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ORIGINAL RESEARCH

Clinicopathological Factors and Nomogram Construction for Lymph Node Metastasis in Locally Advanced Gastric Cancer

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Background: The research on lymph node metastasis (LNM) in locally advanced gastric cancer (LAGC) infiltrating the subserous tissue and serous membrane (T3-4a) is significantly inadequate. This study aims to explore the clinicopathological factors related to LNM in stages T3 and T4a LAGC, while also developing predictive nomograms.

Methods: After systematic searching and rigorous screening, 1995 T3 and 1244 T4a LAGC cases who underwent surgery without neoadjuvant or perioperative chemotherapy were selected. The risk factors associated with LNM were identified using both univariate and multivariate logistic regression analyses. Subsequently, the independent variables identified through the multivariate analyses were utilized to construct a nomogram.

Results: The incidence of LNM in T3 and T4a LAGC was 77.1% (1539/1995) and 83.8% (1043/1244), respectively. The following factors were found to be independently associated with LNM in T3 LAGC: preoperative serum albumin <41g/L (P=0.007), gastrointestinal obstruction (P<0.001), tumor location (P=0.040), tumor size >4cm (P=0.002), mixed (P=0.001) and undifferentiated histological types (P=0.002), presence of lymphovascular invasion (LVI) (P<0.001) and nerve invasion (P<0.001). Additionally, in T4a LAGC cases, serum albumin < 39g/L (P=0.004), tumor size >6cm (P=0.020), mixed (P<0.001) and undifferentiated histological types (P<0.001), presence of gastrointestinal hemorrhage (P=0.016), neuroendocrine differentiation (P=0.024), and LVI (P<0.001) independently influenced the occurrence of LNM.

Conclusion: This study identified the risk factors associated with LNM in T3-4a LAGC cases and constructed nomograms, thereby providing valuable guidance for formulating and implementing a multidisciplinary perioperative treatment program.

Keywords: locally advanced gastric cancer, lymph node metastasis, clinicopathological factors, nomogram

Introduction

The incidence and mortality rates of gastric cancer rank fifth and fourth, respectively, among all malignant tumors worldwide, posing a significant threat to human life and health.[1,2] The situation in China is even more alarming, as it exhibits the third highest incidence and fatality rate. The incidence rate of early gastric cancer (EGC) in China is relatively low, accounting for less than 20% of all cases, with the majority being diagnosed at advanced stages. Even on a global scale, nearly 50% of gastric cancer cases are diagnosed at an advanced stage.[3,4] Locally advanced gastric cancer (LAGC) refers to cases in which the tumor has infiltrated the muscular layer and beyond but without evidence of distant metastasis.[2,5,6] The National Comprehensive Cancer Network (NCCN) recommends preoperative chemotherapy for patients with $cT_{2\text{-}4}N_{0\text{-}3}M_0$ LAGC, based on the findings from the MAGIC and FNCLCC/FFCD studies. Additionally, European Society for Medical Oncology (ESMO) strongly recommends perioperative chemotherapy with a platinum/fluoropyrimidine combination for patients with stage IB-IIIC LAGC.[2,7]

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The distinctive physiological structure of the stomach makes lymph node metastasis (LNM) a crucial pathway for LAGC metastasis. Currently, there has been an increase in the number of lymph node biopsies incorporating clinical, pathological, and adjuvant chemotherapy staging from 15 to 16. Moreover, the extent of lymph node dissection (LND) during radical gastrectomy has undergone further refinement, underscoring the paramount importance of accurate identification of LNM.[3,7,8] Despite efforts to enhance consistency, the number of lymph nodes detected by pathologic screening for LAGC still exhibits variability. The accuracy of LND can be influenced by various factors, including the surgeon and pathologist's expertise and proficiency, as well as the patient's medical condition, tumor status, and the quality of equipment and technology utilized. Therefore, analyzing risk factors associated with LNM will provide valuable reference and supplement to postoperative pathological examination.

Nakamura et al identified significant risk factors for LNM in undifferentiated T1a EGC cases, including the presence of a depressed tumor type, lymphatic tumor invasion, signet ring cell carcinoma component, and large tumor size.[9] Pereira et al's research demonstrated that LNM in EGC is associated with tumor size as well as venous, lymphatic, and perineural invasions.[10] We also utilized EGC cases (T1a-b) to identify risk factors associated with LNM and develop a prediction model, aiming to provide crucial validation and further complement existing indications for endoscopic surgery.[11] However, the existing literature has extensively investigated LNM in EGC, yet lacks sufficient innovation. The current research focus lies in exploring the application of neoadjuvant therapy for T3-4a LAGC cases, as well as unresectable tumors.[3] Neoadjuvant therapy, encompassing preoperative radiotherapy, chemotherapy, and targeted therapy, has emerged as a pivotal component in the management of LAGC cases to enhance patient prognosis. The emergence of sustained release chemotherapeutic drugs and hyperthermic intraperitoneal chemotherapy (HIPEC), besides, offers additional possibilities for advancing comprehensive treatment.[12] The present study not only provides valuable insights for supplementing postoperative pathology, guiding adjuvant therapy and follow-up, but also offers significant implications for the implementation of neoadjuvant therapy, surgical procedures, and intraoperative chemotherapy.

Materials and Methods

Study Participants

The patients diagnosed with gastric cancer who underwent radical surgery without neoadjuvant or perioperative chemotherapy between January 2010 and June 2023 were selected as study population for further screening. The diagnosis of gastric cancer was confirmed through gastroscopic biopsy prior to the surgical procedure. All patients underwent at least one upper abdominal enhanced computed tomography (CT) examination before neoadjuvant therapy or surgery. By assessing the smoothness of the serosal surface, evaluating the characteristics of surrounding adipose tissue on the image, and integrating findings from gastroscopy, the clinical T stage was determined. The lymph nodes were classified as metastatic if their short diameter exceeds 8 mm in the image. The patients with suspected clinical T or N stages should undergo further endoscopic ultrasonography, magnetic resonance imaging (MRI), and other examinations. These results should be discussed by a panel of at least two experienced surgeons to determine the subsequent treatment plan. Neoadjuvant chemotherapy (NACT) was the preferred treatment for LAGC patients with $cT_{3\text{-}4a}N_{1\text{-}3}M_0$ stage, while surgery or endoscopic therapy was recommended for patients with stages I-IIB.

