

The Prognostic Effect of Metastatic Lymph Node Ratio in Operated Gastric Cancer Patients

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ABSTRACT

Objective: To assess the prognostic importance of metastatic lymph node ratio (MLNR) in operated gastric cancer patients.

Study Design: Observational study.

Place and Duration of Study: Health Sciences University, Yildirim Beyazit Diskapi Training and Research Hospital, Department of General Surgery, Ankara, Turkey, between January 2014 and March 2019.

Methodology: Initially, record of a total of 171 patients, operated for gastric cancer, were retrieved. Inclusion criteria involved having gastric adenocarcinoma, undergoing curative-intent surgery, absence of neoadjuvant chemotherapy, dissection of ≥ 15 lymph nodes, negative surgical margins, and no mortality within the first 30 days after surgery. Thirty patients were excluded for various reasons. Thus, clinicopathological features and prognostic factors including MLNR on overall and disease-free survival (DFS) were evaluated for the remaining 141 patients.

Results: The median age of the 141 patients was 63 years (IQR: 54 – 72 years). The median MLNR was 0.18 (IQR: 0 – 0.47). The cut-off value with highest sensitivity and specificity was determined as 0.25 (area under the curve (AUC); 0.724, CI 95%; 0.639-0.808, $p < 0.001$) in ROC curve analysis. Multivariable Cox regression analysis showed MLNR and perineural invasion (PNI) as independent prognostic factors. Patients with MLNR > 0.25 had a 2.39-fold higher risk of disease progression, and 3.76-fold higher risk of shorter survival.

Conclusion: The study contributed to the literature that MLNR is practical and useful as an independent prognostic factor predicting survival even better than tumor/node/metastasis (TNM) staging system.

Key Words: Gastric cancer, Metastatic lymph node ratio, Prognostic factor, Surgery.

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INTRODUCTION

Gastric cancer is the 5th most common cancer in the world, and the third most common cause of cancer related death.^{1,2} Many gastric cancers are in the advanced stage when diagnosed, but still is amenable to treatment by radical gastrectomy with regional lymph node dissection. However, these patients have poor survival compared with early disease.¹ Gastric cancer can be diagnosed at an early stage, even if there is no clinical finding, with the improvement of diagnostic techniques and implementation of intensive screening programmes.³ Surgery is the only proven curative treatment; nevertheless, locoregional recurrence and distant metastasis rates are high.⁴

There is no effective treatment in case of recurrence. Therefore, identifying prognostic and predictive markers would be helpful to evaluate the exact condition of the disease and to plan more effective treatment.^{5,6}

Adequate staging is essential in predicting prognosis. Tumor invasion depth and nodal involvement are important prognostic markers in surgical candidates.⁴ TNM staging is the most commonly used prognostic factor in gastric cancer.⁷⁻⁹ Traditionally, TNM classification is used, based on the number of metastatic lymph nodes.¹⁰ Studies have shown that the classification, according to the number of lymph nodes, is more sensitive; and it has a superior prognostic value than the classification based on lymph node localization.^{9,11,12} In TNM classification, at least 15 lymph nodes have to be removed for accurate staging.^{9,13} However, this rate is seldom achieved.¹⁴

Lymph node-positive patients have a worse prognosis than negative patients.⁷ Despite intensive search for novel prognostic factors such as serum and histopathological markers or molecular information, TNM staging remains to be the most commonly used prognostic factor to date.^{7,15} On the other hand, Japanese Gastric Cancer Association (JGCA) prefers localisation

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for nodal staging.^{9,16} For correct nodal staging, sufficient number of dissected lymph nodes that is representative of geographic location are required. However fulfilling these two requirements, cause complexity and might lead to erroneous staging named stage shift.¹³ Several studies have shown that MLNR can be an excellent independent prognostic marker in both early and advanced gastric cancers.^{8,9,13}

Metastatic lymph node ratio is calculated by dividing the number of metastatic lymph nodes to the number of dissected lymph nodes. This ratio is also known as lymph node density.^{7,17}

Metastatic lymph node ratio varies between 0 and 1. The more the number of metastatic lymph nodes, the higher the MLNR; and it is associated with a worse prognosis.^{1,7,18} Moreover, MLNR can prevent stage migration that is seen with TNM classification.⁹

The aim of the present study was to assess the effect of the prognostic factors on overall and disease-free survival in D1 or D2 type lymph node dissection in gastric cancer patients with special emphasis on the prognostic value of MLNR.

