ORIGINAL ARTICLE

Triple-Negative Breast Cancer (TNBC): Uncommon in Pakistan?

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ABSTRACT

Objectives: To evaluate the incidence of triple-negative breast cancer (TNBC) and elucidate the factors associated with triple-negative breast carcinoma.
Methodology: It is a retrospective study, that includes breast cancer patients presenting to the outpatient department (OPD) for three years from January 2020 to January 2023.
Results: A total of 946 biopsy-proven breast carcinoma cases were included, out of which, 220 (23.2%) were identified as triple-negative breast cancer. The predominant age range among TNBC patients was 40 to 60 years at the time of diagnosis. A total of 58.2% were postmenopausal, while 41.8% were pre-menopausal. Histopathologically, TNBC cases primarily exhibited ductal carcinoma (91.4%), metaplastic carcinoma (7.7%), and lobular carcinoma (0.9%). Tumor grading within the TNBC group revealed that the majority (71.4%) were poorly differentiated (Grade 3), while 26.8% were moderately differentiated (Grade 2), and 1.8% were well differentiated (Grade 1). Concerning family history, 12.7% of TNBC patients had a positive first-degree relative with breast cancer, 5.9% had a positive 2nd-degree family member, and 81.4% had no family history of breast cancer, indicating a significant association with TNBC. This study also revealed the ethnicity of TNBC patients that the majority (85%) identified as Urdu-speaking, Sindhi (6.4%), Pakhtoon (4.1%), Punjabi (3.6%), and Balochi (0.9%) backgrounds.
Conclusion: Our results showed, that TNBC primarily affected individuals aged 40 to 60 with high-grade tumors, showing associations with menopausal status and histopathology. Family history displayed no significant correlation while Urdu-speaking ethnicity was prominent. As TNBC is an aggressive neoplastic entity. By determining the incidence of TNBC, we can adapt interventions and allocate resources more effectively, thereby enhancing patient care and ultimately advancing survival rates.

Key Words: Age, grade, TNBC, postmenopausal

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INTRODUCTION

Triple-negative breast cancer (TNBC) is a subtype of breast cancer characterized by the absence of three receptors commonly found in other types of breast cancer: estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2). TNBC is known for its aggressive behavior, limited treatment options, and higher rates of recurrence compared to other breast cancer subtypes. Understanding the incidence of TNBC holds paramount importance in the realm of healthcare and oncology. According to GLOBACAN 2020, female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer with an incidence worldwide of 2,261,419. Interestingly, Asia is top of the list with a high incidence of 1,026,171 for breast cancer[1]. Breast cancer is a momentous health concern globally, and Pakistan is no exception. In Pakistan, the situation is getting alarming due to the increase in the number of cases. Every 9th woman is prone to get breast cancer in Pakistan[2,3]. In a described data from Karachi, the incidence of breast cancer in 1998- 2002 was 69.1%, however in 2010–2012; it was 79.2%[4].

The immunohistochemistry analysis of ER, PR receptor, and HER 2 neu receptor provides significant prognostic

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and predictive knowledge[5]. Numerous characteristic distinctions manifest among the four molecular subtypes concerning their incidence, responsiveness to therapeutic interventions, disease trajectory, survival rates, and even radiological attributes. Luminal A tumors exhibit the most promising prognosis within the spectrum of breast cancer subtypes, whereas luminal B, HER2-enriched, and basal-like tumors demonstrate inferior clinical outcomes. Among all molecular subtypes of breast cancer, TNBC is considered the more aggressive phenotype[6]. In Western data, Moss JL et al. reported the incidence of TNBC at 13.7 per 100,000 women (range = 4.5–26.3), notably elevated among African American women[7]. On the other hand, our local data indicates a local incidence ranging from 8.98% to 14% of triple-negative breast cancer cases[8]. However, our frequent encounter at OPD with TNBC seems to be higher than reported. Thus, we conducted this study to determine the incidence of TNBC and its associated variables presented to our hospital.

