Journal of Multidisciplinary Healthcare

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ORIGINAL RESEARCH

Predicting Non-Mass Breast Cancer Utilizing Ultrasound and Molybdenum Target X-Ray Characteristics

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Objective: The aim of this study is to investigate the influence of ultrasound and molybdenum target X-ray characteristics in predicting non-mass breast cancer.

Methods: A retrospective analysis was conducted on the clinical data of 185 patients presenting with non-mass breast lesions between September 2019 and 2021. The non-mass lesions were categorized into benign and malignant types based on ultrasonographic findings, which included lamellar hypoechoic, ductal alteration, microcalcification, and structural disorder types. Furthermore, an examination was undertaken to discern variances in molybdenum target X-ray parameters, ultrasonographic manifestations, and characteristics among individuals diagnosed with non-mass breast lesions.

Results: The ultrasonographic depiction of microcalcified lesions and the identification of suspicious malignancy through molybdenum target X-ray evaluation exhibited independent associations with non-mass breast cancer, yielding statistically significant differences ($p < 0.05$). Subsequently, the logistic regression model was formulated as follows: Logit (P) =−1.757+2.194* microcalcification type on ultrasound + 1.520* suspicious malignancy on molybdenum target X-ray evaluation. The respective areas under the receiver operating characteristic curves for microcalcification type on ultrasound, suspicious malignancy on molybdenum target X-ray, and the integrated diagnostic model were 0.733, 0.667, and 0.827, respectively, demonstrating discriminative capacities.

Conclusion: Using both ultrasound and molybdenum target X-ray diagnostics can increase the accuracy of non-mass breast cancer detection. The findings of this study have the potential to augment the detection rate of non-lumpy breast cancer and provide an imaging basis for enhancing the prognosis of individuals with breast cancer.

Keywords: correlation, logistic regression, Molybdenum targeted X-ray, non-mass type, ultrasonographic manifestations

Introduction

Breast pathologies represent prevalent and diverse conditions among women, with both their incidence and malignancy rates demonstrating a gradual increase.[1] In addition, individuals affected by breast disorders tend to be of younger age. Therefore, it is imperative to explore strategies aimed at enhancing the prognosis and quality of life for patients with breast cancer while simultaneously elevating rates of early detection and diagnostic compliance. Breast cancer has a variable presentation on ultrasound, with the mass subtype being predominant.[2–4] However, some breast cancer ultrasonograms deviate from conventional mass characteristics, presenting as a non-mass-type presentation with hazy boundaries and no discernible spatial occupancy impact in two separate vertical views.[5] Based on the current Breast Imaging Reporting and Data System, mass breast cancer was defined as the lesion with a three-dimensional space-occupying effect on two perpendicular sections. However, some breast cancer ultrasonograms deviate from conventional mass characteristics, presenting as a non-mass-type presentation with hazy boundaries and no discernible spatial occupancy impact in two separate vertical views. In addition, Guideline for breast ultrasound

Received: 24 June 2024
Accepted: 20 August 2024
Published: 2 September 2024

diagnosis Results recommended by Japan Association of Breast and Thyroid Sonology described ultrasonography of non-mass breast cancer as no space-occupying effect, no clear boundary, and no growth-oriented lesions in two or more different scanning directions.[6] However, identifying ultrasound images depicting these indicators poses challenges, as they are often inconspicuous, leading to difficulties in accurate recognition and low diagnostic sensitivity.[7] Consequently, there is a risk of missed or erroneous diagnoses.[8–10] Therefore, their ultrasonographic manifestations are still challenging to recognize clinically. To increase the ultrasound diagnostic conformity rate of non-mass breast cancer and provide an imaging basis for identifying the lesions, we conducted a comparative analysis of clinical, ultrasound, and mammographic features between malignant non-mass breast cancer cases and benign non-mass breast lesions.

