

Clinical characteristics of triple negative breast cancer in Egyptian women: a hospital-based experience

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Original Article

Abstract

Purpose: Triple negative breast cancer (TNBC) is an aggressive subtype of breast cancer with poor prognosis despite the high rates of response to chemotherapy. We aim to study the clinical features, factors influencing recurrence and survival outcomes of TNBC patients. **Methods:** We retrospectively studied the charts of patients with biopsy proven TNBC treated at The Clinical Oncology Department Ain-Shams University between 2009 and 2012. **Results:** One hundred and forty five patients fulfilled the eligibility criteria. The incidence of TNBC was 10.5% - 15% with a mean of 12% of all breast cancer patients. The follow-up duration ranged from six months to four years. The age range was 26 to 78 years. Infiltrating ductal carcinoma represented 93.1% of the pathologic types. 87% of patients were free of metastases (M0) at presentation. Clinical stages II and III represented 38 and 39.5% of the patients. 66% of patients had modified radical mastectomy. Following surgery, 77.5% of patients received adjuvant chemotherapy while 61% of the patients had adjuvant radiation therapy. Anthracyclines based chemotherapy was given to 52% of patients. Disease-free survival (DFS) of the M0 patients at 20 and 30 months was 92% and 80% respectively. Relapse occurred in 23% of M0 patients. After a mean duration of DFS of 15.1 months, the most common sites of metastases for relapsed M0 patients were pulmonary (44.8%), bone (41.4%), and locoregional (13.8%). The median overall survival (ORS) of patients was 18 months (1 - 45 months), whereas for the M1 group of patients the median ORS was 9 months (2 - 29 months). **Conclusion:** The incidence, pathological characteristics, and clinical behavior of TNBC were similar to what is mentioned in the literature. Adding taxanes to the chemotherapy protocols and using postoperative radiotherapy were both associated with a significant increase in the mean period of DFS, while did not significantly affect the ORS.

Keywords: Breast cancer, Triple negative, Recurrence, Survival, Hormonal receptors, HER-2.

1. Introduction

Breast Cancer is still the most common malignancy in women worldwide, including Egypt (Cancer registry in Egypt). TNBC (Triple negative breast cancer) is frequently identified by conventional immunohistochemical techniques, as these tumors lack staining for the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor (HER2).¹

The St. Gallen international expert consensus 2011 proposed a new classification system for breast cancer based on its division into five subgroups, namely; normal-like, basal, luminal A&B and HER-2 enriched. A Claudin- low subtype is another described molecular

subtype referring to tumors showing features of mesenchymal and mammary stem cells.² The criteria to identify subtypes were further recently refined at the 2013 conference, in that moderate or a strong expression of PR and Ki - 67 level were both recognized as being important to the surrogate definition of a "Luminal A-like" disease. According to these criteria, the subtypes in question have been defined as: Luminal A - ER positive, HER2 negative, Ki - 67 low, and PR high; Luminal B (HER2 negative) - ER positive, HER2 negative, and either Ki - 67 high or PR low; Luminal B-like (HER2 positive) - ER positive, HER2 over expressed or amplified, any Ki - 67, and any PR; HER2

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positive – HER2 over - expressed or amplified, ER and PR absent; and triple negative – ER and PR absent and HER2 negative.³

TNBC patients have a higher risk of metastases and poor overall survival because TNBC is found to be correlated with mutations of BRCA1 gene, over expression of oncoytogenic kinases such as human epidermal growth factor receptor 2, vascular endothelial growth factor - A, insulin-like growth factor - 1 (IGF - 1) / IGF receptor and transforming growth factor - B1.⁴ These molecular features may have implications for chemotherapy sensitivity to platinum and other directly DNA - damaging agents. Using gene expression analysis, Lehmann *et al* identified six TNBC subtypes namely; basal - like (BL1 & BL20), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem - like (MSL) and a luminal androgen receptor (LAR) subtype.⁵

