Original Article

# Establishing a prediction model of axillary nodal burden based on the combination of CT and ultrasound findings and the clinicopathological features in patients with early-stage breast cancer

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**Background:** Axillary lymph node (ALN) management in early-stage breast cancer (ESBC) patients has become less invasive during the past decades. Here, we tried to explore whether high nodal burden (HNB) in ESBC patients could be predicted preoperatively, so as to avoid unnecessary sentinel lymph node biopsy (SLNB).

**Methods:** The clinicopathological and imaging data of patients with early invasive breast cancer ($cT_{1-2}N_0M_0$) were analyzed retrospectively. Univariate and multivariate analyses were performed for the risk factors of axillary HNB in ESBC patients, and a risk prediction model of HNB was established.

**Results:** HNB was identified in 105 (8.0%) of 1,300 ESBC patients. Multivariate analysis showed that estrogen receptors (ER) status, human epidermal growth factor receptor 2 (HER2) status, number of abnormal lymph nodes (LNs) on computed tomography (CT), and axillary score on ultrasound (US) were the risk factors of HNB (all $P<0.05$). The area under the receiver operating characteristic (ROC) curve in the prediction model was 0.914, with the sensitivity being 85.7% and the specificity being 82.4%. The calibration curve showed that the prediction model had good performance.

**Conclusions:** As a valuable tool for predicting HNB in ESBC patients, this newly established model helps clinicians to make reasonable axillary surgery decisions and thus avoid unnecessary SLNB.

**Keywords:** High nodal burden; early-stage breast cancer (ESBC); sentinel lymph node (SLN); axillary lymph node dissection (ALND)

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## Introduction

Axillary lymph node (ALN) status is one of the most important factors for predicting prognosis and guiding multidisciplinary treatment in early-stage breast cancer (ESBC) patients (1). In patients with clinically lymph node (LN)-negative ESBC, sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) as the standard procedure for ALN staging (2); in contrast, ALND is still routinely recommended for breast cancer patients with positive sentinel lymph nodes (SLNs) (3). However, the results of the American College of Surgeons Oncology Group Z0011 (ACOSOG Z0011) have changed our understanding of the surgical treatment of the axilla in patients with SLN-positive breast cancer (4,5). In the ACOSOG Z0011, ALND was avoided in ESBC ($cT_{1-2}N_0M_0$) women with 1 or 2 positive SLNs who underwent breast-conserving surgery and whole-breast radiotherapy, and the overall survival rate (OS) and local control rate were not affected. ALND was performed only in patients with high nodal burden (HNB: ≥3 metastatic LNs), and up to 21% of patients had HNB. Thus, for breast cancer patients with HNB, SLNB has become unnecessary.

Therefore, identifying HNB accurately and non-invasively before surgery is particularly important for the selection of a feasible axillary surgery (6). Some studies have used clinicopathological data to predict ALN status, but the diagnostic performance of clinicopathological data was poor to predict ALN status (7,8). At the same time, some clinicopathological data like lymphovascular invasion and histological tumor size are available only post-operatively, which may limit the application of clinical prediction model and add a second surgical procedure. With the advancement of preoperative imaging technology, ultrasound (US) and computer tomography (CT) have been routinely applied for preoperative assessment of ALN status (9,10). Preoperative knowledge of ALN status has determined axillary treatment options by imaging technology. A study showed that preoperative axillary imaging results were associated with ALN status in ESBC patients, but a single imaging technology is not enough for predicting ALN status (11). Therefore, it is a hot topic to find accurate and non-invasive preoperative ALN assessment without additional cost.

Our current study was designed to identify the HNB in ESBC patients based on preoperative imaging findings and clinicopathological features and establish a simple HNB risk prediction model in order to help clinicians make reasonable surgical decisions and avoid unnecessary SLNB.

We present the following article in accordance with the STARD reporting checklist (available at http://dx.doi.org/10.21037/gs-20-899).

## Methods

### *General data*

This study was approved by our institutional review board (No.2014156), and the requirement for patients' informed consent was waived due to its retrospective design. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The clinical data of ESBC patients ($cT_{1-2}N_0M_0$) with clinically negative axillary LNs in our center during the period from January 1, 2014 to August 1, 2018 were retrospectively analyzed. The exclusion criteria for patients included the following: (I) with non-invasive breast carcinoma; (II) having received neoadjuvant chemotherapy or endocrine therapy; (III) with bilateral breast cancer; (IV) with an interval between 2 imaging examinations longer than 1 week; (V) with recurrent breast cancer; and (VI) with incomplete data. According to the postoperative pathological results, these patients were divided into non-HNB groups [including a non-positive LN (N0) group and a low nodal burden (LNB) group] (<3 positive LNs) and a HNB group (≥3 positive LNs).

