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Pathology Section

Clinicopathological Profile of Triple Negative Breast Cancer: A Cross-sectional Study

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ABSTRACT

Introduction: Triple Negative Breast Cancer (TNBC) is a subtype of breast cancer, characterised by the lack of expression of Oestrogen Receptor (ER) Progesterone Receptor (PR) and Human Epidermal growth factor Receptor (HER2). TNBC is an aggressive type of invasive breast cancer. The clinical, histopathology, and immunohistochemistry study are vital in diagnosing TNBCs. TNBC have rarely been studied in relation to rare prevalence, diagnostic difficulties, and special histological variants.

Aim: To study the clinicopathological profile of TNBC pateints.

Materials and Methods: The present cross-sectional study, which included all the patients undergoing lumpectomy or modified radical mastectomy received in the the Surgical Pathology Section of tertiary care hospital and department of molecular biology and genetic laboratory, at Krishna Institute of Medical Sciences, Karad, Maharashtra, India from May 2019 to April 2021. During the study period, total of 302 specimens of modified radical mastectomy or lumpectomy that met the inclusion/exclusion criteria were received in the Surgical Pathology department were included in this study. All specimens were analysed using immunohistochemistry for ER, PR, and HER2 Neu expression. Out of these, 100 (33.1%) cases were negative for all three markers, reported as TNBCs. These 100 TNBC cases were evaluated based on the clinicopathological parameters such as patient age, tumour laterality, location, tumour size, histopathological type, histologic Grade, lymphovascular invasion and lymph nodal status of TNBCs and to analyse different histomorphological type.

Results: In this total of 302 specimens of modified radical mastectomy, the Invasive Breast Carcinoma No Special Type (IBC NST) (82.70%, 250 out of 302 specimens) was the commonest histopathological diagnosis, followed by medullary carcinoma seven cases (7.0%), metaplastic carcinoma two cases (2.0%), invasive lobular carcinoma two cases (2.0%), one case of apocrine carcinoma (1.0%), one case of neuroendocrine carcinoma (1.0%) and one case of each (1.0%) as malignant phyllode's tumour, mucinous carcinoma, etc.

Conclusion: Prevalence of TNBC in India is considerably higher compared with that seen in Western populations. Present study included extensive analysis of breast cancer showing increasing in incidence of TNBC and is challenging to treat due to its adverse clinicopathological profile. The TNBC is associated with younger age, larger tumour size, higher histopathological Grades, extensive tumour necrosis, more regional lymph node metastasis, advanced stage at diagnosis and aggressive nature of tumour.

Keywords: High-risk breast cancer subtype, Immunohistochemistry, Invasive breast cancer

INTRODUCTION

Triple Negative Breast Cancers (TNBCs) are an intricate and composite group of cancers and have several molecular subtypes. TNBC is characterised by the lack of expression of ER, PR and HER2 [1]. The overall prognosis in terms of survival and disease-free interval are poor [2,3].

TNBCs display several distinct and aggressive clinicopathological features, such as early age of onset and large tumour size. TNBC prevalence in India varies in between 27 to 35% in literature and is estimated to be around 31 % [4]. TNBCs have multitude of distinctive hostile clinicopathological characters, including young age of onset and large size of tumour [5,6].The histological features include high proliferative activity and Grade, absent infiltrative margin, focal necrosis, lack of gland formation, central scar/fibrotic foci and presence of predominant lymphoplasmacytic infiltrates [5,7,8]. They have a distinctive and peculiar pathological and molecular behaviour. TNBCs lack hormonal receptors rendering hormonal therapy less effective. Thus, chemotherapy is currently considered as the most important systemic therapy [9]. An alarming increase in the number of TNBC cases requires specific attention and organisation's strategic planning goals for patients care. Histopathological and immunohistochemistry diagnosis aids in the selection of optimal treatment and prognosis. Hence, Oncopathologists play a crucial role in identifying TNBCs. This is an observational study on TNBC gives detailed clinicopathological profile of this specific type of breast cancer and provides insights into a high-risk breast cancer subtype that often exhibits an aggressive clinical course.

