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Preoperative Computed Tomography Radiomics Analysis for Predicting Receptors Status and Ki-67 Levels in Breast Cancer

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Background: To assess the prediction performance of preoperative chest computed tomography (CT) based radiomics features for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 ($HER2^+$), and Ki-67 status of breast cancer.

Materials and Methods: This study enrolled 108 breast cancer patients who received preoperative chest CT examinations in our institution from July 2018 to January 2020. Radiomics features were separately extracted from nonenhanced, arterial, and portal-venous phases CT images. The least absolute shrinkage and selection operator logistic regression was used for feature selection. Then the radiomics signatures for each phase and a combined model of 3 phases were built. Finally, the receiver operating characteristic curves and calibration curves were used to confirm the performance of the radiomics signatures and combined model. In addition, the decision curves were performed to estimate the clinical usefulness of the combined model.

Results: The 20 most predictive features were finally selected to build radiomics signatures for each phase. The combined model achieved the overall best performance than using either of the nonenhanced, arterial and portal-venous phases alone, achieving an area under the receiver operating characteristic curve of 0.870 for ER^+ versus ER^-, 0.797 for PR^+ versus PR^-, 0.881 for $HER2^+$ versus $HER2^-$, and 0.726 for Ki-67. The decision curve demonstrated that the CT-based radiomics features were clinically useful.

Conclusion: This study indicated preopreative chest CT radiomics analysis might be able to assess ER, PR, $HER2^+$, and Ki-67 status of breast cancer. The findings need further to be verified in future larger studies.

Key Words: radiomics, computed tomography, breast cancer, receptors

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Breast cancer is the most frequently occurring female malignancy in the world, and, is the second leading cause of cancer deaths among women after lung cancer.[1] According to immunohistochemistry (IHC) or gene expression profiling, breast cancer is classified into several different subtypes which mainly include 4 clinically relevant molecular subtypes: luminal A, luminal B, human epidermal growth factor receptor-2 (HER2) overexpression, and triple-negative (TN) breast cancer.[2–4] Different molecular subtypes have distinct clinical behaviors, therapy methods, treatment responses, and prognoses in clinical practice. Compared with the luminal B subtype, the luminal A subtypes are inclined to be indolent, are more endocrine sensitive, have a better prognosis, and most patients are able to avoid postoperative chemotherapy and only receive adjuvant endocrine therapy.[5] Moreover, neoadjuvant chemotherapy is less effective in some luminal breast cancer patients who need neoadjuvant treatments, and neoadjuvant endocrine therapy should be considered. Meanwhile, patients with TN subtypes who have a worse prognosis, are more sensitive to neoadjuvant chemotherapy and are more likely to achieve a complete pathologic response than luminal cancers,[6–9] whereas most patients with TN breast cancer may undergo adjuvant chemotherapy.[10] Patients with HER2-overexpression can benefit significantly from HER2-targeted therapies.[11,12] Therefore, accurate molecular subtyping is critical for individualized treatment and prognosis evaluation of breast cancer. IHC from postoperative excision samples is the gold standard for breast cancer classification in most hospitals. This said, particularly in patients who are to receive neoadjuvant therapy, it is necessary to accurately carry out the molecular classification before surgery. If the assessment of pretreatment molecular subtypes is inaccurate, the treatment may be ineffective, and the patient may suffer unnecessary side effects of treatment.

Currently, pretreatment molecular subtypes are routinely assessed by IHC on the formalin-fixed paraffin-embedded tissue samples which are obtained from core needle biopsies (CNB).[13,14] It is an invasive procedure and has some limitations. On the 1 hand, the specimen which consists of 4 to 6 pieces of tissue acquired by CNB may not be completely representative of the genetic, epigenetic, and/or phenotypic alterations of the entire tumor.[15,16] Furthermore, IHC results, which are subjectively visually interpreted can lead to mistakes at the cutoff values.[17] A meta-analysis[18] showed that the concordance rates of estrogen receptor (ER) and progesterone receptor (PR) staining between core needle biopsy specimens and excision specimens were 77.7% to 80%($\kappa = 0.52$ to 0.88) and 66.2% to 69.5% ($\kappa = 0.06$ to 0.85). A recent study with the largest sample size showed the concordance rates of ER, PR, HER2 and Ki-67 staining between core needle biopsy specimens and excision specimens were 78.8% ($\kappa = 0.522$), 73.5% ($\kappa = 0.441$), 56% ($\kappa = 0.392$) and 59% ($\kappa = 0.360$), respectively.[19] Therefore, we attempted to explore whether there is an alternative noninvasive method to more accurately predict the total tumor characteristics.

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The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Each patient gave written informed consent and the study protocol was approved by the Clinical Research and Biomedical Ethical Committee of West China Hospital, Sichuan University (Approved No. of ethic committee: 2020-177).

The authors declare no conflicts of interest.

