Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

A Retrospective Analysis: A Predictive Model Using Platelets and Neutrophil-to- Lymphocyte Ratio for the Number of Lymph Node Metastasis in Papillary Thyroid Carcinoma

YuYing Chen
The Fourth Clinical Medical College, Zhejiang Chinese Medical University
Fan Wu
Department of Oncological Surgery, Affiliated Hangzhou First People's Hospital, Westlake University School of Medicine, Hangzhou
Mengqian Ge
The Fourth Clinical Medical College, Zhejiang Chinese Medical University
Tao Hu
The Fourth Clinical Medical College, Zhejiang Chinese Medical University
Shuoying Qian
The Fourth Clinical Medical College, Zhejiang Chinese Medical University
Yuan Cai
The Fourth Clinical Medical College, Zhejiang Chinese Medical University
Xuanwei Huang
The Fourth Clinical Medical College, Zhejiang Chinese Medical University
Kaiyuan Huang
The Fourth Clinical Medical College, Zhejiang Chinese Medical University
Gang Pan
Department of Oncological Surgery, Affiliated Hangzhou First People's Hospital, Westlake University School of Medicine, Hangzhou
Dingcun Luo
ldc65@zju.edu.cn

Department of Oncological Surgery, Affiliated Hangzhou First People's Hospital, Westlake University School of Medicine, Hangzhou

---

Research Article

Keywords:

Posted Date: March 28th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-4147192/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Objective The aim of this study was to investigate the high-risk clinical factors for large-number lymph node metastases (LNLNM) inthyroid papillary carcinoma (PTC).

Methods The clinicopathological data from the 731 PTC patients who underwent thyroid operation between September 2021to October 2022 in the surgical oncology of Affiliated Hangzhou First People's Hospital, Westlake University School of Medicine were collected. Univariate and multivariate logistic analyses were conducted to identify risk factors for LNLNM in PTC. A predictive model for assessing LNLNM in PTC was established and validated by using receiver operating characteristic curves (ROC), the Hosmer-Lemeshow (HL)test, calibration curves, and decision curve analysis (DCA).

Results Age, tumor diameter, platelets and neutrophil-to-lymphocyte ratio (NLR) were identified as independent risk factors for LNLNM in PTC patients. A predictive model was developed to evaluate the risk of LNLNMwith an area under the curve (AUC) of 0.827 (P<0.001, 95%CI: 0.784-0.870) and the specificity and sensitivity were both 75.8%. The AUC of the validation group was 0.824(P<0.001, 95%CI: 0.757-0.890) with a specificity of 79.5% and a sensitivity of 76.0%. Furthermore, themodel demonstrated good calibration through the HL test and favorable diagnostic value by calibration curve and DCA.

Conclusion Age, tumor diameter, platelets and NLRare high-risk factors for LNLNM in PTC, and the predictive model established in combination with the above factors couldeffectively predict the occurrence of LNLNM in PTC. This study provides support for surgeons to accurately predict the possibility of LNLNM and develop personalized treatment plans before surgery.

Introduction

Papillary thyroid carcinoma (PTC) is the one of the most common endocrine tumors with its occurrence experiencing a significant surge over the past decades, leading to widespread public concern[1, 2]. Although the majority PTCs are relatively indolent with a high 10-year survival rate, there still 20–90% of PTC patients will develop lymph node metastasis (LNM), significantly increasing the risk of recurrence and adversely affecting the prognosis[3]. Patients with more LNM have poorer outcomes than patients with fewer LNM, indicating that the number of LNM was significantly associated with prognosis of cancer and the recurrence risk[4–7]. The latest American Thyroid Association (ATA) guidelines have determined that if more than five LNM will reach the intermediate risk or above, the recurrence risk will vary from 4% in fewer than five LNM to 19% in more than five LNM in PTC patients[8]. Therefore, the number of LNM, specifically the number of LNM is more than five which defined as large-number lymph node metastases (LNLNM), will significantly reduce the prognosis of patients[9]. Regrettably, existing conventional methods, such as preoperative cervical ultrasound and computed tomography, could not accurately detected the LNLNM in PTC patients[10]. Consequently, there is an imperative to find a suitable approach for predicting the presence of LNLNM in PTC patients before surgery to enhance clinical decision-making and optimize treatment efficacy.

An increasing findings support that the blood immune indicators are recognized as important factors in the development and prognosis of malignant tumors, including PTC[11–13]. Some inflammatory indicators, including neutrophils (N), lymphocytes (L), monocytes (M), platelets (Plt), lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammatory index (SII) are considered effective predictors in many malignant tumors[14–17]. Notably, a study has established a noteworthy association between heightened Plt levels and cancer metastasis, as well as an unfavorable prognosis[18]. Additionally, an elevated NLR has been found to be correlated with a higher recurrence rate and is considered as a negative prognostic factor for cancer survival[19]. Consequently, blood inflammatory immune indicators are emerging as potentially influential biomarkers for determining cancer prognosis and LNM due to their availability and cheapness. However, the association between blood immune indicators and the prognosis in PTC, particularly in relation to LNLNM, remains uncertain.

The objective of this study is to investigate the potential risk factors associated with LNLNM in PTC patients with a particular emphasis on blood immune indicators, as well as to establish and verify the predictive model. The findings of our study not only offer valuable insights for surgeons, enabling them to accurately predict the possibility of LNLNM before surgery, but also assist surgeons in devising personalized treatment strategies, ultimately leading to improved patient prognosis and quality of life.

Materials and methods

Patient selection

In this study, the relevant data of patients with radical thyroidectomy in Hangzhou First People's Hospital of Westlake University School of Medicine (Hangzhou, China) from September 2021 to October 2022 were collected for retrospective analysis. The inclusion criteria were as follows: (1) initial radical thyroidectomy was performed for PTC, (2) standard surgical procedures included excision of at least one glandular lobe and ipsilateral lymph node dissection, (3) postoperative pathological diagnosis confirmed the presence of PTC, (4) peripheral blood routine examination was conducted within 3 days prior to surgery, (5) no concurrent malignancies were detected. The exclusion criteria were as follows: (1) presence of evident infection or inflammatory disease prior to surgery, (2) history of chemotherapy or exposure to radioactive substances before surgery, (3) incomplete preoperative and postoperative clinical data, (4) history of chronic diseases such as diabetes, hepatitis, tuberculosis or kidney disease. The flowchart of the patient selection process is shown in Fig. 1.