The aim is to conduct a clinicopathological study of TNBCs in a tertiary care centre. The Objectives areto study the clinical profile like age, tumourlaterarity, location, tumour size, histopathological type, histologic Grade, lymphovascular invasion and lymph nodal status of TNBCs and to analyse different histomorphological types.

MATERIALS AND METHODS

The present cross-sectional study included all the patients undergoing lumpectomy or modified radical mastectomy Received to the Surgical Pathology section of tertiary care hospital and Department Of Molecular Biology And Genetic Laboratory, at tertiary care hospital at Krishna Institute of Medical Sciences, Karad, Maharashtra, India, from May 2019 to April 2021. Data was collected over a period of 24 months. The Institutional Ethics Committee approval KIMSDU/ IEC/04/2029was obtained for the study.

Inclusion criteria: All subjects undergoing surgically excised lumpectomy or modified radical mastectomy were included in this study. The cases of TNBC Were taken for detailed study.

Exclusion criteria: Subjects with recurrent breast cancer and patient undergoing chemotherapy were excluded from the study.

Study Procedure

The data including patient's age, clinical presentation, staging, radio imaging and other were obtained from the records. Specimens received were grossed appropriately, fixed in 10% neutral buffered formalin and processed routinely. Sections of 3-4 µm thickness were cut, mounted on a slide using a very thin layer of glycerol egg albumin as an adhesive and stained with Haematoxylin and Eosin (H&E) The slides were studied under light microscopy and the diagnosis was made. Immunohistochemistry procedures were performed using 10% neutral buffered formalin-fixed, paraffin-embedded tissue sections. The sections were immunostained for ER, PR, HER2Neu expression, according to the protocols provided by the manufacturer. The investigators used, ER: ready to use monoclonal rabbit anti-human ER alpha clone EP1 antibody provided in liquid form in a buffer containing stabilising protein and 0.015 mol/L Sodium azide (DAKO autostainer). PR: ready to use monoclonal mouse anti-human PR clone PgR636 in liquid form in a buffer containing stabilising protein and 0.015 mol/L Sodium azide (DAKO autostainer) and HER2/neu: mouse monoclonal anti HER2/neu (c-erbB-2) antibody from tissue culture supernatant diluted in PBS, pH 7.6, containing 1% BSA carrier protein and 0.09% sodium azide (BioGenex) for the study.

In this study, breast cancer tumour cells were classified into groups based on Immunohistochemistry (IHC) profile ER/PR and HER2/neu expression, positive (+) and/or negative (–). In Allred system of scoring, score 0-5 was given to the cells. Score 0 was completely negative staining or membranous staining in less than 10% of the tumour cells. Scores of 0 and 1+ were considered as negative for Her-2/neu expression; while score 3+ as immune-positive while, 2+ were weakly or borderline positive. Positive and negative controls were included in each batch.

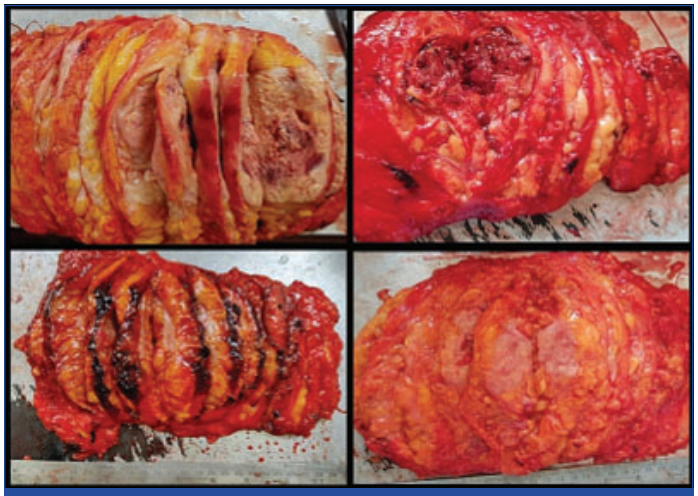
STATISTICAL ANALYSIS

Statistical analysis with qualitative data was presented. Data analysis was performed using Microsoft Excel spreadsheet software.