TNBC is a clinically challenging subtype which accounts for about 9-21% of all breast cancers, including patients with stages, I – IV.⁶ Compared to other types of breast cancer, TNBC is associated with poor prognosis and overall survival.^{1,7,8} TNBC patients tend to be of younger age less than 50 years.^{1,9} TNBC tumors have a shorter median time to relapse and death. TNBC is often locally advanced and of high grade.¹ The patients have increased risk of local recurrence and metastases, mainly in the lung, brain and soft tissue.^{10,11,7,8} TNBC is more chemosensitive, and have higher rates of pathological complete remission following neoadjuvant chemotherapy than in other breast cancer types.⁸ The adjuvant chemotherapy is usually recommended in TNBC and should include anthracyclines, taxanes and an alkylating agent.¹² On the other hand TNBC lacks targeted therapies, and patients do not benefit from anti - estrogen hormonal therapy or trastuzumab.¹

The aim of this retrospective analysis is to study the clinical characteristics, the prognostic factors of recurrence, disease free survival and overall survival in Egyptian TNBC patients treated at the Department of Clinical Oncology, Ain-Shams University.

2. Methods and Materials

We analyzed the institutional medical records, and identified patients who were histopathologically diagnosed with triple negative breast cancer and underwent primary treatment at The Clinical Oncology Department Ain - Shams University between 2009 and 2012. After obtaining approval from the Institutional Review Board at Ain - Shams University Hospitals, a retrospective chart review of patients' demographics, clinical and pathological data was performed. Treatment, follow-up and survival data were obtained from the patients' records. One hundred and forty five patients fulfilled the eligibility criteria which are 18

years or older, immunohistochemistry (IHC) negative expression of ER and PR, and negative HER - 2 neu expression or HER - 2 neu 1+ or 2+ expression on IHC accompanied by a negative fluorescence in situ hybridization (FISH) result.

2.1 Statistical analysis

Data were revised, coded, tabulated and analyzed using the Statistical Software Package for the Social Sciences, for Windows version 18.0 (SPSS / PASW, Inc., 2009, Chicago, IL). Descriptive statistics (mean and standard deviation) were used to evaluate the DFS of the non - metastatic group of patients, and to evaluate the ORS of both metastatic and non-metastatic groups. Chi-square tests were used to assess differences between the DFS and ORS using categorical variables. The overall survival time was calculated in months from the date of diagnosis based on breast biopsy to the date of death or last follow-up. The DFS in months was calculated from the end of the primary treatment until the last date the patient survived without symptoms or signs. Univariate Kaplan - Meier survival curves were plotted, and the log - rank test was used to determine if differences were statistically significant. Statistical significance was defined as alpha less than 0.05.

3. Results

We studied 145 out of the 154 patients diagnosed with TNBC who presented to our department over four - years period where 9 patients had incomplete data in their charts (Table 1). The mean age at diagnosis was 52 years. A positive family history was detected in (7.6%) 11 / 145 of TNBC patients (Table 2).

The most common histopathologic type was infiltrating ductal carcinoma (93.1%) 135 / 145. Most of the tumors were grade II, 73.7% (107 / 145). More than half of the tumors were T2 lesions 52.4% (76 / 145). 96 out of 145 patients had positive lymph nodes (N1, N2, and N3) at diagnosis (66.2%). Majority of patients were diagnosed with stage II and III breast cancer [38% (55 / 145) and 40% (58 / 145) respectively] (Table 3). Most of the patients had modified radical mastectomy (76%) 110 / 145, and the rate of breast conservative surgery was only 11.7% (17 / 145) patients because many patients had stage III cancer (Table 4). Adjuvant chemotherapy was administered in 77.5% (112 / 145) of patients, of whom 25 patients 22.3% (25 / 112) developed recurrence. 14 patients out of 145 (9.7%) received neoadjuvant chemotherapy, with recurrence in 4 patients (28.6%). 89 of 145 patients (61.3%) received adjuvant radiotherapy, followed by recurrence in only 19 / 89 patients (21.3%). Anthracyclines - based regimens were used as adjuvant or neoadjuvant in (52.4%) 76 / 145 of patients.

