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Prevalence of Luminal A, Luminal B, HER2 enriched and triple negative breast carcinoma in population of Sindh: A tertiary care hospital experience

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***Abstract*---**The incidence of breast cancer has increased significantly in Asian countries in comparison to Western countries, and it is now one of the leading causes of cancer-related death among women worldwide. Each year, 1.5 million women (25% of all cancer women) are diagnosed with BC around the world, and this number is expected to rise to 2.2 million by 2025. In particular, breast cancer shows biologic heterogeneity in terms of risk factors, natural histories, responses to therapy, and prognostic features that vary considerably between ethnic and geographical groups. Many studies have focused

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on the distinctions between tumor subtypes because of the importance they play in guiding therapeutic decision making in breast cancer. These factors include histological grade, tumor type and size, and the presence of lymph node metastasis. As a proxy for profiling gene expression, immunohistochemical examination of breast cancer tissue with various biomarkers is employed. This method is cheap, widely accessible, reliable, and technically not demanding. The purpose of this research was to analyze the relationship between molecular subtypes of breast cancer and certain pathological characteristics. Non-probability samples of 622 cases of histologically confirmed invasive breast carcinoma were collected between 2018 and 2021 at the section of histopathology at the Liaquat University of Medical and Health Sciences in Hyderabad. Recurrent cases and cases that had already been treated were not included. FFPE tissues were deparaffinized and rehydrated before being sectioned serially into 4 m for immunohistochemical staining. After the blocking and washing steps, antigen retrieval was conducted. Primary antibodies were first used in a room temperature incubation, then secondary antibodies were added. DAB was used to see the staining, and then haematoxylin was used to counterstain. Allred scoring used for ER and PR. A HER2 score of 3 indicates strong staining of the whole circumferential cytoplasmic membrane in more than 10% of invading malignant cells. Scores of 0 and 1 indicate negativity, 2+ is ambiguous, and FISH was not performed for equivocal cases. Breast cancers were divided into four groups based on their ER, PR, and HER2 status: luminal A, luminal B, HER2 enriched, and triple negative. Quantitative factors were assessed by means and standard deviations, while qualitative variables were quantified by frequencies, using data processed with SPSS version 22. Chi-squared tests of association were used to determine statistical significance between variables. More over half of the 622 patients were under the age of 50, and the majority were married; in terms of breast location, 47.4% of the tumors were found in the left breast. Excisional biopsy, incisional biopsy, and wedge biopsy ranked third, fourth, and fifth, respectively, after trucut biopsy (37.1%) and modified radical mastectomy (30.5%).Most tumors show characteristics typical of invasive ductal carcinoma and, secondarily, invasive lobular carcinoma. Breast tumors are often N1a and then N2a in terms of size, with a range from 0.2 to 24 centimeters. Approximately 60% of tumors tested positive for ER, 50% for PR, and 70% for HER2. Thus, 13.2% were Luminal A, 47.9% were Luminal B, 27.3% were HER2, and 11.6% were Triple negative. Histological grade and molecular subgroups of breast cancer were shown to be very dissimilar. Age, mean tumor size at diagnosis, lymph node metastases at time of diagnosis, and vascular emboli status did not substantially vary amongst molecular subgroups. As a result of our research, we determined that Luminal B is the most prevalent subtype in our region, followed by Her 2 enriched. Different molecular subtypes were shown to correlate strongly with histological grade. Most cases were of invasive ductal carcinoma, and their stages were typically pT2 and N1a.

***Keywords*---**breast carcinoma, breast cancer, immunohistochemical.

Introduction

Cancer of the breast (BC) is a leading cause of death from cancer among women globally, and its prevalence and mortality rates are increasing [1]. According to the American Cancer Society, one in eight women will acquire breast cancer at some point in their lives. The cancer burden is projected to grow by 47% from 2020 levels, reaching a total of 28.4 million new cases by 2040 [3] and 2.2 million new cases annually by 2025 [2]. The World Health Organization estimates that 2,350,000 females will be identified as having BC and that 685,000 will lose their lives as a direct result of the disease worldwide in 2020 [1]. However, in comparison to Western nations, the incidence of breast cancer in Asian countries has increased dramatically. Among Asian women, breast cancer is the most often diagnosed form of the disease. The worldwide distribution of breast cancer cases has shifted, with an increase in the number of diagnoses among women in South America, Africa, and Asia [4].

