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ORIGINAL SCIENTIFIC REPORT

Outcomes of Triple-Negative Breast Cancers (TNBC) Compared with Non-TNBC: Does the Survival Vary for All Stages?

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Abstract

Background Triple-negative breast cancer (TNBC) is associated with aggressive tumor behavior and worse outcomes. In a study at a tertiary care breast unit in a developing country, clinico-pathological attributes and outcomes of patients with TNBC were compared with (c.w.) ER, PR, and/or HER2 expressing tumors (non-TNBC).

Patients and methods Medical records of 1213 consecutive breast cancer patients managed during 2004–2010 were reviewed. An evaluable cohort of 705 patients with complete treatment and follow-up (median 36 months) information was thus identified. Patients were categorized per ER, PR & HER2 status into TNBC, and ER/PR+ and/or HER2+ groups. Clinico-pathological parameters, response to NACT, and OS & DFS were compared between TNBC and non-TNBC groups.

Results TNBC patients ($n = 249$) comprised 35.3 % of the study cohort ($n = 705$), and were significantly younger than non-TNBC patients (mean age 49.1 ± 11.2y c.w. 51.8 ± 11.3, $p = 0.02$). The TNM stage at presentation was similar in the two groups (Stage I and II—37 % c.w. 44.3 %, Stage III—47.5 % c.w. 39.5 %, Stage IV—15.5 % c.w. 16.2 % in TNBC c.w. Non-TNBC; $p = 0.09$). Tumor size (5.7 ± 2.9 cm TNBC c.w. 5.4 ± 2.8 cm non-TNBC, $p = 0.22$) was similar but lymph nodal (cN) metastases were more frequent in TNBC (77.3 % c.w. 69.8 %; $p = 0.03$). TNBC had higher histologic grade (97.1 % gr II/III in TNBC c.w. 91.2 % non-TNBC, $p = 0.01$) and higher incidence of LVI (20.4 % in TNBC c.w. 13.5 %, $p = 0.03$). Patient groups received similar multi-disciplinary surgical, radiation, and systemic treatment. Comparable proportion of patients in 2 groups were treated with NACT (42 % c.w. 38 %), which resulted in pathological complete response (pCR) in 27.5 % TNBC patients c.w. 17.1 % non-TNBC patients ($p = 0.04$). Both OS (81.8 ± 4.52 c.w. 97.90 ± 3.87 months, $p < 0.001$) and DFS (89.2 ± 5.1 c.w. 113.8 ± 4.3 months, $p < 0.001$) were shorter in TNBC than non-TNBC group. On stage-wise comparison, OS differed significantly only in stage III (47.4 ± 5.3 months in TNBC c.w. 74.5 ± 4.4 in non-TNBC; $p < 0.001$). Univariate and multivariate analyses revealed tumor stage and IHC subtyping into TNBC c.w. non-TNBC as most important factors predictive of survival.

Conclusions TNBC occurred at younger age and exhibited aggressive pathology as compared to non-TNBC patients. Although patients with TNBC exhibited better chemo-sensitivity, they had worse DFS and OS compared to the non-TNBC patients. The survival of Stage III TNBC patients was significantly worse compared to non-TNBC group; while in stages I, II, and IV, survival were not significantly different.

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Introduction

Background

Triple-negative breast cancers (TNBC) lack expression of estrogen receptor (ER-negative), progesterone receptor (PR-negative), and human epidermal growth factor receptor 2 (HER2-negative) [1, 2]. These tumors do not respond to hormone treatment or anti-HER2 treatment, and so chemotherapy (CTx) is the main-stay systemic treatment for such patients. TNBC accounts for about 9–21 % of all breast cancers including patients for all the stages of breast cancer [3, 4]. TNBC are known to respond better to CTx, and result in higher rates of pathological complete response (pCR) after neo-adjuvant chemotherapy (NACT) than hormone responsive or HER2 expressing breast cancer subtypes [5]. Yet, they have poorer survival outcomes compared with (c.w.) ER/PR and/or HER2 expressing subtypes [4, 6, 7].

Most of the studies reporting outcomes of TNBC in comparison to non-TNBC patients are from developed countries, in which, the majority of patients are early-stage breast cancers (EBC). Breast cancer patients in India and other developing countries are mostly diagnosed at large operable or locally advanced stages (LABC), and thus NACT is the primary treatment modality employed [8, 9]. There is lack of data from India and other developing countries, comparing the outcomes of TNBC and non-TNBC patients. This retrospective study was conducted at a specialty breast center in north India with the aim of comparing the outcomes of TNBC and non-TNBC patients, and investigating the causes for any differences in their outcomes.

Patients and methods

This retrospective study was carried out at SGPGIMS, Lucknow a tertiary health care center in India, with due clearance from the institute ethics committee. Female breast cancer patients ($n = 1213$) of all stages treated between January 2004 and December 2010 were reviewed. The data were obtained from hospital and follow-up medical records by accessing their electronic medical records, case files in the department of Endocrine and Breast Surgery as well as Department of Radiation Oncology, and the electronic records of Department of Pathology. In addition, all patients were contacted via letters, telephone, and email to derive current follow-up status. Patients for whom one or more clinical, pathological, ER/PR/HER2 information were lacking ($n = 268$) were excluded. Only such surviving patients with minimum 42 months follow-up were included. Those patients for whom current follow-up and outcome information was not available ($n = 240$) were also excluded from the study, thus leaving the study cohort of 705 qualifying patients, who were included in the final analysis.

