Ethnic Differences in the Expression of HER2/neu Phenotype Among Women with Breast Cancer

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Abstract

Background: HER2/neu plays a vital role in the management of breast cancer. Studies have shown differences in the expression of HER2/neu as per ethnicity.

Objectives: To assess the association of HER2/neu positive breast cancer with various ethnicities in Karachi, Sindh, Pakistan.

Methodology: A prospective observational study was conducted at the Department of Oncology, Jinnah Postgraduate Medical Centre between June 2019 to January 2022. All patients referred to the oncology department from the outpatient department and emergency department for the management of breast cancer were eligible to partake in the study. Diagnosis of breast cancer was made on histopathology. Patients' socio-demographics including age, gender, occupation, education, ethnicity (Urdu speaking, Sindhi, Punjabi, Balochi, Pushtoons, and others), and clinical parameters including the site of the tumor, stage, and grade at presentation, and first-line treatment were documented.

Results: A total of 550 patients were included. Overall HER2/neu positivity was seen at the rate of 34.7%(191/550), however as per ethnicity he2neu expression was the most in Pushtoons at the rate of 44.9%, with significant differences seen between the Pushtoons and the Balochis ($p= <0.05$).

Conclusion: We found the highest rate of HER2/neu positivity in Pushtoons and the least in Balochis, however further studies are warranted in larger study populations.

Keywords: Breast carcinoma, ethnicity, HER2/neu, triple-negative breast cancer.

INTRODUCTION

Breast cancer is a heterogeneous group of malignancies in terms of its morphological spectrum, clinical presentation, disease course, and response to treatment [1]. Reported cases of breast cancer rose to 2,002,354 worldwide in 2019 [2].

To better understand the diversities and make specialized treatment plans, breast cancer has been further classified based on molecular studies into subgroups luminal A and luminal B, Basal type, and HER2/neu positive group [3]. HER2/neu accounts for 15 to 20% of all breast cancer. HER2/neu overexpression is linked with a more aggressive course of the disease. Particularly, it is known that HER2/neu overexpressing tumors are resistant to a variety of chemo- and endocrine therapies and are linked with reduced overall survival rates [4-5]. Morphologically they have a higher proliferative index. Up to 75% have a higher histological and nuclear grade and up to 40% have Tp53 mutations [6].

A preliminary examination of breast cancers estimated the proportion of HER-2-positive tumors to be between 20 and 25% [7, 8]. Based on the features of the population under study and how HER-2 positive is defined, further research estimated the prevalence of HER-2 over expression to be between 11 and 30 percent [9, 10]. About 22% of the sample in research employing population-based data from the Carolina Breast Cancer Study were HER-2 positive [11]. In another study rates for HER-2 positivity in women under the age of 50 were 19% and 15%, in women ≥ 50 years respectively [12].

Ethnic variations in breast cancer molecular subtypes, incidences, and outcomes of treatment have been an understudy for decades [13]. Keeping this in mind, the authors of the present study sought to understand the relationship between ethnicity and the expression of HER2-positive breast cancer among the Pakistani population. Our study aimed to highlight the HER2/neu positive group of breast cancer concerning different ethnicities in Karachi, Pakistan.

METHODS AND MATERIALS

A prospective observational study was conducted at the Department of Oncology, Jinnah Postgraduate Medical Centre between June 2019 to January 2022. Ethical approval (F2-81/2017-GEN/430/JPMC) from the institutional review board (IRB) was secured before the data collection.

The sample size was determined using OPENEPI online software by keeping the expected proportion of Her2-positive breast cancer at 22% [13], a margin of error of 5%, and a confidence level of 99%. A sample size of 454 was determined. Using a non-randomized convenience

sampling technique, participants were recruited in the study.

All patients referred from the outpatient department (OPD) for the treatment and management of breast lesions were eligible to partake in the study. Diagnosis of breast cancer was made on histopathology. Individuals with incomplete molecular analysis for ER/PR/or HER2 were excluded from the study.

Patients' socio-demographics including age, gender, occupation, education, ethnicity (Urdu speaking, Sindhi, Punjabi, Balochi, Pushtoons, and others), parity, and clinical findings on examinations were documented in a predefined pro forma. Clinical parameters including the site of the tumor, stage and grade at presentation, and first-line treatment were also documented.

All breast tissue specimens were immunohistochemically analyzed to evaluate the hormone receptor status. The confirmation of HER2/neu was done *via* FISH analysis. FISH was only done in patients who had IHC2 positivity of HER2/neu and if FISH was positive as well, the case was labeled as HER2/neu positive. Estrogen, Progesterone, and HER2/neu status were categorized as either positive or negative. Since our study was based on the positive status of HER2/neu, the cases with negative HER2/neu were excluded.

