Original Article

# Age-related frequency of triple-negative breast cancer in women reporting at AFIP Rawalpindi, Pakistan

Liaquat Ali[1], Mehwish Mehmood[2], Syed Khurram Tariq[3], Samavia Shafique[4], Nabiha Naqvi[5], Manahil Rahat[6], Hassan Mumtaz[7]

[1]National Institute of Health, Islamabad
[2]Resident Plastic Surgeon: Fauji Foundation Hospital, Rawalpindi
[3]Resident Surgeon: Fauji Foundation Hospital, Rawalpindi
[4]Medical Officer, FGPC
[5]House Officer, PIMS
[6]Resident Oral Pathology, Armed Forces Institute of Pathology, Rawalpindi
[7]Public Health Scholar: Health Services Academy, Islamabad

Conflict of interest: None
Funding source: None

Article received: 21-12-22
Article accepted:29-04-23

*hassanmumtaz.dr@gmail.com*
*ORCID: https://orcid.org/0000-0003-2881-2556*

ABSTRACT

Objective: This study aimed to determine the prevalence of triple-negative breast cancer (TNBC) in Pakistani women based on age, focusing on patients at the Armed Forces Institute of Pathology (AFIP) in Rawalpindi, Pakistan.

Methodology: A cross-sectional study was conducted over a five-year period from January 2015 to August 2020 at the Department of Histopathology, AFIP. A retrospective review of TNBC cases during this period was performed. Data were collected and analyzed for 282 breast cancer patients who underwent surgical biopsy.

Results: Among 3138 breast cancer cases, 282 (8.98%) were TNBC. The mean age at diagnosis for TNBC was 42.27 ± 13.69 years, significantly younger than other breast cancer cases with a mean age of 52.90 ± 9.78 years. Of the TNBC cases, 58.9% were aged ≤ 50 years, while 41.1% were aged ≥ 50 years. The highest frequency (29.4%) was recorded among patients aged 41-50 years.

Discussion: This study sheds light on TNBC's prevalence in Pakistani women concerning age at presentation. The observed frequency closely approximates the lower margin of global ranges. TNBC predominantly affected women aged < 50 years. The mean age of TNBC diagnosis in this study is notably younger compared to international data. Previous research showed a higher TNBC proportion among younger patients, consistent with our findings.

Conclusion: A substantial proportion of TNBC cases occurred among premenopausal women and the younger age group. These findings contribute to understanding TNBC demographics and emphasize the need for further research into its causes and effective therapeutic interventions.

Keywords: Triple-negative breast cancer (TNBC), age-related frequency, breast cancer, Pakistan, Armed Forces Institute of Pathology (AFIP), prevalence, diagnosis.

## Introduction

Breast cancer constitutes the most prevalent malignancy among women, ranking as the second leading cause of cancer-related mortality in the female population, with lung cancer occupying the foremost position.[1] Advancement in breast cancer screening and treatment has dramatically improved the survival rates since 1989. Presently, Pakistan registers the highest breast cancer incidence in Asia, often accompanied by advanced disease stages and unfavorable prognoses, particularly among younger women.[2]

Triple Negative Breast Cancer is an aggressive type of breast cancer that lacks receptors for estrogen, progesterone and epidermal-growth-factor; thereby making hormone therapy ineffective. The recommended treatment options for TNBC are chemotherapy and surgical incision, with an excellent prognosis if PCR is achieved after neo-adjuvant chemotherapy

Recent studies indicate that TNBC recurrence risks remain minimal within the subsequent ten years following five years of post-treatment survival. Metastasis is also very common in TNBC with brain and lungs being the most common sites. TNBC is more prevalent in Hispanic and African American women, being more common among the young women. According to research, TNBC was reported to be 57% in patients with BRCA1 mutation while it was 23% in patients with BRCA2 mutation.[3]

A population-based analysis done in Canada in 2020 showed 3277 women (9.5%) had TNBC and the lowest median survival of 8.9 months was present in women with stage IV TNBC.[4]

Another study was conducted in Chicago on "Clinical Characteristics in Patients with Triplenegative Breast Cancer", during the study period, a total of 1964 patients with invasive breast cancer were enrolled in the Breast Cancer Database. The majority of breast cancer patients had tumors that were early stage, stage I or II, (91%) and of ductal histology (81%). Out of a total of 1964 patients, 190 (10%) patients had TNBC and 1774 (90%) had non-TNBC. The median age for both TNBC and non-TNBC was 59 years. There was a significantly higher proportion of African American and Asian patients with BRCA1 and BRCA2 mutations associated with TNBC. A prior history of breast cancer was also significantly associated with triple- negative histology in our study. However, there was no relationship observed between TNBC status and a history of chemoprevention. When compared to patients with non-TNBC, patients with TNBC were more likely to have undergone neo-adjuvant treatment. As compared to patients with non TNBC, patients with TNBC were also more likely to have the later-stage disease, invasive ductal carcinomas, and higher Ki-67.[5]

