CLINICOPATHOLOGICAL CHARACTERISTICS OF BREAST CANCER PATIENTS: A CROSS-SECTIONAL ANALYSIS FROM ZIA UDDIN HOSPITAL, KARACHI.

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ABSTRACT;
Background: Breast cancer is the leading malignancy among women in Pakistan, with late-stage diagnoses and limited systematic data worsening outcomes.
Objective: To analyze clinicopathological features of breast cancer at Zia Uddin University Hospital and highlight needs for early detection and targeted therapy.
Methods: A cross-sectional study of 80 female patients (ages 20–70 years) with invasive ductal carcinoma (IDC). Tumor size, stage, grade, and hormonal profiles (ER, PR, HER2/neu) were assessed.
Results: The majority of patients (61%) were aged 40–60 years, with 63.8% presenting at Stage III, and 71.3% having tumors ≥5 cm. Lymph node involvement was noted in 92.5% of cases, highlighting an aggressive disease profile. All cases were invasive ductal carcinoma (IDC), with poorly differentiated tumors (Grade III) accounting for 61.3%. Hormonal analysis revealed ER negativity in 47.5%, PR negativity in 62.5%, and HER2/neu positivity in 31.3%, indicating a significant subset eligible for targeted therapies.
Conclusion: Findings reveal disease profile requiring early detection, personalized treatments, and HER2/neu-targeted therapies. Systematic cancer registries and public awareness are essential for better outcomes.
Keywords: Age-Standardized Incidence Rate (ASIR), Breast Cancer (BC), Estrogen Receptor (ER), Fine Needle Aspiration Cytology (FNAC), Human Epidermal Growth Factor Rececptor-2 (HER2/neu), Invasive Ductal Carcinoma (IDC). Progestron Receptor (PR), Tumor Node Metastases Staging (TNM Stage).

INTRODUCTION;
Breast carcinoma is the most detected cancer among women worldwide (1). A report published,that more than 2.3 million breast cancer cases were diagnosed worldwide in women in 2020 (2). Breast

cancer is one of the most common cancer types in Pakistan, with a lifetime risk of being diagnosed with breast cancer in Pakistan at 01 in every 09 women (3). Age-standardized breast cancer incidence rate (ASIR) was one of the highest in Pakistan. Sadly, the most common type of cancer in females also contributes to a high mortality rate due to its usual late diagnosis and failure to be referred to the most suitable institutions (4).

Pakistan has among the highest burden of age-standardized incident breast cancer rates in Asia, and mortality is high due to late diagnosis and proper referral. Effective early detection and management can reduce mortality, but systematic approaches and detailed cancer registries in Pakistan are lacking, which aggravates the issue. For example, existing data is limited to out-of-hospital data, and no annualized cases and mortality data is available (4).

Breast cancer is of low incidence in underdeveloped countries but has a high incidence in developed countries (5). Breast cancer increasingly became common worldwide in the last few decades with a significant rise in many developing countries. The gap is largely down to reproductive health, lifestyle, exercise, weight, diet, and high alcohol consumption (6). Breast cancer death rates are globally stable, but new cases rose from 875,657 in 1990 to 2,121,564 in 2021. The age-standardized incidence rate (ASIR) increased from 16.42 to 26.88 per 100,000. In 2021, the highest ASIR was in high SDI regions (66.89 per 100,000) and the lowest in low SDI regions (6.99 per 100,000). Developed nations have registries to track cancer cases, assisting studies (6). According to the 2020 figures, breast cancer remains to be the most common and deadly type of cancer found in Pakistan, with a total of 25,928 women diagnosed with the disease in that particular year, noted to be 14% of all breast cancer cases (4).

In developing countries like Pakistan, diagnosis at a late stage and metastatic spread lead to poor prognosis, with increasing tumor burden and high mortality rates. The scarcity of diagnostic facilities typically leads to women presenting either with early-stage or metastatic breast cancer with poor prognosis. Thus, the cause should always be addressed early, as timely treatment can significantly increase survival and quality of life. Pakistan has a scientific approach to the problem, but the approach is systematic in nature (7). Data for cancer incidence, mortality, incidence rate, and yearly deaths is lacking. Such registries or databases do not exist, and recorded data is limited to hospital records (4).