Breast cancer is no longer seen as an isolated illness. St. Gallen International Expert Consensus calls it a "very complex disease." In 2013, intrinsic molecular subtypes based on ER, PR, HER2, and Ki-67 status divided breast cancer into four molecular subtypes: luminal A, luminal B, HER2 loaded, and triple-negative. All of which demonstrate racial and ethnic differences in risk factors, natural histories, reactions to therapy, and prognostic features due to their biological heterogeneity. [5] [6].

Histological grade, tumor form and size, and lymph node metastasis are only a few of the variables that might affect prognosis and treatment response [5] [7]. Numerous research have been performed on the distinctions between various tumor subtypes [8], and molecular subtypes play a pivotal role in guiding treatment decision making of breast cancer. [5] [4] [9].

The clinical use of gene expression profile has been hampered by high prices, complexity, and technological challenges. Because of its low cost, wide availability, high reliability, and low technical demand, immunohistochemistry examination of breast cancer tissue with various biomarkers is now employed as a stand-in for profiling the gene expression [10]. As new therapies become available, it is essential to validate and, if required, update the tumor stratification by thoroughly re-evaluating the function of traditional markers in huge population-based materials. Such revised findings would greatly aid molecular scientists in their pursuit of novel markers for subsets of patients with inadequate prognostic characterization [11]. The purpose of this research was to analyze the relationship between molecular subtypes of breast cancer and certain pathological characteristics.

Material and Methods

This study was conducted at the section of histopathology, Liaquat university of Medical and Health Sciences Hyderabad from 2018 to 2021, a total of 622 cases

histologically confirmed invasive breast carcinoma were retrieved using a non-probability sampling method while reccurent cases and those who received treatment were excluded.

This is what we gathered: Patient age at diagnosis, tumor size, histopathological subtype, grade, lymph node status, hormonal receptor ER and PR immunohistochemistry, and HER2 immunohistochemistry in invasive malignant cells were extracted from medical records. The Nottingham adaptation of the Bloom-Richardson scale was used to determine the histological grade of the tumor. According to the TNM classification, the tumor's size and nodal status were characterized.

Following deparaffinization in a series of xylene (three changes), graded alcohol (100%, 90%, then 70% ethanol), and rehydration in distilled water, 4 m serial sections of formalin-fixed, paraffin-embedded (FFPE) tissues were prepared for immunohistochemical staining. For 45 minutes, antigens were retrieved at 95 °C in 10 mM citrate buffer (pH 6.0). Then they were blocked with phosphate-buffered, 3% hydrogen peroxide solution and rinsed in Tris-buffered saline. Once that was complete, tissue pieces were blocked using an agent that blocked to prevent any background from showing through. Anti-ER, anti-PR, and anti-HER2 primary antibodies were used, followed by secondary antibodies and room temperature incubation. Diaminobenzadine staining was then counterstained with haematoxylin to see the staining.

Scores for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) were determined using CAPG guidelines. Nuclear staining intensity and percentage of stained cells were determined using the Allred scoring technique for ER and PR. A HER2 score of 3 indicates strong staining of the whole circumferential cytoplasmic membrane in more than 10% of invading malignant cells. With a score of 0 or 1, HER2 negative is indicated, whereas a score of 2+ is equivocal and does not need additional study (FISH was not conducted for equivocal patients). Breast cancer was divided into four molecular subtypes by determining the presence or absence of the receptors for estrogen (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor-2 (HER2). These subtypes were luminal A (ER and/or PR positive but HER2 expression negative), luminal B (ER and/or PR beneficial and HER2 expression positive), HER2 improved (ER as well as PR negative and HER2 favorable), and triple unfavorable (ER, PR, and HER2 negative).

