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Original Article

Machine learning models for prediction of lymph node metastasis in patients with T1b gastric cancer

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Abstract: The prognosis of early gastric cancer (EGC) patients is associated with lymph node metastasis (LNM). Considering the relatively high rate of LNM in T1b EGC patients, it is crucial to determine the factors associated with LNM. In this study, we constructed and validated predictive models based on machine learning (ML) algorithms for LNM in patients with T1b EGC. Data from patients with T1b gastric cancer were extracted from the Korean Gastric Cancer Association database. ML algorithms such as logistic regression (LR), random forest (RF), extreme gradient boosting (XGBoost), and support vector machine (SVM) were applied for model construction utilizing five-fold cross-validation. The performances of these models were assessed in terms of discrimination, calibration, and clinical applicability. Moreover, external validation of XGBoost models was performed using the T1b gastric cancer database of The Catholic University Medical Center. In total, 3,468 T1b EGC patients were included in the analysis, whom 550 (15.9%) had LNM. Eleven variables were selected to construct the models. The LR, RF, XGBoost, and SVM models were established, revealing area under the receiver operating characteristic curve values of 0.8284, 0.7921, 0.8776, and 0.8323, respectively. Among the models, the XGBoost model exhibited the best predictive performance in terms of discrimination, calibration, and clinical applicability. ML models are reliable for predicting LNM in T1b EGC patients. The XGBoost model exhibited the best predictive performance and can be used by surgeons for the identification of EGC patients with a high-risk of LNM, thereby facilitating treatment selection.

Keywords: Machine learning, prediction model, gastric cancer, lymph node metastasis

Introduction

Early gastric cancer (EGC) refers to a tumor confined to the mucosa (T1a) or submucosa (T1b), irrespective of lymph node metastasis (LNM) [1]. Considering that LNM impacts the prognosis of EGC patients, their management depends on the likelihood of lymph node involvement. The overall survival rate of EGC is 70-80% with LNM, and 90-95% without LNM [2]. The LNM rates in EGC depend on the depth of tumor invasions, ranging from 3.2% (0-20.3%) in T1a and 19.2% (10.2-33.3%) in T1b [3]. Considering the relatively high LNM rate in T1b EGC, it is crucial to identify factors associated with LNM.

Several studies have identified independent risk factors associated with LNM in EGC, including age, sex, lymphovascular invasion, and tumor location, size, depth, and differentiation [4-7]. The relationship between LNM and these predictors has been analyzed using Cox proportional hazards model and logistic regression (LR) analysis. However, these relationships are not always linear, making it challenging to describe them using the aforementioned models. In fact, these factors appear to be interconnected in an intricate manner, forming complex relationships with LNM that extend beyond simple linear correlation. Therefore, there is a need to develop more effective and accurate prediction models.

Recently, there has been growing interest in the application of machine learning (ML) to various healthcare issues. Published ML models have the potential to provide clinicians with valuable insights, aiding in diagnostic tasks, predicting clinically significant events, and facilitating clinical decision-making [8]. Due to advancements in statistical theory and computer technology,

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ML is increasingly being utilized to evaluate associations between various cancers and their risk factors. Furthermore, novel ML techniques have been widely used in predictive models for various diseases, outperforming traditional linear relationships and Cox regression analyses. A retrospective study utilized ML algorithms to predict the early risk of gastric cancer based on lifestyle factors [9]. Moreover, a meta-analysis revealed that ML models can enhance the ability of clinicians to diagnose EGC during endoscopy, demonstrating broad clinical utility [10]. However, to the best of our knowledge, no previous studies have investigated the usefulness of ML algorithms in predicting LNM in T1b EGC patients. In this study, we developed and validated multiple ML models for predicting LNM in T1b EGC patients, to identify the model with the highest predictive performance.

Methods

Data source

We used the 2019 Korean Gastric Cancer Association Survey (KGCAS) dataset to train our model. KGCAS is a periodic cross-sectional survey conducted by the Korean Gastric Cancer Association to monitor clinicopathological status and surgical outcomes in the multi-institutionalized Korean population. Approximately 15,000 individuals participate in the KGCAS after every 5 years.

