Original Article

A Combined Nomogram Model to Preoperatively Predict Positive Sentinel Lymph Biopsy for Breast Cancer In Iranian Population

Nahid Nafissi[1], Bushra Zareie[2], Payman Rezagholi[3], Hassan Moayeri[4]

[1]Department of General Surgery, School of Medicine, Hazrat-e Rasool General Hospital, Iran University of Medical Sciences, Tehran, Iran, [2]Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran, [3]Department of Operating Room, Faculty of Nursing and Midwifery, Kurdistan University of Medical Sciences, Sanandaj, Iran, [4]Department of Surgery, School of Medicine, Kowsar Hospital, Kurdistan University of Medical Sciences, Sanandaj, Iran

Abstract

Background: Axillary dissection in breast cancer provides useful information on the degree of axillary nodule involvement, which serves as a reliable indicator for the prognosis and staging of breast cancer in patients. The aim of this study was to develop and validate the nomogram model by combining prognostic factors and clinical features to predict the node status of preoperative breast guard positive node cancer.

Materials and Methods: Subjects consisted of patients referring to hospitals with the diagnosis of breast cancer. Patients were allowed to substitute molecular subtypes with data on breast cancer diagnosis and prognosis as well as sentinel node status. The bootstrap review was used for internal validation. The predicted performance was evaluated based on the area under the receiver operating characteristic curve. According to the logistic regression analysis, the nomograms reported material strength between predictors and final status reliability.

Results: 1172 patients participated in the study, of whom only 539 patients had axillary lymph node involvement. The subtype, family history, calcification, and necrosis were not significantly related to axillary lymph node involvement. Tumor size, histological type, and lymphovascular invasion in multivariate logistic regression were significantly and directly correlated with axillary lymph node involvement.

Conclusion: Nomograms, depending on the population, help make decisions to prevent axillary surgery. It seems that the prediction model presented in this study, based on the results of the neuromography, can help surgeons make a more informed decision on underarm surgery. Moreover, in some cases, their surgical program will be informed by accurate medical care and preclusion of major surgeries such as ALND.

Keywords: Breast cancer, nomogram, sentinel lymph node biopsy

Address for correspondence: Dr. Hassan Moayeri, Department of Surgery, School of Medicine, Kowsar Hospital, Kurdistan University of Medical Sciences, Sanandaj, Iran.
E-mail: moaiery@gmail.com
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Introduction

Axillary dissection in breast cancer provides information on the extent of axillary nodule involvement, which acts as a reliable indicator for the prognosis and staging of breast cancer in patients.[1] Breast cancer surgery has currently lost its momentum. A growing body of studies has shown that, depending on the patient's condition, smaller surgeries can be more efficient than radical surgeries with significantly lower complications.[2] Nonpositive sentinel lymph node biopsy (SLNB) is not required for axillary dissection. It means no metastasis or nonsentinel lymph node (NSLN), although residual disease alone does not affect the rate of local

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recurrence. Recent clinical studies have reported factors that are likely to be associated with metastases of lymph nodes, thereby preventing extensive radical surgeries (axillary lymph node dissection [ALNDs]) in patients with low risk of metastasis or NSLN.[3] Conventionally, ALND is used to determine the rate of lymph nodes involvement, but today, SLNB is recognized as a standard, selective, and noncomplicated method.[4,5] Following a histochemical assessment, patients with a negative SLNB response may not need an ALND. However, there is still a slight chance of NSLN engagement before an SLNB conflict, and surgeons may need an algorithm that measures the risk of NSLN involvement. Considering the possibility of false-negative results in SLNB, it is essential to identify those patients more vulnerable to NSLN and to avoid localized relapses caused by positive lymph nodes behind a precursor missed in the scrutiny.[4] To identify these factors and tools in order to determine the probability of metastasis in nonguarded glands, some medical centers, such as the MD Anderson Cancer Center, have designed a nomogram that predicts the probability of positive NSLN in the case of metastasis in SLNB. Precision medicine is a therapeutic model that personalizes the health-care process by providing medical decisions, exercises, or pharmaceutical products for each individual patient. In this model, diagnostic tests are often employed to identify optimal therapeutic approaches based on the genetic content of a person.[6] Precision instruments include molecular detection and imaging.[7] The precise medical care for breast cancer treatment faces several major challenges, including low frequency of target molecular variations, the feasibility of high-powered technologies, and access to targeted therapy.[8] Precise medical care is also used for breast surgery, and these technologies provide even more precise treatment methods. Nomograms, which are designed to decide on precautions based on data collected from patients, need to be revalidated before application to other areas. Nomogram provides useful information about the possibility of metastasis on the NSLN, though it is an inherently challenging task. When deciding on the application of nomograms in a new facility, caution should be practised in making decisions about positive SLNB patients. The NSLN involvement relies on the characteristics of the tumor and lymph nodes, and several researcher nomograms and scoring systems have been proposed to predict the likelihood of NSLN metastasis. The most common systems include the Memorial Sloan Kettering Cancer Center (MSKCC),[9] Cambridge Nomograms,[10] Stanford Nomograms,[11] Thyon Scores,[12] and Anderson's Cancer Center Score.[13] The accuracy of the nomograms in the prediction of sentinel lymph node (SLN) involvement varies in different societies. Therefore, this study, based on the characteristics of the Iranian patients, designs nomograms to predict SLN involvement to help surgeons in this area.