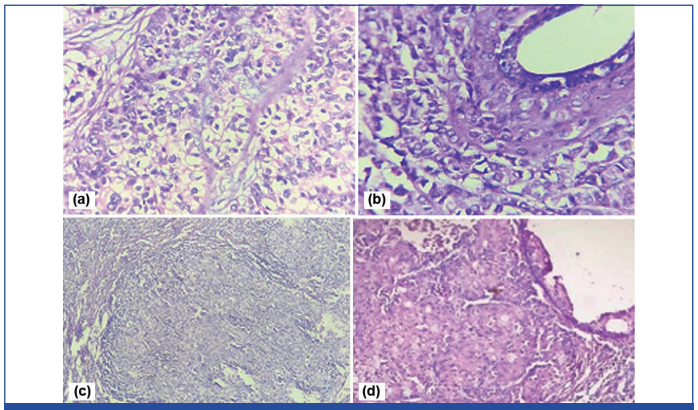
RESULTS

During the study period, a total of 302 specimens of modified radical mastectomy or lumpectomy that fulfilled the inclusion criteria were received in the Department of Surgical Pathology were studied [Table/Fig-1]. The histological types of these specimens were diagnosed as invasive breast carcinoma NST (250 out of 302 specimens (82.7%), followed by medullary carcinoma 7 cases (07.0%), metaplastic carcinoma 2 cases (02.0%), invasive lobular carcinoma 2 cases (02.0%), 1 case of apocrine carcinoma (01.0%) [Table/Fig-2], 1 case of neuroendocrine carcinoma (01.0%) and 1 case of each (01.0%) as malignant phyllode's tumour, mucinous carcinoma, etc., These 302 specimens were further subjected to immunohistochemistry based on ER, PR and HER2 Neu expression [Table/Fig-3], It was observed that 100 out of 302 (33.1%) cases were negative for all the three markers and classified as TNBCs [Table/Fig-3]. These 100 cases were studied in detail based on clinicopathological parameters. Of these 100 cases, 16 were below 40 years (16.0%), 60% were in between 41-60 years (60.0%) and 24 were above 60 years of age (24.0%) [Table/Fig-4]. The youngest patient was 29-year-old whereas the eldest patient was 90-year-old.

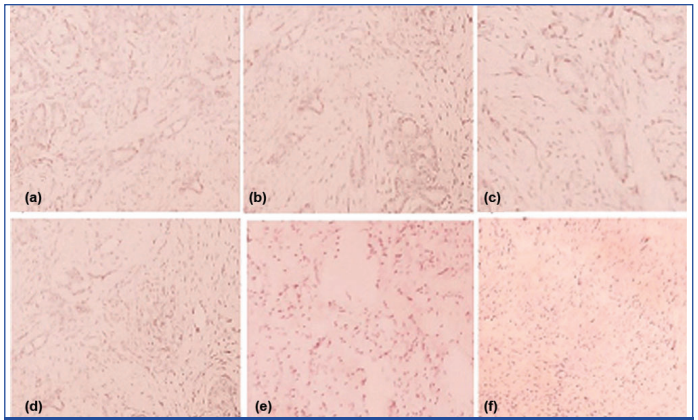
The present study noted that 42% of the patients were premenopausal and 58% were menopausal. The 12 cases (12.0%) of 100 had a positive family history. The investigators found out these patients (40%) had history of hormonal therapy. Tumour was located in the right breast in 60 cases of 100 (60.0%) and in left breast in 40 cases (40%). Of the 100 cases studied, 26 cases showed tumour size less than 2 cm (26.0%). A total of 46 cases had a tumour size between 2-5 cm (46%). A total of 33 cases had a tumour size larger than 5 cm (33.0%). The clinical history of median duration of lump was five months. FNAC was positive for carcinoma cells in 96 of the 100 cases (96%). Sonomammography results showed [Table/Fig-5]: 18 cases in BIRADS IV A (low suspicion of malignancy) category, 44 cases in BIRADS IV B (medium suspicion of malignancy) category, 22 cases in BIRADS IV C (high suspicion of malignancy) category, 14 cases in BIRADS V (suggestive of malignancy) category and two cases had unavailable details. Based on the histological type in the 100 cases studied, the most common type of breast cancer was IBC NST which was seen in 72 (72.0%). The other common types were medullary carcinoma (7.0%) [Table/Fig-3], metaplastic carcinoma (2%) and invasive lobular carcinoma (2.0%). One case of each of apocrine carcinoma, neuroendocrine carcinoma, mucinous carcinoma, and one case of malignant phyllode's tumour (1.0%) were seen [Table/Fig-6].