### *Preoperative imaging*

Before surgery, all patients underwent US and contrast-enhanced chest CT. All films were read independently by 2 radiologists, and any disagreement was settled by a senior radiologist.

#### US

US was performed using a Siemens digital color Doppler US diagnostic instrument, with the probe frequency set at 6–15 MHz. The patient was asked to take a supine position, with both upper limbs naturally raised and abducted to fully expose the axilla bilaterally. The axillary LNs were examined with the probe and scored according to the most abnormal morphology, maximum cortical thickness, and loss of fatty hilum (*Figure 1*). The scoring criteria including the following: long-to-short axis ratio (>2, 0 point; ≤2, 1 point), fatty hilum (evenly present, 0 point; unevenly present, 1 point; absent, 2 points), and maximum cortical thickness (<0.3 cm, 0 point; ≥0.3 cm, 1 point).

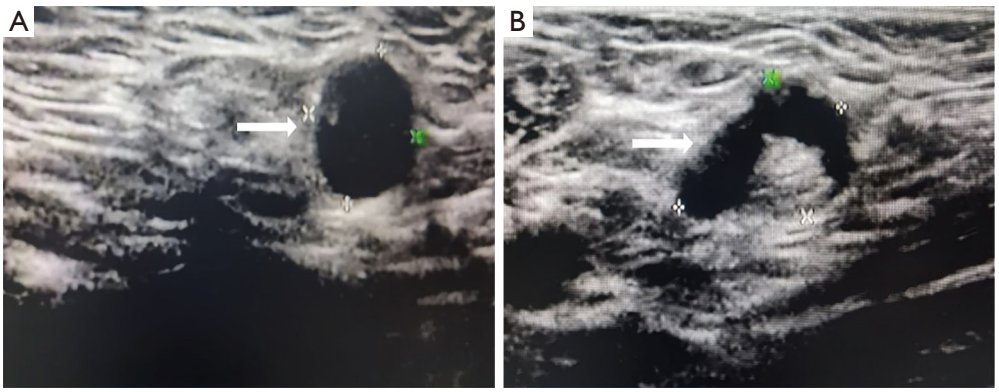


**Figure 1** Sonography of lymph nodes (The green color indicates the starting point of the short axis of the axillary LNs). (A) A 53-year-old woman with invasive carcinoma in her left breast. Horizontal gray scale US of the left axillary LNs shows (I) a long-to-short axis ratio ≤2 (1 point), (II) the loss of fatty hilum (2 points), and (III) a maximum cortical thickness ≥0.3 cm (1 point). The total score of axillary LNs is 4 points on US (arrow). (B) A 47-year-old woman with invasive carcinoma in her right breast. Horizontal grayscale US of the right axillary LNs shows (I) a long-to-short axis ratio ≤2 (1 point), (II) uneven presence of fatty hilum (1 point); and a (III) maximum cortical thickness ≥0.3 cm (1 point). The total score of axillary LNs is 3 points on US (arrow). LN, lymph node; US, ultrasound.