Materials and Methods

General Information

Study participants were enrolled from September 2019 to September 2021 at the First Hospital of Shanxi Medical University. The clinical data were collected from 185 female patients (age range: 24–76 years, mean age: 54.23 ± 10.82 years) diagnosed with non-lumpy breast lesions confirmed through surgical or puncture biopsy pathology. All methods were carried out in accordance with relevant guidelines and regulations in this paper. This study was conducted in accordance with the declaration of Helsinki and approved by the ethics committee/IRB of First Hospital of Shanxi Medical University and the informed consent was obtained from all subjects and/or their legal guardian(s).

Instruments and Inspection Methods

The ultrasound assessments were conducted using GE Logiq E9 and French Acoustics Aixplorer color Doppler ultrasound diagnostic instruments, operating within a frequency range of 7–12 MHz. Mammography evaluations were carried out utilizing a fully digital mammography machine, specifically the Selenia Dimensions model (SDM-05000-2DC) manufactured by Hologic, USA, operating in fully automatic exposure mode.

Basic clinical data encompassing parameters such as age, family history, the age of menarche, and menopausal status, among others, were meticulously compiled prior to the assessment. Subsequently, the patients were arranged in a supine position, ensuring full exposure of both breasts and axillae. The examination included an inspection for any nipple discharge and bilateral palpation of the breasts.

Ultrasound procedure: The nipple served as the focal point for a two-dimensional grayscale ultrasound scan, spanning from the external superior quadrant and proceeding in a radial pattern to the external inferior, internal inferior, and internal superior mammary glands, as well as the nipple and areola regions. The bilateral mammary glands were scanned for comparison and examined for lamellar hypoechogenicity, ductal alterations, microcalcifications, and structural disorders within the glandular tissue. Upon identification of a lesion, optimal display views were selected, and the position of the lesion was recorded, with utilization of the zoom function if deemed necessary. Ultrasound characteristics of the lesion were evaluated, including posterior echogenicity and the presence of abnormal axillary lymph nodes, determined by criteria such as an aspect ratio of 2, lymph node cortical thickness > 4 mm or exhibiting asymmetric thickening, loss of portal structures, nonportal blood flow such as central, peripheral, or mixed, liquefied areas visible within the lymph node, and the presence of visible calcified foci.[2] Following this assessment, the examination transitioned to color Doppler mode and adjusted the sampling frame size, color gain level, and flow rate scale to optimize the Doppler image of the lesion.

Molybdenum target X-ray procedure: Participants adopted an upright stance, ensuring complete chest exposure. Subsequently, the breast was positioned between the X-ray table and a compression device and sequentially photographed in the cephalocaudal, internal oblique, and external oblique positions, utilizing fully automated exposure settings. Localized compression and magnification adjustments were applied as needed during image acquisition. The photographs were automatically uploaded to a workstation for subsequent postprocessing.

Image Analysis

The images, including those obtained through ultrasound and molybdenum target X-rays depicting all lesions, were jointly reviewed by two ultrasound physicians and radiologists possessing extensive experience exceeding 10 years in their respective fields. These experts classified non-mass breast lesions into benign or malignant categories. The ultrasound physicians and radiologists used a double-blind method to analyze the images, ignoring the pathological results of the participants before making the final diagnosis.

Ultrasound image analysis: Combining the current classification methods and the types of cases in this study, non-mass breast lesions were summarized into four distinct types according to their ultrasound findings:[2,5,11,12] ① Lamellar hypoechoic type: characterized by differing echogenicity compared to adjacent glandular tissue or the contralateral breast gland, exhibiting limited asymmetry without clear borders, and lacking clear occupancy on multi-section sweeps ② Ductal alteration type: characterized by localized ductal widening and dilatation parallel to the ductal direction or isolated solid nodules within the ducts, accompanied by uneven changes in ductal wall thickness and variable luminal diameter; ③ Microcalcification type: featuring dotted, linear, or clustered microcalcifications within the lamellar hypoechoic area or the ductal hypoechoic lesions, either in isolation or as the primary lesion manifestation; ④ Structural disorder type: characterized by tangled and distorted glandular structures in the lesion area, with unclear layers, uneven echogenic changes, and blurred borders.

