

Does lymph node ratio (metastasis/total lymph node count) affect survival and prognosis in gastric cancer?

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ABSTRACT

الأهداف: التحقق من تأثير نسبة العقدة الليمفاوية LN / نسبة LN الكلية (N-Ratio) النقيلي على البقاء والتشخيص في حالات سرطان المعدة المعالج جراحياً.

المنهجية: كانت هذه مراجعة بأثر رجعي لـ 73 مريضاً خضعوا لعملية استئصال علاجي. تم استخدام تحليل ROC لحساب القيمة الفاصلة لنسبة N للمرضى. تم تحديد قيمة القطع N-Ratio لتكون 0.32. تم تقسيم المرضى إلى مجموعتين: أقل من 0.32 (المجموعة 1) و 0.32 وما فوق (المجموعة 2).

النتائج: كان لدى مرضى المجموعة 2 متوسط LN إجمالي 13.64 ± 25.10 بينما كان لدى مرضى المجموعة 1 متوسط LN إجمالي قدره 18.77 ± 9.36 ($p=0.04$). في المجموعة 2، كان متوسط LN المنتشر 15.97 ± 10.30 ($p<0.001$). كانت معدلات وفيات المجموعتين 18% و 51.7% على التوالي وكانت ذات دلالة إحصائية ($p=0.0039$). كانت مدة بقاء المجموعة 2 المقدرة 24.22 شهراً، وكانت المجموعة الأولى 48.01 شهراً ($p=0.001$). كان متوسط الوقت المقدر للبقاء على قيد الحياة للمجموعة 2 بأكملها 40.92 شهراً. لقد ميزنا المرضى عن تطوير القيمة الفاصلة للوفيات في تحليل ROC بحساسية 65.2% وخصوصية 72%. تم العثور على هذه النسبة لتكون 0.32، والتي كانت ذات دلالة إحصائية ($p=0.003$). أدت النسب الأكبر من 0.32 إلى زيادة خطر الوفاة بمقدار 4.8 مرة، وهو أمر ذو دلالة إحصائية ($p=0.003$).

الخلاصة: يمكن أن تكون نسبة N مقياساً جديداً لتقييم الإنذار بعد استئصال المعدة العلاجي وتحسين نظام TNM الحالي.

Objectives: To investigate the influence of the metastatic lymph node/total lymph node ratio (N-ratio) on survival and prognosis in surgically treated gastric carcinomas.

Methods: A retrospective review of 73 patients who underwent curative resection at the Department of General Surgery, Hitit University Faculty of Medicine, Turkey. Receiver operating characteristic analysis was used to calculate the cut-off value for the N-ratio of the patients. The N-ratio cut-off value was determined to be 0.32. Patients were divided into 2 groups: below 0.32 (Group 1) and 0.32 and above 0.32 (Group 2).

Results: Group 2 patients had a total lymph node mean of 25.10 ± 13.64 while Group 1 patients had a total lymph node mean of 18.77 ± 9.36 ($p=0.04$). In Group 2, the mean of metastatic lymph node was 15.97 ± 10.30 ($p<0.001$). The mortality rate of Group 1 was 18% while Group 2 was 51.7%, and were statistically significant ($p=0.0039$). The estimated survival duration of Group 2 was 24.22 months, and Group 1 was 48.01 months ($p=0.001$). The mean estimated survival time for the entire group was 40.92 months. We differentiated patients from the development of mortality cut-off value in ROC analysis with 65.2% sensitivity and 72% specificity. This ratio was found to be 0.32, which was statistically significant ($p=0.003$). Ratios greater than 0.32 raised the risk of mortality by 4.8 times, which was statistically significant ($p=0.003$).

Conclusion: The N-ratio could be a new metric to evaluate prognosis following curative gastrectomy and improve the existing tumor lymph node metastasis staging system.

