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Ultrasound radiomics in the assessment of breast cancer molecular subtypes: A systematic review and meta-analysis

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Abstract

Aim: Accurate prediction of preoperative molecular subtypes of breast cancer is crucial for treatment planning and prognosis evaluation of patients. This systematic review aims to investigate the capacity of ultrasound radiomics in accurately identifying the molecular subtypes of breast cancer. **Material and methods:** We conducted a thorough search of PubMed, Embase, and Cochrane databases to identify relevant research up until May 2024. We pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and the area under the curve (AUC) to summarize the ability of ultrasound radiomics to predict Luminal type and triple negative breast cancer (TNBC) type in patient with breast cancer. **Results:** Our meta-analysis found that nine studies provided ultrasound radiomics predictions for TNBC. Pooled sensitivity, specificity, and AUC were 0.64, 0.89, and 0.86, respectively. Four studies have provided the ultrasound radiomics prediction of Luminal molecular subtype breast cancer. Pooled sensitivity, specificity, and AUC were 0.89, 0.79, and 0.90, respectively. There are two studies that predict Luminal A, Luminal B and Her 2+molecular subtype by ultrasound radiology, but they cannot be synthesized quantitatively because of the small number of studies. **Conclusion:** Ultrasound radiomics has a good diagnostic performance in predicting molecular subtypes in breast cancer.

Keywords: ultrasound radiomics; breast cancer; molecular subtype

Introduction

Based on the 2022 report from GLOBOCAN, breast cancer has emerged as the leading malignant tumor affecting women globally. The number of newly diagnosed cases stands at approximately 2.3 million, resulting in 665,684 fatalities [1]. Identifying breast cancer at an early stage is crucial for timely clinical intervention and increasing survival rates [2]. Breast cancer has a high degree of heterogeneity in clinics, and different molecular subtypes have different responses to treatments and prognoses [3,4]. At present, according to the expression of biomarkers estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor -2 (HER2) and Ki-67, breast cancer in clinic can be divided into four molecular subtypes: Lumina A breast cancer (LABC), Lumina B breast cancer (LBBC), human epidermal growth factor receptor-2 overexpression breast cancer (HER2+) and triple negative breast cancer (TNBC) [5]. Luminal subtype is sensitive to hormone therapy because of its high expression of ER and PR [6]. While HER2-enriched cancers may be associated with a poorer prognosis, they can achieve effective treatment by targeting HER2 receptor proteins with drugs such as Herceptin [7]. TNBC lacks ER, PR, and HER2 receptor expression. It is known for its aggressive nature, resistance to standard treatments, high likelihood of recurrence, and unfavorable prognosis [8,9]. If the molecular subtypes of breast cancer can be determined before surgery, it can promote the development of personalized treatment plans, thereby improving the prognosis of patients. Therefore, non-invasive methods for preoperative molecular sub-

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types of breast cancer have become the focus of current study.

In clinical settings, breast cancer is classified into molecular subtypes through the analysis of immunohistochemical markers. Due to the diverse nature of breast cancer, variations exist between preoperative core needle biopsy and postoperative immunohistochemical findings [10-12]. In view of the importance and challenges of identifying molecular subtypes of breast cancer before operation, some studies have explored the relationship between breast ultrasound images and the molecular subtypes of breast cancer [13,14]. Meanwhile, with the advancement of technology, radiomics is an emerging field of medical imaging. It is a novel noninvasive method that rapidly extracts numerous quantitative features imperceptible to the naked eye from traditional medical images through deep mining of medical images. The close relationship between imaging features and potential cancer genetics may provide a biological basis for the clinical application of radiology. Radiomics includes a traditional machine learning method, which extracts quantitative information from images in a high-throughput manner, and deep learning method, a process that simulates analysis by the human brain by building neural networks [15]. Ultrasound, acknowledged for its absence of radiation, real time, and cost-effectiveness, has become a widely adopted method for the screening and diagnosis of breast cancer. Ultrasound radiomics in breast cancer is a rapidly evolving technology with significant challenges and opportunities. It is being used in various aspects of breast cancer management, including the breast diagnosis, evaluation of molecular subtype, assessment of lymph node status, prediction of neoadjuvant chemotherapy response and prediction of survival [15]. Despite the potential of ultrasound radiomics in predicting breast cancer molecular subtypes, the accuracy of current radiomics models varies significantly. This variation may be attributed to different mathematical algorithms, feature extraction methods, image preprocessing and evaluation methods. However, present systematic review focuses on magnetic resonance imaging and mammographic imaging radiomics in predicting breast cancer molecular subtypes [16,17].