The external validation dataset was obtained from eight hospitals affiliated with the Catholic University Medical Center, encompassing the period between January 2007 and December 2017, and used the same criteria as the development set. 705 gastric cancer patients who had undergone curative gastrectomy were included after excluding the patients who did not meet the criteria. The study population included adults (≥ 19 years of age) with T1b gastric cancer, defined as a tumor confined to the submucosa. Age, sex, body mass index (BMI), histological tumor type, the Lauren classification, LVI status, tumor size, tumor location, the number of lesions, endoscopic submucosal dissection (ESD) status within 90 days before surgery, and the extent of lymph node dissection (LND) were all included when applying the external validation. Patient data were retrospectively collected by upper gastrointestinal surgeons and investigators.

The study included adults aged ≥ 19 years with T1b gastric cancer. Consistent with prior research [11], T1b gastric cancer was defined as tumors confined to the submucosa. We excluded patients with other malignancies, those receiving adjuvant chemotherapy or radiation therapy, and those undergoing completion gastrectomy. Moreover, patients with > 20% missing data were excluded. During the 2019 KGCAS survey, 14,076 adults with gastric cancer were identified. Of these, 10,608 participants did not fulfil the inclusion criteria, resulting in 3,468 eligible participants. For the external validation set, 2,125 patients with gastric cancer were identified, of whom 705 fulfilled the inclusion criteria.

Ethical review

The study protocol was approved by the Institutional Review Board of St. Vincent's Hospital, The Catholic University of Korea (VC2 3ZASI0180). The Institutional Review Board waived the need for informed consent.

Data preprocessing

In the preprocessing stage, raw data were extracted from the KGCAS database and transformed into records. Undecipherable values, such as errors in data types and standard formatting, were converted into null representations. Subsequently, the patients' records were structured into a data frame of features and a corresponding class label during the feature extraction stage. The features encompassed demographic, surgical, and pathological information of patients. The class label was a categorical variable, represented as a binary classification of patients: 0 for no, and 1 for yes. Categorical features were encoded with numerical values for analysis.

To develop a data-driven model, all potential variables were extracted from the raw KGCAS dataset to form the preliminary features. The dataset was examined to determine the availability of each variable across specific categories. Based on manual analysis, certain variables were recoded. Subsequently, only 18 of approximately 56 variables from the KGCAS database were found to be available. The data-

set was further analyzed for missing values within the variables, and any variables with > 50% missing values were excluded. Consequently, the number of available variables was further reduced to 11.

Model development

For model development, the original KGCAS dataset was randomly divided into a training set (70%) and a test set (30%). Then, least absolute shrinkage and selection operator (LASSO) regression was applied to the training set to select important features, thereby preventing overfitting. Consequently, 11 features were selected, including sex, age, BMI, histology, Lauren classification, LVI, tumor size, tumor location, number of lesions, ESD within 90 days before surgery, and LND. These features were introduced into four supervised ML models: multivariable LR, random forest (RF) classifier, extreme gradient boosting (XGBoost), and support vector machine (SVM). Subsequently, prediction models were constructed using the training set with aforementioned ML algorithms. During the modeling process, we utilized a grid search algorithm with five-fold cross-validation to tune the optimal hyperparameters. All analyses were conducted using R (R Foundation for Statistical Computing, Vienna, Austria).

Statistical analysis

Continuous variables are presented as means with standard deviation and were compared using Student's t-test or Mann-Whitney U test. Categorical variables are presented as numbers with percentage and were compared using the Chi-square test or Fisher's exact probability method.

