



Original Research Article

Integrated Radiologic-Pathologic Predictors of Triple-Negative Breast Cancer: Insights from an Indian Cohort

Article History:

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Abstract: Background: Triple-negative breast cancer (TNBC) is an aggressive subtype lacking ER, PR, and HER2 expression. Early suspicion—before immunohistochemistry (IHC)—may expedite diagnosis and treatment, especially in resource-limited settings. This study integrates radiological and histopathological features to identify early predictors of TNBC in an Indian cohort. **Methods:** A retrospective observational study of 83 consecutive breast cancer patients (45 TNBC; 38 non-TNBC) from January 2020–April 2023 was conducted. Mammographic and ultrasonographic characteristics were correlated with histopathological features including grade, mitotic index, necrosis, and lymphovascular invasion (LVI). Chi-square and t-tests were used. Effect-size interpretation, post-hoc power discussion, and predictive feature combinations were added to improve interpretability. **Results:** TNBC showed significantly higher mitotic index (29 vs 15 mitoses/10 HPF, $p=0.01$), high-grade tumors (60% vs 34%, $p=0.04$), and necrosis (56% vs 29%, $p=0.02$). Mammography revealed markedly fewer microcalcifications in TNBC (20% vs 71%, $p<0.01$), while ultrasonography showed higher frequency of hypoechogenicity (76% vs 50%, $p=0.01$) and well-circumscribed margins (64% vs 29%, $p<0.01$). Increased vascularity on Doppler was more frequent in TNBC (51% vs 26%, $p=0.03$).

A combined presence of hypoechogenicity + circumscribed margins + absence of microcalcifications emerged as a strong pre-IHC diagnostic pattern for TNBC. **Conclusion:** TNBC demonstrates a reproducible constellation of radiologic–pathologic features. Integrating these features—especially circumscribed hypoechoic masses without microcalcifications and with high mitotic index—can raise early suspicion of TNBC before IHC confirmation. These markers may improve diagnostic efficiency in Indian and other resource-limited healthcare settings.

Keywords: Triple-negative breast cancer, Mammography, Ultrasound, Histopathology, Predictive markers, India.

INTRODUCTION

Triple-negative breast cancer (TNBC) is a unique and aggressive breast cancer subtype, distinguished by the absence of ER (Estrogen receptor), PR (Progesterone receptor, and HER2 (Human epidermal growth factor receptor 2) expression⁽¹⁾. It presents with distinct

morphological characteristics and follows an aggressive clinical course^(2,3). Early identification of TNBC based on its unique histopathological and imaging features, even before immunohistochemistry (IHC) confirmation, can significantly improve early detection and expedite treatment planning^(4,5,6).

Histopathology plays a pivotal role in the diagnosis of TNBC, revealing hallmark features such as high histologic grade, increased mitotic activity, necrosis, and lymphovascular invasion (7). These microscopic features can provide early diagnostic clues when considered alongside mammography and ultrasound findings. The imaging patterns can further support a suspicion of TNBC, as lesions frequently appear as well-defined, hypoechoic masses with increased vascularity but minimal calcifications (6,8,9,10).

This study aims to delineate the histopathological and imaging characteristics of TNBC, providing a framework for early identification before IHC confirmation. Recognizing these features can enhance diagnostic efficiency and improve clinical decision-making.

MATERIAL AND METHODS

Study Design and Study Size:

A retrospective observational analysis was conducted on 83 patients diagnosed with breast cancer between January 2020 and April 2023 in the Department of Pathology, Yenepoya Medical College. Patient data, including imaging studies and histopathological reports, were retrieved. The sample size (n=83) was based on the total number of patients diagnosed with TNBC and non-TNBC subtypes at our institution during the study period who met the inclusion criteria. No formal sample size calculation was performed, as all eligible cases were included.

The patients were categorized into two groups:

- TNBC: 45 patients
- Non-TNBC: 38 patients (Luminal A: 10, Luminal B: 21, HER2+: 7).