Table1: Summary of breast cancer registration in Ain-Shams Oncology Department from 2009 to 2012

Year	No. of all cancer patients	No. of breast cancer patients	No. of TNBC patients	% of TNBC of all breast cancer patients
2009	1441	315	47	15 %
2010	1536	333	40	12 %
2011	1563	294	31	10.5 %
2012	1489	324	36	11%
Total	6029	1266	154	12%

Table 2: Patients characteristics (n= 145)

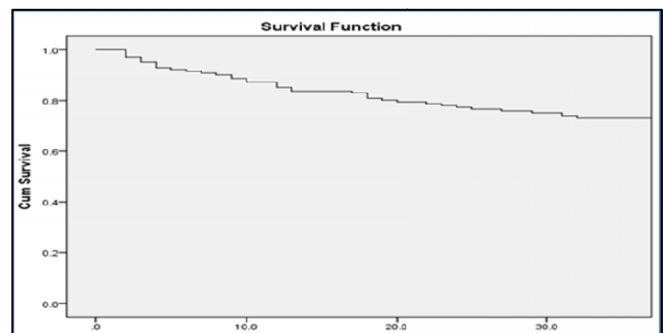
Variable	No. of patients	%
Age at initial diagnosis, years		
Mean	52	
Range	27-78	
Menopausal history		
Premenopausal	70	48.3
Postmenopausal	70	48.3
Perimenopausal	5	3.4
Family History		
Positive	11	7.6
Negative	128	89
Unavailable	6	4

The DFS for the M0 patients (126) at 20 and 30 months was about 92% and 80% respectively (Figure 1). After a mean period of disease - free survival (DFS) of 15.1 months, 29 patients out of 126 (23%) relapsed. The most common sites of relapse were the lung (13 patients, 44.8%), bone (12 patients, 41.4%), and locoregional (4 patients, 13.8%) (Table 8). The overall survival of both M0 and M1 patients at 20 months and 30 months was about 98% and 88% respectively (Figure 2). The median ORS for the M0 group of patients was 18 months (1 - 45 months), whereas for the M1 group of patients the median ORS was 9 months (2 - 29 months) (Table 5).

Except for tumor stage which had direct effect on the recurrence and overall survival ($P < 0.05$), univariate analysis showed that all other risk factors had no statistically significant relationship to either recurrence or overall survival (Tables 6, 7). Patients with stages 0 and I had no recurrence compared to patients with advanced stages. Similarly, the overall survival of patients with early stages was better than with advanced stages as shown in Table (5). The disease stage, the type of chemotherapy and the adjuvant radiation therapy had direct statistically significant effect on the DFS ($P < 0.05$) (Table 6).

Table 3: Tumor characteristics (n=145 patients)

Variable	No of patients	%
Histologic type		
Infiltrating ductal carcinoma	135	93.1
Infiltrating lobular carcinoma	9	6.2
Ductal carcinoma in situ	1	0.7
Histologic grade		
I	4	2.7
II	107	73.7
III	23	16
Unavailable	11	7.6
Tumor size		
Tis	1	0.7
T1	14	9.7
T2	76	52.4
T3	38	26.2
T4	9	6.2
Unavailable	7	4.8
Nodal involvement		
N0	42	29
N1	40	27.5
N2	34	23.5
N3	22	15
Unavailable	7	5
Staging		
Stage 0	1	0.7
Stage 1	9	6.3
Stage 2	55	38
Stage 3	58	40
Stage 4	19	13
Unavailable	3	2
Metastasis at diagnosis		
M0	126	87
M1	19	13

**Figure 1:** Disease Free Survival of M0 triple negative breast cancer patients at Department of Clinical Oncology, Ain Shams University (2009-2012).

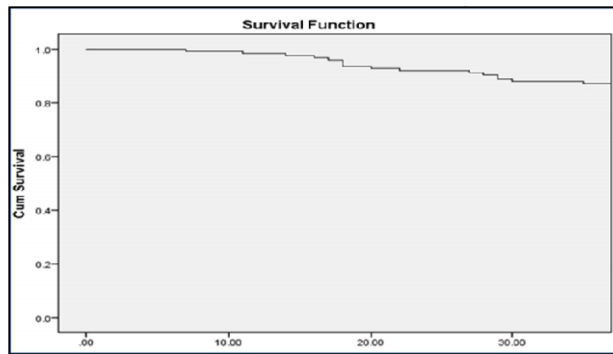


Figure 2: Overall survival of both M1 and M0 triple negative breast cancer patients at Department of Clinical Oncology, Ain Shams University (2009-2012).