Therefore, the objective of this systematic review with meta-analysis was to evaluate the diagnostic performance of ultrasound radiomics in predicting molecular subtypes in patients with breast cancer.

Material and methods

The current research was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2020) guideline.

Literature search

A thorough search was conducted on electronic databases, such as PubMed, Embase, and Cochrane, by two independent reviewers. The aim was to identify relevant studies on the use of ultrasound radiomics in predicting breast cancer molecular subtypes. The search encompassed studies published up to May 22, 2024. The search adopts the theme word or free word method, and the theme word used for the search is (Ultrasound), (Machine learning) and (Breast neoplasms).

Eligibility criteria

The eligibility criteria were established based on the PICO framework, with the following specifications: (P) individuals diagnosed with breast cancer, (I) utilization of ultrasound radiomics techniques for prediction of breast cancer related four molecular subtypes according to 2013 Expert Consensus Guidelines for St. Gallen (Luminal A, Luminal B, HER2, TNBC) [5], (C) confirmation of diagnosis through immunohistochemical assessment (preferably through surgical means), and (O) provision of adequate data to construct a 2x2 table containing true positive (TP), false positive (FP), false negative (FN), and true negative (TN) values for assessing sensitivity and specificity. Exclusion criteria were: 1. Participants did not meet the criteria for any of the molecular subtypes specified in the inclusion criterion; 2. Articles in a non-English language; 3. Review, case reports, animal research, editorial article; 4. Research does not utilize radiology methodologies.

Data extraction

The basic data from the studies were extracted utilizing a data form. Extracted data included: the first author's name, publication year, type of study, country, number of centers, ultrasound type, radiomics methods, number of patients, number of breast lesions, number of patients in each breast cancer molecular subtype. For meta-analysis, these data were extracted as well: TP, FN, TN, and FP. We only include models with optimal diagnostic performance for analysis in study.

Quality assessment

Two independent authors assessed the study quality using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool and the Radiomics Quality Score (RQS scoring system). QUADAS-2 offers a structured approach to assess bias and applicability concerns in diagnostic accuracy studies. QUADAS-2 questions were implemented in the Review Manager software, and diagrams were drawn subsequently. The RQS was used to evaluate the methodological quality of radiomics studies.

Statistical analysis

We used STATA (version 16; MIDAS module) for the meta-analysis. The pooled sensitivity, specificity,

positive likelihood ratios (PLR), negative likelihood ratios (NLR), and diagnostic odds ratio (DOR), with corresponding 95% confidence intervals (CIs), were determined to predict diagnostic accuracy. A forest plot combining sensitivity and specificity was constructed to illustrate the aggregated diagnostic performance of the radiomics investigations. The diagnostic value of the combined studies is assessed by constructing the summary receiver operating characteristic (SROC) curve and calculating the area under the curve (AUC). The AUC scores indicated the level of discrimination as follows: low discrimination for scores between 0.5 and 0.7, moderate discrimination for scores ranging from 0.7 to 0.9, and high discrimination for scores exceeding 0.9. Evaluate publication bias using Deek's funnel plot, where slope coefficients with $p<0.10$ indicated significant publication bias. The clinical utility of ultrasound radiomics in predicting breast cancer molecular subtypes was evaluated with Fagan plot analysis by indicating the posttest probability when pretest probabilities were provided.

