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Prognostic Significance of Immune-Inflammation Markers, Lodds and LNR in Locally Advanced Gastric Cancer

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ABSTRACT

Objective: Gastric cancer continues to be a pressing issue in global health. This research seeks to examine the relationship between immune system-related inflammatory markers.

Methods: The research involved 184 cases of locally advanced gastric cancer diagnosed between January 2010 and January 2021. In light of its retrospective methodology, the study did not necessitate informed consent, as per institutional ethical guidelines. Receiver operating characteristic analysis was applied to establish the optimal threshold values for the systemic inflammatory response index (SIRI), systemic inflammatory index (SII), prognostic nutritional index (PNI), pan-immune inflammation value (PIV), neutrophil-lymphocyte ratio, lymph node ratio (LNR) and log odds of positive lymph nodes (LODDS). In these groups, survival outcomes were analyzed using the Kaplan-Meier method. The association between mortality and risk factors was assessed using Cox regression analysis. All tests were deemed statistically significant if the $p < 0.05$.

Results: The SIRI, SII, PIV, PNI, LNR and LODDS values were shown to be correlated with overall survival (OS) duration ($p < 0.05$). Cox regression model with multiple variables identified that PNI was an independent determinant of OS ($p = 0.045$).

Conclusion: The conclusions drawn from this research suggest that immune-inflammation markers, along with the LNR and LODDS values of patients with local advanced stage gastric cancer diagnosis may be used as prognostic factors in routine clinical practice. Detection of these immune-inflammation markers, LNR and LODDS values may guide clinicians in prognostic evaluation as well as the creation of personalized treatment approaches.

Keywords: Gastric cancer, LNR, LODDS

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INTRODUCTION

Gastric cancer has the 6th-highest incidence after breast, prostate, lung, colorectal, and cervical cancer, according to GLOBOCAN 2022 predictions for global cancer statistics. With respect to mortality, it ranks 7th, with a rate of 6.1% after lung, breast, colorectal, liver, prostate, and cervical cancers.¹ Accumulating evidence indicates that inflammation plays a crucial role in cancer initiation and progression.² In recent years, immune-inflammation-based markers for patients with cancer have been developed using laboratory parameters that are readily available in routine clinical practice, and their prognostic significance

has been investigated. The systemic inflammatory response index (SIRI), the systemic inflammatory index (SII), the pan-immune inflammation value (PIV), the prognostic nutritional index (PNI), and the neutrophil-lymphocyte ratio (NLR) may be included among these biomarkers.³⁻⁶

Pathological lymph node (pN) classification is determined by the number of lymph nodes removed during gastrectomy that are found to be metastatic on pathological examination. The need to develop different classification systems has emerged with the aim of increasing the reliability of lymph node staging.⁷ The percentage of metastatic lymph nodes relative to the total number of excised lymph nodes,



referred to as the lymph node ratio (LNR), is calculated after surgical resection for locally advanced gastric cancer and serves as a marker of poor prognosis in high-risk patients.⁸⁻¹⁰ The LNR classification system has deficiencies: its prognostic estimation power has been reported to decrease when LNR is 0 or 1. The classification determined using the log odds of positive lymph nodes (LODDS), known as the LODDS value, was identified as better at determining disease prognosis than pN or LNR classifications in gastric cancer. The LODDS value is calculated as the logarithm of the ratio of (metastatic lymph nodes +0.5) to (negative lymph nodes +0.5), and is a novel prognostic factor.¹¹⁻¹⁵

In this study, correlations between the biomarkers SIRI, PIV, NLR, SII, PNI, LNR, and LODDS and prognosis were investigated in patients with locally advanced gastric cancer.