The demographic and clinical features including age, menopausal status, family history of breast or ovarian cancers and other relevant family history, tumor stage at presentation, and treatment details including surgical, radiation, and systemic treatment were recorded. Histopathological characteristics of the tumor including pathological tumor size and lymph nodal status, tumor grade, lymphovascular invasion (LVI), margins (involved/not involved), and peri-nodal involvement (yes/no) were captured. Based on immuno-histochemical (IHC) analysis of tumor ER, PR, HER2 results, patients were divided broadly into TNBC and non-TNBC groups. ER, PR immunostaining was done on formalin fixed, paraffin embedded tissues using well-standardized techniques. Any immunostaining for ER and/or PR was taken as positive. The clone used for HER2 detection was a polyclonal (HER2 Hercep Test Kit) and the detection system was a polymer. The CAP/ASCO guideline criteria were used for the interpretation of results: HER2 score 0 (No staining observed, or membrane staining in <10 % of the tumor cells) or 1+ (faint/barely perceptible membrane staining detected in >10 % of the tumor cells; cells only stained in part of the membrane) was interpreted as negative. Score 2+ (weak to moderate complete membrane staining observed in >10 % of tumor cells) was interpreted as weak positive, and further evaluated for HER2 by fluorescent in situ hybridization (FISH) in about half of such patients. All patients with HER2 IHC score 3+ (strong and complete membrane staining observed in >30 % cells) and those with HER2/CEP17 ratio (FISH) of >2.2 were interpreted as HER2 positive tumors.

Patients with inoperable locally advanced (T4 and/or N2/3) and large operable (T3) cancers were treated with NACT. In patients treated with NACT, response was recorded as per RECIST criteria. In patients undergoing breast conservation surgery, any infiltrated margins detected either on intra-operative frozen section or post-operative paraffin section histology were re-excised. Outcomes recorded were Overall survival (OS)—defined as time period from the date of diagnosis to the date of death from any cause; and Disease-free survival (DFS)—defined as time period for which a patient survived without evidence of disease, i.e., the time duration from the first definitive treatment to the date of first event in the form of loco-regional or distant recurrence in surviving patients; or

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death from any cause in patients with no documented recurrence or metastases. Patients alive (for OS analysis)/or free of loco-regional or distant recurrence (for DFS analysis) at the end of study period (or those for whom there was no evidence to show that either has occurred) were considered to have "censored" survival times.

Statistical analysis

Differences in patient and tumor characteristics were analyzed using variance for continuous variables and Chi-square for categorical variables. The Kaplan–Meier product limit method was used for OS and DFS analysis. Log-rank test was used to compare the OS and DFS of subtypes. Univariate and multivariate analyses were done using Cox proportional hazard model to identify factors influencing OS and DFS in TNBC patients. Statistical analyses were performed using a SPSS-16 software package (SPSS, Inc., Chicago, IL). p values were considered significant if <0.05.

Results

TNBC patients constituted 35.3 % (249 of 705) of the entire study cohort. A comparison of TNBC and non-TNBC patients revealed that TNBC patients were younger (mean age of 49 ± 11.2 years, c.w.51.8 ± 11.3 years in non-TNBC group, $p = 0.002$), and more often pre-menopausal (47 % in TNBC c.w. 38.4 % in non-TNBC group, $p = 0.03$). Mean tumor size was similar in the two groups (5.7 ± 2.9 cm in TNBC c.w. 5.4 ± 2.8 in non-TNBC, $p = 0.15$). However, a higher proportion of TNBC patients had lymph node metastases (cN status) at presentation (77.3 % in TNBC c.w. 69.8 % in non-TNBC group, $p = 0.03$). 110 (15.6 %) patients had undergone some prior surgical procedure in the form of incisional or excisional biopsy or mastectomy elsewhere before presenting to our hospital, and they were equally distributed between TNBC and non-TNBC groups. Higher proportion (47.5 %) of TNBC patients presented as LABC compared to 39.5 % in non-TNBC group ($p = 0.06$). The proportion of TNBC and non-TNBC patients in early (stages I and II, 37 % TNBC c.w. 44 % non-TNBC, $p = 0.09$) and metastatic (stage IV, 15.5 % TNBC c.w. 16.2 % non-TNBC, $p = 0.82$) disease at presentation were comparable.

Infiltrating ductal carcinoma (IDC) was the commonest histo-pathological subtype in both the groups (94.2 % in TNBC, 93 % in non-TNBC group; $p = 0.33$). The histological grade III tumor proportion was higher in TNBC (56.4 %) compared to non-TNBC group (31.4 %, $p = 0.002$). The two groups were treated in comparable manner: 42.1 % of TNBC and 37.6 % of non-TNBC patients underwent NACT, with anthracyclines containing combination chemotherapeutic regimen being the commonest one—used in 66.2 % of TNBC and 61.8 % of non-TNBC patients ($p = 0.29$). Combination of

Table 1 Univariate and multivariate analysis of factors affecting overall survival

	Univariate analysis			Multivariate analysis		
	Odd's ratio	p value	CI	Odd's ratio	p value	CI
Age ≤50/>50 years	0.898	0.416	0.692–1.16			
TNM stage (I/II/III/IV)	2.475	<0.001	2.12–2.18	3.15	0.001	1.5–6.3
pT	1.35	<0.001	1.14–1.59	1.472	0.025	1.0–2.1
pN	1.47	<0.001	1.28–1.7			
Histological grade	1.51	0.007	1.12–2.05	2.907	<0.001	1.6–5.2
Group (TNBC vs non-TNBC)	1.59	0.001	1.25–2.1	1.992	0.017	1.1–3.5

CI confidence interval, *pT* pathological tumor stage, *pN* pathological nodal stage, *TNBC* triple-negative breast cancer

Table 2 Univariate and multivariate analysis of factors affecting disease-free survival

