Clinicopathological Factors Associated with Lymph Node Metastasis in Gastric Cancer

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Abstract

Aim: The aim of this study was to evaluate clinicopathological factors associated with lymph node metastasis in patients undergoing surgical treatment for gastric cancer, with particular emphasis on biological invasion parameters.

Methods: This retrospective study included patients who underwent surgical treatment for gastric cancer between 2010 and 2020 at a single tertiary center. Patients with distant metastasis or those who received neoadjuvant therapy were excluded. Demographic, clinical, and pathological variables were recorded. Lymph node metastasis was defined as the presence of at least one metastatic lymph node. Univariate analyses were performed to identify factors associated with lymph node metastasis, followed by multivariable logistic regression analysis to determine independent predictors.

Results: A total of 122 patients were included. In univariate analysis, tumor diameter, number of retrieved lymph nodes, lymphovascular invasion, and perineural invasion were significantly associated with lymph node metastasis (all $p < 0.05$). Age, sex, body mass index, hemoglobin, and serum albumin levels were not significantly associated with lymph node metastasis. In multivariable analysis, lymphovascular invasion emerged as the only independent predictor of lymph node metastasis (odds ratio 6.91, 95% confidence interval 2.67–17.89, $p < 0.001$), whereas tumor diameter and perineural invasion lost statistical significance after adjustment.

Conclusions: Lymphovascular invasion is the strongest independent predictor of lymph node metastasis in patients undergoing surgery for gastric cancer. These findings highlight the importance of tumor biological behavior and careful pathological assessment for postoperative risk stratification.

Keywords: *Gastric cancer; lymph node metastasis; lymphovascular invasion; pathology; risk factors*

1. Introduction

Gastric cancer remains a major global health problem and continues to be one of the leading causes of cancer-related mortality worldwide.[1] Despite advances in surgical techniques and perioperative management, prognosis largely depends on pathological stage, with lymph node metastasis (LNM) representing one of the most important determinants of survival.[2,3] Accurate identification of factors associated with LNM is therefore critical for appropriate staging, treatment planning, and prognostic stratification in patients with gastric cancer.

Numerous clinicopathological factors have been investigated as potential predictors of lymph node metastasis, including tumor size, depth of invasion, histological features, and invasion patterns.[3,4] Tumor diameter has frequently been reported as a significant risk factor for LNM, particularly in early gastric cancer and endoscopic resection–eligible cohorts.[3] However, the predictive value of tumor size varies across studies, and tumor diameter is increasingly regarded as a surrogate marker reflecting underlying tumor aggressiveness rather than a direct driver of nodal spread.[4]

Among the proposed risk factors, lymphovascular invasion (LVI) has emerged as one of the most consistent and biologically plausible predictors of lymph node metastasis. Recent systematic reviews and meta-analyses have demonstrated a strong association between LVI and the presence of nodal metastasis, supporting its role as a marker of aggressive tumor behavior and metastatic potential.[5] Nevertheless, the relative contribution of LVI compared with other clinicopathological parameters remains incompletely defined, particularly in surgically treated cohorts excluding patients with distant metastasis or neoadjuvant therapy.

In this context, the present study aimed to evaluate clinicopathological factors associated with lymph node metastasis in patients undergoing curative-intent gastrectomy at a single tertiary center. By focusing on biological invasion parameters and excluding patients with distant metastasis or neoadjuvant treatment, we sought to identify independent predictors of lymph

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node metastasis and to better delineate the role of tumor biology in nodal spread.

2. Materials and Methods

Study Design and Patient Selection

This retrospective cohort study included patients who underwent surgical treatment for gastric cancer between January 2010 and December 2020 at the Department of General Surgery, Mersin University Faculty of Medicine. All patients were operated on and followed up at the same institution. Patients were identified from a prospectively maintained institutional database and hospital medical records. Only patients with histopathologically confirmed gastric adenocarcinoma who underwent curative-intent gastrectomy with lymph node dissection were considered eligible for inclusion. Patients with distant metastasis detected during preoperative evaluation, as well as those who received neoadjuvant chemotherapy, were excluded from the study. Patients with incomplete clinicopathological data were also excluded.

Ethical Approval

The study was approved by the Ethics Committee of Mersin University Faculty of Medicine (Approval No: 2026/03) and conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived.

Clinicopathological Variables

Demographic data, including age and sex, were collected. Preoperative laboratory parameters, including hemoglobin and serum albumin levels, were recorded. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Tumor-related variables included tumor diameter, pathological T stage, lymphovascular invasion (LVI), and perineural invasion (PNI). Lymphovascular invasion and perineural invasion were assessed on routine hematoxylin–eosin–stained sections by experienced gastrointestinal pathologists, according to standard pathological criteria. The number of retrieved lymph nodes and the presence of metastatic lymph nodes were obtained from final pathological reports. Lymph node metastasis (LNM) was defined as the presence of at least one metastatic lymph node on histopathological examination and was analyzed as a binary variable (present vs. absent).