Keywords: gastric cancer, N-ratio, survival, prognosis

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Gastric cancer is the fourth most common cancer worldwide and the third leading cause of cancer-related death.¹ The most common treatment for stomach cancer is surgery with chemotherapy (CT) or radiation (RT), and lymph node metastases is regarded the most important factor of postoperative survival.² As a result, lymph node dissection is considered an important prognostic factor in gastric cancer.

For lymph node staging, at least 15 lymph nodes must be excised according to the American Joint Committee on Cancer (AJCC) staging standard for malignant tumors (pN stage).³ In clinical practice, certain variables have resulted in an insufficient number of lymph nodes being dissected. The number of metastases diagnosed using normal pN staging was found to be affected by increasing the number of lymph nodes dissected. This could lead to a modification in the TNM (tumor lymph node metastasis) classification of cancer, which could impact prognostic accuracy.⁴⁻⁶

The AJCC-accepted TNM classification is the best prognostic classification approach for assessing the survival of gastric cancer patients in Western countries. In 1997, the number of metastatic lymph nodes (MLN) rather than their location became the basis for lymph node classification.⁷ In addition to being more useful and practical, classification based on the number of metastatic lymph nodes is superior and sensitive in terms of prognostic value versus classification based on the location of metastatic lymph nodes in many studies.^{8,9} To determine the right stage of the disease, the TNM classification requires the removal of at least 15 lymph nodes.³ According to studies, the average number of lymph nodes examined after radical resection in instances of stomach cancer in Western countries is 10, and only 30% of patients have at least 15 lymph nodes removed. This is a component that can have a negative impact on proper staging.¹⁰ Furthermore, for both categories, a phase shift event is observed with a frequency of more than 15%.¹¹ With these problems, some investigators have proposed to use the metastatic lymph node ratio (N-ratio: number of metastatic lymph nodes/total number of lymph nodes evaluated [TLN]) instead of the total number of positive nodes in lymph node evaluation. The N-ratio is an independent prognostic factor in radically resected gastric cancer cases according to studies conducted over the previous 20 years.^{12,13} This study aims to examine the influence of N-ratio on survival and prognosis in curative resection of gastric cancers.

Methods. A total of 103 patients were treated for stomach cancer between January 2014 and December

2017 at the Department of General Surgery, Hitit University Faculty of Medicine, Turkey and were retrospectively searched from the hospital database and clinical archive system after receiving approval from the Hitit University Clinical Research Ethics Committee (20.01.2021-No: 375).

Of the 103 patients studied, 30 patients were excluded from the research because they were unresectable, had gastrointestinal stromal tumors as a result of pathology, and had undergone palliative surgery. A retrospective review of the clinical records, pathology reports, and surgical reports of 73 patients who underwent curative resection was then carried out.

Patients' demographics, tumor localization, surgical types and findings, post-operative histopathological types, presence, and types of postoperative complications, length of hospital stay, preoperative or postoperative CT or RT, total lymph node counts and metastatic lymph node counts, follow-up times, and mortality were all assessed. Cases that did not have any of these data were excluded. The cut-off value for the N-ratio computation of the patients was calculated using a receiver operating characteristic (ROC) analysis. The N-ratio cut-off value was determined to be 0.32. Patients were divided into 2 groups: below 0.32 (Group 1) and 0.32 and above 0.32 (Group 2). The statistical difference between the 2 groups was examined using estimated mean survival analysis.

Categorical variables such as gender, number of additional diseases, tumor location, extent of surgery, presence of additional organ resections (such as: cholecystectomy or splenectomy), pathology results, presence and types of complications, presence of chemotherapy, and presence of mortality was reported as numbers and percentages. Numerical variables such as age, length of hospital stay, TLN, MLN, N-ratio ratio, follow-up time, and mean survival time were reported as mean value, standard deviation (\pm), and median value. Pearson and Spearman correlation coefficients were used to examine the relationships between variables. By drawing the ROC curve and computing the area under it and the Youden index, the cut-off value for the MLN/TLN ratio that best distinguishes the groups according to mortality and has optimal sensitivity and specificity was determined.