Statistical software was used for the data analysis (SPSS version 26). The averages were calculated for each continuous variable, including age, weight, height, and body mass index. Frequency and percentages for each categorical variable were calculated. The Chi-Square test was used to evaluate the relationship between ethnicity and the HER2/neu-overexpression cases. The threshold for statistical significance was set at a p-value of below 0.05.

RESULTS

A total of 550 patients were enrolled in the study. The mean age of 46.52 ± 10.86 years. About 44.5% of the population were Urdu speaking (245) while approximately 17.1% were Punjabi (94), 13.8% were Sindhi, 8.9% were Pushtoon (49), and 7.8% were balochi (43) as shown
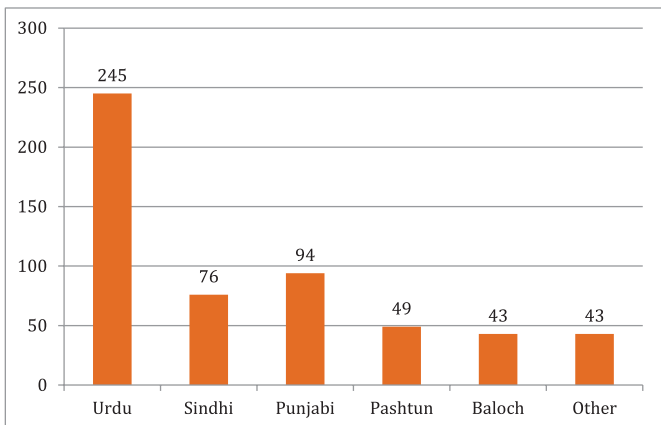

Fig. (1): distribution of patients according to ethnicities.

in **Fig. (1)**. Majority had the IDC tumor (504, 91.6%) (**Table 1**).

Table 1: Sociodemographic and Clinical Characteristics of patients (N=550).

Parameters	Mean / N (%)
Age (years)	46.75 ± 10.86
Grade	
1	5 (0.9%)
2	313 (56.9%)
3	232 (42.2%)
Tumor type	
Invasive Mucinous Carcinoma	5 (0.9%)
Invasive ductal carcinoma (IDC)	504 (91.6%)
Invasive lobular carcinoma (ILC)	11 (2%)
Metaplastic	5 (0.9%)
Infiltrating Mixed D & L carcinoma	1 (0.2%)
IDC with PD	5 (0.9%)
IDC bifocal	4 (0.7%)
IDC with focal micropapillary component	1 (0.2%)
IDC with Mucinous differentiation	7 (1.3%)
IDC with papillary pattern	2 (0.4%)
IDC with focal squamous differentiation	4 (0.7%)
Invasive micropapillary carcinoma	1 (0.2%)
Ethnicities	
Urdu	245 (44.5%)
Punjabi	94 (17.1%)
Sindhi	76 (13.8%)
Pashtun	49 (8.9%)
Baloch	43 (7.8%)
Other	43 (7.8%)
Estrogen Receptor +	302 (54.9%)
Progesterone Receptor +	263 (47.8%)
HER2/neu +	191 (34.7%)
Triple Negative	139 (25.3%)
Triple Positive	80 (14.5%)
ER+PR-HER2+	20 (3.6%)
ER-PR+HER2+	1 (0.2%)
ER-PR-HER2+	90 (16.4%)

Overall HER2/neu was positive in 191 out of 550 cases (34.7%) and was the most prevalent in Pushtuns at a
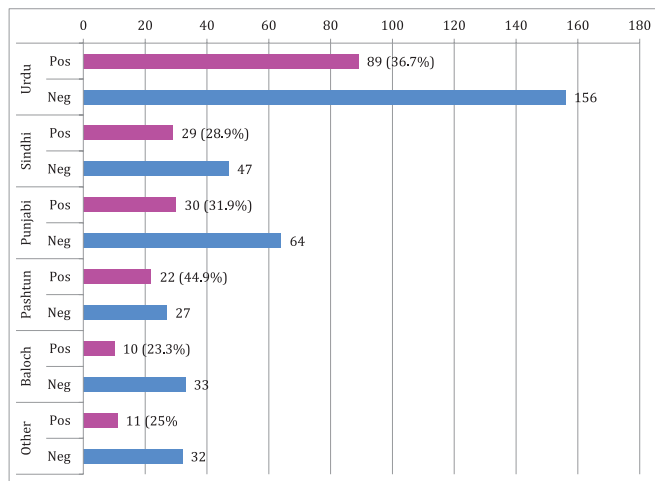

Fig. (2): Showing HER2/Neu positivity against different ethnicities.

rate of 44.9% as shown in **Fig. (2)** as compared to other ethnicities. Statistically, the Pushtoons were compared to the rest of the four ethnicities evaluating the expression of the HER2/neu phenotype. A significant difference was seen between the Pushtoon and the Balochis as shown in Table **2**.