Data collection

Fasting peripheral blood was collected in the morning 3 days before radical thyroidectomy. The blood samples were processed by using the Mindary BC-6800 automatic blood cell analyzer (Shenzhen Mairui Biomedical Electronics Co., Ltd., Shenzhen, China) to obtain the absolute values of N, M, Plt, and L. The NLR, PLR, LMR and SII were calculated based on the ratios of the aforementioned inflammatory indicators. The pathological data included tumor diameter, multifocality, and the number of LNM. In

cases of multifocal tumors, analysis was performed on the largest tumor. LNLNM referred to the presence of more than five metastatic lymph nodes. Additionally, general patient information such as gender and age was collected.

Statistical Analysis

Since our data were non-parametric distributed, the median (M) and inter quartile range (IQR) was used for the continuous variables, while categorical variables were presented as frequency and percentage. We perform the Wilcoxon tests for continuous variables and Pearson's Chi-square test or Fisher's exact test for categorical variables. Variables with a significance level of $P < 0.05$ in the univariate analysis were selected for inclusion in the multivariate analysis. Binary logistic regression analysis was employed to establish the risk prediction model and construct the nomogram. Receiver operating characteristic curve (ROC) and area under curve (AUC) were used to evaluate the discrimination of the above model. A higher AUC value indicates better model performance. Sensitivity and specificity of the models were calculated at the maximum Youden index. Furthermore, the Hosmer-Lemeshow (HL) test is employed for the purpose of forecasting the calibration of the model. When the $P > 0.05$ in HL test indicates that the prediction model has a good fit. Additionally, a calibration diagram was constructed to assess the performance of the predictive model. Finally, the decision curve analysis (DCA) was used to verify the clinical net benefit rate of the predicted model. All statistical analysis and figures were were conducted utilizing R studio (version 4.3.2).

Result

General information

This study included 731 PTC patients based on inclusion and exclusion criteria, including 200 males (27.35%) and 531 females (72.64%). A total of 176 patients (24.07%) with LNLNM while 555 patients (75.92%) without LNLNM. A random distribution of 7:3 was used to divide the PTC patients into a model group and a validation group. The model group consisted of 531 patients while the validation group consisted of 218 patients. Specifically, 124 patients (24.17%) with LNLNM and 389 patients (75.82%) without LNLNM in the model group, while 52 patients (23.85%) with LNLNM and 166 patients (76.14%) without LNLNM in the validation group. The general characteristics of the patients are shown in Table 1.

Table 1
General information of thyroid papillary carcinoma (PTC) patients in model and validation groups

		Model group		Validation group	
		Without LNLNM	With LNLNM	Without LNLNM	With LNLNM
		(N = 389)	(N = 124)	(N = 166)	(N = 52)
Gender	Female	289 (74.2%)	77 (62.1%)	126 (75.9%)	39 (75.0%)
	Male	100 (25.7%)	47 (37.9%)	40 (24.1%)	13 (25.0%)
Age	M (IQR)	46.000 (35.000-55.500)	36.000 (30.000–47.000)	48.000 (36.000–58.000)	40.000 (30.000–49.000)
Tumor Diameter (mm)	M (IQR)	8.000 (6.000–12.000)	14.000 (10.000–22.000)	8.000 (6.000–12.000)	13.000 (9.250–23.500)
Multiplicity	Yes	104 (26.7%)	40 (32.3%)	122 (73.5%)	18 (34.6%)
	No	285 (73.3%)	84 (67.7%)	44 (26.5%)	34 (67.3%)
Plt	M (IQR)	215.000 (184.000-255.000)	233.500 (198.000-274.800)	226.500 (196.800-259.300)	224.000 (194.300–264.000)
N	M (IQR)	3.000 (2.400–3.850)	3.300 (2.800–4.100)	3.200 (2.600–3.900)	3.645 (3.645–4.650)
L	M (IQR)	1.800 (1.500–2.200)	1.830 (1.500–2.200)	1.800 (1.500-2.000)	1.900 (1.503–2.155)
M	M (IQR)	0.300 (0.295-0.400)	0.400 (0.300-0.495)	0.300 (0.300–0.400)	0.400 (0.300–0.500)
PLR	M (IQR)	117.500 (92.340–143.300)	121.300 (102.500-154.800)	123.500 (99.230–153.800)	126.700 (100.800-156.900)
NLR	M (IQR)	1.692 (1.325–2.106)	1.760 (1.381–2.333)	1.769 (1.413–2.351)	1.890 (1.564–2.573)
LMR	M (IQR)	5.667 (4.500-7.292)	5.333 (4.250–6.650)	5.708 (4.333–7.050)	5.000 (4.000-6.500)

		Model group		Validation group	
		Without LNLNM	With LNLNM	Without LNLNM	With LNLNM
		(N = 389)	(N = 124)	(N = 166)	(N = 52)
SII	M (IQR)	361.500 (265.600-485.300)	431.200 (325.900-589.900)	399.100 (295.200-537.600)	452.400 (376.700-616.600)

Screening of predictive model variables

The results of the univariate analysis demonstrated that age, gender, tumor diameter, Plt, N, M, NLR, LMR, PLR, and SII are significant predictors of LNLNM in PTC patients, with a statistically significant correlation ($P < 0.05$). Conversely, there was no statistically significant correlation in multiplicity and L ($P > 0.05$). The corresponding P-values could be found in the Table 2.

Significant factors in the univariate analysis were then included in the multivariate analysis. Multivariate logistic regression analysis demonstrated that age ($P < 0.001$ OR: 0.959, 95%CI: 0.939–0.978), tumor diameter ($P < 0.001$ OR: 1.149, 95%CI: 1.111–1.193), Plt ($P < 0.01$ OR: 1.006, 95%CI: 1.002–1.011) and NLR ($P < 0.01$ OR: 1.604, 95%CI: 1.166–2.198) were the independent risk factors for LNLNM in PTC patients. The specific values are shown in Table 2

Table 2
Results of univariate regression analysis and logistic multivariate regression analysis

	P-value(Univariate analysis)	P-value(Logistic analysis)	OR(Logistic analysis)	95%CI(Logistic analysis)
Gender	0.014			
Age	< 0.001	< 0.001	0.959	0.939–0.978
Tumor Diameter (mm)	< 0.001	< 0.001	1.149	1.111–1.193
Multiplicity	0.249			
Plt	< 0.001	< 0.01	1.006	1.002–1.011
N	0.002			
L	0.361			
M	0.499			
PLR	0.038			
NLR	0.021	< 0.01	1.604	1.166–2.198
LMR	0.045			
SII	< 0.001			