Statistical Analysis

Statistical analysis was conducted using SPSS software (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test. Normally distributed continuous variables were summarized as mean ± standard deviation, whereas non-normally distributed variables were presented as median with interquartile range (IQR). Given that most variables did not demonstrate a normal distribution, continuous data were summarized as median values with interquartile ranges (IQR) and analyzed using the Mann–Whitney U test. Categorical variables were presented as frequencies and percentages and were compared using Fisher's exact test. Factors showing an association with lymph node metastasis at a significance level of $p < 0.10$ in univariate analyses were subsequently entered into a multivariable logistic regression model to determine independent predictors. The results of the regression analysis were expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). All statistical tests were two-tailed, and a p value < 0.05 was considered to indicate statistical significance.

Table 1

Baseline Characteristics of the Study Population

Variable	Total cohort (n=122)
Number of patients	122
Age (years), mean ± SD	65.9 ± 10.5
Male sex, n (%)	67 (54.9%)
Female sex, n (%)	55 (45.1%)
BMI, mean ± SD	25.6 ± 6.0
Hemoglobin (g/dL), mean ± SD	11.7 ± 2.6
Albumin (g/dL), mean ± SD	4.0 ± 0.6
Retrieved lymph nodes, median [IQR]	22 [16–31]
Lymphovascular invasion, n (%)	69 (56.6%)
Perineural invasion, n (%)	66 (54.1%)
Tumor diameter (cm), mean ± SD	5.1 ± 3.5

Table 2

Comparison of Clinicopathological Variables According to Lymph Node Metastasis

Variable	LNM (–)	LNM (+)	p value
Age (years)	65.5 [63.0–72.0]	66.0 [58.0–73.2]	0.460
BMI	24.5 [20.0–28.3]	25.0 [21.2–28.7]	0.562
Hemoglobin (g/dL)	11.1 [10.7–13.3]	12.1 [10.2–13.5]	0.595
Albumin (g/dL)	4.2 [3.8–4.4]	4.0 [3.7–4.3]	0.114
Tumor diameter (cm)	2.5 [1.5–5.0]	5.0 [3.0–7.0]	0.000
Retrieved lymph nodes	17.5 [13.0–27.5]	25.5 [18.8–33.0]	0.005
Male sex, n (%)	24 (57.1%)	43 (53.8%)	0.848
Lymphovascular invasion, n (%)	9 (21.4%)	60 (75.0%)	0.000
Perineural invasion, n (%)	13 (31.0%)	53 (67.1%)	0.000

Footnote: LNM, lymph node metastasis; BMI, body mass index; LVI, lymphovascular invasion; PNI, perineural invasion.

Table 3

Multivariable Logistic Regression Analysis for Lymph Node Metastasis

Variable	OR	95% CI	p value
Tumor diameter (cm)	1.11	0.93–1.33	0.246
Lymphovascular invasion	6.91	2.67–17.89	0.000
Perineural invasion	2.28	0.89–5.85	0.086
Albumin (g/dL)	1.16	0.50–2.67	0.730

3. Results

Patient Characteristics

A total of 122 patients who underwent curative-intent gastrectomy were included in the study. The mean age was 65.9 ± 10.5 years, and 67 patients (54.9%) were male. The median number of retrieved lymph nodes was 22 [interquartile range (IQR): 16–31]. Lymphovascular invasion and perineural invasion were present in 56.6% and 54.1% of patients, respectively. Baseline demographic, clinical, and pathological characteristics of the study population are summarized in Table 1.

Univariate Analysis of Factors Associated with Lymph Node Metastasis

Lymph node metastasis was identified in a substantial proportion of patients. In univariate analysis, tumor diameter, number of retrieved lymph nodes, lymphovascular invasion, and perineural invasion were significantly associated with the presence of lymph node metastasis (all $p < 0.05$). In contrast, age, sex, body mass index, hemoglobin, and serum albumin levels were not significantly associated with lymph node metastasis. Detailed comparisons between patients with and without lymph node metastasis are presented in Table 2.

Multivariable Analysis

Variables demonstrating a potential association with lymph node metastasis in univariate analyses ($p < 0.10$) were included in a multivariable logistic regression model. Within this model, lymphovascular invasion was identified as the sole factor independently associated with lymph node metastasis (OR: 6.91, 95% CI: 2.67–17.89, $p < 0.001$). In contrast, tumor diameter and perineural invasion lost their statistical significance after adjustment for confounding variables. A detailed summary of the multivariable logistic regression findings is provided in Table 3.