Table 4: Treatment of M0 and M1 (n=145)

Variable	No. of patients	%
Surgery		
Modified radical mastectomy	110	76
Conservative	17	11.7
Simple mastectomy	7	4.8
Only biopsy	11	7.5
Chemotherapy		
Adjuvant	112	77.2
Neoadjuvant	14	9.7
Palliative	16	11
Unavailable	3	2.1
The chemotherapy regimen		
Anthracyclines based		
Sequential	76	52.4
Anthracyclines/Taxanes	60	41.4
Other regimens	6	4.1
Unavailable	3	2.1
Radiotherapy		
Adjuvant	89	61.3
Palliative	10	7
Not given	46	31.7

Table 5: Treatment outcome

Variable	No. of patients	%
Disease free survival for M0 patients (n =126)		
No recurrence	97	77
Recurrence	29	23
Progression free survival for M1 patients (n = 19)		
Progression or new metastatic site	7	36.8
No Progression or new metastatic site	12	63.2
Overall survival for M0 (n =126)	115	91.26
Overall survival for M1 (n =19)	13	68.4

4. Discussion

The current study is a retrospective review of 145 patients with TNBC in our institution over a 4-year period (2009 - 2012). It is one of the few studies of TNBC in non - Western countries. In our study, the rate of TNBC was 12%, which is comparable to other studies (9 - 21%) in non - Western countries^{10, 13, 14}, and in Western countries.^{15, 11,6,16} Triple - negative breast tumors have been characterized by several aggressive clinicopathologic features including onset at younger age, higher mean tumor size, higher-grade tumors, and, in some cases, a higher rate of node positivity.^{1,17}

The mean age at diagnosis in this study is 52 years, similar to the mean age at presentation documented by many studies.^{18,19,1,20} Some studies showed different mean ages of TNBC patients 44 - 45 years in Korea and Turkey^{21,22}, and 56 years in Japan.²³

Ghosn *et al*¹⁰ and Fakhoury²⁴ reported a positive family history in 10% of patients with TNBC in Lebanon compared with 1% of patients with breast cancer when all phenotypes are included. In our study, a positive family history was documented in 7% of patients. Similar incidence of less than 10% was found by Rais *et al*.¹³ Higher incidence of positive family history was documented by other studies, both Kwan *et al*, and Fayaz *et al*^{20,25} 20% and 28% in Phipps *et al*.²⁶

The histological characteristics in this current study showed that invasive ductal carcinoma represented 93.3% in accordance with 90% in many studies.²⁷⁻³² Invasive ductal carcinoma was most predominant in Singapore and Japan (93% and 95%, respectively).^{23,33} Invasive lobular carcinoma was interestingly reported in 2% of TNBC patients in Singapore²³, 4% in Kuwait²⁵, 2.3% in Italy³⁴ vs. 6% in our study. This may represent the pleomorphic subtype of lobular carcinoma.³⁵ Triple negative breast cancers are mainly high- grade tumors with high mitotic index and marked cellular proliferation.^{1, 21, 28, 36-38} Most studies reported predominance of high histologic grade that ranged from 55-62%. Contrary in our study, grade II tumors represented 74%, while grade III was 16%.

The aggressiveness of this type of breast cancer and its highly proliferating nature mean that it also tends to be diagnosed at a later stage.^{18,39} Our analysis found that stages 0 - I represented 45% while stages III and IV represented 52.5%. This is comparable to some publications, which reported 34% stage III vs. 15% stage I in a study by Pogoda *et al*⁴⁰, 8% stage I vs. 28% stage III in a study by Rais *et al*.¹³ Fayaz *et al*²⁵ reported 56% of patients with stages, I and II while stage III represented 37 %. Stark *et al*⁴¹, studied a series of 1236 patients with invasive ductal carcinoma, they concluded that women with stages III and IV were 16 times more likely to have triple - negative tumors than those with early stages

[odds ratio (OR) 16.4; 95% confidence interval (CI): 7.8 – 34.2].

Triple - negative breast cancers are commonly of large size at presentation.^{29,36-38,42-45} Tumor size was the most relevant prognostic factor for survival in some studies. In a study by Pogoda *et al*, the hazard ratio of recurrence in patients with a tumor > 5 cm was 16 times higher than in patients with tumor > 2 cm. The authors also found a higher hazard for death in patients with large tumors (HR = 8.21 in tumors > 5 cm).⁴⁰ Similarly, Hamm *et al* reported that the tumor size was the most important prognostic factor.¹⁵ Moreover, tumors < 2 cm with negative nodes were documented to have a high recurrence rate.^{38,45} The current study documented predominance of T2 tumors.

