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Predictors of Negative Sentinel Lymph Node Biopsy Results in Early Breast Cancer: a Retrospective Cohort Study

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ABSTRACT

Objective: To identify clinicopathologic predictors of negative sentinel lymph node biopsy (SLNBx) in clinically node-negative breast cancer patients at a tertiary center in Pakistan.

Study Design: Retrospective cohort study. ***Place and Duration of Study:*** Breast Surgery Department, Combined Military Hospital Rawalpindi, Pakistan, from Jan to Dec 2024. ***Methodology:*** Women with early-stage, clinically node-negative invasive breast cancer undergoing SLNBx were included. Data on tumor size, grade, receptor profile, Ki-67, comorbidities, and family history were analyzed. Chi square test was applied and p-value of ≤ 0.05 was considered as statistically significant.

Results: Of 186 patients, 142 had complete data; 120 (84.5%) had negative SLNBx. There was a statistically significant association found between SLN and Menopause ($p < 0.001$), diabetes ($p < 0.001$), hypertension ($p < 0.001$), family history ($p = 0.026$), tumor grade ($p < 0.001$) and histology ($p = 0.005$).

. ***Conclusion:*** A negative family history was the only independent predictor of SLNBx outcome. The high rate of pathologic node negativity supports selective de-escalation of axillary surgery in this subgroup.

Keywords: Ki-67 Antigen, Neoplasm, Sentinel Lymph Node Biopsy, Tumor Receptor Status

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INTRODUCTION

Sentinel lymph node biopsy (SLNBx) is the standard procedure for axillary staging in early-stage breast cancer, replacing axillary lymph node dissection (ALND) in most patients. This transition has markedly reduced surgical morbidity without compromising oncological outcomes.[1] Current de-escalation strategies increasingly explore whether SLNBx itself may be safely omitted in selected patients predicted to have pathologically negative nodes.[2]

Despite its less invasive nature compared with ALND, SLNBx carries risks including shoulder stiffness, seroma, and lymphedema.[3] Predictors of sentinel node involvement consistently reported in the literature include tumor size, histological grade, molecular subtype, lymphovascular invasion, and proliferation indices.[4–5] For example, up to 74% of T1 tumors are node-negative, compared with approximately 50% of T3 tumors.[6] Increasing patient age has also been associated with a higher likelihood of negative SLNBx.[7] Hormone receptor status further modifies axillary risk, with estrogen receptor (ER) and progesterone receptor (PR) positive tumors showing lower nodal involvement, while triple-negative and HER2-positive cancers are associated with higher risk.[8] Ki-67, a proliferation marker, has been evaluated as a potential predictor, although its role remains debated.[9] Imaging also contributes to preoperative risk assessment, as patients with no suspicious nodes on ultrasonography or MRI are more likely to have negative SLNBx.[9]

In resource-constrained settings, validation of these predictors is limited. A recent study from Bahrain found that high tumor grade, lymphovascular invasion, and larger tumor size were significantly associated with sentinel node metastasis.[6] From Pakistan, Zaman *et al.* demonstrated the feasibility and accuracy of SLNBx using radioguided mapping, supporting its adoption in local surgical practice.[7] Gong *et al.* further reported reduced morbidity and comparable oncologic outcomes with SLNBx combined with breast-conserving surgery.[8]

However, very few institutional or multicenter studies from South Asia specifically evaluate predictors of sentinel node negativity, hence institutional data from Pakistan can provide critical insights in our local context.

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METHODOLOGY

This retrospective cohort study was conducted at the Breast Surgery Department of Combined Military Hospital (CMH), Rawalpindi, Pakistan from January to December 2024, following approval from the Institutional Review Committee (IRC approval no. 888, dated: 10/06/2025). This approval was granted retrospectively for the analysis of routinely collected clinical data.

Inclusion Criteria: Adult females diagnosed with early-stage breast cancer (T1–T3, N0–1, M0) according to the American Joint Committee on Cancer (AJCC) staging system, having clinically and radiologically node-negative axillae determined by physical examination and axillary ultrasound, were included.

Exclusion Criteria: Patients with multicentric breast carcinoma, recurrent tumors, those who received neoadjuvant chemotherapy, and those with incomplete clinicopathological or imaging data were excluded.

We reviewed records of women with early-stage breast cancer treated at CMH Rawalpindi, a tertiary care military hospital with dedicated breast surgery and on-site histopathology services. Non-probability convenience sampling was used to include all eligible patients. Sample size was calculated with the Cleveland Clinic online sample size calculator, assuming 13.64% prevalence of negative sentinel lymph node (SLN) biopsy in clinically node-negative, early breast cancer, which came to 135.[10,11] To compensate for missing or incomplete records, 186 patients were included.