Statistical analysis. The Chi-square test was used to assess the statistical difference in categorical variables between groups. The Shapiro-Wilks test was used to assess the normal distribution of numerical data. The mean ages of the 2 groups were compared using student's t-test. The Mann-Whitney U test was used to compare hospitalization time, TLC, MLN, N-ratio ratio, and

follow-up duration between the 2 groups. The Kaplan-Meier survival analysis was used for survival analysis, and the log-rank test was used to determine statistical significance between the 2 groups. A p -value of <0.05 was considered significant. The Statistical Package for Social Sciences for Windows, version 26. (IBM Corp., Armonk, N.Y., USA) was used to conduct all statistical analyses.

Results. In the 73 patients included in the research, standard curative resection and D2 lymph node dissection were performed by a surgical team with similar surgical experience. Most patients were men ($n=56$, 76.7%). The mean age was 66.49 ± 11.75 years. No additional disease was found in most patients (54.8%). **Table 1** shows the demographic characteristics of the patients. Most lesions (41.09%) were located in the antrum, and the most common surgical procedures were subtotal gastrectomy and D2 lymph node dissection (57.5%). In 73 cases, simultaneous cholecystectomy was performed; gastrectomy was carried out in 8 (10.95%) patients and splenectomy in 4 (5.47%) patients tumors were least differentiated adenocarcinoma (50.68%) and least differentiated adenosquamous carcinoma (1.36%). Wound infection (5.47%) and pulmonary embolism (1,36%) were the most common complications. The patients' mean hospital stay was determined to be 10.11 ± 4.77 days. There were 62 (84.9%) patients who received adjuvant chemotherapy. The mean number of total lymph nodes removed during surgery was 21.29 ± 11.59 , while the average MLN removed was 7.63 ± 9.56 . The N-ratio average was 0.32 ± 0.31 . The patients were followed for a mean of 19.38 ± 15.84 months, and the overall mortality rate was 31.5% ($n=23$) over that time (**Table 1**).

Patients were separated into 2 groups according to the N-ratio ratio: Group 1 with a cut-off value of <0.32 and Group 2 with a cut-off value of 0.32 and >0.32 . (**Table 2**). In terms of gender distribution ($p=0.889$), mean age ($p=0.947$), and comorbidity ($p=0.669$), there was no statistically significant difference between the 2 groups. Subtotal gastrectomy was performed in 16 patients and total gastrectomy in 12 patients in Group 1; subtotal gastrectomy was performed in 26 patients and total gastrectomy in 18, out of 44 patients in Group 2. No statistically significant difference was determined between the groups in terms of the method of surgery ($p=0.74$). In terms of additional organ resection, there were no statistically significant differences between Group 2 ($p=0.892$) and Group 2 ($p=0.536$).

No statistically significant difference was found between both groups in terms of length of hospital stay

Table 1 - Demographic characteristics of the patients (N=73).