Patients were additionally assessed for eligibility based on predetermined inclusion and exclusion criteria. The inclusion criteria were as follows: (1) patients underwent a radical resection of the proximal, distal, or total stomach along with D2 LND; (2) postoperative pathological examination confirmed tumor infiltration extending to the subserous tissue (pT3) or serous membrane (pT4a); (3) complete outcome indicator data was available. This study was reviewed and approved by the Medical Ethics Committee of the First Medical Center of the Chinese PLA General Hospital (S2021-022-01) and was performed in accordance with the Declaration of Helsinki.

Data Collection and Outcome Evaluation

The dependent variables being evaluated and analyzed in this study encompassed the LNM status of T3 and T4a LAGC, respectively. The visualization of all metastatic lymph nodes on CT scan poses challenges, while the differentiation between reactive hyperplasia and metastasis remains elusive, with certain lymph nodes being non-detectable on CT imaging. To ensure the precision and persuasiveness of the analysis findings, we employed the postoperative pathological tumor stage as the dependent variable. Moreover, the clinicopathological data collected and evaluated, which may be related to dependent variables, encompassed sex, age, body mass index (BMI), preoperative levels of serum hemoglobin (HGB) and albumin (ALB), presence of hypertension, diabetes, gastrointestinal obstruction, gastrointestinal hemorrhage, smoking and drinking history, significant weight loss, preoperative American society of Anesthesiologists (ASA) score, tumor location, number, size, histological types, presence of ulceration, necrosis, neuroendocrine differentiation (NED), lymphovascular invasion (LVI), and nerve invasion.

The T and N stages were evaluated according to the TNM staging criteria (the 8th edition) developed collaboratively by the Union Internationale Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC), based on pathological findings obtained from surgical specimens.[13] In cases presenting with clinical symptoms such as dysphagia, nausea, and vomiting, gastrointestinal obstruction should be confirmed through digestive endoscopy. The presence of symptoms such as hematemesis, hematochezia, and melena during the disease course indicated a diagnosis of gastrointestinal hemorrhage. Furthermore, significant weight loss was defined as a reduction of more than 3kg in the month preceding the surgery. The tumor size for a single lesion referred to the longest diameter of the tumor, while for multiple lesions, it was calculated as the sum of the longest diameters of each individual lesion. The highly, highly-moderately, and moderately differentiated histological types were all categorized into the differentiated group, while the undifferentiated group consisted of poorly differentiated and signet-ring cell carcinoma. Additionally, the term "mixed group" denoted the coexistence of both differentiated and undifferentiated pathological types. The diagnosis of NED was achieved through immunohistochemical detection of specific neuroendocrine markers in surgical tissue samples, such as synapse (Syn), chromogranin A (CgA), and neuro-specific enolase (NSE).[14]

Statistical Analysis

The statistical analyses were conducted using SPSS software (version 26.0) and R software (version 4.2.2). Categorical data was presented as numbers (percentages) and compared using either a Chi-square or Fisher's exact test. The normality of continuous variables were assessed by visually inspecting histograms and Q-Q plots. Continuous normally distributed variables were expressed as mean with standard deviation (SD) and compared between groups using an independent-samples *T*-test. Continuous non-normally distributed variables were expressed as median with interquartile range (IQR) and compared between groups using a Mann–Whitney *U*-test. The cut-off values for quantitative variables were determined by plotting receiver operating characteristic (ROC) curves, and subsequently converting the quantitative variables into qualitative variables based on the identified cut-off values. Following this, univariate analyses were conducted to examine the correlations between covariates and dependent variables, with appropriate covariates being included in a multivariate logistic regression model. Variables with a p-value <0.05 in the multivariate analysis were considered independent predictors and utilized to construct nomograms. ROC and calibration curves were both drawn to evaluate the predictive accuracy and discriminative ability of the nomograms.

Results

Patients Selection and Characteristics

A total of 6319 patients diagnosed with gastric cancer ($T_{1\text{-}4}N_{0\text{-}3}M_0$) who underwent radical surgery were retrieved using the electronic medical record (EMR) system. Among them, 828 patients received NACT or EMR/ESD prior to surgery, while 114 cases lacked the necessary outcome indicators. Additionally, a total of 2367 LAGC cases were identified with neoplasms infiltrating the mucosal layer, submucosa, muscular layer, or adjacent tissues. After excluding ineligible cases, 1995 T3 LAGC cases and 1244 T4a LAGC cases were selected as the subjects for further analysis (Figure 1). Regarding T3 LAGC cases, the median number of LND was 29 (22, 39), while the median number of positive lymph nodes was 3