METHODS

Patient Population

From January 2010 to January 2021, the study included 184 patients who were diagnosed with locally advanced-stage gastric cancer and had tests and treatment planned at Dokuz Eylül University, Oncology Clinic; they were aged 18 years or older and had no history of secondary solid or hematological tumors. Our study had a retrospective design, and the clinical information, laboratory and pathology results, and treatments administered to patients were recorded. Overall survival (OS) was defined as the interval from the surgical procedure to death or last follow-up. Locally advanced-stage gastric cancer was defined as cT1b-T4 disease in patients without clinically detectable distant metastasis, with or without lymph node involvement.¹⁶

Immune-Inflammation Markers

Scores for immune-inflammation-based markers were calculated in accordance with definitions and calculation methods reported in the literature, using patients' hematological and biochemical parameters obtained before treatment. The following formulas were used:

NLR: neutrophil ($10^3/\mu\text{L}$)/lymphocytes ($10^3/\mu\text{L}$)

SIRI: [neutrophil ($10^3/\mu\text{L}$) x monocytes ($10^3/\mu\text{L}$)]/lymphocytes ($10^3/\mu\text{L}$)

PIV: [neutrophil ($10^3/\mu\text{L}$) x monocytes ($10^3/\mu\text{L}$) x platelets ($10^3/\mu\text{L}$)]/lymphocytes ($10^3/\mu\text{L}$)

SII: [neutrophil ($10^3/\mu\text{L}$) x platelet ($10^3/\mu\text{L}$)]/lymphocyte ($10^3/\mu\text{L}$)

PNI: [albumin(g/dL) x 10] + [lymphocytes ($10^3/\mu\text{L}$) x 0.005]

To determine cut-off values for SIRI, PIV, NLR, SII, PNI, LNR, and LODDS, receiver operating characteristic (ROC) curve analysis was used, and OS analysis was performed. The analysis results in accordance with the ROC curve determined the mean cut-off values were 1.45 [area under the curve (AUC): 0.574 (95% confidence interval (CI): 0.50-0.64, $p=0.04$)] for SIRI, 391.9 [AUC: 0.567 (95% CI: 0.49-0.63, $p=0.06$)] for PIV, 2.4 [AUC: 0.603 (95% CI: 0.53-0.67, $p=0.004$)] for NLR, 637.5 [AUC: 0.593 (95% CI: 0.52-0.66, $p=0.01$)] for SII, 48 [AUC: 0.606 (95% CI: 0.53-0.67, $p=0.003$)] for PNI, 0.28 [AUC: 0.731 (95% CI: 0.66-0.79, $p<0.001$)] for LNR and 0.40 [AUC: 0.740 (95% CI: 0.67-0.80, $p<0.001$)] for LODDS.

LNR and LODDS Classification

LNR is determined by dividing the number of metastatic lymph nodes by the total number of lymph nodes removed. In addition to cases where LNR is 0 or 1, the LNR value is divided into 5 groups in intervals of 0.1. The LNR classification is LNR 1 (LNR =0), LNR 2 ($0 < \text{LNR} \leq 0.10$), LNR 3 ($0.1 < \text{LNR} \leq 0.2$), LNR 4 ($0.2 < \text{LNR} \leq 0.5$) and LNR 5 ($\text{LNR} > 0.5$). The LODDS value is determined by calculating the logarithm of the ratio of (metastatic lymph nodes +0.5) to (negative lymph nodes +0.5). The categorization of LODDS classes uses intervals of 0.5 and follows a structure comparable to that of LNR classes. The LODDS classification is LODDS 1 ($\text{LODDS} \leq -1.5$), LODDS 2 ($-1.5 < \text{LODDS} \leq -1$), LODDS 3 ($-1 < \text{LODDS} \leq -0.5$), and LODDS 4 ($-0.5 < \text{LODDS} \leq 0$).

Statistical Analysis

Data were analyzed using SPSS 22.0. After descriptive analysis, the normality of quantitative variables was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Comparisons of quantitative variables that did not follow a normal distribution between the mortality and progression groups were performed using the Mann-Whitney U test for independent samples. Comparisons of quantitative variables with a bell-shaped distribution were performed using the Student's t-test. Results are reported as median (range) and mean (standard deviation). Comparisons of categorical variables were performed using Fisher's exact test and the chi-square test. Data are reported as numbers (percentages).

Predictive values of immune-inflammatory markers for mortality and progression/recurrence were determined by analysis of the ROC curve. AUC measurements were determined using the Youden index (YI) for parameters with p value < 0.05 . For each parameter, the value with the highest YI was determined as the cut-off, and the true positive and true negative rates for these cut-offs were calculated. According to these threshold values, patients

were divided into low- and high-risk groups. Survival analysis for these groups was performed using the Kaplan-Meier method. The log-rank test was used to compare median OS values between different risk groups for each parameter. Identification of factors influencing mortality or progression was performed using Cox regression analysis. Findings are reported with 95% confidence. For all tests, $p < 0.05$ was considered statistically significant.

