Triple-Negative Breast Cancer: Clinical Characteristics, Prognostic Features, and Long-Term Outcome: a Comparative Study

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Abstract

Introduction: Because of the reported poor prognosis and absence of effective and specific therapeutic approaches, triple-negative breast cancer (TNBC) tumors have remained as an important area of investigations for clinicians and researchers. The aim of this study was to determine the clinical, pathological, histological, prognostic features, and outcome associated with this type of breast cancer in Iran. We also tried to identify main determinants of long-term survival in women suffered from TNBC tumor type.

Methods: This is a historical cohort study of 546 consecutive female breast cancer patients with known status of gene receptors and diagnosed at the Rasoul-e-Akram University Hospital of Iran between January 2009 and June 2011. Baseline data were collected from patient records and hospital charts. Long-term outcome was determined from clinic records when available or by means of written correspondence with patients' physicians and telephone interviews directly with the patients or with family members. Follow-up data were collected by our research personnel for a mean follow-up duration 5.7 years.

Results: A total of 86 of 546 final included participants with breast cancer were identified as having TNBC (15.8%).The patients with TNBC diagnosis were significantly younger than non-TNBC group and family history of breast cancer was more prevalent in former group. Regarding histopathological feature, medullary feature was more prevalent in TNBC group, while other features were similarly revealed in both groups. With respect to tumor grading, TNBC group was graded higher than non-TNBC group that grade III of tumor was reported in 51.1% of the TNBC patients, but in 15.9% of another group. Also, the stage of tumor was significantly higher in the TNBC group. Tumor size > 50 mm was observed in 18.6% of the TNBC and 14.8% of non-TNBC groups. Metastasis to liver as well as concurrent metastasis to brain and pulmonary was more prevalent in TNBC compared with another group. The Kaplan-Meier curves based showed the survival probability at 1-year, 3-year, and 5-year of follow-up in TNBC group was 95.2%, 86.1%, and 76.4%, respectively. This survival rates in non-TNBC group was 97.7%, 87.2%, and 75.6%, respectively. Multivariable logistic regression analysis showed that TNBC diagnosis could strongly predict long-term mortality in breast cancer patients. Besides, tumor size, number of involved lymph nodes and higher tumor grade were other determinants of cancer-related long-term mortality.

Conclusion: The present study on Iranian TNBCs population shows that TNBCs account for about 15.8% of all invasive breast cancers, and they usually have a high histological stating and metastasis susceptibility.

Keyword: Triple-Negative Breast Cancer, Prognosis, HER2 gene, Estrogen receptors, Progestron receptors

Introduction

Breast cancer is the most frequent malignancy among women whole of the world and the second most common cause of cancer-related death, especially in middle age women.(1) Breast tumors are usually classified on their histological type, morphological features, and its severity based on tumor grading. In this context, identifying tumor molecular and cellular markers including the estrogen receptor (ER), progesterone receptors (PR), and the human epidermal growth factor receptor 2 (HER2) has offered additional value for differentiating and classifying breast cancers as well as predicting their prognosis and outcome.(2-5)

According to the absence of these biomarkers, triple-negative breast cancer (TNBC) has been recently described as a subtype of breast cancer that lacks expression of the ER, and PR markers as well as does not over-express HER2 protein. This type of tumors accounts for about 15% of breast cancers that is frequently diagnosed in younger and premenopausal women.(6-12) This type of breast cancers are biologically aggressive and is usually associated with increased risk for visceral metastases such as lung, liver and, notably, brain metastasis, early replace, and shorter post-recurrence survival.(13,14) Because of the reported poor prognosis and absence of effective and specific therapeutic approaches, TNBC tumors have remained as an important area of investigations for clinicians and researchers.

Although breast cancer is one of the most frequent malignancies among Iranian women, the epidemiological aspects, histopathological features, and long-term outcome of breast cancer especially TNBC type are already uncertain in our country.(15,16) The aim of this study was to determine the clinicopathological, histological, prognostic features, and outcome associated with this type of breast cancer in Iran. We also tried to identify main determinants of long-term survival in women suffered from TNBC tumor type.

