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Original Article

Predictive value of ultrasound assessment of axillary and brachial artery parameters for lymph node metastasis in breast cancer patients

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Abstract: Objective: This study aimed to assess the predictive value of ultrasound assessment of axillary and brachial artery parameters for lymph node metastasis (LNM) in breast cancer (BRCA) patients. Methods: The clinical data of 172 cancer patients were reviewed, and the patients were stratified into two groups based on the presence or absence of axillary LNM. Ultrasound assessment was employed to evaluate axillary and brachial artery parameters using specific techniques, and arterial characteristics were analyzed. Results: Significant differences were observed in the ultrasound parameters of both axillary and brachial arteries between the non-LNM and LNM groups. Specifically, axillary and brachial artery diameters and resistive index exhibited significant differences and correlations with axillary LNM. Furthermore, molecular markers such as human epidermal growth factor receptor 2 (HER2) status, estrogen receptor (ER) status, and progesterone receptor (PR) status were found to be significantly correlated with LNM. Additionally, a nomogram was constructed, demonstrating the predictive value of the integrated arterial parameters. The combined model, incorporating axillary and brachial artery parameters, exhibited a higher predictive capability for axillary LNM compared to individual arterial parameters (AUC = 0.984). Conclusion: Ultrasound assessment of axillary and brachial artery parameters, in conjunction with molecular markers, holds promise as a non-invasive tool for predicting LNM in BRCA patients. The observed correlations provide insights into the potential clinical relevance of arterial parameters in risk stratification and treatment planning. Further research in larger, prospective cohorts is warranted to validate the findings and enhance the precision of BRCA management.

Keywords: Ultrasound, axillary artery parameters, brachial artery parameters, lymph node metastasis, breast cancer

Introduction

Breast cancer (BRCA) is a significant public health concern, accounting for nearly a quarter of all cancers diagnosed in women worldwide. It is the most commonly diagnosed cancer and the leading cause of cancer-related deaths among women globally [1, 2]. The impact of BRCA extends beyond its high incidence, posing substantial emotional, physical, and financial burdens on patients, their families, and healthcare systems [3]. Early detection and accurate assessment of the disease's extent are pivotal for guiding treatment decisions and improving patient outcomes. Lymph node metastasis (LNM) in BRCA is a critical indicator of disease advancement and plays a significant role in treatment planning and prognosis [4]. The dissemination of cancer cells to the regional lymph nodes not only reflects the aggressive nature of the disease but also signifies the staging of BRCA according to widely accepted classification systems such as the TNM (Tumor, Node, Metastasis) staging system [5]. The status of lymph node involvement informs the selection of therapeutic interventions, including

surgical approaches, adjuvant chemotherapy, and radiation therapy [6, 7].

Historically, the gold standard methods for evaluating lymph node status, including axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB), have been instrumental in informing treatment decisions and guiding patient care [8]. However, these approaches are not without limitations. ALND, while fundamental in staging BRCA, is associated with substantial morbidity, including the risk of lymphedema, sensory deficits, and shoulder dysfunction [9, 10]. Similarly, though less invasive than ALND, SLNB is not devoid of potential complications, such as lymphedema, seroma formation, and nerve injury. Furthermore, both procedures necessitate anesthesia, surgical expertise, and postoperative recovery, making them resource-intensive and potentially burdensome for patients. Against this backdrop, the quest for non-invasive, low-risk approaches to predicting and assessing LNM has gained prominence [11, 12].

The clinical application prospect of ultrasound examination in predicting LNM is promising and multifaceted. By providing real-time imaging without exposure to ionizing radiation, ultrasound can be used as an initial screening tool for identifying patients who may benefit from further diagnostic workup or more aggressive treatment planning [13, 14]. Moreover, it can facilitate personalized medicine by enabling clinicians to tailor therapeutic strategies based on individual patient characteristics. For instance, patients with a high risk of LNM identified through ultrasound might undergo earlier surgical intervention or receive neoadjuvant chemotherapy to reduce tumor burden before surgery [15]. Additionally, ultrasound can play a role in monitoring response to therapy, thereby informing decisions about the continuation or modification of treatment regimens [16]. In summary, the non-invasive nature and cost-effectiveness of ultrasound make it a valuable adjunct to existing diagnostic protocols, potentially leading to improved patient outcomes and resource allocation.

Ultrasound assessment of axillary and brachial artery parameters has emerged as a non-invasive and potentially valuable tool in identifying LNM in BRCA patients [17]. By leveraging ultrasound technology, clinicians can assess not only the anatomical characteristics of the lymph nodes but also the hemodynamic changes in the adjacent arterial vasculature, offering comprehensive insight into regional anatomical and physiological alterations indicative of lymphatic involvement [18]. Moreover, ultrasound allows for real-time, dynamic evaluation, enabling the potential identification of subtle changes and enhancing the sensitivity of lymph node assessment.

While ultrasound offers several advantages over traditional methods such as ALND and SLNB, it also has its limitations. One major advantage of ultrasound is its non-invasive nature, which avoids the use of general anesthesia. It allows for dynamic assessment of lymph nodes and adjacent vasculature, providing immediate feedback that can guide decision-making at the point of care. Furthermore, ultrasound is relatively inexpensive and widely available, making it accessible even in resource-limited settings. However, compared to ALND and SLNB, ultrasound has lower specificity and sensitivity, particularly in detecting small or occult metastases [19]. This limitation underscores the importance of combining ultrasound with other diagnostic modalities or molecular markers to enhance predictive accuracy. Moreover, the interpretation of ultrasound images requires specialized training and experience, which may not be uniformly available across different healthcare settings [20]. Despite these challenges, the integration of ultrasound into the diagnostic algorithm for LNM represents a step towards less invasive, patient-centered care in breast oncology.

The integration of ultrasound assessment into the clinical paradigm holds the promise of augmenting risk stratification, informing treatment decisions, and potentially reducing the necessity for invasive procedures, thus minimizing associated morbidities and healthcare resource utilization [21]. By exploring the predictive value of ultrasound assessment of axillary and brachial artery parameters, this study endeavors to shed light on the potential of this non-invasive modality to enhance precise and personalized management of BRCA, ultimately striving to improve patient care and clinical outcomes in this challenging domain.