	Univariate analysis			Multivariate analysis		
	Odd's ratio	p	CI	Odd's Ratio	p	CI
Age ≤50/>50 years	0.686	0.036	0.48–0.97	0.480	0.004	0.29–0.78
TNM stage (I/II/III/IV)	1.864	<0.001	1.4–2.3			
pT	1.275	0.020	1.0–1.5			
pN	1.648	<0.001	1.3–1.9	1.558	<0.001	1.2–1.9
Histological grade	1.549	0.030	1.0–2.2			
Group (TNBC vs non-TNBC)	2.162	<0.001	1.5–3.1	1.991	0.005	1.2–3.2

CI confidence interval, *pT* pathological tumor stage, *pN* pathological nodal stage, *TNBC* triple-negative breast cancer

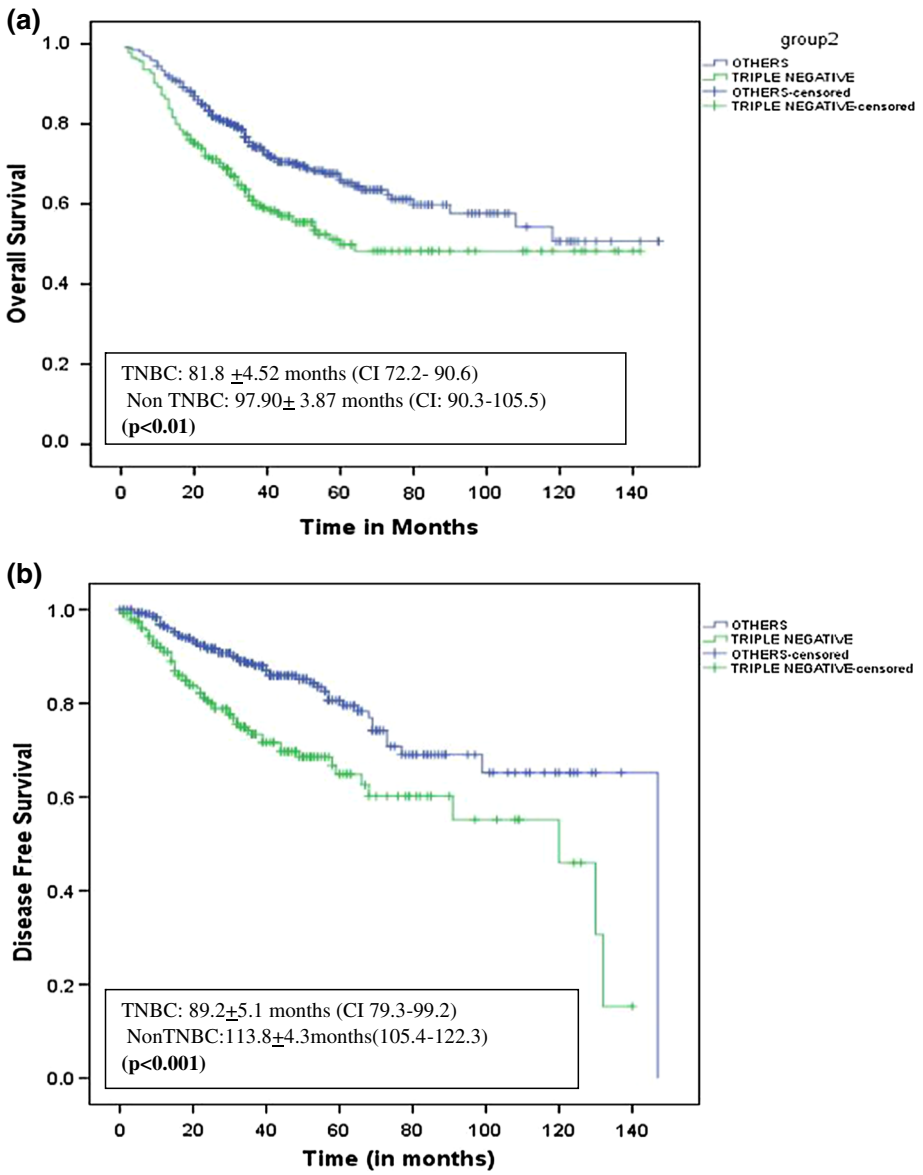

Fig. 1 Comparison between TNBC and non-TNBC patients: **a** overall survival, **b** disease-free survival

anthracyclines and taxanes were used in 28.4 % of TNBC and 33.1 % of non-TNBC patients ($p = 0.24$). In the 238 patients treated with NACT, clinical complete response (cCR) was seen in 35.9 % TNBC and 24.5 % non-TNBC patients ($p = 0.03$). Pathological complete response (pCR) was seen in 27.5 % TNBC patients and 17.1 % of non-TNBC patients ($p = 0.04$). Further details of clinical, pathology, and treatment-related variables, and their comparisons between TNBC and non-TNBC groups are provided in supplementary Table 1. Comparison of clinical, pathologic, and treatment characteristics between patient groups who were treated with adjuvant and neoadjuvant chemotherapy is provided in supplementary Table 2.

Survival data

Over a median follow-up of 36 months (range: 1–147 months; minimum follow-up in surviving patients 42 months), the mean OS {Fig. 1(A)} with 95 % CI in TNBC patients was 81.8 ± 4.5 months (CI 72.3–90.7) which was significantly ($p < 0.001$) shorter compared to the OS in non-TNBC group (97.9 ± 3.9 months, CI 90.3–105.5). The estimated mean DFS {Fig. 1(B)} with 95 % CI in TNBC patients (89.2 ± 5.1, CI 79.3–99.2) was shorter ($p < 0.001$) c.w. that in non-TNBC patients (113.8 ± 4.3, CI 105.4–122.3). The OS (Fig. 2) varied significantly between subgroups based on ER, PR, and HER2 status ($p < 0.001$). The estimated OS was longest in subgroup with ER/PR expressing but HER2

