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PREVALENCE OF BRCA1/2 PATHOGENIC VARIANTS AND THEIR ASSOCIATION WITH CLINICOPATHOLOGICAL FEATURES IN PATIENTS WITH TRIPLE NEGATIVE BREAST CANCER AT A TERTIARY CARE HOSPITAL IN KARACHI

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ABSTRACT

Background: Triple-negative breast cancer is a highly aggressive type of breast cancer in which the estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2) are not present. Clinically relevant identification of genetic and biochemical factors associated with disease aggressiveness is important due to the lack in targeted treatment options. Pathogenic mutations in BRCA1 and BRCA2 affect homologous recombination repair, may lead to genomic instability and contribute to oxidative stress, DNA damage and aggressive tumor behavior.

Objective: To determine the prevalence of BRCA1/2 pathogenic variants and evaluate their association with clinicopathological features and biochemical markers among patients with triple-negative breast cancer.

Methods: This cross-sectional analytical study was conducted from January 2024 to January 2025 at Tertiary Care Hospital in Karachi. Non-probability consecutive sampling was used to include 72 patients with triple-negative breast cancer whose cases were pathologically confirmed. Clinico-pathological parameters were noted such as age, menopausal status, family history, tumor size, tumor grade, tumor stage, lymph node status and ki-67 index. Samples of peripheral blood were taken for both the BRCA1/2 mutation and biochemical evaluation. Serum malondialdehyde, total antioxidant capacity, C-reactive protein, interleukin-6 and 8-hydroxy-2′-deoxyguanosine were determined. SPSS version 25 was used to analyze data. The analysis was performed using chi-square test, independent sample t-test and multivariate logistic regression. A p value <0.05 was declared to be statistically significant.

Results: Out of 72 patients, 20 patients (27.8%) were BRCA-positive, while 52 patients (72.2%) were BRCA-negative. BRCA1 pathogenic variants were more common than BRCA2 variants. BRCA positivity was significantly associated with positive family history, larger tumor size, grade III tumor, and advanced-stage disease. BRCA-positive patients showed significantly higher mean levels of malondialdehyde, C-reactive protein, interleukin-6, and 8-hydroxy-2′-deoxyguanosine, while total antioxidant capacity was lower compared with BRCA-negative patients. On logistic regression, positive family history, grade III tumor, advanced stage, raised malondialdehyde, and raised 8-hydroxy-2′-deoxyguanosine were independent predictors of BRCA1/2 mutation positivity.

Conclusion: BRCA1/2 pathogenic variants were identified in a considerable proportion of patients with triple-negative breast cancer. BRCA-positive status was associated with aggressive clinicopathological features and altered biochemical markers reflecting oxidative stress, inflammation, and DNA damage. Routine BRCA testing in triple-negative breast cancer patients may support genetic counseling, risk assessment, family screening, and personalized treatment planning.

KEYWORDS: BRCA1, BRCA2, triple-negative breast cancer, oxidative stress, DNA damage, inflammatory markers, Pakistan.

INTRODUCTION

Breast cancer has emerged as one of the most frequent cancer types in women globally and is a leading cause of cancer-related morbidity and mortality. One molecular subtype is triple-negative breast cancer, a clinically aggressive type of breast cancer which doesn't express estrogen receptor, progesterone receptor or human epidermal growth factor receptor 2. Due to the lack of response to endocrine therapy and HER2 targeted drugs, treatment options are limited

and primarily rely on chemotherapy, immunotherapy (in specific cases) and targeted therapy (when molecular eligibility exists) (1, 2).

Triple negative breast cancers are more frequently diagnosed at a younger age, are more likely to be of high grade and exhibit a higher proliferation index, to have early recurrence, and to have a worse prognosis than HR+ breast cancers. The biological features of TNBC are heterogeneous, but there is a strong association of TNBC with hereditary breast cancer, especially those linked with pathogenic variants in the BRCA1 gene. BRCA1 and 2 are tumor suppressor genes that are crucial to the homologous recombination repair pathway, which repairs double-strand breaks in DNA. If pathogenic variants occur in these genes, the DNA repair system breaks down and genomic instability leads to malignant transformation (3, 4).