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Radiomics, which can extract large amounts of high-dimensional features from multimodality medical images to provide quantitative and objective support for diagnosis, prognosis, and prediction, especially in oncology,[20–22] are a rapidly developing form of image analysis. Previous studies[23–25] have shown that radiomics features from magnetic resonance imaging (MRI) or simultaneous positron emission tomography (PET) can potentially be used to assess ER/PR receptor states and molecular subtypes of breast cancer. However, MRI or PET is time-consuming and costly, and PET has not been recommended for routine clinical breast examinations at the guideline. Computed tomography (CT) images can be obtained in a quick scanning time and more cheaply than MRI or PET images. Chest CT is recommended.[26] The initial purpose of chest CT is to assess the stage of the disease, which is different from mammography, ultrasound for breast cancer according to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines, and MRI in breast lesions. Several studies have demonstrated the value of CT radiomics analysis in the evaluation of clinical breast cancer characteristics. Yang et al[27] demonstrated that radiomics CT analyses could help clinicians predict sentinel lymph node metastasis in patients with breast cancer. However, the role of CT radiomics signatures in predicting the histopathological features of breast cancers has rarely been investigated. Breast cancer molecular subtype is determined by the status of ER, PR, and HER2, as well as Ki-67 levels. We assumed that CT radiomics methods can be used to assess the status of ER, PR, HER2, and Ki-67 in patients with breast cancer.

The aim of this study was to investigate whether radiomics features extracted from preoperative chest CT images could be useful in predicting the status of ER, PR, HER2, and Ki-67 in patients with breast cancer.

MATERIALS AND METHODS

Patients

This prospective study involving standard care was performed in West China Hospital, at Sichuan University. Ethical approval was obtained for this prospective analysis, and all patients signed the informed consent. Patients were enrolled in our study between July 2018 and January 2020. All patients underwent a chest CT examination before surgery. The inclusion criteria were: (1) at an age older than 18 years, (2) CNB-proven invasive breast cancer; (2) no pregnancy or breast-feeding; (3) patients were scheduled to undergo surgery within 2 weeks; (4) they were all female; (5) had a single lesion. The exclusion criteria were as follows: (1) standard contraindications to CT and/or allergy to contrast agent injection; (2) previous oncological disease; (3) tumor diameter under 1 mm.

Pathologic Evaluation

IHC was used to assess the status of ER, PR, HER2, and the Ki-67 index. A cutoff value of 1% was used to define ER and PR positivity.[28] HER2 expression was initially assessed by IHC staining (IHC staining of 0 or 1^+ was defined as $HER2^-$ whereas tumors with IHC staining of 3^+ were defined as $HER2^+$), and tumors with an IHC staining value of 2^+ were further assessed by fluorescence in situ hybridization (nonamplified results were considered $HER2^-$ and amplified results were considered $HER2^+$). According to the 2013 St. Gallen Consensus Recommendations, the cut-point of the Ki-67 index was set to 20%.[3] The excision specimen was considered the standard of reference for histologic analysis. Three breast pathologists with at least 10 years of breast pathology experience in our institution interpreted the IHC results.

CT Imaging Acquisition and Region of Interest (ROI) Segmentation

The imaging analysis and data processing workflow are illustrated in Figure 1.

All patients underwent a 64-slice multidetector spiral chest CT examination preoperatively using a Somatom Definition Flash CT scanner. After a nonenhanced (NE) CT scan, 80 mL to 100 mL of iodinated contrast agent (Omnipaque 350 mgI/mL, GE Healthcare) was injected using a power injection at a flow rate of 3.0 mL/s. The arterial phase (AP) and portal-venous phase (PVP) images were obtained with a postinjection delay of the

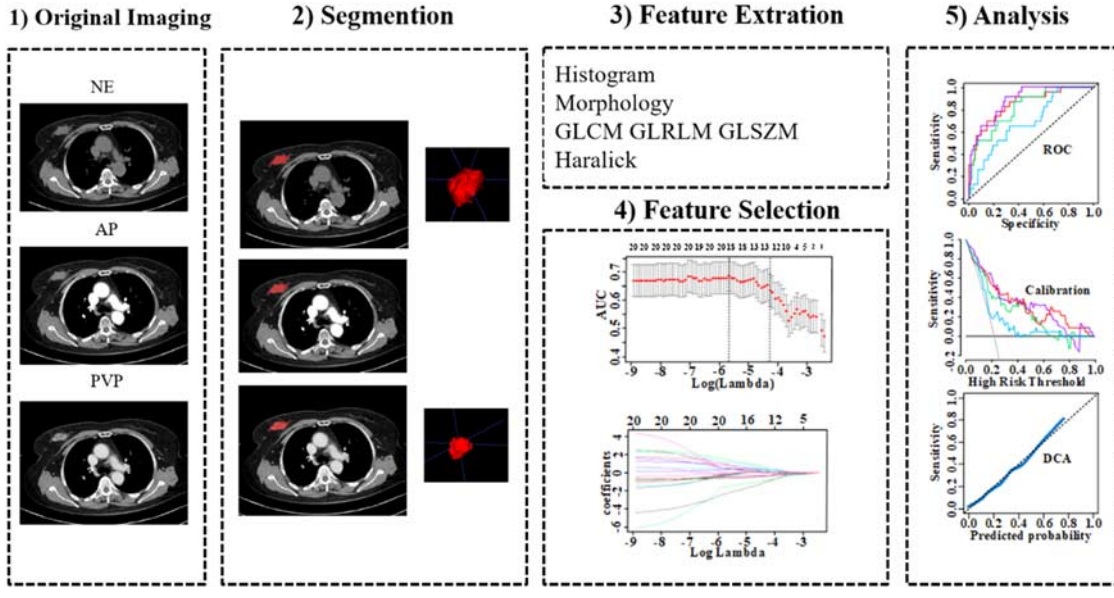

FIGURE 1. Radiomic workflow. AP indicates arterial-phase imaging; DCA, decision curve analysis; GLCM, gray-level cooccurrence matrix; GLRLM, gray-level run-length matrix; GLSZM, gray-level size zone matrix; NE, nonenhanced images; PVP, portal-venous phase imaging. full color online

30s, and 60s, respectively. The slice thickness of the reconstructed images was 1.0 mm. A 3-dimensional ROIs segmentation was conducted by ITK-SNAP (version 3.6.0, http://www.itksnap.org). Two radiologists (P.X.L. and Y.F., with 12 and 9 years of experience in chest imaging, respectively) delineated the ROIs separately in the images of NE, AP, and PVP along the area of maximal tumor extension layer-by-layer, avoiding necrosis, air, and calcification areas. The 2 radiologists delineated the ROIs independently and if their results were inconsistent, a third senior radiologist arbitrated and helped reach an agreement.