Statistical Package for the Social Sciences version 22 was used for analysis; frequency counts were used to synthesize qualitative data, while means and standard deviations were used for quantitative data. Associations between age groups, histological grade, and BC subtypes were calculated using chi-squared tests, with significance set at p 0.05.

Results

The age ranged among 622 cases from 17 to 85 years with a mean age at diagnosis 46.16 years and the standard deviation of 11.9. More than half of

patients were under 50 years i.e in age category of 41–49 years. Most of them were with married marital status while in context to laterality the tumor involved the left breast in 295 patients (47.4%), the right breast in 264 patients (42.4%). Around 37.1% had trucut biopsy, 30.5 % had modified radical mastectomy followed by other procedures like excisional biopsy, incisional biopsy and wedge biopsy (Table 1).

Table No. 1 The distribution of demographic characteristics

Total Cases	622
Age (mean)	46.16 ± 11.9 Years
Age (Range)	17-85 Years
Age Groups	
15-40 years	240 (38.6%)
41-49 Years	321(51.6%)
50-59 years	61(9.8%)
Marital Status	
Married	607 (97.6%)
Unmarried	15 (2.4%)
Specimen Type	
Mastectomy	190 (30.5%)
lumpectomy	48 (7.7%)
Trucut Biopsy	231(37.1%)
Excisional Biopsy	88(14.1%)
Incisional Biopsy	32(5.1%)
Wedge Biopsy	33(5.3%)

Most tumors are Histological grade II, then advanced histological grade, and 92.6% of all cases were invasive ductal carcinoma. Invasive lobular carcinoma accounted for 1.9% of all cases, and metastatic carcinoma was rare. Breast tumors, on average, were 3 cm 2.47 cm in size, with a range of 0.2–24 cm. Patients with lymph node metastasis typically exhibit N1a and N2a nodal subtypes, LVI in only 19.6%, DCIS in 16.1%, calcification in 13.7%, perinodal extension in 9.5%, skin involvement in 5.3%, and dermal lymphatic invasion in 4% (Table 2).

Table No. 2 The distribution of histopathological characteristics

Histological Type	Invasive Ductal Carcinoma	576 (92.6%)
	Invasive Lobular Carcinoma	14(2.3%)
	Metastatic Carcinoma	12 (1.9%)
	Metaplastic Carcinoma	5 (0.8%)
	Mucinous Carcinoma	4(0.6%)
	Invasive Papillary Carcinoma	2(0.3%)
	Others	9 (1.5%)
Grade	1	7(1.1%)
	2	335(53.9%)
	3	265(42.6%)
Stage	pT1	45 (7.2%)
	pT2	174 (28.0%)
	pT3	99 (15.9%)
	pT4	30 (4.8%)
	pN0	39 (6.4%)
	pN1	60 (9.6%)
	pN2	43 (6.9%)
	pN3	08 (1.3%)
DCIS	Identified	100 (16.1%)
	Absent	511 (82.2%)
Lymphovascular Invasion	Identified	122 (16.1%)
	Absent	486 (82.2%)
Microcalcification	Identified	85 (13.7%)
	Absent	537 (86.3%)
Skin Involvement	Involved	33 (10.31%)
	Un-involved	284 (88.75%)
	Pagetoid	3 (0.94%)
Extranodal Extension	Identified	59 (33.88%)
	Absent	101 (63.12)

Immunohistochemical markers status revealed that, the estrogen receptor was positive (ER+) in 60.9% of tumors, progesterone receptor was positive (PR+) in 50.5% of tumors and 70.1% of tumors were HER2 positive (HER2+). Consequently, 13.2% of the cases were classified as luminal A, 47.9% as luminal B, 27.3% as HER2 enriched, while 11.6% as triple negative subtype of the breast cancer (Table 4).