This linkage of pathogenic variants of BRCA1/2 with TNBC has great implications for diagnosis, therapy, and prevention. A study of Pakistani population reported that the prevalence/preponderance of the BRCA1 germline mutations among patients with triple negative breast cancer (TNBC) was high, making it relevant for local population (5). International studies have also revealed that BRCA testing of TNBC patients aids in the identification of patients who may benefit from genetic counselling, family screening, surveillance and risk reducing interventions (6).

The clinical usefulness of BRCA testing has improved even more as patients with the positive test result might be eligible to receive a poly-ADP ribose polymerase inhibitor (PARPi). In the OlympiA trial, high-risk, HER2-negative early breast cancer patients with germline mutations of BRCA1/2 showed better results with adjuvant olaparib. The detection of pathogenic variants of BRCA1/2 is no longer restricted to a "hereditary risk" aspect, but also has direct relevance in personalized treatment planning (7-10).

Besides genetic changes, biochemical processes like oxidative stress, inflammation and DNA damage can also play a role in the progression of breast cancer. Malondialdehyde is another indicator of lipid peroxidation, and the total antioxidant capacity is an indicator of the overall antioxidant defense status. The levels of C-reactive protein (CRP) and interleukin-6 (IL-6) are markers of systemic inflammatory activity, whereas the level of 8-hydroxy-2′-deoxyguanosine (8-OHdG) is an index of oxidative damage to DNA. These biomarkers could be used to gain insights into the biology of the tumour, such as in the context of cancers associated with BRCA which are related to an impairment of DNA repair at the centre of tumour biology (11).

The information on pathogenic variants of BRCA1/2 in TNBC in the Pakistani population is still limited and very few studies have assessed their correlation with clinicopathological parameters and biochemical markers in the same population. This is a gap that is relevant, as genetic background, family structure, consanguinity patterns, access to genetic testing, and clinical presentation may be different from Western populations. BRCA testing strategies, counseling services and risk-based treatment decisions, therefore, require local evidence to guide these decisions in Pakistani TNBC patients (12).

The present study was conducted to determine the prevalence of BRCA1/2 pathogenic variants among patients with triple-negative breast cancer at a tertiary care hospital in Karachi and to assess their association with clinicopathological features and selected biochemical markers of oxidative stress, inflammation, and DNA damage.

METHODOLOGY

This was a cross-sectional analytical study conducted from January 2024 to January 2025. The study was carried out at Tertiary Care Hospital in Karachi. The study was designed to determine the prevalence of BRCA1 and BRCA2 pathogenic variants among patients diagnosed with triple-negative breast cancer and to assess their association with clinicopathological characteristics and selected biochemical markers.

Patients who presented with triple negative breast cancer (TNBC), breast carcinoma that was negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) in immunohistochemistry, were the subjects of the study. Patients who came in during the study period and met the inclusion criteria were all included. 72 patients were included in the study.

The number of patients in the sample was 72. Triple-negative breast cancer was identified during the study period in all patients who met the inclusion criteria, and the number of patients identified in this study was sufficient to complete the study, using a non-probability consecutive sampling technique. A sampling method was chosen as this test is only performed for triple-negative breast cancer (TNBC) when diagnosis has been confirmed, blood samples are available and full clinicopathological data is available.

The study included female patients who had been diagnosed with triple negative breast cancer on a biopsy of their primary breast tumor and were treated for the first time for breast cancer between the ages of 20 and 65. The patient population included only those who had immunohistochemistry confirmation of their ER, PR and HER2 status. Institutional review board consent for a blood sample, biochemical analysis, and genetic testing as well as written informed consent were obtained from patients.

Those who were not the patients of non-triple-negative breast cancer or those who had recurrent breast cancer, inadequate blood sample or incomplete histopathological records were excluded. Patients that had received chemotherapy, radiotherapy or targeted therapy prior to sampling of blood were also excluded to prevent treatment-

induced changes of biochemical markers. Chronic inflammatory disease, autoimmune disease, active infection, chronic liver disease, chronic kidney disease, and current antioxidant supplementation were excluded to avoid the influence of these factors on oxidative stress and levels of inflammatory markers.