The clinicopathological features of breast cancer based on different cancer types, tumor grade, lymph node involvement,histologica grade, the status of the ER and PR receptors, TNM staging, receptors, oncogenes, and lymphovascular invasion, overall survival provide useful prognostic information (8). Breast cancers are diverse and are classified by origin, grade, stage, and receptor status, which inform both prognosis and treatment response. Histopathological examination continues to be the gold standard for diagnosis and evaluation, with FNAC providing important information for the triple assessment of breast lumps on clinical examination (9). FNAC is helpful in predicting tumor factors like hormone receptor status (10).

This study summaries the demographic profile as well as the clinicopathological attributes of the 80 patients with Invasive Ductal Breast Carcinoma. This study was carried out to analyze the cytological and histopathological correlation in breast cancer diagnosis, focusing on tumor size, stage, lymph node metastasis, histological grade, and positivity for Estrogen receptor, Progesterone receptors, and HER2/neu.

MATERIAL AND METHODS;
Study Design:
A cross-sectional comparative study was conducted at the histopathology and molecular diagnostics laboratories of Zia Uddin University Hospital over 12 months. Ethical approval was obtained from the Ethics Review Committee.

Participants:
Eighty female patients aged 20–70 years with newly diagnosed primary breast cancer confirmed by biopsy were included. Exclusion criteria encompassed metastasis, prior anti-cancer treatment, incomplete records, and inadequate biopsy samples.

Data Collection:
Tumor tissues were processed using standard histopathological techniques, including formalin fixation, paraffin embedding, and hematoxylin-eosin staining. Tumor grading followed the Scarff-Bloom-Richardson method. Molecular markers (ER, PR, HER2/neu) were analyzed, and tumor staging adhered to TNM criteria (AJCC) (11).

Statistical Analysis:
Data were analyzed using SPSS (version 21). Frequencies and percentages were calculated for categorical variables to assess associations between tumor grade, size, and lymph node metastasis.

RESULTS;
In this study, we enrolled 80 female patients with breast cancer. Age distribution was 20–70 years, with a majority (61%) in the 40–60 years age group. A much lower percentage (30%) fell into the 20–40 years cohort, and just 09% were 60–70 years old.

TABLE 01. DEMOGRAPHIC DATA IN FEMALE BREAST CANCER PATIENTS. (N=80)

Age group	Number of cases	Percentage %
20-40	24	30
40-60	49	61
60-70	07	09

The clinicopathological features of the patients are listed in table 02. Tumor laterality was more common in the left breast (48%) than in the right breast (36%), with 16% having irregular involvement. In tumor staging, the majority of cases were diagnosed as Stage III (63.7%), followed by Stage II (28.8%) and Stage I (7.5%), with advanced-stage presentations dominating.

It was also noted that a significant number of cases, 71.2%, had tumors ≥ 5 cm, while 28.8% had tumors < 5 cm, denoting a trend toward larger tumor sizes at the time of presentation. Nodal involvement was observed in 92.5% of patients, reflecting a high rate of nodal positivity and an aggressive disease profile.

Histopathologically, 100% of the tumors were of Invasive Ductal Carcinoma (IDC) type, the most frequently observed subtype of breast cancer. Further grading showed that most were Grade III (61.2%), followed by Grade II (36.3%) and Grade I (2.5%), indicating an overall dominance of poorly differentiated tumors. The hormonal receptor status is also reported in table 02. For ER status, 47.5% of cases were ER-negative, 38.8% were ER-positive, and 13.7% showed low positivity. Similarly, PR negativity was observed in 62.5% of cases, with 30% being PR-positive and 7.5% weakly positive. HER2/neu was positive in 31.3% of cases and negative in 68.7%, suggesting an important subgroup of patients who can potentially benefit from targeted therapies against HER2.

Hormone receptor expression by tumor grade is shown in Table 03. ER and PR positivity in Grade I tumors was 50%, and HER2/neu negativity was 100%. Among Grade II tumors, 55.2% were ER-positive, and 37.9% were PR-positive. HER2/neu negativity was observed in 72.4% of cases compared to 27.6% positivity.

In Grade III tumors, which represented the majority (61.3%), ER positivity was 51%, PR positivity 36.7%, and HER2/neu positivity 34.7%. The more aggressive nature of higher-grade tumors is demonstrated by the increased negativity of hormone receptors and the higher positivity of HER2/neu status.

TABLE 02:CLINCOPATHOLOGICAL DATAIN THE BREAST CANCER PATIENTS (N=80).