Results

Literature search

PRISMA flowchart in figure 1 summarizes the search and selection results of the relevant studies. We searched 924 articles through the electronic database, and after eliminating 102 duplicate articles, we screened the remaining 822 articles in the next step. By reading the titles and abstracts, 777 articles were excluded. The remaining 45 articles were evaluated in full text. Among them, 34 studies were excluded due to the following reasons: 1. The subjects of 26 studies are not relevant to the molecular subtyping of breast cancer; 2. Three radiomics models contain other imaging data or clinical information; 3. Three non-English studies. 4. Two cannot extract the same units 2X2 table as those included in the study. The remaining 11 studies were included in the meta-analysis [11,18-27].

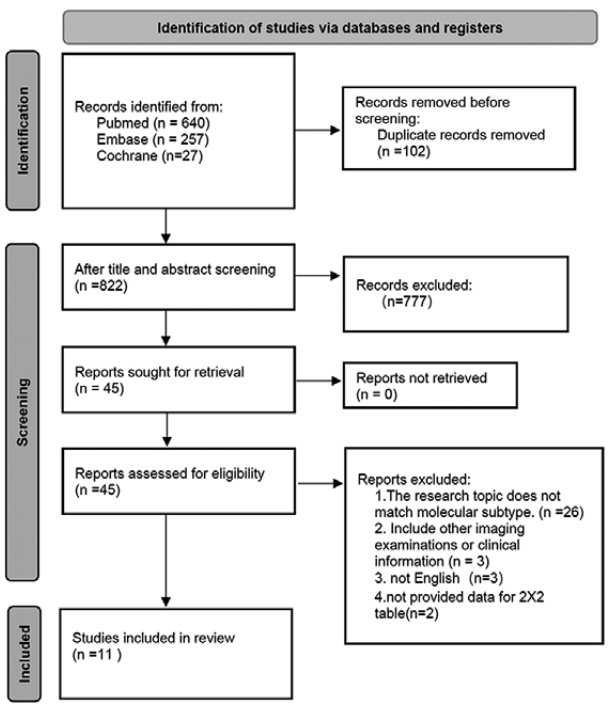

Fig 1. Flow diagram of study selection for meta-analysis according to PRISMA.

Study characteristics

Table I displays the fundamental features of the 11 studies that were included. Out of the four molecular subtypes of breast cancer in ultrasound-related radiology, TNBC is the most extensively researched, with 9 articles [11,18-21,23,25-27]. Most of them were retrospective studies, and 3 studies were prospective. Three studies utilized multimodal ultrasound radiomics methods, including two-dimensional ultrasound combined with contrast-enhanced ultrasound, elastography, or color Doppler flow imaging [11,21,25]. One study collected color Doppler flow imaging and gray scale imaging, but the final feature extraction was converted into two-dimensional gray scale, which did not constitute multimodal analysis [18]. Four of these studies were multicenter [11,21,22,27]. Three studies adopted cross validation other than independent validation [20,21,25]. Among the two mainstream methods of ultrasound radiology, 5 studies use deep learning algorithm, and 6 studies use machine learning algorithm.

Quality assessment

The included 11 diagnostic studies were scored with QUADAS-2, and presence of risk of bias and application concerns are shown in figure 2. The applicability of all studies is insignificant risk. In the flow and timing section, some studies do not provide the time interval between immunohistochemistry and ultrasound examination, so it is unclear. All the studies were scored with RQS, and the specific scores are shown in Supplementary Table S1. The highest score of these studies was 20, and the lowest score was 8.

Prediction performance of TNBC

Nine studies included meta-analysis to predict TNBC. The pooled sensitivity, specificity, PLR, NLR and DOR with 95%CI were 0.64(0.43,0.8), 0.89(0.78,0.95), 5.8(3.1,10.9), 0.41(0.25,0.67) and 14(6,32) respectively. Figure 3A depicts a coupled forest map showing sensitivity, specificity, and heterogeneity of the cohort (I^2 and Cochran's Q). The figure indicates a high rate of heterogeneity for both sensitivity (I^2=81.71[81,94.41])

Table I. Baseline characteristics of included studies.