After obtaining informed consent, demographic and clinical information was recorded on a predesigned proforma. The data collected consisted of age, menopausal status, family history of breast or ovarian cancer, laterality of tumor, tumor size, lymph node status, histological type, tumor grade, tumor stage, and Ki-67 index. Histopathology reports, immunohistochemistry records and patient medical files were used to extract the relevant clinicopathological data.

Immunohistochemistry was used to confirm triple negative breast cancer. Triple negative tumors were defined by the lack of expression by the laboratory for estrogen receptor and progesterone receptor and the lack of expression for HER2. Tumor grade was designated based on the histopathology report and tumor stage was recorded based on the clinical and pathological staging information available.

Venous blood samples were taken from all patients before the beginning of systemic therapy, under sterile conditions. A portion of the blood was drawn into an EDTA tube for extraction of genomic DNA and a portion was drawn into a plain tube for separation of the serum. The serum was separated by the centrifugation process and then stored at proper temperature for biochemical analysis. Confidentiality and prevention of sample mix-up were ensured using proper labelling and coding.

Peripheral blood leukocytes (PBL) genomic DNA was obtained by a standard DNA extraction method or commercially available DNA extraction kit, following the manufacturer's instructions. Before genetic analysis the quality and concentration of extracted DNA was evaluated. Targeted NGS was performed for the detection of pathogenic variants in the BRCA1 and BRCA2 genes. Variants identified were characterized as pathogenic, likely pathogenic, variant of uncertain significance, or negative based on established guidelines for genetic interpretation. Pathogenic or likely pathogenic variants of either the BRCA1 or BRCA2 genes were considered as BRCA+ and patients without pathogenic variants were considered BRCA-.

To assess oxidative stress, inflammatory status, and DNA damage, serum biochemical markers were assessed. Malondialdehyde (MDA) and total antioxidant capacity (TAC) were included in the oxidative stress profile. Inflammatory markers were C-reactive protein and interleukin-6. 8-hydroxy-2′-deoxyguanosine was used for the evaluation of oxidative DNA damage. These markers were quantified by enzyme-linked immunosorbent assay kit following the manufacturers' instructions. The samples were all analyzed in the same laboratory with the same conditions and the results were reported in their units.

BRCA1/2 mutation status (positive or negative) was the primary outcome variable. Independent variables were age, age group, menopausal status, family history, tumor size, tumour grade, tumour stage, lymph node status, Ki-67 index and laterality. Biochemical parameters were measured as malondialdehyde, total antioxidant capacity, C-reactive protein, interleukin-6 and 8-hydroxy-2′-deoxyguanosine.

The data were inputted and analysed with SPSS version 25. Categorical variables including BRCA status, family history, tumor grade, tumor stage, lymph node status and menopausal status were calculated for frequencies and percentages. Continuous variables (such as the levels of biochemical markers and age) were expressed as mean and standard deviation. The prevalence of pathogenic BRCA1/2 was determined by dividing the number of cases that tested positive for the BRCA by the number of triple-negative breast cancer patients.

Association between categorical clinicopathological variables and the presence of BRCA mutations was tested using chi-square test or Fisher's exact test. The means of the biochemical markers were compared with another independent sample t-test between the BRCA positive and BRCA negative groups. We used multivariate logistic regression to assess independent predictors of BRCA1/2 mutation positivity. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

A total of 72 histologically confirmed triple-negative breast cancer patients were included in the study. The average age of the patients was 42.8 ± 10.6 years ranging from 24 to 65 years. The age group with the highest number of patients was 31-40 years of age and 41-50 years of age. In 26.4% (19) of women, the disease had been documented in the family. The majority of patients (43, 59.7%) were premenopausal and 29 (40.3%) were postmenopausal.

Table 1: Baseline demographic and clinical characteristics of TNBC patients

Variable	Frequency	Percentage
Age group		
20–30 years	9	12.5%
31–40 years	27	37.5%
41–50 years	22	30.6%
51–65 years	14	19.4%

Menopausal status		
Premenopausal	43	59.7%
Postmenopausal	29	40.3%
Family history of breast/ovarian cancer		
Yes	19	26.4%
No	53	73.6%
Laterality		
Right breast	38	52.8%
Left breast	32	44.4%
Bilateral	2	2.8%

Out of 72 patients, 20 patients (27.8%) were found to have pathogenic BRCA1/2 variants. Pathogenic variants in BRCA1 were more prevalent than BRCA2 (14 patients, 19.4% and 5 patients, 6.9% respectively). Pathogenic variants in both BRCA1 and BRCA2 were found in one patient (1.4%). Of the 52 patients (72.2%), 52 were not found to be BRCA negative.