Model construction and validation

The logistic multiple regression analysis findings were incorporated into the construction of the prediction model, which identified age, tumor diameter, NLR, and Plt. Consequently, these independent predictors were combined to construct a predictive model for LNLNM in PTC patients (Fig. 2). The ROC curve was generated based on the logistic multiple regression outcomes. The area under the curve (AUC) of the model was 0.827 ($P < 0.001$, 95%CI: 0.784–0.870), which indicates excellent discrimination. When the Youden index was the highest, the specificity and sensitivity were 75.8% (Fig. 3a). The HL test showed good goodness-of-fit ($P = 0.464$), indicating that the predictive model had good calibration in predicting the probability of LNLNM. Besides, the calibration curves showed good agreement between the predicted and observed probabilities of LNLNM, with a mean absolute error of 0.014 (Fig. 4a). Additionally, the DCA demonstrated the effectiveness of the nomograms across a wide range of clinical utility (Fig. 5).

A total of 218 validation data were included to verify the generalization of the model. The results showed that the AUC of the validation group was 0.824 ($P < 0.001$, 95% CI: 0.757–0.890). The specificity was 79.5% and the sensitivity was 76.9% at the maximum Youden index, which means the model has good repeatability and wide applicability (Fig. 3b). The HL test showed a great calibration in the validation group ($P = 0.219$). In addition, the calibration curve and the DCA of the validation group also indicated that the model had good diagnostic value (Fig. 4b and 5).

Discussion

Universally acknowledged, PTC is the most prevalent malignant disease in the endocrine system, with 20–90% of cases experiencing the LNM. The occurrence of LNM not only elevates the risk of recurrence but also significantly diminishes the patient's prognosis and overall quality of life[3, 20, 21]. Patients exhibiting a greater number of LNM tend to experience inferior outcomes compared to those with a less quantity, especially the recurrence risk in PTC significantly increases 5 times when there are more than five metastatic lymph nodes[8, 22, 23]. Similarly, another study discovered that recurrence occurred in up to 37.3% of patients with more than five LNM[24]. Notably, the number of LNM greater than 5 will significantly reduces the prognosis in PTC patients, arousing the attention of clinicians. Therefore, in this study, we artificially defined the presence of LNM more than five as LNLNM referring to previous studies, and explore the risk factors of LNLNM[9]. Analysis found that age, tumor diameter, NLR, and Plt were independent risk factors for LNLNM in PTC patients. Also, the prediction model provides precise predictions for LNLNM in PTC patients, thereby offering enhanced guidance for clinical practice.

It has been documented that blood immune indicators is closely linked to cancers, holding significant research value[25, 26]. Many indicators have demonstrated effective predictive capabilities for the presence and prognosis of malignancies across various types of cancers[27–29]. NLR, as a more popular and reliable blood immune indicators compared to others, had been extensively utilized as a long-term predictor of outcomes across various malignancies[30, 31]. Preoperatively elevated NLR has been identified as a negative prognostic factor for survival in various types of cancers[19, 32–34]. In addition, it was discovered that NLR was associated with the clinicopathologic aggressiveness of PTC and could be used as marker for risk assessment in patients with PTC[29]. Similarly, our investigation found that higher NLR levels tended to be present in patients with LNLNM, which was indicative of a poor prognosis. Interestingly, Natalia's study found that it is the increased neutrophils rather than decreased lymphocytes that drive the predictive value of NLR.[35]. Neutrophils play a critical role in the metastasis of cancer cells[36, 37]. This may be because neutrophils have the ability to promote cancer growth by releasing growth factors and granular proteins, as well as inducing the dissociation of tumor cells through remodeling of the extracellular matrix, thus preparing the tumor cells for metastasis[34, 38]. Additionally, the neutrophils will induce the metastasis of tumor cells by secreting tumor necrosis factor and Cathepsin G[39]. Furthermore, the neutrophils may suppress the immune system, allowing tumor cells to avoid being killed by immune cells during metastasis[40]. Based on these findings, it is suggested that high levels of neutrophils and NLR may be associated with the metastasis of PTC, making them potential markers for predicting LNLNM in PTC patients.

Platelets are a crucial component of the circulatory system that play a significant role in maintaining hemostasis and various pathological processes, such as inflammation, atherosclerosis, and cancer metastasis[41, 42]. Clinically, high level of platelets has been associated with an unfavorable prognosis in a number of malignancies, including ovarian, lung, gastric and breast cancers[18, 43–45]. Our study reveals that a high level of platelets is associated with LNLNM in PTC, indicating a poor prognosis. Additionally, previous research has reported that platelets can serve as useful predictors of thyroid cancer

malignancy and LNM[46]. The mechanistic process by which elevated levels of platelets contribute to the metastasis to lymph nodes by forming the platelet coating, increasing surface P-selectin expression and promoting lymphatic and blood vessel formation[47–51].This suggests that an increase in platelets levels plays a crucial role in facilitating cancer metastasis. Furthermore, platelets may serve as a valuable predictor for the presence of LNLNM in PTC and assessing the risk stratification of the disease.

Moreover, previous research has predominantly relied on ultrasound characteristics to develop models for predicting the number of LNM in PTC patients[9]. Notably, ultrasound factors such as nodule size, multifocal disease and taller-than-wide shape, of LNM have been identified as independent predictors with superior predictive efficacy. Nevertheless, ultrasound has a low sensitivity in the diagnosis of cervical LNM[10]. According to various studies, the false-positive and false-negative rate of ultrasound to palpable LNM both range from 20–30%[52]. Conversely, blood inflammation indicators offer widely applicable and ease of acquisition, having a significant and potential value[53]. In this study, we used preoperative blood inflammation indicators for the first time to predict the presence of LNLNM in PTC. The ROC and HL tests showed the prediction model of LNLNM in PTC patients has good discrimination and calibration. The calibration curve and DCA, both in model and validation group, indicate that the model had a good predictive ability. In summary, this prediction model improves the prediction of LNLNM in PTC patients, aiding surgeons in evaluating patients' conditions and determining personalized treatment plans.