Materials and Methods

The participants included patients diagnosed with breast cancer referring to Rasool Akram and Khatam-ol-Anbia hospitals in Tehran, Iran. Patients were allowed to substitute molecular subtypes with data on breast cancer prognosis. Those who met the following criteria were included in the study: initial diagnosis of breast cancer after pathologic confirmation, no systemic neoadjuvant or mastectomy treatment, successful SLNB and AXLND in case of SLNB involvement, and willingness to participate in the study. Pathological clinical parameters were also recorded. Preoperative imaging including mammography and breast ultrasound was performed for all patients. Tumor size was determined based on the largest size measured in mammography or ultrasound. Furthermore, if the multicenteric tumor in the breast was suspected on mammography or ultrasound, it was confirmed by pathology. All patients underwent a core needle biopsy (CNB) for a definitive diagnosis preoperatively. The following assessments were carried out for all samples. This study was approved by the Ethics Review Board of Iran University of Medical Sciences. The histologic grade, estrogen receptor status, progesterone receptor status, human epidermal growth factor receptor 2 status, and Ki-67 index were based on U. S. National Comprehensive Cancer Network guideline.[6] Based on regression analysis, Nomograms were designed to predict the NSLN status of breast cancer according to the binary logistic regression coefficient. The variables that with P value < 0.2 in tables 2 were entered into regression analysis. Also significant variables based on P value < 0.05 were selected for the multivariate analysis. Confidence intervals of odds ratio were processed with Bootstrap 1000 times. to increase the validity of the final model. Statistical analysis was performed using nomolog package of the Stata14.0 software (StataCorp, College Station, TX).

Results

A total of 1172 people with breast cancer participated in the study, of which 633 (54.01%) had no axillary lymph node involvement, and only 539 (45.99%) reported axillary lymph node involvement. Moreover, 629 (53.67%) participants were over 50 years old and 858 (73.21) had no family history of breast cancer. Tumor size in most cases (525) was between 21 and 40 mm. Histological grade in most cases (555) was II [Table 1]. In addition to age, the prevalence of axillary lymph node involvement was approximately identical in individuals over 50 years of age and those under 50 (46.10 vs. 45.49) ($P > 0.05$). Other variables such as subtype, family history, calcification, and necrosis were not significantly correlated with axillary lymph node involvement ($P > 0.05$) [Table 2]. Tumor size (mm), histological type, and vascular invasion in multivariate logistic regression were significantly and directly related to axillary lymph node involvement ($P < 0.05$). Also, histological grade and multicentric variables were associated with axillary lymph node involvement. In addition, a significant and direct relationship was observed with univariate logistics ($P < 0.05$) [Table 3]. According to the results of multivariate regression, the highest odds ratio was tumor invasion (adjusted odds ratio AOR: 4.56; 3.39–6.13;

Table 1: Characteristics of the patients with positive sentinel lymph node (*n*=1172)

Variable	*n* (%)
Age	
>50	629 (53.67)
≤50	499 (42.58)
Missing	44 (3.75)
Tumor size (mm)	
≤20	489
21-49	525
≥50	107
Missing	51
Family history	
No	858 (73.21)
Yes	211 (18.00)
Missing	103 (8.79)
Histological type	
Ductal	843
Lobular	157
Other	106
Mix	59
Missing	7
Histological grade	
I	100
II	555
III	438
Missing	79
LVI	
No	753
Yes	394
Missing	25
Regional lymph node metastases	
N_0	633 (54.01)
N_+	539 (45.99)
1-2 positive nodes	258
≥3 positive nodes	281
Subtype	
LumA	619
LumB/HER+	88
HER+/nonluminal	37
Triple negative	200
LumB/HER−	43
Missing	185
Calcification	
No	904
Yes	215
Missing	53
Multi centric	
Yes	31
No	1073
Missing	68
Necrosis	
No	759
Yes	362
Missing	51