METHODOLOGY

This was a retrospective study carried out at our oncology department in a tertiary care hospital in Karachi, from January 2020 to January 2023 after the approval of the ethical review committee (ERC). It included the breast cancer patients who presented in our department with their histopathological reports. The data was collected for estrogen receptor (ER), progesterone receptor (PR), and HER-2 neu receptor. Reports with complete records of all three receptors were considered for study. The incidence of TNBC with its associating factors including age, menopausal status, and family history, and the association of grading of tumor at the time of diagnosis, was assessed. The sample size (n) was calculated with Open Epi version 3, according to the formula: n = z2 * p * (1 - p) / e2, (with Z=1.96 for 95% CI), resulting in a total sample size of 220. The inclusion criteria were biopsy-proven triple-negative breast cancer, age above 18 years, weak ER/PR status i.e. ER/PR status less than 3 was considered negative, patients with HER 2 neu 0-2 or FISH amplification of HER 2 neu not detected along with negative ER/PR receptors. The exclusion criteria were patients who were on any hormonal therapy and the patients whose ER/PR and HER 2 neu statuses were not clear.

RESULTS

Out of 946 biopsy-confirmed cancer patients with biopsy-confirmed breast carcinoma with complete ER, PR, and HER 2 neu receptors status, two hundred and twenty patients (23.2%) were identified with TNBC. The majority age array of TNBC patients was 40 to 60 years in our study. The mean age of diagnosis of TNBC was 49.64 ± 14.46 years. Out of 220 patients, about 128 patients were postmenopausal (58.2%) and 92 patients were pre-menopausal (41.8%) with a p-value of 0.0001 (Table 2). Regarding histopathology, 201 patients (91.4%) had ductal carcinoma; however, 17 patients (7.7%) had metaplastic carcinoma and only 2 patients (0.9%) were diagnosed with TNBC lobular carcinoma (Table 3). Concerning grading of TNBC, 157 patients (71.4%) were diagnosed with poorly differentiated (Grade 3) tumors, 59 patients (26.8%) had moderately differentiated (Grade 2) and 4 patients (1.8%) had well differentiated (Grade 1) tumors (p-value 0.005) (Table-4). Relating family history, 28 patients (12.7%) had positive 1st-degree relative breast cancer, 13 patients (5.9%) had positive 2nd-degree relative breast cancer, and 179 patients (81.4%) had no family history for breast cancer (p-value 0.001) (Table-5). As we included the ethnicity of only TNBC patients in this study, about 187 patients (85%) were Urdu speaking, 14 patients (6.4%) were Sindhi, 9 patients (4.1%) were Pakhtoon, 8 patients (3.6%) were Punjabi, and 2 patients (0.9%) were Balochi.

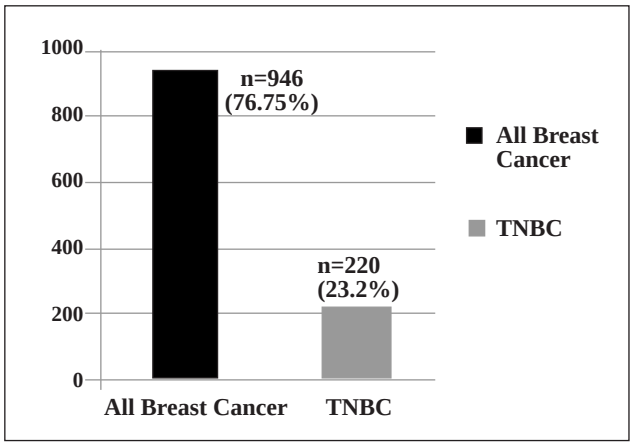

Fig. 1: Incidence of TNBC

Table 1. Frequency of TNBC According to Age

Age	Frequency	Percent	Cumulative Percent
18-30 Years	19	8.6	8.6
31-40 Years	42	19.1	27.7
41-50 Years	55	25.0	52.7
51-60 Years	56	25.5	78.2
61-70 Years	30	13.6	91.8
71-80 Years	14	6.4	98.2
Above 80 Years	4	1.8	100.0
Total	220	100.0	