Table 2: Prevalence and distribution of BRCA1/2 pathogenic variants among TNBC patients

BRCA status	Frequency	Percentage
BRCA-negative	52	72.2%
BRCA1-positive	14	19.4%
BRCA2-positive	5	6.9%
Both BRCA1 and BRCA2 positive	1	1.4%
Total BRCA-positive	**20**	**27.8%**
Total	**72**	**100%**

BRCA1/2 mutation status was more likely to be positive among younger patients. In patients younger than 40 years old, 13 (36.1%) were found to be BRCA-positive while 7 (19.4%) were BRCA-positive in those 40 years old or older. But this correlation was not significant ($p = 0.112$). There was a significant correlation between positive family history and BRCA positivity, with 10/19 (52.6%) of the positive family history patients being positive for the BRCA compared to 10/53 (18.9%) of the negative family history patients ($p = 0.006$). The majority of the tumors were invasive ductal. There were 44 patients with grade III (61.1%) and 31 cases of stage III (43.1%) disease. In 46 patients (63.9%) lymph node involvement was detected. A high Ki-67 index was found in most patients with 49 patients (68.1%) having Ki-67 ≥30.

Table 3: Association of clinicopathological features with BRCA1/2 mutation status

Variable	BRCA-positive n = 20	BRCA-negative n = 52	p-value
Age group			
<40 years	13	23	0.112
≥40 years	7	29	
Family history			
Yes	10	9	**0.006**
No	10	43	
Tumor size			
≤2 cm	3	15	0.041
>2–5 cm	10	28	
>5 cm	7	9	
Tumor grade			
Grade II	4	24	0.031
Grade III	16	28	
Tumor stage			
Stage I–II	6	27	0.048
Stage III–IV	14	25	
Lymph node status			
Positive	16	30	0.076
Negative	4	22	

Ki-67 index			
<30%	3	20	0.061
≥30%	17	32	

The biochemical markers demonstrated significant differences between the two groups (BRCA-positive and BRCA-negative) of patients. Patients with BRCA had higher concentrations of the MDA, CRP, IL-6 and 8OHdG in the serum and lower concentrations of TAC in the serum. The results indicate increased oxidative stress, inflammation and DNA damage in patients with pathogenic variants of BRCA1/2.

Table 4: Comparison of biochemical markers between BRCA-positive and BRCA-negative TNBC patients

Biochemical marker	**BRCA-positive n = 20 Mean ± SD**	**BRCA-negative n = 52 Mean ± SD**	**p-value**
Malondialdehyde, MDA — nmol/mL	7.82 ± 1.46	5.91 ± 1.28	**<0.001**
Total antioxidant capacity, TAC — mmol/L	0.74 ± 0.18	1.02 ± 0.24	**<0.001**
C-reactive protein, CRP — mg/L	12.36 ± 4.15	8.41 ± 3.62	**<0.001**
Interleukin-6, IL-6 — pg/mL	18.92 ± 6.34	13.27 ± 5.18	**<0.001**
8-hydroxy-2′-deoxyguanosine, 8-OHdG — ng/mL	15.48 ± 4.72	10.96 ± 3.86	**<0.001**

Positive family history, grade III tumor, advanced stage, elevated level of MDA and elevated level of 8-OHdG were independently predictive of BRCA1/2 mutation positivity on multivariate logistic regression analysis. There was an approximately 4-fold increased risk of having a pathogenic BRCA1/2 variant in patients with a positive family history compared with those with no family history.