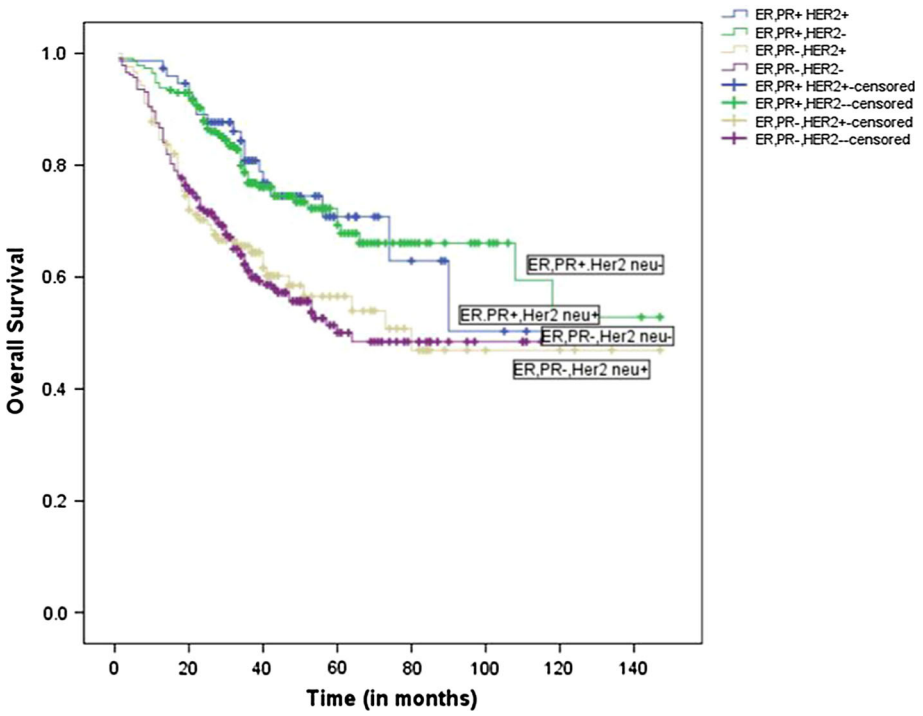

Fig. 2 Comparison of Overall survival in patient groups based on hormone receptors and HER2 status

	ER,PR+,Her2-	ER,PR+,Her2+	ER,PR-,Her2+	ER,PR-,Her2-
Mean overall survival with CI	113.8±4.3months CI:(105.4-122.3)	91.6±7.8months (CI 71.7- 98.4)	85.6±6.8 months (CI: 71.3-97.8)	81.8±4.52 months (CI: 72.260- 90.68)

deficient (ER/PR+, HER2-) tumors {103.8 ± 5.2 months (CI 93.7–114.0)}, and the worst in TNBC patients {81.8 ± 4.52 months (CI 72.3–90.7)}. The estimated DFS (Fig. 3) too varied significantly between the groups ($p < 0.001$) and was longest for ER, PR+ HER2− patients {119.9 ± 5.6 (CI 108.8–131.0) months} and shortest {89.3 ± 5.1 (CI 79.3–99.2)} for TNBC patients. Supplementary Table 3 provides a comparative list of the site of distant metastasis in TNBC and non-TNBC patient groups.

Figures 4 (A), (B), and (C) provide a comparison of OS according to stage groups, namely EBC (TNM stages I and II), LABC (TNM stage III), and MBC (TNM stage IV). There was no significant difference in OS in EBC (non-TNBC 99.1 ± 6.1 months, CI 87.1–111.1 c.w. TNBC 102.6 ± 7.2 months, CI 88.5–116.6; $p = 0.308$) and MBC (TNBC 21.1 ± 3.8, CI 13.6–28.5 c.w. non-TNBC 28.4 ± 3.0, CI 22.4–34.4; $p = 0.116$). However, the OS was significantly different in stage III patients, with the mean OS in TNBC patients being 47.4 ± 5.3 months (CI 37.0–57.8) and 74.5 ± 4.4 (CI 65.924–83.092) in non-TNBC; $p < 0.001$. Figure 5 (A) and (B) shows the difference in OS and DFS, respectively, in patients who achieved pCR following NACT. The OS ($p = 0.158$) and DFS ($p = 0.40$) were similar in such TNBC and non-TNBC patients. However, comparing the OS {Fig. 6 (A)} and DFS {Fig. 6 (B)} in patients who achieved partial response to NACT, the mean OS in TNBC group was 57.4 ± 7.8 (CI 42.0–72.9) months, c.w. 79.4 ± 9.2 (CI 61.27–97.64) months in non-TNBC patients; $p < 0.001$. The DFS in partial responders TNBC patients was 67.6 ± 9.64 (CI 48.75–86.57) months, as compared to 81.45 ± 6.9 months in non-TNBC partial responders (CI 67.92–94.98; $p = 0.007$).

On univariate analysis of factors affecting OS (Table 1), TNM stage at presentation, ($p < 0.001$), pathological tumor (pT) stage ($p < 0.001$), pathological lymph nodal (pN) stage ($p < 0.001$), histo-pathological grade of the tumor ($p = 0.007$), and subtyping based on ER, PR, HER2 status, i.e., TNBC c.w. non-TNBC ($p = 0.001$) were the factors affecting OS, while the response to CTx ($p = 0.31$) and age ($p = 0.41$) had no significant impact on OS. However, on multivariate analysis, only TNM stage at presentation ($p < 0.001$), pT stage ($p = 0.025$), histo-pathological grade ($p < 0.001$), and ER, PR, HER2 subtyping (TNBC c.w. non-TNBC, $p = 0.017$) remained significant predictors of OS. On univariate analysis, the DFS