To evaluate the predictive performance of the models, receiver operating characteristic (ROC) curves were plotted to determine the area under the curve (AUC), sensitivity, specificity, positive predictive value, negative predictive value, accuracy, F1 score, and Brier score. The Brier score serves as a proper score function that measures the accuracy of probabilistic predictions, particularly in tasks involving the assignment of probabilities to a set of mutually exclusive discrete outcomes. A score closer to zero indicates greater model accuracy. Following the identification of the best prediction model based on predictive performance, we used SHapley Additive exPlanations (SHAP) to visualize and determine the importance of variables. This method is used to interpret the output of ML models, elucidating the influence of characteristic variables on outcomes to estimate the contribution of each feature to the final event. Furthermore, decision curve analysis was used to assess the clinical usefulness and net benefit of the best prediction model. Finally, the best prediction model was applied to the external validation cohort, to evaluate its predictive performance and clinical usefulness using the aforementioned indicators and decision curve analysis.

Results

Clinicopathological characteristics

Table 1 presents the clinicopathological data of the study cohort. Among the 3,468 patients with T1b gastric cancer, 2,426 were included in the training cohort and 1,042 in the test cohort. In the training cohort, 550 patients (22.7%) had LNM and 1,876 (77.3%) did not. In the test cohort, 231 patients (22.2%) had LNM and 811 (77.8%) did not. The training and test cohorts had significant differences in terms of the tumor location.

In the external cohort, 185 patients (26.2%) had LNM and 520 (73.8%) did not. There were significant differences between the internal and external cohorts in terms of the Lauren class, LVI, tumor location, ESD within 90 days before surgery, extent of LND, and LNM.

Feature selection for modeling

To determine the predictors of LNM, we used LASSO L1 regularization, which demonstrated the most substantial reduction in the number of features and achieved the optimal predictive performance. Consequently, our models are primarily based on features selected using the LASSO L1 regularization method, including age, sex, BMI, histologic type, Lauren classification, LVI, tumor size, tumor location, number of lesions, ESD before surgery, and extent of LND.

ML analysis for predictive modeling

Table 2 presents a comparison of accuracy scores of various models for LNM prediction in