While the calculation was based on T1 node negativity rates, the outcome measure was SLN negativity across all eligible T stages. This difference is acknowledged as a limitation. Data were extracted from operative notes, histopathology records, and imaging reports using a standardized form. Missing data were handled through complete case analysis; no imputation was performed. To minimize bias in this retrospective cohort study, we employed strict eligibility criteria, used consecutive sampling to reduce selection bias, and extracted data from structured medical records. Operational definitions were standardized, and data were abstracted by trained investigators using uniform templates. Potential confounders were identified a priori and adjusted for using multivariable logistic regression. Missing data were transparently reported, and cases with incomplete covariates were excluded from regression models with caution given the limited event count.

Data was analyzed by using Statistical Package for Social Sciences (SPSS) version 22. Quantitative data was represented using Mean±Sd deviation and qualitative data was represented by using percentage and frequency. Chi square test was applied and p-value of ≤ 0.05 was considered as statistically significant

RESULTS

Of the 186 patients who underwent sentinel lymph node biopsy (SLNBx), complete clinicopathological and histopathology data were available for 142 patients. SLNBx was negative in 120(84.5%) and positive in 22(15.5%). The mean age was 51.6±13.0 years (range: 24–83), with 55.6% (n=79) aged ≥50 years. Most participants were postmenopausal 81(57.5%). Comorbidities included diabetes mellitus in 15(10.6%) and hypertension in 19(13.38%). A family history of breast or ovarian cancer was present in 30(21.13%) of patients and family history of breast cancer was present in 10(7.1%) of patients (Table-I).

Table-I. Baseline characteristics of the study population (n = 142)

Characteristic	Values
Mean Age (years) Mean±SD	51.5±13.0
Menopausal status	
Premenopausal Postmenopausal	61(42.9%) 81(57.1%)
Diabetes mellitus	15(10.6%)
Hypertension	19(13.38%)
Family history of any malignancy	30(21.13%)
Family history of breast cancer	10(7.1%)

Most cases were invasive ductal carcinoma (n=105; 73.9%). Nottingham grading revealed 21(14.1%) Grade I, 75(52.8%) Grade II, and 46 (32.4%) Grade III tumors.

Clinical staging (AJCC) distribution was T1 (n=54; 38.0%), T2 (n=83;58.5%), and T3 (n=53; 3.5%). Hormone receptor positivity (ER or PR) was seen in 66.9%, HER2 positivity in 11.9%, and triple-negative phenotype in 25.0%. Ki-67 data were available for 114 patients (61.3%), with a median of 20% (IQR 5–50); 58.8% of those were classified as high Ki-67 (≥20%). Tumor characteristics are summarized in Table-II

Table-II. Tumor Characteristics of the Study Population (N=142)

Characteristic	n (%)
Histology	
Invasive ductal carcinoma	105(73.9)
Invasive lobular carcinoma	37(26.1)
Tumor grade	
Grade I	21(14.8)
Grade II	75(52.8)
Grade III	46(32.4)
Clinical stage (T)	
T1	54(38.0)
T2	83(58.5)
T3	5(3.5)
Pathological stage	
Stage IIA	85(59.9)
Stage IA	42(29.6)
Stage 0	9(6.3)
Stage IIB	6(4.2)
Proliferation	
Low Ki-67 (%); median (IQR)	20(5.5)
High Ki-67: Median (IQR)	84(58.9)
Receptor status	
ER positive	93(65.7)
PR positive	78(55.0)
Hormone receptor positive (ER or PR)	95(66.9)
HER2 positive	17(11.9)
Triple-negative	36(25.0)

**ER = estrogen receptor; PR = progesterone receptor; HR = hormone receptor (ER or PR); HER2 = human epidermal growth factor receptor 2; IQR = interquartile range.*

Table-III results shows that there was a statistically significant association found between SLN and Menopause ($p < 0.001$), diabetes ($p < 0.001$), hypertension ($p < 0.001$), family history ($p= 0.026$), tumor grade ($p < 0.001$) and histology ($p = 0.005$).