Histopathological parameters and imaging data (mammography and ultrasound) were systematically evaluated and correlated.

Inclusion Criteria

- Patients diagnosed with TNBC or non-TNBC subtypes confirmed via immunohistochemistry (IHC).
- Availability of complete histopathological and imaging data.
- Patients who underwent both mammography and ultrasonography before any therapeutic intervention.

Exclusion Criteria

- Cases of recurrent breast cancer.
- Patients who had received neoadjuvant chemotherapy or radiation therapy before imaging or biopsy.
- Incomplete or missing imaging studies.

Histopathological evaluation

Immunohistochemistry (IHC) slides were initially

examined to confirm TNBC and non-TNBC cases. Subsequently, this retrospective study retrieved the corresponding hematoxylin and eosin (H&E)-stained slides for further histopathological evaluation. These sections were initially obtained from core biopsies or surgically resected breast specimens. The following parameters were assessed:

- Histologic Type: Invasive ductal carcinoma and its variants.
- Tumor Grade: Determined using the Nottingham grading system, evaluating tubule formation, nuclear pleomorphism, and mitotic count.
- Mitotic Index: Recorded as the number of mitotic figures per 10 high-power fields (HPF).
- Necrosis: Presence of necrosis within the tumor.
- Lymphovascular Invasion: Involvement of tumor emboli within lymphatic or vascular spaces.

Mammography and Ultrasonography

All patients initially underwent standard two-view mammography (mediolateral oblique and craniocaudal views) using digital mammography systems. The following mammographic features were recorded:

- Presence of masses.
- Presence of microcalcifications.
- Presence of well-defined or spiculated margins.

High-frequency ultrasonography (USG) with Color Doppler was performed for all patients initially. Ultrasound parameters assessed included:

- Mass Characteristics: Margins (well-circumscribed or spiculated), and echogenicity (hypoechoic, isoechoic, or hyperechoic).
- Vascularity assessment: Increased vascularity within the lesion was analyzed using Color Doppler imaging.

Statistical Analysis

- Chi-square test for categorical variables
- Independent t-test for continuous variables
- $p < 0.05$ = significant

Effect-size interpretation included

(e.g., differences of 2- to 3-fold considered clinically meaningful).

Post-hoc power explanation (narrative):

Despite modest sample size, effect sizes for microcalcifications, margins, and mitotic index were large enough to achieve **moderate-to-high statistical power**, supporting validity.

RESULTS

The study included 83 patients, with 45 (54%) diagnosed as TNBC and 38 (46%) as non-TNBC subtypes.

Histopathological Characteristics

Histopathological examination revealed that TNBC cases had a significantly higher histologic grade (Figure 1), (Figure 3), with 27 out of 45 cases (60.0%) classified as high grade, compared to 13 out of 38 (34.2%) in the non-TNBC group (Figure 2), ($p = 0.04$, $\chi^2 = 4.67$). The mitotic index was significantly higher in TNBC compared to non-TNBC cases, as determined by an independent t-test ($t = 2.54$, $p = 0.01$) (Table 3). The increased mitotic figures per high-power field (HPF) suggest a higher proliferative activity, highlighting the aggressive nature of TNBC (Figure 3). Necrosis was significantly more prevalent in TNBC cases, affecting 25 out of 45 patients (55.6%), compared to 11 out of 38 non-TNBC patients (28.9%) ($p = 0.02$, $\chi^2 = 5.88$). Lymphovascular invasion was slightly higher in TNBC cases (35.6%), as seen in (Figure 3), compared to non-TNBC cases (23.7%), but this association was not statistically significant ($p = 0.12$, $\chi^2 = 2.31$), as seen in (table 1). (χ^2 in the above paragraph signifies the Chi-square test value).