Clinicopathological data in 80 breast cancer patients	Number of cases	Percentage
Laterality		
Left	38	48
Right	29	36
Irregular	13	16
Tumor Stage		
I	06	7.5
II	23	28.8
III	51	63.7
Tumor Size		
< 5 cm	23	28.8
≥ 5 cm	57	71.2
Lymph Node Involvement Status		
Positive	74	92.5
Negative	06	7.5
Histological Grade		
I	02	2.5
II	29	36.3
III	49	61.2
Estrogen Receptor (ER) Status		
Negative	38	47.5
Positive	31	38.8
Low Positive	11	13.7
Progesterone Receptor (PR) Status		
Negative	50	62.5
Positive	24	30
Low Positive	06	7.5
HER2/neu Status		
Negative	55	68.7
Positive	25	31.3

TABLE 03. TUMOR GRADE AND EXPRESSION OF VARIOUS HORMONE (N-80)

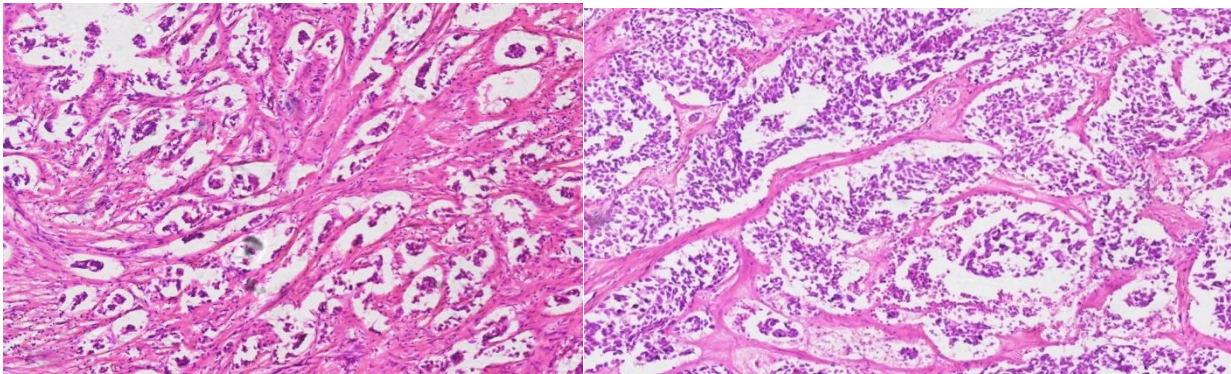| Tumor Grade	No of Cases	ER Negative (%)	ER Positive (%)	PR Negative (%)	PR Positive (%)	HER2/neu Negative (%)	HER2/neu Positive (%)
I	02 (2.5%)	01 (50.0%)	01 (50.0%)	01 (50.0%)	01 (50.0%)	02 (100.0%)	00 (0.0%)
II	29 (36.3%)	13 (44.8%)	16 (55.2%)	18 (62.1%)	11 (37.9%)	21 (72.4%)	08 (27.6%)
III	49 (61.2%)	24 (49.0%)	25 (51.0%)	31 (63.3%)	18 (36.7%)	32 (65.3%)	17 (34.7%)
Total	**80**	**38 (47.5%)**	**42 (52.5%)**	**50 (62.5%)**	**30 (37.5%)**	**55(68.7%)**	**25 (31.3%)**