Table 1. Baseline characteristics of patients

Characteristics	All patients			Training Cohort			Test Cohort		
	Training Cohort (N = 2,426)	Test Cohort (N = 1,042)	*P* value	No LNM (N = 1,876)	LNM (N = 550)	*P* value	No LNM (N = 811)	LNM (N = 231)	*P* value
Age, years									
< 60	809 (33.3)	365 (35.0)	0.357	630 (33.6)	179 (32.5)	0.049	274 (33.8)	91 (39.4)	0.107
≥ 60	1,617 (66.7)	677 (65.0)		1,246 (66.4)	371 (67.5)		537 (66.2)	140 (60.6)	
Gender									
Male	1,625 (67.0)	679 (65.2)	0.317	1,318 (70.3)	307 (55.8)	< 0.001	555 (68.4)	124 (53.7)	< 0.001
Female	801 (33.0)	363 (34.8)		558 (29.7)	243 (44.2)		256 (31.6)	107 (46.3)	
BMI (kg/m^2)									
< 18.5	74 (3.1)	28 (2.7)	0.788	60 (3.2)	14 (2.5)	0.412	24 (3.0)	4 (1.7)	0.199
18.5-24.9	1,404 (57.7)	597 (57.3)		1,071 (57.1)	330 (60.0)		473 (58.3)	124 (53.7)	
≥ 25	951 (39.2)	417 (40.0)		745 (39.7)	206 (37.5)		314 (38.7)	103 (44.6)	
Histologic type									
Differentiated	1,315 (54.2)	555 (53.3)	0.636	1,032 (55.0)	283 (51.5)	0.155	449 (55.4)	106 (45.9)	0.013
Undifferentiated	1,111 (45.8)	487 (46.7)		844 (45.0)	267 (48.5)		632 (44.6)	125 (54.1)	
Lauren classification									
Intestinal	1,301 (53.6)	580 (55.7)	0.453	1,072 (57.1)	229 (41.6)	< 0.001	477 (58.8)	103 (44.6)	< 0.001
Diffuse	718 (29.6)	294 (28.2)		607 (32.4)	111 (20.2)		255 (31.4)	39 (16.9)	
Mixed	407 (16.8)	168 (16.1)		197 (10.5)	210 (38.2)		79 (9.7)	89 (38.5)	
LVI									
No	1,707 (70.4)	764 (73.3)	0.085	1,524 (81.2)	183 (33.3)	< 0.001	674 (83.1)	90 (39.0)	< 0.001
Yes	719 (29.6)	278 (26.7)		352 (18.8)	367 (66.7)		137 (16.9)	141 (61.0)	
Tumor size, cm									
< 2.5	1,063 (43.8)	460 (44.1)	0.887	900 (48.0)	163 (29.6)	< 0.001	390 (48.1)	70 (30.3)	< 0.001
≥ 2.5	1,363 (56.2)	582 (55.9)		976 (52.0)	387 (70.4)		421 (51.9)	161 (69.7)	
Tumor location									
Upper third	509 (21.0)	190 (18.2)	0.03	397 (21.2)	112 (20.4)	0.386	153 (18.9)	37 (16.0)	0.446
Mid third	691 (28.5)	345 (33.1)		547 (29.2)	144 (26.2)		271 (33.4)	74 (32.0)	
Lower third	1,195 (49.3)	497 (47.7)		907 (48.3)	288 (52.4)		378 (46.6)	119 (51.5)	
Whole	31 (1.3)	10 (1.0)		25 (1.3)	6 (1.1)		9 (1.1)	1 (0.5)	
No of lesions									
Single	2,308 (95.1)	985 (94.5)	0.507	1,783 (95.0)	525 (95.5)	0.778	767 (94.6)	218 (94.4)	1
Multiple	118 (4.9)	57 (5.5)		93 (6.0)	25 (4.5)		44 (5.4)	13 (5.6)	
Extent of dissection									
D1	1,240 (51.1)	546 (52.4)	0.511	970 (51.7)	270 (49.1)	0.303	436 (53.8)	110 (47.6)	0.115
D2	1,186 (48.9)	496 (47.6)		906 (48.3)	280 (50.9)		375 (46.2)	121 (52.4)	
ESD before surgery									
No	1,643 (67.7)	693 (66.5)	0.508	1,190 (63.4)	453 (82.4)	< 0.001	489 (60.3)	204 (88.3)	< 0.001
Yes	783 (32.3)	349 (33.5)		686 (36.6)	97 (17.6)		322 (39.7)	27 (11.7)	

Table 2. Performance comparison for the prediction of LNM risk factors in the training cohort

	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	F1 score	Brier score
Logistic regression	0.8413 (0.8215-0.8589)	0.3876	0.9585	0.731	0.8432	0.8298	0.5066	0.1189241
Random forest	0.8353 (0.8148-0.8557)	0.4364	0.9728	0.8247	0.8548	0.8512	0.5708	0.1287359
XGBoost	0.9019 (0.8881-0.9158)	0.5127	0.9622	0.7989	0.8707	0.8603	0.6246	0.09709869
Support Vector Machine	0.8876 (0.8704-0.9049)	0.4691	0.9691	0.8165	0.8616	0.8557	0.5959	0.1033602

Table 3. Performance comparison for the prediction of LNM risk factors in the test cohort

	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	F1 score	Brier score
Logistic regression	0.8284 (0.797-0.8597)	0.4348	0.9594	0.7519	0.857	0.8436	0.551	0.1195243
Random forest	0.7921 (0.7566-0.8276)	0.4026	0.9655	0.7686	0.8502	0.8407	0.5284	0.1323223
XGBoost	0.8776 (0.8534-0.9018)	0.4632	0.9556	0.7483	0.8621	0.8464	0.5722	0.1062113
Support Vector Machine	0.8323 (0.7994-0.8653)	0.3983	0.9716	0.8	0.8501	0.8445	0.5318	0.1554702