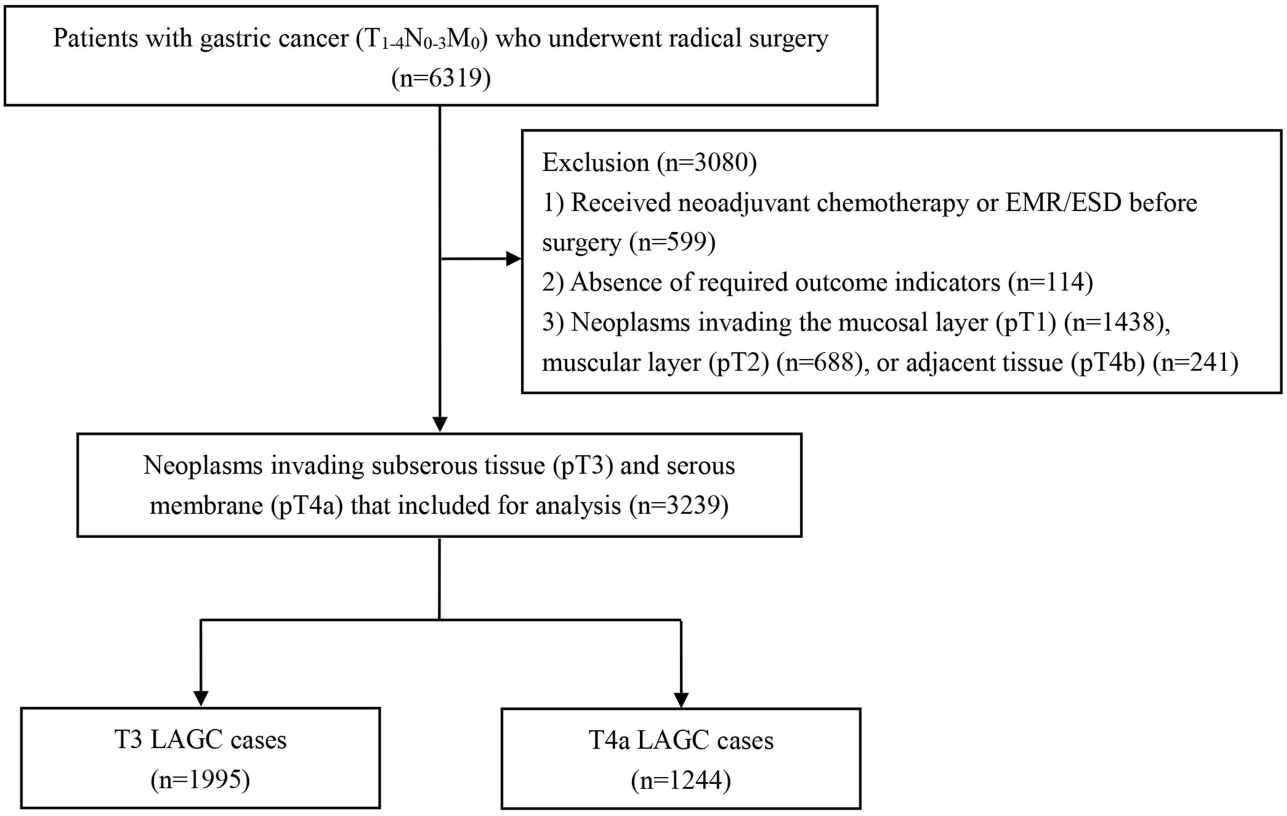

Figure 1 The flowchart of patient inclusion and exclusion.
Abbreviations: EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

(1, 9). Additionally, the number of N0, N1, N2, N3a, and N3b stages in T3 LAGC were 456 (22.9%), 395 (19.8%), 470 (23.6%), 428 (21.5%), and 246 (12.2%) respectively. As for T4a LAGC cases, the median number of LND and LNM were found to be respectively at 28 (20, 37) and 6 (2, 14). LNM was present in 1043 (83.8%) of the 1244 T4a LAGC patients: 173 (13.9%) were classified as N1, 254 (20.4%) as N2, 341 (27.4%) as N3a, and 275 (22.1%) as N3b.

Clinicopathological Factors Related to LNM in T3 LAGC

Univariate and multivariate logistic regression analyses were conducted to investigate the clinicopathological factors associated with LNM in T3 LAGC, comparing 456 LNM-negative cases with 1539 LNM-positive cases. The univariate analyses indicated that the preoperative serum ALB level [odds ratio (OR)=0.967, P=0.015], presence of gastrointestinal obstruction (OR=1.837, P=0.001), significant weight loss (OR=1.253, P=0.040), tumor location (P=0.006), tumor size (OR=1.150, P<0.001), mixed (OR=2.027, P<0.001) and undifferentiated histological types (OR=2.004, P<0.001), presence of LVI (OR=4.355, P<0.001) and nerve invasion (OR=2.010, P<0.001) were all significantly correlated with LNM in T3 LAGC (Table 1).

The cut-off values for preoperative serum ALB level and tumor size were determined by constructing ROC curves, followed by converting the aforementioned outcome indicators into categorical variables. Subsequently, the covariates including preoperative serum ALB < 41 g/L, tumor location, number of tumors, tumor size >4 cm, histological types, presence of gastrointestinal obstruction, significant weight loss, LVI, and nerve invasion were incorporated into a multivariate binary logistic regression model. Preoperative serum ALB < 41 g/L (OR=1.383, P=0.007), gastrointestinal obstruction (OR=1.981, P<0.001), tumor location (P=0.040), tumor size > 4 cm (OR=1.447, P=0.002), mixed (OR=1.695, P=0.001) and undifferentiated histological types (OR=1.576, P=0.002), presence of LVI (OR=3.694, P<0.001) and nerve invasion (OR=1.621, P<0.001) were identified as independent predictors (Table 2). In addition, the acquired independent predictors were utilized to construct a nomogram model to estimate the risk of LNM in T3

Table 1 Univariate Analysis of Clinicopathological Factors Related to LNM for pT3 Locally Advanced Gastric Cancer

	LNM Positive (*n*=1539), *n* (%)	LNM Negative (*n*=456), *n* (%)	OR (95% CI)	*P* Value
Sex				0.401
Female	326 (21.2)	105 (23.0)	Reference	
Male	1213 (78.8)	351 (77.0)	1.113 (0.867, 1.429)	
Age (years)				0.251
≤ 60	662 (43.0)	210 (46.1)	Reference	
> 60	877 (57.0)	246 (53.9)	1.131 (0.917, 1.395)	
BMI (kg/m^2)				0.884
≤ 28	1384 (89.9)	409 (89.7)	Reference	
> 28	155 (10.1)	47 (10.3)	0.975 (0.691, 1.375)	
Preoperative serum HGB (g/L)	123.34±23.21	124.73±23.28	0.997 (0.993, 1.002)	0.264
Preoperative serum ALB (g/L)	39.09±3.93	39.60±4.12	0.967 (0.942, 0.994)	**0.015**
Hypertension				0.846
Absence	1094 (71.1)	322 (70.6)	Reference	
Presence	445 (28.9)	134 (29.4)	0.977 (0.777, 1.230)	
Diabetes				0.528
Absence	1322 (85.9)	397 (87.1)	Reference	
Presence	217 (14.1)	59 (12.9)	1.105 (0.811, 1.504)	
Gastrointestinal obstruction				**0.001**
Absence	1308 (85.0)	416 (91.2)	Reference	
Presence	231 (15.0)	40 (8.8)	1.837 (1.290, 2.615)	
Gastrointestinal hemorrhage				0.266
Absence	1251 (81.3)	360 (78.9)	Reference	
Presence	288 (18.7)	96 (21.1)	0.863 (0.666, 1.119)	
Smoking history				0.849
Absence	1083 (70.4)	323 (70.8)	Reference	
Presence	456 (29.6)	133 (29.2)	1.023 (0.813, 1.287)	
Drinking history				0.885
Absence	971 (63.1)	286 (62.7)	Reference	
Presence	568 (36.9)	170 (37.3)	0.984 (0.793, 1.222)	
Significant weight loss				**0.040**
Absence	882 (57.3)	286 (62.7)	Reference	
Presence	657 (42.7)	170 (37.3)	1.253 (1.011, 1.554)	
Preoperative ASA score				0.945
I-II	1372 (89.1)	406 (89.0)	Reference	
III-IV	167 (10.9)	50 (11.0)	0.988 (0.707, 1.381)	
Location				**0.006**
Upper	626 (40.7)	214 (46.9)	Reference	
Middle	205 (13.3)	52 (11.4)	1.348 (0.958, 1.896)	0.087
Lower	634 (41.2)	183 (40.1)	1.184 (0.945, 1.485)	0.143
Multiple parts	74 (4.8)	7 (1.5)	3.614 (1.639, 7.966)	**0.001**
Number of tumors				0.096
Single	1493 (97.0)	449 (98.5)	Reference	
Multiple (≥2)	46 (3.0)	7 (1.5)	1.976 (0.886, 4.408)	
Tumor size (cm)	5.26±2.40	4.58±2.11	1.150 (1.093, 1.211)	**<0.001**
Histological types				**<0.001**
Differentiated	234 (15.2)	121 (26.5)	Reference	
Mixed	584 (37.9)	149 (32.7)	2.027 (1.526, 2.692)	**<0.001**
Undifferentiated	721 (46.8)	186 (40.8)	2.004 (1.527, 2.632)	**<0.001**