Characteristics	n (%)
Gender	
Male	56 (76.7)
Female	17 (23.3)
Age	
Mean \pm SD	66,49 \pm 11,75
Min-max (median)	43-91 (67)
Presence of comorbidities	
No	40 (54.8)
Yes	33 (45.2)
Tumor localization	
Cardia	3 (4.1)
Corpus	16 (21.91)
Big curvature	9 (12.32)
Small curvature	14 (19.17)
Antrum	30 (41.09)
Pylorus	1 (1.36)
Surgery technique	
Subtotal gastrectomy+D2 lymph node dissection	42 (57.5)
Total gastrectomy + D2 lymph node dissection	31 (42.5)
Additional organ resection	
Cholecystectomy	8 (10.95)
Splenectomy	4 (5.47)
Pathology	
Well differentiated adenocarcinoma	2 (2.73)
Moderately differentiated adenocarcinoma	22 (30.13)
Poorly differentiated adenocarcinoma	37 (50.68)
Signet ring cell	5 (6.84)
Mucinous adenocarcinoma	6 (8.21)
Adenosquamous carcinoma	1 (1.36)
Complication	
Wound site infection	4 (5.47)
Pulmonary embolism	1 (1.36)
Pneumonia	3 (4.1)
Pleural effusion	1 (1.36)
Hospitalization period (days)	
Mean \pm SD	10,11 \pm 4,77
Min - Max (median)	7 -40 (9)
Adjuvant chemotherapy	
Total number of lymph nodes	62 (84.9%)
Mean \pm SD	21,29 \pm 11,59
Min-max (median)	4-56 (19)
Number of metastatic lymph nodes	
Mean \pm SD	7,63 \pm 9,56
Min-max (median)	0-44 (5)
N-ratio	
Mean \pm SD	0,32 \pm 0,31 (0,25)
Min-max (median)	
Follow-up (month)	
Mean \pm SD	19,38 \pm 15,84
Min-max (median)	1 - 61 (14)
Mortality	23 (31.5%)
Average estimated survival time (months)	40.921

Values are presented as number and percentages (%). SD: standard deviation

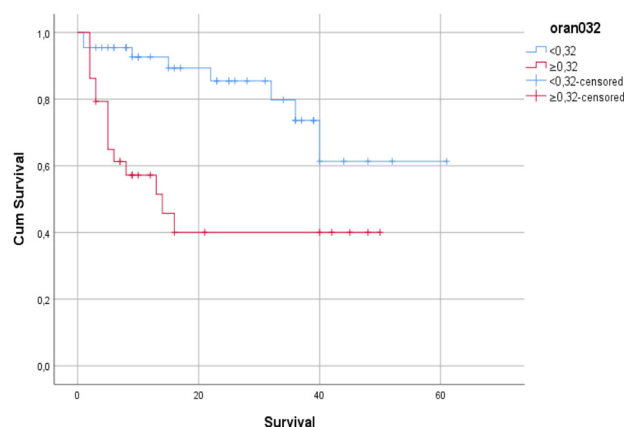
Table 2 - Comparison between Group 1 and Group (N=73).

Characteristics	Group 1 Ratio <0.32 (n=44)	Group 2 Ratio ≥0.32 (n=29)	P-value
<i>Gender</i>			
Male	34 (77.3)	22 (75.9)	0.889
Female	10 (22.7)	7 (24.1)	
Age	66.57±12.31 (67.50)	66.38 ± 11.06 (67)	0.947
<i>Presence of comorbidities</i>			
No	24 (54.5)	16 (55.2)	0.669
yes	20(45.5)	13(44.8)	
<i>Operation width</i>			
Subtotal gastrectomy + D2 LN Dissection	26 (59.1)	16 (55.2)	0.74
Total gastrectomy + D2 Lymph node dissection	18 (40.9)	12 (44.8)	
Cholecystectomy	5 (11.4)	3 (10.3)	0.892
Splenectomy	3 (6.8)	1 (3.4)	0.536
Hospitalization period (days)	10.68±5.91 (9)	9.24±1.92 (9)	0.485
Chemotherapy	36 (81.8%)	26 (89.7)	0.36
TLN	18.77±9.36 (19)	25.10±13.64 (24)	0.04
MLN	2.14±2.51 (1)	15.97±10.30 (13)	<0.001
Follow-up	22.84±15.47 (22.5)	14.14±15.19 (8)	0.009
Mortality	8 (18.2)	15 (51.7)	0.003
Average estimated survival time (months)	48.01	24.22	0.001

Values are presented as number and percentages (%). TLN: total number of lymph nodes, MLN: number of metastatic lymph nodes

($p=0.485$). The rate of postoperative chemotherapy treatment was similar in both groups (81.8% vs. 89.7%). The average TLNs retrieved from the patients were 25.10 ± 13.64 in Group 2 patients and 18.77 ± 9.36 in Group 1 patients ($p=0.04$). In Group 2, the MLN averages removed were determined to be 15.97 ± 10.30 and 2.14 ± 2.51 in Group 1 ($p<0.001$). The mortality rates between the 2 groups were 18% and 51.7%, respectively, and were highly statistically significant ($p=0.003$). There was a significant difference in the average estimated survival analysis for both groups: Group 2's expected survival time was 24.22 months, and Group 1's was 48.01 ($p=0.001$) (Table 2). For the overall group, the average estimated survival time was 40.92 months (Figure 1).

