The Egyptian Journal of Hospital Medicine (October 2025) Vol. 101, Page 5001-5009

Identification of Triple Negative Breast Cancer Based on Sonomammographic Findings

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ABSTRACT

Background: Breast cancer (BC) is a heterogeneous disease with various morphologic, biologic, and molecular features. Ultrasonographic imaging provides valuable predictive signs for different molecular subtypes. Triple-negative breast cancer (TNBC) represents about 12.5% of BC cases and is characterized by the absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2).

Objective: This study aimed to evaluate the role of sono-mammography in predicting TNBC and differentiating it from other molecular subtypes and benign lesions.

Patients and methods: This prospective cohort study included 72 patients diagnosed with breast cancer. Diagnostic processes involved clinical examinations, history-taking, digital mammography, and high-resolution ultrasound (US), with biopsies sent for pathological analysis.

Results: Significant differences were observed between TNBC and other molecular subtypes in terms of lesion size and characteristics. Lesions smaller than 3 cm typically showed benign features (oval shape, microlobulated margins), while larger lesions exhibited malignant characteristics (irregular shape, speculated margins).

Conclusions: Sono-mammographic findings are promising tools for distinguishing TNBC from other breast cancer subtypes, particularly in small lesions.

Keywords: Molecular subtypes, Breast cancer, TNBC, Mammography, Ultrasonography.

INTRODUCTION

Breast cancer (BC) is a heterogeneous disease with various morphologic, biologic, and molecular features. Molecular subtyping, based on gene expression, is essential for individualized management and prognosis prediction [1].

Ultrasonographic imaging provides valuable predictive signs for different molecular subtypes of BC, including tumor shape, margin, boundaries, and calcification. Despite advancements in ultrasound (US) technology, distinguishing between benign and malignant lesions, it remains challenging. Understanding imaging descriptors for different molecular subtypes can help reduce false diagnoses [2]. Triple-negative breast cancer (TNBC) represents about 12.5% of BC cases and is characterized by the absence of ER, PR, and HER2. TNBC is more common in younger females and those with a BRCA1 mutation, and is known for its aggressive nature and poor prognosis [3].

PATIENTS AND METHODS

This is prospective study included 72 female patients, their ages ranged from 22 to 78 years and was conducted at Mansoura Oncology Center from May 2023 to May 2024.

- **Inclusion criteria:** Clinically suspicious breast symptoms.
- **Exclusion criteria:** Pregnant or breastfeeding women and those with breast implants.

Patients underwent clinical examinations, mammography and ultrasound with biopsies analyzed pathologically.

Ethical considerations: The study was conducted after approval by The Research Ethics Committee of the Faculty of Medicine, Mansoura University. All participants provided written informed consents prior to enrolment. The consent form clearly stated their agreement to participate in the study and for the publication of anonymized data, with assurance of confidentiality and privacy protection. This work was performed in accordance with the ethical standards of the institutional research committee and with the principles of the World Medical Association Declaration of Helsinki for studies involving human participants.

Statistical analysis

SPSS version 23.0 was utilized for data management and data analysis. Qualitative data were expressed as count and percent. Using the Kolmogorov-Smirnov and Shapiro-Wilk tests, quantitative data were first examined for normality; if $p > 0.050$, the data were considered normally distributed. If the quantitative data were normally distributed, they were expressed as mean ± SD and if not, it was expressed as median and IQR. One-Sample Chi-Square test was utilized to assess Qualitative data for one group. Chi-Square test (or Fisher's exact test) was utilized to assess Qualitative data

Received: 10/05/2025
Accepted: 12/07/2025

for two groups (2X2 table). Regarding Qualitative data for more than two groups (e.g., 2X3 table), Chi-Square test (with Bonferroni method to adjust p values when comparing column proportions) was utilized. Regarding Quantitative data between two groups, Independent-Samples t-test was utilized if data were normally distributed in both groups. The non-parametric alternative Mann-Whitney U test was utilized if not. Results were considered as statistically significant if p value ≤ 0.05.