Table 2. Frequency of TNBC According to Menopausal Status

Menopausal Status	Frequency	Percent	Cumulative Percent	p-value
Pre-menopausal	92	41.8	41.8	<0.0001
Post-Menopausal	128	58.2	100.0	
Total	220	100.0		

Table 3. Histopathological Types Among TNBC

Histopathology Type	Frequency	Percent	Cumulative Percent	p-value
Ductal Carcinoma	201	91.4	91.4	=0.04
Lobular Carcinoma	2	.9	92.3	
Metaplastic Carcinoma	17	7.7	100.0	
Total	220	100.0		

Table 4. Grade of Tumor According to Age

Tumor Grading	Age (Years)					Percent (%)	p-value
	18-30	31-40	41-50	51-60	61-70		
Well Differentiated	2	1	1	0	0	1.8	=0.005
Moderately Differentiated	9	11	16	12	8	26.8	
Poorly Differentiated	8	30	38	44	22	71.4	
Total	19	42	55	56	30	100	

Table 5. TNBC Relation with Family History

Family History	Frequency	Percent	Cumulative Percent
1st Degree Relative Positive for Breast Cancer	28	12.7	12.7
2nd Degree Relative Positive for Breast Cancer	13	5.9	18.6
Negative for Breast Cancer	179	81.4	100.0
Total	220	100.0	

DISCUSSION

Early detection and intervention are paramount in improving patient outcomes and reducing mortality rates associated with TNBC. Besides, recognizing the incidence of TNBC enables healthcare providers to allocate resources effectively, develop targeted screening programmes, and implement preventive measures to mitigate the burden of this aggressive subtype of breast cancer on our healthcare system and society. By gaining insights into the epidemiology of TNBC, we can adapt interventions and allocate resources more efficiently to optimize patient care and ultimately improve survival rates for individuals affected by this challenging disease.

The National Cancer Registry of Pakistan collected data to reveal the top ten cancers in Pakistan from 2015 to 2019, in which breast cancer ranked as the number one malignancy in females with a total of 38.8% of cases[9]. Research regarding the prevalence of TNBC in Asia remains relatively scarce as compared to the West. However, according to Wang et al, the incidence of TNBC in Asia is 10-17% of all breast cancer[10]. Moreover, gaining insights into the distribution of TNBC cases across various demographic groups and geographical regions, facilitates the identification of potential risk factors and disparities, subsequently informing the development of public health initiatives and targeted interventions. Ultimately, an accurate grasp of TNBC incidence empowers the medical community to address this challenge with precision, offering improved patient outcomes and a more comprehensive approach to breast cancer management. TNBC exhibits substantial heterogeneity, both at the histological and molecular levels, resulting in distinct behavioral variations among its subtypes[11].

In our comprehensive analyses, it was revealed that the incidence of TNBC was approximately 23.2% (Table-1); when we compare our study of a greater sample size with another local study of only 120 patients, it showed a 14% incidence of TNBC[12]. Another study in Pakistan regarding the prognostic factors of TNBC showed approximately 45 patients (16.07%) with TNBC out of 280 patients[13]. Given the unfavorable prognostic associations with TNBC as a breast carcinoma subtype, it is noteworthy that Pakistan exhibits a relatively low prevalence of TNBC patients as compared to non-TNBC. This epidemiological observation can be considered a favorable aspect, as it suggests a lower burden of this aggressive malignancy within the population.