Study	Study design	Region	Center	US type	Radiomics Used	P	L	LABC	LBBC	HER2	TNBC
Boulenger 2023	Ret	China	1	2D CDFI	DL	145	145	23	90	16	16
Cai 2024	Ret	Germany	1	2D	ML	1161	1161	-	-	-	283
Ferre 2023	Ret	Canada	1	2D	ML	88	88	-	-	21	22
Gong 2023	Pro	China	1	2D CEUS	ML	119	120	33	56	15	16
Huang 2023	Pro	China	3	2D	DL	693	693	-	-	-	-
Jiang 2021	Ret	China	3	2D	DL	2120	2120	528	1125	253	214
Wu 2019	Ret	China	1	2D CDFI	ML	140	140	30	62	25	23
Wu 2022	Ret	China	1	2D	ML	264	264	138	62	28	36
Xu 2024	Ret	China	1	2D	ML	454	454	62	238	68	86
Zhang 2021	Ret	China	2	2D	DL	790	790				158
Zhou 2021	Pro	China	3	2D CDFI SWE	DL	807	818	138	464	100	116

US: ultrasound, P: patients, L: lesions, LABC: luminal A breast cancer, LBBC: luminal B breast cancer, HER2: human epidermal growth factor receptor-2 overexpressing, TNBC: triple negative breast cancer, Ret: retrospective, Pro: prospective, DL: deep learning, ML: machine learning, 2D: two-dimensional ultrasound, CDFI: color Doppler flow imaging, SWE: shear-wave elastography

and specificity (I^2=92.77[89.38,96.15]). The AUC from the summary receiver SROC curve analysis was calculated to be 0.86(0.82-0.88) (fig 4A). The funnel diagram showed no publication bias (p=0.46) in figure 5A. As to clinical applicability, using ultrasound radiomics to predict TNBC would increase the posttest probability to 59% from 20% with a positive LR of 6 when the pretest was positive. Conversely, they reduced the posttest probability to 9%, with a negative LR of 0.41 when the pretest was negative (fig 6A).

Prediction performance of Luminal subtype

Four studies conducted meta-analysis to differentiate between luminal and non-luminal breast cancer. The pooled sensitivity, specificity, PLR, NLR, DOR were 0.89(0.76,0.96), 0.79(0.62,0.89), 4.2(2.4,7.5), 0.13(0.06,0.29) and 31(16,63), respectively. The summary of sensitivity and specificity are shown in Figure 3B. Significant heterogeneity was observed for sensitivity (I^2 = 93.83[89.41-98.25]) and specificity (I^2 =81.19[63.13-99.24]). In addition, the SROC with pooled AUC value of the validation cohorts is illustrated in Figure 4B. Pooled AUC estimates were 0.9[0.87-0.93]. The funnel diagram showed no publication bias (p: 0.22) in Figure 5B. Figure 6B shows that ultrasound radiomics to predict Luminal subtype would increase the posttest probability to 51% from 20% with a positive LR of 4 when the pretest was positive and would reduce the posttest probability to 3% with an NLR of 0.13 when the pretest was negative.

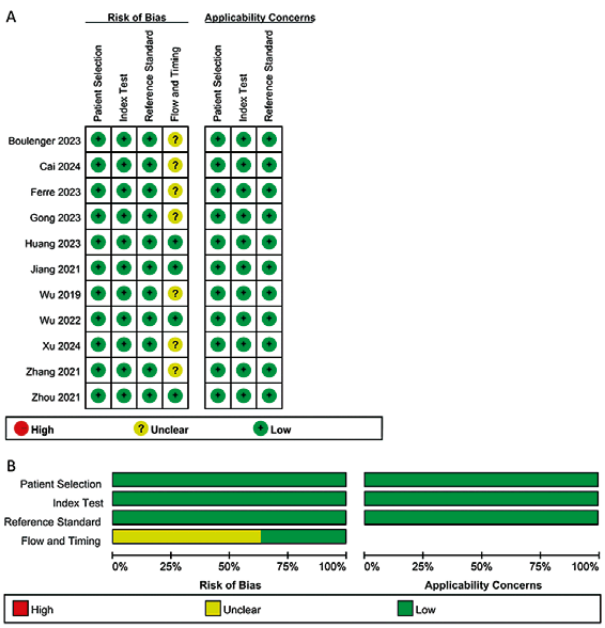

Fig 2. QUADAS quality assessment per study (A) and per domain (B).