(*Continued*)

Table 1 (Continued).

	LNM Positive (*n*=1539), *n* (%)	LNM Negative (*n*=456), *n* (%)	OR (95% CI)	*P* Value
Ulceration				0.719
Absence	163 (10.6)	51 (11.2)	Reference	
Presence	1376 (89.4)	405 (88.8)	1.063 (0.762, 1.484)	
Necrosis				0.121
Absence	1422 (92.4)	411 (90.1)	Reference	
Presence	117 (7.6)	45 (9.9)	0.751 (0.524, 1.078)	
NED				0.601
Absence	1395 (90.6)	417 (91.4)	Reference	
Presence	144 (9.4)	39 (8.6)	1.104 (0.762, 1.598)	
LVI				**<0.001**
Absence	886 (57.6)	390 (85.5)	Reference	
Presence	653 (42.4)	66 (14.5)	4.355 (3.292, 5.761)	
Nerve invasion				**<0.001**
Absence	842 (54.7)	323 (70.8)	Reference	
Presence	697 (45.3)	133 (29.2)	2.010 (1.604, 2.519)	

Notes: Bold values indicate *P*<0.05.
Abbreviations: LNM, lymph node metastasis; OR, odds ratio; CI, confidence interval; BMI, body mass index; HGB, hemoglobin; ALB, albumin; ASA, American society of Anesthesiologists; NED, neuroendocrine differentiation; LVI, lymphovascular invasion.

Table 2 Multivariate Logistic Regression Analysis of Clinicopathological Factors Related to LNM for pT3 LAGC

Covariates	OR (95% CI)	*P* Value
Preoperative serum ALB		**0.007**
≥ 41 g/L	Reference	
< 41 g/L	1.383 (1.094, 1.749)	
Gastrointestinal obstruction		**<0.001**
Absence	Reference	
Presence	1.981 (1.364, 2.877)	
Significant weight loss		0.527
Absence	Reference	
Presence	1.077 (0.855, 1.358)	
Location		**0.040**
Upper	Reference	
Middle	1.373 (0.956, 1.971)	0.086
Lower	1.301 (1.017, 1.666)	**0.037**
Multiple parts	2.630 (0.983, 7.035)	0.054
Number of tumors		
Single	Reference	0.951
Multiple (≥2)	1.033 (0.368, 2.896)	
Tumor size (cm)		**0.002**
≤ 4 cm	Reference	
> 4 cm	1.447 (1.150, 1.821)	
Histological types		**0.001**
Differentiated	Reference	
Mixed	1.695 (1.256, 2.286)	**0.001**
Undifferentiated	1.576 (1.177, 2.110)	**0.002**

(*Continued*)

Table 2 (Continued).

Covariates	OR (95% CI)	*P* Value
LVI		**<0.001**
Absence	Reference	
Presence	3.694 (2.771, 4.925)	
Nerve invasion		**<0.001**
Absence	Reference	
Presence	1.621 (1.274, 2.062)	

Notes: Bold values indicate *P*<0.05.
Abbreviations: LNM, lymph node metastasis; LAGC, locally advanced gastric cancer; OR, odds ratio; CI, credible interval; ALB, albumin; LVI, lymphovascular invasion.

LAGC (Figure 2A). The ROC curve and the area under the ROC curve (AUC) of the nomogram were presented in Figure 2B. Additionally, the calibration curve (Figure 2C) for this nomogram model also demonstrated excellent accuracy and calibration.

Clinicopathological Factors Related to LNM in T4a LAGC

The clinicopathological factors associated with LNM in T4a LAGC were identified by comparing 201 cases with negative LNM and 1043 cases with positive LNM. As shown in Table 3, BMI > 28 kg/m^2 (OR=0.576, P=0.018), presence of gastrointestinal hemorrhage (OR=0.596, P=0.003), multiple tumor location (OR=2.182, P=0.037), tumor size (OR=1.235, P<0.001), mixed (OR=3.352, P<0.001) and undifferentiated histological types (OR=4.184, P<0.001), presence of LVI (OR=4.730, P<0.001) and nerve invasion (OR=2.050, P<0.001) were related to LNM in T4a LAGC.

Further, variables with a P-value <0.15 in univariate analysis were included in multivariate analysis, and the serum ALB < 39 g/L (OR=1.734, P=0.004), gastrointestinal hemorrhage (OR=0.629, P=0.016), tumor size > 6 cm (OR=1.610, P=0.020), mixed (OR=2.673, P<0.001) and undifferentiated histological types (OR=3.634, P<0.001), presence of NED (OR=0.485, P=0.024) and LVI (OR=3.882, P<0.001) were identified as independent factors (Table 4). A nomogram for T4a LAGC was constructed incorporating appropriate covariates identified through multivariate analysis (Figure 3A). ROC curve and the AUC of the nomogram were presented in Figure 3B. The calibration curve (Figure 3C) also showed that our nomogram had a good calibration.