Table No. 3 Frequency of Hormonal status and molecular subtypes

ER	
Positive	379 (60.9%)
Negative	243 (39.1%)
PR	
Positive	314 (50.5%)
Negative	308 (49.5%)
Her2-neu	
Positive	436 (70.1%)
Negative	186 (29.9%)
Molecular Subtypes	
Luminal A	82 (13.2%)
Luminal B	298 (47.9%)
Her2neu Enriched	170 (27.3%)
Triple Negative	72 (11.6%)

Triple-negative cases were diagnosed at a younger age (15-40 years) than cases of other subtypes (41-40 years), although the difference was not statistically significant. There was a statistically significant difference (p=0.004) between the molecular subtypes and the histological grade. In contrast to the advanced histological grade shown in the HER2 or Triple Negative subtypes, the Luminal subtype showed the largest proportion of intermediate grade. Tumor size, lymph node status, and the presence or absence of vascular emboli were not factors that differentiated the molecular subgroups. (Table 4).

Table No. 4 Association of molecular subtypes with clininopathological parameters

		Molecular Subtypes				P-Value
		Luminal A	Luminal B	Her2neu Enriched	Triple Negative	
Age Group	15-40	27	108	70	35	.146
	41-49	46	153	89	33	
	50-59	9	37	11	4	
Histological Type	Invasive Ductal Carcinoma	71	276	164	65	**0.012**
	Invasive Lobular Carcinoma	5	8	1	0	
	Metastatic Carcinoma	1	0	1	3	
	Metaplastic Carcinoma	1	8	2	3	
	Mucinous Carcinoma	1	2	1	0	
	Invasive Papillary Carcinoma	0	1	0	1	

	Others	3	3	1	0	
Grade	1	1	3	3	0	**.004**
	2	59	165	79	32	
	3	20	122	86	37	
pT stage	pT1	3	13	7	4	.392
	pT2	25	91	39	17	
	pT3	19	40	24	13	
	pT4	3	8	10	5	
pN stage	pN0	5	23	7	4	.107
	pN1	7	32	13	8	
	pN2	11	20	10	2	
	pN3	0	3	5	0	
Lymphovascular Invasion	Identified	18	52	43	9	.167
	Absent	63	238	125	60	
Skin Involvement	Involved	3	12	13	5	.190
	Un-involved	45	138	63	39	
	Pagetoid	0	1	2	0	
DermalLymphatic Invasion	Identified	2	11	11	1	.071
	Absent	47	141	68	43	

Discussion

More than half of our patients were under the age of 50, a finding that is in line with observations from China, Africa, and Indonesia [12, 8, 7, and 6], but at odds with those from the West, where 65.1% of reported cases were found in women aged 55 to 65. It's possible that the younger average age of the population in developing nations is related to ethnic and genetic factors, or it might simply be the consequence of the inverted age pyramids seen in wealthy nations. [8][6]. Although we found no statistically significant association between age and molecular subtypes in our patient population, we did find that Luminal A, Luminal B, and Her 2 subtypes were more prevalent in women aged 41–49 years old, while TNBC was highest in women aged less than 40 years old, which is consistent with previous research [13, 10]. However, contrary to our findings, other studies have found that Her 2 is more common in older women [12, 6].

According to the published literature [5][10][12], invasive ductal carcinoma was the most common histological subtype, accounting for 92.6% of all cases. This was followed by invasive lobular carcinoma (2.3%), metastatic carcinoma (1.9%), metaplastic carcinoma (0.8%), mucinous carcinoma (0.6%), papillary carcinoma (0.3%), and other histological subtypes (1.5% of cases). The molecular subtypes of malignancies closely mirrored the histological classifications of the diseases. Our results are consistent with those of previously published research [10].