Fig 01; H&E (40x) Grade-I Infiltrating Ductal (IDC). Fig 02; H&E (40x) Grade-II IDC
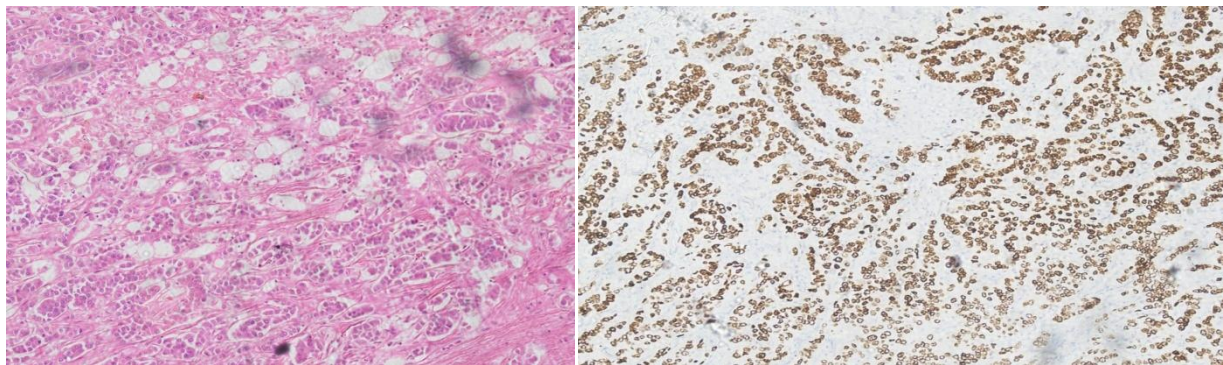
Fig 03; H&E (40x) Grade-III Infiltrating Ductal Ca. Fig 04; HER2/neu Positive expressions
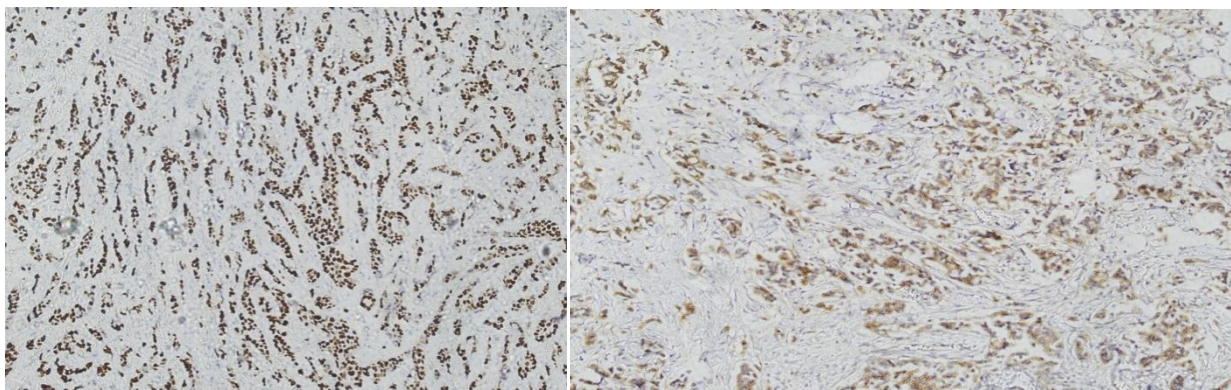

Fig 05; ER Positive expressions (IDC). Fig 06; PR Positive expressions (IDC)

FIGURE 07: DISTRIBUTION OF VARIOUS HORMONE RECEPTOR AND HER2/neu STATUS ACROSS TUMOR GRADEES IN BREAST CANCER

According to the study, most patients had advanced-stage breast cancer, with large tumors and lymph node involvement. Hormone receptor negativity, particularly for PR, was predominant, and a larger subset was HER2/neu-positive, suggesting the need for tailored approaches, including chemotherapy and techniques such as HER2/neu-positive inhibitors.

DISCUSSIONS;
Breast cancer is the most common form of cancer in females. It is reported the highest frequency in the National Cancer Registry of Pakistan (12). Pakistan has one of the highest spectrum of Breast cancer in Asian countries (13). Its prevalence in Pakistan is 2.5 times higher than its prevalence in

neighbouring countries like Iran and India (14). Breast cancer is the most prevalent cancer in third-world countries, and Pakistan bears a significant burden. According to the Karachi Cancer Registry report, Karachi has the highest incidence of breast cancer of any Asian population (15).

In Pakistan, breast cancer appears at a younger age than is commonly seen in the West, where it typically occurs in older age. Late presentation of the disease is a common practice, primarily due to socio-religious taboos, making this a major factor contributing to the high cancer burden in Pakistan (16). The very high rates of breast cancer in the region, which affect over 90,000 women a year, are attributed to the increasing population rate and socio-economic and political instability in all Asian countries (17, 18).

According to a report from the Shaukat Khanum Memorial Cancer Hospital and Research Center in Lahore, Pakistan is one of the largest public sector cancer hospitals 46% of all malignant female diagnoses treated there were breast cancers (19). This reflects an enormous burden of the disease on the country and highlights Pakistan's status as a third-world nation. While several reasons have been mentioned for the relatively higher breast and ovarian cancer rates in Pakistan, they are undocumented, as are lifestyle and reproductive factors as potential contributors. Mutations in genes associated with breast and ovarian cancer susceptibility, including BRCA-1 and BRCA-2, can explain a substantial fraction of cancer susceptibility (20, 21).

Moreover, cousin marriages, which are among the highest in the world, may also play a role in the duplication of these genes (22, 23, 24). In Pakistan, cousin marriages account for 60–76%. Family marriages also increase the risk of mutations in recessive genes that cause certain diseases (22).

