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RESEARCH ARTICLE

Survival Analysis of Non-metastatic Triple Negative Breast Cancer Patients in a Tertiary Care Centre in North Karnataka, India

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Abstract

Aim: The aim of this study is to examine the demographic and clinicopathological characteristics, treatment modalities, and survival statistics of triple negative breast cancer (TNBC) patients at our institution, along with analysing the correlation between these variables and clinical outcomes. **Methodology:** A cohort of non-metastatic TNBC patients treated from January 2017 to June 2023 was analysed, utilizing descriptive statistics to report characteristics and employing the cox proportional hazard model for assessing prognostic factors in overall survival (OS) and disease free survival (DFS). **Results:** Total149 patients underwent analysis, with a median follow-up period of 32.5 months; the mean age was recorded at 47.4 years, 67.7% categorized as premenopausal and 42.28% at stage III. 72% underwent upfront surgery and among those receiving neoadjuvant chemotherapy (NACT), 80.9% achieved a pathological complete response (pCR). At time of analysis, 10% patients had died and 22.8% experienced disease recurrence with 55.8% of recurrences being distant metastasis. The median OS & DFS was 51 months & 47 months with significant differences in OS and DFS noted between stage I/ II and stage III patients. A high ki67 index (>30%) correlated with significantly poorer OS and DFS while specific chemotherapy regimens yielded notable survival rates. Multivariate analysis identified high stage, lymphovascular invasion (LVI), extra nodal extension (ENE) and high ki 67 index as significant poor prognostic factors. **Conclusion:** TNBC predominantly affects younger women and is diagnosed at advanced stages. Most patients experienced relapse within 3-5 years post-treatment. Identified poor prognostic factors impacting survival include disease stage, LVI, ENE, and high ki-67 index. The relatively short median follow-up in our study, necessitates further studies for a comprehensive understanding of outcomes in survivors.

Keywords: Triple negative breast cancer (TNBC)- Breast cancer- Survival- Prognosis

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Introduction

Triple-negative breast cancer (TNBC) is identified as a specific subtype of breast cancer characterized by absence of estrogen and progesterone receptor, staining less than 1% with negative human epidermal growth factor receptor 2 (HER2) [1-3]. The lack of these hormonal receptors makes it resistant to hormonal therapies and HER2 targeted treatments, thereby significantly limiting treatment options. TNBC accounts for 12-17% of all breast cancer cases globally, while its incidence in India may reach as high as 30% of total breast cancer diagnoses [2-4]. It is more frequently diagnosed in younger females where it is correlated with more aggressive clinical profile and an increased risk of recurrence particularly within first five years post-diagnosis [5, 6]. Upfront surgery was traditionally considered the primary treatment for operable TNBC until neoadjuvant chemotherapy(NACT) emerged as preferred approach with significant benefits in TNBC [7, 8]. The five-year survival rate is based upon the stage at diagnosis and high risk features like LVI, ENE and high ki 67 proliferative index [5, 6, 9]. Here we present data of non-metastatic TNBC patients treated at our institute.

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Objectives

To study demographic profile, clinical and pathological features and treatment given to TNBC patients in our institute. To assess their survival outcomes and to analyse relationship between these factors and their clinical outcomes.

Materials and Methods

Consecutive non metastatic TNBC patients who were treated at our hospital from January 2017-June 2023 were analysed. Last follow up of patients was done till June 2024. Details of each patient were obtained from patient's clinical records. Information on current disease status was collected during follow up visit in OPD or through telephonic communication in patients who have not come for follow up. Patients who could not be contacted and had not been seen in the preceding 1.5 year were classified as lost to follow-up. During follow up, clinical examination was done every 3 monthly and annual mammogram was done. If patient was symptomatic, imaging like CT scan or PET CT scan was done to look for evidence of recurrence or metastasis.

Descriptive statistics were used for reporting patient, tumour and treatment related characteristics. Collinearity was checked for all variables with overall survival (OS) and disease-free survival (DFS). Cox proportional hazard model was used to evaluate prognostic factors for OS and DFS in multivariate analysis. The survival analyses were performed using the Kaplan-Meier method. Log Rank test was used to compare the survival. Significance was assessed using 0.5 % level of significance and p-value<0.05 was considered significant.