LVI: Lymphovascular invasion, HER: Human epidermal growth factor receptor

Table 2: Multivariate logistic regression to estimate the final model

Variable	N_0	N_+	*P**
Tumor size (mm)			
≤20	312 (63.80)	177 (36.20)	0.001
21-49	247 (47.05)	278 (52.95)	
≥50	38 (35.51)	69 (64.49)	
Histological type			
Ductal	429 (50.89)	414 (49.11)	0.001
Lobular	87 (55.41)	70 (44.59)	
Other	87 (82.08)	19 (17.92)	
Mix	25 (42.37)	34 (57.63)	
Family history			
No	448 (52.21)	410 (47.79)	0.333
Yes	118 (55.92)	93 (44.08)	
Histological grade			
I	73 (73.00)	27 (27.00)	0.001
II	293 (52.79)	262 (47.21)	
III	199 (45.43)	239 (54.57)	
LVI			
No	505 (67.07)	248 (32.93)	0.001
Yes	109 (27.66)	285 (72.34)	
Multi centric			
Yes	9 (29.03)	22 (70.97)	0.005
No	583 (54.33)	490 (45.67)	
Missing			
Calcification			
No	488 (53.98)	416 (46.02)	0.618
Yes	112 (52.09)	103 (47.91)	
Necrosis			
No	416 (54.81)	343 (45.19)	0.182
Yes	183 (50.55)	179 (49.45)	
Subtype			
LumA	333 (53.80)	286 (46.20)	0.450
LumB/HER+	42 (47.73)	46 (52.27)	
HER +/nonluminal	21 (56.76)	16 (43.24)	
Triple-negative	118 (59.00)	82 (41.00)	
LumB/HER-	25 (58.14)	18 (41.86)	

*Result from Chi-square test. Variables with P<0.2 in the Chi-square test were entered into multivariate logistic regression to estimate the final model. LVI: Lymphovascular invasion, HER: Human epidermal growth factor receptor

$P < 0.001$). The probabilistic nomogram suggested that vascular invasion and pathologic mixing had the highest scores and the greatest impact on increasing the likelihood of cancer spread to the axilla.

Discussion

In the 1971 National Surgical Adjuvant Breast and Bowel Project, a study was conducted to determine whether less invasive (less extensive) treatments could be as effective as radical mastectomy. The results suggested that axillary dissection did not increase the survival of patients in the long term. The sentinel lymph node hypothesis for lymph node

Table 3: Result from logistic regression models for N_0 and N_+

Variable	OR (95% CI)	*P*	AOR (95% CI)	*P*
Tumor size (mm)				
≤20	Reference	-	Reference	-
21-49	1.98 (1.54-2.55)	0.00	1.75 (1.32-2.32) (1.33–2.31)	0.001
≥50	3.20 (2.07-4.95)	0.00	3.06 (1.89-4.97) (1.91-4.92)	0.001
Histological type				
Other	Reference	-	Reference	-
Ductal	4.42 (2.64-7.39)	0.00	3.52 (1.91-6.47) (1.90-6.50)	0.001
Lobular	3.68 (2.05-6.63)	0.00	2.90 (1.45-5.77) (1.45–5.76)	0.003 0.002
Mix	6.23 (3.04-12.75)	0.00	4.00 (1.73-9.27) (1.68-9.56)	0.001 0.002
Histological grade				
I	Reference	-	-	-
II	2.42 (1.51-3.88)	0.00	-	-
III	3.25 (2.00-5.25)	0.00	-	-
LVI				
No	Reference	-	Reference	-
Yes	5.32 (4.07-6.96)	0.00	4.56 (3.44-6.05) (3.39-6.13)	0.001
Multi centric				
No	Reference	-	Reference	-
Yes	2.91 (1.33-6.37)	0.008	2.49 (1.005-6.17) (0.76-8.12)	0.049 0.131
Necrosis				
No	Reference		-	-
Yes	1.19 (0.92-1.52)	0.182	-	-

Vascular invasion (OR: 5.32, 95% CI: 4.07-6.96) and histological grade (OR: 1.58, 95% CI: 1.30-1.92) had a correlation with each other. The variables with higher significant OR were entered into multivariate logistic regression model. OR: Odds ratio, CI: Confidence interval, LVI: Lymphovascular invasion, AOR: Adjusted odds ratio

gradation is based on biopsy-based morbidity (SNLB) to determine the first target of metastatic cells.[14]

Even 10-year survival outcomes from the American College of Surgeons Oncology Group Z0011 and International Breast Cancer Study Group 23-01 trials corroborated non-inferiority of SLNB alone compared to ALND for patients with limited positive SLN(s).[15,16]