Materials and methods

Study subjects

A retrospective case-control investigation was carried out involving the clinical records of 172 cancer patients who were treated at Taizhou People's Hospital between January 2019 and June 2020. The patients were classified into two categories based on whether they had axillary LNM. The group with axillary LNM consisted of 87 patients, while 85 patients formed the non-LNM group. Approval for the study was granted by the Medical Ethics Committee of Taizhou People's Hospital (KY2020-217-01), and obtaining informed consent from patients was deemed unnecessary. The research adhered to the principles outlined in the Helsinki Declaration.

Grouping criteria

In this study, the presence of axillary LNM was determined based on the findings of postoperative ALND and fine-needle aspiration biopsy. The absence of axillary LNM was mainly determined based on the results of postoperative ALND and intraoperative SLNB. Patients with negative results in the intraoperative SLNB were directly considered as not having axillary LNM.

The inclusion was determined based on the availability of complete ultrasound evaluation data and confirmed axillary LNM status from medical records (n = 172). Post-hoc power analysis revealed that our sample size provides adequate statistical power to detect significant differences in arterial parameters between patients with and without LNM, assuming an effect size derived from preliminary analyses, a power of 80%, and an alpha level of 0.05, leading us to conclude that a minimum of 128 patients would be necessary for sufficient statistical power [22].

Inclusion and exclusion criteria

Inclusion criteria: Female patients who met the diagnostic criteria for BRCA as outlined in the *Chinese Anti-Cancer Association Guidelines for the Diagnosis and Treatment of Breast Cancer*: presence of a fixed, hard breast lump with irregular margins [23]; presence of prominent and tortuous blood vessels around the lump; small dimpling of the breast skin; nipple retraction; palpable ipsilateral axillary lymph node enlargement, or palpable lymph nodes in the supraclavicular area and contralateral axilla.

Exclusion criteria: Patients with abnormal heart, liver, or kidney function [24]; those with severe mental illness; those with malignancies in other locations; those who had undergone neoadjuvant chemotherapy, radiotherapy, or endocrine therapy [25]; those with comorbidities or medical conditions that might significantly impact arterial parameters, such as peripheral vascular disease, severe hypertension, or significant peripheral artery disease [26].

Methods for axillary and brachial artery examination

The axillary and brachial artery examinations were performed preoperatively using the Mindray Resona R9S ultrasound diagnostic apparatus equipped with a linear array transducer operating at a frequency of 3 to 12 MHz and incorporating elasticity contrast index (ECI) functionality. Patients were positioned supine with both arms raised to expose the axilla for multiplanar scanning. The investigation aimed to identify the position, size, boundaries, length-to-width ratio, cortical-medullary structure, internal echo, and lymph node blood flow in the axillary region. Additionally, the examination involved recording the shortest distance from the center of the lymph node to the center of the ipsilateral axillary artery and the shortest distance from the lymph node center to the body surface. Upon identifying the lymph nodes in 2D ultrasound, the transducer was lightly placed on the skin surface without pressure. The largest cross-section of the lymph node was selected, and the ECI software was activated. Patients were instructed to hold their breath for 2 to 3 seconds until the color strain ratio bar turned completely green. Subsequently, a strain sequence of the lymph node under the pressure of the ipsilateral axillary artery was obtained, and the image was frozen. To avoid cystic changes and large calcification areas, the region of interest (ROI) was extracted, and the ECI value was annotated. This process was repeated three times, and the average values were recorded. All procedures were conducted by a physician with over 5 years of experience in ultrasound diagnostics [27, 28]. Typical Doppler pictures of axillary artery from patients with and without LNM are shown in **Figure 1**.

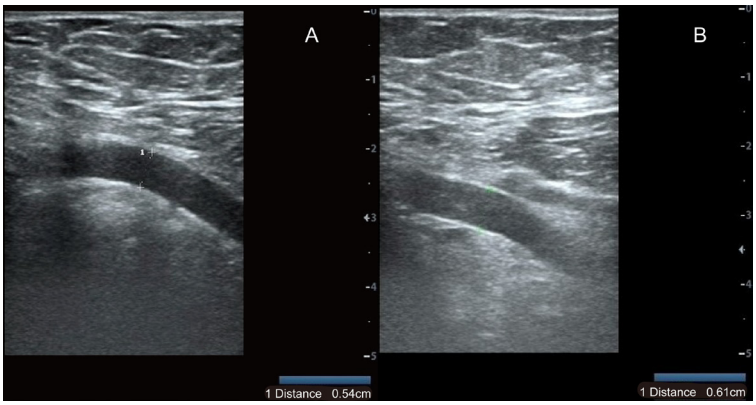

Figure 1. Typical Doppler images of axillary artery in patients, with and without lymph node metastasis. (A) Doppler ultrasound image of the axillary artery in a patient without lymph node metastasis. The vessel appears normal, with no signs of abnormal flow or structural changes; (B) Doppler ultrasound image of the axillary artery in a patient with lymph node metastasis. Structural changes and altered blood flow are visible compared to the normal appearance in (A).

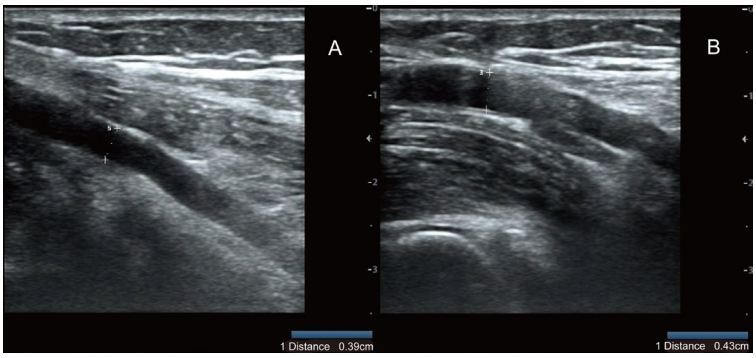

Figure 2. Typical Doppler images of the patient's brachial artery, with and without lymph node metastasis. (A) Doppler ultrasound image of the brachial artery in a patient without lymph node metastasis. The vessel appears normal, with no signs of abnormal flow or structural changes; (B) Doppler ultrasound image of the brachial artery in a patient with lymph node metastasis. Structural changes and altered blood flow are visible compared to the normal appearance in (A).

