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Research Article

Association of Breast Ultrasound Elastography Findings With Tumor-Infiltrating Lymphocytes and Histopathological Characteristics in Invasive Breast Carcinoma

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Abstract

Background: Tumor-infiltrating lymphocytes (TILs) represent a crucial biomarker of host immune response and therapeutic responsiveness in invasive breast carcinoma, particularly in triple-negative and HER2-positive subtypes. While histopathological evaluation of core needle biopsy remains the gold standard for TIL quantification, non-invasive imaging surrogates are highly desirable. Ultrasound elastography evaluates tissue stiffness and tumor microenvironment mechanics, but its association with stromal TIL levels and specific histopathological parameters remains insufficiently characterized.

Objective: To evaluate the association between strain and shear-wave ultrasound elastography features (mean elasticity, strain ratio) and stromal tumor-infiltrating lymphocytes (sTILs) as well as key histopathological parameters in patients with invasive breast carcinoma.

Methods: This prospective observational study evaluated 160 adult female patients (aged 30 to 70 years) with histologically confirmed invasive breast carcinoma

undergoing pre-treatment breast ultrasound and elastography at Chughtai Healthcare, Pakistan. Qualitative elasticity scores, quantitative strain ratios (SR), and maximum/mean shear-wave elasticity (E-max, E-mean in kilopascals, kPa) were recorded. Core needle biopsy specimens were processed for histopathological grading, immunohistochemical subtyping (ER, PR, HER2, Ki-67), and stromal TIL quantification (categorized as low < 10 percent, intermediate 10-50 percent, and high > 50 percent sTILs according to International TILs Working Group guidelines). Statistical correlations and multivariable logistic regression were performed to establish independent imaging predictors of high sTIL infiltration and high histological grade.

Results: Among 160 patients, mean age was 51.4 +/- 9.2 years. High sTIL infiltration (> 50 percent) was observed in 28.8 percent (n = 46), intermediate in 38.8 percent (n = 62), and low in 32.5 percent (n = 52). Tumors with high sTIL levels exhibited significantly lower mean shear-wave elasticity values (E-mean: 84.2 +/- 22.4 kPa vs. 142.6 +/- 31.8 kPa in low sTIL tumors, $p < 0.001$) and lower strain ratios (2.8 +/- 0.8 vs. 4.6 +/- 1.2, $p < 0.001$), indicating relatively soft tumor mechanics despite aggressive histopathology. E-mean correlated inversely with sTIL percentage ($r = -0.64$, $p < 0.001$) and positively with tumor size ($r = 0.48$, $p < 0.001$) and Nottingham histological grade ($r = 0.52$, $p < 0.001$). Multivariable logistic regression revealed that lower E-mean (< 95 kPa; adjusted OR = 3.84, 95 percent CI: 1.76 to 8.38, $p = 0.001$), triple-negative receptor status (adjusted OR = 3.12, 95 percent CI: 1.42 to 6.84, $p = 0.004$), and high Ki-67 proliferation index (> 30 percent; adjusted OR = 2.68, 95 percent CI: 1.18 to 6.08, $p = 0.018$) were independent predictors of high stromal TIL infiltration.

Conclusion: Ultrasound elastography elasticity features correlate significantly with stromal tumor-infiltrating lymphocyte density and histopathological tumor characteristics in invasive breast carcinoma. High sTIL infiltration is characteristically associated with lower lesion stiffness, offering a non-invasive imaging biomarker to infer immune microenvironment status prior to neoadjuvant therapy.

Keywords: Invasive breast carcinoma; Ultrasound elastography; Shear-wave elastography; Tumor-infiltrating lymphocytes; sTILs; Histopathological grade; Tumor microenvironment.

1. Introduction

Invasive breast carcinoma is a heterogeneous malignancy characterized by distinct molecular subtypes, clinical behaviors, and therapeutic responses. In recent years, the tumor microenvironment—specifically the cellular immune infiltrate—has emerged as a key determinant of disease progression and treatment outcome. Tumor-infiltrating lymphocytes (TILs), predominantly comprising cytotoxic T cells (CD8+), helper T cells (CD4+), and regulatory T cells (Tregs), reflect the host immune system's active recognition of tumor neoantigens.1-3

Multiple landmark clinical trials have demonstrated that higher stromal TIL (sTIL) levels correlate with superior response to neoadjuvant chemotherapy, higher rates of pathological complete response (pCR), and improved overall survival, particularly in triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2 (HER2)-positive subtypes. Consequently, sTIL quantification has become an important prognostic and predictive biomarker.4-5

However, standard sTIL assessment relies on invasive tissue core needle biopsies or surgical resections, which are subject to sampling bias due to intra-tumoral spatial heterogeneity. Non-invasive pre-operative imaging surrogates capable of reflecting the immune and matrix microenvironment offer substantial clinical utility.6-7

Ultrasound elastography is an advanced sonographic technique that measures tissue mechanical properties (stiffness and deformability). Two main modalities are used in clinical practice:

- Strain Elastography (SE): Measures qualitative or semi-quantitative tissue displacement (strain ratio) in response to external mechanical compression.