In our studied population, comprising 220 individuals diagnosed with TNBC, the predominant demographic consisted of subjects within the age range of 40 to 60 years, exhibiting a central tendency represented by a mean age of 49.6 years. Hussain.S. et al.'s study which is comparable to our study, also showed the peak age of TNBC ranging from 46 to 60 years of age[12]. About the age of TNBC diagnosis, it is frequently observed in women who are under the age of 40, of Black racial background, and who possess BRCA1 gene mutations[14]. In an Indian meta-analysis, 20 of the 34 studies reported mean age at incidence for TNBC as 47.52 ± 3 years, which is meaningfully younger than that for non-TNBC[15]. TNBC diagnosed at a young age can exhibit an exceptionally aggressive nature. A meta-analysis of 36 studies verified that patients with an established diagnosis of TNBC at less than 40 years of age are at

greater risk of locoregional and distant recurrences linked to those identified as older than 40 years of age[16].

A majority—128 individuals (58.2%)—were identified as postmenopausal, whereas 92 patients (41.8%) were classified as premenopausal in our study group (Table 2). The statistical analysis yielded a highly significant p-value of 0.0001, indicating a substantial association or difference between menopausal status and the patient population under investigation. Regrettably, the study lacks a sufficient quantity of data to establish a meaningful association between menopausal status and TNBC. However, a study published from China revealed, that out of 249 TNBC patients, 196 patients (78.7%) were pre-menopausal and 53 patients (21.3%) were postmenopausal[17]. An Indian cohort analysis of hazard risk between pre and postmenopausal breast cancer revealed a significant relation of TNBC with postmenopausal patients with a p-value of 0.001, but TNBC tumors within the premenopausal group did not show any relationship with the hazard in multivariate analysis[18]. Conclusively, it is essential to consider the menopausal status as a crucial factor when contemplating the breast cancer phenotype.

Next, we analyzed the relationship of the histopathology of TNBC and the grading of the tumor in our population. A majority of patients i.e. 91.4%, exhibited intraductal carcinoma (IDC) pathology, while 7.7% presented with metaplastic carcinoma, and only 0.9% were diagnosed with lobular carcinoma (Table-3). It is a significant investigating point to explore the association between metaplastic and non-metaplastic pathologies in the context of TNBC because, in comparison to the triple-negative invasive ductal carcinoma (TN-IDC), the triple-negative metaplastic breast carcinoma (TN-MBC) group exhibits a notably inferior prognosis[19,20]. A congruent study from Punjab, Pakistan has unveiled results that align with our findings regarding the prevalence of IDC within the landscape of TNBC[21]. Nonetheless, it is accurate to acknowledge that IDC remains a prevalent histopathological subtype, even within the context of TNBC[22-24].

Regarding grading of tumors, it is noteworthy that TNBC is frequently diagnosed as a high-grade tumor, characterized by poor differentiation of cells. TNBC is recognized for its aggressive behavior, characterized by rapid cell proliferation, high mitotic activity, and a tendency for early metastasis. These aggressive features often contribute to a higher histological grade. Likewise, it has also come to our attention through clinical observation that the diagnosis of Grade 1 or Grade 2 TNBC is an infrequent phenomenon. In the context of this cohort analysis, it was determined that about 71.4% of patients presented with TNBC characterized by poor differentiation (Grade 3), while 26.8% of patients exhibited moderate differentiation (Grade 2) (Table 4). A minority of patients i.e. 1.8% were diagnosed with well-differentiated (Grade 1) tumors. In a comprehensive database encompassing 38,628 patients diagnosed with TNBC and published in 2016, it was ascertained that approximately 79.8% of these patients exhibited Grade 3 disease[25]. Furthermore, in the Pakistani study, it was observed that among the 246 cases analyzed, a significant portion of 56.5% was diagnosed with Grade 3 tumors[22]. Certainly, a discernible correlation exists between TNBC and high-grade tumors, given that TNBC is commonly recognized as an aggressive malignancy. Unfortunately, there is an inadequacy of studies that provide a comprehensive assessment of prognostic differences between low-grade and high-grade TNBC, however, it has been observed in several studies that TNBC, majority of the time was diagnosed as a high-grade tumor.