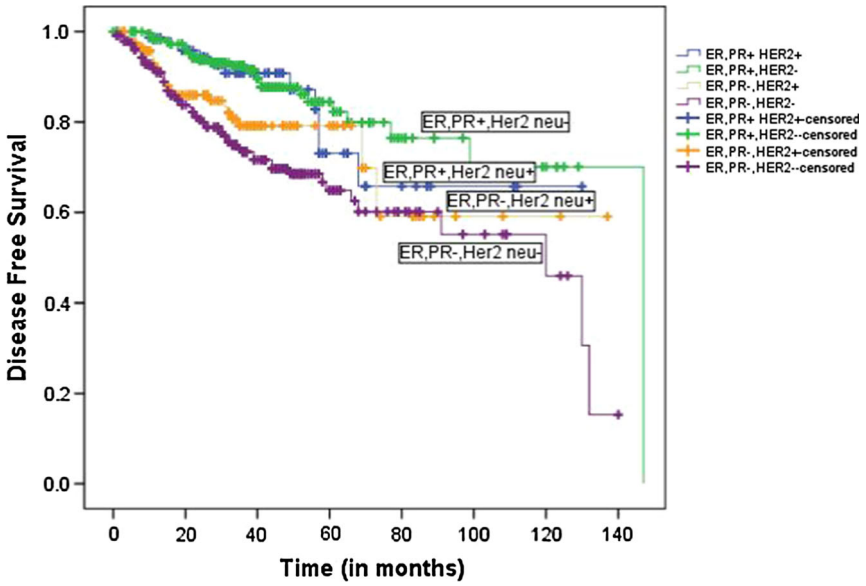

Fig. 3 Comparison of Disease-free survival in patient groups based on hormone receptors and HER2 status

	ER,PR+,Her2-	ER,PR+,Her2+	ER,PR-,Her2+	ER,PR-,Her2-
Mean disease free survival with CI	119.9±5.6months CI:(108.9-131.0)	102.2±7.6months (CI: 87.2-117.3)	98.9±7.1months (CI: 84.8-113.0)	89.3±5.1months (CI: 79.3-99.2)

(Table 2) was predicted by age (< 50 c.w. >50 years age groups, $p = 0.036$), TNM stage at presentation ($p < 0.001$), pT stage ($p = 0.020$), pN stage ($p < 0.001$), histo-pathological grade ($p = 0.030$), and ER, PR, HER2 subtype (TNBC c.w. non-TNBC, $p < 0.001$). On multivariate analysis; age ($p = 0.036$), pN stage ($p < 0.001$), and ER, PR, HER2 subtyping, i.e., TNBC c.w. non-TNBC ($p = 0.005$) turned out to be important determinants of DFS. Thus, subtyping patients into TNBC and non-TNBC groups was an important determining factor for both OS and DFS.

Discussion

Breast cancer is a disease of biologically variable heterogeneous forms, with marked variation in the outcomes. Molecular classification of breast cancer by multi-gene expression studies using DNA microarrays provides robust prediction of outcomes and response to therapy. The commercially available assays for molecular classification are expensive, and beyond reach of most breast cancer patients, more so in countries with limited resources. Based on the IHC evaluation of ER, PR, and HER2 expression, breast cancer patients can be classified, which is relatively easy, and useful in clinical practice. The IHC classification of patients has been shown to correlate well with intrinsic classification using gene expression microarrays: ER/PR+, HER2+ with Luminal B; ER/PR+, HER2− with Luminal A; ER/PR−, HER2+ (ER−/HER2+); and ER/PR−, HER2− with triple-negative/basal-like tumors [5, 14]. TNBC has emerged as a group of breast cancer patients with unique therapeutic challenges and worst outcomes, and forms an important area of research interest.

In this retrospective study, perhaps the largest one on Indian TNBC patients treated and followed-up for intermediate to long term at a tertiary care breast center in north India, TNBC constituted 35.3 % of the whole study cohort of breast cancer patients. Previous Indian studies have documented that rates of ER negativity is higher among Indian breast cancer women [10–13]. It has been suggested that besides technical faults in detection of ER, factors contributing to high ER negativity could be younger age of patients, advanced stage at presentation, and higher grade tumors [11]. In an Indian study that compared Indian patients with those from SEER database, the ER negativity rates of Indian patients was found to be higher across all age groups, perhaps due to advanced stage of breast cancer presentation [12]. Our study found higher incidence of TNBC in younger, pre-menopausal women, which corroborates findings in other studies [14, 15]. Unlike other studies which suggest TNBC to present in more advanced stages [16], we found comparable stages at presentation in the TNBC and non-TNBC groups, which can be attributed to the late presentation of breast cancer in general in India [8, 9]. Overall, around