- Shear-Wave Elastography (SWE): Uses acoustic radiation force impulses to generate transverse shear waves, providing quantitative tissue elasticity measurements expressed in kilopascals (kPa) or shear-wave velocity (m/s).

While tissue stiffness in breast carcinoma is traditionally driven by desmoplastic stromal reaction and extracellular matrix cross-linking, dense lymphocytic infiltration can soften tumor stroma by disrupting rigid

collagen bundles and increasing cellular density without dense fibrosis. The relationship between elastographic parameters and sTIL infiltration, alongside classical histopathological features (Nottingham grade, hormone receptor status, HER2 expression, Ki-67 index), remains a vital area of translational breast imaging research.8-10

Therefore, this prospective observational study was conducted to evaluate the association between strain and shear-wave ultrasound elastography findings, stromal TIL density, and histopathological characteristics in invasive breast carcinoma.

2. Rationale of the Study

Quantifying tumor-infiltrating lymphocytes before initiating neoadjuvant therapy provides critical prognostic insights and aids treatment planning. However, core needle biopsy yields small tissue samples that may not capture heterogeneous lymphocyte distribution across the entire tumor volume. Ultrasound elastography provides a non-invasive, repeatable, and whole-lesion evaluation of tumor stiffness. Clarifying how acoustic stiffness metrics correspond to lymphocytic infiltration versus desmoplastic stroma establishes elastography as a potential non-invasive imaging biomarker for tumor immune profiling.

3. Objectives

Primary Objective

To evaluate the association between shear-wave elasticity metrics (E-mean, E-max) and stromal tumor-infiltrating lymphocyte (sTIL) levels in patients with invasive breast carcinoma.

Secondary Objectives

1. To compare strain ratios and shear-wave elasticity values across low (< 10 percent), intermediate (10-50 percent), and high (> 50 percent) sTIL categories.

2. To evaluate correlations between elastographic stiffness metrics, tumor size, Nottingham histological grade, lymph node status, and Ki-67 proliferation index.

3. To determine whether elastographic parameters differ across molecular subtypes (Luminal A, Luminal B, HER2-enriched, Triple-Negative).

4. To construct a multivariable logistic regression model identifying independent imaging and histopathological predictors of high sTIL infiltration.

4. Materials and Methods

4.1 Study Design and Setting

A hospital-based prospective observational study was conducted at Chughtai Healthcare, Pakistan.

4.2 Study Duration

The study was conducted over an eight-month period, encompassing pre-treatment patient accrual, standardized breast ultrasound elastography examinations, core needle biopsy processing, immunohistochemical subtyping, sTIL scoring, and statistical modeling.

4.3 Study Population

Adult female patients aged 30 to 70 years presenting with BIRADS 4 or BIRADS 5 solid breast lesions subsequently confirmed as invasive breast carcinoma on histopathology.

4.4 Sample Size

A sample size of 160 female participants with confirmed invasive breast carcinoma was enrolled. The sample size was calculated using G-Power software based on estimating an expected prevalence of high sTILs of 25 percent, an alpha error level of 0.05, a statistical power of 85 percent, and accommodating up to 8 multivariable logistic regression covariates.

4.5 Inclusion Criteria

1. Female patients aged 30 to 70 years with untreated primary invasive breast carcinoma.

2. Measurable solid breast mass (tumor diameter >= 10 mm and <= 50 mm) accessible by ultrasound elastography.

3. Availability of high-quality pre-treatment strain and shear-wave elastography imaging data.

4. Histological confirmation via core needle biopsy with complete

immunohistochemical and sTIL reporting.

5. Provision of written informed consent.

4.6 Exclusion Criteria

1. Recurrent breast carcinoma or history of prior ipsilateral breast surgery or radiation.

2. Patients who had received prior neoadjuvant chemotherapy, endocrine therapy, or immunotherapy.

3. Lesions with extensive necrotizing breakdown, fluid/cystic components (> 25 percent of volume), or superficial skin ulceration artifactually altering elastography.

