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ORIGINAL ARTICLE

# Prediction of nonsentinel lymph node metastasis in breast cancer patients with one or two positive sentinel lymph nodes

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**KEYWORDS**
breast cancer;
non sentinel lymph node;
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extracapsuler invasion;
Her-2 status;
clinically node negative

*Objective:* The aim of the present study was to investigate the association between non sentinel lymph node metastasis (NSLNM) and clinicopathological factors, particularly in the case of sentinel lymph node (SLN) metastasis in one or two, in clinically node negative patients with breast cancer.
*Methods:* Between 10/2010 and 10/2014, 350 sentinel lymph node biopsy (SLNB) were performed in patients with histologically proven primary breast cancer in our clinic. The data collection includes the following characteristics: age, pathological tumor size, histological type, histological grade, lymphovascular invasion (LVI), number of positive SLN, size of the SLN metastasis (macrometastasis, micrometastasis, isolated tumor cells), multifocality (MF), extracapsuler invasion (ECI) of the SLN, the estrogen receptor (ER) status, the progesterone receptor (PR) status and the Her 2 receptor status, Ki 67 reseptor status. Data were collected retrospectively and then analyzed.
*Results:* A successful SLN biopsy were performed in 345 (98.5%) cases. SLN metastases were detected in 110 (31.8%) cases. These patients then underwent axillary dissection; among these patients, 101 (91.8%) had only one to two positive SLNs. Of the 101 patients with positive SLN biopsies, 32 (31.6%) had metastases in the NSLNs. Univariate and multivariate analysis showed that lymphovascular invasion, extracapsular invasion (ECI), Her-2 receptor positive, and Ki-67 $>$ 14% were related to NSLNM ($p<.0.05$).

Conflicts of interest: The authors declare that they have no conflicts of interest.

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*Conclusion:* The predicting factors of NSLNM were LVI, ECI, Ki-67 level, Her-2 reseptor positive and but should be further validated in our institutions, different institutions and different patient groups prospectively.


## 1. Introduction

The status of the axillary lymph node (LN) is one of the most important prognostic markers for invasive breast cancer. Sentinel LN biopsy (SLNB) is an accepted method for identification of pathologic axillary status in early cancer cases with clinically negative axilla, which allows for correct and reliable staging of the axillary nodal status with significantly decreased shoulder arm morbidity.[1–4] When positive LN metastasis is detected by SLNB, the patient undergoes complete axillary LN dissection (ALND). However, previous reports suggest that additional LN metastasis is not found on axillary dissection in approximately 40–60% of clinically node-negative patients.[5–7] Furthermore, in a recent prospective randomized study, omitting ALND did not affect local control or prognosis for SLN-positive patients. The Z0011 trial found that omitting ALND did not result in poor survival or local control in SLN-positive patients with low T stage, no more than two SLNs, and no gross extracapsular extension in the involved nodes. The trial also indicated that ALND should be avoided if SLN metastases (SLNMs) are detected in only one or two nodes.[8] Several authors have suggested using nomograms and scoring systems to predict the risk of non-SLMs (NSLNMs) to omit ALND and increase the quality of life in the optimal management of patients with early breast cancer.[9–17] Although numerous studies have been performed in this regard, it is not yet clear in which subgroup of patients with a positive SLN ALND can be safely omitted.

The aim of this study was to investigate the association between NSLNM and clinicopathologic factors, particularly in the case of SLNM in one or two nodes of clinically node-negative patients with breast cancer.

## 2. Methods

Between October 2010 and October 2014, 350 SLNBs were performed in patients with histologically proven primary breast cancer in our clinic. Histological diagnosis was confirmed by core-needle biopsy preoperatively ($n = 330$) or by frozen section ($n = 20$) during the surgical procedure. SLNBs were performed using blue dye and radiocolloid injections. All patients received a lymphoscintigraphy either on the day prior to or on the day of surgery. The dose of the injected radioisotope was 20–30 MBq (on the day before surgery) or 10–12 MBq (on the day of surgery). Patients were surgically treated by either total mastectomy or breast-conserving surgery. ALND was performed for Level I and II LNs if any macrometastases or micrometastases in SLN were detected in the frozen section analysis. In the case of false negativity, ALND was performed in a second operation. However, if SLNB failed, ALND was considered ineludible. ALND was avoided in patients with isolated tumor cells in SLN.

