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The authors aimed to develop and validate a nomogram based on the clinical characteristics and inflammatory indicators related to the non-SLNs metastasis to predict the risk of non-SLNs metastases in patients with positive SLNs. The developed and validated nomogram achieved high performance for prediction of non-SLNs metastases. They concluded that the nomogram could assist clinicians to decide whether to perform ALND in early-stage breast cancer patients with positive SLNs. The comments below may be considered.

1) Which patients do the authors think this nomogram should be indicated for? Patients who have undergone breast-conserving surgery and are scheduled to receive postoperative systemic therapy and radiation therapy do not require ALND for 1-2 SLN metastases, so the benefit of using this nomogram to predict non-SLN metastases would be small. On the other hand, for patients who have undergone total mastectomy with 1-2 SLN metastases or breast-conserving surgery with 3 or more SLN metastases, this nomogram may be useful to predict non-SLN metastases and to consider the need for ALND. How many of the patients in this study met these criteria (i.e., those who underwent total mastectomy with one or two SLN metastases or breast-conserving surgery with three or more SLN metastases)? And what is the accuracy of the prediction in patients who met these criteria?

Reply 1): Thank you very much for your constructive comments which could enrich our manuscript. After the Z-0011 trial, ALND was unnecessary for patients with 1 or 2 SLN metastases who had undergone breast-conserving surgery and were scheduled to receive postoperative radiotherapy and systemic adjuvant therapy. The Z-0011 trial is of great significance, but there are limitations either. Thus, our novel nomogram included the patients who do not meet the criteria of the Z-0011 trial. The number of the patients in our study met these criteria was 87 (i.e., those who underwent total mastectomy with one or two SLN metastases or breast-conserving surgery with three or more SLN metastases). The ROC curve and calibration curve are drawn below, and the AUC is 0.828 (95% CI: 0.7405-0.9154). We have added these contents in the **Introduction and Results** section of our revised manuscript.

Table and figure:

Table 4. Area under the receiver operating characteristic (ROC) curve.

Model	AUC	95% CI	Sensitivity	Specificity
Five-factors	0.867	0.788 to 0.945	0.900	0.786
MSKCC	0.754	0.646 to 0.862	0.925	0.595
External validation	0.727	0.576 to 0.878	0.556	0.895
All without Z-0011	0.828	0.741 to 0.915	0.881	0.682

Abbreviations: All without Z-0011, the patients in original and validation cohort who do not meet the

criteria of the Z-0011 trial; AUC, area under the receiver operating characteristics curve; CI, confidence interval.
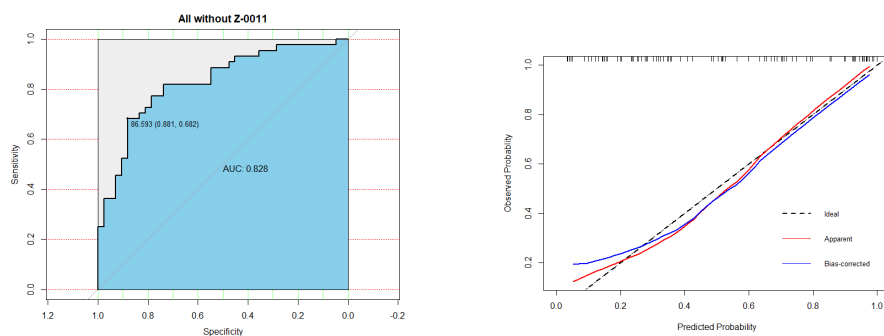

Figure 6. Receiver operating characteristic (ROC) curve (A) and calibration curve (B) for all the patients who do not meet the criteria of the Z-0011 trial.

Changes in the text:

Introduction, paragraph 2:

Management of early breast cancer (cT1-2N0M0) met a new stage, following the development of adjuvant therapy. The American College of Surgeons Oncology Group Z-0011 trial further changed the status of ALND. The early-stage patients with SLNB and standard adjuvant therapy would obtain favorable prognosis, even if harboring a few involved sentinel lymph nodes (SLN)(6). Thus, patients with 1-2 SLN metastases would suffer less ALND and fewer complications, who have undergone breast-conserving surgery and are scheduled to receive postoperative systemic therapy and radiation therapy. However, the necessity of complete ALND is under debate in those who underwent total mastectomy with the willingness of radiotherapy or breast-conserving surgery with three or more SLN metastases. A tool to demonstrate which patients cannot omit ALND may be needed, especially for the patients who do not meet the criteria of the Z-0011 trial.

Results, paragraph 7:

Each patient's information from the external validation cohort was calculated with the five-factor nomogram for performing validation of the predictive model. The ROC curve and the calibration curve was given in Figure 5. The external validation AUC was 0.727 (95% CI = 0.5763 to 0.8779, Table 4), and the consistency between actual observation and predicted probability was good. The accuracy of the prediction in patients who do not meet the criteria of the Z-0011 trial was evaluated. The ROC curve and calibration curve are drawn in Figure 6, and the AUC is 0.828 (95% CI: 0.7405-0.9154, Table 4).