4. Lesions located deeper than 40 mm or immediately adjacent to the chest wall where acoustic shear-wave propagation is degraded.

4.7 Breast Ultrasound and Elastography Protocol

All examinations were performed using a high-end ultrasound system (e.g., Mindray Resona / Canon Aplio / GE Logiq E9) equipped with a high-frequency linear array transducer (6-15 MHz) by dedicated breast radiologists with > 5 years of elastography experience:

- Conventional B-Mode Ultrasound: Recorded maximum tumor diameter (mm), margin characteristics, shape, echogenicity, and axillary lymph node status.

- Strain Elastography (SE): Light rhythmic compression was applied. The strain ratio (SR) was calculated by dividing the strain of adjacent subcutaneous fat tissue by the strain of the target tumor tissue.

- Shear-Wave Elastography (SWE): A real-time SWE box was placed over the tumor including surrounding tissue. A 2-mm to 3-mm region-of-interest (ROI) was positioned over the stiffest area of the tumor and peritumoral region. System software automatically calculated maximum elasticity (E-max in kPa) and mean elasticity (E-mean in kPa).

4.8 Histopathological and Immunohistochemical Evaluation

Ultrasound-guided 14-gauge core needle biopsies were obtained immediately following imaging. Biopsy cores were fixed in 10 percent neutral buffered formalin, paraffin-embedded, and cut into 4-micrometer sections:

- Histological Grading: Graded according to the Nottingham modification of the Bloom-Richardson system (Grade I, II, III).
- Immunohistochemistry (IHC): Evaluated for Estrogen Receptor (ER), Progesterone Receptor (PR), HER2 expression, and Ki-67 proliferation index. Standard molecular subtypes were defined: Luminal A (ER+/PR+, HER2-, low Ki-67), Luminal B (ER+, HER2- or HER2+, high Ki-67), HER2-enriched (ER-/PR-, HER2+), and Triple-Negative (ER-/PR-/HER2-).
- Stromal Tumor-Infiltrating Lymphocytes (sTILs): Quantified according to the International TILs Working Group guidelines. Stromal area occupied by mononuclear inflammatory cells (lymphocytes and plasma cells) was evaluated on hematoxylin and eosin (H&E) sections and scored as a percentage. sTILs were categorized as: Low (< 10 percent), Intermediate (10-50 percent), and High (> 50 percent).

4.9 Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY). Continuous variables were tested for normality using the Kolmogorov-Smirnov test and expressed as mean +/- standard deviation (SD). Categorical variables were presented as absolute numbers and percentages (n, percent).

Comparisons across sTIL categories were conducted using One-Way Analysis of Variance (ANOVA) with Tukey's post-hoc test or Kruskal-Wallis test. Bivariate linear relationships were evaluated using Pearson's or Spearman's rank correlation coefficients (r). Multivariable binary logistic regression models were developed to identify independent predictors of high sTIL infiltration (> 50 percent). Statistical significance was defined as a two-sided p-value < 0.05.

5. Results

5.1 Baseline Demographic and Tumor Characteristics

The study cohort comprised 160 women with invasive breast carcinoma (mean age 51.4 +/- 9.2 years; mean tumor size 24.6 +/- 8.4 mm). Invasive ductal carcinoma (NOS) accounted for 83.8 percent (n = 134) of cases. High sTIL infiltration (> 50 percent) was identified in 28.8 percent (n = 46), intermediate in 38.8 percent (n = 62), and low in 32.5 percent (n = 52). Baseline clinicopathological features across sTIL groups are detailed in Table 1.

Clinicopathological Parameter	**Low sTILs (< 10%) (n = 52)**	**Intermediate sTILs (10-50%) (n = 62)**	**High sTILs (> 50%) (n = 46)**	**Total Cohort (n = 160)**	**p-value**
Patient Age (years)	53.2 +/- 8.8	51.6 +/- 9.4	48.8 +/- 8.6	51.4 +/- 9.2	0.042
Tumor Size (mm)	22.4 +/- 6.8	24.8 +/- 8.2	26.8 +/- 9.4	24.6 +/- 8.4	0.028
Nottingham Grade I, n (%)	18 (34.6)	8 (12.9)	2 (4.3)	28 (17.5)	<0.001
Nottingham Grade II, n (%)	26 (50.0)	34 (54.8)	12 (26.1)	72 (45.0)	<0.001
Nottingham Grade III, n (%)	8 (15.4)	20 (32.3)	32 (69.6)	60 (37.5)	<0.001
Axillary Node Positive, n (%)	22 (42.3)	28 (45.2)	24 (52.2)	74 (46.3)	0.542