Patients were positioned on their backs, with the arms raised and turned outward while the elbows were bent. We conducted imaging of the axillary and brachial vessels, examining each structure in both transverse and longitudinal planes. In the longitudinal view, we assessed the axillary vessels located just distal to the junction of the axillary and subclavian arteries. For the brachial vessels, evaluations were performed near the elbow, prior to their bifurcation into the radial and ulnar arteries in the forearm. A real-time, continuous assessment of blood flow velocities was obtained using spectral Doppler, and the average values - which were automatically generated by the ultrasound machine - were recorded during three stable Doppler waveforms. The angle of insonation was consistently maintained at less than 60°, ensuring proper alignment with the vessel's axis. Typical Doppler pictures of brachial artery from patients with and without LNM are shown in **Figure 2**.

These assessments were conducted preoperatively to avoid any influence of surgical intervention or postoperative changes on vascular parameters. The ultrasound examination did not affect the decision-making process for surgery nor interfere with pathological evaluations, as it was strictly observational and non-invasive.

Statistical analysis

Data analysis was performed using SPSS version 29.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were displayed as frequencies and percentages [n (%)], and the chi-square test was utilized for comparisons. The Shapiro-Wilk test was conducted to evaluate the normality of continuous variables. Continuous data that followed a normal distribution were expressed as means with standard deviations (Mean ± sd). A significant threshold of $P < 0.05$ was set for all statistical tests. To reduce possible biases, any missing data were excluded from the analysis. Logistic regression was applied to identify risk factors, and the results were illustrated using receiver operating characteristic (ROC) curves and nomograms.

Results

Baseline data

As shown in **Table 1**, the comparison of baseline characteristics between BRCA patients

Table 1. Baseline data of non-LNM and LNM groups

Parameters	Non-LNM (n = 87)	LNM (n = 85)	t/χ^2	*P* Value
Age (years)	52.87 ± 6.23	54.32 ± 7.05	1.431	0.154
BMI (kg/m^2)	24.45 ± 2.56	24.89 ± 3.12	1.000	0.319
Tumor Size (cm)	3.27 ± 0.65	3.45 ± 0.78	1.606	0.110
Multifocality (Y/N)	37/50	46/9	2.313	0.128
Menopausal state (Y/N)	47/40	42/43	0.366	0.545
Clinical tumor size staging [n (%)]			0.740	0.864
cT1	5 (5.75%)	6 (7.06%)		
cT2	69 (79.31%)	64 (76.47%)		
cT3	10 (11.49%)	9 (10.59%)		
cT4	3 (3.45%)	5 (5.88%)		

LNM: Lymph Node Metastasis; BMI: Body Mass Index; cT: Clinical Tumor Size Staging (cT1, cT2, cT3, cT4).

Table 2. Mean ER, PR and HER2 status in non-LNM and LNM groups

Parameters	Non-LNM (n = 87)	LNM (n = 85)	χ^2	*P* Value
HER2 Status (positive/negative)	19/68	34/51	6.651	0.01
E R (positive/negative)	67/20	52/33	5.057	0.025
P R (positive/negative)	61/26	47/38	4.042	0.044

HER2: human epidermal growth factor receptor 2; ER: estrogen receptor; PR: progesterone receptor; LNM: Lymph Node Metastasis.

with and without LNM revealed no significant differences in age (52.87 ± 6.23 years vs. 54.32 ± 7.05 years; t = 1.431, *P* = 0.154), BMI (24.45 ± 2.56 kg/m^2 vs. 24.89 ± 3.12 kg/m^2; t = 1.000, *P* = 0.319), tumor size (3.27 ± 0.65 cm vs. 3.45 ± 0.78 cm; t = 1.606, *P* = 0.110), multifocality (37/50 vs. 46/9; χ^2 = 2.313, *P* = 0.128), menopausal state (47/40 vs. 42/43; χ^2 = 0.366, *P* = 0.545), or clinical tumor size staging (cT1: 5 (5.75%) vs. 6 (7.06%), cT2: 69 (79.31%) vs. 64 (76.47%), cT3: 10 (11.49%) vs. 9 (10.59%), cT4: 3 (3.45%) vs. 5 (5.88%); χ^2 = 0.740, *P* = 0.864). Thus, the groups were comparable.

Mean Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor 2 (HER2) status

The mean ER, PR, and HER2 statuses were significantly different between the non-LNM and LNM groups. Specifically, there was a higher proportion of HER2 positive cases in the LNM group (34/51) compared to the non-LNM group (19/68; χ^2 = 6.651, *P* = 0.01); there was a lower proportion of ER positive cases in the LNM group (52/33) relative to the non-LNM group (67/20; χ^2 = 5.057, *P* = 0.025); and there were fewer PR positive cases observed in the LNM group (47/38) than in the non-LNM group (61/26; χ^2 = 4.042, *P* = 0.044) (**Table 2**). These results suggest that the HER2 status, ER status, and PR status significantly differed between the non-LNM and LNM groups, indicating potential associations with metastatic status.

Mean ultrasound parameters of axillary artery

The ultrasound parameters of the axillary artery were compared between the non-LNM and LNM groups (**Figure 3**). The axillary artery diameter was significantly larger in the LNM group (5.98 ± 0.85 mm) compared to the non-LNM group (5.59 ± 0.78 mm; t = 3.141, *P* = 0.002). The end-diastolic velocity was also significantly higher in the LNM group (27.89 ± 4.12 cm/s) compared to the non-LNM group (25.45 ± 3.54 cm/s; t = 4.172, *P* < 0.001). The pulsatility index was significantly increased in the LNM group (2.45 ± 0.38) compared to the non-LNM group (2.24 ± 0.32; t = 3.779, *P* < 0.001). Additionally, the resistive index was significantly higher in the LNM group (0.73 ± 0.11) compared to the non-LNM group (0.68 ± 0.10; t = 2.934, *P* = 0.004). However, there was no significant difference in peak systolic velocity between the two groups (60.43 ± 7.24 cm/s vs.