Molybdenum target X-ray image analysis: The normalized terminology outlined in the fifth edition of the ACR BI-RADS was used to classify the breast glands into four distinct types: adipose, scattered glandular, non-uniform glandular, and dense glandular. Molybdenum target X-ray findings were further categorized into four specific signs: negative, calcified, distorted or asymmetrical, and distorted or asymmetrical with associated calcification, along with unilateral ductal dilatation. In this study, the results of molybdenum target X-ray evaluations were divided into two primary groups: negative and suspicious for malignancy. Categories 1, 2, or 3 were assessed as negative for malignancy, while categories 0, 4, or 5 were assessed as suspicious for malignancy based on the BI-RADS guidelines.

Statistical Analysis

Statistical analysis was conducted using SPSS version 25.0 software. Measurement data were tested for distribution normality, and are presented as the mean ± standard deviation (x ± s) for normally distributed variables. An independent sample *t*-test was used for comparisons between the two groups. The chi-squared test, or Fisher's exact test, was employed. Counting data are reported as instances or rates (%). Multifactorial analysis was performed using binary multifactorial logistic regression analysis. Factors closely associated with the diagnosis of non-mass breast cancer were screened to establish a binary logistic regression model to determine the best predictive characteristics. Receiver operating characteristic (ROC) curves were plotted, and the area under the curve (AUC) was calculated. Statistical significance was determined at a threshold of $p < 0.05$.

Results

Pathology Results

Among the 185 non-mass breast lesions examined in this study, 100 were classified as benign, while 85 were deemed malignant. The malignant lesions encompassed various subtypes, including 36 cases of ductal carcinoma in situ (42.4%), 29 cases of invasive ductal carcinoma (34.1%), 5 cases of invasive lobular carcinoma (6.9%), and 15 cases of ductal carcinoma in situ combined with invasive ductal carcinoma (17.6%). Histological type distribution of non-mass breast lesions in the benign and malignant group was presented in Supplementary Table 1 and comparisons of baseline characteristics between patients in the benign and malignant group were demonstrated in Supplementary Table 2.

Ultrasonographic Manifestation Typing

Among the 185 non-mass breast lesions, the lamellar hypoechoic type was the most prevalent ultrasonographic manifestation, observed in 71 cases (38.4%), followed by the microcalcification type in 56 cases (30.3%), the ductal alteration type in 36 cases (19.4%), and the structural disorder type in 22 cases (11.9%) (Figure 1). The difference in the proportion of microcalcification type between the benign group and malignant group was statistically significant ($p < 0.05$) (see Table 1).