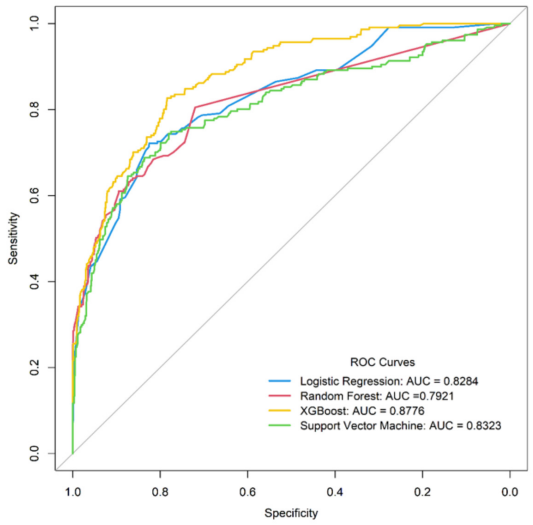

Figure 1. ROC curves for four machine learning models in predicting LNM. Five-fold cross-validation was used to build and evaluate the prediction models. Different colors represent the different machine learning models used in this study. The gray line is the reference corresponding to the performance of a model that completely and randomly classifies the condition.

the training cohort. Significant differences in the performance were observed among the various models. In the training cohort, XGBoost achieved the highest AUC (0.9019), sensitivity (0.5127), precision (0.8707), accuracy (0.8603), F1 score (0.6246), and Brier score (0.0970) in predicting LNM, whereas RF demonstrated the highest specificity (0.9728) and positive predictive value (PPV) (0.8247) for predicting LNM.

Table 3 presents the AUC, sensitivity, specificity, PPV, negative predictive value (NPV), accuracy, F1 score, and Brier score for each model in the test cohort. All four models demonstrated excellent performance, with accuracy rates reaching up to 0.80. Among the models, XGBoost achieved the highest AUC (0.8776), sensitivity (0.6632), NPV (0.8621), accuracy (0.8464), F1 score (0.5722), and Brier score (0.1062). Conversely, SVM achieved the highest specificity (0.9716) and predictive value (0.80) for predicting LNM.

The performance of the four ML models based on features selected using LASSO L1 regularization is demonstrated in an ROC curve (**Figure 1**). XGBoost achieved the highest AUC (0.8776) for predicting LNM. Notably, all ML models achieved higher classification accuracy than the gray diagonal line, indicating AUC of 0.5000 (**Figure 1**).

Figure 2 presents the importance of 11 variable datasets for LNM prediction using feature importance scores for the XGBoost model. The results are based on the average error rate, calculated by the number of misclassifications of observations across sequential trees in an XGBoost classifier. A cutoff of 15 features was determined by developing models ordered by importance and applying a cutoff of a ≤ 2% drop in the cross-validation AUC value.

Internal and external validation of the XGBoost model for LNM prediction

In the training cohort, the AUC was 0.9019 (95% confidence interval: 0.8881-0.9158) (**Figure 3A**). In the test cohort, the AUC was 0.8776 (95% confidence interval: 0.8534-0.9018) (**Figure 3B**). The decision curve analy-

