

# Triple Negative Breast Cancer in Iranian Women: Clinical Profile and Survival Study

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## Abstract

**Background:** Triple negative breast cancer (TNBC) is characterized by negative result of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) in immunohistochemical (IHC) staining and an interesting topic of research today. Various studies have been reported in western countries on TNBC, all insisted of the poorer prognostic of TNBC than other subtypes of breast cancer. However extensive data from Iran is lacking.

**Objectives:** The aim of this study was to analyze the clinical, pathological profile and survival of TNBC patients at our institute.

**Methods:** Medical records of 1910 breast cancer patients in the Shahid Beheshti University of Medical Sciences cancer research center database with data on 180 patients of TNBC patients was collected between September 2002 and December 2014 and reviewed for clinicopathological profile and survival analysis.

**Results:** The median age at diagnosis was 48 years. Fourteen patients (7.8 %) had stage I, 88 patients (48.9%) had stage II, 57 (31.7 %) had stage III, 8 (4.4%) patients had stage IV at first diagnosis and 13 patients (7.2%) with unknown stage. The median follow-up time was 41 months. 149 patients were without any with recurrences at the last follow up and 31 patients were with recurrence. Median interval for recurrence development was 39 months. Five years disease free survival (DFS) was 71%. Overall survival (OS) at 5 years for all patients was 56%. According to univariate cox regression 5-year DFS analysis, unfavorable prognostic factors in our study were as follows: grade III of tumor, positive LVI, presence of lymph node positive, stage II and stage III at diagnosis. According to multivariate cox regression 5-year OS analysis unfavorable prognostic factors were as follows: age: 40, grade III versus grade I of tumor, stage III at diagnosis versus Stage I, and visceral recurrence.

**Conclusions:** We observed that most clinical and pathological TNBC characteristics in Iranian patients are consistent with others findings in literature, such as younger age at diagnosis, high grade tumors, advanced stage at diagnosis, and short time of 5-year DFS and 5-year OS. Longer follow-up of these patients is required for more mature data on these cancers.

**Keywords:** Triple Negative, Breast Cancer, Survival

## 1. Background

Breast cancer is the most frequent diagnosed solid cancer and the second leading cause of cancer death in the world and Iran among females. It comprises 25% of all cancer new cases (1). There are 9,795 new cases annually in Iran based on the cancer registry system with 24.8% distribution, it is among the most prevalent cancer types in women (2).

Breast cancer is a heterogeneous disease clinically and is affected by a variety of risk factors such as tumor size, lymph node involvement, estrogen, progesterone and human epidermal growth factor receptor 2 (HER2) receptors, prognostic factors that have important roles in recurrence, metastasis and breast cancer patients' death (3).

Triple negative breast cancers (TNBCs) are negative for estrogen receptor (ER), progesterone receptor (PR) and HER-2 that can be diagnosed in the lab by immunohistochemistry (IHC) (4).

They constitute 12% - 24% of breast cancers; in addition, they have been found to be more common in younger women and are more aggressive cancers with shorter relapse free survival (RFS), a tendency to visceral rather than bone metastases as an easily recognizable prognostic group of breast cancer with aggressive behavior that commonly lack the benefit of any specific targeted therapy. Various studies have been reported in western countries on TNBC, all insisted on the poorer prognostic of TNBC than other subtypes of breast cancer (5-7).

To date, studies on Iranian women patients with TNBC have been limited by small sample sizes and short follow-up duration.

## 2. Objectives

In the current study, we aimed to determine retrospectively the incidence, clinicopathological profile and sur-

vival of TNBC patients and to find the factors effective in recurrence in breast cancer patients and compared them with patients without recurrence, and prognostic factors effective in the patients' death at Shahid Beheshti University of Medical Sciences, cancer research center, Iran.

### 3. Methods

Shahid Beheshti University of Medical Sciences, cancer research center database was used to identify patients with triple negative breast cancer between September, 2002 and December, 2014. Medical records of 1910 patients with data on 180 patients of TNBC was collected and reviewed for clinicopathological profile and survival study.

We excluded from the study patients who had not follow up after initial diagnosis. Breast cancer diagnosis was made by biopsy or surgery of the breast tumor.

Breast cancer patient information such as age at diagnosis (in years), marital status, number of pregnancies, familial history of breast cancer in first or second degree, education, tumor type, tumor grade, lymphovascular invasion (LVI), lymph node positive or negative, pathologic tumor size in centimeters, TNM staging, type of surgery (breast conserving surgery or modified radical mastectomy), chemotherapy, radiation therapy and type of hormone therapy, follow up duration, location of recurrence (if present), and overall survival was recorded.