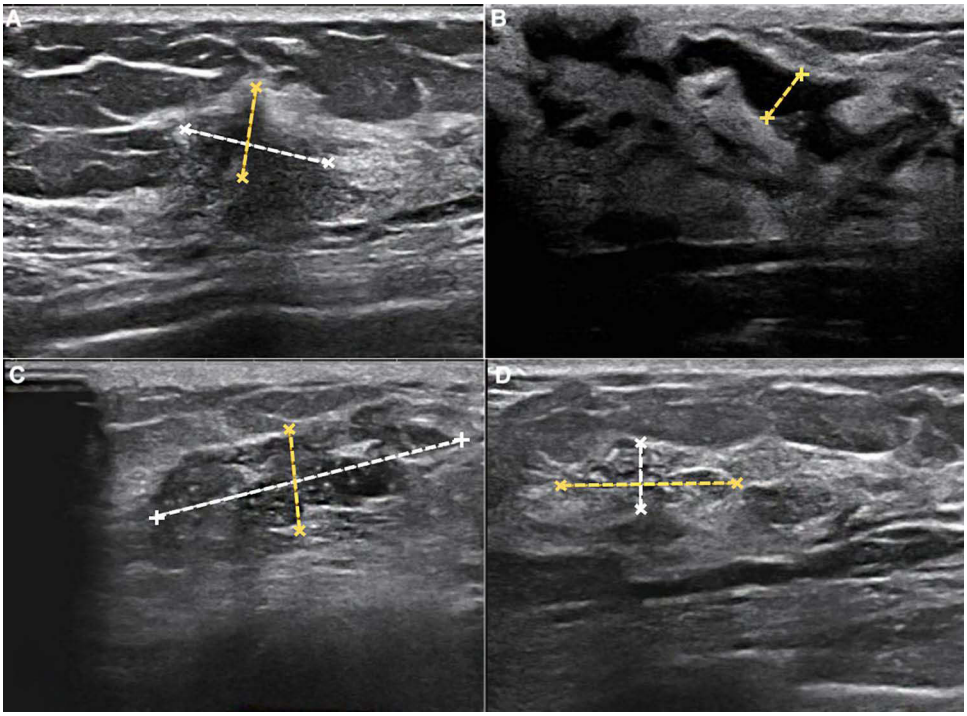

Figure 1 Ultrasonographic Manifestations of Non-Mass Breast Cancer. (**A**) Lamellar Hypoechoic Type; (**B**) Ductal Alteration Type with Hypoechogenicity; (**C**) Microcalcification Type with Lamellar Hypoechogenicity; (**D**) Structural Disorder Type. The lines depict the location of non-mass breast cancer.

Ultrasound Characteristics

The characteristics related to the posterior echogenicity among non-mass breast lesions exhibited no statistically significant differences between the benign and malignant groups (all $p > 0.05$). However, there was a statistically significant difference between the two groups regarding the presence of abnormal axillary lymph nodes and the grade of the blood flow signal (all $p < 0.05$) (refer to Table 2).

Molybdenum Target X-Ray Parameters

No statistically significant differences were observed between the benign group and the malignant group in terms of breast gland type ($p > 0.05$). Furthermore, among the various molybdenum target X-ray signs, no statistically significant differences were noted between the two groups in terms of negative findings, the presence of calcifications, structural distortion or asymmetry, or unilateral ductal dilatation types (all $p > 0.05$). However, a statistically significant difference was identified between the benign group and the malignant group in terms of distorted or asymmetrical structures

Table 1 Comparison of Ultrasonographic Manifestations of Patients with Non-Mass Breast Lesions (Benign and Malignant Groups)

	Benign n (%)	Malignant n (%)	Total n (%)	χ^2	*P* value
Lamellar hypoechoic type	42 (42.0)	29 (34.1)	71 (38.4)	1.207	0.272
Ductal alteration type	23 (23.0)	13 (15.3)	36 (19.4)	1.741	0.187
Microcalcification type	21 (21.0)	35 (41.2)	56 (30.3)	8.861	0.003*
Structural disorder type	14 (14.0)	8 (9.4)	22 (11.9)	0.923	0.337

Note: *$P<0.05$.

Table 2 Comparison of Ultrasound Characteristics of Patients with Non-Mass Breast Lesions

Parameters	Benign n (%)	Malignant n (%)	Total n (%)	χ^2	*P* value
Posterior echo					
No change	40 (40.00)	37 (43.53)	77 (41.62)		
Enhancement	32 (32.00)	18 (21.18)	50 (27.03)	2.909	0.234
Attenuation	28 (28.00)	30 (35.29)	58 (31.35)		
Lymph nodes					
Abnormal	23 (23.00)	37 (43.53)	60 (32.43)	8.837	0.003*
Normal	77 (77.00)	48 (56.47)	125 (67.57)		
Blood signal classification					
Class 0/1	59 (59.00)	33 (38.82)	92 (49.73)	7.482	0.006*
Class 2/3	41 (41.00)	52 (61.18)	93 (50.27)		

Note: *$P<0.05$.

associated with calcifications ($p < 0.05$). Notably, when molybdenum target X-ray was used to evaluate suspicious malignancy, the pathological result was significantly more likely to be malignant ($p < 0.05$) (Table 3 and Figure 2).