Discussion

The 5-year survival rate of LAGC is widely acknowledged to be approximately 30%, with LNM being identified as an independent risk factor for unfavorable prognosis in LAGC. The prevalence of LNM in patients with LAGC can reach up to 80%. The administration of NACT in LAGC cases is advantageous, particularly in those with LNM, as it effectively reduces tumor size and facilitates complete (R0) resection.[8,15,16] Consequently, the identification of risk factors for LNM can aid in assessing the necessity for NACT and provide guidance for surgical procedures, postoperative multidisciplinary treatment, and follow-up. The ESMO and NCCN guidelines for gastric cancer express a more favorable stance towards neoadjuvant chemotherapy compared to the Chinese guidelines, due to variations in incidence rates, biological and behavioral characteristics, as well as the prevalence of D2 lymph node dissection among European, American, and Asian populations. Consequently, the recommendations of the ESMO and NCCN guidelines should be considered as a point of reference rather than blindly adhered to.[3,7] The optimal utilization of neoadjuvant chemotherapy for LAGC remains a subject of debate in China. The domestic guidelines recommended the use of neoadjuvant chemotherapy for LAGC classified as cT3-4aN1-3M0 stage over an extended duration. In China, the slow adoption of neoadjuvant therapy can be attributed to the high prevalence of LAGC, patients' treatment preferences, and inaccurate preoperative clinical staging.[1,3] The TNM staging criteria (the 8th edition), regardless of pathological or clinical staging criteria, both designated LNM as the primary determinant for classifying T3-4a LAGC into stage II or III. The search for clinicopathological factors influencing LNM in T3-4a LAGC cases is of immense significance; however, there is a dearth of

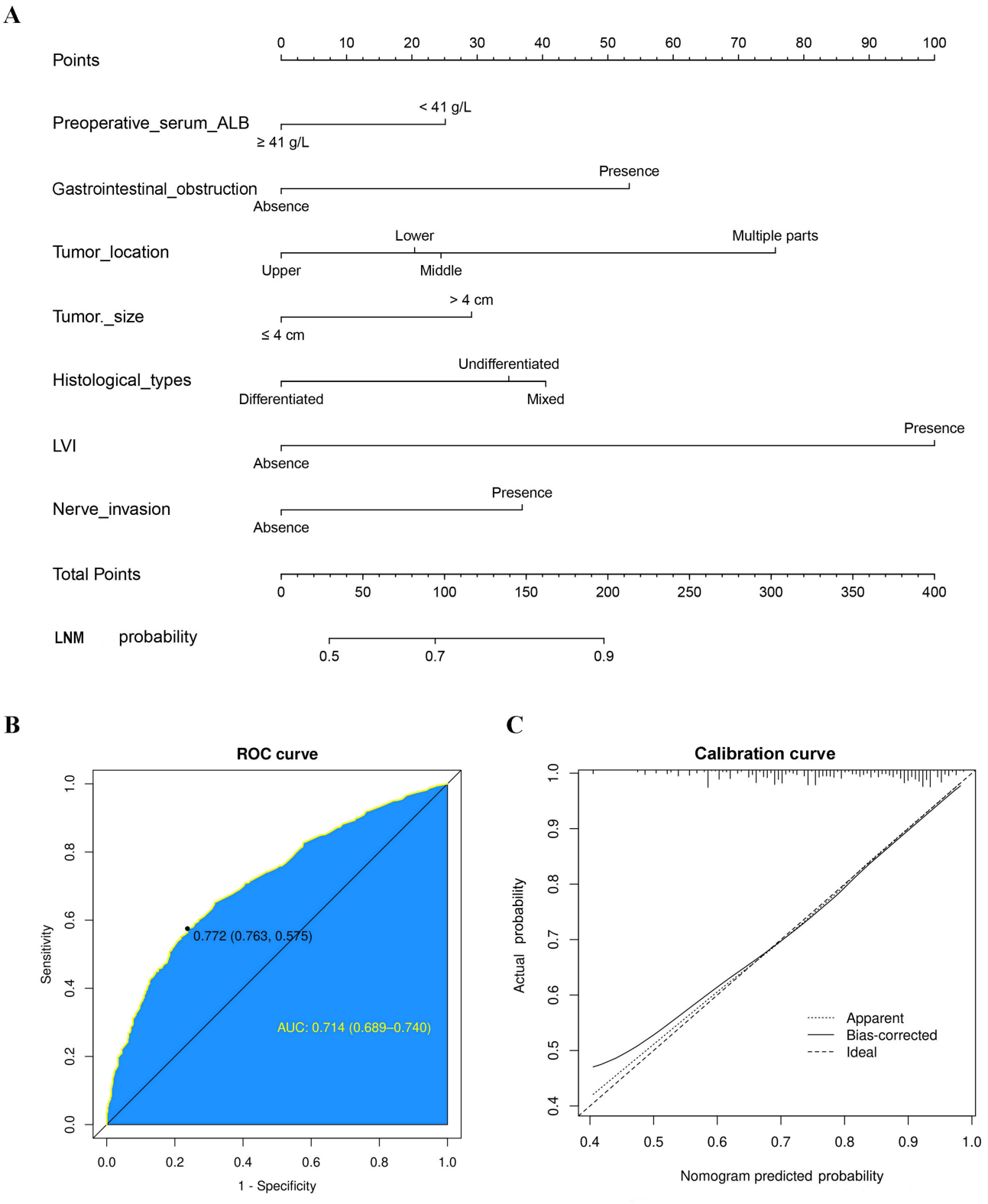

Figure 2 (**A**) The nomogram model constructed to estimate the risk of lymph node metastasis (LNM) in T3 locally advanced gastric cancer (LAGC) cases. (**B**) Receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) of the nomogram. (**C**) Calibration of the evaluation for nomogram model.
Abbreviations: ALB, albumin; LVI, lymphovascular invasion.