Radiomics Features Extraction

AK software (GE Healthcare, version 3.2.5) was used to extract radiomics features from each segmented ROI. All image analyses and calculations were performed separately for NE, AP, and PVP CT images. The consistency and reproducibility of the intra and interobserver agreement of the radiomics features were assessed by intra and interclass correlation coefficients (ICC). Two radiologists (P.X.L. and Y.F.) initially delineated the ROI for 20 random CT images. P.X.L. repeated the same procedure 1 week later. An ICC >0.75 was considered reflective of good reproducibility and consistency.

Feature Selection and Radiomics Signatures Construction

An ICC value >0.75 of radiomics features was selected for further data analysis. The reserved radiomics features were preprocessed by replacing missing values with median values, *z*-score normalizing, and deleting features with zero variance. To overcome overfitting, a least absolute shrinkage and selection operator (LASSO) logistic regression method with 10-fold cross-validation was applied for further feature selection. The features with nonzero coefficients were further selected by stepwise regression analysis with the minimum Akaike Information Criterion. According to their respective LASSO coefficients, a radiomics score (Rad-score) was calculated for each patient through a linear combination of selected features. The radiomics signature (Rad-score) of the NE Rad-score, AP Rad-score, and PVP Rad-score was constructed using selected features based on the logistic regression coefficients to predict the status of ER, PR, HER2, and Ki-67 levels. In addition, the combination model was also constructed using the Rad-scores of such 3 phases.

Assessment of Signatures and Model Performance

The discrimination performance of the radiomics signatures and model was quantified by calculating the area under the receiver-operator characteristic (ROC) curve (AUC) with 5-fold cross-validation. Thereafter, the calculation of radiomics signatures and prediction model was assessed with a calibration curve. Decision curve analysis (DCA) curves were measured to assess clinical benefits.

Statistical Analysis

A 2-sided Mann-Whitney *U* test was used for continuous variables and 2 independent samples *t* tests were used for categorical variables. The Delong test examined the differences in predictive performance between the combined model and the radiomics signatures. All these statistical analyses were conducted in SPSS Software (Version 25, IBM) and R software (Version: 3.5.3, https://www.r-project.org). The following R packages were mainly utilized: "glmnet" for logistic regression including the LASSO algorithm, "pROC" for ROC analyses, and "rmda" for DCA. A *P*-value under 0.05 was considered statistically significant.

RESULTS

Patients Characteristics

A total of 158 patients met our study criteria. Fifty patients were excluded for pathology results demonstrating types of cancer other than invasive carcinoma, before treatment and incomplete IHC reports. The study eventually enrolled 108 breast cancer patients (with a mean age of 53 years old, ranging from 32 to 85). The patients' clinicopathological characteristics are provided in Table 1.

Radiomicss Analysis

A total of 396 radiomics features were extracted from each CT image (NE, AP, and PVP images), including the following features: (1) 42 histogram features; (2) 9 morphologic features; (3) 144 gray-level cooccurrence matrix features; (4) 180 gray-level run-length matrix features; (5) 11 gray-level size zone matrix features; and (6) 10 haralick features. Of these features, 20 features with a potential predictive value were finally selected through the LASSO method. The intraobserver ICCs ranged from 0.796 to 0.893 and the interobserver ICCs ranged from 0.819 to 0.926, both achieving satisfying feature extraction reproducibility. The Rad-score for each patient was calculated by a linear calculation formula. There were significant differences among the Rad-scores of ER, PR, HER2 receptors, and Ki-67 levels ($P<0.01$).

Radiomics Signatures of ER, PR, HER2, and Ki-67 at Nonenhanced, Arterial and Portal-venous Phases, and the Combined Model

The combined model demonstrated better performance for the prediction of breast cancer molecular subtypes related indicators than each of the 3 radiomics signatures, as shown in Figure 2. Table 2 summarizes the ROC analysis results in a combined model.

TABLE 1. Clinical Characteristic of Patients

Characteristic	All patients, N = 108
Age (y), mean (range)	53 (32-85)
BMI	23.6 (17.6-34.4)
Menopausal, n	
Premenopausal	43
Postmenopausal	65
Tumor type, n	
Ductal carcinoma	95
Lobular carcinoma	7
Mucinous carcinoma	3
Endocrine carcinoma	1
Mixed carcinoma	2
Tumor size (cm), mean (range)	2.4 (0.6-9.0)
Axial lymph nodes, n	
Positive	38
Negative	70
Receptor status, n	
ER+	83
ER-	25
PR+	75
PR-	33
HER+	23
HER-	85
Ki-67, n	
$<20\%$	40
$\geq 20\%$	68

BMI indicates body mass index; ER, estrogen receptor; HER, human epidermal growth factor receptor; PR, progesterone receptor.