Multifactor Logistic Regression Analysis

Multifactor logistic regression analysis revealed that both the ultrasonographic manifestation of microcalcification type and the molybdenum target X-ray assessment indicating suspicious malignancy were independently and significantly associated with the diagnosis of non-mass breast cancer (with regression coefficients of 2.194 and 1.520, respectively; both $p < 0.05$) (see Table 4). A multifactorial logistic regression model was established as follows: Logit (P) = −1.757 +2.194*ultrasonographic manifestation of microcalcification type·+1.520*molybdenum (Mg) target X-ray assessment of suspicious malignancy. Using the pathological findings as the gold standard, the model yielded an accuracy rate of 69.7% (refer to Table 5). Additionally, the AUC for the ultrasonographic manifestation of microcalcification type, the molybdenum target X-ray assessment of suspicious malignancy, and the diagnostic model were calculated as 0.733, 0.667, and 0.827, respectively (Figure 3).

Table 3 Comparison of Molybdenum Target X-Ray Parameters of Patients with Non-Mass Breast Lesions (Benign and Malignant Groups)

Parameters	Benign n (%)	Malignant n (%)	Total n (%)	t/χ^2	*P* value
Molybdenum target X-ray gland type					
Fatty type	21 (21.00)	11 (12.94)	32 (17.30)	3.069	0.387
Scattered glandular type	27 (27.00)	31 (36.47)	58 (31.35)		
Heterogeneous glandular type	20 (20.00)	17 (20.00)	37 (20.00)		
Dense glandular type	32 (32.00)	26 (30.59)	58 (31.35)		
Molybdenum target X-ray characteristics					
Negative	32 (32.00)	17 (20.00)	49 (26.49)	14.832	0.004*
Calcified	40 (40.00)	23 (27.06)	63 (34.05)		
Distorted or asymmetrical structure	15 (15.00)	18 (21.18)	33 (17.84)		
Distorted or asymmetrical structure with calcification	12 (12.00)	24 (28.24)	36 (19.46)		
Unilateral ductal dilatation	1 (1.00)	3 (3.52)	4 (2.16)		
Molybdenum target X-ray evaluation					
No suspicious malignancy	76 (76.00)	18 (21.18)	94 (50.81)	55,253	<0.001*
Suspicious malignancy	24 (24.00)	67 (78.82)	91 (49.19)		

Note: *$P < 0.05$.