[Table/Fig-1]: Gross of Modified Radical Mastectomy specimens showing grey white solid tumours.



[Table/Fig-2]: H & E stain photomicrograph of: a) Invasive breast carcinoma NST (100x); b) Invasive lobular carcinoma (40x); c) Medullary carcinoma (100x); d) Apocrine carcinoma (100x).



[Table/Fig-3]: IHC photomicrographs (40x) of: a) ER negativity on IHC of invasive breast carcinoma NST; b) PR negativity on IHC of invasive breast carcinoma NST; c) HER2 negativity on IHC of invasive breast carcinoma NST; d) ER negativity on IHC of invasive lobular carcinoma; e) PR negativity on IHC of invasive lobular carcinoma; f) HER2 Negativity on IHC of invasive lobular carcinoma.

Age at presentation (years)	Present study (N=100) and %
≤40 years	16 (16.0%)
41-60 years	60 (60.0%)
>60 years	24 (24.0%)

[Table/Fig-4]: Age at presentation of Triple Negative Breast Cancer (TNBC) patients.

BIRADS	Cases N=100
IV A	18 (18%)
IV B	44 (44%)
IV C	22 (22%)
V	14 (11%)
NA	2 (2%)

[Table/Fig-5]: Sonomammography and classification as per Breast Imaging-Reporting and Data System (BIRADS).

Histological types of breast tumour	Present study N=100, n (%)
Invasive Breast Cancer of No Special Type- (IBC NST)	72 (72.0%)
IBC with medullary differentiation	7(7.0%)
IBC with neuroendocrine differentiation	1(1.0%)
BC with apocrine differentiation	1 (1.0%)
BC with squamous differentiation	1 (1.0%)
IBC with mucinous change	1 (1.0%)
BC with clear cell morphology	1 (1.0%)
Invasive lobular carcinoma	2(2.0%)
Medullary carcinoma	7 (7.0%)
Metaplastic carcinoma	2 (2.0%)
Apocrine carcinoma	1(1.0%)
Neuroendocrine Carcinoma	1(1.0%)
Malignant Phyllode's tumour	1 (1.0%)
Primary sarcoma	1(1.0%)
Malignant spindle cell tumour	1(1.0%)

[Table/Fig-6]: Histological types of Triple Negative Breast Cancer (TNBC) patients.

