A nomogram for predicting prognosis of internal mammary lymph node metastasis in breast cancer patients with neoadjuvant chemotherapy

Jinzhao Liu

The Fourth Hospital of Hebei Medical University

Wei-Fang Zhang

The Fourth Hospital of Hebei Medical University

Yi-Fei Li

The Fourth Hospital of Hebei Medical University

Guo-Zhong Cui

Cangzhou Central Hospital

Chao Yang

The Fourth Hospital of Hebei Medical University

Geng Zhang

The Fourth Hospital of Hebei Medical University

Shuo Zhang

The Fourth Hospital of Hebei Medical University

Xiang-Mei Zhang

The Fourth Hospital of Hebei Medical University

Yun-Jiang Liu (✉ lyj818326@outlook.com)

The Fourth Hospital of Hebei Medical University

Research Article

Keywords: breast cancer, nomogram, overall survival, internal mammary lymph node metastasis, neoadjuvant chemotherapy

Posted Date: January 20th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1264743/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Breast cancer patients with internal mammary lymph node (IMLN) metastasis have been shown to have poor prognosis, and the overall survival of patients was significantly different. The nomogram was developed to predict prognosis of IMLN metastasis in breast cancer patients who received neoadjuvant chemotherapy and divide the patients into different risk groups.

Methods: This retrospective study included 218 breast cancer patients with IMLN metastasis who underwent neoadjuvant chemotherapy. Based on the multivariate Cox regression model, we determined independent prognostic factors in breast cancer patients with IMLN metastasis and developed a predictive nomogram using these factors. The discrimination and performance of the nomogram was assessed by C-index, the calibration curves and decision curve analyses. Patients were stratified into the high-risk group and low-risk group based on the best cut-off risk score. The Kaplan-Meier analyses were performed between the two different risk groups to assess the predictive ability of the nomogram.

Results: Menopausal status, clinical T stage, pathological Complete Response, axillary lymph node metastasis and Ki-67 were independent prognostic factors in breast cancer patients with IMLN metastasis. These prognostic factors were determined for the development of the nomogram. The C-index of the nomogram was 0.77, which showed the nomogram provided good discernment. The calibration curves demonstrated optimal agreement between prediction by the nomogram and actual observation. The decision curve analyses further demonstrated that the nomogram had the best net benefits. The patients with IMLN metastasis were divided into high-risk group (total score ≥ 206.9733) and low-risk group (total score < 206.9733), and the risk group stratification confirmed that the nomogram had great capacity for distinguishing the prognosis.

Conclusions: The nomogram was developed and validated to predict prognosis of IMLN metastasis in breast cancer patients with neoadjuvant chemotherapy. It might help clinicians to identify patients who need individualized treatment and active post-operative surveillance. However, it is necessary to further mine the unknown prognostic factors to optimize the nomogram, and more external validation is still required.

Background

Breast cancer is the most common cancer in women, and has surpassed lung cancer as the most common cancer worldwide [1]. Internal mammary lymph node (IMLN) and axillary lymph node belong to the "first station" lymph node of breast cancer lymphatic drainage, and IMLN is also one of the important metastatic pathways of breast cancer [2]. A Meta-analysis of IMLN metastasis in breast cancer found that approximately 23% of patients developed IMLN metastasis [3]. With the development of imaging diagnostics and new diagnostic techniques, the incidence of IMLN metastasis will be further increased.

IMLN metastasis is not only a major component of breast cancer staging, but also an independent prognostic indicator of breast cancer [4]. A study has shown that breast cancer patients

with IMLN metastasis have a higher risk of recurrence and a worse prognosis [5]. Although some studies found that the 5-year overall survival (OS) of patients with IMLN metastasis received neoadjuvant chemotherapy (NAC) was 75.5%-84.2%, there were corresponding differences in the prognosis of different patients [6-9]. However, TNM staging may not be able to predict the prognosis of all breast cancer patients [10], and there is currently no nomogram that can predict long-term survival in patients with IMLN metastasis. In the era of precision medicine, a more effective method to predict the survival of breast cancer patients with IMLN metastasis is needed to identify patients with long-term survival risk so as to provide optimized treatment plans.