DISCUSSION

This retrospective cohort study evaluated predictors of sentinel lymph node (SLN) negativity in early breast cancer patients at a South Asian tertiary care center. The observed SLN-negative rate of 84.5% closely matches findings from large international trials such as ACOSOG Z0011 and AMAROS, which reported SLN negativity rates of 83% and 85%, respectively.[12,13] A recent Pakistani study by Siddiqui et al. reported a slightly lower rate of 78%, which may reflect differences in patient selection, imaging protocols, or nodal assessment.[14]

Table-III: Association of Study Parameters and Sentinel Lymph Node (n=142)

Parameters	Sentinel Lymph Node		*p*-value
	Positive (n=22) n (%)	Negative (n=120) n (%)	
Menopausal status Pre Post	20(90.9%) 2(9.1%)	41(34.2%) 79(65.8%)	*< 0.001*
Diabetes Yes No	9(40.9%) 13(59.1%)	6(5.0%) 114(95.0%)	*< 0.001*
Hypertension Yes No	11(50.0%) 11(50.0%)	8(6.7%) 112(93.3%)	*< 0.001*
Family history Yes No	4(18.2%) 18(81.8%)	6(5.0%) 114(95.0%)	*0.026*
Clinical T stage T1 T2 T3	13(59.1%) 8(36.4%) 1(4.5%)	41(34.2%) 75(62.5%) 4(3.3%)	0.071
Tumor grade I II III	2(9.1%) 2(9.1%) 18(81.8%)	19(15.8%) 73(60.8%) 28(23.4%)	< 0.001
Histology Invasive ductal carcinoma Invasive lobular carcinoma	11(50.0%) 11(50.0%)	94(78.3%) 26(21.7%)	0.005

Among examined predictors, family history of malignancy was the only variable that retained statistical significance in multivariable analysis. While this suggests a potential link between family history and greater nodal involvement, the wide confidence interval and limited number of events mean the association should be interpreted cautiously. Our findings are consistent with reports from India and China, where familial cancer history has been linked with higher nodal burden and aggressive tumor biology.[8,15] Prior research also shows that BRCA1/2 mutation carriers and patients with strong familial clustering are more likely to present with multifocal tumors and lymphatic spread.[16,17] In the absence of genetic testing in our cohort, family history may serve as a pragmatic, low-cost surrogate for hereditary risk, but further validation is needed before it can guide clinical decision-making.

Comorbidities such as diabetes mellitus and hypertension showed significant associations with SLN status in univariate analysis but not after adjustment, echoing findings by Peairs et al. and Aroner *et al.*, who found no independent effect of metabolic comorbidities on nodal burden.[18,19] Although chronic inflammation may influence tumor progression, nodal involvement appears to be primarily driven by tumor-intrinsic factors.

The relationship between Ki-67 and SLN status was counterintuitive in our cohort. High Ki-67, usually associated with aggressive disease, showed a non-significant trend toward higher SLN negativity. Possible explanations include residual confounding, misclassification of Ki-67, or biological differences across subtypes. For instance, triple-negative tumors often have high Ki-67 but may present with smaller primaries that are node negative. A meta-analysis of over 12,000 patients by de Azambuja et al. reported a clear association of high Ki-67 with worse outcomes, but our smaller, incomplete dataset (Ki-67 available for 61% of patients) limited the power to confirm or refute this association.[20]

These results reinforce global shifts in axillary management. The SOUND and INSEMA trials demonstrated the safety of omitting SLNBx in selected patients with negative axillary imaging and favorable biology.[2,21] Likewise, the IBCSG 23-01 and long-term ACOSOG Z0011 results confirmed no survival benefit from axillary clearance in cases of minimal nodal disease.[12,22] While our cohort differed in surgical patterns (many underwent mastectomy rather than breast-conserving surgery), the high rate of SLN negativity aligns with the rationale for tailoring axillary surgery according to risk.

Clinically, these findings are relevant for low-resource settings where advanced genomic testing is unavailable. Family history, routinely obtainable in outpatient clinics, may provide an additional lens for SLNBx triage when combined with imaging and clinicopathological predictors. This pragmatic approach could reduce unnecessary interventions and the morbidity associated with axillary surgery.

LIMITATION OF STUDY

Several limitations should be acknowledged. The retrospective design is prone to selection and information bias, as data were abstracted from records rather than collected prospectively. Missing or incomplete biomarker data (e.g., ER, PR, HER2, Ki-67) limited inclusion of potentially important predictors in adjusted models. The number of SLN-positive cases (n = 22) constrained statistical power, and the regression model had fewer than 10 events per variable, raising the risk of overfitting. Finally, recruitment from a single military hospital may limit generalizability, since patient demographics and access to care may differ from the broader population.

CONCLUSION

In our study, the majority of clinically node-negative breast cancer patients were also pathologically node negative, with an SLN-negative rate of 84.5%. Family history of malignancy was the only factor that retained statistical significance in adjusted analysis, although the limited number of positive events warrants cautious interpretation. Conventional variables such as age, menopausal status, comorbidities, and Ki-67 index did not independently predict SLN status.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SN & AJ: Data acquisition, data analysis, critical review, approval of the final version to be published.

SRN & AS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

ZJ & SSQN: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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