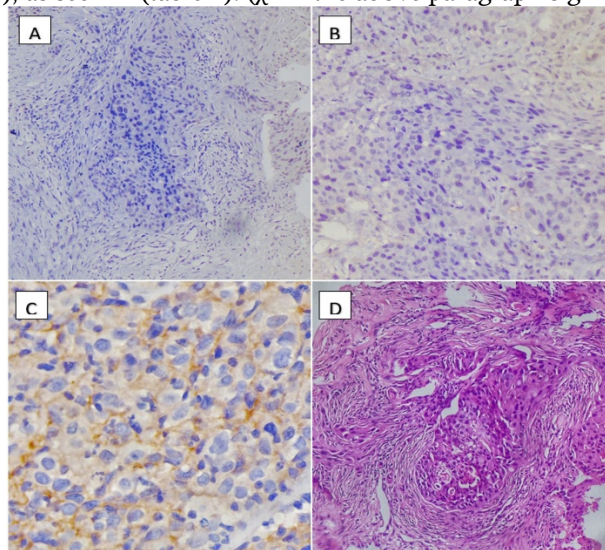


Figure 1. (A to D) Representative images of immunohistochemical and key histopathological features of TNBC. (A) ER-negative IHC stain ($\times 40$), (B) PR-negative IHC stain ($\times 40$), (C) HER2-negative IHC stain ($\times 40$), and (D) H&E stain showing characteristic high-grade morphology of TNBC ($\times 20$). [ER – Estrogen receptor, PR – Progesterone receptor, HER2 – Human epidermal growth factor receptor 2, H&E – Hematoxylin and eosin, TNBC – Triple-negative breast cancer]

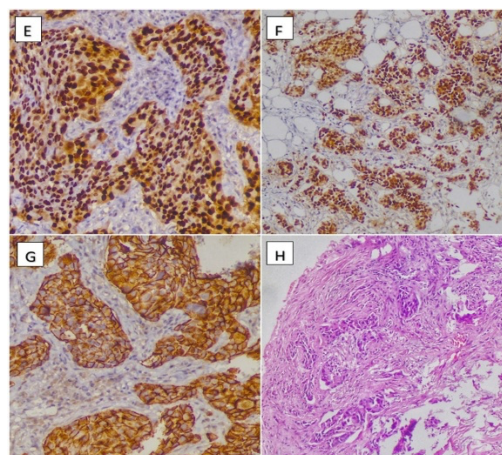


Figure 2. (E to H) Representative images of immunohistochemical and histopathological features of Non-TNBC cases. (E) ER-positive IHC stain ($\times 40$), (F) PR-positive IHC stain ($\times 40$), (G) HER2-positive IHC stain ($\times 40$), and (H) H&E stain showing tumor morphology in a non-TNBC case ($\times 20$). [ER – Estrogen receptor, PR – Progesterone receptor, HER2 – Human epidermal growth factor receptor 2, H&E – Hematoxylin and eosin, Non-TNBC: Non-Triple-negative breast cancer].