Results

149 non metastatic TNBC patients from January 2017-June 2023 were analysed with median follow up 32.5 months. Maximum patients were between 30-50 years age group with mean age 47.4 years and median age 48 years. 67.7 % (101) patients were premenopausal, 32.2% (48) patients were postmenopausal. Majority (59%) patients had T2 stage disease. 36.2 % had N1 disease followed by 24.8 % in N2 whereas 26 % had N0 disease. 34.8 % patients were in stage IIB & 26.1% in Stage IIIA (Figure 1).

More than half (52.3%) patients in our study had grade 3 disease. 68.4% patients had ki67<=30% whereas 31.5 % had ki67 >30%. 71.8 % patients were treated by upfront surgery whereas neoadjuvant chemotherapy was given as first line treatment in 28.1 % patients. Out of those 28.1% (42) patients who received neoadjuvant chemotherapy (NACT), 80.9% (34) had pathological complete response. Median OS and DFS for entire study population is 51 months and 47 months. (Figure 2, Figure 3).

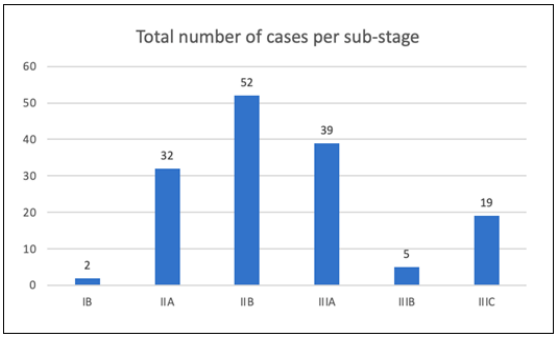

Figure 1. Distribution Based on Sub-stages

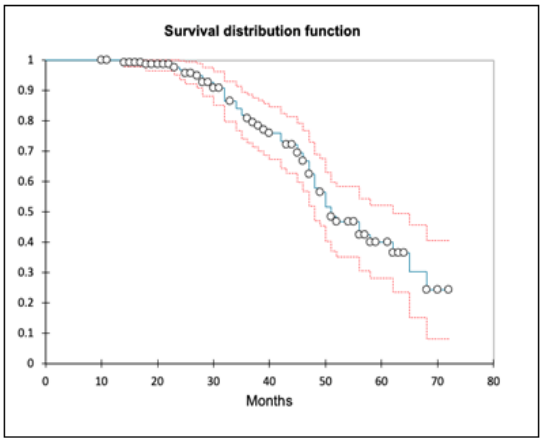

Figure 2. Kaplan Meier Curve for Overall Survival Analysis of Entire Study Population.

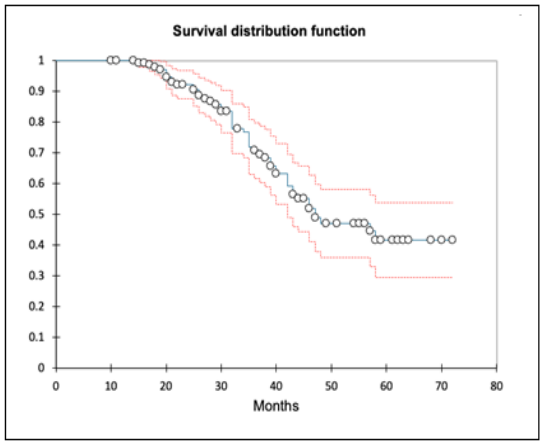

Figure 3. Kaplan Meier Curve for Disease free Survival Analysis of Entire Study Population

4 cycles Adriamycin, cyclophosphamide (AC) q3 weekly followed by 12 cycles weekly paclitaxel was the most commonly used regimen in 83 patients with 3 years OS & DFS 88.3 % & 84 %.OS & DFS at 5 years was 49.5 % & 41.5 % in patients who received this chemotherapy regimen. 40 patients received 4AC q3 weekly followed by 4 docetaxel q3 weekly. 3 year OS & DFS was 88.5 % & 70.6 %, 5 year OS & DFS was 52 % & 56 % in patients who received this regimen.

15 patients died & 34 patients had recurrence at the time of analysis. 93.8 % patients failed within 5 years of treatment, out of which 48.9 % failed within first 3 years of treatment. 53% developed distant metastasis in which 25% had multiple organs involved, 34% were local recurrences &13% patients had both local recurrence and distant metastasis. Most common site of metastasis was lung (25%) followed by bone (20%), brain (15%) and liver (15%) (Figure 4).