Prediction performance of other molecular subtypes

Two studies incorporated in this meta-analysis projected Luminal A, Luminal B, and Her2. Nevertheless, this is insufficient to concentrate on the effect magnitude for quantitative analysis. Gong et al used conventional ultrasound (CUS) and contrast-enhanced ultrasound

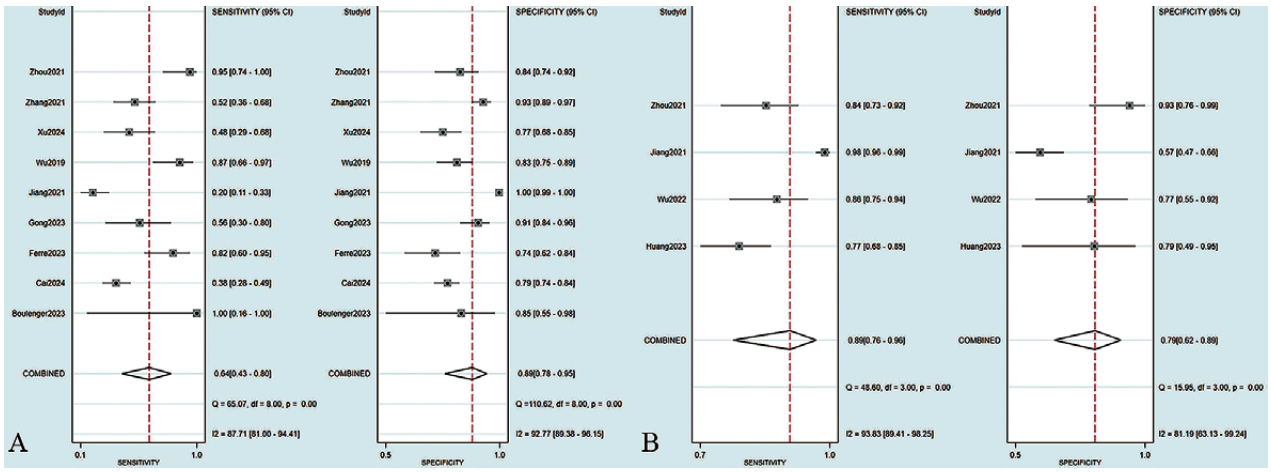

Fig 3. Forest plots of the sensitivity and specificity of ultrasound radiomics in predicting (A) TNBC and (B) Luminal breast cancer

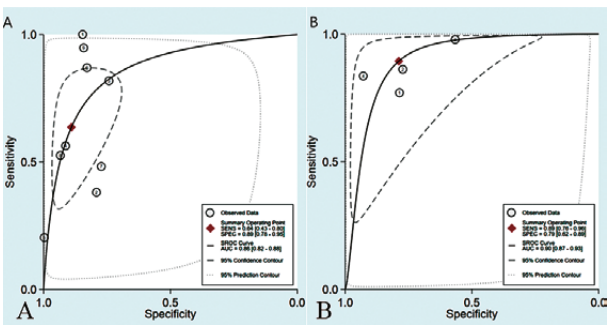

Fig 4. The summary receiver operating characteristic (SROC) curve of the diagnostic accuracy of ultrasound radiomics in predicting (A) TNBC and (B) Luminal breast cancer

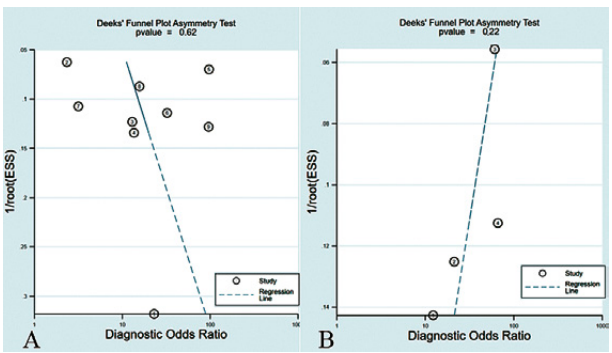

Fig 5. Funnel plot of ultrasound radiomics in predicting (A) TNBC and (B) Luminal breast cancer