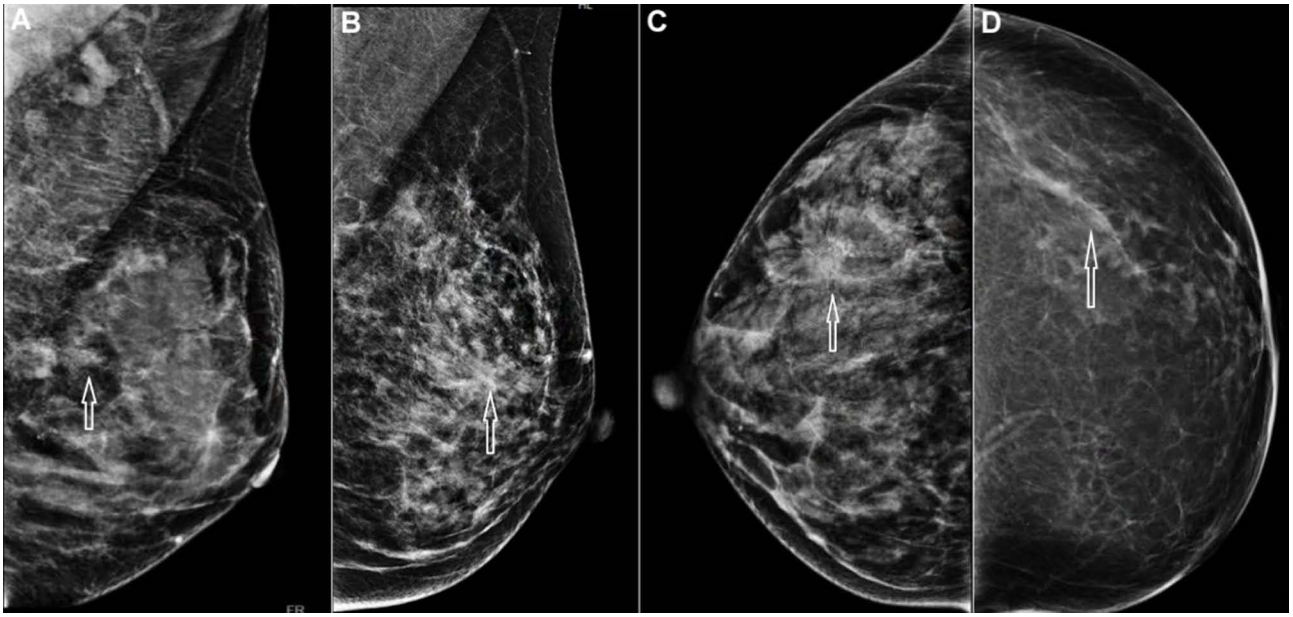

Figure 2 Depiction of Molybdenum Target X-ray Signs. (**A**) Calcification (arrow); (**B**) Distorted or Asymmetrical Structure (arrow); (**C**) Distorted or Asymmetrical Structure with Calcification (arrow); (**D**) Unilateral Ductal Dilatation (arrow).

Discussion

The ultrasonographic manifestations of breast cancer are complex and varied, with mass type being the most typical.[1,13] However, ultrasound images of some breast cancer lack typical mass characteristics, showing unclear boundaries and non-mass manifestations without clear space occupying effect in two vertical sections in different directions. Breast ultrasound related signs (structural disorders, catheter changes, etc.) may be the only ultrasonic features of non-mass breast cancer, which make it difficult to identify correctly and cause missed diagnosis and misdiagnosis of the disease. Molybdenum X-ray has a good diagnostic ability for the early lesion morphology and microcalcification of breast cancer, which makes up for the deficiency of ultrasound diagnosis.[14] Li et al[15] founded that the combination of the two methods may have a synergistic effect on the early diagnosis of breast cancer. In recent years, non-mass breast cancer has attracted

Table 4 Multivariate Logistic Regression Analysis of Factors Influencing Non-Mass Breast Cancer

Factor	B	SE	χ^2	*P*	OR	95% Confidence Interval	
						Upper Bound	Lower Bound
Axillary lymph nodes (normal or abnormal)	1.150	0.799	2.070	0.150	3.159	0.659	15.138
Blood signal	0.423	0.677	0.391	0.532	1527	0.405	5.761
Ultrasonographic manifestation: microcalcification type	2.194	0.710	9.555	0.002*	8.973	2.232	36.073
Molybdenum target X-ray sign: Distorted or asymmetrical structure with calcification	0.468	0.745	0.394	0.530	1.597	0.370	6.882
Molybdenum target X-ray evaluation: Suspicious malignancy	1.520	0.706	4.628	0.031*	4.571	1.145	18.252
Constant	−1.757	0.589	8.893	0.003*	0.173		

Note: *P<0.05.

Table 5 Logistic Regression Model Prediction

		Pathology Result of Nonmass Breast Lesions	
		Benign Lesions (n)	Malignant Lesions (n)
Prediction result	Benign lesion	69	25
	Malignant lesion	31	60
Prediction accuracy		69.7%	

more and more attention from clinicians and become a research hotspot, but its understanding and understanding are still limited, and there are still few studies on ultrasonographic manifestations of the disease.[16,17]

The results of this study revealed that non-mass breast lesions were significantly more likely to exhibit malignancy ($p < 0.05$) if they demonstrated ultrasonographic features such as abnormal axillary lymph nodes, abundant lesion blood flow signal, and the microcalcification type. Furthermore, molybdenum target X-ray indicators, including the presence of distorted or asymmetrical structures with calcification and assessments indicating suspicious malignancy, were associated with elevated likelihoods of malignancy. These results corroborate the findings reported by Ko et al.[18]