In this work, we aimed to evaluate the clinicopathologic features to predict NSLNM in breast cancer patients with one to two positive SLNs.

The following data were collected from all patients: age (<50 years or ≥50 years), pathological tumor size (≤2 cm, 2–5 cm, or >5 cm), histological type (invasive ductal, invasive lobular, or mixed), histological grade (I, II, or III), lymphovascular invasion (LVI; yes or no), number of positive SLNs, size of the SLNM (macrometastasis, micrometastasis, or isolated tumor cells), multifocality (yes or no), extracapsular invasion (ECI) of the SLN (yes or no), estrogen receptor (ER) status (negative or positive), progesterone receptor (PR) status (negative or positive), HER2 receptor status (negative or positive), and Ki-67 receptor status (<14% or >14%). Data were collected retrospectively and then analyzed.

Informed consent was obtained from all patients. Data were collected retrospectively. Exclusion criteria were as follows: ductal carcinoma *in situ*, palpable regional LNs, neoadjuvant chemotherapy, known allergic reactions to blue dye or isotope, previous surgery in the ipsilateral breast, pregnancy, and distant metastasis at diagnosis. Informed consent was obtained from all patients.

Multiple breast cancer included both multifocal and multicentric breast cancers. Multifocal breast cancer is defined as a case in which multiple invasive foci existed in the same quadrant, and multicentric cancer was defined as one in which the multiple invasive lesions were interspersed in the pleural quadrants.

Breast cancer was considered multifocal if two or more lesions were located in the same quadrant and the distance between each lesion was <5 cm. If nodules arise in different quadrants of the breast and/or if the distance between each lesion was >5 cm, the cancer was considered multicentric. Treatment decision making was made in a multidisciplinary tumor board setting attended by surgeons, medical oncologists, and radiation oncologists specializing in breast cancer. Based on size, metastasis was divided into macrometastases, micrometastases, or isolated tumor cells, according to the American Joint Committee on Cancer Staging Classification (AJCC) of Breast Cancer.[18] Macrometastasis was defined as a cancer focus measuring over 2 mm in the greatest diameter within SNs. Micrometastasis was defined as a cancer focus measuring between 0.2 mm and 2 mm in the greatest diameter within SLN, and isolated tumor cells were defined as cancer foci smaller than 0.2 mm across their greatest diameter within SLN.

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In this study, the pathologic invasion size for multiple breast cancer was based on the maximum diameter of each invasive component, and total tumor size for multiple breast cancer was defined as the maximum diameter of the lesions.[19] Diagnosis was made according to the AJCC and World Health Organization criteria. Assessment of pathological parameters followed standard guidelines.

ER, PR, and HER2 receptor statuses were established on the resected primary tumor or on the core biopsy sample. PR and ER statuses were assessed by Allred scores, with an Allred score of 3 or more indicating ER or PR positivity.[20,21]

HER2 expression was examined by immunohistochemical (IHC) analysis. A gene amplification assay using fluorescence *in situ* hybridization was used in cases where it was difficult to decide the HER2 status by IHC. Ki-67 protein expression was also examined by IHC, and the results are expressed as the percentage of tumor cells stained by the antibody, as described previously.[22]

Hematoxylin–eosin staining was used to assess lymphatic and vascular involvement, as well as histologic grading, which was defined according to the Scarff–Bloom–Richardson system.[23] ECI was defined as positive if extracapsular tumor growth was present in an SLN section. Each SLN was bisected at two levels for hematoxylin–eosin staining with IHC staining for cytokeratin.