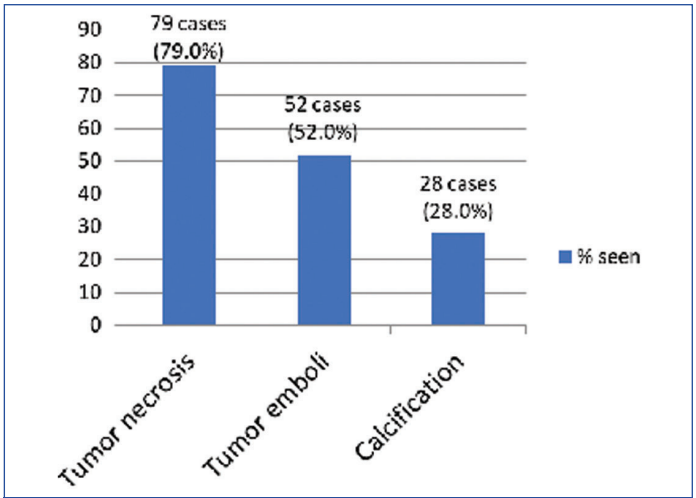
All tumours were classified as per modification of Scarff-Bloom-Richardson grading system, based on the histological Grade this study of 100 cases showed one case of Grade I (01.0%), 11 cases showed Grade II (11.0%), 85 cases showed Grade III (85.0%) as shown in [Table/Fig-7]. Of the 100 cases studied, 79 cases had infiltrating tumour borders (79.0%) and 21 cases showed pushing borders (21.0%). Tumour necrosis was seen in 79 cases (79.0%), Tumour emboli were seen in 52 cases (52.0%), calcification was seen in 28 cases (28.0%) [Table/Fig-8]. Positivity of lymph node metastases was noted in 62 cases (62.0%) [8]. The 66 (66.0%) cases showed DCIS component which was observed in association high tumour Grade.

Tumour Grades	Present Study n=100
I	01 (1.0%)
II	11 (11.0%)
III	85 (85.0%)
Not assessable	03 (03.0%)

[Table/Fig-7]: Histological Grades in Triple Negative Breast Cancer (TNBC) patients.

DISCUSSION

Breast cancer is the most common cancer in India. The prevalence of TNBC observed is 12-17% of all invasive breast cancers in Western populations [10]. Sandhu GS et al., study showed the prevalence of TNBC in India ranged from 27% to 35% across studies, with a summary estimate of 31% [11]. The current study showed that prevalence of TNBC is raising i.e., 33.1% cases were negative for all the three markers. TNBC Was a subtype of breast cancer based on immunohistochemistry study related to negative for ER, PR and



[Table/Fig-8]: Percentage of cases with tumour necrosis, tumour emboli and calcification.

HER2neu. In this study, of the 302 specimens included the most common histological type was IBC NST (250 out of 302 specimens, 82.7%).

TNBC cases shows symptoms which are the same as other more common breast cancers. Most common age of presentation was between 41-60 years (60%), followed by above 60 years of age (24.0%), and least by age group below 40 years (16.0%). Age range was 29-90 years. The mean age of presentation was 52.3 years which showed concordance with studies by Verma S et al., 2012, Doval DC et al., 2015, noted mean age at 52.1 years, 41.9% premenopausal and Singh R et al., 2014, noted median age at 50 years [12-14]. The present study noted that 42.0% of the patients were premenopausal and 58% were menopausal. This finding was concordant with studies by Nigam JS et al., 2014, Doval DC et al., 2015, Akhtar M et al., 2015 observed in premenopausal 41.9% cases and Ambroise M et al., in 2011, noted mean age at 53.8 years as shown in [Table/Fig-9] [13,15-17].

Menopausal Status	Present Study	Nigam JS et al., [15] 2014	Doval DC et al., [13] 2015	Akhtar M et al., [16] 2015	Ambroise M et al., [17] 2011
Premenopausal	42.0%	45.0%	41.9%	41.2%	39.3%
Menopausal	58.0%	55.0%	58.1%	58.8%	60.7%

[Table/Fig-9]: Menopausal status of TNBC patients in various studies [13,15-17].

The history of hormonal therapy was noted in 40 patients of 100 (40%). The 12 (12%) cases of 100 showed a contributory family history. The median duration of lump was five months. Tumour showed laterality to right breast in 60 cases of 100 (60.0%) more than in left breast (40.0%). Of the 100 cases studied, most cases had a tumour size between 2-5 cm (46 of 100 cases, 46.0%) which showed concordance with study by Gaopande VL et al., 2015 [18]. A total of 26 cases showed tumour size less than 2 cm (26%). This finding is concordant with study by Thike AA et al., 2010 [19]. A total of 33 cases had a tumour size larger than 5 cm (33%). This finding was concordant with studies by Sen S et al., 2012 and Nandi M et al., 2014 [20,21]. FNAC was positive for carcinoma cells in 96 of the 100 cases (96.0%). Sonomammography results in this study showed 44 cases in BIRADS IV B (medium suspicion of malignancy) category (44.0%). Based on the histological type in the 100 cases studied, the most common type of breast cancer was IBC NST which was seen in 72 (72.0%) cases. And others along with other literature studies as shown in [Table/Fig-10].