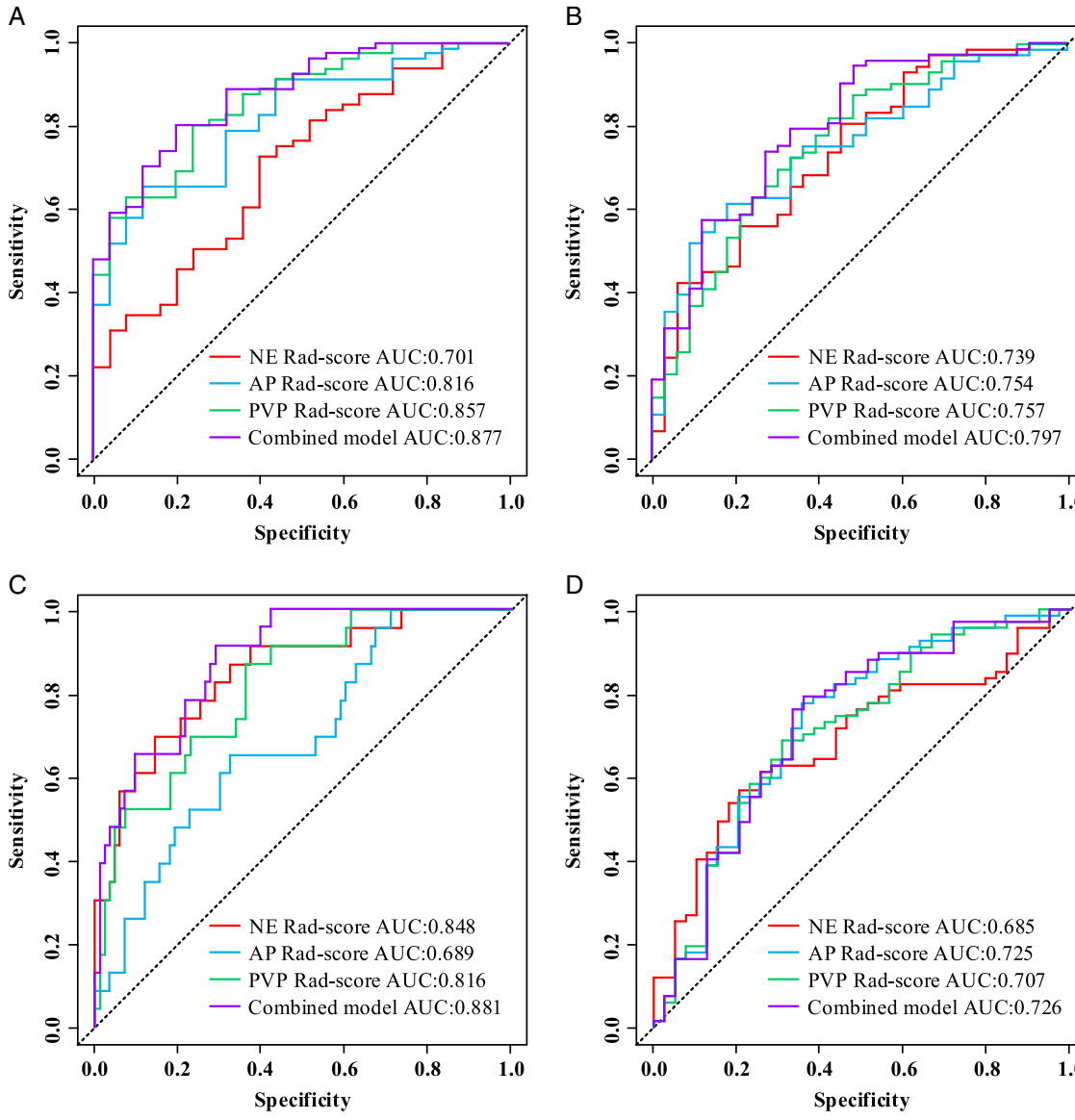

FIGURE 2. Receiver-operator characteristic curve analysis showing the ability of each Rad-score and combined model to discriminate among receptors statue and Ki-67 level of breast cancer: (A) ER$^+$ versus ER$^-$, (B) PR$^+$ versus PR$^-$, (C) HER2$^+$ versus HER2$^-$, (D) high Ki-67 versus low Ki-67. full color online

For the assessment of ER state (ER$^+$ vs ER$^-$), we obtained the following prediction accuracies: AUC values were 0.701 (95% CI, 0.526-0.770, based on NE images), 0.816 (95% CI, 0.730-0.903, based on AP images), 0.857 (95% CI, 0.780-0.934, based on PVP images), and 0.877 (95% CI, 0.749-0.942, based on the combination of the 3), respectively.

For the assessment of PR state (PR$^+$ vs PR$^-$), we obtained the following prediction accuracies: AUC values were 0.739 (95% CI, 0.637-0.841, based on unenhanced images), 0.754 (95% CI, 0.659-0.850, based on AP images), 0.757 (95% CI, 0.656-0.858, based on PVP images), and 0.797 (95% CI, 0.704-0.917 based on the combination of the 3), respectively.

TABLE 2. The Diagnostic Performance of Combinated Model

Set	AUC	Sensitivity (95% CI)	Specificity (95% CI)	Cutoff value
ER	0.870	0.60 (0.496-0.704)	0.92 (0.739-0.989)	> 1.955349099
PR	0.797	0.74 (0.628-0.827)	0.70 (0.525-0.828)	> 0.900829986
HER2	0.881	0.91 (0.720-0.988)	0.70 (0.593-0.737)	>−1.437605357
Ki-67	0.726	0.79 (0.678-0.833)	0.62 (0.459-0.751)	> 0.063262441

AUC indicates area under the ROC curve; ER, estrogen receptor; HER, human epidermal growth factor receptor; PR, progesterone receptor.