Within this study, we also attempted to recognize the impact of a family history of breast cancer on the occurrence of TNBC. In this analysis, our outcomes have not revealed a substantial correlation between a family history of breast cancer and the occurrence of TNBC. Only 12.7% of patients had 1st degree family history positive for breast cancer, 5.9% had a positive 2nd degree relative to breast cancer, and about 81.4% had no family history of breast cancer (Table 5). Multiple research studies have demonstrated an inverse relationship between TNBC and a positive family history of the disease[26-28]. Moreover, the prevalence of BRCA mutations in TNBC was also found to be lower among patients, in contrast to those who were non-BRCA carrier TNBC patients[29]. Remarkably, the presence of a germline BRCA mutation emerges as a favorable prognostic factor for individuals diagnosed with TNBC[30].

Umair-ul-Islam et al studied the incidence of TNBC among Pakistani ethnicity and 160 TNBC patients; Urdu-speaking and Punjabis were the most affected ethnic groups[31]. Our study showed that among 220 TNBC-diagnosed patients, about 85% of patients were Urdu speaking followed by Sindhi 6.4%, Pakhtoon 4.1%, Punjabi 3.6%, and Balochis 0.9% (Table 6). This phenomenon may be attributed to the predominant geographical locations. An additional study published in March 2022 indicated a higher incidence of breast cancer, inclusive of all subtypes, among Urdu-speaking patients when compared to other ethnic groups[32]. Despite the multitude of studies conducted in Pakistan concerning TNBC, the influence of ethnicity specifically

within the Pakistani population remains an enigmatic aspect that warrants further investigation with a larger sample size.

CONCLUSION

The conclusion drawn from our study is that TNBC predominantly affected individuals aged 40 to 60 years, often presenting as high-grade tumors. Menopausal status and histopathology showed significant associations with TNBC and displayed no significant correlation between family history and TNBC. Ethnicity distribution highlighted a predominant Urdu-speaking population. These findings provide valuable insights into the demographic and clinical characteristics of TNBC in the study cohort. The cornerstone of enhancing patient outcomes and decreasing mortality rates linked to TNBC lies in early detection and intervention. This necessitates the establishment of targeted screening initiatives and the implementation of preventive measures to alleviate the burden posed by TNBC.

Limitation of study: The study's limitations include single-center data collection and its retrospective nature.

Conflict of interest: Authors declare that there is no conflict of interest.