This finding is concordant with studies by Nigam JS et al., 2014 observed (IBC NST) as most common type in 81.4% cases [15] and Rao C et al., 2013, noted in 67.4 % of cases [22]. The other common types reported in this study were medullary carcinoma (07.0%). Budzik MP et al., observed that medullary carcinoma is

Histological subtypes	n (%)	Author and year of the study
Invasive Breast Cancer of No Special Type- (IBC NST)	72 (72.0%)	81.4% (Nigam JS et al., 2014) [15] 67.4% (Rao C et al., 2013) [22]
IBC with medullary differentiation	7 (7.0%)	Budzik MP et al., (2019) [23]
IBC with neuroendocrine differentiation	1 (1.0%)	7.0%, Wang J et al., (2014) [27]
BC with apocrine differentiation	1 (1.0%)	0.3% Thomas A et al., (2023) [25]
BC with squamous differentiation	1 (1.0%)	0.6% Thomas A et al., (2023) [25]
IBC with mucinous change	1 (1.0%)	1.32% Marrazzo E et al., (2020) [26]
BC with clear cell morphology	1 (1.0%)	3.6% Kuroda H et al., (2005) [30]
Invasive lobular carcinoma	2 (2.0%)	1.0% Thike AA et al., (2010) [19]
Medullary carcinoma	7 (7.0%)	2.0% Thike AA et al., (2010) [19]
Metaplastic carcinoma	2 (2.0%)	1.0% Okada N et al., (2010) [24]
Apocrine carcinoma	1 (1.0%)	0.2% Thomas A et al., (2023) [25]
Neuroendocrine carcinoma	1 (1.0%)	1.0% Wang J et al., (2014) [27]
Malignant Phyllode's tumour	1 (1.0%)	5% Tse GM et al., (2002) [32]
Primary sarcoma	1 (1.0%)	<1.0%, Magdoud K et al., (2024) [28]
Malignant spindle cell tumour	1 (1.0%)	<1.0%, Magdoud K et al., (2024) [28]

[Table/Fig-10]: Histological types of Triple Negative Breast Cancer (TNBC) patients in our study compared with others literature studies [15,22,23,25-28,30,32].

uncommon breast cancer subtypes, representing 1-7% of all cases [23]. Okada N, et al., observed that the expression of hormone receptors and HER2 have low in medullary carcinoma [24]. In The present study, metaplastic carcinoma were reported in 2% cases having triple negativity.

The present study showed invasive lobular carcinoma 2% cases of TNBC, which showed concordance with study by Thike AA et al., 2010 [19]; while in our study, IBC with squamous differentiation, BC with apocrine differentiation, and apocrine carcinoma were reported in 1.0% of cases, study from Thomas A et al., observed in 0.6%, 0.3%, 0.2% of cases. A total of 25 IBC with mucinous change was noted in 1.32% in study from Marrazzo E et al., [25,26]. The neuroendocrine breast carcinoma cases were 1.0 % in study by Wang J et al., [27]. In The current study, 1.0% cases were of Malignant Phyllode's Tumour. The study by Wang J, et al., (2002) noted 5% cases of Malignant Phyllode's Tumour [27]. The cases of primary sarcoma of breast were reported very rarely accounting <1.0% patients [28]; while clear cell carcinoma of the breast is rare, accounting for 1.4-3% of all breast tumours [28].