Therefore, the aim of the present study was to identify clinicopathologic characteristics and to develop and validate a nomogram to predict the prognosis of patients with IMLN metastasis. The patients are divided into high-risk group and low-risk group by using the nomogram, which has important guiding significance for clinicians to accurately evaluate the prognosis of patients and formulate personalized treatment strategies.

Patients And Methods

Patients

We retrospectively analyzed breast cancer patients who received treatment at The Fourth Hospital of Hebei Medical University between 1 August 2010 and 31 August 2020. Among a total of 18025 breast cancer patients, 279 patients who pathologically confirmed IMLN metastasis without distant metastasis were enrolled. The inclusion criteria were as follows: (a) Eastern Cooperative Oncology Group performance status of 0 or 1; (b) histopathological confirmation of invasive breast cancer before ANC; (c) IMLN metastasis confirmed by histopathology or cytopathology; (d) intact clinicopathological and follow-up data; and (e) patients who received at least two cycles of NAC and surgical treatment and postoperative radiotherapy. The exclusion criteria were as follows: (a) distant metastasis; (b) previous or concurrent other malignant disease; (c) bilateral breast cancer; (d) male patients. 279 patients were screened, and finally, 218 patients fulfilling all inclusion and exclusion criteria were included in the study.

Clinicopathologic characteristics

The clinical characteristics include age at diagnosis, menopausal status, tumor location, supraclavicular lymph node (SLN) status and clinical T staging. In this study, all patients were clinically staged according to the 2010 American Joint Committee on Cancer (AJCC) staging system for breast cancer. Clinical T stages were clinically determined according to physical examination and imaging at initial diagnosis. Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and Ki67 status were determined by immunohistochemistry (IHC). Positive staining for ER or PR was defined as $\geq 1\%$ of tumor cell nuclei staining, HER2 positive was defined as 3+ receptor overexpression on IHC staining or gene amplification on fluorescence in situ hybridization. Ki-67 high expression was defined as Ki-67 levels above 30%, and low expression as levels below 30%. For pathological evaluation of primary

lesion and axillary lymph node metastasis after breast cancer NAC, the results of routine paraffin section examination were used. Pathological Complete Response (pCR) was defined as the complete disappearance of all invasive tumor cells from breast tissue regardless of the presence of residual ductal carcinoma in situ in the breast (ypT0/is).

Comprehensive Treatment

All patients received at least two cycles of NAC. NAC regimens were as follows: anthracycline plus taxane, anthracycline-based, and taxane-based. Accurately grasped the indications and contraindications of breast conserving surgery (BCS) and breast reconstruction surgery (BRS), patients deemed eligible for BCS and BRS were carefully selected. All patients also underwent axillary lymph node dissection, but IMLN dissection could be selected according to the surgeon's preference and experience. All patients received radiotherapy to the breast or chest wall and regional lymph nodes (axillary node and IMLN) while supraclavicular radiotherapy was performed for patients with SLN metastasis suggested by imaging or pathologically confirmed. All patients who were hormone receptor positive received adjuvant endocrine therapy. All HER2 positive patients received anti-HER2 targeted therapy, except those who refused to apply targeted medicine.

Follow-up

Clinical follow-ups were conducted by medical record review, out-patient medical record review or telephone interview. The last follow-up date was 12 September 2021, and the median follow-up duration was 50.3 (range, 2.6-131.2) months. 205 breast cancer patients received complete follow-up among of 218 patients, with a follow-up rate of 94%. OS was defined as the period from the date of surgery to the date of death or the last follow-up.

Statistical analysis

Statistical analysis was performed using the SPSS 25.0 (IBM Corporation, Armonk, NY, USA) and R 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). A P -value <0.05 was considered statistically significant. All statistical tests were two-sided.