An important characteristic that can differentiate between benign and malignant non-mass breast lesions is the involvement of the axillary lymph nodes.[19,20] As infiltration of tumor cells into axillary lymph nodes signifies a certain degree of advancement of breast cancer to intermediate or advanced stages, the presence of abnormal axillary lymph nodes alongside non-palpable breast cancer lesions warrants consideration of malignancy.[5,21] However, the number of patients in this study with abnormal axillary lymph nodes among those diagnosed with malignant lesions was 37 (43%), which is insufficient to prove definitively that abnormal axillary lymph nodes are an indicator of non-mass breast cancer. Furthermore, it has been observed that significant overlap exists in ultrasound imaging features between benign hyperplastic or enlarged lymph nodes and metastatic, abnormal axillary lymph nodes. Consequently, relying solely on axillary lymph node abnormalities presents limitations in accurately distinguishing between benign and malignant non-mass breast lesions.[19]

Angiogenic factors secreted by tumor cells in non-mass breast cancer initiate neovascularization, facilitating tumor cell growth and proliferation.[22] Choi et al found that high vascular density was linked to malignant non-mass breast lesions,[23] whereas low vascular density was linked to benign non-mass breast lesions. In the present study, a notably higher proportion of malignant non-mass breast lesions (61.2%) exhibited blood flow signals classified as grade 2/3

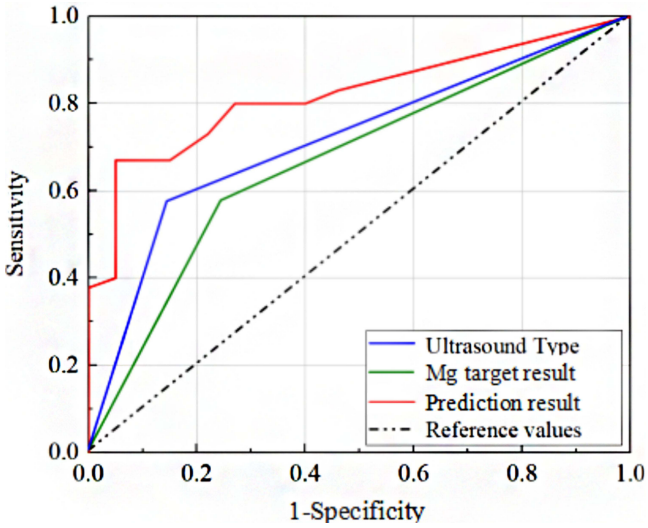

Figure 3 The receiver operating characteristic (ROC) curves. The area under the curve for the ultrasonographic manifestation of microcalcification type, the molybdenum target X-ray assessment of suspicious malignancy, and the diagnostic model were calculated as 0.733, 0.667, and 0.827, respectively.

compared to benign lesions (41.0%; $p < 0.05$), indicating a heightened blood flow signal in malignant non-mass breast lesions, consistent with findings reported by Zhang et al.[24]

The ultrasound results of this study revealed that among the various ultrasonographic manifestations observed in non-mass breast lesions, the malignant group exhibited a significantly higher propensity for the manifestation of the microcalcification type compared to the benign group ($p < 0.05$). This observation underscores the potential of microcalcified breast lesions to serve as valuable indicators in the detection of non-lumpy breast cancer, which is consistent with the findings of Kim et al.[25] Furthermore, Keränen et al[26] observed that ultrasound had a higher detection rate for microcalcified non-mass breast malignant lesions compared to benign lesions. The lack of nutrients in non-mass breast cancer lesions leads to massive tumor cell necrosis and lysis, consequently precipitating calcium ion accumulation and subsequent deposition of calcium salts, forming calcification foci.[27] Microcalcifications thus emerge as pivotal indicators of non-mass breast cancer[28,29] and may even be the sole ultrasound characteristic of malignant non-mass breast lesions.[30] Kim et al[25] additionally highlighted that the detection of microcalcifications via molybdenum target X-ray imaging in non-mass breast lesions enhances the accuracy of differential diagnosis for such lesions.