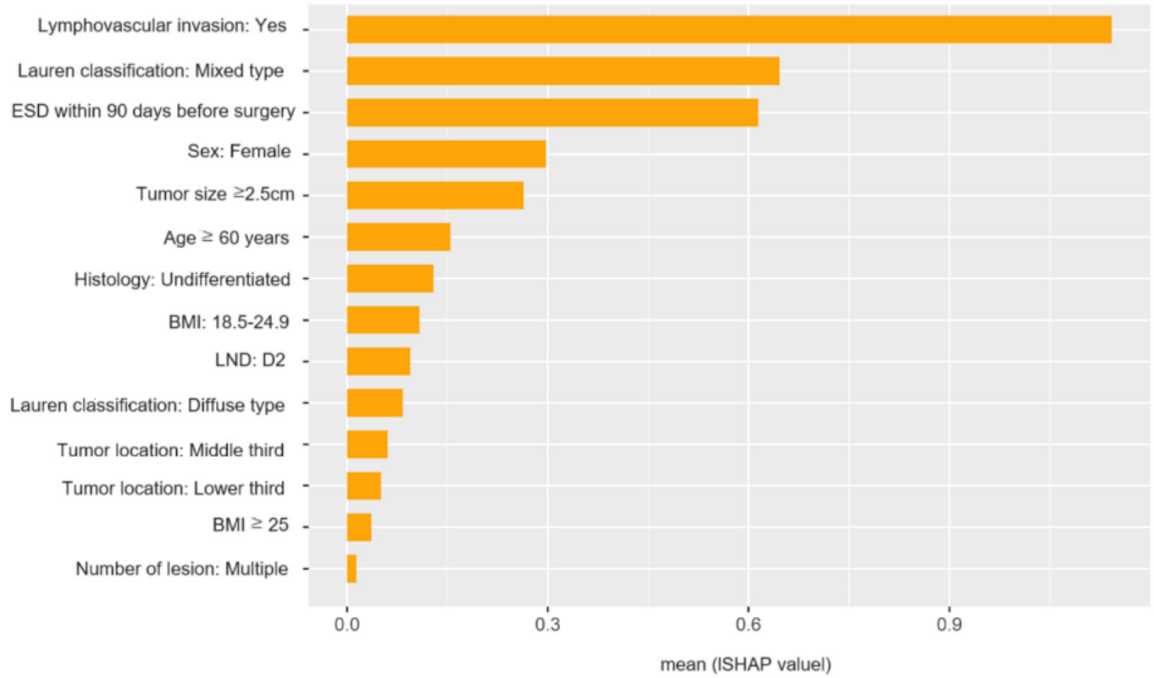

Figure 2. Average feature importance for LNM. This graph shows the most important features for predicting LNM.

sis (**Figure 3C**) demonstrated that the XGBoost model exhibited favorable net benefit and threshold probability, indicating that this was the optimal model with good clinical utility.

To overcome the limitations of internal validation, we conducted external validation to assess the generalizability of the prediction model using a validation cohort. In the external validation, the AUC was 0.8050 (95% confidence interval: 0.7647-0.8454) (**Figure 4A**). Furthermore, decision curve analysis for XGBoost showed good agreement between the predicted and actual observations (**Figure 4B**).

Discussion

In this study, we developed effective ML models (LR, RF, XGBoost, and SVM) to predict LNM in T1b gastric cancer patients using the KGCAS dataset. Among these models, XGBoost exhibited the best predictive performance for LNM. Considering that the predictors included in the model consisted of 11 features related to preoperative clinicopathological data, XGBoost could be used to predict LNM and guide optimal treatment planning before the surgery.

In Korea, national screening programs have progressively facilitated the early detection of EGC, with ESD performed for EGC with a minimal risk of LNM meeting the endoscopic resection criteria [11]. The curability of endoscopic resection is categorized as eCuraA, B, and C [12]. While no additional treatment is needed for patients with eCuraA, controversy exists regarding whether additional surgery should be performed for those with eCuraB and C. Cases categorized as eCuraC-1, where the horizontal margin is positive or cancer is not resected en bloc, may undergo repeat ESD [12]. However, for cases categorized as eCuraC-2, including cancer with LVI, additional surgery is recommended due to the high risk of LNM. Therefore, predicting LNM in patients with EGC is essential. Introducing ML-based predictive models for identifying EGC patients with a high probability of LNM offers a potential solution to the aforementioned challenges.