Continuous and categorical variables were presented as mean $\pm$ standard deviation and counts(percentages), respectively. Multivariate analysis was performed using the Cox regression model for variables which were found to be significant in univariate analysis, and the prognostic factors of OS were determined. The nomograms based on the multivariate Cox regression models were developed to estimate 3-year and 5-year OS probabilities. The discriminatory performance of the OS nomogram was evaluated by concordance index (C-index). In addition, the calibration curves were constructed with the bootstrap resampling (1000 bootstrap samples) method and compared whether the prediction probability and observation probability in the queue have good consistency. The clinical value of the predictive models was tested using decision curve analyses (DCAs). The scores of each variable were calculated using the nomogramEx package in R. On the basis of the scores of each variable, the total scores for

each patient could be calculated. The "surv_cutpoint" function in R package "survminer" was used to find the best cut-off risk score. According to the cut-off of the risk-score, patients were assigned to the low-risk and high-risk groups. The Kaplan–Meier method was carried out to produce the survival curves of the two different risk groups.

Results

Clinicopathologic characteristics of patients

A total of 218 patients were finally enrolled in this study and the clinicopathologic characteristics of the patients are shown in Table 1. The mean age of the patients was 48.0 years (range 25-70 years), and 98 patients (45.0%) were postmenopausal. Clinical T stages were cT1-2 in 147 patients (67.4%), cT3-4 in 71 patients (32.6%), respectively. There were 68 patients (31.2%) with 1-3 axillary lymph node metastases, 75 patients (34.4%) with >3 axillary lymph node metastases, and 37 patients (17.0%) with SLN metastasis. The positive rates of ER, PR and HER2 were 58.7%, 49.1% and 37.6%, respectively. Ki67 was highly expressed in 133 patients (61.0%). Overall, 64(29.4%) patients showed breast pCR, 210(96.3%) patients underwent mastectomy, while only 71 patients (32.6%) underwent IMLN dissection. Triple negative breast cancer (TNBC) accounted for 22.9% of 218 patients with IMLN metastasis. Due to economic reasons and availability of drugs, only 56.1% of HER2 positive patients received targeted medicine in neoadjuvant therapy.

Independent prognostic factors of patients

Univariate analysis showed that menopausal status, clinical T stage, ER status, PR status, TNBC, Ki67, breast PCR and the number of axillary lymph node metastasis were significantly associated with OS (Table 2). Multivariate regression analysis confirmed that menopausal status (hazard ratio [HR]=2.090, 95% CI:1.181–3.698, P=0.011), clinical T3-4 stage (HR=1.878, 95% CI:1.058–3.333, P=0.031), breast PCR (HR=0.331, 95% CI:0.117–0.939, P=0.038), Ki67 high expression (HR=2.612, 95% CI:1.282–5.325, P=0.008) and > 3 axillary lymph node metastasis (HR=3.336, 95% CI:1.236–9.005, P=0.017) were independent prognostic factors (Table 2).

Development and validation of the nomogram

Based on the independent risk factors that were statistically significant in multivariate analysis, the nomogram was developed (Fig.1). The prediction of 3-year and 5-year OS probability of patients with IMLN metastasis can be calculated by this nomogram.

The C-index of the nomogram was 0.77 (95% CI: 0.73-0.80), which showed the nomogram provided good discernment. Additionally, the acceptable agreement between the predictions of nomogram and actual observations was illustrated by calibration curves for 3-year and 5-year OS (Fig.2A-B). Therefore, the prediction performance of the nomogram for OS probability showed good predictive value. In this study, the 3-year and 5-year OS DCA curves indicated that the nomogram yielded clinical net benefits (Fig.3A-B).

Performance of the nomogram in risk stratification of patients

The total score of each patient was calculated based on the nomogram, and patients were divided into two subgroups: low-risk group (total score < 206.9733) and the high-risk group (total score $\geq$ 206.9733). In the whole study population, the 5-year survival rates of patients in low-risk group and high-risk group were 82.8% and 43.3% respectively. As shown in Fig.4, OS of the low-risk group and the high-risk group is different (P-value <0.0001).