RESULTS

A total of 72 cases were included in the study, with 37 classified as TNBC and 35 as non-TNBC. Statistical significance of associations between TNBC status and imaging characteristics was assessed using appropriate tests, including the Chi-square test and Fisher exact test. In this study we found that oval lesions with circumscribed margins exhibited a significant association with TNBC (P=0.0004*), indicating their relevance in TNBC diagnosis. **Sensitivity:** Lesions with oval shape and circumscribed margin demonstrated high sensitivity in identifying TNBC (91.4% and 96.9% respectively).

Specificity: Specificity for oval shape and circumscribed margin was moderate (54.1% and 55.9% respectively) indicating their ability to identify non-TNBC lesions. Table (1) presented significant findings related to TNBC cases and their lesion characteristics. In terms of lesion shape, TNBC cases predominantly exhibited oval and rounded shapes, contrasting significantly with non-TNBC cases where irregular shapes were more common (45.9% and 100% respectively, p=0.001). Regarding other aggressive findings, non-TNBC cases showed higher rates of intraductal extension (70% vs. 42.9%, p=0.001) compared to TNBC cases. However, there were no statistically significant differences between TNBC and non-TNBC cases according to site (retroareolar zones A, B, AB, BC, and C). The study employed statistical tests including Mann-Whitney U test and Monte Carlo test to evaluate these differences. *Statistically significant.

Table (1): Comparison of tumor characteristics, site, shape, and aggressive imaging findings between triple-negative and non–triple-negative breast cancer cases

	Triple negative		Test of significance
	No N=35(%)	**Yes N=37(%)**	
Size			
Width (mm) **Median (range)**	28.2 (13.4-67)	30 (9-75)	Z=0.255 P=0.799
Length(mm) **Median (range)**	18 (7.5-54)	20.2 (5-78)	Z=1.48 P=0.144
Site **Retro areolar** **Zone A** **Zone B** **Zone AB** **ZONE BC** **Zone C**	 3 (8.6) 5 (14.3) 14 (40.0) 2 (5.7) 5 (14.3) 6 (17.1)	 2 (5.4) 12 (32.4) 11 (29.7) 7 (18.9) 1 (2.7) 4 (10.8)	 MC=9.24 P=0.100
Shape **Irregular** **Rounded** **Oval**	 35(100.0) 0 0	 20(54.1) 2 (5.4) 15 (40.5)	 MC=22.70 P=0.001*
Other aggressive findings **Intraductal extension** **Parenchymal distortion** **Skin retraction with smaller satellite** **Infiltrative retro areolar ducts** **Infiltrating the nipple areolar complex**	 14 (70.0) 3 (15.0) 1 (5.0) 1 (5.0) 1 (5.0)	 3 (42.9) 0 0 1 (14.3) 3 (42.9)	 P=0.001* P=0.109 P=0.486 P=1.0 P=0.614

Table (2) Illustrated significant sonographic findings related to non-TNBC compared to TNBC cases. Non-TNBC lesions were significantly more hypoechoic (78.4% vs. 10.8%, pcompare while well-circumscribed (29.7% vs. 97.1%, p=0.0004) is significantly associated with TNBC compared to non-TNBC lesions. On the other hand, non-TNBC exhibited higher rates of speculated margins (43.2% vs. 29.7%, p=0.001) and vascularity (51.4% vs. 48.6%, p=0.001).

Table (2): Comparison of ultrasonographic features between triple-negative and non–triple-negative breast cancer cases

	Triple negative		**Test of significance**
	No N=35(%)	**Yes N=37(%)**	
Echogenicity			
Isoechoic	0	4(10.8)	P=0.11
Hypoechoic	35(100)	29(78.4)	P=0.02*
Heterogeneous	0	2(5.4)	P=0.163
Anechoic with soft tissue	0	2(5.4)	P=0.163
Margin			
well circumscribed	0	11(29.7)	P=0.0004*
Speculated	34(97.1)	16(43.2)	P=0.001*
non circumscribed	0	4(10.8)	P=0.115
Obscured	1(2.9)	2(5.4)	P=1.0
lobulated	0	4(10.8)	P=0.11
Vascularity			
No	0	18(48.6)	χ^2=22.70
Yes	35(100)	19(51.4)	P=0.001*
Orientation to skin			
Not Parallel	35(100)	19(51.4)	χ^2=22.70
Parallel	0	18(48.6)	P=0.001*
Calcification			
No	30(85.7)	33(91.7)	χ^2=0.629
Yes	5(14.3)	3(8.3)	P=0.428
Affected lymph node			
No	15(42.9)	16(43.2)	χ^2=0.001
Yes	20(57.1)	21(56.8)	P=0.974