METHODOLOGY

Patients with gastric cancer, who underwent gastric surgery between January 2014 and March 2019 at the Department of General Surgery Health Sciences University, Yildirim Beyazıt Diskapi Training and Research Hospital were evaluated retrospectively. Inclusion criteria involved having gastric adenocarcinoma, undergoing surgery with a curative intent, absence of neoadjuvant chemotherapy, dissection of at least 15 lymph nodes, negative surgical margins, and no mortality within the first 30 days after surgery. Exclusion criteria included having a non-gastric adenocarcinoma or neuroendocrine differentiation, palliative surgery, having received neoadjuvant chemotherapy, dissection of less than 15 lymph nodes, positive surgical margins, and mortality within the first 30 days.

A total of 171 patients were detected during initial screening. Thirty patients were excluded based on inclusion and exclusion criteria. Finally, 141 patients, who were operated with a curative intent, were included in the analyses. Patient charts and electronic records were used to collect study data including age, gender, tumor localisation, histological subtype, degree of differentiation, TNM stage, presence of lymphovascular invasion (LVI), perineural invasion (PNI), MLNR, type of gastric surgery and lymph node dissection, and presence of adjuvant chemoradiotherapy. Follow-up data, including time of death and disease progression, were retrieved from outpatient hospital database.

All patients included in the study had undergone D1 or D2 type lymph node dissection. MLNR was calculated by the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes. This ratio varies between 0 and 1.

Data were presented as median (IQR), number and percentage. In the survival analysis, DFS was defined as the time between the operation date and the first progression date. Overall

survival (OS) was accepted as the period between the date of operation and the date of exitus or last follow-up date for surviving patients. In addition, the follow-up period was defined between the date of diagnosis and the last control date.

Survival rates were calculated by the Kaplan-Meier method. The univariate analyses were performed using log-rank test. In the multivariate analysis, independent factors predicting survival were analysed by using Cox regression analysis with the backward selection. Results were evaluated in a 95% confidence interval and $p < 0.05$ was found to be a significance level.

The absolute cut-off value of MLNR in predicting disease progression was analysed by the receiver operating characteristics (ROC) curve analysis. According to the analysis, the cases with a sensitivity and specificity limit of less than 5% of the type 1 error in the evaluation of the area under the curve were interpreted to be statistically significant.

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences for Windows) version 18.0.

RESULTS

The median age of the 141 patients was 63 years (IQR: 54 – 72 years). Males comprised 71.6% ($n=101$) of the study population. Adenocarcinoma was located in cardia in 48 (34.0%) patients, in gastroesophageal junction in 46 (32.6%), in corpus in 35 (24.8%), and in antrum in 12 (8.5%) patients. Regarding differentiation, 7 (5.0%) patients had well differentiated tumor, 45 (31.9%) had moderately differentiated, and 89 (63.1%) had poorly differentiated tumor. Lymphovascular invasion was present in 76 patients (53.9%); whereas, PNI was positive in 77 patients (54.6%). Subtotal gastrectomy was performed in 22 (15.6%) patients, and total gastrectomy was performed in 119 (84.4%) patients. Table I states demographic and clinicopathological features of the whole study population.

The median number of extracted lymph nodes was 28 (IQR: 20 – 38), the median number of metastatic lymph nodes was 6 (IQR: 0 – 12), and the median MLNR was 0.18 (IQR: 0 – 0.47). The cut-off value with highest sensitivity and specificity was determined as 0.25 (area under the curve (AUC); 0.724, CI 95%; 0.639-0.808, $p < 0.001$) in ROC curve analysis. The patients performed D2 dissection were not received adjuvant chemoradiotherapy.