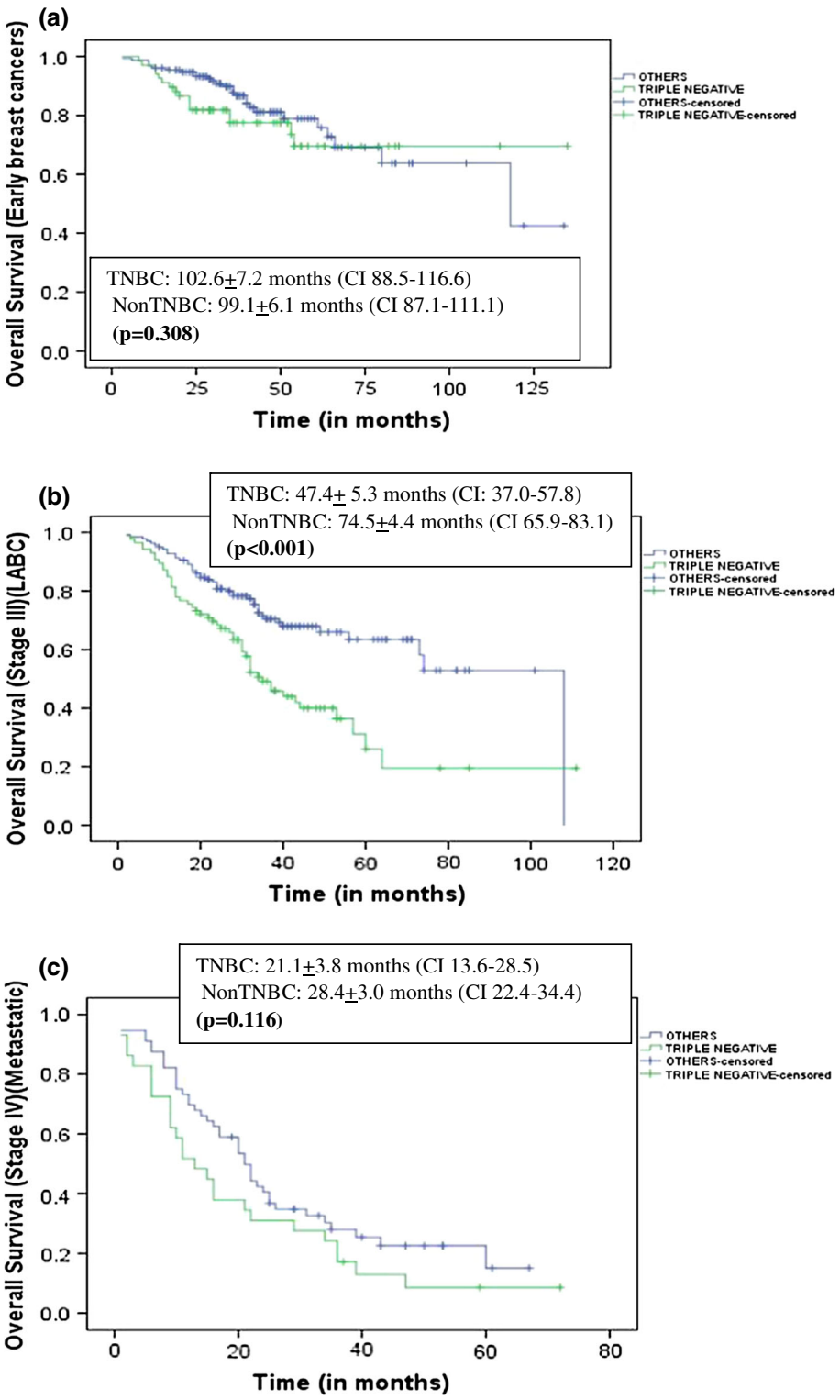

Fig. 4 Comparison of Overall survival in TNBC and non-TNBC patients: **a** Stage I and II patients, **b** stage III patients, **c** Stage IV patients

50–55 % of our patients present as LABC or metastatic breast cancers.

The mean clinical tumor size of TNBC patients (5.7 cm) in our study was similar to that in non-TNBC patients (5.4 cm). However, higher proportion of TNBC patients had clinically enlarged lymph nodes, perhaps due to large tumor size and late stage at presentation, similar to what has been reported by others [9], though some others, wherein the mean tumor size varied from 1.8 to 2.2 cm, have reported lesser incidence of nodal involvement in

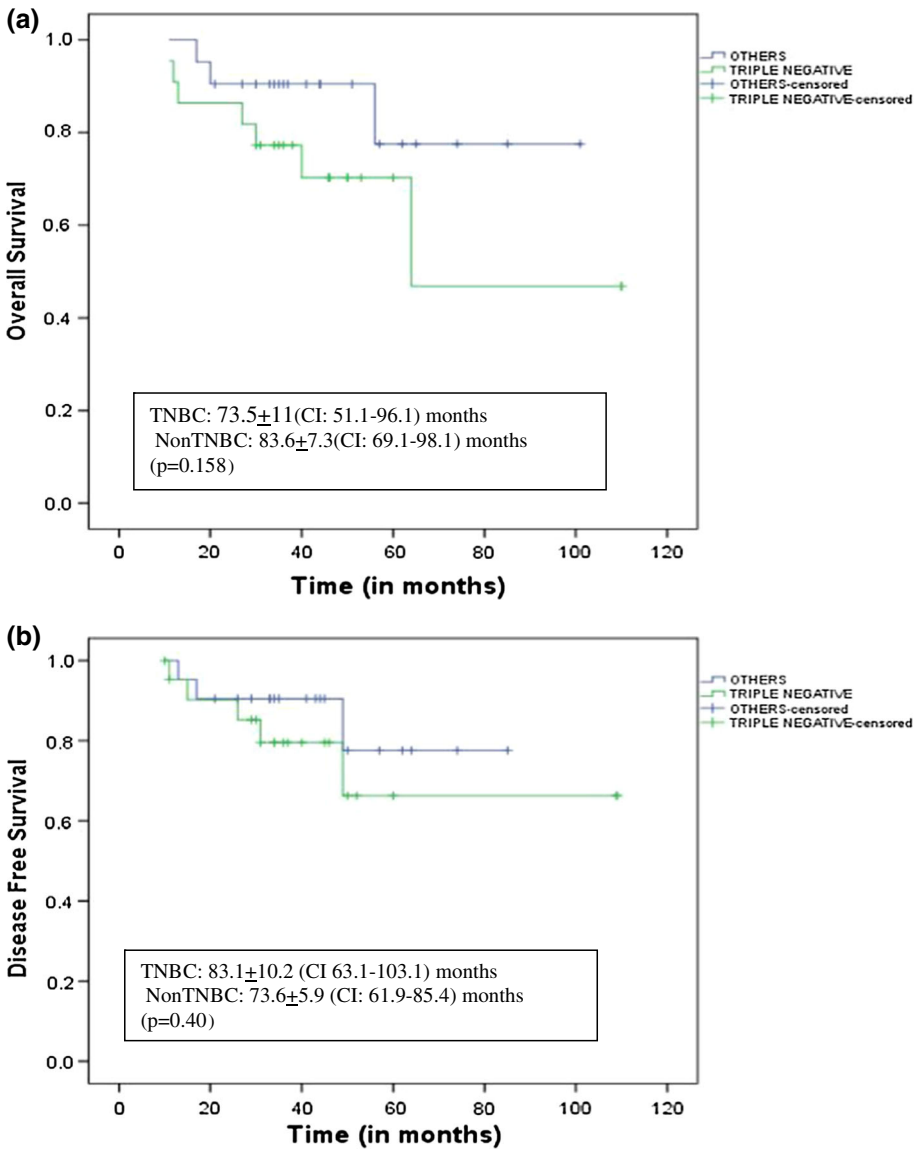

Fig. 5 Comparison between TNBC and non-TNBC patients with pathological complete response to neo-adjuvant chemotherapy: **a** overall survival, **b** disease-free survival