### 2.1. Statistical analysis

The associations between NSLNM and clinicopathologic factors including age, invasive tumor size, nuclear grade, lymphatic or venous involvement, ECI, ER and/or PR status, HER2 status, and Ki-67 labeling index were examined. All statistical analyses were performed using the IBM SPSS Statistics 22.0 package program (IBM Corporation, Armonk, NY, USA). Data were expressed as frequencies or median (minimum–maximum). Shapiro–Wilk test was used and a histogram and the $q$–$q$ plot were examined to assess data normality. Statistical analyses were performed using Mann–Whitney $U$ test and the Chi-square test. Univariate and multiple binary logistic regression analyses were performed for predicting NSLNM using independent factors, such as HER2 status, Ki-67 labeling index, ECI, and LVI. Each of the predictive variables (obtained by binary logistic regression analysis) of sensitivity, specificity, positive predictive values, negative predictive values, and accuracy values was calculated to determine NSLNM. A two-sided $p$ value $< 0.05$ was considered to indicate statistical significance. Confidence interval (CIs) were set at the 95% level.

## 3. Results

A successful SLN biopsy was performed in 345 (98.5%) cases. SLNMs were detected in 110 (31.8%) patients. These patients then underwent ALND; among these patients, 101 (91.8%) had only one to two positive SLNs. Of the 101 patients with positive SLN biopsies, 32 (31.6%) had metastases in the NSLNs. After ALND, five patients had SLNM on the final pathology despite negative SLN during frozen section analysis. Therefore, the false-negative rate was 4.3% (5/115) in our study. The average number of harvested SLN

**Table 1** Results of univariate analysis of clinicopathologic factors associated with NSLNM.

| Variables | Non-SLN (−) | Non-SLN (+) | $p$ |
|---|---|---|---|
| Patients ($n$) | 69 | 32 | |
| Age (y), median | 50.9 ± 1.4 | 52.4 ± 2.1 | 0.553 |
| >50 | 38 (55.1%) | 17 (55.1%) | 0.885 |
| <50 | 31 (44.9%) | 15 (46.9%) | |
| Tumor size (cm) | 2.9 ± 2.1 | 3.2 ± 3 | 0.564 |
| <2 cm | 22 (31.9) | 12 (37.5%) | 0.537 |
| 2–5 cm | 40 (58%) | 15 (46.9%) | |
| >5 cm | 7 (10.1%) | 5 (15.6%) | |
| Tumor type | | | 0.797 |
| Ductal | 64 (92.75%) | 31 (96.88%) | |
| Lobular | 2 (2.9%) | 1 (3.12%) | |
| Mixed | 3 (4.35%) | 0 | |
| Histological grade | | | 0.537 |
| I | 15 (21.7%) | 4 (12.5%) | |
| II | 33 (47.8%) | 18 (56.3%) | |
| III | 21 (30.5%) | 10 (31.2%) | |
| Lymphovascular invasion | | | <0.001* |
| Yes | 10 (14.5%) | 17 (56.25%) | |
| No | 59 (85.5%) | 15 (43.75%) | |
| Multifocality | | | 0.549 |
| Yes | 9 (13%) | 6 (18.8%) | |
| No | 60 (87%) | 26 (81.2%) | |
| ER | | | 0.991 |
| Positive | 56 (81.2%) | 26 (81.3) | |
| Negative | 13 (18.8%) | 6 (18.7%) | |
| Progesterone receptor | | | 0.087 |
| Positive | 55 (79.7%) | 20 (62.5%) | |
| Negative | 14 (20.3%) | 12 (37.5%) | |
| HER2 | | | 0.043* |
| Positive | 12 (17.4%) | 12 (37.5%) | |
| Negative | 57 (82.6%) | 20 (62.5%) | |
| Triple negative | | | 0.929 |
| Yes | 4 | 2 | |
| No | 65 | 30 | |
| Ki-67 | | | 0.011* |
| <14 | 41 (59.4%) | 10 (31.2%) | |
| >14 | 28 (40.6%) | 22 (68.8%) | |
| Removed SLN number, median | 2.0 ± 0.1 | 2.2 ± 0.1 | 0.145 |
| Positive SLN, $n$ | | | |
| 1 | 53 (76.8%) | 20 (62.5%) | 0.156 |
| ≥2 | 16 (23.2%) | 12 (37.5%) | |
| Size of metastasis in SLN | | | 0.173 |
| Macrometastasis | 62 (90%) | 31 (96.9%) | |
| Micrometastasis | 5 (7.2%) | 0 | |
| Isolated tumor cells | 2 (2.8%) | 1 (3.1%) | |
| Extracapsular invasion | | | 0.003* |
| Yes | 9 (13%) | 13 (40.6%) | |
| No | 60 (87%) | 19 (59.4%) | |
| Surgery | | | |
| Mastectomy | 26 (39.13%) | 16 (50%) | 0.305 |
| Breast-conserving surgery | 43 (60.87%) | 16 (50%) | |

* Statistically significant ($p < 0.05$).
ER = estrogen receptor; NSLNM = nonsentinel lymph node metastasis; SLN = sentinel lymph node.
Bold values signifies statistically significant ($p < 0.05$).

