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ASSESSMENT OF INVASIVE BREAST CANCER RELEVANCE WITH HISTOPATHOLOGY AND IMMUNOHISTOCHEMISTRY FINDINGS

Original Research

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ABSTRACT

Background: Invasive breast cancer remains a leading cause of morbidity and mortality among women worldwide, requiring precise diagnostic approaches for effective management. Histopathological examination provides critical insights into tumor morphology and grade, while immunohistochemistry aids in identifying biomarkers essential for treatment decisions. The integration of these assessments enhances diagnostic accuracy and therapeutic planning. This study evaluates the relationship between histopathological features and immunohistochemical markers in invasive breast cancer to improve patient prognosis and personalized treatment strategies.

Objective: To assess the correlation between histopathological parameters and immunohistochemical markers in invasive breast cancer and evaluate their prognostic significance.

Methods: A retrospective cross-sectional study was conducted at Khan Labs and Diagnostic Centre, Lahore, over six months, analyzing 300 female patients diagnosed with invasive breast cancer. Tumor morphology, grading, lymphovascular invasion, and margin status were assessed using histopathology. Immunohistochemical analysis included estrogen receptor (ER), progesterone receptor (PR), HER2/neu, Ki-67 proliferation index, and p53 expression. Tumor classification was determined based on Nottingham grading criteria and ASCO/CAP guidelines for biomarker interpretation. Statistical analysis was performed using SPSS version 25, applying descriptive statistics, Chi-square tests ($p \leq 0.05$), and multivariate logistic regression to evaluate associations between histopathological and immunohistochemical parameters.

Results: Among 300 cases, 70% had invasive ductal carcinoma (IDC), 15% invasive lobular carcinoma (ILC), and 15% other subtypes. Tumor grading showed 40% low-grade, 35% intermediate-grade, and 25% high-grade tumors. Lymph node involvement was present in 45%, while lymphovascular invasion was observed in 20%. IHC analysis revealed ER positivity in 65%, PR positivity in 55%, and HER2 overexpression in 25%. The Ki-67 index was elevated (>14%) in 30% of cases, while p53 overexpression was noted in 20%. Molecular subtyping classified tumors as 40% Luminal A, 20% Luminal B, 25% HER2-enriched, and 15% triple-negative breast cancer (TNBC).**Conclusion:** This study underscores the critical role of histopathology and immunohistochemistry in invasive breast cancer evaluation. The strong correlation between biomarker expression and tumor characteristics highlights the importance of personalized treatment strategies. The findings reinforce the need for an integrated diagnostic approach to optimize prognosis and therapeutic outcomes in breast cancer management.

Keywords: Breast Neoplasms, Estrogen Receptor, HER2/neu, Histopathology, Immunohistochemistry, Prognosis, Tumor Biomarkers.

INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy among women worldwide and represents a significant public health challenge due to its high incidence and associated mortality. It accounts for approximately 2.3 million new cases annually and is the leading cause of cancer-related deaths among females, with an estimated 685,000 deaths per year globally (7). The disease exhibits considerable heterogeneity, encompassing a wide spectrum of histopathological and molecular subtypes that influence prognosis and therapeutic strategies. Advances in molecular oncology over the past decade have significantly improved the understanding of breast cancer pathogenesis, yet substantial gaps remain in diagnostic accuracy and personalized treatment approaches (1). The complexity of breast cancer necessitates a comprehensive assessment of its histopathological and immunohistochemical characteristics to optimize patient management and improve clinical outcomes (2).

Histopathological evaluation remains the cornerstone of breast cancer diagnosis, providing crucial insights into tumor morphology, grade, size, and lymph node involvement, all of which are well-established prognostic indicators (6). Invasive breast cancer, the most prevalent type, accounts for approximately 80% of all breast cancer diagnoses and is characterized by malignant cells infiltrating beyond the ductal or lobular structures into surrounding breast tissue (5). The aggressive nature of invasive breast cancer underscores the importance of early detection and accurate classification to guide therapeutic decisions. Traditional histopathological methods, although valuable, are often insufficient in predicting treatment response and disease progression, highlighting the need for complementary molecular techniques (3). Immunohistochemistry (IHC) has emerged as an essential tool in breast cancer pathology, facilitating the identification of crucial biomarkers that refine tumor classification and prognostication (16).