A study was also conducted in Tehran, Iran in which 214 pathology samples of patients with malignant breast cancer, TNBCs account for 14% of cases. The mean age in the N-TNBC group was 50 ± 12 years. A significant difference was seen between the age of the two groups (p=0.03). No significant difference was observed regarding the number of involved lymph nodes between the two groups (p=0.058). The presence of vascular and nerve invasion and involvement of surgical margins at the time of diagnosis were significantly more frequent in the TNBC group comparing with N- TNBC. Grade III of histologic and nuclear grading was significantly more common in TNBC.[6]

A study regarding breast cancer was published in the International Journal of Medical and Health Research India. It showed a total of 65 (23.3%) cases identified as triple-negative, out of 279 cases with known receptor status. Most of these were less than 50 years old (67.7%) with a mean age of 46 years and most patients were premenopausal (50.8%). Most of the patients in TNBC were grade 3 tumors (53.8%).[7]

Another study was conducted in the Department of Pathology, AIIMS, New Delhi, India on Triple-negative breast cancer which showed that TNBC constituted 21.8% of all patients. Patients with triple-negative subtype were significantly younger and more likely to be premenopausal. The higher proportion of TNBC presented in the locally advanced stage and had a higher proportion of node-positive patients compared to their non- TNBC counterparts. Although taxane-based neoadjuvant therapy was associated with significantly higher pathological complete responses, recurrences occurred earlier in TNBC. Even though inferior overall and DFSs were encountered in TNBC, statistical significance could not be derived.[8]

A study was also conducted in AFIP, CMH, Rawalpindi where the mean age of diagnosis of TNBC was found to be 46.26 ± 12.22 years while other breast cancers had a mean age 52.90 ± 9.78 years ($p < 0.001$).[9]

Considering the increasing rates of TNBC in women in Pakistan every year and the scant amount of data available regarding frequency of TNBC among the local population, this research aims to determine age-related frequency of TNBC among Pakistani population. This study aimed to report age-related frequency among women presenting at AFIP, Pakistan. The objectives of the research are to report overall frequency of TNBC reported at AFIP, Pakistan and to determine the relation of TNBC with age.

## Methodology

A cross-sectional study design was conducted, and the study duration spanned from January 2015 to August 2020. The study was conducted at the Department of Histopathology at AFIP, which is affiliated with the Armed Forces Post Graduate Medical Institute from Jan 2015 to August 2020. It was a five-year retrospective review of triple-negative breast cancer cases, from January 2015 to August 2020. The data available during the period were collected and analyzed.

282 Patients presenting with breast cancer at AFIP and underwent surgical (open) biopsy were included in the study. This study was done as a follow-up of study conducted in AFIP, CMH, Rawalpindi in 2014.[9] The samples were then received at Histopathology Department AFIP for pathological examination and diagnosis of carcinomas. Non-probability universal sampling technique was used to collect the data.

Inclusion & Exclusion Criteria: True cut biopsies of breast suspected of breast tumor were included in the study. All tumor biopsies other than breast were excluded from our study.

The immunohistochemistry (IHC) technique was used for the study. Immunohistochemistry (IHC) is a method for detecting antigens or haptens in cells of a tissue section by exploiting the principle of antibodies binding specifically to antigens in biological tissues. The antibody-antigen binding can be visualized in different manners. Enzymes, such as Horseradish Peroxidase (HRP) or Alkaline Phosphatase (AP), are commonly used to catalyze a color-producing reaction. Polyclonal- produced by injecting a specific antigen into a rabbit and taking its serum.

Primary: Specific monoclonal antibodies are produced by the Hybridoma Technique. Secondary: This is raised against the primary and binds with it. Results are interpreted in light of the appropriate staining of negative and positive controls. A positive reaction is indicated by brown staining at a specific site of the cellular antigen.

The data were analyzed by using Statistical Package for Social Sciences (SPSS) version 22 and Excel. Descriptive statistics were applied to qualitative variables as frequency and percentages.

Permission was sought for the conduction of the study from the institutional review board of Armed Forces of Pathology Rawalpindi and the following ethical considerations were applied.

Informed consent sought for accessing the data, Confidentiality and anonymity of the data was maintained. The results of the data were only used for academic purpose

Our study is fully compliant with the STROCSS 2021 guidelines.[10] A complete STROCSS 2021 checklist has been provided as a supplementary file. Our study has been registered on Research Registry with the following UIN: research registry 8197.[11] Our study is in accordance with the Declaration of Helsinki.