Table 5: Multivariate logistic regression analysis for predictors of BRCA1/2 mutation positivity

Predictor	**Adjusted OR**	**95% CI**	**p-value**
Age <40 years	1.86	0.61–5.65	0.273
Positive family history	4.21	1.36–13.02	**0.013**
Tumor size >5 cm	2.48	0.78–7.89	0.123
Grade III tumor	3.16	1.01–9.87	**0.048**
Stage III–IV disease	2.91	1.02–8.34	**0.046**
Raised MDA level	2.74	1.18–6.38	**0.019**
Raised 8-OHdG level	3.08	1.24–7.66	**0.015**

The overall prevalence of pathogenic BRCA1/2 variants in TNBC was 27.8% (BRCA1 was the main mutation type). BRCA-positive patients were more likely to have a biochemical evidence of oxidative stress and DNA damage, a biochemical evidence of detoxification, a high grade tumour, advanced stage disease, and a positive family history. These results suggest that there are clinicopathological aggressive features and biochemical changes related to BRCA1/2 mutation status in TNBC.

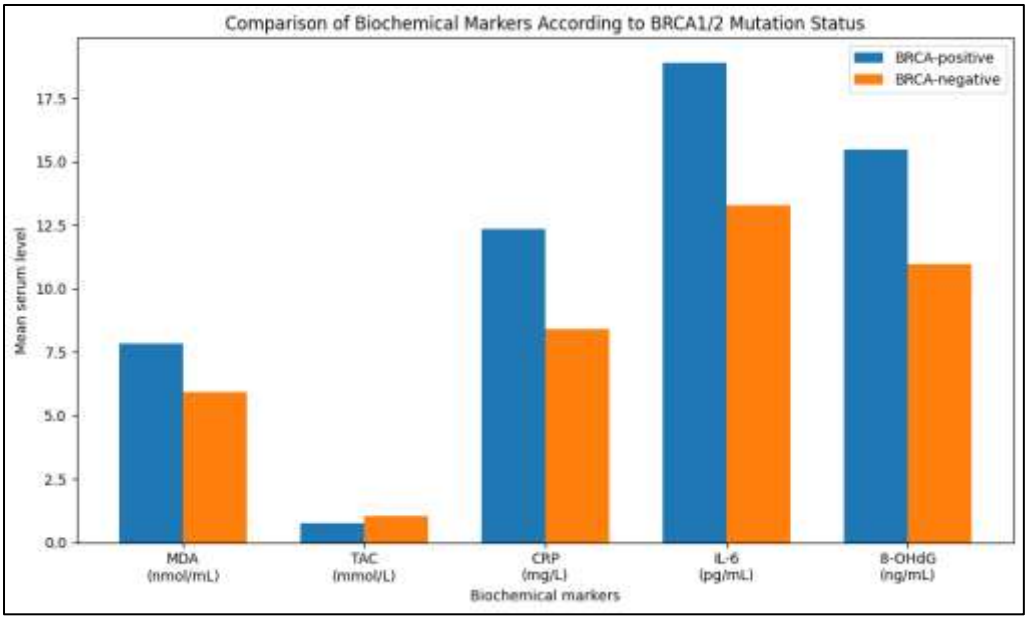

Figure 1: Comparison of biochemical markers according to BRCA1/2 mutation status among TNBC patients.

The graph shows higher mean MDA, CRP, IL-6, and 8-OHdG levels among BRCA-positive patients, while TAC was lower compared with BRCA-negative patients.

DISCUSSION

The present study found that 27.8% of patients with triple-negative breast cancer carried pathogenic BRCA1/2 variants, with BRCA1 variants more frequent than BRCA2. This finding is clinically important because TNBC has a stronger hereditary component than many other breast cancer subtypes, particularly in younger women and in patients with a family history of breast or ovarian cancer. In a Pakistani TNBC cohort, Rashid et al. reported a high frequency and predominance of BRCA1 germline mutations, supporting the relevance of BRCA testing in Pakistani patients with TNBC(5). Similarly, a prospective evaluation of universal BRCA testing in TNBC reported that women with TNBC may have an approximately 11–31% likelihood of carrying a BRCA pathogenic variant, which is close to the prevalence observed in the present study (6).