(CEUS) radiomics to predict Luminal A, Luminal B and HER2. The AUC values are 0.73(0.69-0.77), 0.89(0.86-0.91) and 0.65(0.61,0.69) respectively [21]. Jiang et al evaluate the prediction performance of deep convolutional neural network (DCNN) based on ultrasound (US) images for the assessment of breast cancer molecular subtypes. The AUC values of Luminal A, luminal B and Her2 are 0.99(0.98-1.00), 0.93(0.91-0.95), 0.94(0.89-0.98) respectively [23].

Discussion

This study conducted a thorough investigation and assessment of the effectiveness of ultrasound radiomics in accurately identifying the molecular subtypes of breast cancer. The results found that ultrasound radiomics has moderate to high predictive power in predicting TNBC and Luminal molecular subtypes. Ultrasonography has shown immense potential in predicting molecular subtypes of breast cancer, which may become one of the non-invasive methods for predicting molecular subtypes before surgery.

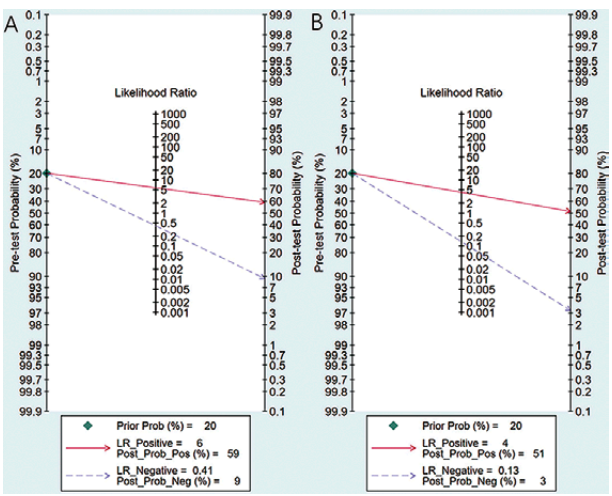

Fig 6. Fagan plots for assessing the clinical utility in predicting (A) TNBC and (B) Luminal breast cancer

Previous studies have found that specific features in ultrasound images are closely related to the molecular subtypes of breast cancer. HER2 overexpression subtype is more likely to show calcification, posterior echo en-

hancement and vascularity on ultrasound images [14,28]. Triple negative breast cancer often presents benign manifestations in ultrasound images. It is more likely to present with regular shape, markedly hypoechoic, no calcifications, posterior acoustic enhancement and hypovascularity [14,29-31]. Besides, spiculated margins, an echogenic rim and posterior shadowing were observed more commonly in luminal disease, but luminal B cancers have higher vascularity than the luminal A subtype [14,32]. These observations reveal the intrinsic biological characteristics of tumors and provide important clues for ultrasound radiomics.

Due to various factors, we found that there is a significant difference in the ability of ultrasound radiomics to predict TNBC results among different studies, AUC value from 0.64 to 0.98. So, we conducted a meta-analysis and found that the pooled AUC value was 0.86, sensitivity was 0.64, and specificity was 0.89. Some of the studies included used multimodal ultrasound imaging, which has a higher diagnostic efficacy than two-dimensional ultrasound radiomics [11,21,25]. It may be that different modes of ultrasound images contain unique features of breast cancer [33,34]. Liu et al included 2272 multimodal ultrasound images, and the average AUC value of triple negative breast cancer prediction by deep learning algorithm was 0.98, and the average accuracy rate of four molecular subtypes prediction was 85.19% [35]. Ye et al developed a deep convolutional neural network to distinguish TNBC from non-TNBC, the AUC was 0.9 [36]. Although the above two studies were not included in our meta-evaluation because they could not extract 2X2 table, we can see that ultrasound radiomics in the studies has a high accuracy in predicting TNBC. Ultrasound radiomics also can differentiate between TNBC and fibroadenoma and reduce the number of invasive biopsies [37].