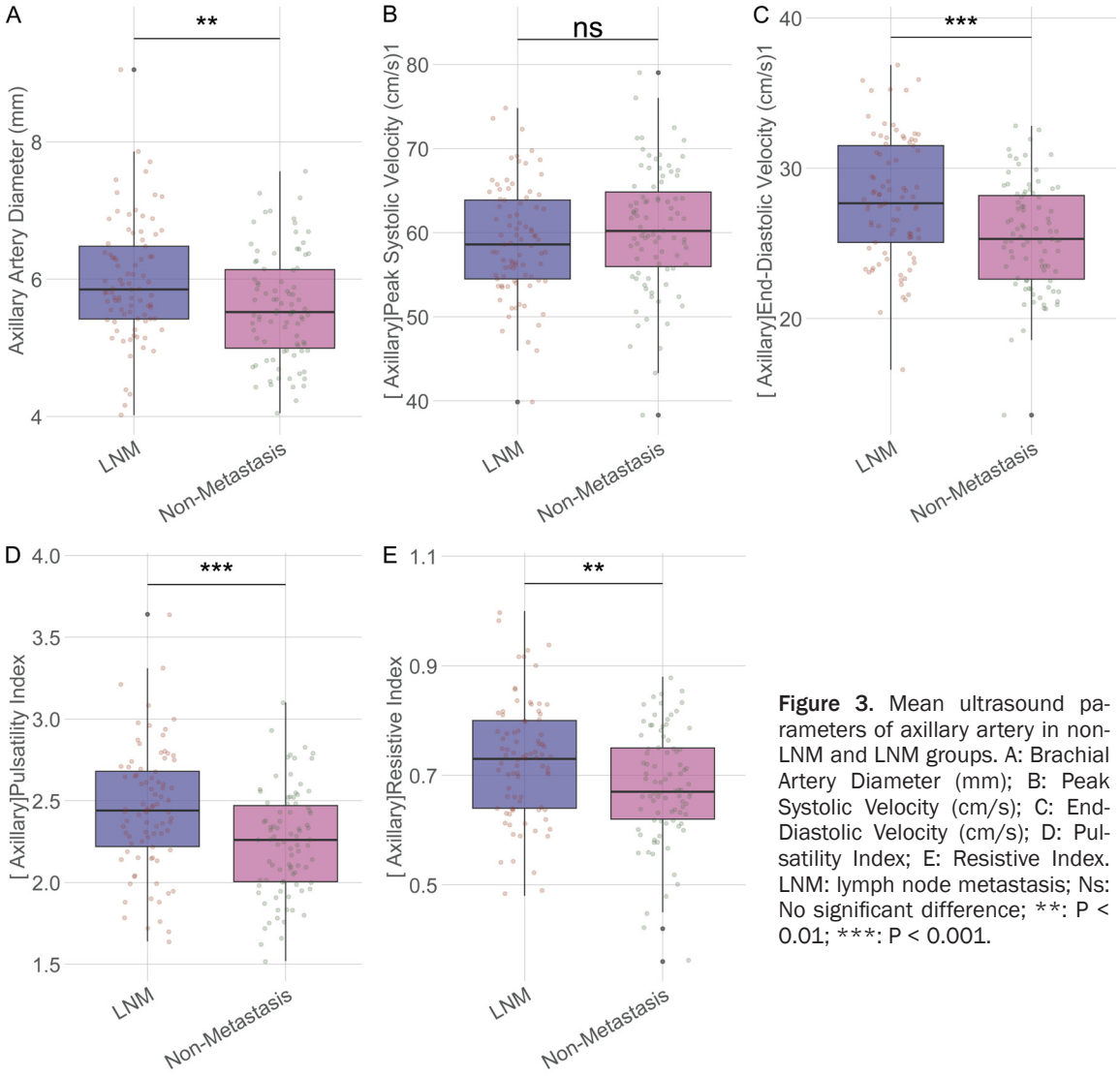

Figure 3. Mean ultrasound parameters of axillary artery in non-LNM and LNM groups. A: Brachial Artery Diameter (mm); B: Peak Systolic Velocity (cm/s); C: End-Diastolic Velocity (cm/s); D: Pulsatility Index; E: Resistive Index. LNM: lymph node metastasis; Ns: No significant difference; **: P < 0.01; ***: P < 0.001.

58.97 ± 6.55 cm/s; t = 1.388, *P* = 0.167). These findings indicate that several ultrasound parameters of the axillary artery, including diameter and resistive index, differed significantly between the non-LNM and LNM groups, suggesting potential diagnostic and prognostic value in assessing axillary artery characteristics in the context of LNM.

Mean ultrasound parameters of brachial artery

The ultrasound evaluation parameters of the brachial artery were compared between the non-LNM and LNM groups. The brachial artery diameter was found to be significantly larger in the LNM group (4.31 ± 0.78 mm) compared to the non-LNM group (3.97 ± 0.65 mm), with a statistically significant difference (*t* = 3.260, *P* = 0.001) (**Figure 4**). However, peak systolic velocity did not differ significantly between the non-LNM (73.56 ± 8.43 cm/s) and LNM (71.25 ± 7.89 cm/s) groups (*t* = 1.854, *P* = 0.065). End-diastolic velocity and pulsatility index were both significantly higher in the LNM group compared to the non-LNM group (*t* = 3.602, *P* < 0.001 and *t* = 2.811, *P* = 0.0026, respectively). Additionally, the resistive index was significantly higher in the LNM group (0.67 ± 0.10) compared to the non-LNM group (0.63 ± 0.10) (*t* = 2.855, *P* = 0.005). These findings suggest that several ultrasound parameters of the brachial artery, including diameter, end-diastolic velocity, pulsatility index, and resistive index, differed significantly between the non-LNM and LNM