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**Table 2** Multiple binary logistic regression analysis for predicting clinicopathologic factors associated with nonsentinel lymph node metastasis.

| Variables | Odds ratio (95% confidence interval) | *p* |
|---|---|---|
| LVI | 6.1 (2.1–17.69) | 0.010 |
| HER2 positive | 3.2 (1.07–9.55) | 0.037 |
| Ki-67 index > 14 | 3.2 (1.53–9.27) | 0.026 |
| ECI | 4 (1.24–12.7) | 0.020 |

According to multiple logistic regression analysis, we obtained the following equation:
$P(\text{NSLNM}=1)=\frac{1}{1+\exp(-2.683+1.185\ \text{Ki}{-}67+1.165\ \text{HER2}+1.382\ \text{ECI}+1.804\ \text{LVI})}$

ECI = extracapsular invasion; LVI = lymphovascular invasion.

was 2.0 ± 0.1 in patients with negative NSLN and 2.2 ± 0.1 in patients with positive NSLNM ($p = 0.145$).

The results of univariate analysis of clinicopathologic factors associated with NSLNM are presented in Table 1. Based on the results obtained, we investigated which factors were predictive of NSLNM in clinically node-negative patients with breast cancer.

Histological type of the primary tumor was invasive ductal carcinoma in 95 patients (94%), invasive lobular carcinoma in three patients (3%), and mixed invasive breast carcinoma in three patients (3%). There was no statistically significant between the groups ($p = 0.797$). The mean ages (±standard deviation) were 50.9 ± 1.4 years in patients with negative NSLN and 52.4 ± 2.1 years in patients with NSLNM ($p = 0.553$).

The median invasive tumor size was larger in patients with NSLNM compared with metastasis-negative patients (3.2 ± 3 vs. 2.9 ± 2.1, respectively; $p = 0.564$), but there was no statistical significance.

Characteristics of study patients and results of the histopathological evaluation of the primary tumor are presented in Table 1. Demographics of study patients and histopathological features of the primary tumor that were likely to predict metastatic involvement of NSLN are presented in Table 2.

Univariate analysis showed that LVI, ECI, positive HER2 receptor, and Ki-67 index over 14% were associated with NSLNM ($p < 0.05$; Table 1). There was no significant association between NSLNM and invasive tumor size, nuclear grade, ER and/or PR status, triple negative, multifocality, positive SLN, and size of metastasis in SLN ($p > 0.05$, Table 1).

**Table 3** Overall prediction of nonsentinel lymph node metastasis using variables obtained by multiple binary logistic regression analysis in patients with clinically node-negative breast cancer.

| Variables | Truly positive NSLNM | Truly negative NSLNM | Total |
|---|---|---|---|
| Predicted positive NSLNM | 17 | 8 | 25 |
| Predicted negative NSLNM | 15 | 61 | 76 |
| Total | 32 | 69 | 101 |

Variables obtained by multiple binary logistic regression analysis are presented in Table 2.
NSLNM = nonsentinel lymph node metastasis.

Binary logistic regression analysis also showed that LVI [odds ratio (OR) = 6.1, 95% CI = 2.1–17.69, $p = 0.01$], HER2 receptor positivity (OR = 3.2, 95% CI = 1.07–9.55, $p = 0.037$), ECI (OR = 4, 95% CI = 1.24–12.7, $p = 0.02$), and Ki-67 index over 14% (OR = 3.2, 95% CI = 1.53–9.27, $p = 0.026$) were independent predictors for NSLNM (Table 2).