Table 3 Univariate Analysis of Clinicopathological Factors Related to LNM for pT4a Locally Advanced Gastric Cancer

	LNM Positive (*n*=1043), *n* (%)	LNM Negative (*n*=201), *n* (%)	OR (95% CI)	*P* Value
Sex				0.851
Female	289 (27.7)	57 (28.4)	Reference	
Male	754 (72.3)	144 (71.6)	1.033 (0.738, 1.444)	
Age (years)				0.315
≤ 60	520 (49.9)	108 (53.7)	Reference	
> 60	523 (50.1)	93 (46.3)	1.168 (0.863, 1.581)	
BMI (kg/m^2)				**0.018**
≤ 28	954 (91.5)	173 (86.1)	Reference	
> 28	89 (8.5)	28 (13.9)	0.576 (0.366, 0.908)	
Preoperative serum HGB (g/L)	122.71±21.97	122.79±21.95	1.000 (0.993, 1.007)	0.964
Preoperative serum ALB (g/L)	39.24±3.66	39.75±3.64	0.962 (0.922, 1.003)	0.070
Hypertension				0.232
Absence	779 (74.7)	142 (70.6)	Reference	
Presence	264 (25.3)	59 (29.4)	0.816 (0.584, 1.139)	
Diabetes				0.403
Absence	912 (87.4)	180 (89.6)	Reference	
Presence	134 (12.6)	21 (10.4)	1.231 (0.756, 2.005)	
Gastrointestinal obstruction				0.078
Absence	872 (83.6)	178 (88.6)	Reference	
Presence	171 (16.4)	23 (11.4)	1.518 (0.954, 2.414)	
Gastrointestinal hemorrhage				**0.003**
Absence	844 (80.9)	144 (71.6)	Reference	
Presence	199 (19.1)	57 (28.4)	0.596 (0.423, 0.840)	
Smoking history				0.266
Absence	791 (75.8)	145 (72.1)	Reference	
Presence	252 (24.2)	56 (27.9)	0.825 (0.587, 1.158)	
Drinking history				0.688
Absence	722 (69.2)	142 (70.6)	Reference	
Presence	321 (30.8)	59 (29.4)	1.070 (0.769, 1.490)	
Significant weight loss				0.190
Absence	565 (54.2)	119 (59.2)	Reference	
Presence	478 (45.8)	82 (40.8)	1.228 (0.904, 1.668)	
Preoperative ASA score				0.169
I-II	928 (89.0)	172 (85.6)	Reference	
III-IV	115 (11.0)	29 (14.4)	0.735 (0.474, 1.140)	
Location				0.060
Upper	340 (32.6)	63 (31.3)	Reference	
Middle	155 (14.9)	30 (14.9)	0.957 (0.596, 1.539)	0.857
Lower	442 (42.4)	99 (49.3)	0.827 (0.585, 1.169)	0.283
Multiple parts	106 (10.1)	9 (4.5)	2.182 (1.050, 4.536)	**0.037**
Number of tumors				0.070
Single	984 (94.3)	196 (97.5)	Reference	
Multiple (≥2)	59 (5.7)	5 (2.5)	2.350 (0.931, 5.932)	
Tumor size (cm)	6.10±3.02	4.75±2.48	1.235 (1.151, 1.326)	**<0.001**
Histological types				**<0.001**
Differentiated	88 (8.4)	53 (26.4)	Reference	
Mixed	295 (28.2)	53 (26.4)	3.352 (2.140, 5.252)	**<0.001**
Undifferentiated	660 (63.4)	95 (47.2)	4.184 (2.796, 6.261)	**<0.001**

(*Continued*)

Table 3 (Continued).

	LNM Positive (*n*=1043), *n* (%)	LNM Negative (*n*=201), *n* (%)	OR (95% CI)	*P* Value
Ulceration				0.249
Absence	219 (21.0)	35 (17.4)	Reference	
Presence	824 (79.0)	166 (82.6)	0.793 (0.535, 1.176)	
Necrosis				0.863
Absence	989 (94.8)	190 (94.5)	Reference	
Presence	54 (5.2)	11 (5.5)	0.943 (0.484, 1.837)	
NED				0.135
Absence	988 (94.7)	185 (92.0)	Reference	
Presence	55 (5.3)	16 (8.0)	0.644 (0.361, 1.148)	
LVI				**<0.001**
Absence	570 (54.7)	171 (85.1)	Reference	
Presence	473 (45.3)	30 (14.9)	4.730 (3.150, 7.103)	
Nerve invasion				**<0.001**
Absence	608 (58.3)	190 (94.5)	Reference	
Presence	435 (41.7)	11 (5.5)	2.050 (1.461, 2.877)	

Notes: Bold values indicate *P*<0.05.

Abbreviations: LNM, lymph node metastasis; OR, odds ratio; CI, confidence interval; BMI, body mass index; HGB, hemoglobin; ALB, albumin; ASA, American society of Anesthesiologists; NED, neuroendocrine differentiation; LVI, lymphovascular invasion.

relevant literature evidence.[6,17,18] Consequently, we conducted this retrospective cohort study utilizing case data from one of the nation's largest medical centers, aiming to explore clinicopathological factors and develop nomograms for predicting LNM in T3-4a LAGC.

The existing literature primarily focuses on risk factors for LNM in EGC. Yang's research findings indicated that the presence of submucosal invasion, positive vertical margin, ulceration, and LVI could serve as independent risk factors for LNM or distant spread following non-curative endoscopic resection of undifferentiated-type EGC.[18] Oh's study found that tumor size larger than 3 cm, undifferentiated histologic type, and the presence of lymphatic and submucosal invasion were significantly associated with LNM in EGC.[19] Additionally, our previous research revealed that tumor size >2cm, submucosal invasion, mixed and undifferentiated histological types, the presence of LVI, and NED were factors associated with a higher incidence of nodal involvement in EGC.

The incidence of positive LNM in T3 and T4a LAGC was found to be 77.1% (1539/1995) and 83.8% (1043/1244), respectively, in this study. These findings were consistent with previous research.[2,3] Furthermore, the present study identified several independent risk factors for LNM in T3-4a LAGC, including reduced serum ALB levels, lower tumor location, lager tumor size, mixed and undifferentiated histological types, the presence of gastrointestinal obstruction, LVI, and nerve invasion. Malignant tumors are characterized by high metabolic activity and cachexia. In addition to weight loss as a clinical manifestation, tumor patients often experience concurrent reductions in muscle mass, adipose tissue, and cellular volume. The progression of the tumor is accompanied by metabolic alterations such as decreased activity of mitochondrial complex, impaired phosphocreatine synthesis, increased intracellular calcium flow, elevated protein degradation, and impaired synthesis. The alterations in body composition also increase the susceptibility to anemia and hypoalbuminemia among tumor patients. Moreover, protein deficiency can impair immune function, diminish the body's capacity to withstand trauma and infection, hinder tumor resistance, and promote tumor progression.[20,21] The preoperative diagnosis of gastrointestinal obstruction in this study was established through a combination of clinical symptoms such as abdominal distension and vomiting, along with the utilization of CT and gastroscopy. The majority of patients with gastrointestinal obstruction presented with concurrent electrolyte imbalances, anemia, hypoproteinemia, malnutrition, and compromised immune function. The occurrence of gastrointestinal obstruction frequently indicates an advanced stage of tumor progression. Our previous study also found that the presence of gastrointestinal obstruction is associated with an increased risk of developing postoperative gastroparesis syndrome.[22,23] The distal stomach wall