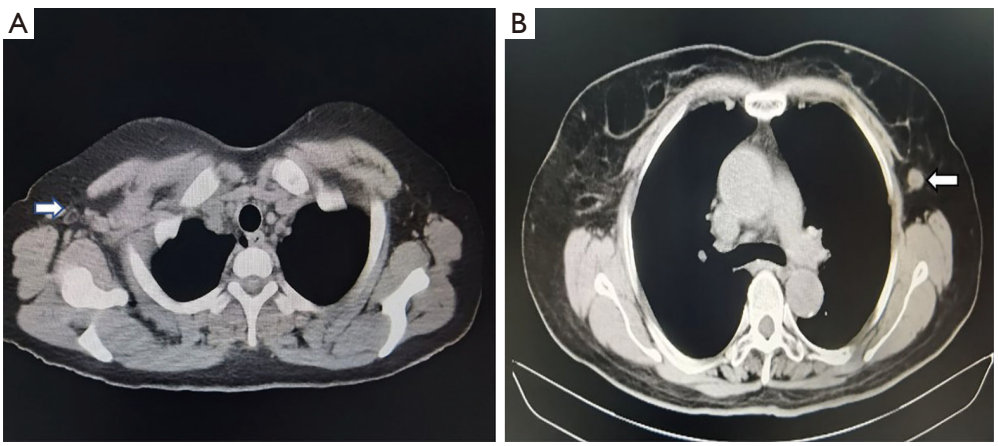


**Figure 2** Lymph nodes on CT. (A) A 50-year-old woman with invasive carcinoma of the right breast. Axial CT shows that the level I LNs at the right axillary are normal, the fatty hilum are evenly present, and the maximum cortical thickness is <0.3 cm (arrow). (B) A 48-year-old woman with invasive carcinoma of the left breast. Axial CT shows that the level I LNs at the left axillary are abnormal, the fatty hilum has disappeared, and the maximum cortical thickness is ≥0.3 cm (arrows). CT, computed tomography; LN, lymph node.

### Computed tomography

For the plane CT scan, the slice spacing and thickness were 4 mm, with the upper boundary of the scan being the lower edge of the fourth cervical vertebra and the lower boundary being the lower edge of the diaphragm. The contrast bolus (90 mL of ioversol) was intravenously infused using an injection flow rate of 3 mL/s. If the maximum cortical thickness of axillary LNs was ≥0.3 cm or the fat hilum was absent, it was considered an abnormal LN (*Figure 2*).

### *SLNB and ALND*

The $^{99m}$Tc-labeled sulfur colloid was injected into the subcutaneous and intradermal tissues of the primary tumor, the subcutaneous tissue in the areola area, or the surrounding glands of the primary tumor 3–18 hours before the surgery. After anesthesia, 0.2–0.4 mL of methylene blue was injected into the subcutaneous and intradermal tissues of the primary tumor, the subcutaneous tissue in the areola area, or the surrounding glands of the primary tumor. SLNB was

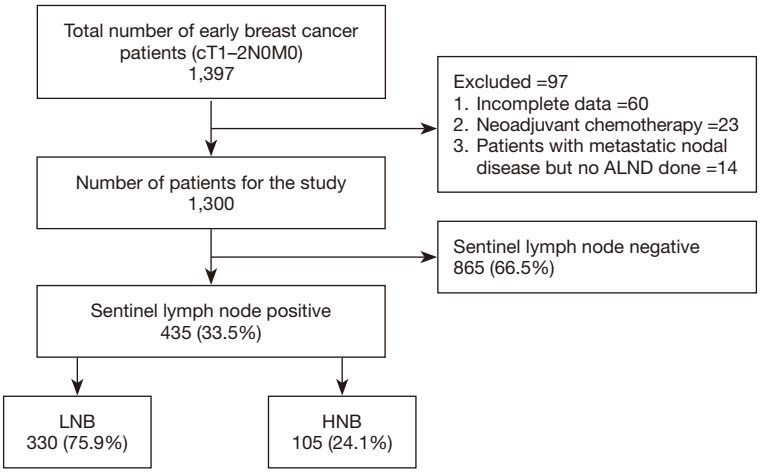


**Figure 3** Study flow. ALND, axillary lymph node dissection; HNB, high nodal burden; LNB, low nodal burden.

performed 10–12 minutes later. Intraoperative radioactive SLN localization was performed using a gamma photon detection probe (Neoprobe 2000, Neoprobe Corporation, Dublin, OH, USA) and the blue dye method. Intraoperative evaluation of SLNs was performed using the combination of frozen section (FS) analysis and imprint cytology. Non-sentinel LNs and the remaining tissues were detected by using serial-section hematoxylin and eosin (HE) staining. Patients with SLNB-positive ESBC further received ALND, and failed SLNB cases underwent ALND directly.

### *Statistical analysis*

All the statistical analyses were performed using SPSS 24.0 software package (IBM Corp., Armonk, NY, USA). The comparisons of the clinicopathological features and imaging findings between the HNB group and non-HNB groups were based on chi-square test. Factors with statistical significance in the univariate analysis were further analyzed using multivariate stepwise logistic regression analysis. A nomogram predicting the probability of involvement of HNB was then developed based on the multivariate logistic regression model. Simple graphs were produced with the R (R Foundation for Statistical Computing, Vienna, Austria). Receiver operating characteristic (ROC) curves were used to evaluate the performance of the prediction model. A standard curve was drawn to evaluate the agreement between observed actual outcomes (axillary tumor burden) and nomographically predicted values (ALN metastasis rate). A P value of less than 0.05 was considered statistically significant.