Methods

This is a historical cohort study of 700 consecutive female breast cancer patients diagnosed at the Rasoul-e-Akram University Hospital of Iran between January 2009 and June 2011. Baseline data were collected from patient records and hospital charts. Data were primarily collected on the presence of estrogen receptor, progesterone receptor, and human endothelial growth factor receptor 2 (Her2) and the participants were categorized as “triple-negative breast cancer” (TNBC) and non-TNBC. Those with unknown status of noted gene receptors were not included into the study and thus 546 consecutive female breast cancer patients with known status of gene receptors were included. Triple-negative breast cancer was defined as estrogen receptor/progesterone receptor <10% and HER2 1+ or 2+ (with negative fluorescence in situ hybridization) on immunohistochemistry.(17) Also, data on clinical variables identified through a literature review as potential important predictors of mortality and poor outcome in study patients were collected. These included patient and tumor characteristics present at the time of original breast cancer diagnosis, such as age, types of tumors (Invasive ductal, Invasive lobular, Medullary, or Mucinous), tumor-node-metastasis (TNM) stage, grade, histopathological features of tumors including lymphovascular invasion, tumor size, history of ovary cancer or family history of breast cancer, involvement of opposite breast, lymph node metastasis, and details on surgical therapy administered. Institutional research ethics board approval was obtained before study initiation.

Long-term outcome was determined from clinic records when available or by means of written correspondence with patients' physicians and telephone interviews directly with the patients or with family members. Follow-up data were collected by our trained research personnel by telephone interviewing and related data involved follow-up on long-term survival in both study groups. The mean follow-up duration was 5.7 years. Descriptive statistics were reported as mean ± SD for continuous variables and as absolute frequencies and percentages for categorical variables. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than 5 were observed. Quantitative variables were compared using t test. Multivariate logistic regression analysis was used to compare between-group differences in long-term mortality and determine its main determinants. Survival rate was determined by using the Kaplan-Meier method. For the statistical analysis, the statistical software SPSS version 19.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

Results

A total of 86 of 546 final included participants with breast cancer were identified as having TNBC (15.8%).Totally, 64.5% of the patients were positive estrogen receptor, 68.3% were positive progesterone receptor, and 46.5% were positive HER2 receptor. The patients with TNBC diagnosis were significantly younger than non-TNBC group and family history of breast cancer was more prevalent in former group (Table- 1). Regarding histopathological feature, medullary feature was more prevalent in TNBC group, while other features were similarly revealed in both groups. With respect to tumor grading, TNBC group was graded higher than non-TNBC group that grade III of tumor was reported in 51.1% of the TNBC patients, but in 15.9% of another group. Also, the

stage of tumor was significantly higher in the TNBC group.

Lymph node involvement in TNBC group was more prevalent compared with non-TNBC patients (82.6% versus 67.4%) and the mean number of involved lymph nodes was 4.08 and 3.64, respectively. Tumor size > 50 mm was observed in 18.6% of the TNBC and 14.8% of non-TNBC groups.

With respect to metastasis location (Table- 2), metastasis to liver as well as concurrent metastasis to brain and pulmonary were more prevalent in TNBC compared with another group.

The Kaplan-Meier curves based showed the survival probability at 1-year, 3-year, and 5-year of follow-up in TNBC group was 95.2%, 86.1%, and 76.4%, respectively. This survival rates in non-TNBC group was 97.7%, 87.2%, and 75.6%, respectively (Figure- 1).

Multivariable logistic regression analysis showed that TNBC diagnosis could strongly predict long-term mortality in breast cancer patients. Besides, tumor size, number of involved lymph nodes and higher tumor grade were other determinants of cancer-related long-term mortality (Table- 3).