However, our study has several limitations that should be acknowledged. Firstly, it is important to note that our prediction model is a single-center study, which may limit the generalizability of our findings. In the follow-up study, we should include more centers for large-sample verification to improve the accuracy of the prediction model. Secondly, it is worth mentioning that our study is a retrospective study, introducing the possibility of selection bias in the sample selection process. To address this limitation, we recommend to combine prospective studies in the future. Finally, the diameter of metastatic lymph nodes was not included in the analysis due to its difficult to measure their diameter accurately. In subsequent studies, it is crucial to incorporate both the size and number of lymph nodes to obtain a more comprehensive evaluation of the prognosis.

Conclusions

In conclusion, age, tumor diameter, NLR and Plt are identified as significant risk factors for LNLNM in PTC patients, and the utilization of a prediction model incorporating these aforementioned factors can yield accurate predictions for LNLNM in PTC patients, thereby offering improved guidance for clinical practice.

Abbreviations

LNLNM large-number lymph node metastases

PTC thyroid papillary carcinoma

ROC receiver operating characteristic curves

HL Hosmer-Lemeshow

DCA decision curve analysis

NLR neutrophil-to-lymphocyte ratio

AUC area under the curve

LNM lymph node metastasis

ATA American Thyroid Association

N neutrophils

L lymphocytes

M monocytes

Plt platelets

LMR lymphocyte-to-monocyte ratio

PLR platelet-to-lymphocyte ratio

SII systemic immune-inflammatory index

M median

IQR inter quartile range

Declarations

Ethics approval and consent to participate

This study was approved by Ethics Committee of Hangzhou First People's Hospital and written informed consent was obtained from all patients.

Acknowledgements

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare no competing interests.

Funding

This work was supported by Zhejiang Provincial Basic Public Welfare Research Project (grant numbers: LGF22H160082), Zhejiang Provincial Medical and Health Technology Project (grant numbers: 2022KY939), and the Medical and Health Technology Projects of Hangzhou (grant numbers: Z20210025).

Author contribution statement

Yuying Chen and Fan Wu conceptualized and designed the study. Shuoying Qian, Yuan Cai, Xuanwei Huang and Kaiyuan Huang collected and analyzed the data. Yuying Chen wrote the original draft. Mengqian Ge and Tao Hu revised the manuscript. Dingcun Luo and Gang Pan reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

Author details

[1]The Fourth Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China, 310053; [2]Department of Surgical Oncology, Hangzhou First People's Hospital, Westlake University School of Medicine, Hangzhou, Zhejiang, China, 310006.

References

1. Du L, Wang Y, Sun X, Li H, Geng X, Ge M, et al. Thyroid cancer: trends in incidence, mortality and clinical-pathological patterns in Zhejiang Province, Southeast China. BMC Cancer. 2018;18:291.
2. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. JAMA. 2017;317:1338-48.
3. Zheng CM, Ji YB, Song CM, Ge MH, Tae K. Number of Metastatic Lymph Nodes and Ratio of Metastatic Lymph Nodes to Total Number of Retrieved Lymph Nodes Are Risk Factors for Recurrence in Patients With Clinically Node Negative Papillary Thyroid Carcinoma. Clin Exp Otorhinolaryngol. 2018;11:58-64.
4. So YK, Kim MJ, Kim S, Son YI. Lateral lymph node metastasis in papillary thyroid carcinoma: A systematic review and meta-analysis for prevalence, risk factors, and location. Int J Surg. 2018;50:94-103.
5. Ito Y, Fukushima M, Tomoda C, Inoue H, Kihara M, Higashiyama T, et al. Prognosis of patients with papillary thyroid carcinoma having clinically apparent metastasis to the lateral compartment. Endocr J. 2009;56:759-66.
6. Wei WJ, Lu ZW, Wen D, Liao T, Li DS, Wang Y, et al. The Positive Lymph Node Number and Postoperative N-Staging Used to Estimate Survival in Patients with Differentiated Thyroid Cancer:

Results from the Surveillance, Epidemiology, and End Results Dataset (1988-2008). World J Surg. 2018;42:1762-71.

7. Lee J, Song Y, Soh EY. Prognostic significance of the number of metastatic lymph nodes to stratify the risk of recurrence. World J Surg. 2014;38:858-62.
8. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26:1-133.
9. Zhang M, Zhang Y, Qiu Y, Wei H, Lyu S. A nomogram based on ultrasound characteristics to predict large-number cervical lymph node metastasis in papillary thyroid carcinoma. Endocr J. 2023;70:481-8.
10. Wang W, Yang Z, Ouyang Q. A nomogram to predict skip metastasis in papillary thyroid cancer. World J Surg Oncol. 2020;18:167.
11. Pu W, Shi X, Yu P, Zhang M, Liu Z, Tan L, et al. Single-cell transcriptomic analysis of the tumor ecosystems underlying initiation and progression of papillary thyroid carcinoma. Nat Commun. 2021;12:6058.
12. Lopes N, Lens H, da Silva Brito WA, Bianchi JK, Marinello PC, Cecchini R, et al. Role of papillary thyroid carcinoma patients with Hashimoto thyroiditis: evaluation of oxidative stress and inflammatory markers. Clin Transl Oncol. 2022;24:2366-78.
13. Wang G, Ma Y, Liu Y, Fan Y, Miao X, Zhang Y, et al. Predictive value of systemic inflammatory markers for recurrence of papillary thyroid cancer. J Surg Oncol. 2023;128:743-8.
14. Tan D, Fu Y, Tong W, Li F. Prognostic significance of lymphocyte to monocyte ratio in colorectal cancer: A meta-analysis. Int J Surg. 2018;55:128-38.
15. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106:dju124.
16. Schobert IT, Savic LJ, Chapiro J, Bousabarah K, Chen E, Laage-Gaupp F, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as predictors of tumor response in hepatocellular carcinoma after DEB-TACE. Eur Radiol. 2020;30:5663-73.
17. Zhou LH, Luo XF. Platelet to lymphocyte ratio in biliary tract cancer: Review and meta-analysis. Clin Chim Acta. 2017;474:102-7.
18. Taucher S, Salat A, Gnant M, Kwasny W, Mlineritsch B, Menzel RC, et al. Impact of pretreatment thrombocytosis on survival in primary breast cancer. Thromb Haemost. 2003;89:1098-106.
19. Seretis C, Gourgiotis S, Gemenetzis G, Seretis F, Lagoudianakis E, Dimitrakopoulos G. The significance of neutrophil/lymphocyte ratio as a possible marker of underlying papillary microcarcinomas in thyroidal goiters: a pilot study. Am J Surg. 2013;205:691-6.
20. Hay ID, Hutchinson ME, Gonzalez-Losada T, McIver B, Reinalda ME, Grant CS, et al. Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. Surgery. 2008;144:980-7;