## Results

### *Clinical features*

A total of 1,300 eligible ESBC patients were included in this study (*Figure 3*). SLNs were negative in 865 patients (66.5%) and positive in 435 patients (33.5%). Among patients with positive SLNs, 330 patients (75.9%) had LNB and 105 patients (24.1%) had HNB. The median number of SLNs resected during SLNB was 3 (range, 0–8), and the median number of SLNs resected during ALND was 18 (range, 15–34). The median age of the enrolled patients was 53 years (range, 24–78 years). The median tumor size was 23 mm (range, 0–48 mm).

### *Results of univariate analysis of HNB*

Univariate analysis of the HNB group and non-HNB (N0 and LNB) groups showed that tumor location, tumor size, and patient's age were not significantly correlated with HNB in ESBC patients (all P>0.05), whereas menstrual, estrogen receptors (ER), human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), and Ki-67 status, along with number of abnormal LNs on CT and axillary US score was significantly correlated with HNB in ESBC patients (all P<0.05) (*Table 1*).

### *Results of multivariate analysis*

Logistic regression analysis was performed with axillary nodal burden as the dependent variable. For those factors showing correlation with axillary nodal burden in the

**Table 1** Correlations between clinicopathological features and nodal tumor burden (%)

| Clinicopathological features | $N_0$ | LNB | Non-HNB ($N_0$ and LNB) | HNB | P |
|---|---|---|---|---|---|
| Age (years) | | | | | 0.100 |
| ≤50 | 485 (68.8%) | 155 (22.0%) | 640 (90.8%) | 65 (9.2%) | |
| >50 | 380 (63.9%) | 175 (29.4%) | 555 (93.3%) | 40 (6.7%) | |
| Tumor size | | | | | 0.574 |
| $T_1$ | 515 (72.0%) | 145 (20.3%) | 660 (92.3%) | 55 (7.7%) | |
| $T_2$ | 350 (59.8%) | 185 (31.6%) | 535 (91.5%) | 50 (8.5%) | |
| Tumor location | | | | | 0.075 |
| Outer upper | 365 (58.8%) | 195 (31.4%) | 560 (90.2%) | 61 (9.8%) | |
| Inner upper | 128 (66.7%) | 47 (24.4%) | 175 (91.1%) | 17 (8.9%) | |
| Outer lower | 201 (67.8%) | 79 (26.5%) | 280 (94.3%) | 17 (5.7%) | |
| Inner lower | 84 (77.8%) | 16 (14.8%) | 100 (92.6%) | 8 (7.4%) | |
| Central | 59 (73.1%) | 21 (25.6%) | 80 (98.7%) | 2 (2.4%) | |
| Menstrual state | | | | | 0.005 |
| Yes | 445 (59.4%) | 230 (30.7%) | 675 (90.1%) | 74 (9.9%) | |
| No | 420 (76.3%) | 100 (18.1%) | 520 (94.4%) | 31 (5.6%) | |
| ER status | | | | | <0.001 |
| Negative | 245 (79.0%) | 55 (17.8%) | 300 (96.8%) | 10 (3.2%) | |
| Positive | 620 (62.6%) | 275 (27.8%) | 895 (90.4%) | 95 (9.6%) | |
| PR status | | | | | <0.001 |
| Negative | 290 (78.4%) | 70 (18.9%) | 360 (97.3%) | 10 (2.7%) | |
| Positive | 575 (61.8%) | 260 (28.0%) | 835 (89.8%) | 95 (10.2%) | |
| HER2 status | | | | | <0.001 |
| Negative | 590 (67.4%) | 240 (27.5%) | 830 (94.9%) | 45 (5.1%) | |
| Positive | 275 (64.7%) | 90 (21.2%) | 365 (85.9%) | 60 (14.1%) | |
| KI-67 | | | | | <0.001 |
| ≤14 | 125 (88.7%) | 15 (10.6%) | 140 (99.3%) | 1 (0.7%) | |
| >14 | 740 (63.8%) | 315 (27.2%) | 1,055 (91.0%) | 104 (9.0%) | |
| No. of abnormal LNs on CT | | | | | <0.001 |
| 0 | 485 (80.8%) | 110 (18.4%) | 595 (99.2%) | 5 (0.8%) | |
| 1 | 270 (60.7%) | 145 (32.6%) | 415 (93.3%) | 30 (6.7%) | |
| 2 | 100 (50.0%) | 65 (32.5%) | 165 (82.5%) | 35 (17.5%) | |
| 3 | 10 (28.6%) | 5 (14.3%) | 15 (42.9%) | 20 (57.1%) | |
| ≥4 | 0 (0.0%) | 5 (25.0%) | 5 (25.5%) | 15 (75.0%) | |
| Axillary US score | | | | | <0.001 |
| 0 | 385 (81.9%) | 80 (17.0%) | 465 (98.9%) | 5 (1.1%) | |
| 1 | 275 (64.7%) | 130 (30.6%) | 405 (95.3%) | 20 (4.7%) | |
| 2 | 155 (68.9%) | 55 (24.4%) | 210 (93.3%) | 15 (6.7%) | |
| 3 | 30 (30.0%) | 45 (45.0%) | 75 (75.0%) | 25 (25.0%) | |
| 4 | 20 (25.0%) | 20 (25.0%) | 40 (50.0%) | 40 (50.0%) | |