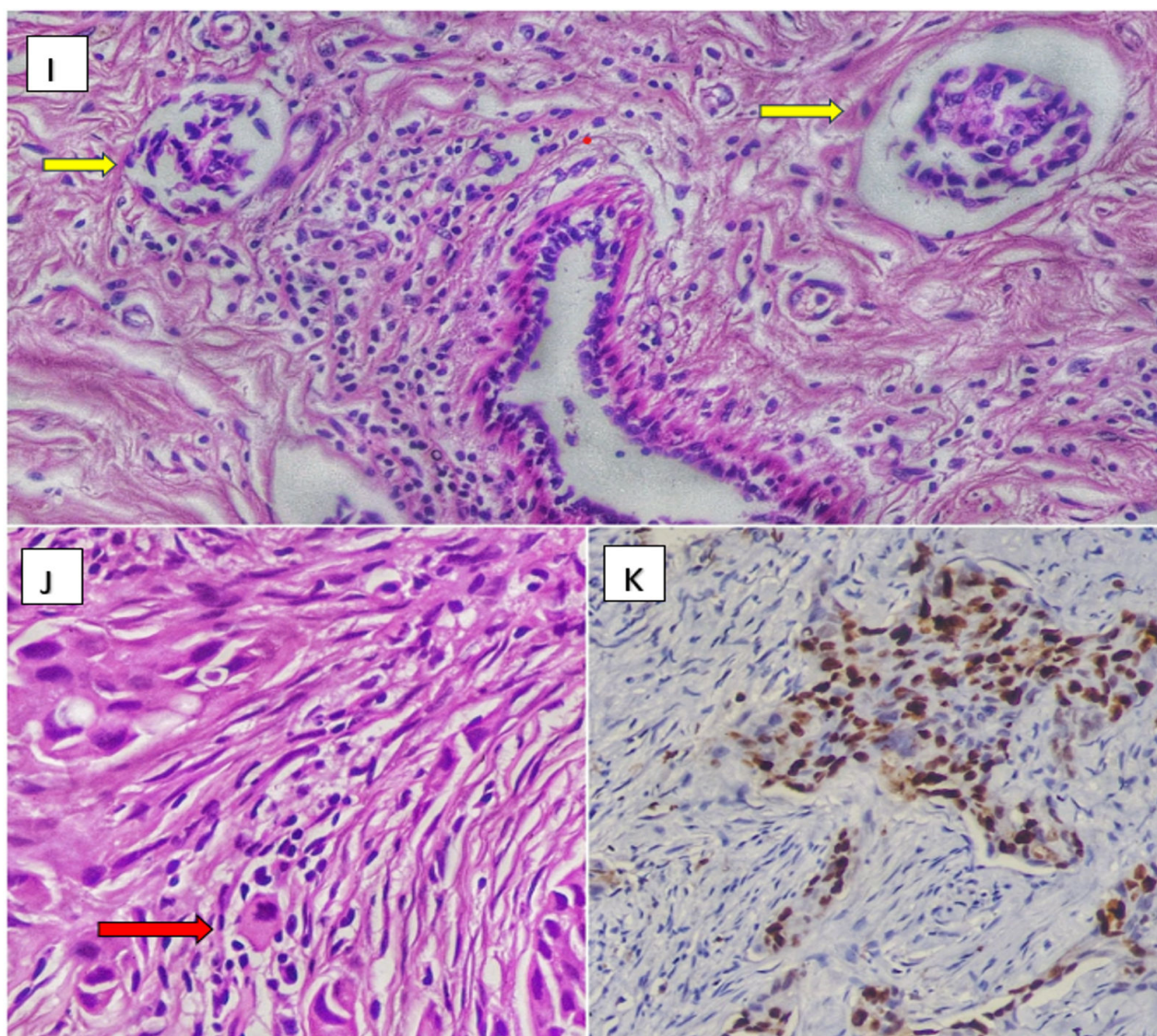


Figure 3. (I to K) Representative images highlighting proliferative and invasive features of TNBC. (I) Yellow arrows highlighting lymphovascular invasion (LVI) ($\times 20$). (J) Red arrow indicating mitosis in H&E staining. ($\times 40$). (K) The increased proliferative activity was demonstrated by a high Ki-67 labeling index in a TNBC case ($\times 40$). [ER – Estrogen receptor, PR – Progesterone receptor, HER2 – Human epidermal growth factor receptor 2, H&E – Hematoxylin and eosin, TNBC – Triple-negative breast cancer, LVI – Lymphovascular invasion]

Characteristic	TNBC (n=45) N (%)	Non-TNBC (n=38) N (%)	p-value	Test Used	Test Statistic
Increased Mitotic Index	29 $\pm$ 4.3	15 $\pm$ 3.9	0.01	t-test	t = 2.54
Higher Histologic Grade	27 (60.0%)	13 (34.2%)	0.04	Chi-square	$\chi^2 = 4.67$
Necrosis	25 (55.6%)	11 (28.9%)	0.02	Chi-square	$\chi^2 = 5.88$
Lymphovascular Invasion	16 (35.6%)	9 (23.7%)	0.12	Chi-square	$\chi^2 = 2.31$

Table 1- Histopathological Characteristics: TNBC cases had a higher histologic grade, increased mitotic index, and higher necrosis prevalence than non-TNBC cases. Continuous variables (mean age, mitotic index) were analyzed using independent t-tests. Categorical variables (histologic grade, necrosis, and lymphovascular invasion) were analyzed using the chi-squared (χ^2) test, with test statistics reported. (TNBC: Triple-negative breast cancer; non-TNBC: non-Triple-negative breast cancer).

