

Prediction of prognosis with neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and pathological parameters in operated gastric cancer

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Abstract

Objective: Inflammatory markers are of prognostic importance in many malignancies. This study aimed to examine the effects of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and pathological parameters on survival in preoperative complete blood counts in patients with operated gastric cancer.

Material and Methods: Between 2012 and 2017, 281 patients were analyzed after total/subtotal gastrectomy. According to the ROC curve, we determined the cut-off values for NLR as 2.5 and PLR as 158. Overall survival (OS) was calculated from surgery to the last interview or to death.

Results: In univariate analysis age ≥ 55 ($p = 0.028$), non-adenocarcinoma histology ($p = 0.003$), lymphovascular invasion (LVI) positivity ($p = 0.003$), perineural invasion (PNI) positivity ($p < 0.001$), T 3-4 stage ($p = 0.006$), lymph node involvement (LN) 2-3 ($p < 0.001$), metastatic stage ($p < 0.001$), NLR ≥ 2.5 ($p < 0.001$) and PLR ≥ 158 ($p < 0.001$) were statistically significant for OS. In multivariate analysis age (HR 0.652, 95% CI: 0.475-0.895; $p = 0.008$), PNI positivity (HR 0.493, 95% CI: 0.337-0.720; $p < 0.001$), more lymph node involvement (HR: 0.608, 95% CI: 0.412-0.896, $p = 0.012$), metastatic stage (HR 0.377, 95% CI: 0.265-0.537; $p < 0.001$) and PLR ≥ 158 (HR: 0.610; 95% CI: 0.433-0.859; $p = 0.005$) were found to be independent prognostic factors affecting OS.

Conclusion: Age ≥ 55 , PNI positivity, more lymph node involvement, metastatic stage, and PLR ≥ 158 are independent prognostic factors for shorter overall survival. Given the high morbidity and mortality of gastric cancer, besides classical known prognostic factors, parameters such as preoperative PLR may have benefits for forecast the prognosis of gastric cancer.

Keywords: Gastric cancer, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, prognosis

Introduction

Gastric cancer is the fifth most common malignancy worldwide (1). Surgery is considered the main curative treatment for gastric cancer, but survival is fairly low (2). Even if gastric surgery is performed, distant metastasis or local recurrence will be seen in approximately 35-70% of patients within 5 years (3). The TNM stage is the gold standard for predicting the prognosis of patients with gastric cancer, still. However, the TNM stage is determined postoperatively. Laboratory parameters showing systemic inflammation were researched as prognostic biomarkers in many cancers (4-6). Compared to other factors, NLR and PLR are easily, routinely, and almost cheaply achieved. Some indexes of inflammatory cells, such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), have become prognostic factors and are used to predict survival (7).

With the reduction of vascular perfusion, the endothelium is activated, which causes inflammation. Pro-inflammatory factors are secreted from platelets, which also contributes to inflammation and tumor progression (8). Neutrophils have different duties in the process from the onset of the tumor to its growth and metastasis. Tumor manufactures granulocyte colony-stimulating factor (G-CSF) and the number of neutrophils in the peripheral blood increases (9). One of the highest tumor burden sicknesses is gastric cancer. Blood count parameters such as PLR can be used to predict survival along with known prognostic factors in patients with operated gastric cancer. We aimed to be able to forecast the prognosis with simple assays that can be performed before surgery and with clinicopathological parameters after surgery in this study.