HNB, high nodal burden; LNB, low nodal burden; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; LNs, lymph nodes; CT, computed tomography; US, ultrasound.

**Table 2** Logistic regression analysis of factors associated with HNB

| Clinicopathological features | Odds ratio | 95% CI | P |
|---|---|---|---|
| Menstrual state | 1.668 | 0.944–2.948 | 0.078 |
| ER | 8.003 | 2.169–29.533 | 0.002 |
| PR | 1.404 | 0.395–4.992 | 0.600 |
| HER2 | 3.842 | 2.243–6.580 | <0.001 |
| Ki-67 | 10.052 | 0.463–218.215 | 0.142 |
| No. of abnormal LNs on CT | | | <0.001 |
| 1 | 6.321 | 1.968–20.304 | 0.002 |
| 2 | 17.357 | 4.999–60.274 | <0.001 |
| 3 | 25.936 | 5.665–118.752 | <0.001 |
| ≥4 | 86.456 | 15.933–469.140 | <0.001 |
| Axillary US score | | | <0.001 |
| 1 | 1.114 | 0.337–3.678 | 0.859 |
| 2 | 1.068 | 0.303–3.764 | 0.919 |
| 3 | 2.709 | 0.718–10.221 | 0.141 |
| 4 | 11.770 | 3.09–44.795 | <0.001 |

HNB, high nodal burden; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; LNs, lymph nodes; CT, computed tomography; US, ultrasound.

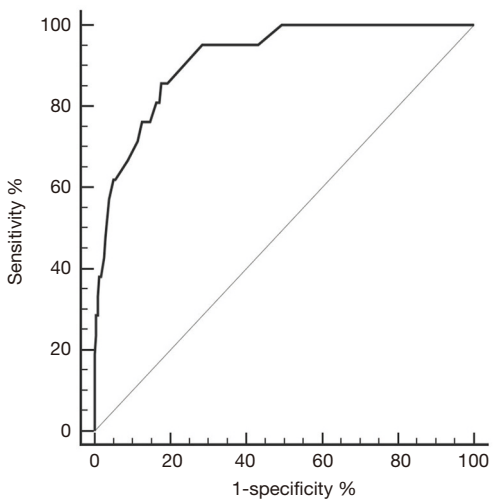


**Figure 4** ROC curve for predicting high nodal burden in early-stage breast cancer. The AUC was 0.914. ROC, receiver operating characteristic; AUC, area under the curve.

univariate analysis as the dependent variables, multivariate logistic regression analysis was further performed. As shown in *Table 2*, multivariate analysis was performed for factors showing statistical significances in *Table 1*. The standard method of entry was applied to include these variables in the regression model. The results showed that ER status, HER2 status, number of abnormal LNs on CT, and axillary score on US were the risk factors of HNB (all P<0.05). In contrast, PR, Ki-67, and menopausal status were not significantly correlated with HNB (all P>0.05).