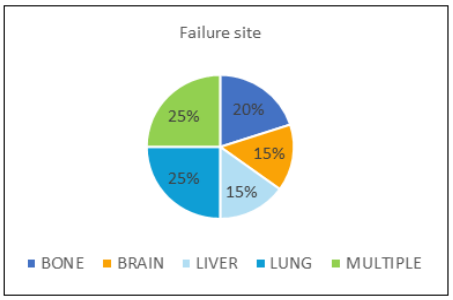

Figure 4. Distribution of Distant Metastasis

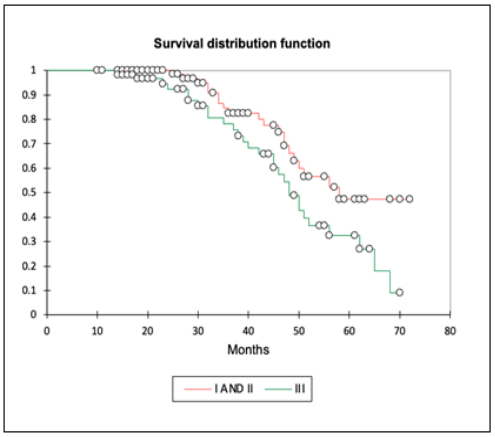

Figure 5. OS Analysis of Stage I and II vs Stage III Patients

Table 1. OS Analysis of Atage I and II vs Atage III Patients

Cohort	Test	Variables	p-value
OS	Stages	I & II vs III	0.027

For stage I/II vs III, 3 year OS was 82.4 % vs 78.2 %, 5 year OS was 47.4 % vs 32.5% (p 0.027) 3 year DFS was 81 % vs 57.8 %, 5 year DFS was 57.6 % vs 23.3 % (p 0.007) (Figure 5 and 6) (Table 1) (Table 2).

5 year OS & DFS in pre menopausal women was 36.5 % & 37.1 % & for postmenopausal women it was 49 % & 52.6% (Figure 7 and 8).

Significant survival difference was seen in OS as well as DFS in patients with ki 67 <=30% vs ki 67 >30%. 5 year OS was 57.5 % vs 14.2 % (p<0.0001) & DFS was 56.5 % vs 15.2 % (Figure 9 and 10).

In multivariate analysis, p value for OS in stage I& II vs III was 0.031 with hazard ratio (HR) of 1.87 at 95 % confidence interval (1.06-3.31) & for DFS HR was 2.21 (1.20-3.76) with p value 0.01. For lymphovascular invasion (LVI) & extra nodal extension (ENE), pvalue was significant (p<0.0001) for both OS & DFS. OS hazard ratio for ki 67 index was 0.334 (0.00-0.596) p<0.0001, DFS for ki 67 was 0.34 (0.00-0.60) p<0.0001 (Table 3).

Discussion

Median age of patients in our study was 48 years with 67.7 %(101) premenopausal patients. It is similar to multiple studies [2, 3, 6, 10, 11] stating that TNBC occurs commonly in young females <50 years. This presentation at early age highlights importance of screening & early detection.

Nishimura et al. [1] stated that premenopausal women have aggressive course of TNBC compared to postmenopausal. This was reflected in our study also where 5year OS & DFS was better in postmenopausal group, suggesting poor prognosis in premenopausal patients.

Multiple studies [2, 3, 5, 12-14] quote that TNBC generally presents in advanced stage, our study also had majority patients with locally advanced disease with 12.7 % in stage IIIC with N3 disease. 7 patients had positive supraclavicular lymph node, 9 patients had >10 axillary lymph nodes positive on axillary lymph node dissection (AXLND) & 3 patients had both internal mammary & axillary nodes positive.

The initial presentation in high grade and stage may be due to limited access to cancer centres in peripheries and ignorance of symptoms in general population leading to delayed presentation. Our data corelates with aggressive behaviour of TNBC at presentation, also reported in various studies [5, 6, 9, 14]. Early diagnosis and timely treatment is important because of the aggressive nature of disease at presentation, with higher stages corelating with poor prognosis and inferior survival outcomes.