Authors' Contributions: HS wrote original manuscript and data analysis; ZM supervise, provided guidance, and final manuscript; TL and AA worked on data collection; JAM worked on validation.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Frequency and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249. PMID: 33538338.: doi.org/10.3322/caac.21660
2. Arif M, Javed M, Raza H. Breast Cancer in Pakistan: Alarming Situation of Breast Cancer in Near Future. Iran J Public Health. 2020;49(4):812-813.: doi.org/10.18502/ijph.v49i4.3193
3. Sadia S. bShaikh RS, Tariq N, Kausar T. Analysis of P4 receptors polymorphisms in the development of breast cancer: A study of Southern Punjab (Pakistan). Pure and Applied Biology. 2022 ;11(1): 81-190,.doi.org/10.19045/bspab.2022.110020.
4. Zubair M, Hashmi SN, Afzal S, Muhammad I, Din HU, Ahmed R. Immunohistochemical Expression of B Cell Lymphoma2 with Clinicopathological Correlation in Triple Negative Breast Cancers in Northern Pakistan. Asian Pac J Cancer Prev. 2016;17(7):3619-22.
5. Hou Y, Peng Y, Li Z. Update on prognostic and predictive biomarkers of breast cancer. Semin Diagn Pathol. 2022; 39(5):322-332. doi.org/10.1053/j.semdp.2022.06.015
6. Baranova A, Krasnoselskyi M, Starikov V, Kartashov S, Zhulkevych I, Vlasenko V, et al. Triple-negative breast cancer: current treatment strategies and factors of negative prognosis. J Med Life. 2022;15(2):153-161doi.org/10.25122/jml-2021-0108
7. Moss JL, Tatalovich Z, Zhu L, Morgan C, Cronin KA. Triple-negative breast cancer incidence in the United States: ecological correlations with area-level sociodemographics, healthcare, and health behaviors. Breast Cancer. 2021;28(1):82-91. https://pubmed.ncbi.nlm.nih.gov/32671723/
8. Ali L, Mehmood M, Tariq SK, Shafique S, Naqvi N, Rahat M, Mumtaz H. Age-related frequency of triple-negative breast cancer in women reporting at AFIP Rawalpindi, Pakistan. Mirpur J Med Sci. 2023;1(1):9-13. https://mjms.org.pk/index.php/mjms/article/view/4/4
9. Ikram A, Pervez S, Khadim MT, Sohaib M, Uddin H, Badar F, et al. National Cancer Registry of Pakistan: First Comprehensive Report of Cancer Statistics 2015-2019. J Coll Physicians Surg Pak. 2023;33(6):625-632. doi.org/10.29271/jcpsp.2023.06.857
10. Wang C, Kar S, Lai X, Cai W, Arfuso F, Sethi G, et al. Triple negative breast cancer in Asia: An insider's view. Cancer Treat Rev. 2018;62:29-38. doi.org/10.1016/j.ctrv.2017.10.014.
11. Derakhshan F, Reis-Filho JS. Pathogenesis of Triple-Negative Breast Cancer. Annu Rev Pathol. 2022 ;17:181-204. doi.org/10.1146/annurev-pathol-042420-093238
12. Hussain S, Durrani F, Khan A. Frequency and Clinicopathologic Characteristics of Triple-Negative Breast Cancer Among Breast Cancer Patients Presenting to Medical Oncology Department, Hayatabad Medical Complex Peshawar, Pakistan. Cureus. 2023 ;15(2): e34581. doi.org/10.7759/cureus.34581
13. Langah IA, Shah SM, Khushk M, Rehman A, Owais MA, Ahmed M. Prognostic Markers Related to Triple-Negative Breast Cancer. Pak J Med & Health Sci. 2023; 17(2):354. doi.org/10.53350/pjmhs2023172354
14. Borri F, Granaglia A. Pathology of triple negative breast cancer. Semin Cancer Biol. 2021 ;72:136-145. doi.org/10.1016/j.semcancer.2020.06.005
15. 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 Frequency in Indian Patients With Breast Cancer. JCO Glob Oncol. 2020;6:1052-1062. doi.org/10.1200/go.20.00054
16. Basmadjian RB, Chow K, Kim D, Kenney M, et al. The Association between Early-Onset Diagnosis and Clinical Outcomes in Triple-Negative Breast Cancer: A Systematic Review and Meta-Analysis. Cancers (Basel). 2023;15(7):1923. doi.org/10.3390/cancers15071923

17. Ye S, Xu Y, Li J, Zheng S, Sun P, Wang T. Prognostic role of GPER/Ezrin in triple-negative breast cancer is associated with menopausal status. Endocr Connect. 2019;8(6):661-671.doi.org/10.1530/ec-19-0164

18. Nimbalkar VP, Rajarajan S, Snijesh V P, Alexander A, Kaluve R, Selvam S. et al. A comparative analysis of clinicopathological features and survival between pre and postmenopausal breast cancer from an Indian cohort. Sci Rep. 2023;13(1):3938. doi.org/10.1038/s41598-023-30912-5

19. Li Y, Zhang N, Zhang H, Yang Q. Comparative prognostic analysis for triple-negative breast cancer with metaplastic and invasive ductal carcinoma. J Clin Pathol. 2019 Jun;72(6):418-424. doi.org/10.1136/jclinpath-2018-205544