However, this data provides no insight into whether these recessive genes have any role in adult cancers, especially breast cancer. Another study reported a connection between consanguinity and breast cancer in Pakistan, while other studies highlighted alarmingly high levels of breast cancer in the reproductive-age group in Pakistan (24). Common practices such as early marriages, multiple births, and extended breast feeding cannot be considered primary risk factors. Other possible risk factors include reproductive age, menopause, the role of reproductive hormones, and dietary factors such as obesity (21). Histological biopsy findings correlated closely with cytological diagnoses, and Invasive Ductal Carcinoma was the histopathological subtype in all cases in this study of 80 breast cancer lesions with follow-up over 12 months, 100% cytohistological concordance for ductal carcinomas.

This study comprised 80 female patients age 20–70 years. The majority (61%) was aged in the range of 40–60 years, 30% of patients were aged between 20–40 years, whereas only 09% of patients were between 60–70 years old. For tumor staging, the majority of cases were found to be at Stage III (63.7%), followed by Stage II (28.8%) and Stage I (7.5%), showing predominance of advanced stage of presentation. More than two-thirds of tumors (71.2%) were ≥5 cm, and 28.8% were <5 cm, indicating larger tumors at the time of diagnosis. High rates of nodal positivity and an aggressive disease profile were evident in 92.5% of cases. Further grading revealed that most were poorly differentiated: Grade III (61.2%), Grade II (36.3%), and Grade I (2.5%). These findings align with studies by *Hanif et al.,2015*, which also reported a significant association between lymph node metastasis and tumor histological grade (25).

Hormonal receptor status showed that 47.5% of cases were ER negative, 38.8% ER positive, and 13.7% low ER positive. Similarly, 62.5% of cases were PR negative, 30% PR positive, and 7.5% low PR positive. A total of 68.7% of patients had negative HER2/neu expression, and 31.3% were HER2/neu positive, indicating a significant patient subset eligible for HER2/neu targeted therapies. Correlations were made between hormonal expressions and tumor grades. In Grade I tumors, ER and PR positivity were each 50%, with HER2/neu negativity in all cases. Among Grade II tumors, 55.2% were ER positive, 37.9% PR-positive, and 72.4% HER2/neu negative. In Grade III tumors, comprising 61.3% of cases, ER positivity was 51%, PR positivity 36.7%, and HER2/neu positivity 34.7%.

These data highlight that higher-grade tumors frequently exhibit hormone receptor negativity and HER2 positivity, underscoring their more aggressive nature.Similar findings were reported by *Hanif*

et al., 2015, who observed that Grade I tumors, which were ER and PR positive, had good prognoses, while Grade III tumors, characterized by HER2 positivity and ER/PR negativity, were associated with poor prognoses (25). In brief, breast cancer patients have a crucial plan, management, and follow-up according to the parameters tumor size, lymph node status, histological grade, and hormonal expression of ER, PR, and HER2/neu. Most patients had advanced-stage disease, larger tumor sizes, and lymph node involvement, the study reports.

AJCC staging revealed that 50% of patients were in Stage III, followed by 37% in Stage II, 07% in Stage I, and 06% in Stage IV. These findings emphasize that late-stage presentations are common in this region, likely due to low awareness, ignorance, and inadequate primary healthcare facilities, contrary to studies from other countries, where early-stage diagnosis is more typical (11). The high prevalence of hormone receptor negativity, particularly for PR, as well as a significant group of HER2-positive tumors, highlights the need for personalized treatment strategies, including chemotherapy and HER2 inhibitors, especially in endocrine-resistant cases.

CONCLUSION;
o This study highlights the clinicopathological features of breast cancer patients from a tertiary care setting in Karachi, with a significant proportion presenting with advanced-stage tumors, larger size, lymph node metastasis, and poor differentiation.
o The combination of high HER2/neu positivity and low PR expression highlights the need for therapy approaches that focus on these particular pathways, such as HER2-directed treatments.
o These results draw attention to structural issues such as delayed diagnosis, restricted access to diagnostic resources, and deficiencies in the healthcare system.

RECOMMENDATION;
o Establish well-organized tumor registries to track the trends, advancement, and results of treatment for breast cancer.
o Begin educating the people about the importance of early detection, self-examination, and prompt medical consultation.
o Make targeted treatments more widely available and enhance access to advanced diagnostic tools and molecular profiling.
o Implement innovative breast cancer screening programs with an emphasis on high-risk groups.

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o **Authors' Contribution:**
o **SZ & QJ:** Conceived/ designed, analysis and editing of manuscript and agreement to be accountable**.**
o **SZ, BW& SU:** Help in data collection, drafting the manuscript and statistical analysis.

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