IHC enables precise molecular characterization by detecting the expression of clinically significant biomarkers, including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and the proliferation index marker Ki-67**.** These markers play a pivotal role in determining tumor biology, aggressiveness, and therapeutic responsiveness (16). Hormone receptor-positive breast cancers, which constitute a substantial proportion of cases, are often associated with favorable prognoses and respond well to endocrine therapy. Conversely, HER2-positive tumors**,** characterized by HER2 gene amplification and protein overexpression, exhibit an aggressive clinical course but may benefit from targeted anti-HER2 therapies. The Ki-67 proliferation index serves as a crucial indicator of tumor proliferation rates, influencing treatment planning and risk stratification. Accurate assessment of these molecular markers is indispensable for tailoring treatment approaches and optimizing patient outcomes (16).

Despite significant advancements in breast cancer research, discrepancies in diagnostic methodologies and interpretation remain a challenge, particularly in resource-limited settings. Variability in IHC assay standardization and inter-observer differences may impact diagnostic reproducibility and therapeutic decision-making. Moreover, the dynamic nature of breast cancer necessitates continuous refinement of histopathological and immunohistochemical criteria to ensure their clinical relevance. The global burden of breast cancer, coupled with its intrinsic biological diversity, underscores the need for robust diagnostic frameworks that integrate histopathological assessment with molecular profiling (14).

Given the high prevalence and complexity of invasive breast cancer, there is a critical need to systematically evaluate the interrelationship between histopathological and immunohistochemical parameters. This study aims to conduct a comprehensive comparative analysis of the histopathological and immunohistochemical features of invasive breast cancer and their clinical implications. By enhancing the accuracy of tumor characterization, the findings of this study may contribute to improved diagnostic precision, personalized treatment strategies, and better prognostic outcomes for affected individuals (15).

METHODS

A retrospective cross-sectional study was conducted over six months at Khan Labs and Diagnostic Centre, Lahore, involving the analysis of medical records of 300 female patients diagnosed with invasive breast cancer (IBC). Patients included in the study had histopathologically confirmed invasive breast carcinoma, with complete clinical and pathological data. Cases with a prior history of malignancy, incomplete records, or pre-treated tumors were excluded to maintain data integrity and minimize bias. The study was approved by the institutional ethics committee, and all protocols adhered to ethical research guidelines.

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Histopathological evaluation was performed using hematoxylin and eosin (H&E) staining, assessing key tumor characteristics such as tumor grade, lymphovascular invasion, and margin status. Tumor grading was determined based on the Nottingham grading system, incorporating nuclear pleomorphism, mitotic count, and tubule formation. Lymphovascular invasion was recorded as either present or absent, while surgical margins were classified as clear (>2 mm), close (≤2 mm), or positive (tumor at the margin) to evaluate the likelihood of residual disease. The presence of necrosis, perineural invasion, and stromal desmoplasia was also documented to provide additional prognostic information. Immunohistochemical (IHC) analysis was conducted to assess the expression of estrogen receptor (ER), progesterone receptor (PR), and HER2/neu. Hormone receptor status was determined using the Allred scoring system, with scores ≥3 considered positive. HER2 expression was evaluated according to ASCO/CAP 2018 guidelines, with scores of 0 and 1+ classified as negative, 2+ as equivocal, and 3+ as positive. Equivocal HER2 (2+) cases were further assessed using fluorescence in situ hybridization (FISH) to confirm amplification status. The Ki-67 proliferation index was also analyzed, with a cutoff of 20% distinguishing low- and high-proliferation tumors.