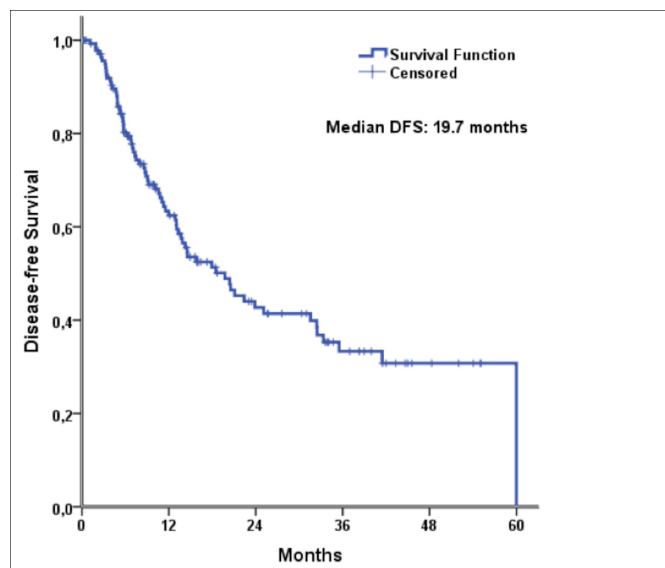
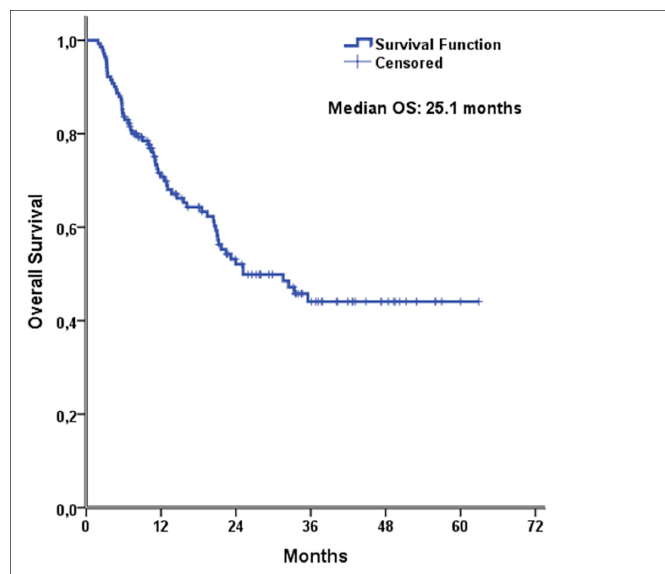
In a median of 15.3 months (IQR: 8.0-32.8) follow-up duration; median DFS was 19.7 months (95% CI: 13.1-26.4), and median OS was 25.1 months (95% CI: 13.5-36.8, Figures 1-a and b). Due to small sample sizes, when each parameter was taken alone, some parameters were grouped as follows: Age was categorised as ≤ 60 and > 60 years, type of differentiation (poorly differentiated and not poorly differentiated), stage (early stage I-II and advanced stage III a-b-c), and receiving adjuvant therapy or not. Initially, a univariate regression analysis was performed to determine the independent predictors of OS and DFS. While age seemed to be a significant predictor of reduced OS, gender had no effect neither for OS nor DFS.

Table I: Clinicopathological characteristics of patients.

Patient characteristics	Number (N)	Percent (%)
Gender: Female / male	40/101	28.4/71.6
Age: ≤60 / >60	60/81	42.6/57.4
Location: Cardia Gastroesophageal junction Corpus Antrum	48 46 35 12	34.0 32.6 24.8 8.5
Adenocarcinoma subtype: Rignet cell Mucinous Diffuse Classic	35 13 3 90	24.8 9.2 2.1 63.8
Differentiation: Poor Moderate Well	89 45 7	63.1 31.9 5.0
Lymphovascular invasion: Positive Negative	76 65	53.9 46.1
Perineural invasion: Positive Negative	77 64	54.6 45.4
Operation: Subtotal gastrectomy Total gastrectomy	22 119	15.6 84.4
Dissection type: D1 D2	9 132	6.4 93.6
Adjuvant chemotherapy: Received Non-received	108 33	76.6 23.4
Adjuvant chemoradiotherapy: Received Non-received	64 77	45.4 54.6
Metastatic lymph node ratio: ≤0.25 >0.25	85 56	60.3 39.7
Tumor: T1a T1b T2 T3 T4a T4b	4 9 20 39 66 3	2.8 6.4 14.2 27.7 46.8 2.1
Node: N0 N1 N2 N3a N3b	37 14 24 33 33	26.2 9.9 17.0 23.4 23.4
Stage: Ia Ib IIa IIb IIIa IIIb IIIC	9 14 16 9 15 30 48	6.4 9.9 11.3 6.4 10.6 21.3 34.0

Since the number of patients, who underwent total and subtotal gastrectomy was quite different, the type of operation was not evaluated in the univariate analyses due to imbalance of the patient numbers.