Table (3) reported significant mammographic findings associated with TNBC compared to non-TNBC cases. TNBC lesions were equally oval, rounded in shape (45.9%, p=0.001) and showed significantly higher rates of well circumscribed margins (38.2%, p=0.0shapein spite of Non-TNBC, which demonstrated speculated margins (44.1 p=0.0001). They also exhibited higher density (97.1% hyperdense vs. 100% isodense, p=1.0), although this difference was not statistically significant. There were no grouped microcalcifications observed in TNBC cases, whereas one non-TNBC case had this feature (p=0.486). Asymmetry (focal/global) was equally distributed between TNBC and non-TNBC cases (p=1.0).

Table (3): Comparison of mammographic features between triple-negative and non–triple-negative breast cancer cases

Mammogram	Triple negative		Test of significance
	No N=35(%)	Yes N=37(%)	
Shape **Rounded/ oval** **Irregular**	 0 32(91.4)	 17(45.9) 17(45.9)	 P=0.001* P=0.001*
Grouped microcalcification	1(2.9)	0	P=0.486
Asymmetry (focal/ global)	2(5.7)	3(8.1)	P=1.0
Margin **Well circumscribed** **Speculated** **Partially obscured** **Microlobulated**	N=32 0 31(96.9) 1(3.1) 0	N=34 13(38.2) 15(44.1) 2(5.9) 4(11.8)	 P=0.0009* P=0.0001* P=1.0 P=0.114
Density **isodense** **hyperdense**	N=32 0 32(100)	N=34 1(2.9) 33(97.1)	 FET=0.956 P=1.0

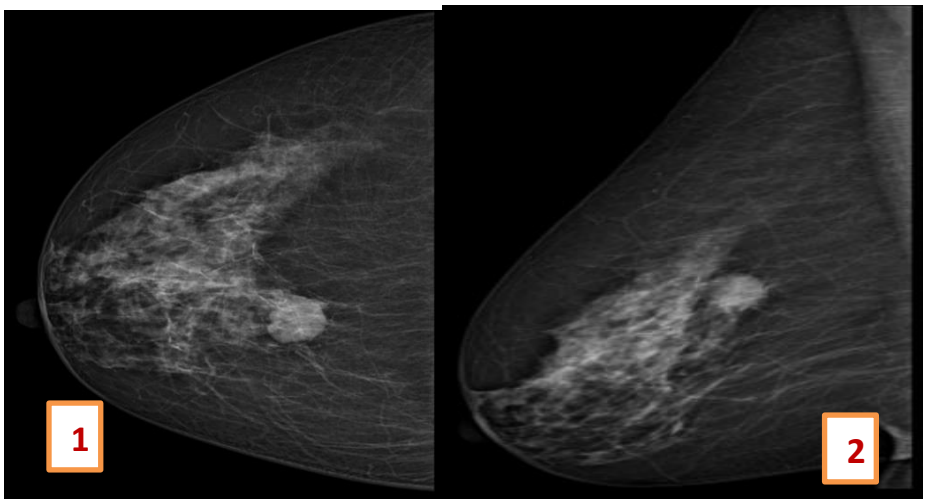
Table (4) presented the diagnostic performance of sono-mamographic features in distinguishing triple-negative breast cancer (TNBC) lesions. High sensitivity is observed for shape (91.4%) and margin (96.9%), indicating their effectiveness in identifying TNBC. However, specificity varied across features, with margin showing 55.9% specificity and echogenicity only 21.6%. Features like vascularity and orientation to skin exhibited perfect sensitivity (100%) but moderate specificity (48.7%), contributing to an overall accuracy ranging from 58.3% to 76.4%. Calcification and affected lymph nodes showed lower sensitivity (91.7% and 56.8% respectively) and specificity of 14.3% and 42.9%, resulting in lower predictive values and accuracy (PPV: positive predictive value, NPV: Negative predictive value).