discussion 987-8.
21. Malterling RR, Andersson RE, Falkmer S, Falkmer U, Niléhn E, Järhult J. Differentiated thyroid cancer in a Swedish county–long-term results and quality of life. Acta Oncol. 2010;49:454-9.
22. Randolph GW, Duh QY, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid. 2012;22:1144-52.
23. Adam MA, Pura J, Goffredo P, Dinan MA, Reed SD, Scheri RP, et al. Presence and Number of Lymph Node Metastases Are Associated With Compromised Survival for Patients Younger Than Age 45 Years With Papillary Thyroid Cancer. J Clin Oncol. 2015;33:2370-5.
24. Gao L, Li X, Xia Y, Liu R, Liu C, Shi X, et al. Large-Volume Lateral Lymph Node Metastasis Predicts Worse Prognosis in Papillary Thyroid Carcinoma Patients With N1b. Front Endocrinol (Lausanne). 2021;12:815207.
25. Manatakis DK, Tseleni-Balafouta S, Balalis D, Soulou VN, Korkolis DP, Sakorafas GH, et al. Association of Baseline Neutrophil-to-Lymphocyte Ratio with Clinicopathological Characteristics of Papillary Thyroid Carcinoma. Int J Endocrinol. 2017;2017:8471235.
26. Tong YS, Tan J, Zhou XL, Song YQ, Song YJ. Systemic immune-inflammation index predicting chemoradiation resistance and poor outcome in patients with stage III non-small cell lung cancer. J Transl Med. 2017;15:221.
27. Qi J, Zhang J, Ge X, Wang X, Xu L, Liu N, et al. The Addition of Peripheral Blood Inflammatory Indexes to Nomogram Improves the Predictive Accuracy of Survival in Limited-Stage Small Cell Lung Cancer Patients. Front Oncol. 2021;11:713014.
28. Shui Y, Li M, Su J, Chen M, Gu X, Guo W. Prognostic and clinicopathological significance of systemic immune-inflammation index in pancreatic cancer: a meta-analysis of 2,365 patients. Aging (Albany NY). 2021;13:20585-97.
29. Ceylan Y, Kumanlıoğlu K, Oral A, Ertan Y, Özcan Z. The Correlation of Clinicopathological Findings and Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in Papillary Thyroid Carcinoma. Mol Imaging Radionucl Ther. 2019;28:15-20.
30. Lin N, Li J, Yao X, Zhang X, Liu G, Zhang Z, et al. Prognostic value of neutrophil-to-lymphocyte ratio in colorectal cancer liver metastasis: A meta-analysis of results from multivariate analysis. Int J Surg. 2022;107:106959.
31. Cupp MA, Cariolou M, Tzoulaki I, Aune D, Evangelou E, Berlanga-Taylor AJ. Neutrophil to lymphocyte ratio and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies. BMC Med. 2020;18:360.
32. Unal D, Eroglu C, Kurtul N, Oguz A, Tasdemir A. Are neutrophil/lymphocyte and platelet/lymphocyte rates in patients with non-small cell lung cancer associated with treatment response and prognosis. Asian Pac J Cancer Prev. 2013;14:5237-42.

33. Jin H, Zhang G, Liu X, Liu X, Chen C, Yu H, et al. Blood neutrophil-lymphocyte ratio predicts survival for stages III-IV gastric cancer treated with neoadjuvant chemotherapy. World J Surg Oncol. 2013;11:112.
34. Noh H, Eomm M, Han A. Usefulness of pretreatment neutrophil to lymphocyte ratio in predicting disease-specific survival in breast cancer patients. J Breast Cancer. 2013;16:55-9.
35. Popowicz N, Cheah HM, Gregory C, Miranda A, Dick IM, Lee Y, et al. Neutrophil-to-lymphocyte ratio in malignant pleural fluid: Prognostic significance. PLoS One. 2021;16:e0250628.
36. Coffelt SB, Kersten K, Doornebal CW, Weiden J, Vrijland K, Hau CS, et al. IL-17-producing γδ T cells and neutrophils conspire to promote breast cancer metastasis. Nature. 2015;522:345-8.
37. Yang L, Liu Q, Zhang X, Liu X, Zhou B, Chen J, et al. DNA of neutrophil extracellular traps promotes cancer metastasis via CCDC25. Nature. 2020;583:133-8.
38. Xiong S, Dong L, Cheng L. Neutrophils in cancer carcinogenesis and metastasis. J Hematol Oncol. 2021;14:173.
39. Morimoto-Kamata R, Yui S. Insulin-like growth factor-1 signaling is responsible for cathepsin G-induced aggregation of breast cancer MCF-7 cells. Cancer Sci. 2017;108:1574-83.
40. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. Oncology. 2007;73:215-20.
41. Borsig L. The role of platelet activation in tumor metastasis. Expert Rev Anticancer Ther. 2008;8:1247-55.
42. Haemmerle M, Stone RL, Menter DG, Afshar-Kharghan V, Sood AK. The Platelet Lifeline to Cancer: Challenges and Opportunities. Cancer Cell. 2018;33:965-83.
43. Stone RL, Nick AM, McNeish IA, Balkwill F, Han HD, Bottsford-Miller J, et al. Paraneoplastic thrombocytosis in ovarian cancer. N Engl J Med. 2012;366:610-8.
44. Pedersen LM, Milman N. Prognostic significance of thrombocytosis in patients with primary lung cancer. Eur Respir J. 1996;9:1826-30.
45. Ikeda M, Furukawa H, Imamura H, Shimizu J, Ishida H, Masutani S, et al. Poor prognosis associated with thrombocytosis in patients with gastric cancer. Ann Surg Oncol. 2002;9:287-91.
46. Wang X, Liu W, Zhao M. [Correlation between preoperative platelet parameters and clinicopathological features of differentiated thyroid cancer]. Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2023;37:796-800.
47. Kim YJ, Borsig L, Varki NM, Varki A. P-selectin deficiency attenuates tumor growth and metastasis. Proc Natl Acad Sci U S A. 1998;95:9325-30.
48. Placke T, Salih HR, Kopp HG. GITR ligand provided by thrombopoietic cells inhibits NK cell antitumor activity. J Immunol. 2012;189:154-60.
49. Nieswandt B, Hafner M, Echtenacher B, Männel DN. Lysis of tumor cells by natural killer cells in mice is impeded by platelets. Cancer Res. 1999;59:1295-300.