A total of 59 (58.4%) patients underwent breast-conserving surgery and 42 (41.6%) received mastectomy. There was no difference between the two groups regarding the surgical method (positive NSLN vs. negative NSLN, $p = 0.305$; Table 1). Macrometastasis was observed in 93 (92%) patients, micrometastasis in five (5%) patients, and isolated tumor cells in three (3%) patients.

The overall prediction of NSLNM based on variables obtained in multiple binary logistic regression analysis (Table 2) is shown in Table 3. The overall sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of the prediction model were 53.1%, 88.4%, 80.2%, 68.0%, and 77.2%, respectively (Table 4). Table 4 also shows each independent predictor for NSLNM.

## 4. Discussion

The aim of our work was to evaluate the risk factors of NSLNM in clinically node-negative breast cancer patients with one to two SLNMs and examine the likelihood of NSLN prediction. Our study results show that LVI, HER2 receptor positivity, ECI, and Ki-67 index over 14% were independent predictors for NSLNM.

Axillary nodal status is an important prognostic and predictive factor for the staging and treatment of breast cancer. SLNB is accepted as a standard procedure for axillary lymph node staging in clinically axillary-negative breast cancer patients?.[24–26] However, 40–70% of patients with positive SLN do not have further axillary metastasis.[27,28] Therefore, axillary dissection could be avoided in these patients.[9,12] Although ALND has been the standard procedure if patients are positive for SLNM, a recent clinical trial suggests that ALND is unnecessary if positive SLNM is detected in one or two nodes. The ACOSOG Z0011 trial[8] showed that SLNB alone without ALND results in extremely low locoregional recurrence and excellent overall survival comparable to that in patients undergoing ALND if SLNM is present in two or fewer nodes. In addition, the Dutch AMAROS trial[29] compared ALND with radiotherapy in T1–T2 patients with a positive SLNB. The trial authors obtained similar results in terms of axillary control between the two treatments. In that trial, patients treated with

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**Table 4** Rates of specificity and sensitivity, PPV, NPV, and accuracy of values obtained by univariate binary logistic regression analysis to predict NSLNM for each independent predictor.*

| Variables | Lymphovascular invasion | HER2 positive | Ki-67 index > 14 | Extracapsular invasion | Overall[a] |
|---|---|---|---|---|---|
| Sensitivity (%) | 53.1 | 37.5 | 68.7 | 40.6 | 53.1 |
| Specificity (%) | 85.5 | 82.6 | 59.4 | 86.9 | 88.4 |
| PPV (%) | 62.9 | 50 | 44 | 40.6 | 68 |
| NPV (%) | 79.7 | 80.3 | 80.3 | 75.9 | 80.2 |
| Accuracy (%) | 75.2 | 68.3 | 62.3 | 72.2 | 77.2 |

NPV = negative predictive value; PPV = positive predictive value.
[a] The overall specificity, sensitivity, PPV, NPV, and accuracy values obtained by multiple binary logistic regression analysis to predict NSLNM, which were calculated using Table 3.

**Table 5** Studies demonstrating independent predictors of NSLNM in clinically node-negative breast cancer, with different rates of NSLNM, ER+, T1, and MF.