Material and Methods

The study was approved by the Ethical Committee of the our hospital and complied with the standards of the Declaration of Helsinki (1993/2019). This was a retrospective study. The inclusion criteria as follows: (1) Karnofsky performance status being ≥ 80 ; (2) not in the metastatic stage. The exclusion criteria as follows: (1) another synchronous or metachronous malignity (2) chronic inflammatory disease (3) blood transfusion before surgery (4) receive neoadjuvant chemotherapy. Between 2012 and 2017, 281 patients were included in this retrospective study after total/subtotal gastrectomy. The patients were followed at the Department of Radiation Oncology at the University of Health Sciences, Istanbul Training, and Research Hospital. Radiotherapy was planned three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT). After gastric surgery for radiotherapy, tumor bed and nodal volumes were structured with preoperative/postoperative imaging and surgical clip location. If lymph nodes were involved, for all resection and anastomosis fields, and nodal drainage areas uses to 45 Gy radiotherapy doses. If surgical margins positive, the dose is raised to 50.4 Gy to the surgical bed or at risk areas. Systemic chemotherapy as infusional 5-fluorouracil and orally capecitabine were administered. In the first two years, patients were watched over with three monthly periods and then each six months in the third year and annually afterward. For complete blood counts was used XN-900 hematology analyzer (Symex, Japan). The normal reference range for neutrophils $1,56-6,13 \times 10^9 / L$, for lymphocytes to $1.18-3,57 \times 10^9 / L$ and platelets for $142-424 \times 10^9 / L$. The NLR and PLR respectively were found as follows: NLR = Neutrophil / Lymphocyte; and PLR = Platelet / Lymphocyte. Complete blood count was performed before surgery.

Statistical analysis

Categorical variables were analyzed using the Pearson Chi-square test, and non-categorical variables were analyzed using Fisher's exact test. The relationship between NLR, PLR, and pathological parameters were evaluated by ROC curves, Kaplan-Meier analyses, and Cox regression survival analyses and used to calculate overall survival (OS) characteristics. OS was calculated from surgery to the last interview or to death. The SPSS 22.0 (Chicago, IL, USA) program was used in all analyses. A p-value of <0.05 was considered statistically significant.

Results

According to the ROC curve, we determined the cut-off values for NLR 2.5 (AUC: 0.687; 95% CI: 625-749; $p < 0.001$) and the cut-off values for PLR 158 (AUC: 0.648; 95% CI: 583-714; $p < 0.001$). The median age was 57 (range: 22-80). Female/male ratio of the patients was: 78/203, approximately 1/3. There were 178 (63%) patients diagnosed with adenocancer and 103 (rignet cell: 84, mucinous type: 19) patients of other hystological subtypes. The location of tumor was antrum ($n=80$; 29%), small curvature ($n=76$; 27%), corpus ($n=49$; 17%), cardia ($n=45$; 16%), pilor ($n=19$; 7%) and big curvature

($n=12$; 4%), respectively. Two hundred forty-eight (78 %) patients had total gastrectomy and 63 (22 %) patients had subtotal gastrectomy. Postoperative lenfovascular invasion (LVI) positive patients were 210 (75 %) and perineural invasion (PNI) positive patients were 193 (69 %). There were patients at the T1-2 stage ($n=36$; 13%) and T3-4 stage ($n=245$; 87%); patients at the N0-1 stage ($n=96$; 34%) and N2-3 stage ($n=185$; 66%). Metastasis present patients were 119 (42%) and metastasis absent were 162 (58%). There were TNM stage 2 ($n=87$; 31%) and TNM stage 3 ($n=194$; 69%) patients. The radiation was applied by 1.8 Gy fractions/day 45 Gy in 25 fractions in 269 (96%) patients and 1.8 Gy fractions/day 50.4 Gy in 28 fractions in 12 (4%) patients. All patients were completed radiotherapy. FUFA (5-Fluorourasil and calcium folinate) regimen was administered 222 (79%) patients, infusional 5-fluorouracil was administered to 32 (12%) patients and orally capecitabine in 21 (7%) patients as a cycle before and after radiotherapy (RT). There were 6 (2%) patients have not receiving (because of advanced age) concomitant chemoradiotherapy (CCRT). And all advanced age patients were performed radiotherapy. The most common metastasis was to the peritoneum ($n=37$), liver ($n=36$) and lung ($n=16$), bone ($n=11$), lymph nodes ($n=10$) and others ($n=9$) respectively. Patients overall survival rate was 54 % for 2-years and 28 % in 5-years.

When the patients were evaluated according to $NLR \geq 2.5$ and $NLR < 2.5$ levels; LVI positivity ($p=0.014$), advanced T stages ($p=0.004$), LN 2-3 ($p < 0.001$), metastatic stage ($p < 0.001$) were statistically significant.