2) How did the authors measure the resected tumor size intraoperatively? If they measured the resected tumor size by US, why was there no significant difference in preoperative clinical tumor size in US (1.90 cm vs 1.80 cm, p=0.863), but a significant difference in the resected tumor size (2.00 cm vs 2.50 cm, p=0.004)?

Reply 2): This is a very important and valuable suggestion which really make our manuscript more accurate. The resected tumor size was defined according to the widest diameter of the largest tumor, and calipers measured the maximum section width during operation. Tumors are usually irregular rather than standard spherical, which makes ultrasound measurements more difficult. Thus, the resected tumor size is more accurate than clinical tumor size in US. On the

other hand, it is easy for the resected size to be obtained during operation, compared with pathological size. In summary, we decided to use the resected tumor size to describe the size of tumors. We have added these contents in the **Materials and Methods and Discussions** section of our revised manuscript.

Changes in the text:

Materials and Methods, paragraph 5:

The resected tumor size was defined according to the widest diameter of the largest tumor, and calipers measured the maximum section width during the operation. The tumor size in ultrasound (US) and the pathologic tumor size were reported by authoritative ultrasonographers and pathologists.

Discussions, paragraph 4:

Number of positive SLNs and of negative SLNs were powerful risk predictive factors, which included in nearly all the previously published models(7-9, 21, 22). In our nomogram, number of positive SLNs made a significant contribution, due to the length of the line in Figure 1. Age was included in previous models as a protective predictor, which is consistent with this study(21, 22). Age here was divided into two groups based on two following reasons. On the one hand, neither age > 50-year nor menopause status was confirmed as an independent predictor of non-SLN metastases in previous models(21, 22, 28). On another hand, the elder patients would hardly tolerate ALND and its adverse effects and omitting ALND may not affect their OS benefits. In our model, size of resected tumor was chosen as a predictive factor. Tumors are usually irregular rather than standard spherical, which makes ultrasound measurements more difficult. Thus, the resected tumor size is more accurate than clinical tumor size in US. On the other hand, it is easy for the resected size to be obtained during operation, compared with pathological size. In present study, there were no significant differences in resected positive SLN size. It was acceptable for accidental omission of micrometastasis in frozen section.

3) According to Figure 1, patients aged 65 years were assigned more than 20 points. However, Table 3 shows that Age (≥65 years) has an odds ratio=0.171, p=0.032, which means that age 65 years was not a risk factor. Please clarify this discrepancy.

Reply 3): We fully appreciate your concerns. Age was a protective predictor in our five-factor nomogram. In our study, we found that women >65 years old appear to have a lower risk of non-SLN involvement, which is consistent with previous studies(1-2). Caywoodh et al. found that older patients(>66 years) were 45% less likely to have SLN metastasis than younger patients, and there was a steady decline in the rates of SLN metastasis with increasing age(3). In our opinion, the older patients have more risks and complications and would hardly tolerate ALND and its adverse effects and omitting ALND may not affect their OS benefits.

References:

1. J. BEVILACQUA, M. KATTAN, J. FEY, H. CODY, P. BORGEN and K. VAN ZEE: Doctor, What Are My Chances of Having a Positive Sentinel Node? A Validated Nomogram for Risk Estimation. J. Clin. Oncol., 25(24), 3670-3679 (2007) doi:10.1200/JCO.2006.08.8013.

2. J. Chen, J. Chen, B. Yang, Z. Liu, X. Huang, G. Liu, Q. Han, W. Yang, Z. Shen, Z. Shao and J. Wu: Predicting sentinel lymph node metastasis in a Chinese breast cancer population: assessment of an existing nomogram and a new predictive nomogram. Breast Cancer Res. Tr., 135(3), 839-848 (2012) doi:10.1007/s10549-012-2219-x.

3. J. Caywood, R. Gray, J. Hentz, B. Pockaj: Older age independently predicts a lower risk of sentinel lymph node metastasis in breast cancer. Ann Surg Oncol., 12(12), 1061-1065 (2005). doi: 10.1245/ASO.2005.02.013.

4) In the Results section, the authors did not describe a statistical comparison of the AUC value of the five-factor model to the AUC value of the MSKCC model. However, in the Abstract section, they described "The AUC was 0.867 in our nomogram, which was significantly higher than that of the MSKCC model." How did they confirm the statistical significance between the two models? If a statistical comparison was made, please describe the results in the Results section.

