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**Original Article**

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

**KILINÇ et al. Immune Markers in Advanced Gastric Cancer**

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**Abstract**
**Introduction:** Gastric cancer continues to be a pressing issue in global health. This research seeks to examine the relationship between immune system-related inflammatory markers.
**Material and Method:** 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. ROC 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 (NLR), 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 duration ($p<0.05$). Cox regression model with multiple variables identified that PNI was an independent determinant of overall survival ($p=0.045$).
**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

## INTRODUCTION

Gastric cancer is the cancer with 6th highest incidence after breast, prostate, lung, colorectal and cervical cancer according to GLOBOCAN 2022 predictions for global cancer statistics. For mortality, it is in 7th place with 6.1% rate after lung, breast, colorectal, liver, prostate and cervical cancer.[1] Evidence is increasing that inflammation plays a crucial role in the initiation and spread of cancer.[2] In recent years, immune-inflammation-based markers have been created for cancer patients using laboratory parameters easily accessed in routine clinical practice and the prognostic significance of these markers has been researched. The systemic inflammatory response index (SIRI), systemic inflammatory index (SII), pan-immune inflammation value (PIV), prognostic nutritional index (PNI) and neutrophil-lymphocyte ratio (NLR) may be listed among these biomarkers.[3-6]

Pathological lymph node (pN) classification is evaluated by the quantity of lymph nodes removed during the gastrectomy procedure and assessed as metastatic as a result of pathological investigation. The need to develop different classification systems has emerged with the aim of increasing the reliability of lymph node staging.[11] The percentage of metastatic lymph nodes relative to the total count of excised lymph nodes is referred to as the Lymph Node Ratio (LNR), which is calculated after surgical resection of locally advanced-stage gastric cancer and serves as a marker predicting poor prognosis in high-risk patients.[7-9] There are deficiencies in the LNR classification system with the estimation power for disease prognosis reported to reduce when LNR is 0 or 1. Classification is determined using the log odds of positive lymph nodes, known as the LODDS value was identified to determine disease prognosis better compared to pN or LNR classifications in gastric cancer. The LODDS (Log Odds of Positive Lymph Nodes) value is determined by calculating the log value of the ratio between metastatic lymph nodes + 0.5 to negative lymph nodes + 0.5 and is a new prognostic factor.[10-15]

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

## MATERIAL AND METHOD

### Patient Population

From January 2010 to January 2021, the study included 184 patients, with tests and treatment planned for locally advanced-stage gastric cancer diagnosis in xxx Oncology Clinic, aged 18 years and older without secondary solid or hematological tumor history. Our study had retrospective design and the clinical information, laboratory and pathology results and treatments given to patients were recorded. Overall survival (OS) was described by the period extending from the surgical procedure to either death or the last follow-up. Locally advanced stage gastric cancer was defined in cT1b-T4 patients without clinically distant metastasis, with or without any lymph node involvement.[16]

### Immune-Inflammation Markers

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

NLR: neutrophil ($10^3$/μL) / lymphocytes ($10^3$/μL)

SIRI: [neutrophil ($10^3$/μL) x monocytes ($10^3$/μL)] / lymphocytes ($10^3$/μL)

PIV: [neutrophil ($10^3$/μL) x monocytes ($10^3$/μL) x platelets ($10^3$/μL)] / lymphocytes ($10^3$/μL)

SII: [neutrophil ($10^3$/μL) x platelet ($10^3$/μL)] / lymphocyte ($10^3$/μL)

PNI: [albumin (g/dL) x 10] + [lymphocytes ($10^3$/μL) x 0.005]

To determine cut-off values for SIRI, PIV, NLR, SII, PNI, LNR and LODDS measurements, the ROC curve 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 (AUC: 0.574 (95%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 count of the quantity of metastatic lymph nodes in comparison to the overall number of lymph nodes removed. Along with situations where LNR is 0 and 1, the LNR value is divided into 5 groups at 0.1 intervals. The LNR classification is LNR 1 (LNR=0), LNR 2 (0<LNR≤0.10), LNR 3 (0.1<LNR≤0.2), LNR 4 (0.2<LNR≤0.5) and LNR 5 (LNR>0.5). The LODDS value is determined by calculating the log value of the ratio between metastatic lymph nodes + 0.5 to negative lymph nodes + 0.5. The categorization of LODDS classes follows a comparable structure to that of LNR classes, using intervals of 0.5. The LODDS classification is LODDS 1 (LODDS ≤-1.5), LODDS 2 (<-1.5 LODDS ≤-1), LODDS 3 (<-1 LODDS≤-0.5), and LODDS 4 (-0.5<LODDS≤0).