Table 2: Comparison of Pushtoon ethnicity with others.

Ethnicities	HER2/Neu +ve %age	p-value
Pashtoon	44.9%	0.283
Urdu-Speaking	36.7%	
Pashtoon	44.9%	0.068
Sindhi	28.9%	
Pashtoon	44.9%	0.126
Punjabi	31.9%	
Pashtoon	44.9%	0.030
Balochi	23.3%	

DISCUSSION

Breast cancer is not only the most frequently diagnosed invasive cancer but it also happens to be the second leading cause of death among females worldwide [14]. There is evidence in the literature that most of the risk factors associated with breast cancer are non-modifiable. Recent studies also report that ethnicity/ race has an influence on the prevalence and clinical characteristics of breast cancer emphasizing the immense need for studies in all ethnic groups [15].

Breast cancer carries a relatively greater prevalence among younger age groups (middle age) in Pakistan than in the West [16]. Gene pool, environmental settings, racial disparities, reproductive aspects, the regulatory effects of female hormones, immunological status changes, and biological characteristics are all significant determinants of the development of breast cancers [17].

In the present research, we determined HER2/neu overexpression in a large number of women with histologically diagnosed breast malignancy and its association with ethnicity. Following our study, Kumar *et al.* revealed that in 46.37% of cases, HER2/neu overexpression was found [18].

Cronin revealed that in women ≤49, after adjusting for other factors, HER-2 status was correlated with tumour grade and race in women under the age of 50. Age, race, and tumour all affect HER-2 levels in older women [12].

An investigation by Shah *et al.* in the year 2022 explored the receptor status distribution by ethnicity and revealed that HER2/neu positive expression was proportionally higher in Pushtoon patients, with a prevalence of 75.7% as opposed to other ethnicities [19]. Our study also indicated the highest percentage of HER2/neu positivity among the Pushtoons, and the lowest in the Balochi population with a statistically significant difference between the Pushtoon and Balochis.

A study conducted by Telli *et al.* reports that there is a significant ethnic disparity in HER2-positive breast cancer among Asian women in a large, population-based cancer registry. Their analysis shows that in contrast to the 19% frequency of HER2+ breast cancer in Non-Hispanic Whites, Korean, Filipina, and Vietnamese women had increased frequencies of HER2+ disease, 36% (95% CI 32-40%), 31% (95% CI 29–32%), and 29% (95% CI 26–33%), respectively. Their analyses also showed that Korean women were 80% more likely than NH White women to be diagnosed with HER2+ as opposed to HR+/HER2-breast cancer. This was similar to our study where we also observed that Pushtoon women expressed the HER2/Neu gene more as compared to women of the rest of the ethnicities [20].

Another such study conducted by Mandeep *et al.* showed that Indian Indian, Hispanic and Chinese women in the younger group demonstrated significantly higher numbers of HER2/neu positive breast cancer than Non-Hispanic Women and African American women. This variation was highest among Indian women (p = 0.0006) followed by Hispanic (p = 0.0099) and Chinese women (p = 0.053) [21].

Molecular breast cancer features related to epidemiology and survival, such as hormone receptor status and histopathology, have indeed been found to differ across women of different races and ethnicities in a handful of international publications [20, 21]. However, there seems to be only one native research that we are aware of that correlates ethnicities in Pakistan with hormone receptor status, hence the limitations [22].

There are certain limitations in our study. The researchers did not evaluate survival and recurrence status among the study population. We urge that more researchers conduct such studies that can further shed some light on the relationship between ethnic groups and HER2/neu gene over-expression.

Another limitation is that it is a single-center study. Multiple multicenter, long-term, and large-scale studies must be carried out that also follow up on the treatment outcomes, to assess the true equation amid the ethnic disparity and its prognostic value.

CONCLUSION

The current study explored the ethnic differences in individuals with overexpression of HER2/neu in breast tissue. We found a high proportion of HER2/neu expression in our study *i.e.* 34.7% as compared to the western world. The highest rate of HER2/neu positivity was found in Pushtoon ethnicity and the least in Balochis showing a statistical significance between the two. However larger sample size studies need to be conducted to further explore such findings.

ETHICAL APPROVAL

A prospective observational study was conducted at the Department of Oncology, Jinnah Postgraduate Medical Centre between June 2019 to January 2022. Ethical approval (F2-81/2017-GEN/430/JPMC) from

the institutional review board (IRB) was secured before the data collection. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration.

CONSENT FOR PUBLICATION

Written informed consent was taken from the participants.

AVAILABILITY OF DATA

Data supporting the article's results are available upon request from the Corresponding author's email.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR'S CONTRIBUTION

Dr. Shumyla Beg contributed to conceptualization and data acquisition. Dr. Ejaz Khan contributed to the draft write-up and literature review.

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