Immunohistochemical (IHC) analysis to determine estrogen (ER) and progesterone receptor (PR) status was performed using standard procedures on paraffin embedded tissue specimens stained. Over expression of HER2 status was determined positive if HER2 was 3+ by IHC and negative if HER2 score of 0 or 1. Confirmation by Fluorescence in-situ hybridisation (FISH) was carried out for all those with receptor status 2+.

Once all the treatments were over, the breast cancer patients were examined every three to six months for five years and annually afterwards. In case of clinical suspicion or detection of any symptoms, patients would have undergone tests to identify recurrence; Patients were followed up until April, 2015. Disease free survival (DFS) was determined as the time interval among diagnosis, and recurrence. Overall survival (OS) was defined as the time interval among diagnosis, and death.

The ethical regulations dictated in the act provided by Shahid Beheshti University of Medical Sciences, cancer research center were strictly observed and they approved the retrospective review of the medical records for the purposes of our study (ethical code: IR.SBMU.MSP.REC.1396.221).

The data acquired from the patients was analyzed by SPSS version 19. The effects of variables on recurrence and

death, and then their effects on recurrence were evaluated by univariate and multivariate cox regression model analysis. OS and DFS rates were estimated by Kaplan-Meier analysis.

### 4. Results

The Her2 status overexpression and gene amplification was performed in one thousand and nine hundred teen breast cancer patients treated in the Shahid Beheshti University of Medical Sciences, cancer research center between September, 2002 and December, 2014. A total of one hundred and eighty patients with breast cancer were identified as having triple-negative breast cancer (9.4%). The median age at diagnosis ( $\pm$  standard deviation) was 48 years (range 23 - 85 years). Teen patients (5.5%) had a family history of breast cancer in their first degree relatives and eighteen patients (10%) had a family history of breast cancer in their second degree relatives. Thirty-one patients (17.2%) had college education.

One hundred and sixty-nine patients (93.9%) had infiltrating ductal carcinoma, seven patients (3.9%) had infiltrating lobular carcinoma and four patients (2.2%) had mixed ductal and lobular carcinomas. 104 cases (57.8%) were grade III, 58 patients (32.2%) were grade II and only eighteen (10%) were grade I. Lymph vascular invasion was found in 104 patients (58%). For the lymph node involvement: 93 patients (51.7%) had pathologic positive lymph nodes.

According to TNM staging, 14 patients (7.8%) had stage I, 88 patients (48.9%) had stage II, 57 (31.7%) had stage III, 8(4.4%) patients had stage IV at first diagnosis and 13 patients (7.2%) with unknown stage. Among the metastatic patient group, three had bone metastases only, 3 had bone and lung metastases and 2 patients had brain metastases. [Table 1](#) summarizes baseline characteristics and the clinical-pathological features of 180 adult patients with triple negative breast cancer.

After breast cancer diagnosis, surgical treatment was done in all patients. 110 patients (61.1%) underwent breast conserving surgery and seventy patients (38.9%) underwent modified radical mastectomy. Neo adjuvant chemotherapy was administered to 14 patients and 166 patients received adjuvant chemotherapy. Five patients did not received adjuvant radiotherapy, 131 patients received adjuvant radiotherapy, and 44 patients with unknown situation. Hormonal therapy with Tamoxifen was done in 30 patients (16.6%) and with Letrozole in four patients despite hormone receptor negative patients.

The median follow-up time was 41 months (range 4.2 - 208 months). 149 patients were without any recurrences at the last follow up and 31 patients were with recurrence.

**Table 1.** Baseline Characteristics and the Clinical-Pathological Features of 180 Adult Patients with Triple Negative Breast Cancer

Characteristics	Value (%)
<b>Gender</b>	
Male	0 (0)
Female	180 (100)
<b>Median age at diagnosis</b>	
48 years	
<b>Age (years)</b>	
40	43 (23.9)
> 40	123 (68.3)
Unknown	14 (7.7)
<b>Family history of breast carcinoma</b>	
Yes	28 (15)
No	152 (75)
<b>Hsiotological type</b>	
Invasive ductal carcinomas	169 (93.9)
Invasive lobular carcinomas	7 (3.9)
Others types	4 (2.2)
<b>Tumor size</b>	
2 cm	15 (8.3)
2 - 5 cm	95 (52.8)
> 5 cm	30 (16.7)
Unknown	40 (22.2)
<b>Grade</b>	
I	18 (10)
II	58 (32.2)
III	104 (57.8)
<b>Lymphovascular invasion</b>	
Positive	78 (43.3)
Negative	72 (40)
Unknown	30 (16.7)
<b>Lyrnphe nodes</b>	
Positive	93 (51.7)
Negative	74 (41.1)
Unknown	13 (7.2)
<b>Stage</b>	
Stage I	14 (7.8)
Stage II	88 (48.9)
Stage III	57 (31.7)
Stage IV	8 (4.4)
<b>Total patients</b>	13 (7.2)