Patients with positive BRCA had not been as old as those without, but this difference was not statistically significant in this study. This could be because of the small sample size. The biological and clinical significance is that BRCA related breast cancers tend to present at a younger age and are commonly associated with aggressive breast cancer types. In a large study of young women with breast cancer, breast cancer in young women was found to be more likely to display high-risk features and to be related to BRCA1/2 mutations in the genes (13). A strong association between positive family history and BRCA positivity has been found in the present study, which further reinforces the importance of hereditary risk assessment. In the Turkish population, pathogenic variants of the BRCA1 and BRCA2 genes were also significantly associated with having a family history of breast or ovarian cancer (14).

The present study also revealed that the number of patients with the presence of more aggressive clinicopathological characteristics such as larger tumour size, grade III tumours, advanced stage, and high Ki-67 index was higher among BRACA positive patients. This is consistent with the biology of TNBC known to be associated with BRCA. BRCA1 abnormalities result in genomic instability, fast tumor growth and high tumor proliferation. In a large study based on the pathology, pathogenic variants of BRCA1 were found to be associated with triple-negative disease more strongly than other breast cancer types (15). Another study examining the expression of BRCA1 in breast cancer also revealed a correlation with ER, PR and HER2 negative status, and a high Ki-67 proliferation index, indicative of the very aggressive biological nature of these BRCA related tumors (16).

The biochemical results of this study revealed that serum MDA, CRP, IL-6 and 8-OHdG were significantly higher in BRCA-positive patients than in BRCA-negative patients, whereas TAC was significantly lower in BRCA-positive patients. This suggests an upregulation of lipid peroxidation, inflammation, oxidative DNA damage and decreased antioxidant defense in mutation-positive TNBC patients. In the study, Doneleva et al. found the changes in the oxidant-antioxidant status in breast cancer patients and pointed out that MDA is one of the important markers of oxidative damage. Likewise, in breast cancer patients, (17) Yahia et al. reported that serum IL-6 and oxidative stress related markers were detectable by ELISA and correlated to clinicopathological parameters and molecular-subtypes (18). The

results provide evidence for a possible role of oxidative stress and inflammatory activation in the progression of a tumor, especially in the case of biologically aggressive breast cancer phenotypes.

This is particularly relevant because the increased levels of 8-OHdG in the BRCA-positive cases of the present study is a measure of oxidative damage to DNA. Pathogenic variants in the genes that repair damaged DNA, like BRCA1/2, can lead to ongoing DNA damage, which can help cause genomic instability and tumour growth. The simultaneous rise in MDA and fall in TAC level also points to a balance of oxidants and antioxidants is not being achieved. High levels of IL-6 and CRP levels also indicate a general inflammatory response and might be associated with tumor burden and advanced stage, and with poor biological behavior. A study involving breast cancer patients found that levels of cytokines, such as IL-6, IL-8, and TNF-α, were related to the stage of the disease and whether or not it had spread to the lymph nodes, making these cytokines a useful marker of disease prognosis (19).

It is a clinically relevant finding to discover pathogenic variants of BRCA1/2 in TNBC. BRCA testing can help inform genetic counseling, family screening, risk reduction, and treatment. The OlympiA trial revealed that adjuvant olaparib was beneficial in patients with high-risk early breast cancer with a germline BRCA1/2 mutation who did not have HER2 positivity (20). Hence, detection of patients with BRCA mutation in Karachi might enable the selection of patients that may benefit from PARP inhibitor treatment if available. The present study however, was limited by a single center study and small sample size. More large multi-center trials from Pakistan are needed to validate these findings and to create screening strategies for TNBC patients that are applicable in the Pakistani context.

CONCLUSION

This study showed that pathogenic BRCA1/2 variants were present in 27.8% of patients with triple-negative breast cancer, with BRCA1 mutations being more frequent than BRCA2**.** BRCA positivity was significantly associated with positive family history, high tumor grade, advanced stage, and biochemical evidence of increased oxidative stress, inflammation, and DNA damage. BRCA-positive patients had higher MDA, CRP, IL-6, and 8-OHdG levels and lower TAC levels than BRCA-negative patients. These findings suggest that BRCA1/2 pathogenic variants are important contributors to the biological aggressiveness of TNBC and may be linked with altered biochemical profiles. Routine BRCA testing in TNBC patients can support genetic counseling, risk stratification, family screening, and personalized treatment planning, including consideration of PARP inhibitor therapy.

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