4. Discussion

In the present study, lymph node metastasis was strongly associated with several clinicopathological variables in univariate analysis. Patients with lymph node metastasis had significantly larger tumors (median 5.0 cm vs 2.5 cm, $p < 0.001$), a higher number of retrieved lymph nodes (median 25.5 vs 17.5, $p = 0.005$), and markedly higher rates of lymphovascular invasion (75.0% vs 21.4%, $p < 0.001$) and perineural invasion (67.1% vs 31.0%, $p < 0.001$). However, the association between the number of retrieved lymph nodes and lymph node metastasis should be interpreted with caution, as this parameter likely reflects surgical extent and pathological examination quality rather than representing a direct biological risk factor for nodal spread. In contrast, age, sex, body mass index, hemoglobin, and serum albumin levels were not significantly associated with lymph node metastasis (all $p > 0.05$). Importantly, in multivariable logistic regression analysis, lymphovascular invasion remained the only independent predictor of lymph node metastasis, conferring nearly a sevenfold increased risk (OR 6.91, 95% CI 2.67–17.89, $p < 0.001$). Tumor diameter and perineural invasion lost statistical significance after adjustment for other clinicopathological variables, suggesting that their effects on nodal spread may be mediated through underlying tumor biological aggressiveness rather than acting as independent determinants. Nevertheless, the borderline association observed for perineural invasion suggests a potential relationship with lymph node metastasis that may reach statistical significance in larger, adequately powered cohorts.

Lymphovascular invasion has been consistently identified as a major determinant of lymph node metastasis in gastric cancer. A recent systematic review and meta-analysis demonstrated a strong association between lymphovascular invasion and nodal involvement, reporting a markedly increased risk of lymph node metastasis in tumors with lymphovascular invasion.[5] In line with these findings, large retrospective surgical series have shown that lymphovascular invasion remains independently associated with lymph node metastasis in multivariable analyses, whereas traditional clinicopathological parameters such as tumor size or depth of invasion often lose statistical significance after adjustment.[6,7] Consistent with the existing literature, lymphovascular invasion emerged as the only independent predictor of lymph node metastasis in the present study, supporting the concept that direct lymphatic permeation reflects intrinsic tumor aggressiveness and plays a central role in nodal spread.

Tumor diameter has frequently been reported as a significant risk factor for lymph node metastasis in gastric cancer, particularly in early-stage disease and endoscopic treatment–eligible cohorts.[8,9] However, increasing evidence suggests that tumor size may function primarily as a surrogate marker reflecting underlying tumor aggressiveness rather than acting as an independent biological driver of nodal spread. Several studies have demonstrated that although tumor diameter is associated with lymph node metastasis in univariate analyses, its significance often diminishes after adjustment for invasion-related parameters such as lymphovascular invasion or depth of invasion in multivariable models.[9,10] These observations are consistent with our findings, in which tumor diameter was strongly associated with lymph node metastasis in univariate analysis but did not remain an independent predictor after adjustment for biological invasion parameters. This supports the concept that the effect of tumor size on nodal metastasis is largely mediated through tumor biological behavior rather than size alone.

The identification of lymphovascular invasion as the sole independent predictor of lymph node metastasis has important clinical implications. Several predictive models and nomograms have incorporated lymphovascular invasion to improve risk stratification for nodal involvement and to guide postoperative management strategies.[11] In this context, the presence of lymphovascular invasion may warrant closer postoperative surveillance and could support consideration of more aggressive adjuvant treatment strategies in appropriately selected patients. Furthermore, recognizing lymphovascular invasion as a key biological marker may aid in refining pathological reporting and risk assessment beyond conventional size-based or stage-based parameters.[12] In surgically treated cohorts excluding neoadjuvant therapy, as in the present study, emphasis on biological invasion patterns may provide a more accurate reflection of metastatic potential. These findings highlight the potential value of integrating lymphovascular invasion into individualized decision-making processes, particularly in patients with otherwise borderline or intermediate-risk clinicopathological features.

Several limitations of the present study should be acknowledged. First, the retrospective design and single-center nature of the study may limit the generalizability of the findings. Second, although pathological evaluation was performed according to institutional standards, interobserver variability in the assessment of lymphovascular and perineural invasion cannot be completely excluded. In addition, patients who received neoadjuvant therapy were deliberately excluded, which restricts the applicability of our findings to neoadjuvant-treated populations.[13] Despite these limitations, the study has several notable strengths. The analysis was conducted in a relatively homogeneous cohort of patients undergoing curative-intent gastrectomy without distant metastasis or neoadjuvant treatment, allowing a focused evaluation of biological invasion parameters. Furthermore, the comprehensive pathological assessment and

multivariable analytical approach enabled identification of lymphovascular invasion as a robust independent predictor of lymph node metastasis. These strengths support the validity of our findings and their potential relevance to surgical decision-making and postoperative risk stratification.[14]

5. Conclusion

In conclusion, lymphovascular invasion was identified as the strongest and only independent predictor of lymph node metastasis in patients undergoing curative-intent gastrectomy for gastric cancer. While tumor size and perineural invasion were associated with nodal involvement in univariate analyses, their effects were not independent after adjustment for biological invasion parameters. These findings emphasize the central role of tumor biology in lymph node dissemination and highlight the importance of careful pathological assessment of lymphovascular invasion for postoperative risk stratification and clinical decision-making.