Breast cancer surgery has currently been scaled down. Many studies have shown that, depending on the patient's condition, smaller surgeries could be more effective than radical surgeries with lower complications.[17,18] The first and most important prognosis of invasive breast cancer is in the proximal tumor of the axillary lymph nodes. Indeed, 40 to 70% of these patients do not have metastatic non-sentinel lymph nodes (NSLN).[19,20] According to the results of this study, the prevalence of axillary lymph node involvement is almost identical in patients below 50 years of age who had SLND ($P = 0.837$). However, as reported by Dihge L *et al*. (2017), 1 year of age difference was associated with 0.02 times higher risk of axillary involvement ($P = 0.013$ (AOR: 1.02, 95% confidence interval [CI] (1.00)–1.04) This could be ascribed to the fact that Iranian women, like the study Wang XY *et al*., develop breast cancer one to two decades earlier, which can neutralize this difference.[21,22] As reported in the literature, lymphovascular invasion (LVI) is one of the main determinants of SLN metastases.[23] It has the highest risk among other variables in both raw and multivariate logistic models ($P < 0.001$ AOR: 4.56; 3.39–6.13). Similar studies have been performed on LVI tumors. Similar AOR values can be found in the study of Dijeji *et al*. (2017) (AOR: 4.67; 2.70–8.09; $P < 0.001$). As depicted by nomograms, LVI has the longest relevant tumor, and patients with LVI have a higher score with a significantly higher chance of lymph node involvement. This finding is consistent with the results reported in previous studies. Given the fact that LVI may not be evaluated in the CNB, this variable is often treated with caution. Multicentricity significantly increases the risk of tumor risk (odds ratio [OR]: 2.91; 1.33–6.37; *P*: <0.001) in raw analysis and multivariate analysis (OR: 2.49; 0.76–8.12; $P = 0.131$). Few studies have evaluated the impact of this variable on the involvement of the axillary nodes. Evaluation of patients' histological type factor and the incorporation of this variable based on specific categories into the multivariate analysis can significantly increase the accuracy of predictions. According to the results of pathology, lobular and ductal tumors and a combination both can significantly increase the likelihood of axillary lymph node involvement compared to pathological results of other types. Most people with a combined type of tumor have adjusted odds ratio: 4.00; 1.68–9.56; $P = 0.002$. In other words, lobular and combined tumors are least and most likely to be pathologically involved in axillary lymph nodes, respectively.[24] In light of the histological results reported in the raw logistic model, the increased tumor grade raises the likelihood of tumor development, but the effect of this variable on multivariate analysis has not been evaluated

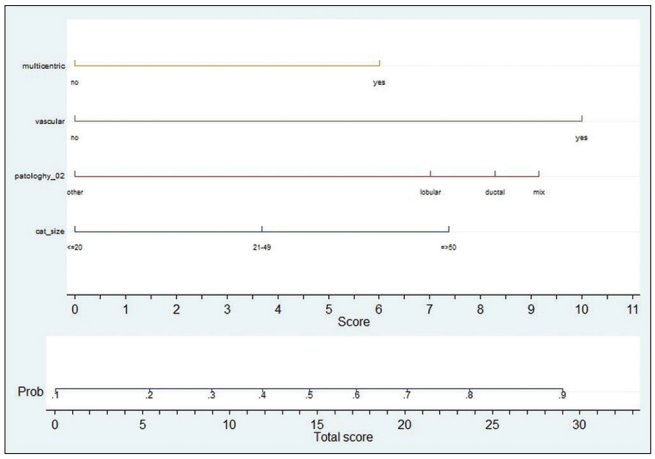

Figure 1: Nomogram for predicting Positive Sentinel Lymph Biopsy for Breast Cancer (Instructions for use of the nomogram: First, assign the points of each characteristic of the patient by drawing a vertical line from that variable to the points scale. Then, sum all the points and draw a vertical line from the total points scale to the predict to obtain the probability of Positive SLNs. Multicentric, multicentric breast cancer; vascular, Lympho vascular invasion; pathology, Histological type; cat_size, Tumor size (mm); prob, probabilistic)

due to its association with other variables and the lack of cross-correlations between variables. In other studies, this may not be sufficiently accurate. Contrary to the results reported by Dihge L *et al*. (2017), subtypes do not play a significant role in the breast cancer spread and metastasis in the axillary lymph node involvement (P = 0.450). Investigating the factors underlying the likelihood of lymph node involvement in breast cancer patients can prevent unnecessary dissection of the axillary lymph node that causes pain and swelling and restricts shoulder movements.

Conclusion

However, in this study, all patients were measured on a CNB sample (LVI) before surgery. This study evaluated the variables regardless of their sensitivity and specificity. According to the results of this study and using the nemogram drawn in Iran to predict the presence of nonmetastatic lymph nodes in patients, surgeons are recommended to use this device to perform unnecessary surgeries and complications refrain more. Of course, standard examinations such as preoperative LVI examinations seem necessary [Figure 1].

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Conflicts of interest

There are no conflicts of interest.

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