The results of molybdenum target X-ray in this study confirmed the hypothesis of Kim et al[25] indicating that molybdenum target X-ray characteristics serve as guiding parameters in the differential diagnosis of non-mass breast lesions. Specifically, the results revealed significantly fewer patients in the benign group presented with the molybdenum target X-ray sign of distorted or asymmetrical structures with calcification and the molybdenum target X-ray evaluations indicating suspicious malignancy compared to the malignant group ($p < 0.05$).[31] An important reference for diagnosing non-mass breast cancer is provided by Ko et al,[19] who demonstrated a substantial correlation between molybdenum target X-ray evaluations suggestive of malignancy and non-mass breast cancer.

This study encompassed various ultrasound types of non-mass breast lesions within a multifactorial logistic regression analysis. The results revealed the ultrasonographic manifestation of microcalcification type as an independent risk factor for non-mass breast cancer,[32,33] a perspective not addressed in the research conducted by Ko et al.[18] Additionally, the multifactorial logistic regression[34–36] analysis demonstrated that factors such as abnormal axillary lymph nodes, blood flow signal grade, and the molybdenum target X-ray sign of structural distortion or asymmetry with calcification, which exhibited statistical significance in the univariate analysis, did not retain significance in the regression analysis. Conversely, the molybdenum target X-ray evaluation of suspicious malignancy and the ultrasonographic manifestation of microcalcifications were identified as significant risk factors for non-mass breast cancer.

The AUCs, according to the regression model created in this study, were 0.733 for the ultrasonographic manifestation of microcalcification type, 0.667 for molybdenum target X-ray suspicious malignancy, and 0.827 for the diagnostic model, indicating superior diagnostic efficacy compared to individual factors. Studies conducted in other countries have indicated that segmental or aggregated calcifications, microcalcifications within dilated ducts, and microcalcifications within hypoechoic zones are all easily detected on ultrasonography, indicating a greater risk of malignancy.[25] Therefore, the identification of suspected malignant lesions on molybdenum target X-ray imaging and the presence of microcalcification-type non-mass breast lesions on ultrasound warrant heightened suspicion of malignancy, necessitating vigilant patient monitoring.

However, the present study is subject to certain limitations: (i) The sample size was relatively small and did not include rare non-mass breast cancer types such as breast lymphoma and breast mucinous carcinoma. Future research endeavors should aim to address this limitation by expanding the sample size to include such cases; (ii) a single molybdenum target X-ray imaging result was included in this study. However, future investigations should endeavor to combine this result with MRI and other ultrasound techniques to facilitate a more comprehensive comparative analysis.

Conclusion

Notable distinctions exist between benign non-mass breast lesions and non-mass breast cancer in terms of ultrasound characteristics, including abnormalities in axillary lymph nodes, blood flow signal grade, and the presence of microcalcifications, as well as molybdenum target X-ray characteristics, such as the identification of distorted or asymmetrical structures with calcifications and the presence of suspicious malignancy on molybdenum target X-ray imaging. Hence,

the diagnostic precision for non-mass breast cancer could be enhanced through the combined use of ultrasound and molybdenum target X-rays. However, it is imperative to acknowledge the limitation of the study's small sample size, underscoring the necessity for further investigations with larger cohorts to validate and corroborate these findings.

Acknowledgment

This paper has been uploaded to Research Square as a preprint: https://www.researchsquare.com/article/rs-3230407/v1.

Funding

Correlation between contrast-enhanced ultrasound features and molecular biological prognostic indicators of breast cancer, Key Research and Development Program of Shanxi Province (Social development, No.: 201803D31097).

Disclosure

The authors have no conflicts of interest in this work.

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