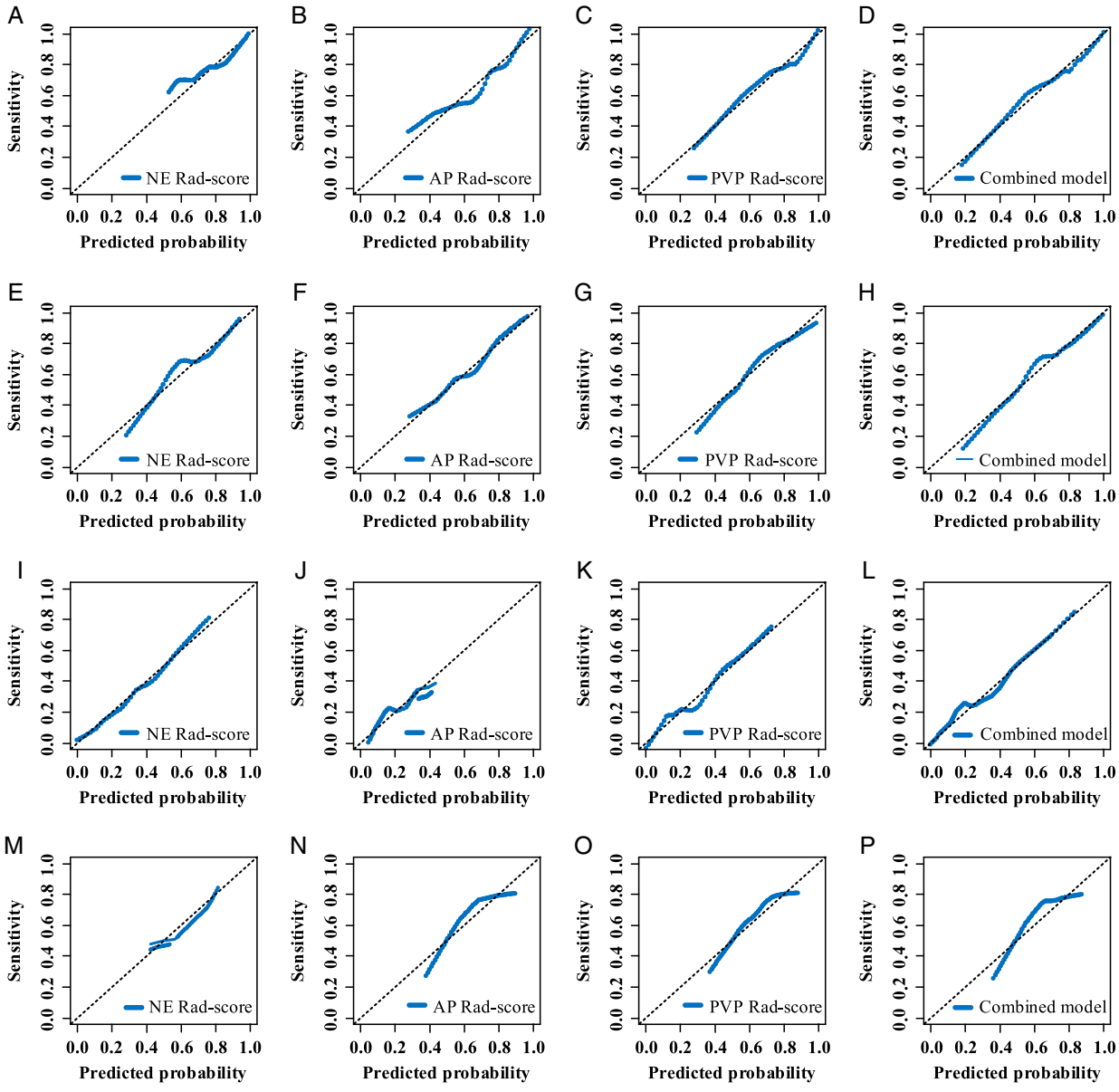

FIGURE 3. Calibration curves of each Rad-score and combined model (from left to right in each row are NE, AP, and PVP Rad-score and model). A–D, ER^+ versus ER^-, (E–H) PR^+ versus PR^-, (I–L) $HER2^+$ versus $HER2^-$, (M–P) high Ki-67 versus low Ki-67. Calibration curves indicate the calibration of the Rad-score and combined model in terms of the agreement between the predicted value and the IHC results. The 45 degrees gray line represents a perfect prediction and the blue lines represent the predictive performance. The closer the blue line fit is to the ideal line, the better the predictive accuracy is. full color online

For the assessment of the HER2 state ($HER2^+$ vs $HER2^-$), we obtained the following prediction accuracies: AUC values were 0.848 (95% CI, 0.757-0.939, based on unenhanced images), 0. 689 (95% CI, 0.570-0.807, based on AP images), 0.816 (95% CI, 0.724-0.909, based on PVP images), and 0.881 (95% CI, 0.812-0.921 based on the combination of the 3), respectively.

For the recognition of Ki-67 levels (high and low Ki-67 proliferation), we obtained the following prediction accuracies: AUC values were 0.685 (95% CI, 0.582-0.787, based on NE images), 0.725 (95% CI, 0.619-0.830, based on AP images), 0.707 (95% CI, 0.601-0.813, based on PVP images), and 0.726 (95% CI, 0.657-0.859 based on the combination of the 3), respectively.