Reply 4): This is a very valuable suggestion which really make our manuscript more accurate. We used AUC and decision curve analyses (DCA) to compare our five-factor model with MSKCC model (see in Figure 3-4). The ROC curves were drawn in Figure 3. The five-factor model gained an AUC of 0.867 (95% CI: 0.7878-0.9455, Table 4), whereas the MSKCC model gained 0.754 (95% CI: 0.6464 to 0.8620, Table 4) (see in Results, paragraph 4). The DCA of the models was drawn in Figure 4.

5) Please provide the result of the number of positive non-SLN in Table 1 and 2.

Reply 5): We fully appreciate your concerns. We have added these contents in the **Table 1 and 2** of our revised manuscript.

6) Please describe the result of the Hosmer-Lemeshow test in the validation cohort (Chi-square value and p-value).

Reply 6): Thank you very much for your constructive comments which could enrich our manuscript. We have added these contents in the **Results** section of our revised manuscript.

Results, paragraph 3:

A nomogram model named five-factor was developed in Figure 1. The calibration curve was generated by 1,000 times resample via the bootstrap method for predicting value of the nomogram for non-SLN metastases. The calibration curve exhibited good consistency between actual observation and predicted probability (Figure 2). The Hosmer-Lemeshow test also showed a nonsignificant goodness of fit in the nomogram (Chi-square = 8.2236, P = 0.4119).

7) Regarding with ethics approval and consent to participate, please describe the approval number of this study. Also, please describe about the consent to participate.

Reply 7): We fully appreciate your concerns. Informed consent was waived because of the nature of retrospective study, and the patient data were kept confidentially. We have added these contents in the **Declarations** section of our revised manuscript.

Declarations, paragraph 1:

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. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Informed consent was waived because of the nature of retrospective study, and the patient data were kept confidentially.

8) Please provide a definition of "resected tumor size" in the Materials and Methods section, not in the Discussion section.

Reply 8): Thank you very much for your constructive comments which could enrich our manuscript. We have added these contents in the **Materials and Methods** section of our revised manuscript.

Changes in the text:

Materials and Methods, paragraph 5:

The resected tumor size was defined according to the widest diameter of the largest tumor during the operation. The tumor size in ultrasound (US) and the pathologic tumor size were reported by authoritative ultrasonographers and pathologists.

9) In the Discussion section, the authors described "In our study, no statistically significant relations were detected between molecular subtypes and non-SLNs metastases. The AUC of the model including molecular subtypes was 0.870, which was similar to our initial model." However, there was no description about molecular subtypes in the Results section nor Tables.

Reply 9): We appreciate your concerns. As you mentioned, there was no description about molecular subtypes in the Results section nor Tables. Thus, we have carefully considered your proposal. We did not descript about molecular subtypes in the results section, due to there were no statistically significant relations between molecular subtypes and non-SLNs metastases in our study. We have deleted these contents in the **Discussions** section of our revised manuscript.

10) In the Discussion section, the authors described "After reviewing the previous models, we found molecular subtypes were not included in most of them." Please add the references of the "previous models".

Reply 10): Thank you for your constructive comments. As stated in the ninth question, we have deleted these contents in the **Discussions** section of our revised manuscript.

Reviewer B

1) Table 1, please indicate how data are presented in the table.

Age (year)				0.098
≤65 years	29 (70.7%)	36 (85.7%)	65 (78.3%)	
>65 years	12 (29.3%)	6 (14.3%)	18 (21.7%)	
BMI (kg / m^2)	25.00 ± 4.24	24.21 ± 3.05	24.59 ± 3.67	0.221
Type of surgery				0.006

No. of positive non-SLN [M (Q_1, Q_3)]		4.5 (1,9)		
Resected positive SLN size (cm)	1.48 ± 0.52	1.58 ± 0.60	1.53 ± 0.56	0.399
Resected tumor size (cm) [M (Q_1, Q_3)]	2.00 (1.80,2.50)	2.50 (2.10,3.30)	2.20 (1.80,3.00)	0.004

2) Table 2, please indicate how data are presented in the table.

Age (year)			
≤65 years	22 (81.5%)	15 (78.9%)	37 (80.4%)
>65 years	5 (18.5%)	4 (21.1%)	9 (19.6%)
BMI (kg / m^2)	26.03 ± 4.58	25.23 ± 3.56	25.70 ± 4.16
Type of surgery			

3) table 4, please check the number circled to see if any adjustments should be made.

203   The ROC curves were drawn in Figure 3. The five-factor model gained an AUC of

204   0.867 (95% CI: 0.7878-0.9455, Table 4), whereas the MSKCC model gained 0.754

Table 4. Area under the receiver operating characteristic (ROC) curve.

Model	AUC	95% CI	Sensitivity	Specificity
Five-factors	0.867	0.788 to 0.945	0.900	0.786
MSKCC	0.754	0.646 to 0.862	0.925	0.595

4) All abbreviations in tables and figures should be explained in table footnote and figure legends.

Answer: Thank you for the reminder. We have indicated how data are presented in the table 1 and 2, and revised the manuscript about the number circled in Line 204.