Ethics Committee Approval

The study was completed after receiving approval from the Dokuz Eylül University Non-Interventional Research Ethics Committee (dated 10.05.2023 and numbered 8059-GOA).

RESULTS

Among patients diagnosed with locally advanced gastric cancer, 118 male and 66 female patients were included. The median age of the 184 patients was 61 years (range 23–85). According to the Eastern Cooperative Oncology Group (ECOG) performance classification, 48.9% of patients were categorized as ECOG 0, 38% as ECOG 1, 11.4% as ECOG 2, and 1.6% as ECOG >2. Regarding treatment, 52.2% of patients had neoadjuvant chemotherapy, 91.8% had surgical treatment, and 63% had adjuvant radiotherapy. When pathological subtypes were evaluated, the most frequent subtype was adenocarcinoma (77.2%), followed by signet ring cell carcinoma (15.2%). Table 1 provides the clinical and pathological details of the study cohort; Table 2 provides the laboratory parameters used to calculate the immune-inflammation-based markers.

Age median, years (min-max)	61.0 (23-85)
Sex, n (%)	
Man	118.0 (64.1)
Woman	66.0 (35.9)
Performance status, n (%)	
ECOG 0	90.0 (48.9)
ECOG 1	70.0 (38.0)
ECOG 2	21.0 (11.4)
ECOG >2	3.0 (1.6)
Comorbid disease, n (%)	
HT	47.0 (25.5)
DM	26.0 (14.1)
CAD	4.0 (2.2)
COPD	18.0 (9.8)
Operation, n (%)	169.0 (91.8)
LNR, n (%)	
LNR 1 (LNR =0)	30.0 (17.9)
LNR 2 (0 < LNR ≤ 0.10)	50.0 (29.8)
LNR 3 (0.1 < LNR ≤ 0.2)	24.0 (14.3)
LNR 4 (0.2 < LNR ≤ 0.5)	45.0 (26.8)
LNR 5 (LNR > 0.5)	19.0 (11.3)

Age median, years (min-max)	61.0 (23-85)
LODDS classification, n (%)	
LODDS 1 (LODDS ≤ -1.5)	32.0 (18.9)
LODDS 2 (-1.5 < LODDS ≤ -1)	35.0 (20.7)
LODDS 3 (-1 < LODDS ≤ -0.5)	43.0 (25.4)
LODDS 4 (-0.5 < LODDS ≤ 0)	59.0 (34.9)
Adjuvant RT, n (%)	116.0 (63)
Neoadjuvant CT, n (%)	96.0 (52.2)
Tumor histopathology, n (%)	
Adenocarcinoma	142.0 (77.2)
Signet ring cell carcinoma	28.0 (15.2)
Other	14.0 (7.6)
LNR, median (min-max)	0.1 (0-1)
LODDS, median (min-max)	-0.8 (-2.1-1.2)

ECOG: Eastern Cooperative Oncology Group, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, LNR: Lymph node ratio, LODDS: Log probability of positive lymph nodes, RT: Radiotherapy, CT: Chemotherapy, min: Minimum, max: Maximum

Parameter	Median	Min-max
NEU	4.5	0.9-24.5
LYM	1.8	0.4-4.1
HB	11.6	6.3-16.3
PLT	250.0	99.0-587.0
Albumin	3.8	1.8-4.8
SIRI	1.4	0.1-26.1
PIV	391.9	8.3-5472
NLR	2.4	0.7-36.5
SII	637.5	82.6-8788
PNI	48.0	21.5-59.5

NEU: Neutrophil, LYM: Lymphocyte, HB: Hemoglobin, PLT: Platelets, SIRI: Systemic inflammatory response index, PIV: Pan-immune inflammation value, NLR: Neutrophil lymphocyte ratio, SII: Systemic inflammatory index, PNI: Prognostic nutritional index, min: Minimum, max: Maximum

The median OS of patients was identified as 35.5±4.6 months. Patients with age under or equal to 61 years had median OS of 44.9±7.8 months, while patients over 61 years of age had median OS of 28.4±4.2 months and a notable statistical variation was detected across the age categories ($p = 0.020$).