Table 4: Diagnostic performance of different imaging features in differentiating triple-negative from non–triple-negative breast cancer

	Sensitivity %	Specificity %	PPV%	NPV%	Accuracy%
Shape	91.4	54.1	65.3	86.9	72.2
Margin	96.9	55.9	67.4	95	75.8
Echogenicity	97.1	21.6	53.9	88.9	58.3
Margin	97.1	56.8	68	95.5	76.4
Vascularity	100	48.7	64.8	100.0	73.6
Orientation to skin	100	48.7	64.8	100.0	73.6
Calcification	91.7	14.3	52.4	62.5	53.5
Affected lymph node	56.8	42.9	51.2	48.4	50.0

Figure legends:

Fig (1, 2, 3 and 4): female patient aged 38 years old married with one offspring presented with right breast lump and positive family history (mother and aunts).



Figures (1 & 2): Mammogram images MLO & CC views, Right breast upper outer quadrant dense lesion with oval shape and partially obscured margin.

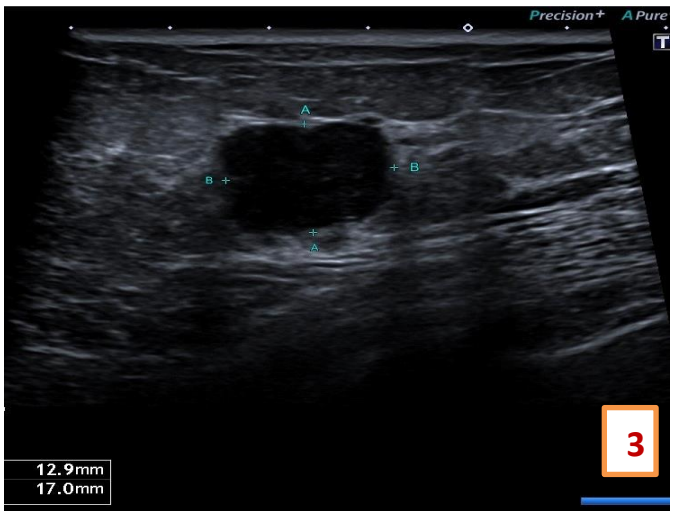


Figure (3): Ultrasound showed microlobulated oval hypoechoic mass.

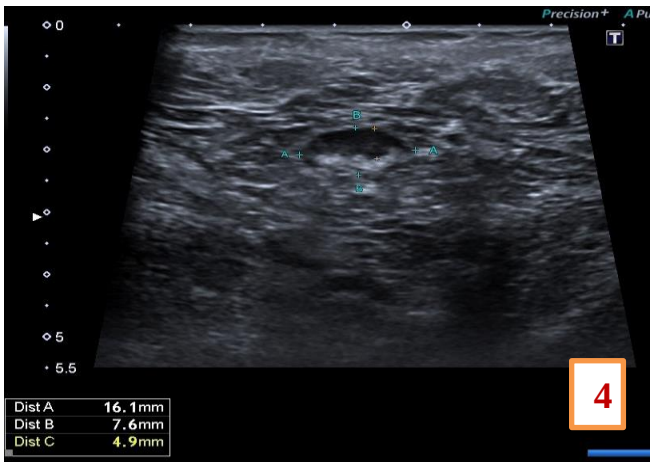


Figure (4): Ultrasound showed single enlarged level 1 axillary lymph node with focal cortical thickness measures 4.9 mm.

Figures (5, 6 and 7): Female patient aged 30 years old not married presented with left breast lump, positive family history (mother and older sister).