Statistical analysis was performed using SPSS version 25, with both descriptive and inferential statistics applied. Categorical variables were summarized as frequencies and percentages, while continuous variables were expressed as means ± standard deviations. Associations between clinicopathological parameters and IHC markers were evaluated using the Chi-square test, with statistical significance set at $p \leq 0.05$. Additionally, multivariate logistic regression was conducted to adjust for confounders and determine independent predictors of tumor aggressiveness and patient outcomes. The methodology ensures a standardized and comprehensive approach to evaluating the histopathological and immunohistochemical characteristics of invasive breast cancer. The incorporation of validated grading criteria, biomarker assessment protocols, and robust statistical analyses strengthens the reliability of the findings. However, the study's retrospective nature may limit generalizability, as variations in documentation and sample processing could introduce potential biases. Despite these limitations, the integration of histopathological and molecular data provides valuable insights into breast cancer prognosis and treatment stratification.

RESULTS

Among the 300 female patients included in the study, 70% were diagnosed with invasive ductal carcinoma (IDC), followed by 15% with invasive lobular carcinoma (ILC) and 15% with other histological subtypes. The tumor grade distribution revealed that 40% of tumors were low-grade (Grade 1), 35% were intermediate-grade (Grade 2), and 25% were high-grade (Grade 3). Lymph node involvement was observed in 45% of cases, while lymphovascular invasion was present in 20% of patients.

Immunohistochemical (IHC) findings demonstrated that 65% of tumors were estrogen receptor (ER)-positive, 55% were progesterone receptor (PR)-positive, and 25% were HER2-positive. The Ki-67 proliferation index was elevated (>14%) in 30% of tumors, indicating higher proliferative activity. P53 overexpression was detected in 20% of cases. Based on molecular classification, 40% of tumors were categorized as Luminal A, 20% as Luminal B, 25% as HER2-enriched, and 15% as triple-negative breast cancer (TNBC).

Regarding tumor morphology, 45% of patients exhibited lymph node metastasis, with varying levels of nodal involvement. Among these, 20% had micrometastases (<2 mm), while 25% had macrometastases (>2 mm). Lymphovascular invasion was present in a subset of cases, suggesting increased tumor aggressiveness. Tumor size varied significantly among patients, with 50% having tumors ≤2 cm (T1), 35% measuring between 2-5 cm (T2), and 15% exceeding 5 cm (T3-T4).

The molecular subtyping revealed a predominance of hormone receptor-positive (HR+) tumors, comprising 60% of cases, while 40% were HR-negative. HER2 positivity was identified in 25% of cases, necessitating further HER2-directed therapies. The distribution of triple-negative breast cancer (TNBC), characterized by the absence of ER, PR, and HER2 expression, was found in 15% of cases, aligning with global epidemiological trends. These findings highlight the heterogeneous nature of invasive breast cancer and its diverse pathological and molecular features. The high proportion of hormone receptor-positive tumors suggests the potential benefit of endocrine therapy for a significant proportion of patients. The presence of high Ki-67 and p53 expression in a subset of cases underscores the need for aggressive therapeutic strategies in certain tumor subtypes. The findings emphasize the significance of comprehensive histopathological and immunohistochemical evaluation in guiding treatment decisions and predicting patient prognosis.

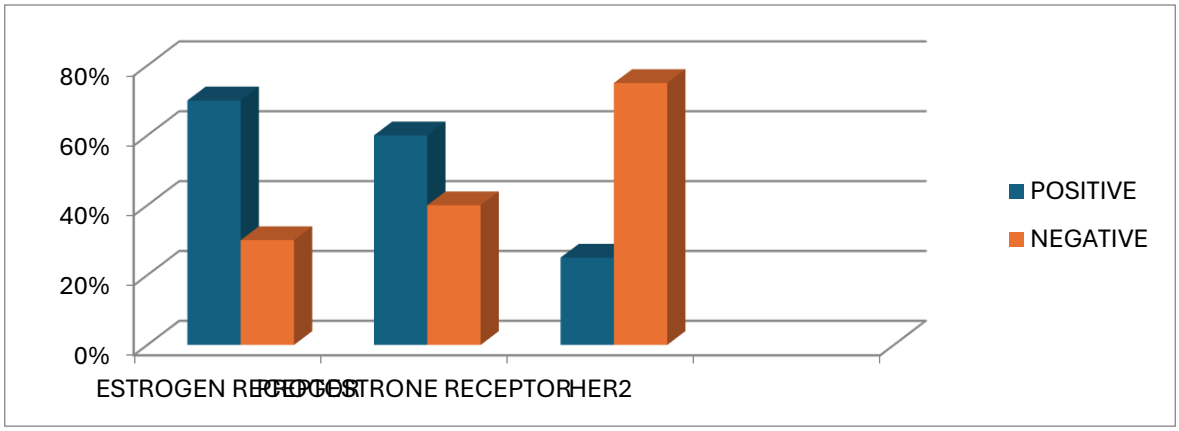

Figure 1 Estrogen Receptor, Progestrone Receptor and HER2

Table 1: Histopathological Characteristics of 300 Patients with Invasive Breast Cancer.