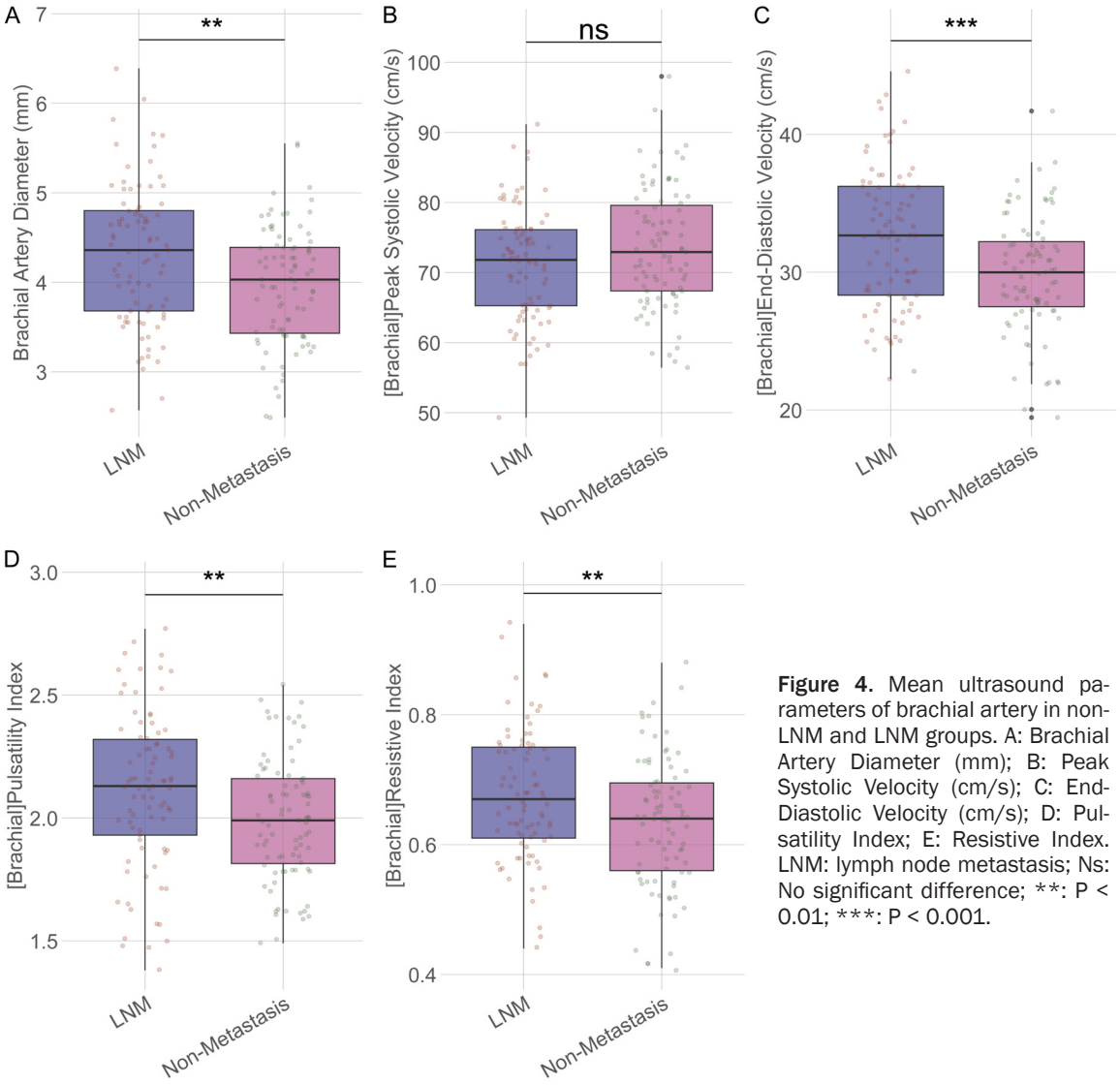

Figure 4. Mean ultrasound parameters of brachial artery in non-LNM and LNM groups. A: Brachial Artery Diameter (mm); B: Peak Systolic Velocity (cm/s); C: End-Diastolic Velocity (cm/s); D: Pulsatility Index; E: Resistive Index. LNM: lymph node metastasis; Ns: No significant difference; **: P < 0.01; ***: P < 0.001.

groups, pointing to potential implications for assessing brachial artery characteristics in the context of LNM.

Correlation analysis

The correlation analysis of axillary and brachial artery parameters with axillary LNM in BRCA patients revealed several significant findings (**Table 3**). Specifically, the axillary artery diameter showed a positive correlation with axillary LNM (r = 0.231, P = 0.002), as did the end-diastolic velocity (r = 0.291, P < 0.001), pulsatility index (r = 0.277, P < 0.001), and resistive index (r = 0.198, P = 0.009). Similarly, the brachial artery diameter (r = 0.225, P = 0.003), end-diastolic velocity (r = 0.243, P = 0.001), pulsatility index (r = 0.220, P = 0.004), and resistive index (r = 0.199, P = 0.009) were positively correlated with axillary LNM. Additionally, the HER2 status (r = 0.197, P = 0.010) was positively correlated with axillary LNM, while the ER (r = -0.171, P = 0.025) and PR (r = -0.153, P = 0.045) statuses were negatively correlated. These findings suggest a potential association between specific arterial parameters and axillary LNM in BRCA patients, providing valuable insights for further research and potential clinical implications.

Logistic regression analysis

The logistic regression analysis of axillary and brachial artery parameters for axillary LNM in BRCA patients revealed significant associations (**Table 4**). Specifically, the axillary artery

Table 3. Correlation analysis of axillary and brachial artery parameters with axillary LNM in breast cancer patients

Variable	rho	*P* Value
HER2 Status	0.197	0.010
ER	-0.171	0.025
PR	-0.153	0.045
Axillary Artery Diameter (mm)	0.231	0.002
[Axillary] End-Diastolic Velocity (cm/s)	0.291	P < 0.001
[Axillary] Pulsatility Index	0.277	P < 0.001
[Axillary] Resistive Index	0.198	0.009
Brachial Artery Diameter (mm)	0.225	0.003
[Brachial] End-Diastolic Velocity (cm/s)	0.243	0.001
[Brachial] Pulsatility Index	0.220	0.004
[Brachial] Resistive Index	0.199	0.009

HER2: human epidermal growth factor receptor 2; ER: estrogen receptor; PR: progesterone receptor; rho: Spearman's rank correlation coefficient; LNM: Lymph Node Metastasis.

diameter (coefficient = 0.598, std error = 0.201, Wald = 2.982, *P* = 0.003, OR = 1.819) was significantly associated with axillary LNM, indicating that a larger diameter is associated with an increased odds of LNM. The axillary artery end-diastolic velocity (coefficient = 0.168, std error = 0.044, Wald = 3.825, *P* < 0.001, OR = 1.183) also showed a significant association, suggesting that higher velocities are linked to a greater likelihood of LNM. The axillary artery pulsatility index (coefficient = 1.673, std error = 0.476, Wald = 3.512, *P* < 0.001, OR = 5.328) and resistive index (coefficient = 4.366, std error = 1.557, Wald = 2.804, *P* = 0.005, OR = 78.763) were strongly associated with LNM, with higher indices indicating a substantially increased risk.

