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# COMPARISON OF CLINICOPATHOLOGICAL CHARACTERISTICS, DISEASE FREE SURVIVAL AND RECURRENCE IN TRIPLE NEGATIVE BREAST CANCER(TNBC) WITH NON-TNBC

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## ABSTRACT

**Introduction:** TNBC is associated with high mortality, morbidity and low survival rates. This study is aimed to study difference in pathological characteristics, disease free survival and recurrence between TNBC and Non-TNBC. **Materials and Methods:** Total 208 patients, who are diagnosed cases of breast carcinoma visiting our out patient department between August 2020 and July 2022 were enrolled. Demographic details, details during the presentation, pathological characterstics including the HPE, grade and receptor status, modality of treatment were taken. Enrolled patients were followed up. At the end of the study period, 2 year disease free survival, overall survival, recurrence of malignancy were noted. 102 patients who lost followup, status unknown or who has not completed a period of 2 years after diagnosis of Breast carcinoma were excluded. 106 patients were finalised, details were entered in excel sheet. Patients were divided into TNBC and Non-TNBC group and compared. **Results:** Prevalence of TNBC in our study was 22.6. Tumor size is more at presentation in TNBC compared to Non TNBC. All patients with TNBC had positive nodes during presentation (100%Vs78%). Presence of metastasis at the time of diagnosis is more in TNBC group(20.8%Vs 8.5%). Both groups has Intraductal Carcinoma as the predominant variant. Most of the TNBC had poorly differentiated grade tumors when compared to Non-TNBC. TNBC has more local(38.8% Vs 18.7%) and metastatic(22.22% Vs 4%) recurrences. 2 year Diseases free survival was more in Non-TNBC group(77.33% Vs 38.88%). **Conclusions:** TNBC has overall lesser disease survival period, more local and metastatic recurrences. Stage at diagnosis in TNBC is more advanced. Hence TNBC has got poor prognosis and high mortality. Early diagnosis and treatment is the key in reducing the mortality and better prognosis.

**KEYWORDS :** Breast Cancer, TNBC, Receptor status

## INTRODUCTION

Breast cancer is the second most common and second leading cause of cancer deaths, most common among females worldwide. Incidence of breast cancer is 11.6% overall and 24.2% in females among the total cancers. Breast cancer contributes 6.6% overall and 15% among females in total cancer deaths. (1) Breast cancers are heterogeneous disease. It consists ofvarious pathological subtypes with different histological appearances, different clinical presentations, prognosis and response to the treatment. (2)

Treatment of breast carcinoma is more successful nowadays because of early detection and use of aggressive multimodality treatment options. Various prognostic factors have been used in the treatment plan like age, axillary lymph node involvement, histopathologic grade, lymphatic and vascular involvement, metastasis, status of hormone receptors, and human epidermal growth factor receptor(HER-2/neu). (3)

Breast cancer can be classified into various groups depending on the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2/neu). Breast cancer which lacks the expression of the above receptors are called as Triple negative breast cancers (TNBC) (4)

TNBC is most heterogeneous and most aggressive subtype. TNBC is linked with younger age of presentation, high tumour grade, poor prognosis and high mortality. (5, 6, 7) TNBC is usually associated with high incidence of metastasis, frequent recurrences and associated with less overall survival. (8) TNBC patients have high chances of recurrence within 3 years and have risk of death within 5 years from diagnosis, despite optimal treatment. (9) Since TNBC lack the expression of receptors, targeted therapies and hormonal therapies are of less useful. Hence there is no effective specific therapeutic strategy for TNBC. Non-Targeted therapy is the main stay of chemotherapy in these individuals. Success rate of targeted therapies for receptor positive breast cancers (non-TNBC) are more when compared to TNBC. (10, 11, 12) There is lack of data regarding the TNBC in Indian population. This study is aimed to understand difference in pathological characteristics, disease free survival and recurrence between TNBC and non-TNBC variants.