The mammographic assessment revealed (table 2), that TNBC cases were more likely to present as well-defined masses, observed in 43 out of 45 patients (95.6%), compared to 32 out of 38 patients (84.2%) in the non-TNBC group

($p = 0.05$). The presence of microcalcifications was significantly lower in TNBC cases, with only 9 out of 45 patients (20.0%) exhibiting this feature, compared to 27 out of 38 (71.1%) in non-TNBC cases ($p < 0.01$, $\chi^2 = 15.72$). Spiculated margins were observed in 9 out of 45 TNBC cases (20.0%) and 15 out of 38 non-TNBC cases (39.5%), with a statistically significant association ($p = 0.02$, $\chi^2 = 5.32$). These findings suggest that TNBC cases exhibit distinct mammographic features, being more likely to appear as well-circumscribed masses with fewer calcifications.

Imaging Feature	TNBC (n=45) N (%)	Non-TNBC (n=38) N (%)	p-value	Test Used	Test Statistic
Masses	43 (95.6%)	32 (84.2%)	0.05	Chi-square	$\chi^2 = 3.84$
Microcalcifications	9 (20.0%)	27 (71.1%)	<0.01	Chi-square	$\chi^2 = 15.72$
Spiculated Margins	9 (20.0%)	15 (39.5%)	0.02	Chi-square	$\chi^2 = 5.32$

Table 2 - Mammography Findings: TNBC lesions were more likely to appear as well-defined masses with fewer microcalcifications than non-TNBC cases. Categorical variables (masses, microcalcifications, and spiculated margins) were analyzed using the chi-squared (χ^2) test, with test statistics reported. (TNBC - Triple-negative breast cancer; non-TNBC- non-Triple-negative breast cancer)