For patients with SIRI value >1.45, the OS was 44.9±19.6 months, while patients with SIRI ≤1.45 had OS of 27.9±3.2 months and the survival durations between the groups were found to be notable statistical variation ($p = 0.009$). Patients with PIV ≤391.9 had OS of 44±8 months, while patients with PIV >391.9 had OS of 28.1±3.2 months and there a notable statistical variation for OS durations across

the PIV risk categories ($p=0.048$). For cases with $NLR >2.4$, the OS was 44.0 ± 7.1 months, while cases with $NLR \leq 2.4$ had OS of 29.2 ± 3.5 months and there was no notable statistical variation across the groups ($p=0.05$). Patients with $SII \leq 637.5$ had median OS of 44.9 ± 8.7 months, while patients with $SII >637.5$ had median OS of 28.4 ± 2.6 months ($p=0.031$). Patients with $PNI >48$ had median OS that was statistically significantly longer compared to patients with $PNI \leq 48$ (44.9 ± 10.0 months and 28.0 ± 4.5 months, respectively, $p=0.017$). Cases having $LNR >0.28$ had survival durations that were statistically significantly shorter compared to those with $LNR \leq 0.28$ ($p < 0.001$). For cases having $LODDS > -0.40$, the survival durations were statistically significantly worse than for those having $LODDS \leq -0.40$ ($p < 0.001$) (Table 3). According to the results of a multivariable Cox regression model developed using immune-inflammation markers PNI values were independent determinants of OS ($p=0.045$) (Table 4).

DISCUSSION

In this study, significant correlations were observed between immune-inflammation-based markers (SIRI, PIV, SII, PNI), LNR, and LODDS and OS in patients with locally advanced gastric cancer.

SIRI is an index derived from levels of neutrophils, monocytes, and lymphocytes, reflecting the relationship between inflammatory processes and immune function.

In our study, those with SIRI values >1.45 had a significantly shorter median OS. This finding is consistent with the literature reporting that elevated SIRI is associated with an unfavorable prognosis in gastric cancer. Ren et al.¹⁷ similarly associated higher SIRI values with poor OS; however, they did not find an optimal cut-off value. Another study proved that the SIRI index was an independent determinant in patients with gastric cancer who underwent radical gastrectomy.¹⁸ In the literature, the five-year survival rate for gastric cancer cases with high preoperative NLR has been reported to be considerably shorter than that for

Table 3. Correlation of immune-inflammation markers, LNR and LODDS with overall survival

Parameter	Kaplan-meier analysis			Cox regression analysis (univariate)	
	Median OS (month)	95% CI	p	HR	p
Age ≤61 years >61 years	44.9±7.8 28.4±4.2	29.6-60.1 20.1-36.7	0.019	1.6 (1.1-2.3)	0.020
Sex Man Woman	42.8±5.9 33.0±3.3	31.3-54.3 26.6-39.5	0.868	1.0 (0.7-1.5)	0.868
SIRI ≤1.45 >1.45	44.9±19.6 27.9±3.2	6.4-83.3 21.6-34.3	0.009	1.7 (1.1-2.5)	0.010
PIV ≤391.9 >391.9	44.0±8.0 28.1±3.2	28.4-59.6 21.8-34.5	0.048	1.5 (1.0-2.2)	0.050
NLR ≤2.4 >2.4	44.0±7.1 29.2±3.5	30.1-57.9 22.3-36.2	0.050	1.5 (1.0-2.2)	0.051
SII ≤637.5 >637.5	44.9±8.7 28.4±2.6	27.9-61.9 23.4-33.5	0.031	1.5 (1.0-2.2)	0.032
PNI >48.0 ≤48.0	44.9±10.0 28.0±4.5	25.3-64.4 19.1-36.7	0.017	1.6 (1.1-2.3)	0.019
LNR ≤0.28 >0.28	103.5±--- 24.4±3.3	---- 17.9-30.8	<0.001	3.7 (2.4-5.6)	<0.001
LODDS ≤-0.40 >-0.40	103.5±--- 24.4±3.3	---- 17.9-30.8	<0.001	3.7 (2.4-5.6)	<0.001