The cut-off value for optimally discriminating patients according to the development of mortality was 0.32 with 65.2% sensitivity and 72% specificity; it was statistically significant in the ROC analysis ($p=0.003$). A ratio greater than 0.32 increased the risk of mortality within 4 years by 4.8-fold, which was statistically significant (AVE 4.821 [95%CI 1.675-13.876], $p=0.003$) (Table 3) (Figure 2).

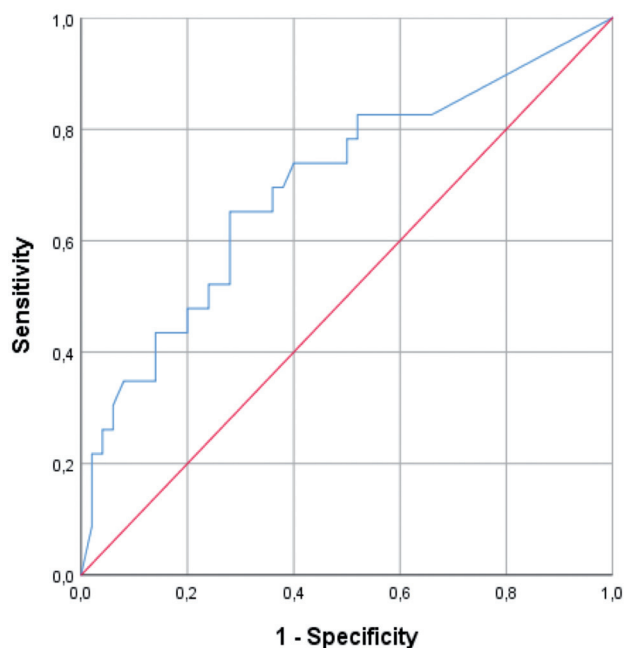
**Figure 1** - Survival curve according to N-ratio ratios.

Discussion. Lymph node dissection is critical not only for gastric cancer treatment, but also for correct staging and prognosis prediction. The clinical effects of lymph node dissection in gastric cancer are rather substantial when compared to other types of gastrointestinal tract cancer.

Table 3 - Relationship to 4-year mortality by N-ratio.

	Cut-off	Diagnostic values				ROC curve			Odds ratio		
		Sensitivity	Specificity	PPV	NPV	Area (SE)	95% CI	P-value	Odds ratio	95% CI	P-value
N-ratio	0.32	65.20%	72.00%	51.70	81.80%	0.700 (0.069)	0.565 - 0.835	0.006	4.821	1.675 - 13,876	0.003

PPV: positive predictive value, NPV: negative predictive value, SE: standard error, CI: confidence interval

**Figure 2** - A 4-year mortality receiver operating characteristics by N-ratio. Diagonal segments are produced by ties.

The American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) staging is widely utilized in daily practice due to its simplicity and repeatability. It has also been questioned due to a potential limitation of stage migration in gastric cancer, and it has been suggested that the lymph node ratio be used to overcome this staging problem for patients with lymph node who have been studied in small numbers; the hypothesis is that the N-ratio may represent the true burden of lymph node metastases.^{14,15} In a large cohort of conventional lymph node dissections, N-Ratio staging was found to be superior to AJCC TNM N-staging.¹⁶ The N-ratio cut-off value in this study was 0.32. Group 2 had dramatically reduced survival with increased mortality and worse prognosis.