When the patients were evaluated according to $PLR \geq 158$ and $PLR < 158$ levels; the metastatic stage ($p=0.001$) were statistically significant. There was no statistical significance found between other parameters and PLR. Age, gender, histology, tumor differentiation, and PNI were not statistically significant in both NLR and PLR groups. The general demographic comparisons of patients according to NLR and PLR values are seen in Table-1.

In univariate analysis; age ≥ 55 ($p = 0.028$), other hystology ($p = 0.003$), LVI positivity ($p = 0.003$), PNI positivity ($p < 0.001$), T 3-4 stage ($p = 0.006$), LN 2-3 ($p < 0.001$), metastatic stage ($p < 0.001$), $NLR \geq 2.5$ ($p < 0.001$) and $PLR \geq 158$ ($p < 0.001$) were statistically significant for OS.

In multivariate analysis, age (HR: 0.652, 95% CI: 0.475-0.895; $p = 0.008$), PNI positivity (HR: 0.493, 95 % CI: 0.337-0.720 $p < 0.001$), more lymph node involvement (HR 0.608, 95 % CI: 0.412-0.896; $p = 0.012$), metastatic stage (HR: 0.377, 95 % CI : 0.265-0.537 $p < 0.001$) and $PLR \geq 158$ (HR: 0.610, 95%CI 0.433-0.859; $p = 0.005$) were found to be independent prognostic factors affecting OS (Table-2).

For patients with $PLR \geq 158$; 2-year survival was 45%; 5-year survival was 16% (Figure-1).

Table 1. The general demographic comparisons of the patients according to NLR and PLR values. (LVI: Lenfovascular invasion, PNI: Perineural invasion, T: Tumor, N: Lymph node)

		NLR<2,5 (n %)	NLR≥2,5 (n %)	p value	PLR<158 (n %)	PLR≥158 (n %)	p value
Age	< 55	49 (40)	70 (44)	0.452	56 (42)	63 (43)	0.777
	≥ 55	74 (60)	88 (56)		79 (58)	83 (57)	
Gender	Female	32 (26)	46 (29)	0.565	36 (27)	42 (29)	0.694
	Male	91 (74)	112 (71)		99 (73)	104 (71)	
Hystology	Adeno	79 (64)	99 (63)	0.786	83 (62)	95 (65)	0.533
	Others	44 (36)	59 (37)		52 (38)	51 (35)	
Tumor differantiation	Well	14 (11)	12 (8)	0.114	15 (11)	11 (8)	0.585
	Moderately	54 (44)	56 (35)		52 (39)	58 (39)	
	Poorly	55 (45)	90 (57)		68 (50)	77 (53)	
LVI	negative	40 (33)	31 (20)	0.014	41 (30)	30 (21)	0.058
	positive	83 (67)	127 (80)		94 (70)	116 (79)	
PNI	negative	46 (37)	42 (27)	0.052	46 (34)	42 (29)	0.338
	positive	77 (63)	116 (73)		89 (66)	104 (71)	
T stage	1	4 (3)	4 (3)	0.004	5 (4)	3 (2)	0.184
	2	21 (17)	7 (4)		18 (13)	10 (7)	
	3	52 (42)	70 (44)		59 (44)	63 (43)	
	4	46 (38)	77 (49)		53 (39)	70 (48)	
N stage	0	33 (27)	14 (9)	<0.001	28 (21)	19 (13)	0.316
	1	27 (22)	22 (14)		23 (17)	26 (18)	
	2	29 (23)	42 (27)		30 (22)	41 (28)	
	3	34 (28)	79 (50)		53 (40)	60 (41)	
M stage	absent	99 (81)	63 (40)	<0.001	91 (67)	71 (49)	0.001
	present	24 (19)	95 (60)		44 (33)	75 (51)	

Table 2. Univariate and multivariate analyses of factors for the prediction of overall survival. (LVI: Lenfovascular invasion, PNI: Perineural invasion, T: Tumor, N: Lymph node, NI: Not included)

		Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value
Age	<55	1	0.028	1	0.008
	≥55	0.711(0.524-0.963)		0.652(0.475-0.895)	
Gender	Female	1	0.684		NI
	Male	0.933(0.669-1.302)			
Hystology	Adeno	1	0.003	0.772(0.561-1.062)	0.112
	Others	0.635(0.471-0.854)			
Tumor differantiation	Well	1	0.751		NI
	Moderately	1.102(0.605-2.005)			
	Poorly	1.732(0.972-3.084)			
LVI	negative	1	0.003	0.881(0.593-1.307)	0.528
	positive	0.578(0.400-0.834)			
PNI	negative	1	<0.001	0.493(0.337-0.720)	<0.001
	positive	0.451(0.316-0.642)			
T stage	1-2	1	0.006	1.053(0.594-1.866)	0.861
	3-4	0.478(0.281-0.811)			
N stage	N0-1	1	<0.001	0.608(0.412-0.896)	0.012
	N2-3	0.428(0.302-0.606)			
M stage	absent	1	<0.001	0.377(0.265-0.537)	<0.001
	present	0.288(0.211-0.394)			
NLR	NLR<2.5	1	<0.001	0.971(0.669-1.410)	0.879
	NLR≥2.5	0.502(0.367-0.687)			
PLR	PLR<158	1	<0.001	0.610(0.433-0.859)	0.005
	PLR≥158	0.549(0.406-0.741)			

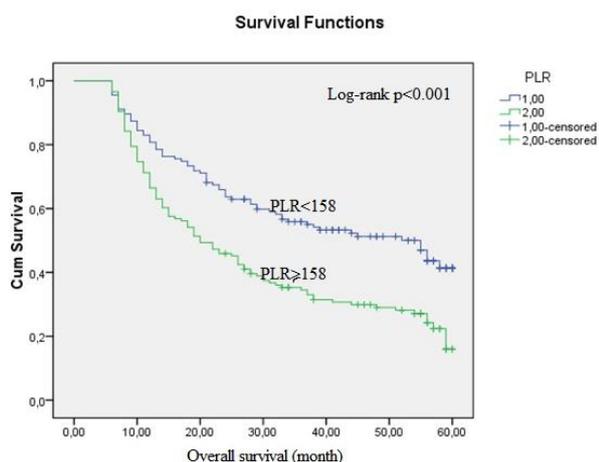


Figure-1. OS for PLR < 158 and PLR \geq 158.

Discussion

The idea that age is a prognostic factor for gastric cancer is contentious. It is most commonly seen in the 50-70 age range (10). In a study of 7762 diseases showing the effect of age on the prognosis of patients with operable gastric cancer, the prognosis was shown to be better in patients diagnosed between 56 and 65 years of age (11). Age was found as a prognostic factor in our study too.

We know that prevalence of gastric cancer is higher among the male than female (12). In our patients, the ratio was in favor of males, too. The WHO classification (13) was used for histopathological classification. And we found 63 % of patients were in adenocarcinoma histology. And when subtypes were evaluated, we did not achieve a statistically significant result that would affect the prognosis.

In Feng et al's study with 3090 patients who treated surgery with a diagnosis of gastric cancer, it was shown that the differentiation status had no prognostic value (14). In this study, we were not found an association with differentiation status and prognosis.

Despite adjuvant treatments administered after surgical treatment, it has not been reported long survival in gastric cancer. This is because most patients have lymph node metastasis or micrometastases during diagnosis. LVI has been described as a beneficial predictor for lymph node involvement or distant metastasis. Lymphovascular invasion was determined to be an independent prognostic factor in many of the studies (15-17). In our study, in univariate analysis lymphovascular invasion was statistically significant, but not prognostic.

In patients with gastric cancer, the stage T, PNI and positive lymph nodes are independent indicators of poor prognosis. More aggressive postoperative treatments should be recommended in PNI-positive patients after surgery (18,19). In our research advanced stage (T3/T4) and the positivity of PNI was statistically important in univariate analysis. But only PNI positivity was found prognostic.