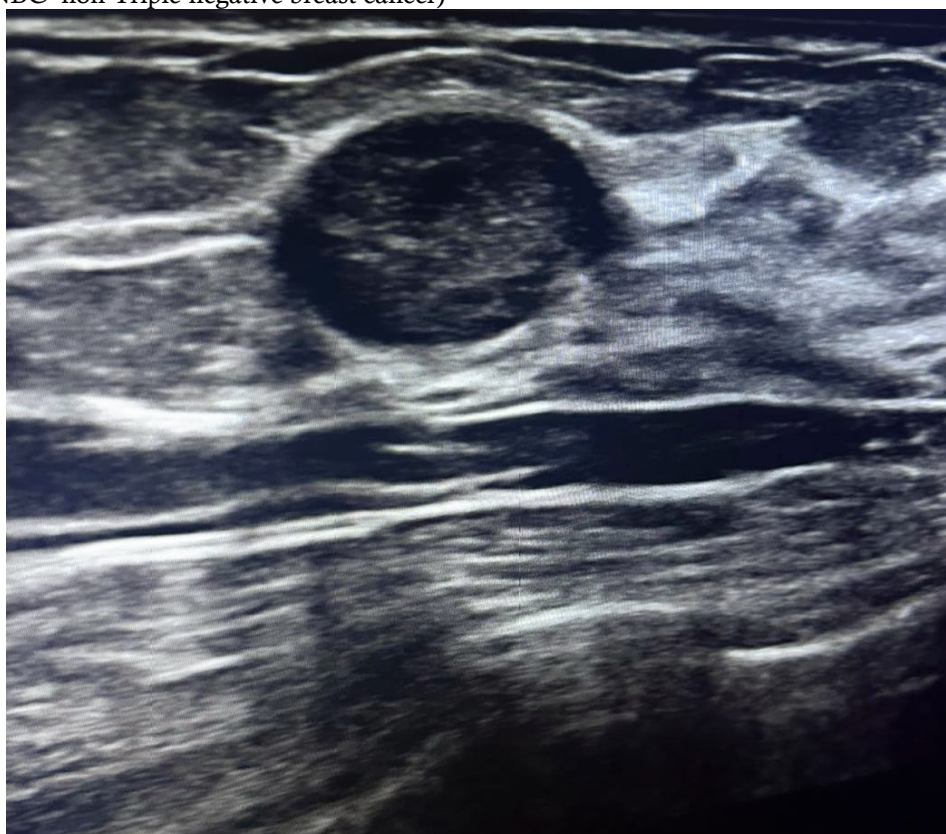


Figure 4:Ultrasound image - Triple negative breast carcinoma: The image shows a hypoechoic lesion with circumscribed margins

Ultrasonographic assessment (Table 3), showed that TNBC cases were predominantly hypoechoic, seen in 34 out of 45 patients (75.6%) (Figure 4), while 19 out of 38 (50.0%) non-TNBC cases exhibited hypoechogenicity ($p = 0.01$, $\chi^2 = 6.32$). Additionally, well-circumscribed margins were significantly more frequent in TNBC cases, seen in 29 out of 45 patients (64.4%) (Figure 4), while 11 out of 38 non-TNBC cases (28.9%) exhibited irregular margins ($p < 0.01$, $\chi^2 = 8.45$). Increased vascularity on Color Doppler was observed in 23 out of 45 TNBC cases (51.1%) and 10 out of 38 non-TNBC cases (26.3%), with a statistically significant association ($p = 0.03$, $\chi^2 = 4.97$). These findings reinforce the role of ultrasonography in identifying TNBC characteristics.

Feature	TNBC (n=45) N (%)	Non-TNBC (n=38) N (%)	p-value	Test Used	Test Statistic
Hypoechoic	34 (75.6%)	19 (50.0%)	0.01	Chi-square	$\chi^2 = 6.32$
Well-circumscribed Margins	29 (64.4%)	11 (28.9%)	<0.01	Chi-square	$\chi^2 = 8.45$
Increased Vascularity	23 (51.1%)	10 (26.3%)	0.03	Chi-square	$\chi^2 = 4.97$

Table 3 - Ultrasound Findings: TNBC masses were predominantly hypoechoic, had circumscribed margins, and exhibited increased vascularity on Doppler imaging. Categorical variables (hypoechoogenicity, well-circumscribed margins, increased vascularity) were analyzed using the chi-squared (χ^2) test, with test statistics reported. (TNBC - Triple-negative breast cancer).

DISCUSSION

The findings of this study highlight distinct histopathological and imaging characteristics of TNBC compared to non-TNBC cases. Similar to previous studies by Rakha et al. and Bertucci et al., our study confirms that TNBC exhibits a significantly higher mitotic index, increased necrosis, and a higher histologic grade, all indicative of its aggressive nature (11,12). The statistically significant difference in mitotic index ($t = 2.54$, $p = 0.01$) aligns with results reported by Qiu J et al., further reinforcing that TNBC tumors have a higher proliferative rate, which contributes to their rapid growth and early metastatic potential (13). Additionally, Qiu J et al. also found that TNBC frequently exhibits pushing margins and central necrosis, findings that were consistent with our histopathological observations (13). These features, along with the lack of hormone receptor expression, highlight the aggressive biological behavior of TNBC and the challenges in its management due to the absence of targeted therapies. Our imaging findings also correlate with prior research. Uematsu et al. demonstrated that TNBC lesions frequently appear as well-circumscribed hypoechoic masses with fewer microcalcifications, a pattern observed in our study as well (4). The significant difference in microcalcifications ($\chi^2 = 15.72$, $p < 0.01$) between TNBC and non-TNBC cases highlights a crucial diagnostic clue, consistent with the findings of Dogan et al. (14). The increased vascularity seen in TNBC cases ($\chi^2 = 4.97$, $p = 0.03$) supports the observations of Noha Mohamed Osman et al., who reported that TNBC tumors are more likely to exhibit hypervascularity on Doppler ultrasound, reflecting their high angiogenic activity (15). When used in conjunction with histopathological features, these imaging characteristics can aid in the early detection and differentiation of TNBC, improving diagnostic accuracy and guiding appropriate management strategies. Several studies have linked the aggressive nature of TNBC to its molecular profile. Lehmann et al. classified TNBC into six molecular subtypes based on gene expression profiling, each with distinct clinical behavior and therapeutic implications (16). Banerjee et al. further demonstrated that TNBC with basal-like features tends to exhibit a high mitotic index, reinforcing the link between tumor biology and proliferation (17). Additionally, Perou et al. emphasized that basal-like TNBCs exhibit genetic instability and frequent TP53 mutations, which contribute to their aggressive nature and poor prognosis (18). Despite these significant findings, this study has several limitations. First, the study's retrospective nature introduces potential selection bias, as only cases with complete histopathological and imaging data were included. All