Statement of ethics

The study was approved by the Ethics Committee of Mersin University Faculty of Medicine (Approval No: 2026/03) and conducted in accordance with the Declaration of Helsinki.

genAI

No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by both authors.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions

Both authors were involved in the conception and design of the study, literature search, analysis and interpretation of data, and writing of the manuscript. YE additionally performed the data collection. Both authors read and approved the final version of the manuscript.

References

1. Sundar R, Nakayama I, Markar SR, Shitara K, van Laarhoven HWM, Janjigian YY, et al. Gastric cancer. Lancet. 2025;405(10494):2087-2102. **Crossref**
2. Hwang J, Carr J. Lymphadenectomy for gastric cancer. Surg Clin North Am. 2025;105(1):47-54. **Crossref**
3. Yu Z, Liu H, Li R, Hu L, Xiao C, Gao Y, et al. Clinicopathological factors and nomogram construction for lymph node metastasis in locally advanced gastric cancer. Cancer Manag Res. 2024;16:1475-1489. **Crossref**
4. Du J, Shen Y, Yan W, Wang J. Risk factors of lymph node metastasis in the splenic hilum of gastric cancer patients: a meta-analysis. World J Surg Oncol. 2020;18(1):233. **Crossref**
5. Duan M, Li M, He L, Dai S, Zhou L, Liu Z, et al. Risk prediction models for lymph node metastasis in early gastric cancer patients: a systematic review and meta-analysis. BMC Gastroenterol. 2025;25(1):776. **Crossref**
6. HajiEsmailPoor Z, Tabnak P, Baradaran B, Pashazadeh F, Aghebati-Maleki L. Diagnostic performance of CT scan-based radiomics for prediction of lymph node metastasis in gastric cancer: a systematic review and meta-analysis. Front Oncol. 2023;13:1185663. **Crossref**
7. de Jong MHS, Gisbertz SS, van Berge Henegouwen MI, Draaisma WA. Prevalence of nodal metastases in the individual lymph node stations for different T-stages in gastric cancer: a systematic review. Updates Surg. 2023;75(2):281-290. **Crossref**
8. Mao S, Li W, Pan Y, Wu H, Xiang Y, Liu M, et al. Long-term outcomes of additional surgery vs. observation after noncurative endoscopic submucosal dissection for early gastric cancer and application value of the eCura scoring system: a propensity score-matched study. J Gastrointest Surg. 2025;29(6):102030. **Crossref**
9. Xu N, Zhang Y, Ma X, Meng W. Lymph node metastasis and its risk factors for early gastritis individuals who underwent noncurative endoscopic resection: a systematic review and meta-analysis. Iran J Public Health. 2024;53(10):2191-2200. **Crossref**
10. Yang S, Gu X, Tao R, Huo J, Hu Z, Sun F, et al. Relationship between histological mixed-type early gastric cancer and lymph node metastasis: a systematic review and meta-analysis. PLoS One. 2022;17(4):e0266952. **Crossref**
11. Li Y, Xie F, Xiong Q, Lei H, Feng P. Machine learning for lymph node metastasis prediction in patients with gastric cancer: a systematic review and meta-analysis. Front Oncol. 2022;12:946038. **Crossref**
12. Zhao X, Cai A, Xi H, Song Y, Wang Y, Li H, et al. Predictive factors for lymph node metastasis in early gastric cancer with signet ring cell histology: a meta-analysis. ANZ J Surg. 2017;87(12):981-986. **Crossref**
13. Jiang B, Zhou L, Lu J, Wang Y, Guo J. Predictors of lymph node metastasis and residual tumor in early gastric cancer patients after noncurative endoscopic resection: a systematic review and meta-analysis. Therap Adv Gastroenterol. 2020;13:1756284820935033. **Crossref**
14. Varvarousis DN, Marini AA, Ntritsos G, Barbouti A, Kitsoulis PV, Kanavaros PE. Relationship of lymphatic vessel invasion and density with clinicopathological parameters and survival in patients with gastric carcinoma: a systematic review and meta-analysis. Pathol Res Pract. 2025;269:155877. **Crossref**