Jiao et al's research, the involvement of lymph nodes in patients with gastric cancer is one of the principal risk factors for poor prognosis. And mostly recognized which is

related to recurrence of tumors (20). The involvement of the lymph nodes has been found to be an independent prognostic factor for OS, in our research too.

A systemic inflammatory response is known to be associated with poor outcomes in many types of cancer. It's not too clear to forecast the recurrence and prognosis of gastric cancer in gastrectomy patients. The mechanisms caused by the inflammatory response are still not absolutely known. Inflammation and cancer are connected each other (21). The tumor microenvironment is extremely significant in carcinogenesis and supports tumor proliferation and dissemination (22,23). Tumor cells and tumor-associated leukocytes can produce various inflammatory cytokines, such as tumor necrosis factor-alpha, interleukin-6, and vascular endothelial growth factor. These have strong effects on cancer growth, invasion, and metastasis (24). Cancer-related inflammation can activate regulatory T cells and chemokines that suppress antitumor immunity (25,26). Inflammation is related to, lymphocytopenia, neutrophilia, thrombocytosis, and leukocytosis (27,28).

Yu et al' s research of 291 patients, in univariate analysis, showed that T-stage, N-stage, TNM stages, and high NLR \geq 3.5 were statistically significant. NLR was identified as an independent prognostic factor in multivariate analysis (29). And we also identified these three factors statistically significant in univariate analysis. In multivariate analysis, we found advanced N stage as independent prognostic factors.

Deng et al' s study involving 389 patients who underwent gastric surgery found that preoperative NLR \geq 2.3 and PLR \geq 132 were associated with poor prognosis in a significant (30).

Jiang et al' s study of 377 non-advanced resectable gastric cancer patients; NLR \geq 1.4 and PLR \geq 184 values are analyzed. The NLR was found to be the prognostic factor for predicting overall survival (31).

Zhang et al' s recent study involving 182 patients showed that NLR \geq 2.8 is a prognostic factor in overall survival and PLR \geq 172 also has predictive value (32). In our study, only PLR was independent prognostic factor for OS.

Cao et al., in gastric cancer meta analysis PLR correlated meaningful with prognosis, but there was no statistical difference between NLR and prognosis (33). But they noted that the study design, the country in which the study was conducted, sample size, treatment methods, and cut values of PLR can be affected by the quality of the study.

Gu et al., they noted that high PLR \geq 154 level is an independent risk factor for poor prognosis in patients with gastric cancer, and that PLR can predict the response of adjuvant chemotherapy (oxaliplatin / 5-fluorouracil combination) in patients with gastric cancer after surgery (34).

In the meta-analysis, which included 49 studies (51 cohorts) with 28,929 gastric cancer patients, they not only investigated the prognostic value of PLR \geq 160 for OS and DFS, but also investigated the relationships between PLR

and gastric cancer clinicopathological characteristics. This analysis showed that high PLR led to a higher risk of lymph node metastasis, increased risk of T stage, and advanced TNM stage risk in patients with gastric cancer (35).

In a study conducted by Zhou and colleagues for 451 patients with operated gastric cancer, preoperative PLR \geq 167 was identified as an independent prognostic factor, as in our study(36).

The 5-year survival rate of patients is less than 20-30%. Our patient's survival rate was 28 % in 5-years. The estimated survival time was 29 months (95% CI:21.90-36.09).

The main constraints of our study were that it was retrospective, small sample size and single-centered.

Conclusion

Age, PNI positivity, more lymph node involvement, metastasis present and PLR \geq 158 are independent prognostic factors for shorter overall survival. Our findings demonstrated that preoperative higher PLR values may be predictors for gastric cancer patients. Given the high morbidity and mortality of gastric cancer, besides classical known prognostic factors, parameters such as preoperative PLR may have benefits for forecast the prognosis of gastric cancer.

Ethical approval: The study was approved by the University of Health Sciences, Istanbul Training and Research Hospital, Ethics Committee.

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Author's contributions: **OM:** Study design, **BI:** Literatur search, **OM, BI:** Material preparation, **OM, BI:** Data collection, **BI:** Statistics, **OM:** Manuscript preparation and revisions.

Ethical issues: All authors declare originality and ethical approval of research. The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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