## MATERIALS AND METHODS:

This is a observational study conducted at Department of General Surgery, KVG Medical College and Hospital, Sullia, Karnataka. Total 208 patients, who were diagnosed cases of breast carcinoma visiting the oupatient between august 2020 and July 2022 were enrolled in the study. Both old and freshly diagnosed cases were included in the study. Extensive details of all the patients were noted down along with the medical records which included demographic details, details of presentation during the diagnosis, pathological characteristics including histopathology, grade of tumour, lymph node metastasis, status of ER, PR, HER-2 neu overexpression and modality of treatment were noted. Significant events like treatment modality, recurrence(both local and metastatic) and death (both breast carcinoma related and unrelated) were noted in each patient in a period of 2 years from the date of diagnosis of breast carcinoma. Among 208 patients, 102 patients who lost follow up, not having all the significant data and who has not finished 2 years since the time of diagnosis were excluded from the study. Hence 106 patients made it to final enrolment in the study, Subjects were categorised into TNBC-Triple Negative Breast Cancers who were ER negative, PR negative, and HER-2 neu negative and non-TNBC who were positive for any of these markers.Data of all the patients were compiled and tabulated in an excel sheet. Analysis was done to find out prevalence of TNBC in our study. Various clinic-pathological features like tumour size, lymph node status, distant metastasis, staging of tumour, histopathological type of the tumour and grade of tumour at the time of diagnosis between TNBC and non-TNBC were compared. Difference in overall status, 2-year disease free survival rate and recurrence rate were compared between 2 groups.

## RESULTS

Total 106 patients were enrolled for the study. 24 patients out of

106 had TNBC, Prevalence was 22.6%. Mean age of the total study poulation was 52.8 years, TNBC group had 50 years and Non-TNBC group had 53.6years. 56 patients of 106 had right sided breast cancer. (Figure 1)

In TNBC group, most of the patients had tumor size > 5cm (54.2%) followed by 2 to 5 cm size (45.8%). None of them had tumor <2cm. In non-TNBC group, most of the patients had tumor size 2 to 5cm(63.4%), followed by >5cm(25.6%), then <2cm(11%). Tumor size was significantly higher in TNBC(p=0.016, Chi-Square Test). 64 patients(78%) had positive lymph node status in Non-TNBC group, where as all patients had positive lymph node status in TNBC which was statistically significant(p=0.012). At the time of diagnosis, distant metastasis was present in 20.8% of the TNBC patients when compared to 8.5% of Non-TNBC patients (p=0.031). TNM Staging was done according to the American joint committee on cancers. Most of the patients with TNBC presented with Stage 2(45.8%), Followed by stage 3(33.3%) and stage 4(20.8%). None of them were with stage 1 disease. In Non-TNBC, patients presented with stage 2(58.5%) followed by stage 3(23.2%), stage 1(9.8%) and stage 4(8.5%).

Based on the morphological characterstics over histopathology, Intraductal carcinoma was dominant variety in both TNBC and Non-TNBC(79.2% and 73.2% respectively) followed by Intra lobular variant(16.7% and 14.6%). Scarff-Bloom-Richardson grade system was used to grade tumors, which showed 62.5% of the patients with TNBC had poorly differentiated carcinoma when compared to 18.3% in Non-TNBC. Moderately differentiated Carcinoma was predominant in Non-TNBC(46.3%).

Among the study population, ER was positive in 55.7%, PR was positive in 26.4% and Her2/Neu was positive in 43.4%. In the management of Breast cancer, 75% of patients in TNBC and 91.5% of patients in Non-TNBC underwent Surgical removal of the tumour. All patients with TNBC and 98.8% with underwent chemotherapy. 87.5% of TNBC and 81.7% with Non-TNBC had radiotherapy.

At the end of 2 years from the day of diagnosis of Breast carcinoma, 58.3% of TNBC patients and 89% of Non-TNBC patients were alive. 41.7% of TNBC and 8.5% of Non-TNBC patients died of breast cancer.(p=<0.001) 2.4% in Non-TNBC group died of causes other than Breast carcinoma. After excluding metastatic disease in both the groups, 2 year Disease free survival(DFS) rate was 38.88% in TNBC group and 77.33% in Non-TNBC group. 38.88% of TNBC and 18.7% of Non-TNBC had local recurrence. In TNBC, 22.22% had distant metastatic recurrence, whereas Non-TNBC had only 4%.

## DISCUSSION

Among women, Breast cancer is the most common malignancy surpassing lung cancer, contributing to about 11.7% of all cancers(13, 14). In India, Of all cancers breast cancers contributed to 13.5% and 10.6% of all cancer deaths according to Globocan 2020 data(15).