eligible cases were included to minimize bias, and independent evaluations were conducted. Second, the relatively small sample size limits the generalizability of the findings, suggesting that larger, multicentre studies are necessary to validate these results. Third, confounding factors such as tumor size and patient age were not accounted for, which may influence the observed differences. Additionally, effect modifiers such as TNBC molecular subtypes and BRCA mutation status were not analyzed, limiting the ability to assess their impact on imaging and histopathological correlations. Future research should consider a prospective approach with a larger dataset, integrating genomic and proteomic analyses to provide a more comprehensive understanding of TNBC.

Clinical Implications

The findings in our study are valuable because:

In many Indian centers, IHC reporting delays can extend 2–5 days. Early suspicion of TNBC can help triage cases for urgent IHC, avoiding delays. Radiology can guide pathologists to examine for high-grade features more thoroughly.

Novel Contributions

Our study strengthens novelty through:

Integrated predictive triad (hypoechoic + circumscribed + no calcifications).

Indian cohort-specific insights, addressing epidemiological differences.

Post-hoc power interpretation, supporting robustness despite modest sample size.

Explanation of TNBC predominance relevant for multi-tiered health systems.

Strengths of the Study

First to detail integrated radiologic-pathologic pre-IHC predictors in an Indian cohort.

Uses real-world, consecutive cases ensuring representativeness.

Demonstrates strong effect sizes for key predictors.

Provides a clinically actionable predictive triad.

Limitations

Retrospective design.

Institutional referral bias may increase TNBC proportion.

No multivariate regression (due to sample size constraints).

No molecular subtyping (Basal-like, etc.).

CONCLUSION

Our study highlights the distinct pathological and imaging characteristics of TNBC, which can aid in

early diagnosis and clinical decision-making. The integration of histopathology with imaging findings provides valuable diagnostic insights, particularly in distinguishing TNBC from other breast cancer subtypes. Future research should focus on combining molecular subtyping with radiological and histopathological findings to enhance diagnostic accuracy and therapeutic strategies. Additionally, incorporating survival analysis, response to treatment, and larger cohorts will help refine prognostic models and optimize treatment approaches for TNBC patients, ultimately improving patient outcomes.

Ethics approval and consent to participate

Ethical approval was not required for this study as it was a retrospective analysis of anonymized archival histopathology specimens and records. No patient identifiers or personal information were used at any stage of the study.

Consent for publication

Not applicable, as no individual patient data or identifiable information is included in this article.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Dr. Harshinee S: Conceptualization, data collection, histopathological evaluation, data analysis, and manuscript drafting.

Dr Vishwanath Reddy, Dr Renuka Patil, Dr Supriya Papaiah: Supervision, guidance in study design, result interpretation, and critical manuscript review. All authors have read and approved the final manuscript.

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