### *Establishing a prediction model based on the results of multivariate analysis*

According to the results of multivariate binary logistic regression analysis, independent variables with a P value of ≤0.05 were selected for establishing a prediction model. Indicators in the model included ER status, HER2, number

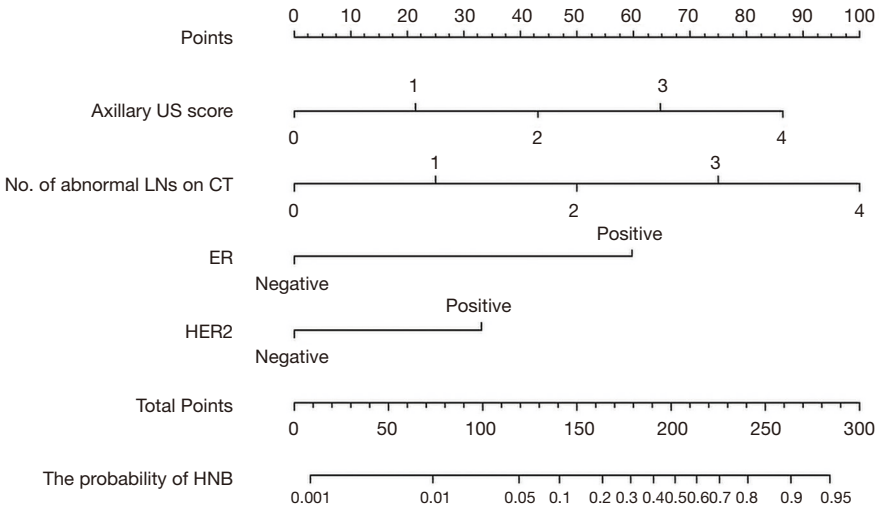


**Figure 5** Nomogram for predicting the probability of HNB in early-stage breast cancer. US, ultrasound; LNs, lymph nodes; CT, computed tomography; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HNB, high nodal burden.

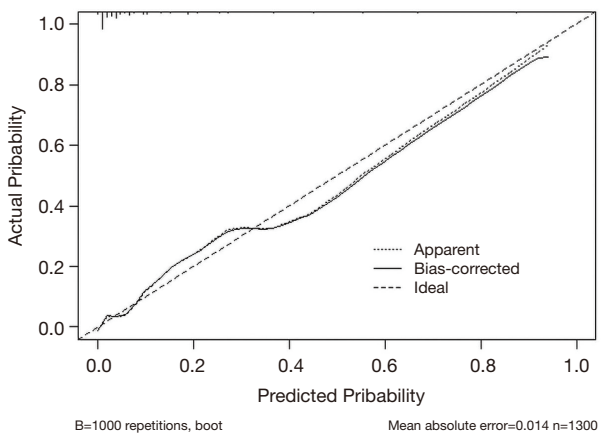


**Figure 6** Calibration plot of the nomogram.

of abnormal LNs on CT, and axillary US score (*Figure 4*). The area under the ROC curve (AUC) was 0.914, the sensitivity was 85.7%, and the specificity was 82.4% (P<0.001). These 4 indicators were quantified, and their sum corresponded to the probability of HNB (*Figure 5*). The calibration curve showed that the prediction model had good performance (*Figure 6*).

## Discussion

In the ACOSOG Z0011 trial, patients who had ESBC with two or fewer SLN metastases had no inferior survival if they underwent SLNB alone versus ALND. While the ACOSOG Z0011 trial increased the threshold of ALND for ESBC patients with positive SLNs, ALND remains the routinely recommended procedure for HNB patients. Unfortunately, assessment of the status of axillary LNs in ESBC patients is a controversial issue. The conventional procedure for axillary evaluation in ESBC patients with clinically negative axillary LNs is SLNB. If SLNs are positive, ALND is often indicated. However, such staging method based on axillary LN increases the risk of unnecessary secondary operations for HNB patients (12). Some other studies have shown that HNB leads to a decrease in the amount of nuclide uptake in SLNs, thereby increasing the false-negative results when performing SLNB (13-15). Thus, direct ALND may be feasible for HNB patients. In the era of precision medicine, accurate pre-operative prediction of the axillary HNB status in ESBC patients enables surgeons to perform ALND directly during the operation.

At present, clinical assessment of the axillary LN status in breast cancer patients mainly relies on a variety of imaging techniques including mammography, positron emission tomography-computed tomography (PET-CT), magnetic resonance imaging (MRI), CT, and US. Mammography is less useful due to its small visual field and low visualization rate during the pre-operative assessment of ALNs. Therefore, mammography is generally not the preferred tool for clinical evaluation of axillary LN status.