Of the 100 cases studied, based on the histological Grade, 1 case showed Grade I (01.0%) concordant with Thike AA et al., 2010 [19], 11 cases showed Grade II (11.0%), 85 cases showed Grade III (85.0%) concordant with Nabi MG et al., 2015 [29], Nandi M et al., 2014 [21], Sen S et al., 2014 observed mean tumour size 4.7±0.21 cm. and Grade III histology, in 16 patients (80%) [20]. Compared with other forms of breast cancer, TNBC is associated with advanced stage at diagnosis, high-Grade TNBC and poorer pathological responses to neoadjuvant chemotherapy [30,31].

Of the 100 cases studied, 79 cases had infiltrating tumour borders (79.0%) and 21 cases showed pushing borders (21.0%).This finding is concordant with the study conducted by Thike AA et al., in 2010, noted infiltrating tumour borders in 84% cases [19].

Tumour necrosis was seen in 79 cases (79%), Tumour emboli were seen in 52 cases (52%), calcification was seen in 28 cases (28%) as shown in [Table/Fig-9].

Positivity of lymph node metastases was noted in 62 cases of the 100 cases studied (62.0%). This finding is concordant with studies by Nigam JS et al., 2014 [15], Sen S et al., study in 2012 observed nodal metastasis in 70% cases [20] and Ambroise M et al., 2011 [17].

Ductal Carcinoma In Situ (DCIS) component was absent in 34 cases of the 100 cases studied (34.0%). This finding is concordant with study by Thike AA et al., 2010 [19]. A total of 66 (66%) cases showed DCIS component which was observed in association high tumour Grade. The stromal ER, PR, was low (05.0% or less) in all phyllodes tumours as observed by Khaoula Magdoud et al., [33].

For TNBC treatment can be challenging. TNBC has fewer treatment options than other types of invasive breast cancer. The surgical resection and chemotherapy is often used. The hormone therapy and anti-HER2 drugs is not effective. For advanced stage IV cases, platinum chemotherapy, targeted drugs like a PARP inhibitor or antibody-drug conjugate, or immunotherapy with chemotherapy are other mode of treatment. Postsurgery radiation therapy helps reduce the chance recurrences [32].

This cross-sectional study on TNBC gives detailed clinicopathological profile of this specific type of breast cancer and provides insights into a high-risk breast cancer subtype that often exhibits an aggressive clinical course. Identifying molecular characteristics offers potential for new therapies, and better predictive biomarkers and targeted drugs are needed to improve outcomes [34,35]. Follow-up of three years showed three cases having recurrence. Five cases showed systemic metastases, three cases to lung and two cases to liver. Within last five years, four cases showed mortality. TNBCs have a more aggressive clinical course than other forms of breast cancer. A study on epidemiology, pattern of recurrence and survival in TNBCs, showed most of patients were locally advanced stage (69.3%) while 30.7% were in the early stage and 29.2% recurrence at 38 months of median follow-up [34]. The Surveillance, Epidemiology, and End Results (SEER) program showed that the survival statistics. The 5-year relative survival rates for triple-negative breast cancer for all stages combined are reported to be 62.0% [36]. While stage IV or distant metastasis patients have poor survival rates at five years after diagnosis. For TNBCs patients, the development of novel strategies to improve outcomes in this subset of breast cancer patients and better outlook due to advances in knowledge and treatment plays significant role.

Limitation(s)

Some recent investigations in breast cancer detection like FISH technics and treatment options are not included in this study. The follow-up was of limited period. Interobserver variations, quality of different reagents, time of fixation, staining, are some of the errors which should be taken care off.

CONCLUSION(S)

Prevalence of TNBC in India is considerably higher compared with that seen in Western populations. In this study, higher prevalence of cases showing Triple-negative breast cancers was observed. The TNBC is associated with younger age, larger tumour size, higher histopathological Grades, extensive tumour necrosis. More regional lymph node metastases and advanced stage at diagnosis having aggressive nature. To improve therapeutic outcome of TNBC, reliable predictive biomarkers and newer drugs against the known molecular pathways are required.

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