SIRI: Systemic inflammatory response index, PIV: Pan-immune inflammation value, NLR: Neutrophil lymphocyte ratio, SII: Systemic inflammatory index, PNI: Prognostic nutritional index, LNR: Lymph node ratio, LODDS: Log probability of positive lymph nodes, CI: Confidence interval, OS: Overall survival, HR: Hazard ratio

Table 4. Cox regression model with multiple variables

	Cox regression model with multiple variables		
	HR	95% CI	p
SIRI ≤1.45 (92.0) vs. >1.45 (92.0)	2.2	1.0-5.2	0.050
PIV ≤391.9 (92.0) vs. >391.9 (92.0)	0.7	0.3-1.8	0.481
NLR ≤2.4 (92.0) vs. >2.4 (92.0)	0.7	0.3-1.5	0.383
SII ≤637.5 (92.0) vs. >637.5 (92.0)	1.4	0.6-2.8	0.421
PNI >48.0 (92.0) vs. ≤48.0 (91.0)	1.5	1.0-2.3	0.045

SIRI: Systemic inflammatory response index, PIV: Pan-immune inflammation value, NLR: Neutrophil lymphocyte ratio, SII: Systemic inflammatory index, PNI: Prognostic nutritional index, CI: Confidence interval, HR: Hazard ratio

cases with low NLR.^{19,20} According to the results of this study, no meaningful relationship was found between NLR and survival (Table 2, $p=0.05$).

With locally advanced gastric cancer, patients with SII >637.5 had shorter median OS duration compared to patients with SII ≤637.5. In the literature, cases with elevated SII exhibited shorter OS.²¹ A study including a broad group of patients found that increased SII prior to surgery is an independent determinant of adverse prognosis in gastric cancer.²⁰

In cases with locally advanced gastric cancer, cases with PNI >48 had statistically significantly longer median OS compared to patients with PNI ≤48. In our study, in light of the results from the Cox regression model with multiple variables developed using immune-inflammation markers, cases with a PNI ≤48 demonstrated a substantial increase in mortality ($p=0.045$). In the literature, increased PNI was associated with longer OS. In these studies, multivariate analyses showed that a low PNI value was an independent determinant of worse OS.^{22,23} Identifying PNI as an independent risk factor for OS reiterates the importance of nutritional status for cancer prognosis. Providing nutritional support to patients with gastric cancer in the preoperative period has the potential to improve survival. Additionally, combining PNI with other inflammation markers may be beneficial in creating stronger prognostic models.

In our study, the LNR and LODDS values, which evaluate lymph node metastasis, were correlated with prognosis. In patients having an LNR >0.28, median OS was statistically

significantly shorter in comparison to those with an LNR ≤0.28. In the literature, the percentage of lymph nodes involved by metastasis has served as a prognostic indicator, independent of the number of lymph nodes removed during the operation. An increase in this proportion was associated with decreased OS.^{24,25} As part of our research, cases with LODDS >-0.40 were found to have statistically significantly shorter median OS relative to cases with LODDS ≤-0.40. Determining pN stages based solely on the lymph node count with metastasis and the classification variation between <15 and ≥15 lymph nodes highlighted the need for stronger prognostic measures, such as LNR and LODDS, to predict outcomes. LODDS accounts for both metastatic and non-metastatic lymph node counts. It was developed to provide an accurate prognostic assessment for patients with pN0 and <15 removed lymph nodes. In the literature, as the LODDS degree increases, prognosis is affected, and LODDS appears to be a more reliable prognostic indicator than pN.²⁶

CONCLUSION

Our study demonstrated the usefulness of the immune-inflammation markers LNR and LODDS as prognostic factors in clinical practice for patients with locally advanced gastric cancer. Due to the ease of measurement using routine blood tests and the number of lymph nodes with and without metastasis in pathology reports, they offer practical and economic benefits. Detection of these immune-inflammation markers, LNR and LODDS values, may guide clinicians in predicting patient prognosis and planning optimal treatment.

Ethics

Ethics Committee Approval: The study was completed after receiving approval from the Dokuz Eylül University Non-Interventional Research Ethics Committee (dated 10.05.2023 and numbered 8059-GOA).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.K., Concept: M.U., İ.T.Ü., Design: M.U., İ.T.Ü., Data Collection or Processing: M.K., Analysis or Interpretation: M.K., M.U., İ.T.Ü., Literature Search: M.K., Writing: M.K.

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