Compared with its role in patients with advanced breast cancer, PET-CT is less valuable for evaluating the axillary LNs in ESBC patients (16,17). In addition, due to its high cost and low coverage, PET-CT is typically not applied in the pre-operative evaluation of axillary LN status in China. Although research has shown that MRI has high sensitivity and specificity for the assessment of axillary LNs (18), breast MRI alone cannot cover the entire regional area, and a combination with chest MRI is often required. Clinically, however, chest MRI is not a recommended routine examination for ESBC patients. Compared with breast MRI, chest CT not only covers all the axillary LNs but also can be used to screen for other metastases (e.g., lung metastases and bone metastases). Liang *et al.* (19) found that the diagnostic performance of CT for axillary LNs was similar to that of MRI. Therefore, in our current study, we also chose chest CT results as an important component of our prediction model.

Depending on the results, a single examination can easily lead to both misdiagnoses and missed diagnoses when assessing the status of ALNs. In the post-Z0011 era, the role of US in assessing axillary LNs has long been controversial. Previous studies (20,21) have found the false-positive rate of suspicious axillary US for detecting axillae with 3 or more nodal metastases ranged from 64.1% to 79.8%, and axillary US could not effectively quantify the number of metastatic ALNs. However, Zhu *et al.* (22) found direct ALND would be required if abnormal LNs were found on US or the possibility of HNB was high after metastases were confirmed by biopsy. In another study of 988 patients with breast cancer, only 1 abnormal LN was visualized on US in 30% of the patients who had 2 or more LN metastases (23). Therefore, in our current study, only the most abnormal LN morphology on US was scored to evaluate the axillary nodal tumor burden.

Many conventional predictive models for axillary LN status are available across the world (24-26). Among these, the Memorial Sloan-Kettering Cancer Center (MSKCC) nomogram is the most popular and has shown substantive clinical value, especially when applied to predicting the non-sentinel LNs in patients with positive SLNs. The Memorial Sloan Kettering Cancer Center (MSKCC) non-sentinel LN prediction model has been validated in many international centers, with a reported AUC of 0.78–0.89 (27). However, the diagnostic performance (i.e., the cutoffs) of MSKCC has been questioned (28,29). The extremely low cutoff value of this model fails to achieve high positive predictive value, whereas an excessively high cutoff requires the support of large-sample studies. In addition, the pathological diagnosis standards and the detection methods vary among different medical institutions in different areas. Finally, the variables of traditional prediction models are often based on postoperative pathological information such as tumor size, vascular invasion, and histological grade (30), and thus it is impossible to effectively use traditional prediction models to guide the pre-operative selection of appropriate axillary surgery.

Therefore, there is an imminent need to establish a simpler and more popular model. Our current model consists of 4 simple variables: ER status, HER2 status, number of abnormal LNs on CT, and axillary US score. This model can accurately identify ESBC patients with HNB, which helps surgeons formulate correct and individualized treatment plans that can shorten operative time and lower the economic burden of patients while offering them more treatment options (i.e., surgery or neoadjuvant chemotherapy). For HNB patients who plan to undergo breast-conserving surgery, ALND may be directly performed to avoid unnecessary SLNB, which not only reduces the increased operative time and costs associated with SLNB but also lowers the incidence of adverse reactions (e.g., skin necrosis, rare but severe allergic reactions, and radiation damage) due to the use of tracers during SLNB (31,32). Another advantage of our model is that all the variables can be obtained before surgery, which is conducive to the promotion of the prediction model. However, our study was limited by its single-center retrospective design. Multicenter studies with larger sample sizes are warranted to prospectively verify our model.

In the era of precision medicine, determining the means to avoid undertreatment or overtreatment is a topic of intense research in the management of axillary LNs in ESBC patients. In our current study, we developed a simple HNB prediction model using imaging techniques and clinicopathological features which may allow direct ALND and avoid unnecessary SLNB in selected patients.

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## Footnote

*Reporting Checklist:* The authors have completed the STARD

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*Data Sharing Statement:* Available at http://dx.doi.org/10.21037/gs-20-899

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/gs-20-899). The authors have no conflicts of interest to declare.

*Ethical Statement:* 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. This study was approved by our institutional review board (No. 2014156), and the requirement for patients' informed consent was waived due to its retrospective design. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).



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