The predictors for LNM identified in this study align with findings from previous studies; furthermore, certain additional emerging predictors were also identified. Vos *et al.* [13] proposed a nomogram for predicting LNM in T1b EGC, highlighting female sex, tumor size, tumor location, and LVI as predictive factors, findings that are consistent with our study. Similarly, Kim *et al.* [14] developed a prediction model for

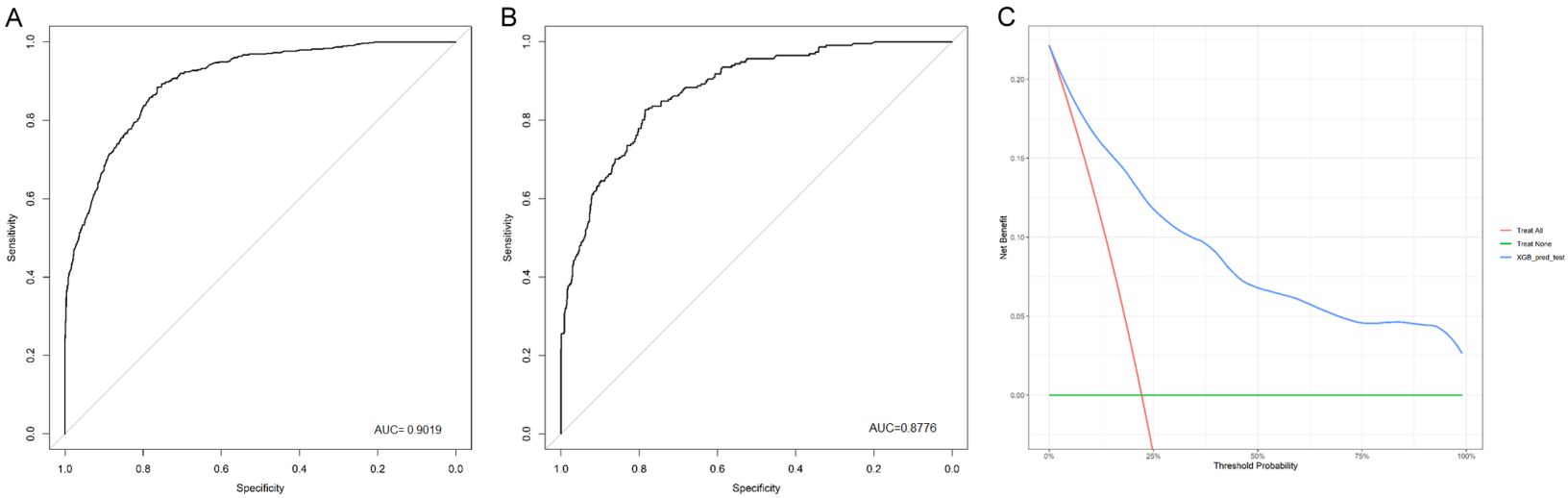

Figure 3. A. Receiver operating characteristic (ROC) curve analysis of XGBoost model in the training cohort. B. ROC curve analysis of XGBoost model in the test cohort. C. Calibration plot of XGBoost decision curve.