Univariate analysis results showed that the type of differentiation and presence of adjuvant therapy did not affect DFS and OS. However, according to TNM staging, presence of an advanced stage was significantly reduced DFS and OS compared with early stage. In addition, the presence of LVI and PNI significantly reduced both OS and DFS. MLNR affected both DFS and OS. In ROC curve analysis, the cut-off value as 0.25 was accepted in keeping with the literature; and it revealed that MLNR greater than 0.25 significantly reduced both DFS and OS. All univariate analyses were given in Tables II and III.

**Figure 1-a: Disease-free survival curve.****Figure 1-b: Overall survival curve.**

The factors affecting DFS in univariate analysis were tumor stage of TNM, MNLN, PNI and LVI. Multivariable Cox regression analysis comprising those showed MLNR and PNI as independent factors for prognosis. Patients with MLNR >0.25 had a 2.39-fold higher risk of disease progression. The presence of PNI increased the risk of progression by 3.47 times. TNM stage was not a significant predictor of DFS.

Table II: Factors affecting disease-free survival in univariate analysis.

Characteristics	Median DFS	95% Confidence interval	p-value
Gender: Female Male	35.5 15.8	12.3-58.7 9.2-22.4	0.249
Age (years): ≤60 >60	20.5 17.9	11.9-29.1 8.2-27.6	0.168
MLNR: ≤0.25 >0.25	35.5 8.8	28.3-42.7 4.8-12.9	<0.001
LVI: Negative Positive	32.5 13.0	19.6-45.3 8.8-17.3	0.002
PNI: Negative Positive	60.0 11.5	NA 7.1-16.0	<0.001
Differentiation: Not poorly Poorly	17.9 20.5	11.2-24.7 11.2-29.9	0.756
Stage: Early Advanced	60.0 13.0	NA 10.1-16.0	<0.001
Adjuvant treatment: Received Not received	18.5 20.5	12.2-24.8 0.0-51.2	0.778

DFS: Disease-free survival, MLNR: Metastatic lymph node ratio, LVI: Lymphovascular invasion, PNI: Perineural invasion, NA: Not applicable.

Table III: Factors affecting overall survival in univariate analyses.

Characteristics	Median OS	95% Confidence interval	p-value
Gender: Female Male	NR 24.0	NA 13.2-34.8	0.353
Age (years): ≤60 >60	NR 23.2	NA 11.2-35.3	0.032
MLNR ≤ 0.25 > 0.25	NR 11.9	NA 6.6-17.4	<0.001
LVI Negative Positive	35.5 20.5	NA 12.1-29.0	0.033
PNI Negative Positive	NR 19.4	NA 11.7-27.1	<0.001
Differentiation Not poorly Poorly	23.2 35.5	18.6-27.9 NA	0.423
Stage Early Advanced	NR 18.5	NA 11.6-25.5	<0.001
Adjuvant treatment Received Not received	24.0 32.5	NA 16.8-48.1	0.912

OS: Overall survival, MLNR: Metastatic lymph node ratio, LVI: Lymphovascular invasion, PNI: Perineural invasion, NR: Not reached, NA: Not applicable.

The factors affecting OS in univariate analyses were MLNR, LVI, PNI, advanced tumor stage, and advanced age (>60 years). In multivariate Cox regression analysis, advanced age and MLNR remained independent poor prognostic factors for OS. Patients with MLNR >0.25 had a 3.76-fold higher risk of shorter OS.

DISCUSSION

The most notable findings of this present study were that MLNR was an independent predictor of progression-free and overall survival in operated gastric cancer patients. When the cut-off label was taken as >0.25, MLNR showed a 2.39-fold higher risk of disease progression and 3.76-fold higher risk of shorter survival.