### Statistical Assessment

The analysis of data was carried out utilizing SPSS 22.0 software. After descriptive analysis, normal distribution of quantitative variables were evaluated with the Shapiro-Wilk and Kolmogorov-Smirnov tests. Comparisons of quantitative variables, which do not follow a bell curve distribution, between mortality and progression groups were made using a test for independent samples with no distributional assumptions (Mann-Whitney U test). Comparisons of quantitative variables with bell curve distribution used the Student T test. Results are reported as median (range) and mean values with standard deviation. The comparison of categorical variables was performed with the Fisher's exact test and chi-square test. Data are reported in number (percentage).

Predictive values of immune-inflammatory markers for mortality and progression/recurrence were determined with analysis of the ROC curve. The measurements of the area under the curve (AUC) were determined with the Youden index (YI) for parameters with p value <0.05. For each parameter, the value with highest YI value was determined as the cut-off and the true positive rate and true negative rate values for these cut-off values were calculated. According to these threshold values, patients were divided into low and high-risk groups. Survival analysis in these groups was performed with Kaplan-Meier analysis. The log-rank test was utilized to assess the median OS values for each parameter across the different risk groups. Identification of factors influencing mortality or progression involved the Cox regression analysis. Findings are reported along with 95% certainty. For every test, p<0.05 was deemed statistically significant.

**Ethics Committee Approval**

The study was completed after receiving ethics committee approval from xxx Non-Interventional Research Ethics Committee dated 10.05.2023 and numbered 8059-GOA.

**RESULTS**

Among patients diagnosed with locally advanced gastric cancer, a total of 118 male and 66 female were included. The median age of the total of 184 patients was calculated as 61 years (23-85). According to ECOG performance classification, 48.9% of patients were categorized as ECOG 0, 38% were ECOG 1, 11.4% were ECOG 2 and 1.6% were ECOG >2. For treatment, 52.2% of patients had neoadjuvant chemotherapy, 91.8% had surgical treatment and 63% had adjuvant radiotherapy. When pathological subtypes are evaluated, the most frequently seen subtype was adenocarcinoma in 77.2%, followed by signet ring cell carcinoma in 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.

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 ≤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 ≤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 ≤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 ≤0.28 (p<0.001). For cases having LODDS>-0.40, the survival durations were statistically significantly worse than for those having LODDS ≤-0.40 (p<0.001) (Table 3). According to the outcomes of the Cox regression model with multiple variables, developed using immune-inflammation markers, PNI values were found to be an independent determinant of OS ($p$=0.045) (Table 4).

**DISCUSSION**

In this study, significant correlations were shown between immune-inflammation-based markers (SIRI, PIV, SII, PNI), LNR, and LODDS values related to overall survival in cases diagnosed with locally advanced-stage gastric cancer.

SIRI is an index derived from neutrophil, monocyte, and lymphocyte levels, illustrating the relationship between inflammatory processes and immune function.

In our study, those with SIRI value >1.45 had statistically significantly shorter median OS. This finding is consistent with the literature reporting that elevated SIRI levels are associated with an unfavorable prognosis in cases of gastric cancer. Ren et al. similarly associated higher SIRI values with poor OS;

however, they did not find an optimal cut-off value.[17] Another study proved that the SIRI index is an independent determinant in cases of gastric cancer who received radical gastrectomy.[18] In the literature, the five-year survival rate for cases diagnosed with gastric cancer and high NLR measured in the preoperative period was reported to be considerably shorter than that of 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 levels exhibited a shorter OS.[21] A study including a broad patient group evaluated that increased SII prior to surgery is recognized as 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 literature, an increased PNI demonstrated a longer OS. In these studies, multivariate analyses showed that low PNI value was an independent determinant of worse OS.[22,23] Determining PNI as an independent risk factor affecting overall survival reveals the importance of nutritional status for cancer prognosis once more. As a result, providing nutritional support in the preoperative period to patients with gastric cancer has the potential to improve survival. Additionally, combining PNI with other inflammation markers may be beneficial to create stronger prognostic models.

In our study, the LNR and LODDS values, evaluating lymph node metastasis, were found to be 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 with metastasis served as a prognostic indicator, independent of all lymph nodes removed during the operation. As this proportion increased, it 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 for accurate prognostic assessment for patients with pN0 and <15 removed lymph nodes. In the literature, as the LODDS degree increases, prognosis appears as well as a more reliable prognostic indicator compared to pN.[27]

**CONCLUSION**

In conclusion, our study showed the usefulness of immune-inflammation markers, LNR and LODDS values as prognostic factors in clinical practice for cases of locally advanced gastric cancer. Due to the ease of measurement with routine blood tests and the amount of lymph nodes with metastasis/without metastasis in pathology reports, they offer practical and economic contributions. Detection of these immune-inflammation markers, LNR and LODDS values may guide clinicians when predicting prognosis for patients and making optimal treatment plans.

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**Table 1. Patient clinical and pathological features**

| | |
|---|---|
| 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) |
| 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

**Table 2. Immune-inflammation markers of patients**

| **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

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

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

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

**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