Discussion

Despite different epidemiological surveys have reported different aspects of TNBCs regarding its determinants and outcome, no published study is available in clinical, epidemiological, and prognosis of Iranian women suffered from TNBC. In this context, the current study has some imports findings. First, the overall range of TNBCs among all type of breast cancers estimates as 15.8% that is in its world range that contribute approximately 10% to 20% of all newly diagnosed breast cancer.(18- 22)

The mean age of our TNBC patients was 42 years lower than non-TNBC ones. Similarly, previous studies showed that the mean age at diagnosis for women with TNBC tends to be younger than those with non-TNBC tumors. Bauer and colleagues,(22) reported that compared with women with non-TNBC, the odds of a woman with TNBC being under the age of 40 years was 1.53. Our another important finding was that the long-term survival of TNBC group was slightly lower than non-TNBC group and regardless of the type of diagnosis, this low survival rate was influenced by some baseline risk factors including tumor grade, tumor size, and extension lymph node involvement. In a Canadian study involving a large population by Dent and colleagues,(23) women with TNBC had an increased risk of death with hazard ratio of 3.2 and distant recurrence with hazard ratio of 2.6 compared with women with non-TNBC. Furthermore, Cheang and colleagues(18) showed that it is probably the proportion of women with 'basal-like' tumors within the TNBC group that drives the negative prognostic impact.

Moreover, Anderson and colleagues(24) reported that the main criteria of poor prognosis were hormone receptor negative, tumor size >2 cm, lymph node positive and high grade.

Review of different studies showed the main risk factors of TNBCs include age at diagnosis <50 years, African American ethnicity, high body mass index, young age at menarche, high parity, young age at time of first birth, lack of breast feeding, and some biological features such as high Ki67, and presence of p53 mutations,(20- 24) on the other hand, the pointed risk factors and death indicators for TNBC may differ from those usually associated with other types of breast cancer.

For instance and based on reviewing literatures, in contrast with the risk of the more common low-grade, the risk of TNBCs rises with increasing parity and an increasing ratio of waist-to-hip circumference,(25, 26) however with did not demonstrate the role of these factors in our study.

Thus, there appears to be a complex interplay of genetic and societal factors that put women at increased risk for TNBCs.

In summary, the present study on Iranian TNBCs population shows that TNBCs account for about 15.8% of all invasive breast cancers, and they usually have a high histological stating and high metastasis susceptibility.

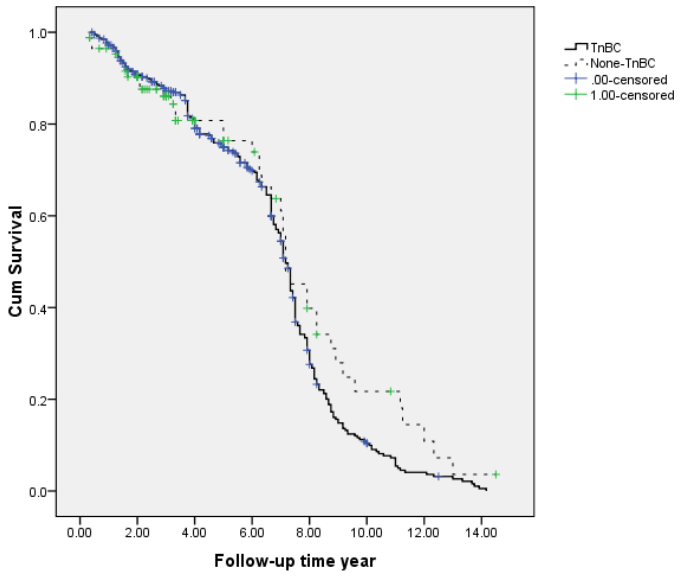

Figure- 1. The Kaplan-Meier curves based showed the survival probability at 1-year, 3-year, and 5-year of follow-up in TNBC group.

Table- 1. Baseline demographic and histopathological data of TNBC and non-TNBC groups.