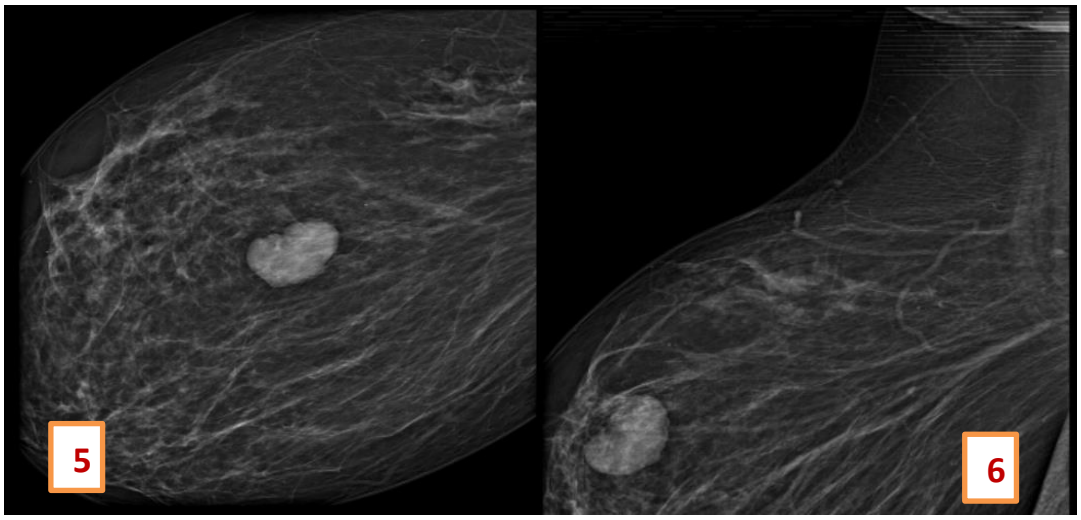


Figure (5 & 6): Showed mammogram of left breast showing upper inner quadrant dense lesion with oval shape and well circumscribed margin.

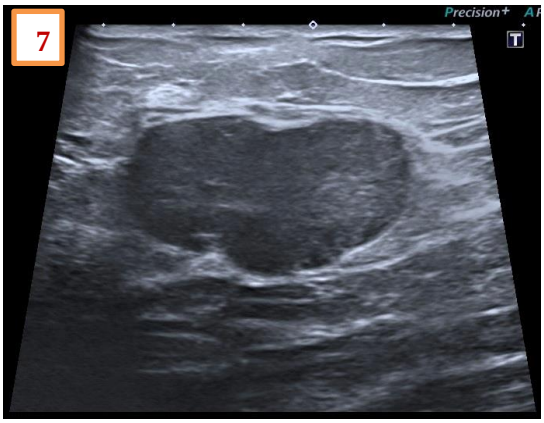


Figure (7): Showed ultrasound showing well circumscribed oval hypoechoic mass with parallel orientation to the skin.

Figures (8, 9 and 10): Female patient aged 59 years old, postmenoupausal, married with two offsprings, presented with left breast lump, positive family history (mother). **<u>Biological markers</u> :** ER: negative, PR: negative , HER2/neu: negative, Ki 67: positive.

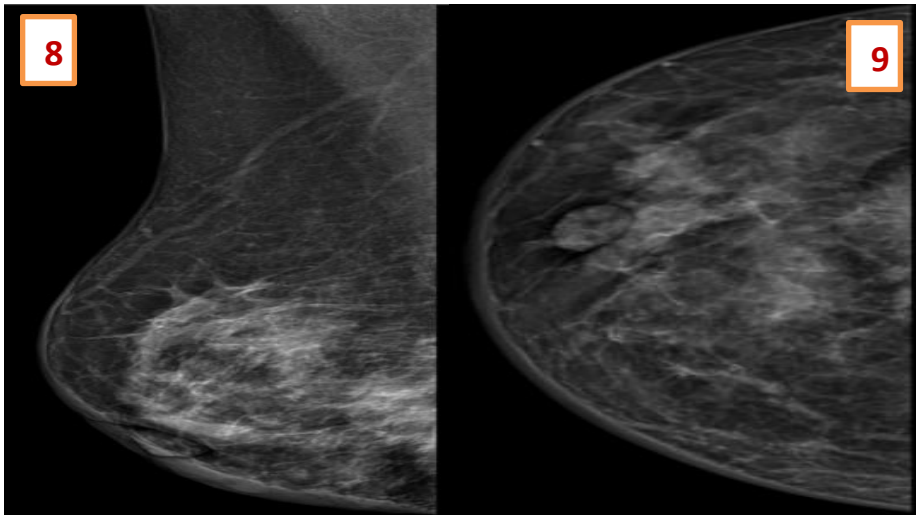


Figure (8 & 9): Showed mammogram images, which showed dense lesion lying on the chest wall with irregular shape and speculated margin.