Clinicopathological Parameter	Low sTILs (< 10%) (n = 52)	Intermediate sTILs (10-50%) (n = 62)	High sTILs (> 50%) (n = 46)	Total Cohort (n = 160)	p-value
Ki-67 Proliferation Index (%)	18.2 +/- 8.4	28.6 +/- 11.2	48.4 +/- 16.2	30.8 +/- 16.4	<0.001
Triple-Negative Subtype, n (%)	4 (7.7)	14 (22.6)	22 (47.8)	40 (25.0)	<0.001

Table 1: Baseline clinicopathological characteristics stratified by stromal tumor-infiltrating lymphocyte (sTIL) category.

5.2 Ultrasound Elastography Features Across sTIL Categories

Tumors with high sTIL infiltration exhibited significantly lower elastographic stiffness metrics compared to tumors with low sTIL levels ($p < 0.001$). Mean shear-wave elasticity (E-mean) was 84.2 ± 22.4 kPa in high sTIL tumors vs. 142.6 ± 31.8 kPa in low sTIL tumors. Strain ratio was similarly reduced in high sTIL cases (2.8 ± 0.8 vs. 4.6 ± 1.2, $p < 0.001$).

Elastographic Parameter	Low sTILs (< 10%) (n = 52)	Intermediate sTILs (10-50%) (n = 62)	High sTILs (> 50%) (n = 46)	p-value
Strain Ratio (SR)	4.6 +/- 1.2	3.6 +/- 0.9	2.8 +/- 0.8	<0.001
SWE E-mean (kPa)	142.6 +/- 31.8	114.2 +/- 26.4	84.2 +/- 22.4	<0.001

Elastographic Parameter	Low sTILs (< 10%) (n = 52)	Intermediate sTILs (10-50%) (n = 62)	High sTILs (> 50%) (n = 46)	p-value
SWE E-max (kPa)	168.4 +/- 38.2	136.8 +/- 32.2	102.4 +/- 28.6	<0.001
Peritumoral E-mean (kPa)	68.4 +/- 18.2	52.6 +/- 14.8	38.2 +/- 11.4	<0.001
Color Map Soft / Deformable Pattern (%)	11.5 percent	35.5 percent	71.7 percent	<0.001

Table 2: Comparison of strain and shear-wave elastography features across sTIL categories.

5.3 Correlation Analysis

Spearman rank correlation analysis demonstrated that shear-wave elasticity (E-mean) correlated inversely with sTIL percentage ($r = -0.64$, $p < 0.001$). Conversely, E-mean correlated positively with Nottingham grade ($r = 0.52$, $p < 0.001$) and tumor size ($r = 0.48$, $p < 0.001$). High sTIL level correlated strongly with Ki-67 index ($r = 0.62$, $p < 0.001$).

Variable Pair	Correlation Coefficient (r)	p-value
SWE E-mean vs. sTIL Percentage	-0.64	<0.001
Strain Ratio vs. sTIL Percentage	-0.58	<0.001
SWE E-mean vs. Nottingham Grade	0.52	<0.001
SWE E-mean vs. Tumor Size (mm)	0.48	<0.001

Variable Pair	Correlation Coefficient (r)	p-value
sTIL Percentage vs. Ki-67 Index	0.62	<0.001
SWE E-mean vs. Ki-67 Index	-0.36	<0.001

Table 3: Bivariate correlation matrix linking elastographic features, sTILs, and histopathology.

5.4 Multivariable Logistic Regression Analysis

In multivariable binary logistic regression modeling for predicting high sTIL infiltration (> 50 percent), lower shear-wave elasticity (E-mean < 95 kPa; adjusted OR = 3.84, 95 percent CI: 1.76 to 8.38, p = 0.001), triple-negative breast cancer subtype (adjusted OR = 3.12, 95 percent CI: 1.42 to 6.84, p = 0.004), high Ki-67 proliferation index (> 30 percent; adjusted OR = 2.68, 95 percent CI: 1.18 to 6.08, p = 0.018), and high Nottingham grade III (adjusted OR = 2.24, 95 percent CI: 1.02 to 4.92, p = 0.044) were established as independent predictors.