The detection of positive lymph nodes at presentation in TNBC patients is interestingly contradictory in different studies. Dent *et al*¹ found that the rate of node positivity was slightly higher in node positive TNBC compared with other types of breast cancer (54.6% versus 45.6%, respectively; $P = 0.02$). Similar results of positive lymph nodes were reported by Fayaz *et al* and Ghosn *et al* (58 and 50% respectively).^{25,10} Lin *et al* and related studies demonstrated that TNBC was less likely to be lymph node positive (38 and 41%, respectively).^{17,7} A much lower incidence of positive lymph nodes was detected in Japanese patients by Ishikawa *et al*.³³ In the current study, positive lymph node was 66% possibly due to the tendency to late presentation of patients in the social stratum that we treat at our center.

Despite the poor clinical outcome and DFS, the more aggressive clinical course in the metastatic setting, TNBC is sensitive to standard chemotherapy. Chemotherapy is the standard treatment of TNBC in the adjuvant, neoadjuvant, and metastatic settings due to the lack of response to traditional hormonal therapies and targeted therapies.¹ TNBC patients have a higher pathologic complete response (pCR) than non - TNBC, and also better survival compared to TNBC patients who do not achieve pCR.⁸ The pCR rate was 29% in patients who received neoadjuvant anthracyclines based chemotherapy and 38% after anthracyclines and taxanes combined treatment.^{46,47} In another study, two thirds of patients received neoadjuvant anthracycline- taxane chemotherapy and only 15% of them achieved pCR; recurrence occurred in almost half of patients in this group.⁴⁰ Our study, showed that the majority of M0 patients ($n = 126$) received adjuvant chemotherapy (89%) in the form of anthracyclines based regimens (52.3%). There was insignificant difference between patients who received adjuvant vs. neoadjuvant chemotherapy as regards the recurrence status (DFS was 15.48 months and 11.75 months respectively) and as regards the overall survival, (ORS was 91.07% and 92.86%, respectively). Similarly the type of

chemotherapy, whether combined anthracyclines and taxanes or taxanes alone in M0 patients ($n = 126$) did not significantly affect both the DFS (76.67% and 77.27% respectively) and the ORS (95% and 87.88% respectively).

Triple negative breast cancers have been associated with lower disease - free survival, a higher predisposition to visceral metastases and poorer outcome when compared to other subtypes of breast cancer.^{18, 148,49} Women with triple negative breast cancer typically tend to develop recurrence during the first 3 years after therapy with a rapid decline thereafter; and the majority of deaths occur in the first 5 years post treatment. Patients with non - TNBC have more consistent rates of recurrence.^{1,8} In both studies by Ghosn *et al*, and Haffty *et al*^{10,50}, the peak of recurrence occurred after 6 - 18 months. Fayaz *et al*²⁵ reported the peak of recurrence at 30 months. We observed the same phenomenon where after a mean period of DFS of 15.1 months, 29 out of 126 metastases - free patients developed recurrence. The lung was the most common site of metastases followed by bone and locoregional recurrence (Table 8). The ORS for the non - metastatic group at presentation of patients was 87% (11 / 126), whereas for the metastatic group of patients M1 the ORS was 31.6% (6 / 19). The Mayo Clinic Study reported an overall survival at 5 years after surgery of 85% vs. 87% in the present study. In Kaplan *et al*.⁶ study, the 5 - year disease - free survival and ORS in TNBC patients were 84% and 81% respectively. The variable results between studies may be dependent on the difference in staging of breast cancer, in the present study majority of patients were stage II and III, whereas in Kaplan's study about 80% of patients presented with stages, I and II.