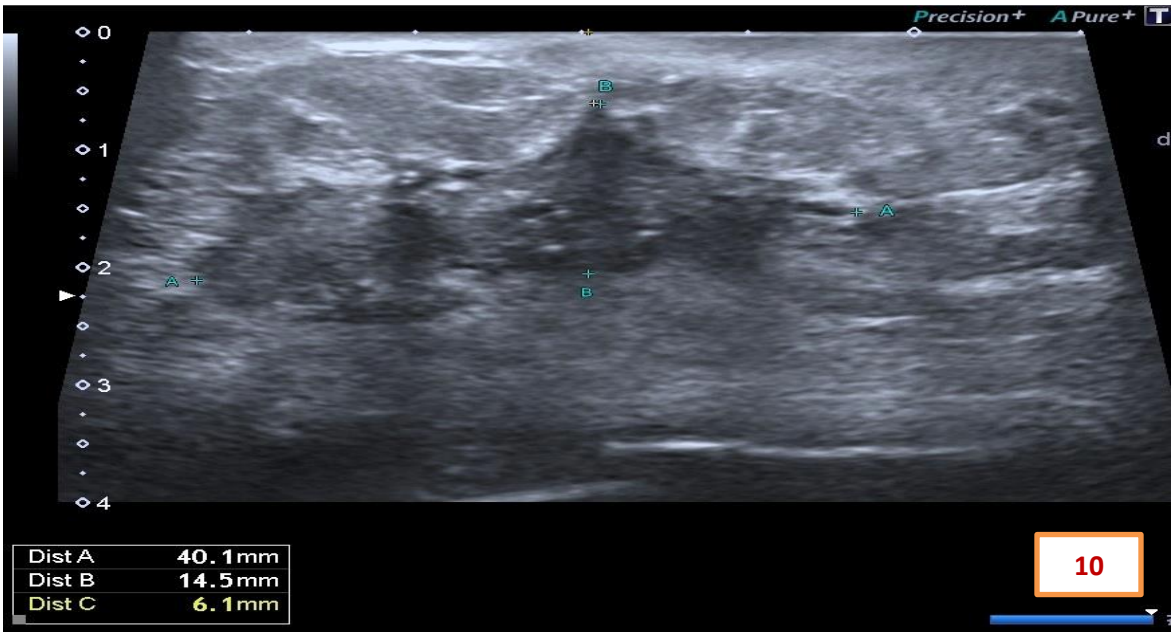


Figure (10): Showed ultrasound images, which showed irregular speculated hypoechoic mass that was seen with not parallel orientation to the skin and posterior shadowing, with intraductal extension and overlying skin thickness and mild edema.

DISCUSSION

Triple-negative breast cancer (TNBC) is a subtype of BC characterized by the absence of three main receptors frequently demonstrated in different forms of BC: ER, PR, and HER2. This lack of receptor expression makes TNBC unique and challenging to treat, as it doesn't give response to hormonal therapies or drugs targeting HER2**.** TNBC is typically more aggressive compared to other types of BC and has a higher likelihood of spreading to other parts of the body (metastasizing). It typically occurs more frequently in younger women, especially those of African American descent**.** Due to the absence of specific molecular targets, therapeutic modalities for TNBC are limited compared to other breast cancer subtypes. Standard treatments often include surgery, chemotherapy and radiation therapy. Research into targeted therapies and immunotherapies specifically designed for TNBC is ongoing, aiming to enhance outcomes and survival rates for patients with this subtype. Rapid detection and precise diagnosis are crucial for effective management of TNBC. We aimed at correlating different U/S and mammographic criteria of histopathological confirmed TNBC and to compare it with other molecular subtyping for better lesion characterization [3].