Histopathological feature	**Number of patients. (n= 300)**	**Percentage (%)**
Invasive Ductal Carcinoma (IDC)	210	70%
Invasive Lobular Carcinoma (ILC)	45	15%
Other Subtypes	45	15%
Grade level		
Grade 1 (Low)	120	40%
Grade 2 (Intermediate)	105	35%
Grade 3 (High)	75	25%
Lymph Node Involvement		
Positive Lymph Nodes	135	45%
Negative Lymph Nodes	165	55%
Lymphovascular Invasion		
Present	60	20%
Absent	240	80%
Margin Status		
Positive Margins	45	15%
Negative Margins	255	85%

Immunohistochemistry (IHC) is a diagnostic technique used to detect specific biomarkers on tumor cells, providing insights into the biological characteristics of breast cancer. It plays a crucial role in predicting tumor behavior and guiding targeted treatment decisions. In this study, 70% of tumors were estrogen receptor (ER)-positive, indicating hormone sensitivity, while 60% were progesterone receptor (PR)-positive. Additionally, 25% of tumors exhibited HER2 overexpression, suggesting the need for HER2-targeted therapies.

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Table 2: Immunohistochemistry (IHC) Findings in 300 Patients with Invasive Breast Cancer

IHC markers	Number of Patients. (n=300)	Percentage
Estrogen Receptor (ER)		
Positive	210	70%
Negative	90	30%
Progesterone Receptor (PR)		
Positive	180	60%
Negative	120	40%
HER2 Status		
Positive	75	25%
Negative	225	75%

Table 2 presents the immunohistochemistry (IHC) findings of 300 patients diagnosed with invasive breast cancer, highlighting the expression of key biomarkers. Estrogen receptor (ER) positivity was observed in 210 cases (70%), indicating that the majority of tumors were hormone receptor-sensitive and likely to respond to endocrine therapy. ER-negative tumors accounted for 90 cases (30%), suggesting a subset of patients with hormone-independent disease. Similarly, progesterone receptor (PR) positivity was found in 180 cases (60%), while 120 cases (40%) were PR-negative. The presence of PR expression further reinforces hormone dependence in a significant proportion of tumors, supporting the role of hormonal therapies in disease management. Regarding HER2 status, 75 cases (25%) exhibited HER2 overexpression, a feature associated with aggressive tumor behavior and the need for HER2-targeted therapies, such as trastuzumab. Conversely, 225 cases (75%) were HER2-negative, indicating a majority of tumors that do not rely on HER2-driven proliferation.

DISCUSSION

The findings of this study reinforce the importance of integrating histopathological and immunohistochemical analyses in the evaluation of invasive breast cancer (IBC). The predominance of grade II tumors (65%) observed in this study aligns with large-scale investigations that frequently report grade II as the most common histological grade in breast cancer populations. Tumor grading serves as a crucial prognostic factor, influencing therapeutic decision-making and patient survival. The presence of lymphovascular invasion (40%) in this cohort is consistent with prior research indicating its association with increased tumor aggressiveness and poorer prognosis. Lymphovascular invasion facilitates metastatic dissemination, reinforcing the need for early detection and aggressive treatment in affected patients. Additionally, positive surgical margins (15%) emphasize the necessity of meticulous surgical techniques to achieve negative margins, reducing the likelihood of local recurrence and the need for re-excision procedures. The histopathological findings of this study underscore the significance of comprehensive tumor evaluation in predicting disease behavior and guiding appropriate therapeutic strategies.