Characteristics	Total (n = 546)	TNBC group (n = 86)	Non-TNBC group (n = 460)	P-value
Age (year)	46.83 ± 11.08	42.42 ± 10.61	47.80 ± 10.65	< 0.001
Number of parity				0.009
Nuliparity	508 (93.4)	73 (86.9)	435 (94.6)	
Multiparity	36 (6.6)	11 (13.1)	25 (5.4)	
Involvement of opposite breast	18 (3.3)	3 (3.5)	15 (3.3)	0.906
History of ovary cancer	6 (1.1)	0 (0.0)	6 (1.3)	0.597
Family history of breast cancer	45 (8.2)	12 (14.0)	33 (7.2)	0.036
Histopathological feature				
Invasive ductal	492 (90.1)	77 (89.5)	415 (90.2)	0.965
Invasive lobular	32 (5.9)	2 (2.3)	30 (6.5)	0.146
Medullary	15 (2.7)	6 (7.0)	9 (2.0)	0.024
Mucinous	4 (0.7)	0 (0.0)	4 (0.9)	0.387
Others	3 (0.5)	1 (1.2)	2 (0.4)	0.406
Tumor grading				< 0.001
I	45 (8.3)	4 (4.7)	41 (9.0)	
II	382 (70.2)	38 (44.2)	344 (75.1)	
III	117 (21.5)	44 (51.1)	73 (15.9)	
	4.66 ± 2.20	5.10 ± 2.53	4.59 ± 2.14	
Tumor staging				0.008
1	48 (8.8)	4 (4.7)	44 (9.6)	
2A	150 (27.6)	22 (25.6)	128 (28.0)	
2B	115 (21.2)	23 (26.7)	92 (20.1)	
3A	134 (24.7)	15 (17.4)	119 (26.0)	
3B	15 (2.8)	3 (3.5)	12 (2.6)	
3C	46 (8.5)	5 (5.8)	41 (9.0)	
4	35 (6.4)	14 (16.3)	21 (4.6)	
Number of involved lymph node	3.71 ± 4.15	4.08 ± 3.29	3.64 ± 4.32	0.285
Metastasis status				0.143
0 – 5 years	150 (81.1)	39 (88.6)	111 (78.7)	
> 5 years	35 (18.9)	5 (11.4)	30 (21.3)	
Tumor size				0.315
≤ 20 mm	113 (20.7)	13 (15.1)	100 (21.7)	
21 to 50 mm	349 (63.9)	57 (66.3)	292 (63.5)	
> 50 mm	84 (15.4)	16 (18.6)	68 (14.8)	

Table- 2. Metastasis location in TNBC and non-TNBC groups

Characteristics	Total (n = 546)	TNBC group (n = 86)	Non-TNBC group (n = 460)	P-value
Brain	13 (7.3)	1 (2.3)	12 (8.9)	0.428
Pulmonary	46 (25.7)	12 (27.3)	34 (25.2)	0.070
Liver	20 (11.2)	7 (15.9)	13 (9.6)	0.023
Bone	23 (12.8)	3 (6.8)	20 (14.8)	0.726
Brain and pulmonary	12 (6.7)	7 (15.9)	5 (3.7)	< 0.001
Brain and liver	2 (1.1)	0 (0.0)	2 (1.5)	0.541
Brain and bone	7 (3.9)	1 (2.3)	6 (4.4)	0.916
Pulmonary and liver	25 (14.0)	6 (13.6)	19 (14.1)	0.273
Pulmonary and bone	19 (10.6)	4 (9.1)	15 (11.1)	0.535
Liver and bone	12 (6.7)	3 (6.8)	9 (6.7)	0.387

Table-3. Main determinants of long-term mortality in a multivariable regression model

Characteristics	Multivariable p-value	Odds ratio	95% Confidence Interval
TNBC versus non-TNBC	0.001	2.272	1.442 – 4.494
Age	0.330	0.990	0.970 – 1.010
Number of parity	0.165	0.518	0.205 – 1.311
Involvement of opposite breast	0.394	0.591	0.176 – 1.985
Family history of breast cancer	0.927	1.038	0.469 – 2.297
Histopathological feature	0.144	0.704	0.439 – 1.128
Tumor grading	0.009	1.795	1.161 – 2.774
Tumor size	0.003	1.016	1.005 – 1.027
Number of involved lymph node	< 0.001	1.136	1.078 – 1.198

Hosmer – Lemeshow goodness of fit: $\chi^2 = 6.217$, $p = 0.623$

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