Discussion

With the continuous development and progress of breast cancer diagnosis and comprehensive treatment, the prognosis of these patients has been significantly ameliorated.⁴ Although patients with IMLN metastasis are a clinical subgroup with particularly poor prognosis, the 5-year OS has increased to nearly 85.0% with the improvement of comprehensive treatment in recent years.⁹ However, patients may still experience early disease recurrence and death. Nomogram that accurately predict OS in breast cancer patients received comprehensive treatment can guide more aggressive surveillance and intensive treatment of high-risk patients. At present, there are still limitations in the accuracy of the TNM staging system. Besides the TNM staging system, the application of nomogram in individual risk prediction has been widely recognized in many cancers [11-14]. As far as we know, there are no reports on the nomogram predicting prognosis of breast cancer patients with IMLN metastasis. In this study, we attempted to develop and validate a model to predict the prognosis of breast cancer patients with IMLN metastasis.

In multivariate analysis, menopausal status, clinical T staging, Ki67, breast pCR and axillary lymph node metastasis were important independent factors for predicting OS in breast cancer patients with IMLN metastasis. Clinical T staging and the number of axillary lymph node metastasis are important reference indicators for TNM staging to assess the prognosis of breast cancer patients, and are widely used in clinical practice. Previous studies have shown that breast pCR was an important prognostic indicator in breast cancer patients [15-16]. In a population-based study, Nathalie LeVasseur et al. [15] found that early breast cancer patients who received NAC and achieved pCR had better prognosis than non-pCR patients. Similarly, María Gion et al. [16] also suggested that the correlation between pCR and long-term prognosis is strongest for breast cancer patients (TNBC or HER2 positive / hormone receptor negative). In our report, we observed that Ki-67 in breast cancer patients before receiving NAC was highly predictive of OS. OS decreased significantly in patients with Ki-67 high expression (HR=2.354, 95% CI: 1.145-4.840, $p=0.020$). Haeyoung Kim et al. [17] found that high expression of Ki-67 was an important risk factor for DFS (HR=2.8, 95% CI: 1.3-6.2, $p=0.010$) in 193 patients of breast cancer with IMLN metastasis. Similarly, in a Meta-analysis involving 14076 patients, Ki-67 high expression before NAC was associated with poor OS (HR = 2.29, 95% CI: 1.42-3.69, $P < 0.001$) and DFS (HR = 1.54, 95% CI: 1.23-1.95, $P < 0.001$) [18]. Elena vissio et al. reported the results of a study evaluating the prognosis of breast cancer patients based on Ki67 combined with the 8th Edition AJCC staging [19]. Ki67 may be a reliable marker for optimizing the 8th Edition AJCC breast cancer prognostic staging evaluation

system. Although Ki-67 has prognostic significance for breast cancer patients, its threshold has great variability and limits the clinical application of Ki-67 [20]. Therefore, it is important to further define the threshold that are better correlated with clinical outcomes.

It may be beneficial to predict which patients are at risk of early death in breast cancer with IMLN metastasis. The potential clinical application of this nomogram is a better risk stratification for breast cancer patients with IMLN metastasis. This enables clinicians to identify high-risk patients who might benefit from more aggressive post-operative surveillance and individualized intensive treatment, and identify low-risk patients who might be safely treated with less intensive treatment regimens. Currently, there is no consensus on adjuvant chemotherapy for patients with IMLN metastasis who received NAC, regardless of the degree of tumor regression or other clinicopathologic features. Julie Labrosse et al. [21] found that adjuvant chemotherapy after NAC was not beneficial in OS outcomes compared with patients treated with NAC alone. However, Julia foldi et al. [22] believed that non-PCR patients after NAC had a higher risk of recurrence, and these high-risk patients tended to improve their prognosis after adjuvant chemotherapy. The CREATE-X trial randomly assigning 910 patients with residual disease after NAC to receive postsurgical treatment either with or without Capecitabine showed that adjuvant Capecitabine significantly prolonged DFS and OS in patients with HER2 negative breast cancer [23]. DFS and OS in patients with HER2 positive breast cancer have improved significantly since the era of dual target therapy with trastuzumab plus pertuzumab [24]. The phase 3 KATHERINE trial demonstrated significantly improved invasive disease-free survival with adjuvant trastuzumab emtansine (T-DM1) in patients with residual invasive disease after NAC plus HER2-targeted therapy [25]. Therefore, it is of great importance to risk stratify breast cancer patients received NAC and individualize treatment for high-risk patients.