The results of our investigation demonstrate that ultrasound radiomics may accurately identify Luminal subtypes. The sensitivity, specificity, and AUC values obtained were 0.89, 0.79, and 0.9, respectively. Our results demonstrated that ultrasound radiomics enables the identification of Luminal subtypes with accuracy. Compared to individuals with luminal-type breast cancer, those with non-luminal subtypes tend to exhibit poorer outcomes in terms of recurrence-free survival and disease-specific mortality [38]. Radiologists distinguish luminal types from other subtypes with the help of mammography and ultrasonography radiology. They found that the average sensitivity, average specificity, and average accuracy of less experienced and more experienced radiologists increased by 0.084, 0.152, 0.159, and 0.020, 0.100, 0.048 [39]. Zhang et al develop a deep learning-based model for predicting the molecular subtypes of breast cancer directly from the diagnostic mammography and ultrasound images. In the diagnosis of Luminal versus other subtypes, the AUC is 0.93 (95%CI:0.90,0.95), result significantly outperforms clinicians' predictions based on radiographic imaging [40]. This shows that radiology can help radiologists improve the accuracy of diagnosis. These pieces of evidence indicate that integrating multimodal data can enhance the predictive performance of the model. Huang et al developed radiopathomics model using ultrasound images and hematoxylin and eosin (H&E)-stained biopsy specimens for distinguishing between luminal and non-luminal tumors. The performance of this model is superior to that of ultrasound radiomics model [22]. Just as mammography shows better performance than ultrasound in observing calcification, especially microcalcification [41]. Combining ultrasonic images with other diagnostic images can improve the accuracy of the model and produce complementarity.

This meta-analysis lacks sufficient research on differentiating the luminal A, luminal B, and HER2 molecular subtypes individually, preventing us from effectively combining them in a quantitative manner. The study conducted by Li et al. obtained an AUC of 0.78 for patients older than 50 years and 0.82 for those with tumor sizes ≤20 mm through a deep convolutional neural network (DCNN) model on ultrasound images together with clinical information for distinguishing luminal A from others [42].The accuracy of Liu et al's multimodal ultrasound radiomics in predicting Luminal A and Luminal B accuracy was 86.7% and 86.1%, respectively [35]. A meta-analysis on ultrasound radiomics predicted the sensitivity and specificity of HER2 biomarkers to be 0.76 and 0.78, respectively, while predicting the sensitivity and specificity of Ki67 biomarkers to be 0.80 and 0.76, respectively [43]. However, from the current research results, we can see that the results of radiomics diagnosis are acceptable. These studies show a promising accuracy of ultrasound radiomics in predicting molecular markers of breast cancer.

There are also some limitations in our study. First, radiomics strategies include conventional machine learning and deep learning. There are significant differences between mechanical learning and deep learning in terms of algorithm structure, data processing methods, and model complexity. Meanwhile, due to the small sample size in some studies, there may be a risk of overfitting in deep learning. In our study, due to the number of studies, we did not evaluate them separately. We look forward to more research in the future to help us distinguish the diagnostic efficacy of different radiomics methods in molecular subtypes. Second, the test or external validation sets used in some studies have small sample sizes,

so larger scale data is needed to study their clinical application value. Finally, this meta-analysis included less research on multimodal ultrasound, and we look forward to more research on multimodal ultrasound in the future, which will further help us to evaluate the effectiveness of ultrasound in molecular subtype prediction.

Conclusion

The results of our meta-analysis demonstrate that ultrasonic radiomics has successfully acquired a promising diagnostic capacity in predicting the molecular subtypes of breast cancer. In the future, we hope that there will be more prospective multi-modal ultrasound radiologic studies to further improve the accuracy of diagnosis and help clinicians to make non-invasive diagnosis before operation.

Conflict of interest: none

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