Similarly, the brachial artery diameter (coefficient = 0.671, std error = 0.225, Wald = 2.986, *P* = 0.003, OR = 1.957) was significantly associated with LNM, suggesting that a larger brachial artery diameter is related to a higher odds of LNM. The brachial artery end-diastolic velocity (coefficient = 0.118, std error = 0.035, Wald = 3.377, *P* < 0.001, OR = 1.125) and pulsatility index (Coefficient = 1.511, Std Error = 0.556, Wald = 2.717, *P* = 0.007, OR = 4.529) also showed significant associations, with higher values indicating a greater risk of LNM. The brachial artery resistive index (coefficient = 4.388, std error = 1.600, Wald = 2.743, *P* = 0.006, OR = 80.512) had a particularly strong association, with a very high odds ratio indicating a significant increase in LNM risk.

These findings underscore the potential predictive value of arterial parameters and molecular markers in identifying axillary LNM in BRCA patients, indicating their clinical relevance and warranting further investigation.

ROC curve analysis: the predictive value of axillary and brachial artery parameters for axillary LNM

This study analyzed a range of arterial parameters to examine the predictive significance of axillary and brachial artery measurements for axillary LNM among BRCA patients (**Table 5**). The analysis of the axillary artery diameter showed a sensitivity of 0.706, specificity of 0.529, an area under the curve (AUC) of 0.633, and a Youden index of 0.235. Among the axillary artery parameters, the resistive index exhibited the highest sensitivity at 0.671, while the pulsatility index had the best specificity at 0.655, with AUCs of 0.614 and 0.66, and Youden indices of 0.246 and 0.267, respectively. The end-diastolic velocity of the axillary artery demonstrated a sensitivity of 0.588, specificity of 0.667, an AUC of 0.668, and a Youden index of 0.255.

For the brachial artery, the end-diastolic velocity provided the most favorable combination of sensitivity (0.553), specificity (0.747), AUC (0.64), and Youden index (0.300). The brachial artery diameter had a relatively low sensitivity of 0.388 but a high specificity of 0.874, contributing to an AUC of 0.630 and a Youden index of 0.262. The pulsatility index of the brachial artery showed similar sensitivity (0.553) and lower specificity (0.701) with an AUC of 0.627 and a Youden index of 0.254. Lastly, the resistive index of the brachial artery had the lowest sensitivity at 0.318 but maintained a high specificity at 0.862, with an AUC of 0.615 and a Youden index of 0.180.

This suggests that while individual parameters have some predictive value, their combined use may offer a more robust approach to predicting axillary LNM in BRCA patients. There-

Table 4. Logistic regression analysis of axillary and brachial artery parameters for axillary LNM in breast cancer patients

Parameters	Coefficient	Std Error	Wald	*P* Value	OR
Axillary Artery Diameter (mm)	0.598	0.201	2.982	0.003	1.819
[Axillary] End-Diastolic Velocity (cm/s)	0.168	0.044	3.825	< 0.001	1.183
[Axillary] Pulsatility Index	1.673	0.476	3.512	< 0.001	5.328
[Axillary] Resistive Index	4.366	1.557	2.804	0.005	78.763
Brachial Artery Diameter (mm)	0.671	0.225	2.986	0.003	2.019
[Brachial] End-Diastolic Velocity (cm/s)	0.118	0.035	3.377	< 0.001	1.125
[Brachial] Pulsatility Index	1.511	0.556	2.717	0.007	4.529
[Brachial] Resistive Index	4.388	1.600	2.743	0.006	80.512

OR: Odds Ratio; LNM: Lymph Node Metastasis.

Table 5. Predictive value of axillary and brachial artery parameters for axillary LNM in breast cancer patients

Parameters	Sensitivities	Specificities	AUC	Youden index
Axillary Artery Diameter (mm)	0.706	0.529	0.633	0.235
[Axillary] End-Diastolic Velocity (cm/s)	0.588	0.667	0.668	0.255
[Axillary] Pulsatility Index	0.612	0.655	0.660	0.267
[Axillary] Resistive Index	0.671	0.575	0.614	0.246
Brachial Artery Diameter (mm)	0.388	0.874	0.63	0.262
[Brachial] End-Diastolic Velocity (cm/s)	0.553	0.747	0.640	0.300
[Brachial] Pulsatility Index	0.553	0.701	0.627	0.254
[Brachial] Resistive Index	0.318	0.862	0.615	0.180

AUC: Area Under the Curve; LNM: Lymph Node Metastasis.

fore, we established a model combining axillary and brachial artery parameters.

Nomogram construction: a prediction model for axillary LNM based on axillary and brachial artery parameters

By incorporating parameters of the axillary and brachial arteries, a nomogram was constructed using the lineplot function (**Figure 5**). The AUC value of the model was found to be 0.984 (**Figure 6**). To further validate the superiority of the combined model over individual parameters, DeLong's test was conducted for each of the eight individual parameters. The results are summarized in **Table 6**. The combined model (AUC = 0.984) showed significantly higher predictive capability compared to each of the individual parameters ($P < 0.05$). These findings support the hypothesis that integrating information from multiple parameters enhances the predictive accuracy for axillary LNM in BRCA patients.

Discussion

BRCA remains a significant global health concern, with LNM playing a crucial role in treatment decisions and prognosis [29]. Historically, the assessment of lymph node involvement in BRCA has relied on invasive procedures such as ALND and SLNB [30]. However, these approaches are not without limitations, necessitating the search for non-invasive and low-risk modalities to predict and assess LNM. This study aimed to evaluate the predictive value of ultrasound assessment of axillary and brachial artery parameters for LNM in BRCA patients.