The calibration curve for the 3 radiomics signatures and the combined model is shown in Figure 3. The DCA is presented in Figure 4.

DISCUSSION

Breast cancer is a heterogeneous disease with different prognoses, treatment protocols, and treatment responses based on tumor subtypes.[7,13,14] It is fundamental to accurately assess the statuses of ER, PR, HER2, and Ki-67 of pretreatment breast cancer patients as they form the basis for the discrimination of different molecular subtypes. In this study, we assessed the availability of radiomics features from preoperative chest CT

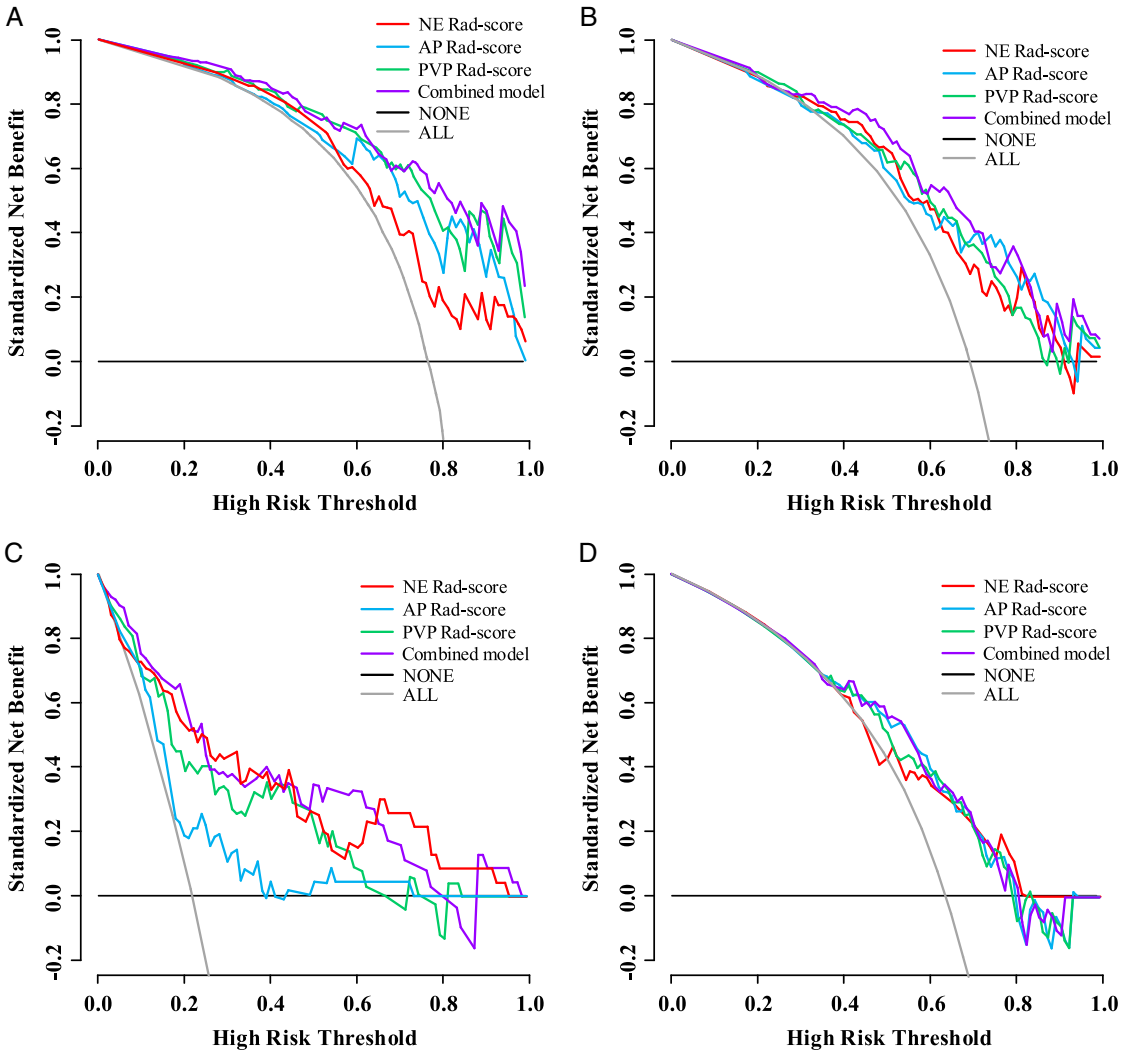

FIGURE 4. DCA for the Rad-scores and combined model. A, ER$^+$ versus ER$^-$, (B) PR$^+$ versus PR$^-$, (C) HER2$^+$ versus HER2$^-$, (D) high Ki-67 versus low Ki-67. full color online

images to noninvasively evaluate breast cancer molecular subtypes related indicators without additional radiation exposure and cost. The best results were obtained for the discrimination of ER$^+$ versus ER$^-$ (AUC, 0.870) and HER2$^+$ versus HER2$^-$ (0.881) by the combined model in our preliminary study.

Previous studies have shown radiomics biomarkers associated with the histologic characteristics of breast cancer.[23–25,29,30] Ma et al[29] respectively selected 11, 10, and 12 radiomics features in 331 breast cancer cases from a craniocaudal view, mediolateral oblique view, and the combination thereof mammogram images using the LASSO method, finding that the AUCs for TN versus non-TN, HER2-enriched versus non-HER2-enriched luminal versus nonluminal subtypes were 0.865, 0.784, and 0.752, respectively. Guo and colleagues extracted ultrasound radiomics features from 215 breast invasive ductal carcinoma patients to distinguish hormone receptor-positive, HER2$^-$ and TN. Results showed a strong correlation with an area under the curve of 0.760.[30] Moreover, several studies[23–25] have demonstrated that MRI-based radiomics features can assess the molecular subtypes related to indicators receptor state of breast cancer. However, published studies of CT radiomics for predicting the molecular subtypes of breast cancer are rarer, our study preliminarily proves CT images can reflect potential tumor traits in helping assess breast cancer receptors from image-derived radiomics features.