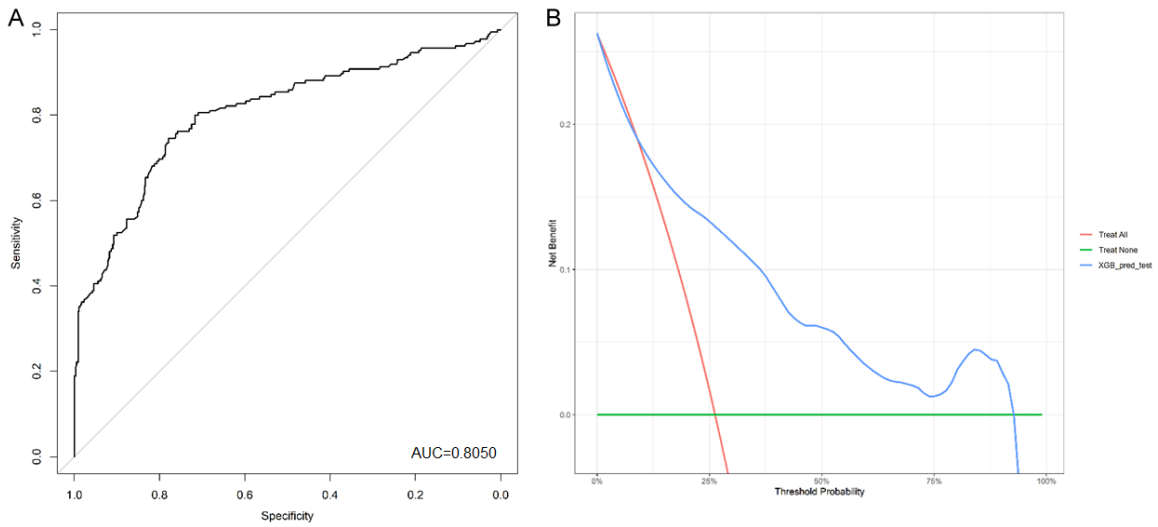

Figure 4. A. Receiver operating characteristic (ROC) curve analysis of XGBoost model in the external validation cohort. B. Calibration plot of XGBoost decision curve.

LNM in EGC, considering female sex, younger age, and LVI as predictive factors. However, their inclusion of both T1a and T1b EGC patients differs from our cohort, potentially explaining why female sex and LVI were the only predictive factors consistent with our study. Notably, our study identified ESD before surgery as a newly identified predictor, along with the presence of a mixed type of Lauren classification. Previous studies have shown that the presence of a mixed type of Lauren classification correlates with a higher risk of LNM and worse prognosis, in line with our findings [15]. Conversely, ESD before surgery was associated with a protective effect on LNM. To the best of our knowledge, the protective effect of ESD before surgery on LNM has not been previously verified. ESD can disrupt the lymphatic network and flow in the submucosal layer of the gastric wall [16], potentially blocking the lymphatic flow of cancer cells and preventing LNM.

Numerous studies have evaluated ML techniques due to their integration of statistics and computer technology. These techniques have garnered significant interest for their ability to develop prediction models for various diseases, outperforming traditional LR or Cox regression models [17]. ML algorithms are accurate tools that play a crucial role in decision-making processes, particularly when analyzing big data [18]. Notably, when a substantial amount of data is available for analysis, ML algorithms consistently demonstrate excellent performance. Considering that we utilized nationwide data to construct our ML-based prediction model, the achieved accuracy is satisfactory. Furthermore, our analysis was based on various models, with XGBoost demonstrating the highest prediction accuracy. Several other studies have also reported that XGBoost, a linear model, outperforms other ML models in terms of accuracy [19-22].

This study had several limitations that should be considered. First, genetic information, such as p53, C-erbB2, and PD-L1 status, was not incorporated, despite their associations with gastric cancer prognosis [23]. The inclusion of genetic information as features for ML model development could potentially enhance the predictive accuracy of LNM in future studies. Second, data were collected retrospectively and participants with missing data were excluded. Third, data were not available for patients who underwent ESD but did not undergo surgery. Only data from patients who underwent ESD followed by surgery for EGC were included, potentially leading to selection bias. Fourth, the sample size of this study was relatively small compared to other population studies. Finally, we only used the data from the same country for external validation. Validating the models using data from other countries would have provided a more comprehensive assessment. Nevertheless, the strength of this study lies in the creation of prediction models using preoperative clinical features, enabling surgeons to

plan treatment for EGC based on factors contributing to a high LNM risk. ML models included pathologic data, making it more helpful for patients requiring surgical treatment after ESD. Furthermore, external validation was performed using a relatively large sample size, demonstrating the model's applicability with high accuracy, similar to internal validation. Based on ML model algorithms in this study, we expect that these can be used to predict LNM in T1b gastric cancer patients and assist clinicians in making treatment decisions. Also, we plan to start a prospective study associated with prediction of T1b gastric patients' LNM before surgery by using the ML models and evaluate the accuracy in the future.

In conclusion, we successfully developed effective ML models for predicting LNM in T1b gastric cancer patients. Among the various ML models examined, the XGBoost model exhibited superior performance in LNM prediction. These findings hold promise for assisting surgeons in identifying patients at high risk of LNM and formulating appropriate treatment plans before surgery.

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Disclosure of conflict of interest

None.

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