TNBC [7]. The predominant histopathology seen in both subtypes was IDC in our study. We found large number of TNBC patients (96 %) presenting with higher tumor grades, i.e., grade II, III similar to other studies [17] which have reported more aggressive histological features such as higher grades, pushing margins, and marked apoptosis in TNBC. The incidence of LVI was also higher in TNBC in our experience, but there was no difference in margin positivity status or peri-nodal spread between subtypes.

Patients in TNBC and non-TNBC groups were offered similar surgical treatment, and around 20 % of the patients underwent BCS. Majority of the patients were treated with anthracycline-based combination adjuvant or neo-adjuvant CTx. Starting 2005, taxanes in combination with anthracyclines—either sequentially or concomitantly are being uniformly administered to TNBC patients. In the patient cohort treated with NACT, 37 % of TNBC patients had cCR and 27 % had pCR, which is comparable to other studies [5]. The OS and DFS of TNBC patients were found to be poorer, as compared to non-TNBC subtypes. On subgroup analysis, we found the highest OS and DFS in luminal subtypes followed by TNBC and HER2 enriched types, which corresponds with findings of most of other studies [14, 15].

On a subgroup analysis to evaluate the stage-wise OS and DFS, the survival rates between TNBC and non-TNBC groups were not found significantly different for stages I, II, and IV. In the stage III patients, the OS and DFS were significantly poorer in the TNBC group as compared to non-TNBC group. These findings suggest that the tumor

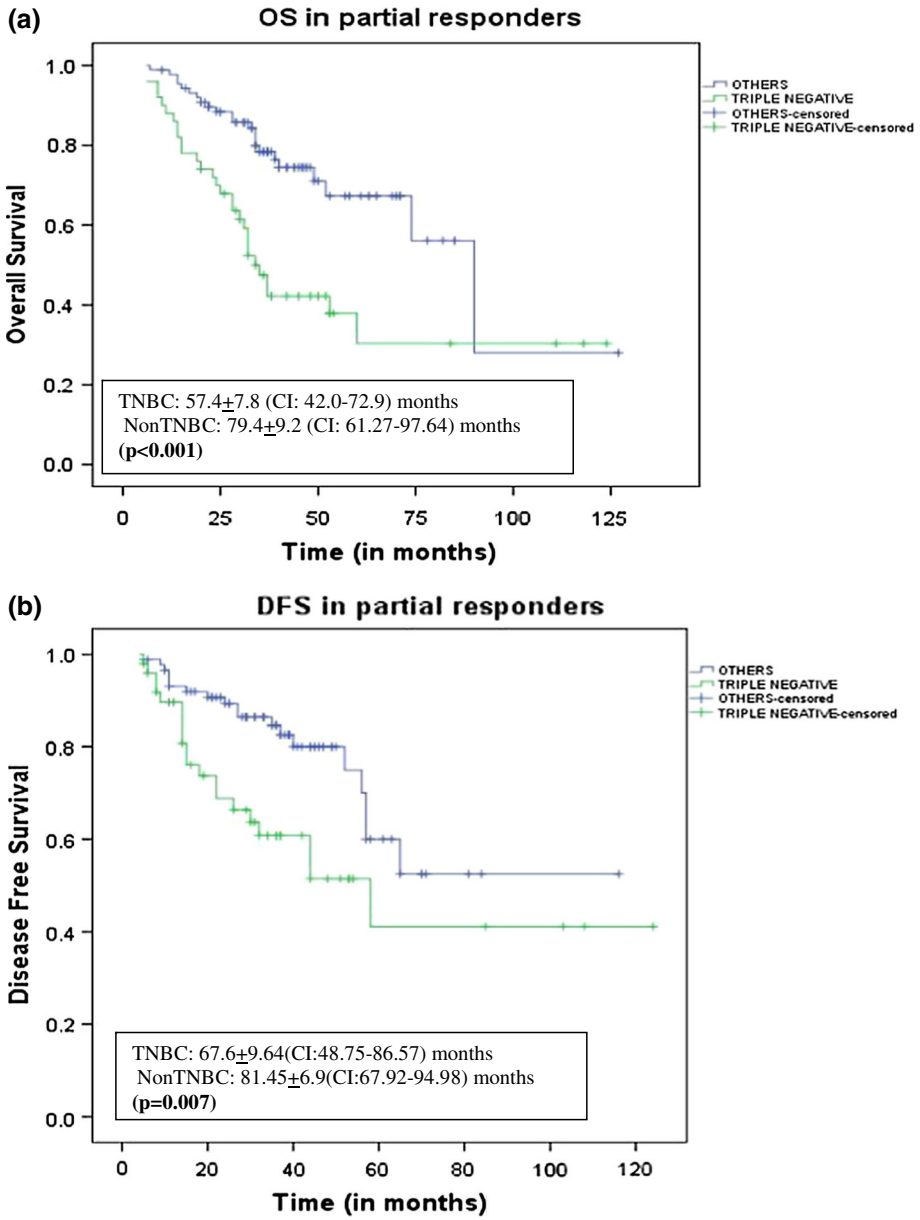

Fig. 6 Comparison between TNBC and non-TNBC patients with partial response to neo-adjuvant chemotherapy: **a** overall survival, **b** disease-free survival