Notably, radiomicss analyses in breast cancer are almost exclusively dominated by MRIs at present, yielding encouraging results.[23,25] However, due to the nature of MRI scanning, which is costly and limited in its availability, or patient ineligibility (pacemakers, metallic implants, claustrophobia, and renal insufficiency), it remains an inappropriate choice for some women. Currently, the NCCN for breast cancer recommends that patients with stage III to IV disease typically need to undergo CT or PET/CT imaging and that early-stage patients with pulmonary symptoms undergo a chest CT.[26] Importantly, it states that there are many other causes (eg, chest pain) in many patients that can warrant a chest CT scan. Preoperative CT examinations can assess not only the extent of the lesion, but also the skin, chest wall, regional lymph nodes, distant organs, and bone metastases, which play a vital role in breast cancer management and have been increasingly performed in clinical practice in our institution. CT is different from MRI as

regards potential imaging traits that they can be readily accessible, our study showed CT-based radiomics analyses could be performed to noninvasively obtain data that could help evaluate breast cancer molecular subtypes related indicators. Besides, these radiomics features are extracted from routine preoperative chest CT, which would not impose extra financial costs and radiation exposure to the patients.

Previous studies have attempted to assess the correlation between ER and PR status and radiomics features, especially using MRI scanning. Saha et al[25] used a machine learning approach based on MRI radiomics features to predict the ER and PR status in 922 patients, yielding an AUC of 0.649 and 0.622, respectively. Castaldo et al[31] achieved excellent results for the differentiation of ER^+ versus ER^- (0.86) and PR^+ versus PR^- (0.93) statuses using 3 machine learning techniques based-MRI radiomics features from the Cancer Imaging Archive. We also achieved favorable results in predicting ER^+ versus ER^- and PR^+ versus PR^- status, yielding an AUC of 0.870 and 0.797, respectively. Our results show that ER and PR status may be discriminated by CT-based radiomics features.

A recent study by Yang et al[27] reported AUCs of 0.829 for predicting HER2 status in breast cancer based on preoperative multidetector CT radiomics features. Compared with their research, although we did not independently validate our results, the AUC was higher than that of their study on HER2 status prediction (AUC, 0.881). Considering the sample size, we used a cross-validation method, which has been applied in multiple studies in this field, without further dividing our population into a training and validation cohort.[24]

Ki-67 not only forms the basis of molecular subtypes discrimination but is also an independent predictor of prognoses and treatment responses in breast cancer patients.[3,7] Many studies have reported that radiomics features were correlated with Ki-67 levels. Zhang et al[32] and Liang et al[33] showed that the Ki-67 levels in breast cancer patients can be predicted by MRI-based radiomics features, with an AUC of 0.750 and 0.762, respectively. Similar to Zhang, we used a 3-dimensional analysis of the entire tumor, which allows for the complete assessment of the heterogeneity of breast cancer tumors. To the best of our knowledge, no research has assessed the relationship between CT image information and Ki-67 levels. Our results demonstrated differentiation of low Ki-67 proliferation from high Ki-67 proliferation with an AUC of 0.726 based on the combination of the 3.

In addition, we compared the abilities of NE, AP, and PVP radiomics imaging signatures and the combination thereof in predicting breast cancer molecular subtypes related indicators in this study. The best results were achieved for the differentiation of ER^+ versus ER^- (AUC 0.870), PR^+ versus PR^- (0.797), $HER2^+$ versus $HER2^-$ (0.881), and high Ki-67 versus low Ki-67 (0.726) in the combination. Our results showed that the combination of the 3 images enabled a better performance, likely due to the fact that the 3 images together were able to provide more information.

Our study has some limitations. First, this was a small sample study carried out in a single institution, which lacked external validation. Some of our results might be the product of overfitting as the dataset is relatively small. We tried to minimize the risk of overfitting by feature normalization[31] and selection by LASSO.[34] It is necessary to recruit more patients from additional medical centers to confirm these results in clinical practice. At present, we are also actively carrying out this work. Second, all of our imaging data originated from the same CT machine. We will assess the robustness of our methods on various imaging data obtained from different machines in the future. Moreover, the ROI was manually drawn by an expert radiologist based on favorable ICC. Although many previous studies[28,30] have achieved good results by manually drawing ROIs, there remains a certain degree of inevitable interrater variability. In future studies, we will try to use semiautomatic or full-automatic methods to draw the ROI to minimize unnecessary variability.