Table 4 Multivariate Logistic Regression Analysis of Clinicopathological Factors Related to LNM for pT4a LAGC

Covariates	OR (95% CI)	*P* Value
BMI (kg/m^2)		0.198
≤ 28	Reference	
> 28	0.721 (0.438, 1.187)	
Preoperative serum ALB		**0.004**
≥ 39 g/L	Reference	
< 39 g/L	1.734 (1.190, 2.526)	
Gastrointestinal obstruction		0.240
Absence	Reference	
Presence	1.359 (0.814, 2.269)	
Gastrointestinal hemorrhage		**0.016**
Absence	Reference	
Presence	0.629 (0.431, 0.919)	
Location		0.635
Upper	Reference	
Middle	0.821 (0.489, 1.378)	0.455
Lower	0.800 (0.548, 1.169)	0.249
Multiple parts	1.144 (0.401, 3.266)	0.801
Number of tumors		0.996
Single	Reference	
Multiple (≥2)	0.997 (0.263, 3.776)	
Tumor size (cm)		**0.020**
≤ 6 cm	Reference	
> 6 cm	1.610 (1.078, 2.404)	
Histological types		**<0.001**
Differentiated	Reference	
Mixed	2.673 (1.659, 4.306)	**<0.001**
Undifferentiated	3.634 (2.350, 5.620)	**<0.001**
NED		**0.024**
Absence	Reference	
Presence	0.485 (0.258, 0.910)	
LVI		**<0.001**
Absence	Reference	
Presence	3.882 (2.542, 5.927)	
Nerve invasion		0.071
Absence	Reference	
Presence	1.404 (0.972, 2.029)	

Notes: Bold values indicate *P*<0.05.
Abbreviations: LNM, lymph node metastasis; LAGC, locally advanced gastric cancer; OR, odds ratio; CI, credible interval; BMI, body mass index; ALB, albumin; NED, neuroendocrine differentiation; LVI, lymphovascular invasion.

exhibits a higher density of blood vessels, lymphatic vessels, and nerves compared to the proximal stomach. Additionally, there are augmented clusters of lymph nodes surrounding the distal stomach. Thus, distal gastric cancer carries a higher risk of LNM compared to proximal gastric cancer, resulting in a greater number of LNM.[24] Furthermore, the incidence of gastrointestinal obstruction is also elevated in cases of distal gastric cancer.

The biological characteristics of a tumor are also determined by its degree of differentiation. Malignant tumors with a lower degree of differentiation generally have a higher risk and extent of LNM. This phenomenon primarily stems from the increased heterogeneity and aggressiveness of inadequately differentiated tumor cells.[5,18,25] Additionally, previous research has primarily categorized histological subtypes as either differentiated or undifferentiated; nevertheless, it is noteworthy that a significant proportion of tumors exhibit mixed histology encompassing both aforementioned