Adequate staging is vital in predicting prognosis in gastric

cancer patients.^{4,5} The minimum number of lymph nodes required for adequate staging is accepted as 15.^{19,20} Inadequate lymph node dissection leads to inadequate evaluation of prognosis.¹⁰ Studies have shown that the higher the number of lymph node examination after gastrectomy, the better the survival.²⁰ MLNR was suggested as a reliable and reproducible method for prognostication as well as reducing the phenomenon of stage migration.¹⁰

In this study, patients were staged according to the TNM staging system and categorised as advanced stage (stage III a-b-c) and early stage (stage I-II) disease. TNM staging appeared not a significant predictor of the overall survival of advanced stage patients. In addition, TNM stage was not a significant predictor of DFS, either. On the other hand, MLNR significantly predicted both survival parameters and was found as an independent prognostic factor. This study showed the prognostic effect of MLNR as more effective than TNM staging, in agreement with the previous studies.

No unanimous consensus has been reached regarding the cut-off value of MLNR in the prevailing studies.^{9,21} In some studies, evaluations were made according to whether the lymph node was negative or positive, and the ratio of negative lymph node and positive lymph node was evaluated.¹⁰ In the study conducted by Hu *et al.*, the cut-off value for the appropriate sensitivity and specificity limit was determined as 0.25, similar to this study.¹ In the later study, MLNR cut-off value was taken as 0.25; and MLNR together with other prognostic factors were examined. In multivariate analyses, advanced age, stage III and MLNR (>0.25) were independent poor prognostic factors for OS. In terms of DFS, stage III and MLNR (>0.25) were found as independent prognostic factors.¹ In this study, the cut-off value of MLNR was 0.25; similarly, as an important prognostic factor for both OS and DFS. In contrast, several cut-off categories of MLNR were used in other studies with comparable analyses additionally.^{8-10,18}

Lymphovascular invasion and PNI are well-known prognostic factors.^{22,23} Therefore, these factors can guide to decide adjuvant treatment for early-stage gastric cancer.²⁴ In this study, in multivariate analysis, PNI was found as an independent prognostic factor for DFS. Similar to This study, Bilici *et al.* showed that in patients with N3 gastric cancer who underwent curative resection MLNR above 0.75, tumor differentiation and LVI were independent prognostic factors for DFS.⁴

It is essential to evaluate the high-risk patient in terms of recurrence potential and to determine which patient would benefit from adjuvant treatment.¹⁸ Kim and colleagues evaluated the survival benefit of MLNR in 719 patients with gastric adenocarcinoma, who underwent curative-intent resection. The authors divided the study population into three groups with two cut-off values; 0.10 and 0.25. Considering the prognostic factors; gastroesophageal junction

tumor, T stage, LVI, and MLNR greater than 0.25 were independent predictors of survival. Besides, patients with MLNR > 0.25 were shown to benefit from adjuvant chemoradiotherapy.¹⁸ In this study, the survival advantage was evident in patients with MLNR >0.25 and with advanced stage. The difference in the present study was that the association between MLNR and adjuvant therapy was not evaluated as a predictive effect of MLNR. In addition, receiving adjuvant therapy did not provide a significant difference in univariate analyses.

In another study, the MLNR evaluated as a prognostic factor and advanced age (>65), tumor size (>10 cm) and MLNR (≥ 0.4) were shown to be independent prognostic factors in operated gastric cancer patients with pathologic N3.²⁵ The differences from this study were inclusion of patients in all stages, not evaluating tumor size, and accepted different cut-off values.

Some limitations of this study are worthy to mention. First, the sample size was small and the follow-up period was relatively short. Second, it would be better if different staging system on prognosis such as TNM and Japanese classification of gastric carcinoma could be compared.¹⁶ Third, the lymph node negativity could not be evaluated independently, which needed a larger sample size.

CONCLUSION

In the current study, it was shown that the presence of MLNR < 0.25 prolongs the DFS time and provides survival advantage regardless of TNM stages. MLNR is useful as an independent prognostic factor predicting survival, even better than TNM staging system.

ETHICAL APPROVAL:

The study was approved by the Ethics Committee of the Health Sciences University, Yildirim Beyazit Diskapi Training and Research Hospital (No. 77-17-2019).

PATIENTS' CONSENT:

Informed consents were obtained from all participants or their family, included in the study.

CONFLICT OF INTEREST:

Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

ST: Substantial contributions to conception and design, acquisition of data, interpretation of data, and reviewed the paper. FBB: Analysis and interpretation of data, drafting of manuscript, advices and final approval, and reviewed the paper.

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