50. Lala PK, Nandi P, Majumder M. Roles of prostaglandins in tumor-associated lymphangiogenesis with special reference to breast cancer. Cancer Metastasis Rev. 2018;37:369-84.
51. Möhle R, Green D, Moore MA, Nachman RL, Rafii S. Constitutive production and thrombin-induced release of vascular endothelial growth factor by human megakaryocytes and platelets. Proc Natl Acad Sci U S A. 1997;94:663-8.
52. Qiu Y, Fei Y, Liu J, Liu C, He X, Zhu N, et al. Prevalence, Risk Factors And Location Of Skip Metastasis In Papillary Thyroid Carcinoma: A Systematic Review And Meta-Analysis. Cancer Manag Res. 2019;11:8721-30.
53. Luo QQ, Wang T, Zhang KH. New indexes derived from routine blood tests and their clinical application in hepatocellular carcinoma. Clin Res Hepatol Gastroenterol. 2022;46:102043.

Figures

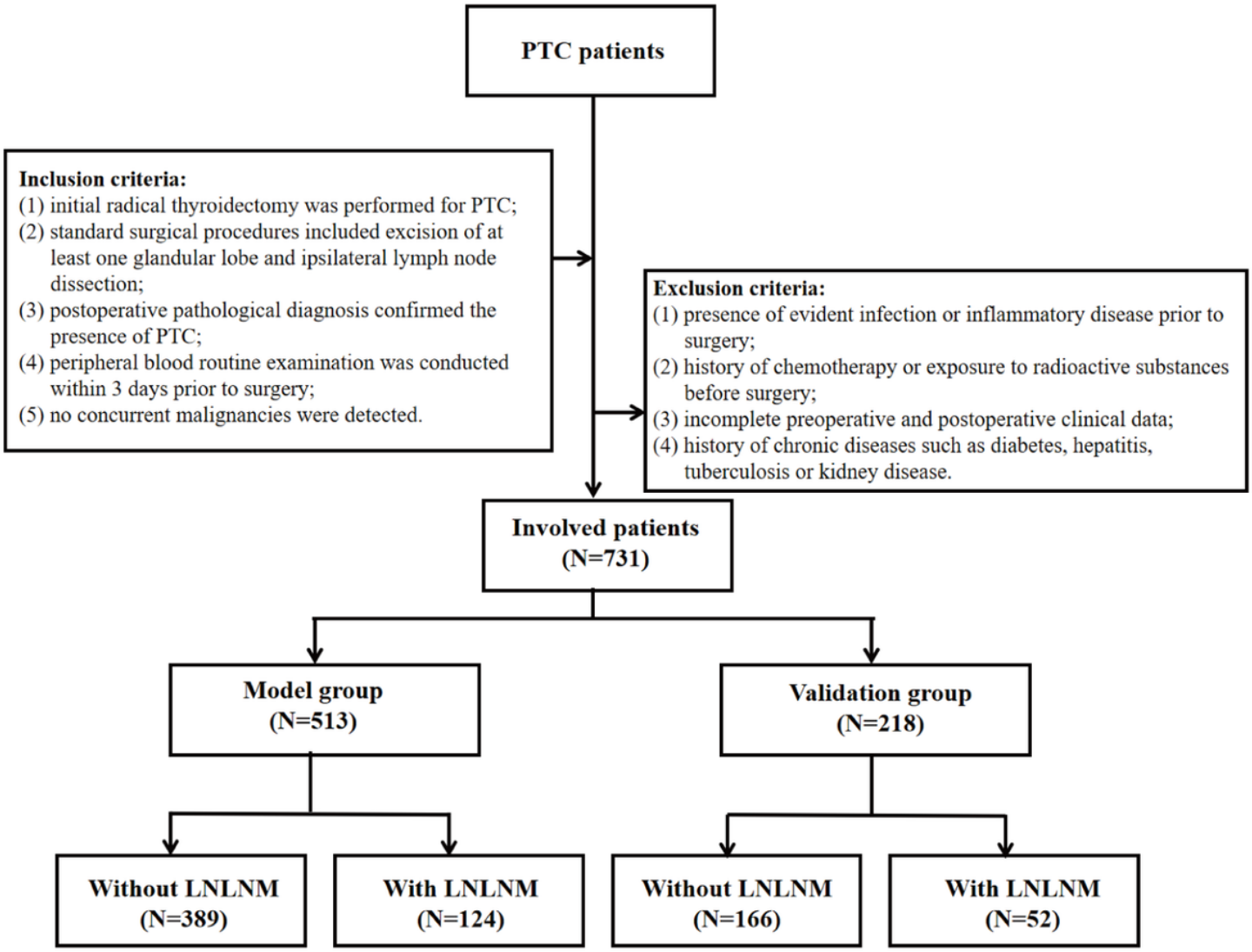


Figure 1

The flowchart of the patient selection process

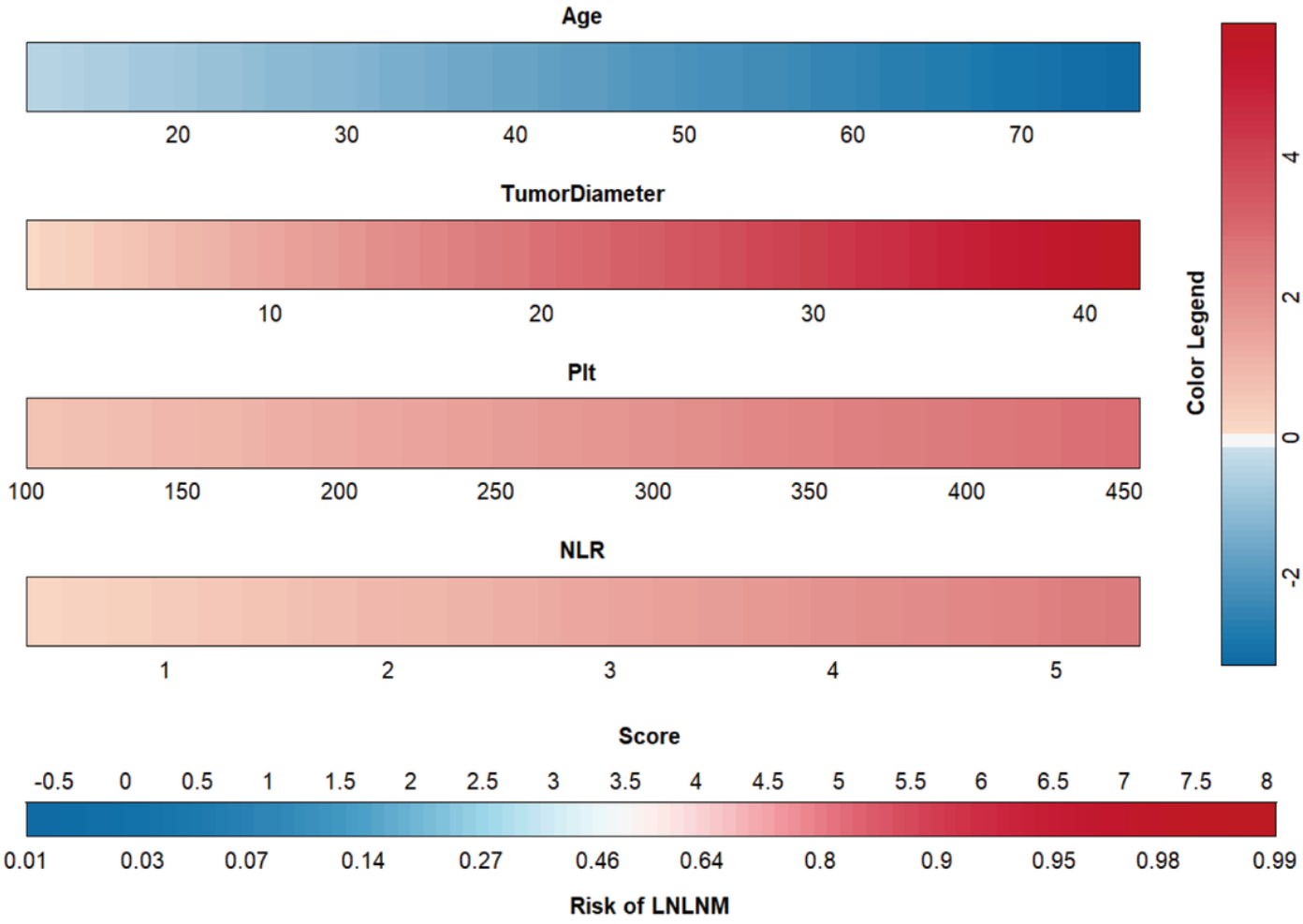


Figure 2

Clinical factor-based nomogram used for preoperatively predicting the LNLNM

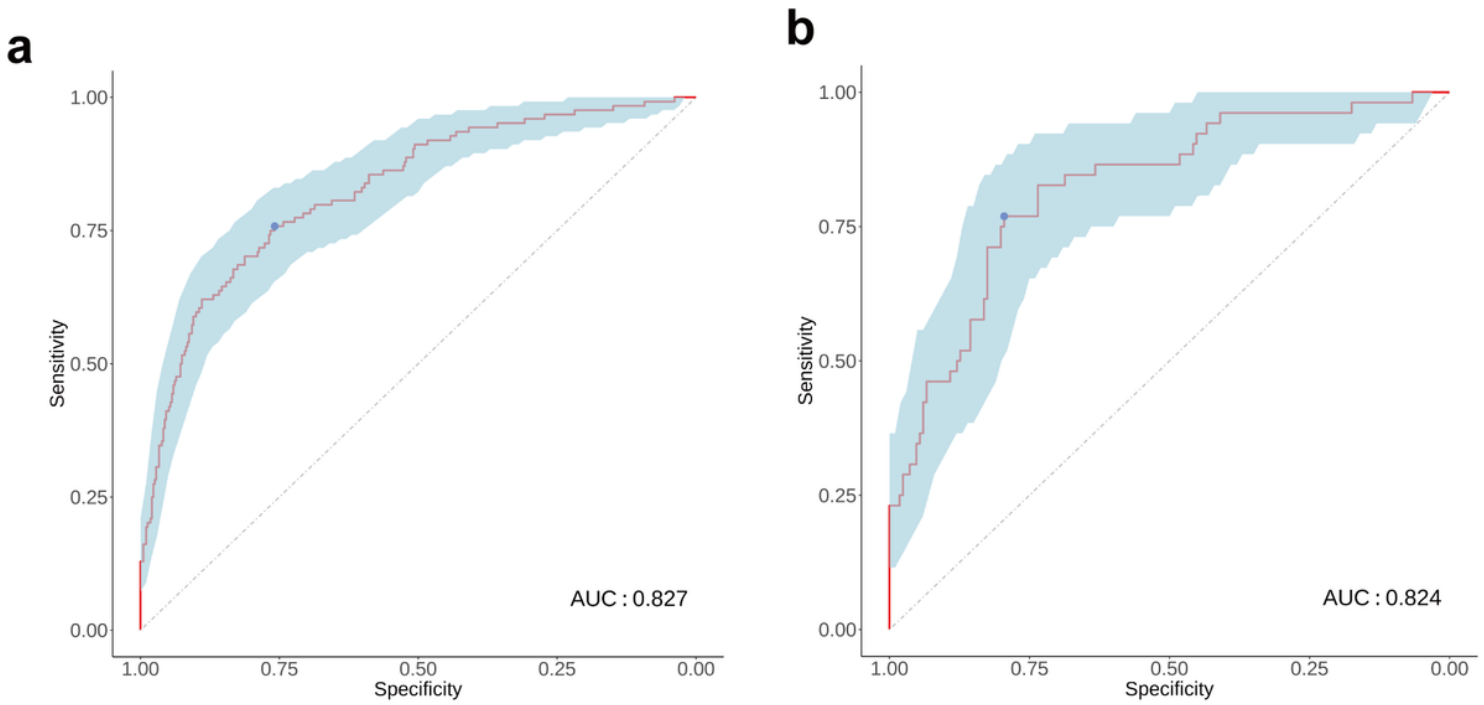


Figure 3

Receiver operator characteristic curve of model group (a) and validation group(b)