There are several limitations to our study. Firstly, the nomogram was developed and validated based on a retrospective analysis. Due to the inherent biases from the study design, such as selection bias and recall bias, these results need to be further validated by prospective studies. Secondly, some potential predictors are not included in the nomogram. It is necessary to further explore the biomarkers or diagnostic modalities related to the prognosis of patients with IMLN metastasis. Thirdly, due to the data are relatively small and from a single institution, these are some limitations on the applicability and generalizability of the nomogram. In order to confirm the reliability and applicability of the nomogram, it is necessary for more other institution external validations.

Conclusions

This study first developed and validated the nomogram for predicting OS in patients with IMLN metastasis of breast cancer. Menopausal status, clinical T stage, Ki67, breast pCR and axillary lymph node metastasis were significant independent predictors of OS. Our prognostic nomogram accurately and reliably predicts 3-year and 5-year OS of IMLN metastasis in breast cancer patients treated with ANC, which provides an effective clinical tool to identify high-risk patients who may benefit from individualized treatment and more aggressive post-operative surveillance. However, it is necessary to further explore the

unknown prognostic factors to optimize the nomogram, and multi-institution external validation is still needed.

Abbreviations

IMLN: Internal mammary lymph node; OS: Overall survival; NAC: Neoadjuvant chemotherapy; AJCC: American Joint Committee on Cancer; HR: Hazard ratio; C-index: Concordance index; DCAs: Decision curve analyses; SLN: Supraclavicular lymph node; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; TNBC: Triple-negative breast cancer; BCS: Breast conserving surgery; BRS: Breast reconstruction; pCR: Pathological complete response; ALNM: Axillary lymph node metastasis; IHC: Immunohistochemistry.

Declarations

Acknowledgement

None.

Authors' contributions

JZL and YJL designed the research. WFZ, YFL, CY and SZ collected the data. GZC, JZL and GZ analyzed the data. All authors wrote the manuscript. WFZ, XMZ, YFL and YJL discussed the results and revised the final manuscript. All authors read and approved the final manuscript.

Funding

None.

Availability of data and materials

Additional data and materials may be requested from the corresponding author on reasonable request.

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of The Fourth Hospital of Hebei Medical University. This study is retrospective analysis, and all the individual patient data is anonymous. No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient

community. Therefore, a statement of informed consent of study participants was institutionally waived because of the retrospective nature of the study and the anonymity of individual patient data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹ Department of Breast Surgery, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, China;² Department of Pathology, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, China;³ The Second Department of Thyroid and Breast Surgery, Cangzhou Central Hospital, Cangzhou 061011, China;⁴ Center of Scientific Research, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, China.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71:209-249.
2. Xie X, Xiong Z, Li X, Huang X, Ye F, Tang H, et al. Nomogram to Predict Internal Mammary Lymph Nodes Metastasis in Patients With Breast Cancer. *Front Oncol*. 2019;9:1193.
3. Li Z, Gu X, Tong J, Liu B, Sun L, Gao X, et al. A meta-analysis of internal mammary lymph node metastasis in breast cancer patients. *Onkologie*. 2013;36:747-752.
4. Chen RC, Lin NU, Golshan M, Harris JR, Bellon JR. Internal mammary nodes in breast cancer: diagnosis and implications for patient management—a systematic review. *J Clin Oncol*. 2008;26:4981-4989.
5. Wang Y, Qi W, Xu H, Zhang M, Han Y, Chen J, et al. Infiltration tendency of internal mammary lymph nodes involvement in patients with breast cancer: anatomical characteristics and implications for target delineation. *Radiat Oncol*. 2019;14:208.
6. Noh JM, Kim KH, Park W, Suh CO, Huh SJ, Choi DH, et al. Prognostic significance of nodal involvement region in clinical stage IIc breast cancer patients who received primary systemic treatment, surgery, and radiotherapy. *Breast*. 2015;24:637-641.
7. Kim J, Chang JS, Choi SH, Kim YB, Keum KC, Suh CO, et al. Radiotherapy for initial clinically positive internal mammary nodes in breast cancer. *Radiat Oncol J*. 2019;37:91-100.
8. Yang K, Kim H, Choi DH, Park W, Noh JM, Cho WK. Optimal radiotherapy for patients with internal mammary lymph node metastasis from breast cancer. *Radiat Oncol*. 2020;15:16.