The molecular characterization of BRCA, including ER status, HER2 status, as well as PR status, emerged as crucial factors associated with LNM [31]. The significant differences observed in these molecular markers between the non-LNM and LNM groups highlight the importance of considering molecular profiles in the assessment of lymph node involvement. Notably, the higher percentage of HER2-positive cases in

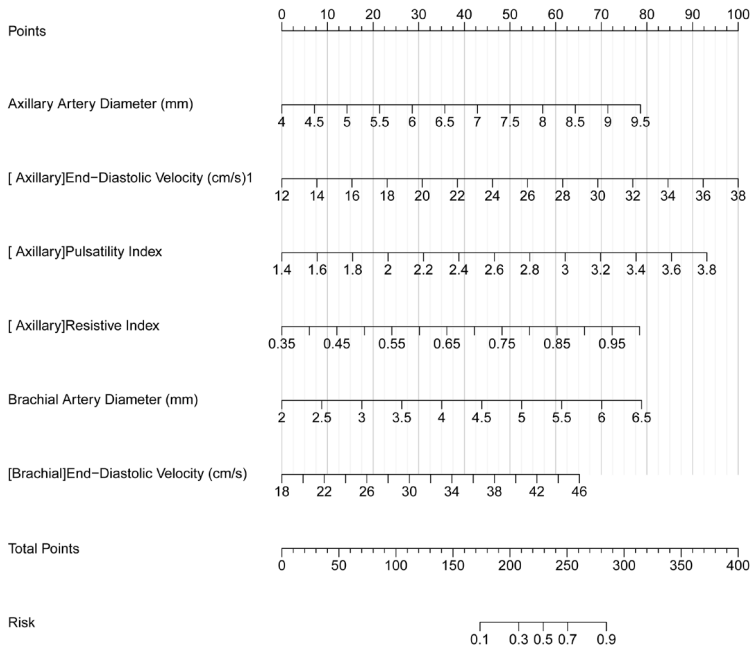

Figure 5. Nomogram depicting the prediction of lymph node metastasis based on parameters of the axillary artery and brachial artery.

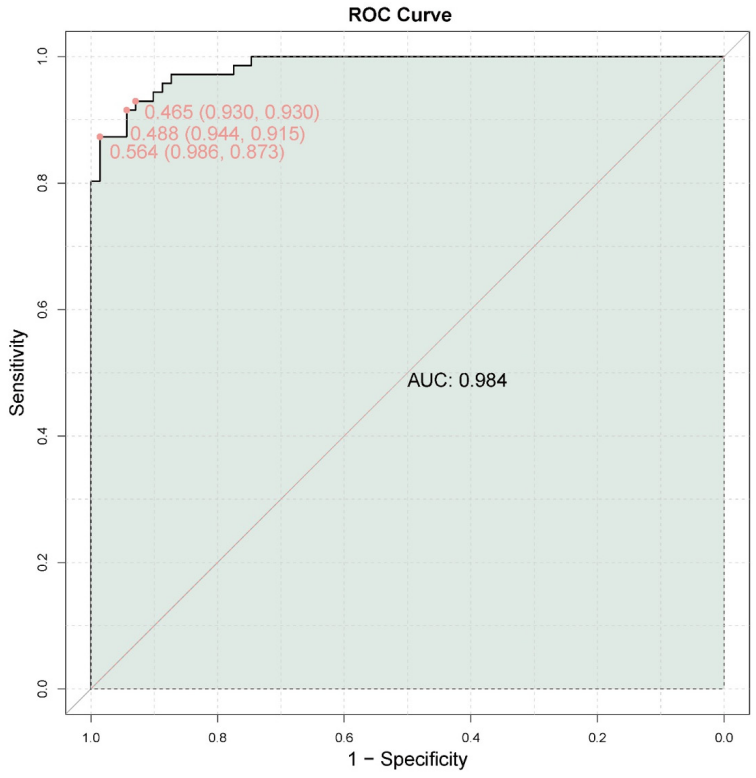

Figure 6. The predictive value of a combined model of axillary and brachial artery parameters for axillary lymph node metastasis in breast cancer patients. AUC: Area Under the Curve.

the LNM group suggests a potential association between HER2 and lymphatic spread. This finding is consistent with previous research indicating the role of HER2 overexpression in BRCA aggressiveness and metastatic potential, emphasizing the relevance of molecular markers in predicting disease progression and informing treatment strategies [32]. ER-negative tumors tend to be more aggressive and have a higher likelihood of LNM compared to ER-positive tumors [33]. Mechanistically, ER signaling can inhibit tumor proliferation and angiogenesis, while its absence may lead to increased cellular motility and invasiveness. PR-positive tumors are generally associated with a better prognosis and lower risk of LNM [34], likely due to PR's role in regulating cell cycle progression and apoptosis. Integrating ER and PR statuses into the prediction model can enhance its accuracy by accounting for these distinct biological behaviors. These findings underscore the importance of incorporating ER, HER2, and PR statuses in evaluating BRCA patients, offering a more comprehensive understanding of the molecular mechanisms underlying LNM and enhancing clinical management.

Ultrasound parameters of the axillary and brachial arteries provided valuable insights into their potential predictive value for LNM. The larger diameter of both the axillary and brachial arteries in the LNM group suggests a relationship between arterial dimensions and lymphatic involvement. These findings are consistent with the

Table 6. DeLong test results for comparing AUCs of individual parameters with the combined model

Parameter	AUC	*P*-value (vs. Combined Model)
Combined Model (Axillary + Brachial)	0.984	-
Axillary Artery Diameter (mm)	0.633	0.003
[Axillary] End-Diastolic Velocity (cm/s)	0.668	0.007
[Axillary] Pulsatility Index	0.660	0.010
[Axillary] Resistive Index	0.614	0.015
Brachial Artery Diameter (mm)	0.63	0.005
[Brachial] End-Diastolic Velocity (cm/s)	0.640	0.012
[Brachial] Pulsatility Index	0.627	0.018
[Brachial] Resistive Index	0.615	0.020

AUC: Area Under the Curve.

concept that tumor-associated angiogenesis and lymphangiogenesis lead to increased vascularization and vessel dilation, potentially contributing to the observed arterial changes [35]. Moreover, the higher resistive index in both the axillary and brachial arteries of the LNM group indicates altered vascular resistance, possibly reflecting the impact of tumor-induced vascular remodeling and impaired hemodynamics associated with lymphatic metastasis. These ultrasound-derived arterial parameters hold promise as non-invasive biomarkers for identifying lymphatic involvement in BRCA, offering a window into the complex interplay between tumor biology and vascular alterations.