## Results

A total of 282 patients (aged 21-80 years) were included in the study to determine the prevalence of TNBC. The demographic data of the included patients are presented in Table I Showing the demographic presentation of 282 patients that show triple negative breast cancer.

Table II Shows the majority of the patients are non-menopause and the age group of 41-50 years is showing the majority of disease, about 29.4%. It also shows the frequency and percentage of TNBC in the different age groups of patients. Out of 3138 cases of breast cancer, 282 (8.98%) are triple-negative breast cancer.

Table I: Demographics of 282 patients presented with TNBC.

| Variable | n (%) |
|---|---|
| Total Breast Cancer Cases | 3138 (100) |
| Triple-negative Female cases | 282 (8.98%) |

Table II: Demographics of patients (aged 21-83 years) presented with TNBC.

| Age groups | n (%) |
|---|---|
| 21-30 | 24(8.5%) |
| 31-40 | 59 (20.9%) |
| 41-50 | 83 (29.4%) |
| 51-60 | 62 (21.9%) |
| 61-70 | 43 (15.2%) |
| 71-80 | 11(3.9%) |

This figure I shows the frequency and percentage distribution of the age group of triple negative breast cancer. 83 cases (29.4%) were the highest recorded in 41-50 years' age group. However, 11 cases (3.9%) were recorded as the lowest in patients having age 71-80 years' age group.

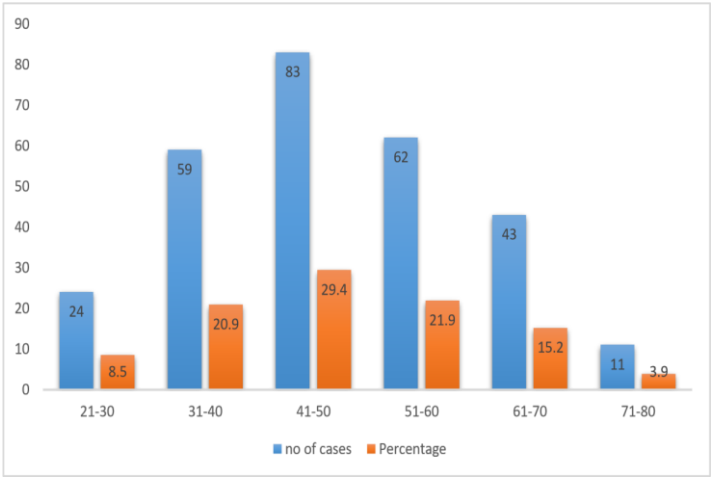



**Figure I. Frequency & percentage distribution of age group.**

Out of 282 (8.98%) are triple-negative breast cancer cases in which 166 (58.9%) cases were found in non-menopausal women aged ≤ 50 years and 116 (41.1%) cases were found in menopausal women age ≥ 50 years.

## Discussion

This study focused on the frequency of TNBC in Pakistani women with the context of age at presentation. A pathological record of 3138 samples was studied. TNBC was found in 282 (8.98%) patients. The frequency revealed was significantly closer to the lower margin of the range quoted worldwide. The majority of the patients had age < 50 years at presentation. The mean age of diagnosis of TNBC is 42.27 ± 13.69 years which is significantly younger than that quoted worldwide. In comparison, a meta-analysis that done in India showed high homogeneity in age –related studies with a mean age of incidence of TNBC of 47.52 ± 3 years.[12]

Another study was also conducted in AFIP, Pakistan between 2005-2010 which showed TNBC to be 17.28% of all breast cancers, our research showed TNBC was 8.98% of all breast cancers. Moreover, percentage of TNBC in patients with age< 50 in our research was 58.87 which was comparable to their study which showed TNBC to be 65.88% in patients with age < 50. Percentage of TNBC in patients age > 50 was 41.1% in our research comparable to their study done in 2005-2010 which showed TNBC to be 34.11% in patients with age > 50.[9]

More than 90% of TNBC fall within basal-like subtype (BBC) so-called for its gene expression type that mimics basal epithelial cells in other parts of the body and characteristics morphology that includes high proliferation rate, central necrosis, and pushing border. Basal-like breast cancers are overrepresented in African- American women and BRCA-I mutation carriers. After adjustment for age and stage at diagnosis, African-American women are almost 3-fold more likely than white women to have TNBC. According to a study published in 2021, younger women had higher proportion of BCRA-1 mutations. It showed that TNBC patients with less than 40 years of age, 82.1% had BRCA-1 mutations. *However, unlike our study the mean age of diagnosis of TNBC was 62 years whereas* our research showed highest frequency (20.9%) of TNBC in the age group of 41-50.[13]

There is a direct association between Ki67 and p53 in TNBC patients, according to a 2015 study from Kermanshah University of Medical Sciences, Kermanshah, Iran; however, further research is needed to draw a definitive conclusion.[14] TNBC accounted for 17.28% of all breast cancers diagnosed in Pakistani women at AFIP between 2005 and 2010.[9] TNBC was shown to occur more frequently in substantially younger people. Even after 5 years, there has been no change in these findings.