TNBC is a subset of breast cancer which is more aggressive, adding high morbidity and mortality. It comprises of 15-20% of all Breast cancers(16). In our study, Incidence of TNBC among breast cancers was 22.6%, which was comparable with other Indian studies by Ambroise et al. (25%)(17) and Krishnamurthy et al. (18.5%)(18). Incidence of TNBC in our study was low in comparision with studies by Saha et al.(30.4%)(19), Keam et al.(32.4%)(20) and Nabi MG et al.(34.4%)(21). Few studies showed overall rate lower than our study also like Chun-Yan Li et al. (12.1%)(22), Bauer et al. (12.5%)(23) and Dent et al. (11.2%)(24).

The mean age at the time of diagnosis was low in TNBC(49.96 years) compared to Non- TNBC(53.65years) in our study which was statistically significant. Several studies showed younger age at the time of diagnosis in cases with TNBC worldwide. Nabi et al.(21) showed mean age of 47.4 years. A study by Saha et al.(19) showed mean age of about 53.6 years involving 1026 patients of which 312 had TNBC. Study by Krishnamurthy et al.(18) showed mean age of 46.6 years. Overall, TNBC has younger age of disease presentation.

In our study, 54.2% of TNBC had tumor size >5cm, followed by 2 to 5 cm (45.8%). Nabi et al.(21) in their study showed 82.2% of tumours were >2cm compared to 67.7% in Non-TNBC. Dent et al.(24) had significantly larger mean tumour size in TNBC. A study by Mouh FZ et al.(25) in Moroccan patients showed no significant changes in tumour size between TNBC and Non-TNBC. Lymph node involvement is the main prognostic factor in breast carcinoma, deciding the adjuvant chemotherapy requirement. In our study, All patients with TNBC had positive lymph nodes compared to 78% in Non-TNBC. Lymph node positivity is a bit controversial in TNBC. Several studies including Nabi et al.(21), Dent et al.(24), and Saha et al.(19) showed significant increase in positive lymph node status in TNBC than in Non-TNBC. Few other studies like Mouh FZ et al.(25) and Albergaria A et al.(26) showed predominantly negative lymph node status than the Non-TNBC. In our study presence of distant metastasis at the time of diagnosis in TNBC than in Non-TNBC, which is comparable to other studies(25). In our study, most of the patients with TNBC had Stage 2 disease followed by Stage 3 and 4. None of TNBC patients presented with Stage 1, where as it was 9.8% in Non-TNBC. There were no statistically significant Changes compared to Non-TNBC. Studies by Nabi et al.(21) and Chun-Yan Li et al.(22) also showed no significant changes between TNBC and Non-TNBC in staging.

Histopathological characterstics were assessed and compared between two groups showed similar morphological pictures in both, Invasive ductal carcinoma being the predominant variant. Chun-Yan Li et al.(22) and Qiu J et al.(27) showed similar results. In our study, most of the patients with TNBC had poorly differentiated carcinoma when compared to Non- TNBC(62.5% Vs 18.3%). Hence the more invasiveness of the tumour in TNBC. Results of the studies by Mouh FZ et al.(25), Nabi et al.(21) and Dent et al.(24) were similar to our study(55.4%, 56.4% and 66% respectively).In our study, Only 58.3% of patients with TNBC were alive compared to 89% in Non-TNBC at the end of 2 years from the date of diagnosis. TNBC had more local recurrences(38.8% Vs 18.7%) and Distant metastatic recurrences(22.58% Vs 4%) compared to Non-TNBC after excluding metastatic disease at the time of diagnosis. Pogoda K et al.(28) in their study stated 1/3$^{rd}$ of TNBC patient had recurrence at the end of 6 years among which 14% had locoregional recurrence. A study by Qiu J et al.(27) showed local recurrence of 7.45% and distant metastasis of 20.5% among TNBC, both were significantly higher compared to Non-TNBC. Our study had more number of recurrences, both and distatnt metastasis compared to other studies. 2 year Disease free survival(DFS) rate in TNBC was 38.88% compared to 77.33% in non-TNBC in our study. Qiu J et al.(27) in their study showed 5-years DFS and Overal survival rates were 72.05% and 88.51% in TNBC compared 86.62% and 95.46% respectively in Non-TNBC which was significant. A study by Chun-Yan Li et al.(22) showed 5-year DFS was 77.78% in TNBC and 88.34% in Non-TNBC. Our study also showed similar trend but 2-year DFS was lower compared to other studies in TNBC.