In conclusion, breast cancer receptor status may be assessed by radiomics signatures based on preoperative CT images. This noninvasive preoperative prediction method can be an important complement to biopsy. These findings need to be further assessed and confirmed in larger studies in the future.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA: Cancer J Clin*. 2022;70:7–30.
2. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature* . 2012;490:61–70.
3. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer. *Ann Oncol*. 2013;24:2206–2223.
4. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer. *Ann Oncol*. 2015;26:1533–1546.
5. Cheang MC, Chia SK, Voduc D, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. *J Natl Cancer Inst*. 2009;101:736–750.
6. Liedtke C, Rody A, Gluz O, et al. The prognostic impact of age in different molecular subtypes of breast cancer. *Breast Cancer Res Treat*. 2015;152:667–673.
7. Howlader N, Cronin KA, Kurian AW, et al. Differences in breast cancer survival by molecular subtypes in the United States. *Cancer Epidemiol Biomarkers Prev*. 2018;27:619–626.
8. Sopik V, Sun P, Narod SA. The prognostic effect of estrogen receptor status differs for younger versus older breast cancer patients. *Breast Cancer Res Treat*. 2017;165:391–402.
9. Johansson A, Trewin CB, Hjerkind KV, et al. Breast cancer-specific survival by clinical subtype after 7 years follow-up of young and elderly women in a nationwide cohort. *Int J Cancer*. 2019;144:1251–1261.
10. Lluch A, Barrios CH, Torrecillas L, et al. Phase III trial of adjuvant capecitabine after standard neo/adjuvant chemotherapy in patients with early triple-negative breast cancer (GEICAM/2003-11_CIBOMA/2004-01). *J Clin Oncol*. 2020;38:203–213.
11. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med*. 2019;380:617–628.
12. Goutsouliak K, Veeraraghavan J, Sethunath V, et al. Towards personalized treatment for early stage HER2-positive breast cancer. *Nat Rev Clin Oncol*. 2020;17:233–250.
13. Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. *Nat Rev Dis Primers*. 2019;5:66.
14. Ahn HJ, Jung SJ, Kim TH, et al. Differences in clinical outcomes between luminal A and B type breast cancers according to the St. Gallen Consensus 2013. *J Breast Cancer*. 2019;18:149–159.
15. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Eng J Med*. 2012;366:883–892.
16. Aerts HJ. The potential of radiomics-based phenotyping in precision medicine: a review. *JAMA Oncol*. 2016;2:1636–1642.
17. Yang X, Knopp MV. Quantifying tumor vascular heterogeneity with dynamic contrast-enhanced magnetic resonance imaging: a review. *J Biomed Biotechnol*. 2011;2011:732848.
18. Li S, Yang X, Zhang Y, et al. Assessment accuracy of core needle biopsy for hormone receptors in breast cancer: a meta-analysis. *Breast Cancer Res Treat*. 2012;135:325–334.
19. Chen J, Wang Z, Lv Q, et al. Comparison of core needle biopsy and excision specimens for the accurate evaluation of breast cancer

molecular markers: a report of 1003 cases. *Pathol Oncol Res*. 2017;23:769–775.
20. Gatenby RA, Grove O, Gillies RJ. Quantitative imaging in cancer evolution and ecology. *Radiology*. 2013;269:8–15.
21. Gillies RJ, Kinahan PE, Hricak H, et al. Radiomics: images are more than pictures, they are data. *Radiology*. 2016;278:563–577.
22. Lambin P, Leijenaar R, Deist TM, et al. Radiomicss: the bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol*. 2017;14:749–762.
23. Leithner D, Horvat JV, Marino MA, et al. Radiomics signatures with contrast-enhanced magnetic resonance imaging for the assessment of breast cancer receptor status and molecular subtypes: initial results. *Breast Cancer Res*. 2019;21:106.
24. Ozkan EE, Sengul SS, Erdogan M, et al. 18F-fluorodeoxyglucose PET/computed tomography in locoregional staging and assessment of biological and clinical aggressiveness of breast cancer subtypes. *Nucl Med Commun*. 2019;40:1043–1050.
25. Saha A, Harowicz MR, Grimm LJ, et al. A machine learning approach to radiogenomics of breast cancer: a study of 922 subjects and 529 DCE-MRI features. *Br J Cancer*. 2018;119:508–516.
26. Gradishar WJ, Anderson BO, Balassanian R, et al. NCCN guidelines insights breast cancer, version 1.2016. *J Natl Compr Canc Netw*. 2015;13:1475–1485.
27. Yang X, Wu L, Ye W, et al. Deep learning signature based on staging CT for preoperative prediction of sentinel lymph node metastasis in breast cancer. *Acad Radiol*. 2020;27:1226–1233.
28. Fujii T, Kogawa T, Dong W, et al. Revisiting the definition of estrogen receptor positivity in HER2-negative primary breast cancer. *Ann Oncol*. 2017;28:2420–2428.
29. Ma W, Zhao Y, Ji Y, et al. Breast cancer molecular subtype prediction by mammographic radiomics features. *Acad Radiol*. 2019;26:196–201.
30. Guo Y, Hu Y, Qiao M, et al. Radiomicss analysis on ultrasound for prediction of biologic behavior in breast invasive ductal carcinoma. *Clin Breast Cancer*. 2018;18:e335–e344.
31. Castaldo R, Pane K, Nicolai E, et al. The Impact of normalization approaches to automatically detect radiogenomic phenotypes characterizing breast cancer receptors status. *Cancers*. 2020;12:518.
32. Zhang Y, Zhu Y, Zhang K, et al. Invasive ductal breast cancer: preoperative predict Ki-67 index based on radiomicss of ADC maps. *Radiol Med*. 2020;125:109–116.
33. Liang C, Cheng Z, Huang Y, et al. An MRI-based radiomicss classifier for preoperative prediction of Ki-67 status in breast cancer. *Acad Radiol*. 2018;25:1111–1117.
34. Pavlou M, Ambler G, Seaman SR, et al. How to develop a more accurate risk prediction model when there are few events. *BMJ*. 2015;351:h3868.