Significant difference in survival outcomes of Stage I & II vs Stage III patients was seen in our study. This was like other studies [2] showing poor survival in stage III patients underscoring the need for detection in early stages. Inferior survival outcomes in stage III also highlights the need for better & newer treatment strategies for advanced stages, where current therapies yield suboptimal results.

ki67> 30% had significantly poorer prognosis compared to ki67<=30% in our study. Li et al [14] suggested that TNBC may be sub categorized according to ki 67 levels, with ki 67 > 45% associated with poorer prognosis. In study by Arafah et al. [9] ki67 was associated

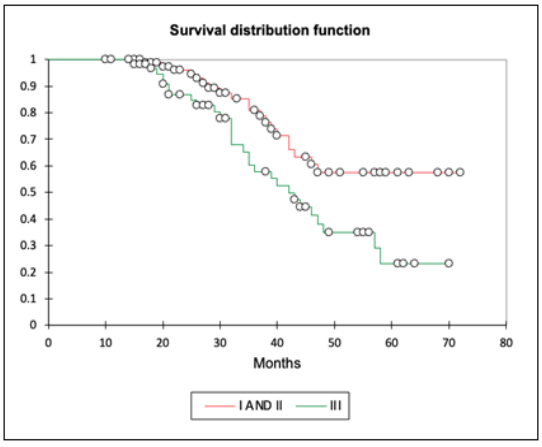

Figure 6. DFS Analysis of Stage I and II vs Stage III Patients

Table 2. OS Analysis of Stage I and II vs Stage III Patients

Cohort	Test	Variables	p-value
DFS	Stages	I & II vs III	0.007

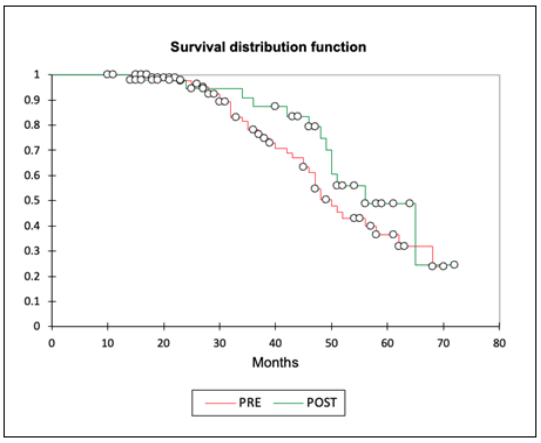

Figure 7. OS in Pre and Post-menopausal Patients

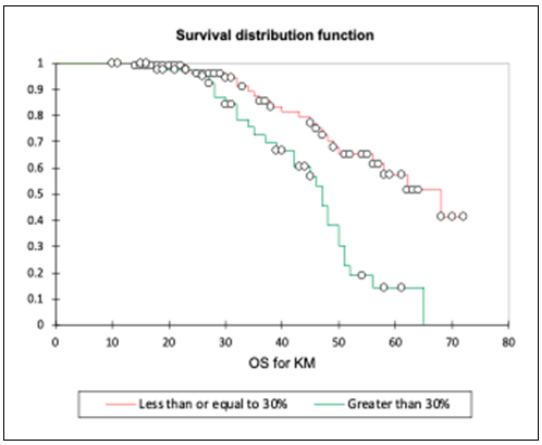

Figure 9. OS Analysis Based on ki 67 Index

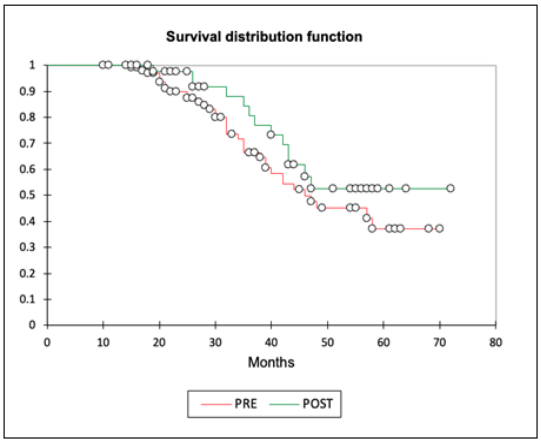

Figure 8. DFS in Pre and Post-menopausal Patients

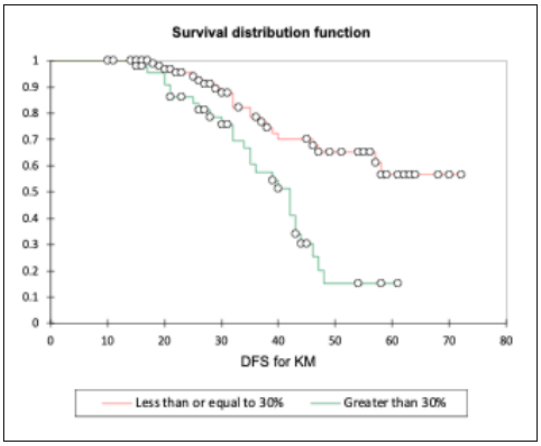

Figure 10. DFS Analysis Based on ki 67 Index

with lymph node metastasis, high grade & stage, poor survival & failure to achieve pathological complete response (pCR). In our study, patients in high ki 67 group were younger with high grade and high stage tumours. High ki 67 index was linked with poorer DFS and OS ($p<0.001$). More studies are needed to standardise & define ki 67 cut off point, so that it can be considered as an indicator for TNBC subgroup analysis.

In our institute, 71.8 % patients underwent upfront surgery. This large number indicates the change in treatment trend over the years. However, in recent years after studies [12-16] quoting the advantage of NACT in TNBC, the sequence of treatment has changed. We treated 28.1 % (42) cases with NACT. These patients had superior surgical outcomes.80.9% (34) patients had pCR when they underwent surgery after NACT, translating into better prognosis and superior outcomes. Though studies [7, 8, 17] have quoted superior outcomes in patients treated by neoadjuvant chemotherapy in TNBC, the survival outcomes did not differ in patients treated by neoadjuvant versus adjuvant chemotherapy in our institute.

Four different chemotherapy regimens have been used over the years in our centre. It corelates with how chemotherapy landscape has evolved over time in breast cancer, with use of taxanes along with anthracyclines. Current recommendation [16] of using platinum in NACT was not used at our centre to avoid additional toxicities. OS & DFS in our patients treated with 4 AC q3weekly followed by 12 weekly paclitaxel & 4 AC q3weekly followed by q3 weekly docetaxel, was like the survival quoted in literature with these regimens [14, 15]