A total of 72 cases were included in the study, with 35 classified as TNBC and 37 as non-TNBC. Statistical significance of associations between TNBC status and imaging characteristics was evaluated using appropriate tests. In this study we found that oval lesions with circumscribed margins exhibited a significant association with TNBC (P=0.0004*), indicating their relevance in TNBC diagnosis. **Sensitivity:** Lesions with oval shape and circumscribed margin demonstrated high sensitivity in identifying TNBC (91.4% and 96.9% respectively). **Specificity:** Specificity for oval shape and circumscribed margin was moderate (54.1% and 55.9% respectively), indicating their ability to identify non-TNBC lesions. Lesions characterized by an oval shape and circumscribed margin on mammography exhibited significant associations with TNBC. These features demonstrated high sensitivity, making them valuable in the detection of TNBC lesions. However, their moderate specificity suggests potential overlap with other breast cancer subtypes. In agreement with **Boisserie-Lacroix *et al.*** [4], TNBC presents with round, oval, and lobular shapes having an unclear or microlobulated contour. Posterior enhancement is detected in 35.5% to 49% of TNBC and fifty percent of hormone receptor-negative HER2+ cancers, and this is approaching the rations described by **Ko *et al.*** [5]. Also, In agreement with **Boisserie-Lacroix *et al.*** [4], **Tandon *et al.*** [6] and **Zhang *et al.*** [7]**,** tumours with well-defined margins and posterior enhancement were highly indicative of TNBC type of BC, which is the most aggressive type of BC with rapid growth and necrosis. Our study is in agreement with **Alghazal *et al.*** [8], who stated that TNBC lesions in the present work were mainly oval in shape with circumscribed margin, the benign looking malignant lesions, which carry the worst prognosis. The reliable radiologist has to be alert about US characteristics of various molecular subtype in order not to under diagnose a malignant breast lesion.

In our study we found that 18 cases demonstrated parallel orientation of the lesion in relation to skin (p=0.001*), this is in accordance with **Schopp *et al.*** [3], who found that masses demonstrated parallel orientation in 8%–57% of cases. Also, we found a significant association between young age (under 40 years) and TNBC diagnosis (P=0.0xx*), indicating a higher likelihood of TNBC occurrence in younger individuals. The findings highlighted a notable association between young age and TNBC diagnosis. So, we should make a focus upon this to avoid underestimation of the possibility of benign looking lesions to be malignant in nature in young females so we have to make close follow up and to consider other factors as family history in assessment of these cases. In agreement with **Anders and Carey** [9] who stated that several studies have focused on TNBC in young BC cases. TNBC constitutes a greater ratio among younger than older BC cases. In the same line, **Guo *et al.*** [10] have displayed that the US scores of BC are closely linked to its pathologic changes, and this has implications for the types of pathologic tissues, biological indicators, and existence of metastasis. As a result, US values might be helpful as a primary pathologic screening approach for BC cases.

Against **Tandon *et al.*** [6], we displayed that triple-negative cancers were hypervascular compared to non-TNBC. Our study displayed that there was significant association between hypervascularity of the lesion and non-TNBC, P=.001.

In agreement with **Çelebi *et al.*** [11] who showed that tumors with posterior shadowing were more likely to be of non-TNBC and having at least one positive receptor, on the other hand, tumours with circumscribed margins were more often TNBC. This is in accordance with **Lehmann *et al.*** [12] and **Choi *et al.*** [13] who displayed that TNBC tumors often appear as irregular masses with indistinct margins, our study also found that there was association with irregular shaped masses P=0.001, but in our study it depended on the size of the lesion as lesions more than 3 cm tends to have irregular shape and speculated margin. This is in disagreement with **Ko *et al.*** [5] and **Choi *et al.*** [13] who found that TNBC tumors frequently exhibit hypoechoic masses with irregular margins and posterior acoustic shadowing, reflecting their aggressive nature. Our study found that lesions with speculated margins were significantly associated with non-TNBC (P=0.0009*), suggesting their utility in identifying TNBC lesions according to the age of the patient and the size of the lesion. This is in agreement with **Candelaria *et al.*** [14] who found that non-TNBC often appears as high-density masses with irregular shapes and indistinct margins.

CONCLUSION

Sono-mammographic features provided valuable insights for the detection and differentiation of TNBC from other breast cancer subtypes. High sensitivity for certain characteristics, such as shape and margin, made them useful in identifying TNBC. Continued research and refinement of imaging protocols are essential to enhance diagnostic accuracy and improve patient outcomes.

Conflict of interest: None.
Fund: None.

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