9. Kim H, Kim SS, Lee IJ, Shin KH, Kim K, Jung J, et al. Outcome of radiotherapy for clinically overt metastasis to the internal mammary lymph node in patients receiving neoadjuvant chemotherapy and breast cancer surgery. *Breast*. 2021;55:112-118.
10. Park YH, Lee SJ, Cho EY, La Choi Y, Lee JE, Nam SJ, et al. Clinical relevance of TNM staging system according to breast cancer subtypes. *Ann Oncol*. 2019;30:2011.
11. Zhang J, Zhao B, Jin F. The assessment of 8th edition AJCC prognostic staging system and a simplified staging system for breast cancer: The analytic results from the SEER database. *Breast J*. 2019;25:838-847.
12. Habraken V, van Nijnatten TJ, de Munck L, Moosdorff M, Heuts EM, Lobbes MB, et al. Does the TNM classification of solitary internal mammary lymph node metastases in breast cancer still apply? *Breast Cancer Res Treat*. 2017;161:483-489.
13. Merritt RE, Abdel-Rasoul M, Souza DM, Kneuert PJ. Nomograms for predicting overall and recurrence-free survival after trimodality therapy for esophageal adenocarcinoma. *J Surg Oncol*. 2021;123:881-890.
14. Song J, Chen Z, Huang D, Wu Y, Lin Z, Chi P, et al. Nomogram Predicting Overall Survival of Resected Locally Advanced Rectal Cancer Patients with Neoadjuvant Chemoradiotherapy. *Cancer Manag Res*. 2020;12:7375-7382.
15. LeVasseur N, Sun J, Gondara L, Diocee R, Speers C, Lohrisch C, et al. Impact of pathologic complete response on survival after neoadjuvant chemotherapy in early-stage breast cancer: a population-based analysis. *J Cancer Res Clin Oncol*. 2020;146:529-536.
16. Gion M, Pérez-García JM, Llombart-Cussac A, Sampayo-Cordero M, Cortés J, Malfettone A. Surrogate endpoints for early-stage breast cancer: a review of the state of the art, controversies, and future prospects. *Ther Adv Med Oncol*. 2021;13:1-30.
17. Kim H, Kim SS, Lee IJ, Shin KH, Kim K, Jung J, et al. Outcome of radiotherapy for clinically overt metastasis to the internal mammary lymph node in patients receiving neoadjuvant chemotherapy and breast cancer surgery. *Breast*. 2021;55:112-118.
18. Li L, Han D, Wang X, Wang Q, Tian J, Yao J, et al. Prognostic values of Ki-67 in neoadjuvant setting for breast cancer: a systematic review and meta-analysis. *Future Oncol*. 2017;13:1021-1034.
19. Vissio E, Metovic J, Osella-Abate S, Bertero L, Migliaretti G, Borella F, et al. Integration of Ki-67 index into AJCC 2018 staging provides additional prognostic information in breast tumours candidate for genomic profiling. *Br J Cancer*. 2020;122:382-387.
20. Liu YP. Interpretation of Ki-67 assessment update of International Ki-67 in Breast Cancer Working Group. *Zhonghua Bing Li Xue Za Zhi*. 2021;50:704-709.
21. Labrosse J, Osdoit M, Hamy AS, Coussy F, Pierga JY, Reyat F, et al. Adjuvant chemotherapy for breast cancer after preoperative chemotherapy: A propensity score matched analysis. *PLoS One*. 2020;15:e0234173.
22. Foldi J, Rozenblit M, Park TS, Knowlton CA, Golshan M, Moran M, et al. Optimal Management for Residual Disease Following Neoadjuvant Systemic Therapy. *Curr Treat Options Oncol*. 2021;22:79.

23. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017;376:2147-2159.

24. Swain SM, Im YH, Im SA, Chan V, Miles D, Knott A, et al. Safety profile of Pertuzumab with Trastuzumab and Docetaxel in patients from Asia with human epidermal growth factor receptor 2-positive metastatic breast cancer: results from the phase III trial CLEOPATRA. Oncologist. 2014;19:693-701.

25. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. KATHERINE Investigators. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019;380:617-628.

Tables

Table 1 Clinicopathologic characteristics of patients(n=218)

Characteristics	Patients, n (%)
Age(years)	
Mean age $\pm$ SD	48.0 $\pm$ 10.9
Menopause	
No	120(55.0%)
Yes	98(45.0%)
Tumor location	
Lateral	96(44.0%)
Central	44(20.2%)
Medial	78(35.8%)
SLN status	
Negative	181(83.0%)
Positive	37(17.0%)
Clinical T stage	
T1-2	147(67.4%)
T3-4	71(32.6%)
ER status	
Negative	90(41.3%)
Positive	128(58.7%)
PR status	
Negative	111(50.9%)
Positive	107(49.1%)
HER2 status	
Negative	136(62.4%)
Positive	82(37.6%)
Ki67	
Low expression	85(39.0%)
High expression	133(61.0%)
TNBC	

No	168(77.1%)
Yes	50(22.9%)
NAC regimens	
Anthracycline plus taxane	189(86.7%)
Anthracycline-based	7(3.2%)
Taxane-based	22(10.1%)
NAC cycles	
≤4	63(28.9%)
>4	155(71.1%)
Neoadjuvant regimen Herceptin received	
No	172(78.9%)
Yes	46(21.1%)
Breast surgery strategies	
Mastectomy	210(96.3%)
BCS+BRS	8(3.7%)
IMLN dissection	
No	147(67.4%)
Yes	71(32.6%)
Breast pCR	
No	154(70.6%)
Yes	64(29.4%)
Number of ALNM	
0	75(34.4%)
1-3	68(31.2%)
>3	75(34.4%)

SLN supraclavicular lymph node, ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth factor receptor 2, TNBC triple-negative breast cancer, NAC neoadjuvant chemotherapy, BCS breast conserving surgery, BRS breast reconstruction, IMLN Internal mammary lymph node, pCR pathological complete response, ALNM axillary lymph node metastasis.

Table 2 Univariable and multivariable analysis of overall survival

Univariable analysis		Multivariable analysis	
Variable	HR (95% CI)	Variable	HR (95% CI)
Age		Age	
<65	1.0	<65	1.0
≥65	1.2 (0.8-1.8)	≥65	1.1 (0.7-1.7)
Sex		Sex	
Male	1.0	Male	1.0
Female	1.3 (0.9-1.9)	Female	1.2 (0.8-1.8)
Stage		Stage	
I	1.0	I	1.0
II	1.5 (1.1-2.0)	II	1.4 (1.0-1.9)
III	2.2 (1.7-2.8)	III	2.1 (1.6-2.7)
IV	3.5 (2.8-4.3)	IV	3.3 (2.6-4.1)
Performance		Performance	
Good	1.0	Good	1.0
Poor	1.8 (1.3-2.4)	Poor	1.7 (1.2-2.3)
ECOG		ECOG	
0-1	1.0	0-1	1.0
≥2	2.5 (1.8-3.4)	≥2	2.4 (1.7-3.3)
Albumin		Albumin	
≥3.5	1.0	≥3.5	1.0
<3.5	1.4 (1.0-1.9)	<3.5	1.3 (0.9-1.8)
LDH		LDH	
<250	1.0	<250	1.0
≥250	1.6 (1.2-2.1)	≥250	1.5 (1.1-2.0)
CRP		CRP	
<10	1.0	<10	1.0
≥10	1.7 (1.3-2.2)	≥10	1.6 (1.2-2.1)
CA125		CA125	
<35	1.0	<35	1.0
≥35	1.9 (1.4-2.5)	≥35	1.8 (1.3-2.4)
CEA		CEA	
<5	1.0	<5	1.0
≥5	1.5 (1.1-2.0)	≥5	1.4 (1.0-1.9)
HER2		HER2	
Not amplified	1.0	Not amplified	1.0
Amplified	1.3 (0.9-1.8)	Amplified	1.2 (0.8-1.7)
EGFR		EGFR	
Not mutated	1.0	Not mutated	1.0
Mutated	1.4 (1.0-1.9)	Mutated	1.3 (0.9-1.8)
PD-L1		PD-L1	
Not expressed	1.0	Not expressed	1.0
Expressed	1.6 (1.2-2.1)	Expressed	1.5 (1.1-2.0)
MSI		MSI	
Stable	1.0	Stable	1.0
Unstable	1.8 (1.3-2.4)	Unstable	1.7 (1.2-2.3)
MMR		MMR	
Intact	1.0	Intact	1.0
Deficient	1.7 (1.3-2.2)	Deficient	1.6 (1.2-2.1)