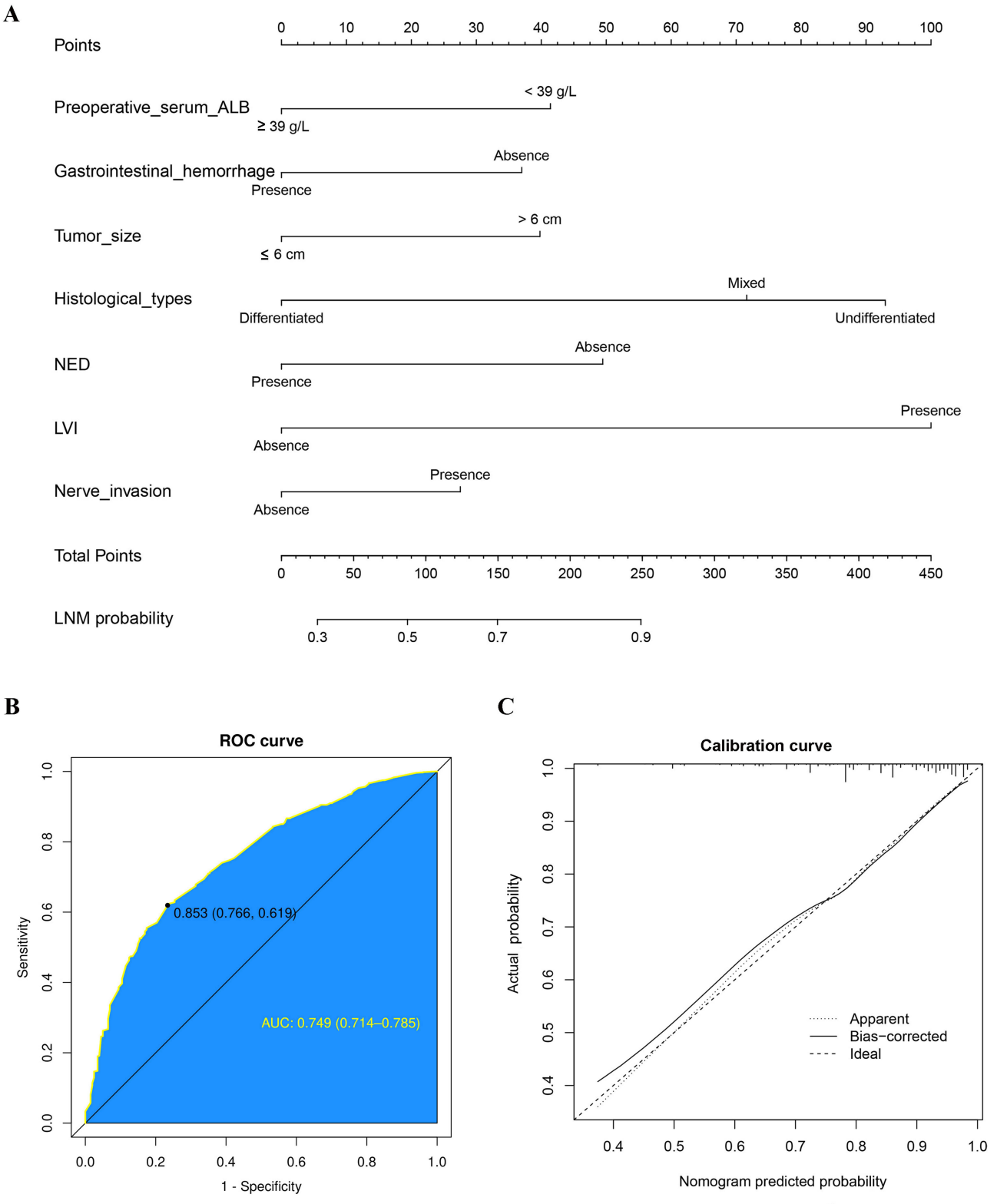

Figure 3 (**A**) The nomogram model constructed to estimate the risk of lymph node metastasis (LNM) in T4a locally advanced gastric cancer (LAGC) cases. (**B**) Receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) of the nomogram. (**C**) Calibration of the evaluation for nomogram model.
Abbreviations: ALB, albumin; NED, neuroendocrine differentiation; LVI, lymphovascular invasion.

categories.[26] The findings of the present study suggested that LAGC with mixed histological subtypes carries a higher risk and extent of LNM and demonstrates more aggressive biological behavior compared to LAGC with differentiated histological subtypes. The presence of undifferentiated components in mixed tumors is believed to account for the aforementioned phenomenon, and it should be managed similarly to undifferentiated tumors until specific therapeutic principles for mixed tumors are established. Consequently, obtaining tumor tissue through endoscopy and subsequent rigorous pathological examination are imperative for LAGC cases in order to establish an accurate treatment plan for follow-up procedures.

The endothelial cells forming the wall of capillary lymphatic vessels are predominantly arranged in an overlapping pattern, lacking a basal membrane and pericytes. As a result, they exhibit heightened permeability compared to capillaries, facilitating easier invasion by cancer cells.[27] This study also revealed that T3-4a LAGC cases with larger tumor size exhibited a higher propensity for progression to positive LNM. Despite still being confined to the subserous tissue or serous membrane, tumors at the T3-4a stage display increased contact areas and interactions with lymphatic vessels, blood vessels, and nerves within the gastric wall. This amplifies the risk of tumor cell infiltration into both bloodstream and lymphatic fluid as well as nerve invasion. Therefore, larger tumor size and higher rates of vascular and nerve invasion are frequently observed in LNM-positive LAGC.[5,18,28] The determination of LVI and nerve invasion prior to surgery poses a significant challenge. In addition to endoscopy and endoscopic ultrasonography, preoperative contrast-enhanced CT and MRI evaluations are also considered crucial for assessing the tumor size as well as the presence of LVI and even LNM. It is imperative to enhance and refine the existing imaging and histopathological examination techniques in order to improve the preoperative detection rate of LVI and nerve invasion.[29]

The analysis of T4a LAGC also revealed a higher incidence of preoperative gastrointestinal bleeding in the LNM negative group. This may be attributed to the fact that the presence of gastrointestinal bleeding symptoms prompts patients to seek medical attention, leading to early detection of tumors and subsequently reducing the risk of LNM. NED refers to a distinct pathological subtype of gastric adenocarcinoma characterized by the presence of less than 30% neuroendocrine cells. This subtype lies between gastric neuroendocrine carcinoma and adenocarcinoma. Until now, the available literature evidence regarding the impact of NED on the prognosis of gastric adenocarcinoma is limited and subject to controversy.[30,31] Due to the low occurrence rate of NED, there is a potential for systematic errors that could affect the findings of this study. Therefore, further expansion is necessary to validate its effectiveness.

Although this study examined the associations between clinicopathological factors and LNM in T3-4a LAGC by analyzing a substantial amount of case data, it is important to acknowledge certain limitations. First, the level of evidence was constrained by administrative and technical disparities between retrospective cohort studies and single-center cases, limiting the robustness of the findings. Second, the accuracy of the predictive model may be compromised if the included cases are divided into modeling and validation sets, thereby limiting the value of the nomogram as it lacks validation from external patient series or internal controls. Third, the retrospective nature of the study and the extensive dataset have resulted in certain medical records being unavailable, such as NLR, etc. The results of this study, therefore, necessitate further validation and supplementation through multicenter prospective studies encompassing a substantial sample size and comprehensive clinicopathological indicators.

Conclusion

The incidence of LNM in T3 and T4a LAGC was 77.1% (1539/1995) and 83.8% (1043/1244), respectively. Reduced serum ALB levels, lower tumor location, larger tumor size, mixed and undifferentiated histological types, presence of gastrointestinal obstruction, LVI, and nerve invasion are clinicopathological factors associated with a higher frequency nodal involvement. Additionally, the nomograms constructed based on the acquired risk factors demonstrated excellent predictive performance. This study identified the risk factors for LNM in stages T3-4a LAGC cases and constructed nomograms, thereby providing valuable insights for supplementing postoperative pathology reports, guiding the formulation and clinical application of multidisciplinary treatment program and follow-up.

Abbreviations

LNM, lymph node metastasis; LAGC, locally advanced gastric cancer; LVI, lymphovascular invasion; EGC, early gastric cancer; ESMO, European Society for Medical Oncology; LND, lymph node dissection; NCCN, National Comprehensive Cancer Network; HIPEC, hyperthermic intraperitoneal chemotherapy; CT, computed tomography; MRI, magnetic resonance imaging; NACT, neoadjuvant chemotherapy; BMI, body mass index; HGB, hemoglobin; ALB, albumin; ASA, American society of Anesthesiologists; NED, neuroendocrine differentiation; UICC, Union Internationale Against cancer; AJCC, American joint Committee on cancer; Syn, synapse; CgA, chromogranin A; NSE, neuro-specific enolase; SD, standard deviation; IQR, hyperthermic intraperitoneal chemotherapy; ROC, receiver operating characteristic; EMR, electronic medical record; AUC, area under the ROC curve.

Data Sharing Statement

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

Ethics Statement

This study was approved by the Medical Ethics Committee of the First Medical Center of the Chinese PLA General Hospital (S2021-022-01). All methods were carried out in accordance with the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of this study and the anonymous processing of patient data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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