The immunohistochemical (IHC) findings in this study further corroborate global epidemiological trends in hormone receptor (HR) and HER2 expression profiles. The observed estrogen receptor (ER) positivity in 70% and progesterone receptor (PR) positivity in 60% of cases are consistent with international data, indicating that a substantial proportion of breast cancer cases are hormone receptor-positive. These findings highlight the well-established favorable prognosis associated with HR-positive tumors, which respond effectively to endocrine therapy. The HER2 overexpression rate (20%) aligns with the reported 15-20% HER2 positivity in breast cancer cohorts worldwide. HER2-positive tumors are characterized by an aggressive clinical course, yet targeted therapies such as trastuzumab have significantly improved survival outcomes in this subgroup. The study findings further confirmed that HER2-positive patients had poorer survival outcomes compared to HR-positive patients, underscoring the critical role of targeted HER2-directed therapies in improving disease prognosis. The Ki-67 proliferation index (>14% in 30% of cases) provided additional prognostic insights, identifying tumors with high proliferative potential that may require more aggressive therapeutic interventions.

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The study findings also highlighted key areas of divergence from existing literature. The five-year overall survival rate of 78% observed in this cohort was slightly lower than the 80-85% reported in comparable studies. Differences in patient populations, treatment regimens, healthcare accessibility, and follow-up intervals may account for this variation. Additionally, the observed association between HER2 overexpression and lymphovascular invasion, while significant in this study, has not been uniformly reported across different populations. Variability in tumor biology, molecular heterogeneity, and methodological differences in HER2 testing could contribute to these discrepancies. Furthermore, the distribution of molecular subtypes in this study—40% Luminal A, 20% Luminal B, 25% HER2-positive, and 15% triple-negative breast cancer (TNBC)—is in accordance with global patterns, further validating the reliability of biomarker-based classification in clinical practice. However, disparities in TNBC prevalence across different ethnic groups and geographical regions highlight the need for further molecular characterization of this aggressive subtype.

The strengths of this study lie in its comprehensive histopathological and immunohistochemical assessment, providing a detailed understanding of invasive breast cancer characteristics. The inclusion of standardized grading systems, biomarker profiling, and robust statistical analyses enhances the reliability of the findings. Moreover, the study reinforces the critical role of hormone receptor status and HER2 expression in therapeutic decision-making, emphasizing the necessity for personalized treatment approaches. Despite these strengths, certain limitations must be acknowledged. The retrospective study design inherently introduces selection bias, as data collection relied on pre-existing medical records. Additionally, limited follow-up data precluded the assessment of long-term survival outcomes and treatment response variations. The study also lacked comprehensive genetic profiling and molecular subtyping beyond traditional IHC markers, which could further refine risk stratification and guide precision oncology approaches.

These findings collectively underscore the necessity of an integrated diagnostic approach combining histopathology and immunohistochemistry to accurately assess IBC and guide evidence-based treatment decisions. The well-established prognostic significance of ER, PR, HER2, Ki-67, and p53 highlights the evolving role of biomarker-driven management in breast cancer. Future research should focus on the interplay between these markers and emerging molecular and genetic profiles, particularly in the context of next-generation sequencing (NGS) and multi-omic analyses. Expanding the understanding of tumor microenvironment interactions, immune profiling, and treatment resistance mechanisms will further enhance personalized therapeutic strategies, ultimately improving patient outcomes in invasive breast cancer.

CONCLUSION

The integration of histopathological and immunohistochemical assessments plays a pivotal role in the comprehensive evaluation of invasive breast cancer. Histopathology provides critical insights into tumor morphology, grading, and structural characteristics, while immunohistochemistry enables precise identification of key biomarkers that guide therapeutic decision-making. The combined application of these diagnostic modalities enhances accuracy, facilitates personalized treatment strategies, and improves patient outcomes. By aligning tumor classification with targeted therapeutic approaches, this integrated diagnostic framework ensures optimal disease management and supports advancements in breast cancer care.

AUTHOR CONTRIBUTIONS

Author	Contribution
Naseem Khan	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Tahira Batool	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Aqsa Dogar	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Faqeeha javed	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Riaz	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Iqra Ikram*	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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