Variables	Univariate analysis			Multivariable analysis		
	HR	95%CI	<i>P</i>	HR	95%CI	<i>P</i>
Age	1.010	0.984-1.037	0.440			
Menopause						
No	Reference			Reference		
Yes	1.842	1.066-3.185	0.029	2.090	1.181-3.698	0.011
Tumor location						
Lateral	Reference					
Central	1.222	0.611-2.444	0.571			
Medial	1.135	0.609-2.115	0.690			
SLN status						
Negative	Reference					
Positive	1.752	0.949-3.234	0.073			
Clinical T stage						
T1-2	Reference			Reference		
T3-4	2.436	1.419-4.180	0.001	1.878	1.058-3.333	0.031
ER						
Negative	Reference			Reference		
Positive	0.525	0.306-0.900	0.019	1.029	0.364-2.910	0.958
PR						
Negative	Reference			Reference		
Positive	0.570	0.329-0.990	0.046	0.811	0.309-2.128	0.671
HER2						
Negative	Reference					
Positive	0.849	0.471-1.532	0.587			
Ki67						
Low expression	Reference			Reference		

High expression	2.582	1.356-4.916	0.004	2.612	1.282-5.325	0.008
TNBC						
No	Reference		Reference			
Yes	1.908	1.077-3.381	0.027	1.513	0.684-3.345	0.307
NAC regimens						
Anthracycline plus taxane	Reference					
Anthracycline-based	1.089	0.264-4.495	0.906			
Taxane-based	1.591	0.630-4.021	0.326			
NAC cycles						
≤4	Reference					
>4	1.020	0.577-1.805	0.945			
Neoadjuvant regimen						
Herceptin received						
No	Reference					
Yes	0.458	0.164-1.275	0.135			
Breast surgery strategies						
Mastectomy	Reference					
BCS+BRS	0.048	0.001-2314.228	0.580			
IMLN dissection						
No	Reference					
Yes	1.374	0.795-2.377	0.255			
Breast pCR						
No	Reference		Reference			
Yes	0.273	0.108-0.686	0.006	0.331	0.117-0.939	0.038
Number of ALNM						
0	Reference		Reference			
1-3	1.982	0.767-5.117	0.158	1.780	0.640-	0.269

					4.950	
>3	4.617	1.916-11.127	0.001	3.336	1.236-9.005	0.017

HR hazard ratio, SLN supraclavicular lymph node, ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth factor receptor 2, TNBC triple-negative breast cancer, NAC neoadjuvant chemotherapy, BCS breast conserving surgery, BRS breast reconstruction, IMLN Internal mammary lymph node, pCR pathological complete response, ALNM axillary lymph node metastasis.

Figures

Figure 1

The nomograms that are used to predict the 3-year and 5-year OS of breast cancer patients with IMLN metastasis. For each patient, we calculated the points of the clinicopathologic characteristics, and summed up the points to obtain the total points. The predicted the 3-year and 5-year OS can be estimated based on the total points of each patient.

A

B

Figure 2

Calibration curves of the nomograms for (A) predicting the 3-year and (B) 5-year OS respectively.

A

B

Figure 3

Clinical decision curve of the nomograms for (A) predicting the 3-year and (B) 5-year OS respectively. The y-axis represented the net benefit. The dotted line represented the nomogram. The net benefit was calculated by subtracting the proportion of all patients who were false positive from the proportion who are truly positive, weighting by the relative harm of giving up treatment compared with the negative consequences of an overtreatment. The x-axis represented the threshold probability.

Figure 4

Kaplan–Meier curves of OS for patients in high-risk and low-risk groups.