| Study | NSLNM (%) | Patients, n | ER+ (%) | T1 (%) | Multifocality (%) | Predictive factors |
|---|---|---|---|---|---|---|
| Toshikawa et al (2015)[39] | 38.6 | 44 | 93.1 | 50 | Unstudied factor | tm size, LVI |
| Yıldız et al (2015)[31] | 48.5 | 70 | 77.1 | 40 | 20 | MF, tm size |
| Gurleyik et al (2011)[34] | 22 | 59 | 71 | 66 | Unstudied factor | tm size, LVI |
| Su et al (2012)[42] | 50.9 | 159 | 81.7 | 62.2 | 10.2 | SLN number, negative SLN number |
| Eldweny et al (2012)[27] | 44.4 | 80 | 80 | 40 | 20 | LVI |
| Dingemans et al (2016)[13] | 58.8 | 158 | 78.4 | 31.6 | 18.9 | tm size, ECI, negative SLN number |
| Tan et al (2014)[43] | 55.2 | 266 | 81.2 | 30.8 | 9 | LVI, negative SLN number, positive SLN number |
| Moosavi et al (2014)[32] | 55 | 167 | 69.4 | 21.5 | 16.1 | age, tm size, LVI, ECI |
| Kuru et al (2014)[33] | 48.5 | 237 | 88 | 37.1 | 14 | tm size, LVI, ECI, multifocality, negative SLN number |
| Yeniay et al (2012)[17] | 40.9 | 244 | 78.1 | 55 | 14.5 | cerb-2, metastasis size |
| Gipponi et al (2013)[40] | 26.1 | 126 | 78.6 | 69.8 | Unstudied factor | tm size, LVI, grade, mitoses number |
| Wang et al (2015)[41] | 38.8 | 509 | 67.7 | 42 | 5 | tm size, grade, LVI, negative and positive SLN number |
| Jinno et al (2008)[35] | 35.1 | 131 | 73.2 | Unstudied factor | Unstudied factor | LVI, positive SLN number |
| Dozin et al (2014)[36] | 35.5 | 397 | 74.6 | 64.7 | Unstudied factor | tm size,grade, HER2 res positive, positive SLN number |
| Cabioglu et al (2012)[30] | 37.9 | 116 | Unstudied factor | 48.2 | 17.2 | metastasis size, ECI |
| Neven et al (2014)[15] | 21.9 | 470 | 91.9 | 10.6 | Unstudied factor | SLNM size |
| Ozmen et al (2006)[37] | 50.6 | 148 | 70.2 | 44 | 10.8 | tm size, ECI, SLNM size |
| Gur et al (2009)[38] | 33.5 | 319 | 86.6 | 49.8 | Unstudied factor | tm size, SLNM size |
| Present study | 31.6 | 101 | 81.1 | 33.6 | 14.8 | LVI, ECI, Ki-67 level, HER2 positive |

ECI = extracapsular invasion; ER = estrogen receptor; LVI = lymphovascular invasion; MF = multifocality; NSLNM = nonsentinel lymph node metastasis; SLN = sentinel lymph node; tm = tumor.

ALND had significantly more morbidities than those treated with radiotherapy. Based on this, many studies have identified factors associated with the histopathological variables of the primary tumor and the SLNM to develop nomograms to predict the risk of NSLNM.[13,15,17,27,30–41] These studies showed that different pathologic characteristics of the primary tumor and the SN were associated with an increased probability of additional positive NSLN.

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However, there is no consensus on the predictive factors of NSLNM until now (Table 5).

Some histopathological variables of the primary tumor and its metastasis have been identified to correlate with the NSLN status. The most commonly analyzed risk factors in other studies include primary tumor size, grade of primary tumor, the maximum size of positive SLN, LVI, ECI in SLN, and ER, PR, and HER2 statuses (Table 5).

The association of tumor size with the probability of NSLNM has been documented in numerous studies where the T1 tumor rates ranged from 10% to 70% in the study group.[15,37–40] Ozmen et al[37] also demonstrated that tumor size over 2 cm was associated with a higher rate of SLNM and NSLNM. Recently, Dingemans et al[13] and Wang et al[41] also reported that the primary tumor size was a predictor of NSLNM. Chen et al[14] have recently developed a new nomogram to predict the probability of a patient with one to two metastatic SLN to have further axillary disease, which is similar to our study, but they could not demonstrate an association between tumor size and NSLN involvement in multivariate analyses. Similarly, there was no correlation between tumor size and NSLNM in our study. Although some studies have shown that tumor size was not associated with a higher rate of NSLNM[17,27,42,43] in parallel to our study, some studies have reported contrasting results.[31,34,37,40]

Some investigations have demonstrated that the presence of micrometastasis in SLN was associated with lower rates of NSLNM, compared with macrometastasis.[17,30,37] It has also been reported that the size of the SLNM had no significant relationship with NSLNM after multivariate analysis.[14,27,32,40] Similarly, in our study, the size of the SLNM was not an independent predictor of NSLNM. The Memorial Sloan Kettering Cancer Center (MSKCC) model, which is the most widely used model to predict NSLNM, also did not include the size of SLNM.[9]

To our knowledge, few studies have shown that age was significantly associated with positive NSLNs in multivariate analyses.[32,44] However, several studies could not find an association of age with NSLNM,[15,34–43] which was the case in this study as well.