Predictor Variable	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
SWE E-mean < 95 kPa	5.82 (2.78–12.18)	<0.001	3.84 (1.76–8.38)	0.001
Triple-Negative Molecular Subtype	4.86 (2.28–10.36)	<0.001	3.12 (1.42–6.84)	0.004
Ki-67 Proliferation Index > 30%	4.24 (2.02–8.88)	<0.001	2.68 (1.18–6.08)	0.018
Nottingham Grade III	3.68 (1.74–7.78)	0.001	2.24 (1.02–4.92)	0.044
Tumor Size > 20 mm	2.18 (1.06–4.48)	0.034	1.48 (0.68–3.22)	0.318

Table 4: Multivariable logistic regression modeling independent predictors of high sTIL infiltration.

6. Discussion

This prospective observational study evaluated the association between ultrasound elastography findings, stromal tumor-infiltrating lymphocytes (sTILs), and histopathological characteristics in invasive breast carcinoma. The primary finding demonstrates that tumors with dense lymphocytic infiltration (> 50 percent sTILs) exhibit significantly lower acoustic stiffness (E-mean 84.2 kPa) compared to immunologically cold tumors (142.6 kPa), despite displaying aggressive histopathological features such as high grade and elevated Ki-67.11-13

6.1 Mechanical Basis of Tumor Softening by Lymphocytic Infiltration

Breast carcinoma stiffness on elastography is traditionally attributed to desmoplastic stromal reaction, dense collagen type I cross-linking, and myofibroblast activity. However, high sTIL infiltration alters this physical microenvironment. Infiltrating mononuclear cells release matrix metalloproteinases (MMPs) and proteolytic enzymes that break down rigid extracellular matrix collagen. Additionally, dense lymphocytic sheets replace dense fibrotic stroma with softer, cellular fluid-rich immune clusters, reducing shear-wave velocity and acoustic elasticity values.14-15

6.2 Subtype-Specific Immune and Mechanical Paradox

High sTILs were enriched in triple-negative breast cancer (47.8%) and high-grade (Nottingham Grade III, 69.6%) tumors. Although high-grade tumors generally present with larger size and central necrosis, the presence of dense sTILs creates a mechanical "softening paradox": an aggressive, high-grade tumor that appears less stiff on elastography due to extensive immune cell flux. Recognizing this pattern prevents misinterpreting soft elastographic features as benign when evaluating highly immunogenic aggressive carcinomas.16-17

6.3 Clinical Value as a Non-Invasive Biomarker

Because sTILs predict neoadjuvant chemotherapy response and suitability for immune checkpoint inhibitor therapy (e.g., anti-PD-1/PD-L1 agents), pre-treatment identification of immune-rich tumors is clinically crucial. SWE E-mean < 95 kPa provided a nearly four-fold increased odds of high sTIL infiltration (aOR $= 3.84$). Incorporating elastography alongside standard B-mode ultrasound offers a real-time, non-invasive method to map immune infiltration across the entire tumor volume, mitigating core needle biopsy sampling error.18-20

6.4 Limitations

Several limitations should be considered. First, elastography evaluates total tumor stiffness, which reflects a composite of desmoplasia, necrosis, cellularity, and lymphocyte infiltration. Second, sTILs were quantified on core biopsies rather than whole surgical resection specimens. Third, inter-observer variation in strain application was minimized but remains a factor inherent to hand-held ultrasound techniques.

7. Conclusion

Ultrasound elastography elasticity metrics correlate significantly with stromal tumor-infiltrating lymphocyte density and histopathological tumor features in invasive breast carcinoma. Tumors with high sTIL infiltration display lower acoustic stiffness (E-mean and strain ratio) compared to immunologically cold tumors. Pre-operative shear-wave elastography serves as a valuable non-invasive surrogate biomarker to infer tumor microenvironment mechanics and immune infiltration status prior to initiating definitive systemic or surgical therapy.

8. Recommendations

1. Incorporate quantitative shear-wave elastography (SWE) in pre-treatment breast ultrasound protocols to evaluate tumor microenvironment stiffness alongside morphological features.

2. Consider lower elasticity values in aggressive or triple-negative tumors as a potential imaging indicator of high stromal tumor-infiltrating lymphocyte (sTIL) density.

3. Combine elastographic E-mean metrics with core needle biopsy histology to minimize sampling error when assessing tumor immune status for neoadjuvant chemotherapy planning.

4. Standardize SWE region-of-interest (ROI) placement to capture both stiff desmoplastic margins and softer immune-rich tumor cores.

5. Conduct multi-center longitudinal studies evaluating whether pre-treatment elastography metrics can directly predict pathological complete response (pCR) following immunochemotherapy.

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