Correlation and logistic regression analyses further elucidated the connections between arterial parameters and LNM. Although all correlations were statistically significant, some correlation coefficients (r values) were relatively low, suggesting moderate relationships. To explore possible mechanisms behind these associations, we referred to existing literature, which indicates that vascular changes might be driven by factors such as hypoxia-induced angiogenesis, inflammation, and tumor-secreted growth factors [36]. The significant positive correlations of axillary artery diameter, end-diastolic velocity, and pulsatility index, as well as brachial artery diameter, with LNM underscore the potential of these parameters as predictors of disease progression. Conversely, the negative correlations of ER and PR statuses with LNM emphasize the role of hormonal receptor expression in modulating lymphatic spread, highlighting the intricate interplay between molecular and vascular factors in BRCA progression.

This study's findings align with previous research demonstrating the role of vascular alterations in cancer progression, emphasizing the potential of non-invasive ultrasound evaluation of arterial parameters as a complementary approach to molecular profiling for prognostication [37]. The non-invasive nature of ultrasound assessment presents a distinct advantage over invasive procedures, offering a more patient-friendly and resource-efficient method for assessing lymphatic involvement in BRCA. The ability to dynamically visualize vascular changes in real-time enhances the sensitivity of lymph node assessment, potentially facilitating early detection and risk stratification.

The predictive value of arterial parameters for LNM was further examined through ROC analysis. While individual arterial parameters demonstrated moderate sensitivity and specificity, the construction of a combined model incorporating axillary and brachial artery parameters resulted in an increased AUC. This model leveraged the unique contributions of distinct vascular parameters, offering a more comprehensive approach to predicting lymphatic involvement in BRCA. The nomogram derived from the combined model provides a practical tool for estimating the risk of LNM based on arterial parameters, fostering personalized risk assessment and treatment decision-making.

To fully assess the clinical utility of our proposed model, it is essential to compare its performance with existing models used for predicting LNM in BRCA. Previous studies have developed various models based on clinical, pathological, and molecular features. For example, an integrative 3' Untranslated Region (UTR)-based model for triple-negative BRCA has

achieved an AUC of around 0.7 [38]. Additionally, a model in the study by Kirienko et al. on gene expression profiles in lung cancer achieved an AUC of 0.87 [39]. Our model, which integrates ultrasound axillary and brachial artery parameters, demonstrated a higher AUC of 0.984, indicating superior predictive capability. However, to establish its clinical superiority, future studies should conduct head-to-head comparisons with established models in larger, multi-center cohorts. Such comparisons will help to determine whether the addition of arterial parameters significantly improves the accuracy and reliability of LNM prediction, thereby enhancing clinical decision-making and patient outcomes.

This study's strengths lie in its comprehensive assessment of both molecular and vascular parameters and its focus on non-invasive ultrasound evaluation, addressing a critical need for alternative modalities to inform BRCA management. Tumor-associated angiogenesis and lymphangiogenesis, which entail the formation of new blood and lymphatic vessels to support tumor growth and dissemination, lead to a complex interplay of vascular changes, comprising vessel dilation, increased vascularization, altered hemodynamics, and modified vascular resistance [40]. As BRCA progresses and involves the lymph nodes, these vascular alterations become more pronounced, reflecting the dynamic interactions between the tumor and the host vasculature [41, 42]. The non-invasive ultrasound assessment of axillary and brachial artery parameters provides insight into these vascular changes by visualizing the dimensions, flow characteristics, and resistance of these arteries, offering real-time, dynamic information about the vascular changes associated with tumor progression [43, 44]. This approach enables valuable insights into the biological behavior of BRCA and its impact on the surrounding vasculature. Moreover, the non-invasive nature of ultrasound assessment presents a distinct advantage over invasive procedures such as lymph node dissection, as it allows for repeated and longitudinal evaluations without imposing significant discomfort or risk on patients [45]. This facilitates the longitudinal monitoring of vascular changes, potentially enabling the early detection of evolving metastatic processes and guiding timely interventions [46]. Additionally, integrating arterial parameters with molecular markers and clinical characteristics provides a multi-dimensional approach to risk assessment in BRCA. This comprehensive strategy allows for a more thorough understanding of disease progression by considering not only the tumor's molecular profile but also its impact on the host vasculature, potentially enhancing precise and personalized BRCA management. The potential of non-invasive ultrasound assessment of axillary and brachial artery parameters as valuable tools for predicting LNM in BRCA is underscored by its ability to bridge the gap between tumor biology and non-invasive diagnostics, representing a confluence of insights from oncology, vascular biology, and imaging sciences [47, 48]. This convergence presents a promising avenue for advancing the prognostication and management of BRCA. By elucidating the interconnectedness of arterial parameters and molecular markers with LNM, this study lays the groundwork for a multi-faceted approach to risk stratification and treatment guidance in BRCA.

While this study offers important insights, it is essential to recognize several limitations. The research data was collected from a single center, and the sample size was relatively small, which may restrict the applicability of the results to broader populations. Additionally, the retrospective design introduces potential biases and confounding variables that may impact the interpretation of results. Future studies encompassing larger, multi-center cohorts and prospective designs are warranted to validate and further refine the predictive value of ultrasound evaluation of arterial parameters for LNM in BRCA. It is well recognized that BRCA metastasis is a multifactorial process involving genetic mutations, immune evasion, epithelial-mesenchymal transition (EMT), and interactions with the tumor microenvironment [49]. Therefore, future research should aim to integrate multiple factors, including molecular profiles, clinical characteristics, and imaging features, to develop a comprehensive model for predicting LNM. While our study focused on ER, PR, and HER2, it is acknowledged that other biomarkers, such as Ki67, also play an important role in predicting LNM. Future studies should consider incorporating a broader range of biomarkers to provide a more comprehensive understanding of the molecular mechanisms underlying LNM. Integrating multiple bio-

markers may offer a synergistic effect, providing a more robust and reliable model for predicting LNM in BRCA.

Conclusion

In conclusion, this study underscores the potential of non-invasive ultrasound assessment of axillary and brachial artery parameters as valuable tools for predicting LNM in BRCA. The findings highlight the intricate interplay between vascular alterations and molecular profiles in disease progression, offering novel insights into the complex landscape of BRCA biology. The integration of arterial parameters alongside molecular markers provides a multidimensional approach to risk assessment and treatment decision-making, paving the way for enhanced precision and personalized care in BRCA management.

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