## CONCLUSION

The incidence of Triple Negative breast Cancer(TNBC) was 22.6% in our study. TNBC occurs at younger age as compared to others and presents with larger tumour size, increased lymph node involvement and distant metastasis. It has more

number of poorly differentiated grade on histopathology, hence more aggressive. Both local recurrence and Metastasis is more in TNBC leading to lesser Overall survival anf Disease free survival compared to Non-TNBC. TNBC is more aggressive variant of breast cancer which is responsible for increased mortality and morbidity. Hence, early detection and treatment is the key to success. Further trials were needed to find definitive therapy for TNBC subtype.

### Conflict of interest

The authors declare that they have no conflict of interest.

### Acknowledgements

The authors declare that they have no competing interests.

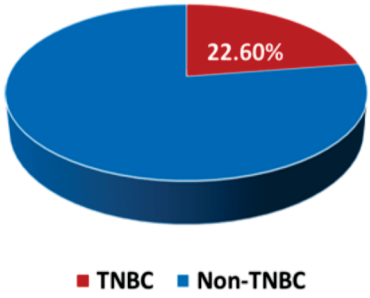


**Figure 1: Incidence of TNBC in our study**

**Table 1: Characteristics compared between TNBC and Non-TNBC**

| | | Groups | | P value | |
|---|---|---|---|---|---|
| Characteristics | Total | Non TNBC (N(%)) | TNBC (N (%)) | Chi-square | |
| Mean Age in years (t-test) | 52.8 | 53.65 | 49.96 | NA | 0.045 |
| Tumour Size | | | | | |
| <2 mm | 9 | 9 (11) | 0 (0) | 8.32 | 0.016 |
| 2-5 mm | 63 | 52 (63.4) | 11 (45.8) | | |
| >5 mm | 34 | 21 (25.6) | 13 (54.2) | | |
| Lymph Node status | | | | | |
| Negative | 18 | 18 (22) | 0 (0) | 6.346 | 0.012 |
| Positive | 88 | 64 (78) | 24 (100) | | |
| Metastasis | | | | | |
| No | 93 | 75 (91.5) | 18 (75) | 4.677 | 0.031 |
| Yes | 13 | 7 (8.5) | 6 (25) | | |
| Stage (TNM) | | | | | |
| Stage I | 8 | 8 (9.8) | 0 (0) | 6.112 | 0.106 |
| Stage II | 59 | 48 (58.5) | 11 (45.8) | | |
| Stage III | 27 | 19 (23.2) | 8 (33.3) | | |
| Stage IV | 12 | 7 (8.5) | 5 (20.8) | | |
| Histopathologic Morphology | | | | | |
| IDC | 79 | 60 (73.2) | 19 (79.2) | 1.59 | 0.662 |
| ILC | 16 | 12 (14.6) | 4 (16.7) | | |
| Both | 7 | 6 (7.3) | 1 (4.2) | | |
| Others | 4 | 4 (4.9) | 0 (0) | | |
| Pathological grade | | | | | |
| Well Differentiated | 28 | 26 (31.7) | 2 (8.3) | 20.498 | <0.001 |
| Moderately differentiated | 43 | 38 (46.3) | 5 (20.8) | | |
| Poorly Differentiated | 30 | 15 (18.3) | 15 (62.5) | | |
| Unclassified | 5 | 3 (3.7) | 2 (8.3) | | |
| ER receptor Status | | | | | |
| Negative | 48 | 24 (29.3) | 24 (100) | 37.488 | <0.001 |
| Positive | 58 | 58 (70.7) | 0 (0) | | |

**Table 2: Recurrence and 2-year DFS comparison between TNBC and Non-TNBC excluding cases with metastasis at presentation**

| Characteristics | Total n = 93(%) | Non-TNBC n = 75(%) | TNBC n = 18(%) | P Value |
|---|---|---|---|---|
| Reccurence | | | | |
| Local | 21(69.89) | 14(18.7) | 7(38.88) | 0.001 |
| Metastasis | 7(22.58) | 3(4) | 4(22.22) | 0.001 |
| 2 year DFS | 65(69.89) | 58(77.33) | 7(38.88) | <0.00 |

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