20. González-Martínez S, Pérez-Mies B, Carretero-Barrio I, et al. Molecular Features of Metaplastic Breast Carcinoma: An Infrequent Subtype of Triple Negative Breast Carcinoma. Cancers (Basel). 2020 Jul 8;12(7): 1832. PMID: 32650408; PMCID: PMC7408634. http://dx.doi.org/10.3390/cancers12071832

21. Shehzad K, Alam S, Shams MU, Riaz S, Khan HA, Khan RU. Frequency and pathologic features of triple negative breast cancer at a tertiary care hospital in Pakistan. Ann Punjab Med Coll. 2021 ;15(2):136-8.

22. Tzikas AK, Nemes S, Linderholm BK. A comparison between young and old patients with triple-negative breast cancer: biology, survival and metastatic patterns. Breast Cancer Res Treat. 2020;182(3):643-654. doi.org/10.1007/s10549-020-05727-x

23. Mohammed AA, Elsayed FM, Algazar M, Rashed HE, Anter AH. Neoadjuvant Chemotherapy in Triple Negative Breast Cancer: Correlation between Androgen Receptor Expression and Pathological Response. Asian Pac J Cancer Prev. 2020 ;21(2):563-568. doi.org/10.31557/apjcp.2020.21.2.563

24. Ba R, Karanam VPK, Mundada AB. Immunohisto chemical Markers in Breast Cancer: A Cross-Sectional Study on Triple-Negative Breast Cancer in a Rural Tertiary Care Hospital. Cureus. 2021;13(11):e19486. doi.org/10.7759/cureus.19486

25. Plasilova ML, Hayse B, Killelea BK, Chagpar AB,Lannin DR. Features of triple-negative breast cancer: Analysis of 38,813 cases from the national cancer database. Medicine (Baltimore). 2016;95(35):e4614. doi.org/10.1097/md.0000000000004614

26. Zhou W, Pan H, Liang M, Xia K, Liang, Jinqiu Xue.et al. Family history and risk of ductal carcinoma in situ and triple negative breast cancer in a Han Chinese population: a case-control study. World J Surg Oncol. 2013; 11:248. doi.org/10.1186/1477-7819-11-248

27. Costa REARD, Oliveira FTR, Araújo ALN ,Vieira SC. Prognostic factors in triple-negative breast cancer: a retrospective cohort. Rev Assoc Med Bras (1992). Rev Assoc Med Bras (1992). 2021;67(7):950-957. doi: 10.1590/1806-9282.20210249.

28. Arranz-Ledo M, Lastra E, Abella L, Ferreira R, M Orozco, L Hernández.et al. Multigene germline testing usefulness instead of BRCA1/2 single screening in triple negative breast cancer cases. Pathol Res Pract. 2023:247:154514. doi: 10.1016/j.prp.2023.154514

29. Pogoda K, Niwiñska A, Sarnowska E, Nowakowska D, Jagie33o-Gruszfeld A, Janusz Siedlecki.et al. Effects of BRCA Germline Mutations on Triple-Negative Breast Cancer Prognosis. J Oncol. 2020;2020:8545643. doi.org/10.1155/2020/8545643

30. Phipps AI, Buist DS, Malone KE, Barlow WE, Porter PL, Kerlikowske K, et al. Family history of breast cancer in first-degree relatives and triple-negative breast cancer risk. Breast Cancer Res Treat. 2011 ;126(3):671-8. doi.org/10.1007/s10549-010-1148-9

31. Pakistan K. Triple negative breast cancer (TNBC), the surgeons and physicians dilemmain Pakistan. Int J.2015;3(1):851-5.

32. Ajaz S, Zaidi SE, Ali S, Siddiqa A, Memon MA. Germline Mutation Analysis in Sporadic Breast Cancer Cases With Clinical Correlations. Front Genet. 2022:13:820610. doi.org/10.3389/fgene.2022.820610