Some investigations have revealed that LVI is a predictor of NSLNM.[27,33,35] In this study, we reported an association between LVI and NSLN involvement. However, Yıldız et al[31] and Dozin et al[36] have recently demonstrated that LVI is not a significant predictor of NSLNM in logistic regression analysis. In our study, LVI at SLN was found to be a predictor of NSLNM, although its sensitivity was low (53.1%) and specificity was high (85.5%).

Recently, Shigematsu et al[45] revealed that ECI at SLN is an independent predictor of both NSLNM and poor prognosis for early stage breast cancer patients with SLNM. Similarly, we demonstrated that the presence of ECI at SLN was a strong predictor of NSLNM, with 86.9% specificity. In addition, several studies have documented ECI to be a predictor of NSLNM,[13,32,33,37] although in some other studies this relationship was not found.[12,42]

Some authors have revealed that multifocality of the primary tumor is a predictor of NSLNM.[31,33] In our study, the relationship between multifocality of the primary tumor and NSLNM was not significant in both univariate and multivariate analyses, as seen in many studies.[12,37,39,41]

Axillary LN involvement has been reported to be higher in ER/PR-positive patients.[46,47] However, in this study, we did not find any relationship between ER/PR positivity and NSLNM. Meretoja et al[28] and Wang et al[48] indicated that there is a significant relation between HER2 expression and NSLNM. Similarly, the results obtained in this study showed that overexpression of HER2 significantly increased the probability of NSLNM. However, several studies did not demonstrate this relationship.[7,10,12,48]

In our study, Ki-67 index over 14 is a predictor of NSLNM in both univariate and logistic regression analyses, but its accuracy (68.7%) and specificity (59.4%) are lower than other predictors. To our knowledge, only one study[36] documented that Ki-67 level over 20% in SLN is significantly related to NSLNM in univariate analyses, but not significant in multivariate analysis. However, some studies could not demonstrate this relationship.[14,17,40] The authors of the present paper opine that an association between Ki-67 level and NSLNM has not been revealed in many studies.[13,27,30–32,42,43,45,49]

Based on the obtained predictors of NSLNM in different studies, several nomograms have been developed to predict the presence of tumor in NSLN in the axilla.[9–12,33] The most widely used nomogram is developed by MSKCC.[9] This nomogram includes primary tumor size, grade, number of positive and negative SLNs, SLN detection method, ER status, LVI, and tumor multifocality to predict NSLNM. Although the predictive accuracy of these nomograms have been validated by some studies,[17,33,41,50] others have not.[42,49,51,52]

In this study, the overall sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of the prediction model were 53.1%, 88.4%, 80.2%, 68.0%, and 77.2%, respectively. Although our sensitivity value is low, both specificity value and negative predictive value are high. These data could better predict the condition of not having an NSLNM in patients with positive SLN, compared with other prediction values.

Recently, many mathematical models have been used to evaluate the predictive factor of NSLNM in SLN-positive patients. A literature review showed that many different studies included various clinicopathologic factors or different study designs (e.g., rate of T1 tumor, ER, multifocality, and NSLNM, as shown in Table 5). However, the results of these studies cannot be applied to specific patient populations as they may have poor accuracy. Therefore, each clinic should establish its own nomograms and utilize the most appropriate nomogram or should determine the likelihood of NSLNM to omit ALND.

The limitation of our study is that it is a retrospective study using a single and small population. Despite these limitations, our predictive model provides a good specificity and negative predictive value for the prediction of NSLNM; however, our model should be further validated in our institutions, different institutions, and different patient groups prospectively.

In our study, the predictive factors of NSLNM were LVI, ECI, Ki-67 level, and HER2 receptor positivity. Based on these results, ALND may be omitted in consequence of positive SLN in one or two nodes in clinically node negative patients with breast cancer. Our results incidate more accurate the patients with no evidence of NSLNM than that of

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NSLNM due to high specificity rate and NPV obtained in the predictive model. These factors should be validated in prospective studies in order to develop a nomogram to predict NSLNM before they can be used generally.

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