Although TNBC is defined by IHC analysis, TNBC is a heterogeneous disease with high recurrence and poor survival rate which poses an important clinical challenge. Few studies to date have focused on etiologic risk factors and currently, little data is available in Pakistan on its true incidence and etiology. It is hoped that these results would be extended further. There is no clear proven effective single agent that targets a driving vulnerability in TNBC. This also provides a wide array for researchers and novel therapeutic options are needed to counter this aggressive tumor affecting women in their peak life.

## Conclusion

In our study, we found that there was a considerably high frequency of TNBC among premenopausal women. TNBC was found to be more common in younger age as compared to the older age.

## References


1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018 Nov;68(6):394-424. https://doi.org/10.3322/caac.21492
2. Menhas R, Umer S. Breast Cancer among Pakistani Women. Iran J Public Health. 1;44(4):586-7.
3. Gonzalez-Angulo AM, Timms KM, Liu S, Chen H, Litton JK, Potter J, Lanchbury JS, Stemke-Hale K, Hennessy BT, Arun BK, Hortobagyi GN. Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clinical Cancer Research. 2011 Mar 1;17(5):1082-9. https://doi.org/10.1158/1078-0432.CCR-10-2560
4. Seung SJ, Traore AN, Pourmirza B, Fathers KE, Coombes M, Jerzak KJ. A population-based analysis of breast cancer incidence and survival by subtype in Ontario women. Current Oncology. 2020 May;27(2):191-8. https://doi.org/10.3747/co.27.5769

5. Yeh J, Chun J, Schwartz S, Wang A, Kern E, Guth AA, Axelrod D, Shapiro R, Schnabel F. Clinical characteristics in patients with triple negative breast cancer. International journal of breast cancer. 2017 ;2017. https://doi.org/10.1155/2017/1796145

6. Abdollahi A, Etemadi M. Pathological Characteristics of Triple-Negative Breast Cancer at Main Referral Teaching Hospital, April 2014 to April 2015, Tehran, Iran. Int J Hematol Oncol Stem Cell Res. 2016 Oct 1;10(4):200-205.

7. Raju G. S., Shantappa R., Jena S. "Triple negative breast cancer: A therapeutic challenge". International Journal of Medical and Health Research, Volume 3, Issue 2, 2017, Pages 12-15

8. Suhani S, Kazi M, Parshad R, Seenu V, Verma E, Mathur S, Gupta SD, Haresh KP. An audit of over 1000 breast cancer patients from a tertiary care center of Northern India. Breast Dis. 2020;39(2):91-99. https://doi.org/10.3233/BD-190435

9. Sajid MT, Ahmed M, Azhar M, Mustafa Q, Shukr I, Kamal Z. Age-related frequency of triple negative breast cancer in women. J Coll Physicians Surg Pak. 2014 Jun 1;24(6):400-3.

10. Mathew G and Agha R, for the STROCSS Group. STROCSS 2021: Strengthening the Reporting of cohort, cross-sectional and case-control studies in Surgery. International Journal of Surgery 2021; 96:106165

11. Research Registry. Available at: https://www.researchregistry.com/

12. Kulkarni A, Kelkar DA, Parikh N, Shashidhara LS, Koppiker CB, Kulkarni M. Meta-analysis of prevalence of triple-negative breast cancer and its clinical features at incidence in Indian patients with breast cancer. JCO global oncology. 2020 Jul;6:1052-62. https://doi.org/10.1200/GO.20.00054

13. Aine M, Boyaci C, Hartman J, Häkkinen J, Mitra S, Campos AB, Nimeus E, Ehinger A, Vallon-Christersson J, Borg Å, Staaf J. Molecular analyses of triple-negative breast cancer in the young and elderly. Breast Cancer Research. 2021 Dec;23:1-9. https://doi.org/10.1186/s13058-021-01392-0

14. Mehrdad Payandeh, Reza Malayeri, Masoud Sadeghi, Edris Sadeghi, Faezeh Gholami. Expression of p53 and Ki67 in the Patients with Triple Negative Breast Cancer and Invasive Ductal Carcinoma. American Journal of Cancer Prevention. 2015; 3(3):58-61.