The results of this investigation showed that, when compared to the high and low groups, moderate differentiation was the norm. In a related research, Mohammed et al. [10] found that low-grade tumors were much rarer than those of intermediate and high grades. Other studies found various outcomes; for example, Paramita et al., Sayed et al., Al Zaman et al., and Al Thoubaity et al. found more cases of mild differentiation (n = 274, 37.1%), than cases of moderate differentiation (n = 248, 33.5%). [6][14][5][7] . Similar to what Al Thoubaity et al. [7] reported about HER2 and TNBC being linked to poorly differentiated tumors,

we found that Grade II was strongly linked to Luminal A and Luminal B, whereas Grade III was linked to HER2. Histological Grade was also shown to be substantially correlated with molecular subtypes [8] by Maseb'a Mwang Sulu et al. Triple negative subtype has been linked to high grade by Al Zaman et al [5].

Furthermore, this study found that the median dimension of breast tumors was 3 centimeters, while other studies have found that the average size for breast tumors is 5 centimeters [6] and that the average size of breast cancers is greater than 2 meters [5][14]; however, in Western nations the majority of breast tumors measure under two centimeters, reflecting the late detection of the illness in our population, which could be due to inadequate awareness in our culture. In keeping with the findings of Ditsatham et al. [13], the T2 stage was the most often seen molecular type. Although our research and others have failed to identify a significant link between genetic subtypes and clinical stages [10], it is known that HER2-enriched or basal-like breast cancers often have bigger tumors than Luminal A patients [1].

Similar to Al Zaman et al. [5], we evaluated the lymph node status of 150 patients and found that the proportion of those with positive lymph node status was higher than that of those with negative lymph node status. Across all molecular subtypes, N1 was the most prevalent presentation, followed by N2a; however, luminal type A is linked to a more advanced nodal stage than the other subtypes, a result that is in agreement with Mohammed et al. [10]. This finding is consistent with previous research by Mohammed et al. and Zhang et al., but contradicts the findings of Al-Thoubaity et al., who found a strong association between the various molecular subtypes and lymph node status [10][1].[7].

Estrogen receptor positivity was found in 60.9% of tumors, progesterone receptor positivity was found in 50.5% of tumors, and HER2 positivity was found in 70.1% of tumors using immunohistochemistry. These results are consistent with those reported by Paramita et al. (50.1%), Maseb'a Mwang Sulu et al. (48.91%), and Sayed et al. (26.7%). In this study, Luminal B was found to be the most common subtype of breast cancer, with 47.1 percent of cases falling into this category compared to 13.2 percent for Luminal A, 27.3 percent for HER2-overexpressed, and 11.6 percent for triple negative. These results are consistent with those found by Mohammed et al. [10], who found that Luminal B was the most common molecular type. Similarly, Ditsatham et al. [13] observed that luminal B accounts for 36.4% of all diagnoses, with luminal A coming in at 28.8%, HER2 at 20%, and Triple Negative at 14.6%. Most cases of breast cancer are of the luminal B kind, which was found by Paramita et al. [6]. Whereas the luminal A subtype was shown to be predominate by Al-Thoubaity et al, Maseb'a Mwang Sulu et al, Al Zaman et al, and L. Vukovi et al [7][8][5][15], this was not the case with the other researchers.

Of the 622 individuals with DCIS, 100 (16.1%) had an in-situ luminal B component, with HER2 coming in second most often. One hundred twenty-two patients (19.6%) had lymphovascular invasion, with luminal B cases being more common than HER2 cases. Elidrissi Errahhali et al. and Sayed et al. [9], 14 found the same thing.

Mohammed et al. [10] found that whereas distant metastasis was more prevalent in luminal B, local metastasis occurred most often in the axillary lymph node, followed by the bone, liver, gut, and cervical lymph node. While Sayed et al. [14] found extranodal extension in 39.5% of cases, we found it in 99 (33.88%). Similar findings regarding microcalcification prevalence in luminal B and HER2enriched subtypes were also obtained by Zhang et al [1]. Briefly elaborating on several pathological aspects, our research provides a comprehensive understanding of BC in our community.

Conclusion

Luminal B and Her 2 enriched are the two most prevalent subtypes here. Different molecular subtypes were shown to correlate strongly with histological grade. Most cases were of invasive ductal carcinoma, and their stages were typically pT2 and N1a.

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