biology plays a major role in patients with substantial disease burden as is the case in stage III. In patients with limited/early disease (stage I and II) or those with systemic metastases, the outcomes are impacted to lesser extent by the hormone receptor and HER2 status of the tumors. It must also be pointed out that the relatively small patient numbers in the EBC (stage I and II) and MBC (stage IV) groups might have had some bearing on the lack of significant difference in outcomes of TNBC c.w. non-TNBC patients in these subgroups. A few other studies have compared the stage-wise outcomes between various subtypes. One such study reported comparable survival rates between tumor subtypes when compared stage wise [7]. Another study reported that the survival is worse for stage II and III TNBC [18], while yet another commented that tumor biology is more important determinant of survival than tumor stage [19]. Most other studies reporting the relative outcomes of TNBC and non-TNBC have mostly included stage I and II patients, with stage III patients constituting 10–22 % of all cases. In contrast, in our study 39–48 % patients in various subtypes were stage III. Our results bring into focus the problems of breast cancer management faced in majority of low- and middle-income countries. Majority of reports in literature comparing TNBC with non-TNBC come from centers in developed nations, which focus on the early-stage disease—which

make the bulk of their patients. The high proportion of LABC in our study, compared to other studies in any set-up and documentation of a significant survival difference between TNBC and non-TNBC groups in stage III patients alone are somewhat unique findings of our study.

Response to CTx plays a major role in determining the survival in breast cancer patients, more so in TNBC patients as these patients lack any targets (ER, PR, HER2) that can be treated. Patients presenting with stage III disease are candidates for NACT, and patients who achieve pCR following NACT are believed to have better OS [20], though this belief is contested by certain other studies which report no significant OS benefit in such patients. It is also widely acknowledged that higher proportion of TNBC patients can achieve pCR with NACT, as compared to non-TNBC patients, as was observed in our study too. Yet, pCR to NACT is achieved only in a small proportion of the patients, and hence the difference in OS between the TNBC and non-TNBC groups could be attributed to a large fraction of partial and poor responders where the survival varies despite NACT. TNBC/basal-like breast cancers respond better to taxane-based CTx compared to other subtypes [21]. In our study conducted on patients treated between 2004 and 2010, about 30 % patients only received taxanes containing combination CTx, though currently, taxanes administered sequentially after anthracyclines is the standard practice in our center. We found that TNBC patients who attained pCR following NACT had comparable DFS and OS to non-TNBC patients, while TNBC patients with partial response to NACT had worse survival compared to non-TNBC partial responders. These observations are consistent with other studies [5, 22].

The basal-like breast cancers or TNBC are characterized by the high expression of the proliferation cluster of genes [23] and other conventional indices of proliferation, which is also reflected in our study with higher grade tumors in TNBC group. A prognostic index that is highly influenced by proliferation genes was shown to predict pCR to doxorubicin/taxane-based CTx [24]. The paradox of higher sensitivity to NACT with anthracyclines in subtypes known to have a poor prognosis is explained by the high relapse among those with residual disease. Our study confirms the well-known TNBC paradox of higher response to CTx, resulting in higher pCR rates to NACT, yet poorer outcomes and survival compared to the ER/PR and/or HER2 expressing breast cancers. The worse outcomes in the TNBC patients may be driven by the higher relapse rates among the partial or poor responder TNBC patients, when compared to non-TNBC patients.

On univariate analysis, our results suggested the tumor stage, tumor size, nodal status, histological grade of the tumor, and the TNBC c.w. non-TNBC classification are factors that predict the OS. However, on a multivariate analysis, only the tumor stage at presentation, size, and histological grade were found to important determinants affecting OS; while the age, nodal status, and TNBC c.w. non-TNBC classification were found to be important factors affecting DFS. Other studies have reported varying determinants of the DFS and OS [25, 26], but a distinction between TNBC and non-TNBC subtypes has remained a strong determining factor for both OS and DFS, similar to our finding.

The limitations of a hospital-based retrospective study from a developing country are reflected in our study. Firstly, almost one-third of breast patients treated during the study period had to be excluded because of the lack of complete clinical, pathologic, and follow-up information. Further, this was a study spanning almost a 11-year period wherein patients treated over a 7-year period, with a rather modest duration of follow-up (median 36 months) were included. During this time period, the practices and protocols of breast cancer have evolved. Such changes include a change from anthracyclines containing combination regimen to combination of taxanes with anthracyclines as standard of care CTx for most breast cancer patients in the last few years of our study. As a result, only about a third of our patients received taxanes. Yet, as the CTx regimen used were the same for the TNBC and non-TNBC patient groups, this should not confound our primary findings. Another limitation is that HER2 evaluation by FISH was done only in selected patients with borderline HER2+ results on IHC due to the financial constraints. This might mean that we may have overestimated the TNBC and HER2 negative cases to a small extent.

In conclusion, this retrospective study comparing the TNBC and non-TNBC patients showed the triple-negative subtype (ER−/PR−, HER2−) patients are younger, have similar clinical presentations, poorer histo-pathological features, and worse overall and disease-free survival compared to the ER/PR and/or HER2 expressing subtypes. The survival varies by the stage at presentation, with significant difference in survival between stage III TNBC c.w. non-TNBC patients. The stage III TNBC patients who achieve pCR with NACT have similar survival rates as non-TNBC patients with pCR to NACT, while survival in partial or non-responder stage III TNBC patients is worse compared to partial or non-responder stage III non-TNBC patients. Stage I/II as well as stage IV TNBC patients did not have significantly worse survival compared to same stage non-TNBC patients.

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