In gastric cancer, lymph node metastases is a significant prognostic factor.¹⁷ Huang et al¹⁸ determined that an N-ratio of less than 0.3 enhanced survival in 236 patients diagnosed with gastric cancer originating from

the cardia and fundus and having D2 curative resection. Know et al¹⁹ classified the number of dissected lymph nodes to metastatic lymph nodes into 4 categories: 0%, 1-25%, 26-50%, and >50%, with 5-year survival rates of 83%, 66%, 30%, and 23%, respectively. In a study of 1654 gastric cancer patients, Siewert et al²⁰ reported that lymph node involvement rates greater than 20% were the most important poor prognostic indication. The MLN removed increases in patients who have undergone extended lymphadenectomy, thus prolonging survival.²¹ Here, the cut-off value was determined as 0.32. The overall survival and prognosis of the patients in Group 1 were significantly better than the other group in this study based on the cut-off value ($p=0.003$).

Nelen et al²² support our conclusions with an LNR greater than 0.3 having a lower survival rate. Their data confirm our Kaplan Meier survival curve, which we acquired when the 2 curves in between were ignored. In addition, a meta-analysis of 27 studies indicated that a high N-ratio was linked to a shorter survival.²³ The LNR ratio in this study was 0.32, which is consistent with the literature. The duration dropped to 48 months in Group 1 and 24 months in Group 2 based on the average survey of the patients. In another study, patients with LNR greater than 0.4 had a median survival period of 20.5 months. Patients with an LNR of less than or equal to 0.4 had a longer median survival time (47.0 months). This implies that the LNR was useful in determining the prognosis of patients with less than 15 lymph nodes evaluated; as the LNR increased, the median survival time fell.²⁰

Various studies have shown that the lymph node in the TNM classification used in gastric cancer staging should be re-determined based on N-Ratio ratios rather than the number of lymph node retained.^{18,21,24} A statistically significant difference was observed when the groups formed using N-ratio cut-offs were compared in terms of total survival time ($p=0.001$) (Figure 2).

One of the important prognostic factors in gastric cancer is the N-ratio ratio, which has been reported in recent studies.²⁵ In survival analyses, the rate of metastatic lymph nodes was found to be an independent factor for survival, and most studies proposed reclassification of

N according to this rate.^{17,25-27} In this study, “the ratio of metastatic to total lymph nodes” was determined to be the factor that had a statistically significant effect on survival in the survival analysis conducted to determine the effect of the data evaluated on survival ($p < 0.001$). Recent research suggests that the positive lymph node ratio (LNR) and the log odds of positive lymph nodes (LODDS) may be more accurate predictors of postoperative survival in gastric cancer patients than the AJCC N stage.^{17,28}

We found a cut-off value of 0.32, and patients exceeding this value have significantly lower survival and higher mortality. A ratio greater than 0.32 statistically raised the mortality risk in 4 years by 4.8 times (AVE 4.821 [95%CI 1.675-13.876], $p = 0.003$). In other words, it has a negative effect on the prognosis. Other studies support this study, but because of the variation in lymph node dissected between centers, determining the lymph node ratio cut-off value for each stage is difficult. More multicenter studies are needed to find universal cut-off values.^{29,30}

Study limitation. This study is a retrospective study with a small number of cases, and the follow-up period is limited to 5 years.

It is possible to use N-ratio as a more significant predictor of survival than N-stage in terms of future TNM (tumor-node-metastasis) staging as well as future staging in patients who are scheduled to have surgical resection and lymph node dissection for gastric cancer. Determining a universally cut-off value in the lymph node ratio is extremely challenging because the number of lymph nodes removed varies substantially between clinics due to varying surgical approach practices. However, this universal cut-off value can be determined with many prospective and long-term follow-up studies conducted in multicenter and even multinational trials. In patients undergoing curative resection for gastric cancer, the LNR level, rather than the LN number, may provide more accurate results in predicting prognosis. As a result, the LNR could become a new indicator for assessing prognosis following curative gastrectomy and improving the current TNM staging system.

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