Sparano et al. [15] stated that, AC followed by weekly paclitaxel was the most effective adjuvant chemotherapy option for TNBC. GeparSixto trial [18] established NACT as the preferred approach to treat stage II or III TNBC with complete pCR as a marker for chemotherapy sensitivity & improved long-term outcomes.

32.8 % (49) patients in our study failed within 5 years of treatment. This early relapse can be due to treatment

Table 3. Multivariate Cox Proportional Hazard Analysis

Variable	HR (95%) for OS	P Value	HR (95%) for DFS	P Value
Stage I and II vs Stage III	1.875 (1.060 - 3.316)	0.031	2.216 (1.202 - 3.760)	0.01
LVI present	6.197 (3.075 - 12.489)	<0.0001	7.569 (3.747 - 15.290)	<0.0001
ENE present	3.681 (2.068 - 6.552)	<0.0001	5.042 (2.828 - 8.991)	<0.0001
Ki 67 index	0.334 (0.000- 0.596)	<0.0001	0.342 (0.000 -0.607)	<0.0001

resistance, aggressive biology & patient associated factors. According to Soares et al. [5], patients who do not achieve pCR, younger patients & those with high tumour burden at diagnosis are more likely to experience early relapse. Similar recurrence pattern was also seen in other TNBC studies[10, 11, 19, 20] in India. In study by Bajpai et al. [2], total death rate was 17 % whereas we saw 10 % death rate in our study. In other study [17], 35% events occurred before third year of treatment. In our data, we saw 38.7 % treatment failures between second and third year post treatment and 93.8 % of the failures occurred within first 5 years after treatment. The involvement of distant sites is same suggesting high chances of visceral metastasis. In our study 8.05% (12) patients were lost to follow up at the time of analysis. Total 10% (15) patients died in our study ,11 deaths were due to cancer and 4 were covid related deaths. 3-year OS & DFS was similar to Bajpai et al. [2] but 5-year survival rates were not comparable. This is due to high number of relapses between third & fifth year post treatment in our study. Significant factors for prognosis were stage, LVI, ENE along with ki-67 index. These independent variables had significant impact on prognosis in multivariate analysis.

The findings from our study are promising regarding the current treatment & prognosis of TNBC in India. 3-year and 5-year survival rates are comparable to global averages. The strength of our study is the contemporary nature of the cohort who were uniformly treated at a single tertiary care centre from India whereas the limitation is the smaller number of patients and minimal follow up duration was less than a year in some patients. The median follow-up was relatively short, so we were unable to study the long-term toxicities and outcomes among survivors.

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The authors declare no conflict of interest.

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