To date, not a single targeted therapy has been approved for the treatment of TNBC, and cytotoxic chemotherapy remains the standard treatment.⁵¹ Novel candidate compounds for TNBC have entered phase II and phase III trials and will likely require patient stratification before therapy. Examples of these tailored approaches include poly (adenosine diphosphate - ribose) polymerase (PARP) inhibitors for BRCA - mutated TNBC, antiandrogens for androgen receptor (AR) - positive TNBC, fibroblast growth factor receptor (FGFR) inhibitors for TNBC harboring FGFR amplifications, and gamma - secretase inhibitors for TNBC with mutations in the PEST domain of NOTCH proteins. Well - designed clinical trials of molecularly targeted therapy for different subgroups of TNBC are necessary.⁵²

Table 6: Factors influencing recurrence and mean duration of DFS for M0 disease (n=126)

Variable	Recurrence	No recurrence	Total number	P value	Mean duration of DFS \pm SD	P value
Stage						
0	0	1	1			
I	0 (0%)	9	9			
II	6 (11%)	49	55			0.002
III	22 (38%)	36	58			
Chemotherapy Type						
Anthracyclines/taxanes	14 (23.3%)	46	60	0.9 (NS)	19.3 \pm 11.7	0.031
Anthracyclines	15 (22.7%)	51	66			
Radiotherapy						
Adjuvant	19 (21.4%)	70	89	0.5 (NS)	18 \pm 10.4	0.027
No adjuvant	10 (27%)	27	37			

SD: standard deviation

Table 7: Factors influencing overall survival (ORS) of M1 and M0 patients (n=145)

	Alive	Dead	OS %	P value
Stage				
0	1	0	100	
I	9	0	100	
II	52	3	95	0.03
III	50	8	86.2	
IV	13	6	68.4	

Table 8: Pattern of recurrence in M0 patients (n = 29/126)

Site	Number	%
Lung	13	44.8
Bone	12	41.4
Locoregional	4	13.8

PARP enzymes are critical to cell recovery from DNA damage. When PARP1, the most abundant member of the PARP family, is inhibited, double - strand DNA breaks accumulate and under normal conditions are repaired via the BRCA pathway-dependent homologous recombination mechanism.⁵³ The efficacy and safety of PARP inhibitors are tested in clinical trials in both BRCA - mutated and triple negative breast cancers because of the shared clinicopathologic characteristics.^{54 -56} In a single arm study olaparib (400 mg orally twice daily) was administered to women with BRCA1 and / or BRCA2 - deficient, advanced breast cancer (of which > 50 percent were triple - negative). Olaparib resulted in an overall response rate of 41 percent and PFS of 5.7 months. The drug was generally well tolerated with the most commonly reported grade 3 adverse events being fatigue, nausea, and vomiting.^{54,57} On the other hand, another study showed that olaparib had no activity in

breast cancer outside of patients with known germline BRCA mutations, although epithelial ovarian cancer appears to respond similarly regardless of germline status.⁵⁸

The role of cetuximab; an anti - EGFR monoclonal antibody in patients with metastatic TNBC was studied⁵⁹ by comparing cetuximab plus cisplatin versus cisplatin alone. The authors demonstrated an overall better response rate of 20% when compared to a 10% overall better response rate with cisplatin alone. Cisplatin plus cetuximab also resulted in longer progression free survival (PFS) compared with cisplatin alone (median, 3.7 vs. 1.5 months) with a corresponding median OS of 12.9 versus 9.4 months. Common grade 3 / 4 adverse events included acne - like rash, neutropenia, and fatigue. Despite the longer PFS and OS, the trial failed to reach its primary endpoint, which is the overall response rate compared to the single regimen. Additionally cetuximab induced diarrhea was a concern when added to chemotherapy as carboplatin and irinotecan despite an increased overall response rate in the TNBC subset of O'Shaughnessy's phase II trial.⁶⁰ The potential efficacy of anti - EGFR strategies needs further investigation with more trials.

5. Conclusion

This study documents the clinical experience of TNBC at our institution. The results of the study accord with the literature data of characteristics of TNBC in terms of young age at presentation, high - grade tumors, late stages at diagnosis, and short disease - free survival. We acknowledge the limitations of this study inherent to most retrospective studies, the relatively small sample

size, and the lack of BRCA gene mutations' studies due to the limited financial resources. However, our results are unique to Egypt, are one of the very few studies of TNBC in the Middle East, and represent a single - institution approach to patient care.

Tumor stage, chemotherapy type and adjuvant radiation therapy statistically influenced the recurrence and the duration of disease - free survival. In addition, the tumor stage statistically influenced the overall survival of both the metastatic and non - metastatic TNBC in our study.

Unfortunately, TNBC as an aggressive subtype of breast cancer has limited treatment options when it does not respond to or progresses after the standard and /or taxanes based regimens. More research should be directed at identifying molecules and pathways that may be effective targets for new drugs.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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