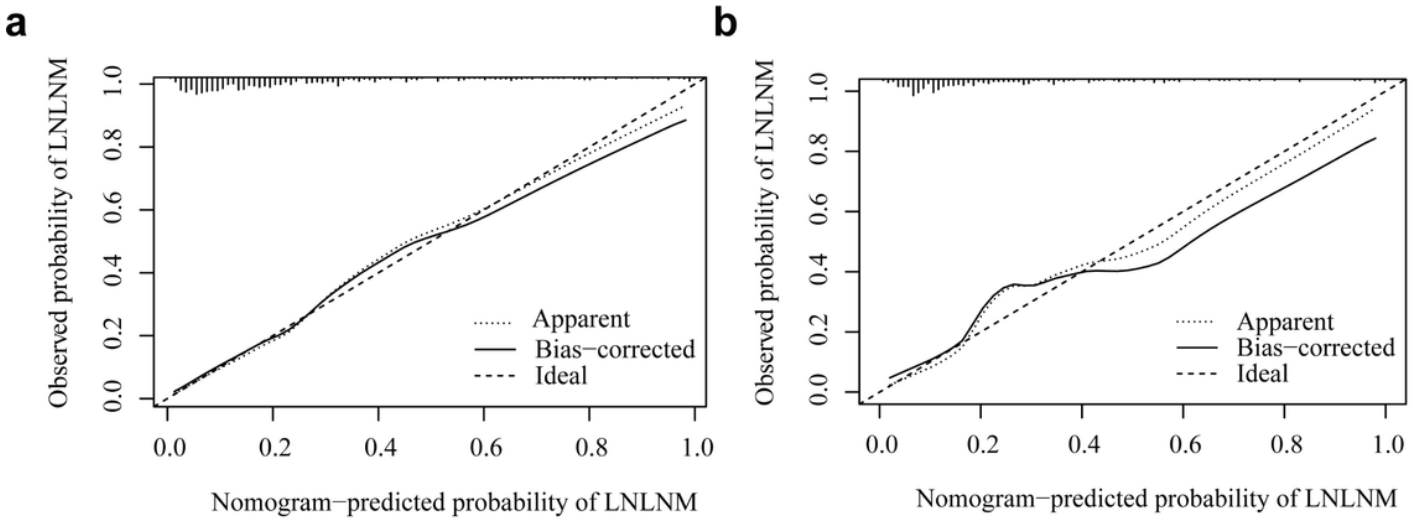


Figure 4

Calibration curve of model group (a) and validation group(b). The X-axis represents the predicted probability, while the Y-axis represents the actual probability of LNLNM. The diagonal dashed line represents the ideal prediction model. The solid line represents the performance of the column chart model, with a higher fit to the diagonal dashed line indicating better predictive capability. LNLNM, large number lymph node metastases.

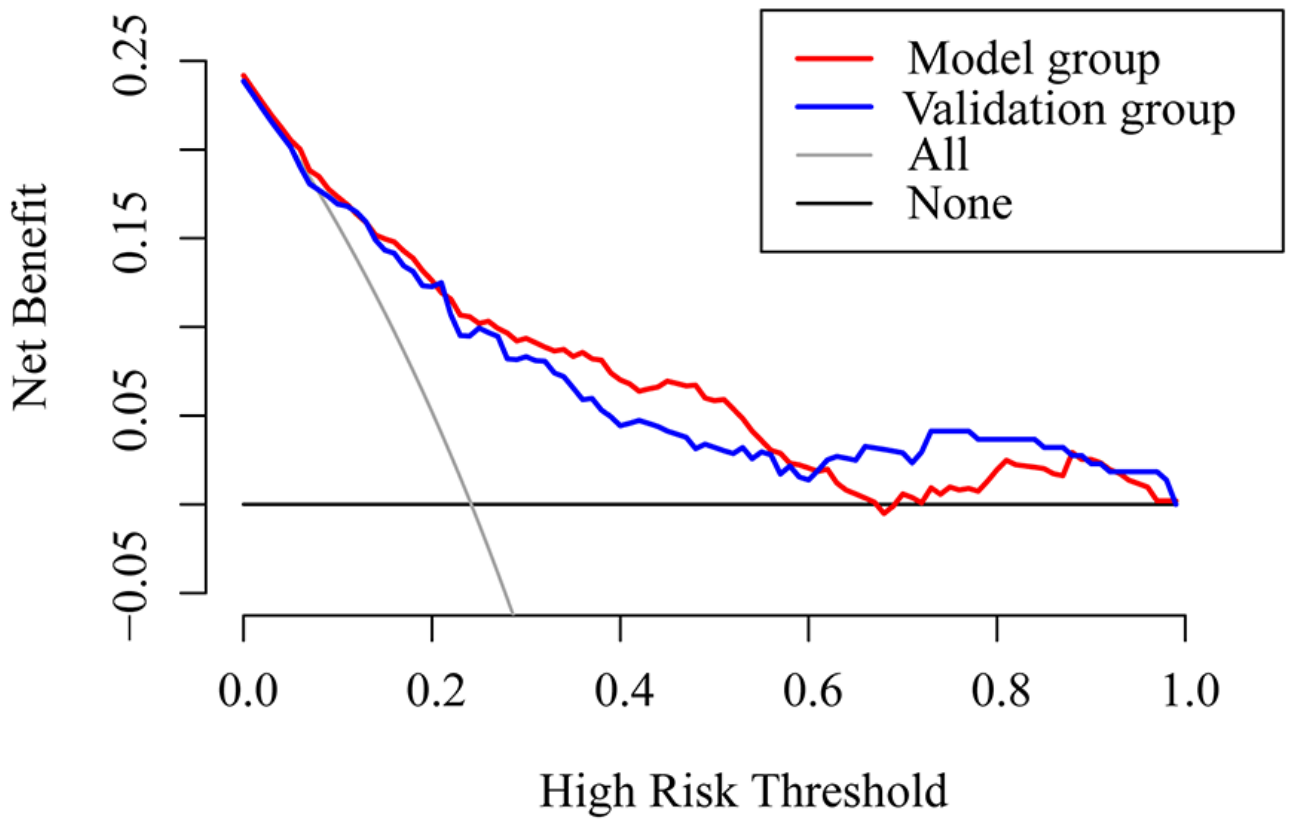


Figure 5

Decision curve analysis of model group and validation group. The net benefit is indicated on the Y-axis. The black line represents the assumption that all patients have severe morbidity. The gray line represents the assumption that no patient has severe morbidity. The red line represents the prediction model. The blue line represents the validation group of the model.