**Table 2.** Treatment Modalities, Recurrence Sites and Outcomes of 180 Patients with Triple Negative Breast Cancer

Characteristics	Value (%)
<b>Surgery</b>	
Radical mastectomy	70 (38.9)
Conservative surgery	110 (61.1)
<b>Chemotherapy</b>	
Neoadjuvant chemotherapy	14 (7.8)
Adjuvant chemotherapy	166 (92.2)
Without chemotherapy	0 (0)
<b>Total recurrence</b>	31 (17.3)
<b>Recurrence site</b>	
Bone	7 (3.9)
Lung	8 (4.4)
Liver	9 (5)
Brain	4 (2.2)
Local recurrence(breast, soft tissue or chest wall)	9 (5)
Unknown	2 (1.1)
<b>Disease free survival at 5 years</b>	71%
<b>Overall survival at 5 years</b>	
Stage I	92.3%
Stage II	86.5%
Stage III	57.8%
Stage IV	9%
<b>Total patients</b>	180 (100)

Among 31 patients with recurrence, nine patients (35.5%) experienced local relapse and nineteen patients (64.5%) had metastatic relapse. The most prevalent distant metastasis was seen in liver 47.3% of distant metastasis and 29% of recurrence patients.

Median interval for recurrence development or DFS was 39 months (range: 2 - 125 months, standard deviation = 32). Five years disease free survival (DFS) was 71%. Overall survival at 5 years for patients with stage I, stage II, stage III and stage IV were 92.3%, 86.5%, 57.8% and 9% respectively. Overall survival at 5 years for all patients was 56%. [Table 2](#) shows treatment modalities, recurrence sites and outcomes of 180 patients with triple negative breast cancer.

According to univariate cox regression 5-year DFS analysis, five factors had a statistically significant relationship with the 5-year DFS. These five factors, determined by univariate analysis ([Table 3](#)) are listed here: 1) grade III versus grade I of tumor ( $P = 0.0001$ ), hazard ratio (HR) = 3.10, 95% CI = 1.71 - 5.59, 2) Positive LVI versus negative LVI ( $P = 0.0001$ ,

HR = 3.33, 95% CI = 2.43 - 4.56), 3) Presence of lymph node positive versus lymph node negative ( $P = 0.0001$ , HR = 2.80, 95% CI = 2.02 - 3.87), 4) stage II at diagnosis versus stage I ( $P = 0.04$ , HR = 1.94, 95% CI = 1.01 - 3.70) and 5), and stage III at diagnosis versus stage I ( $P = 0.0001$ , HR = 5.01, 95% CI = 2.64 - 9.49). Then the unfavorable prognostic factors in our study based on univariate analysis were as follows: grade III of tumor, positive LVI, presence of lymph node positive, stage II at diagnosis and stage III at diagnosis (Table 3). Based on the univariate analysis, there were no statistically significant relationships between 5-year DFS and age 40 years versus age > 40, family history of breast carcinoma, grade II versus grade I of tumor at diagnosis and breast conserving surgery versus modified radical mastectomy (Table 3).

The multivariate analysis indicated that three factors had a statistically significant relationship with 5-year DFS i.e.: 1) age: 40 years versus age > 40 ( $P = 0.0001$ , HR = 0.94, 95% CI = 0.03 - 0.25), 2) positive LVI versus negative LVI ( $P = 0.03$ , HR = 1.95, 95% CI = 1.05 - 2.40), and 3) stage III at diagnosis versus stage I ( $P = 0.04$ , HR = 3.16, 95% CI = 0.98 - 10.20).

Then the unfavorable prognostic factors in our study, based on multivariate analysis, were as follows: age: 40, the presence of positive LVI, and stage III at diagnosis versus stage I. Based on the multivariate analysis, there were no statistically significant relationships between 5-year DFS and family history of breast carcinoma, grade II versus grade I of tumor at diagnosis, grade III versus grade I of tumor, presence of lymph node positive versus lymph node negative, stage II at diagnosis versus stage I, and breast conserving surgery versus modified radical mastectomy (Table 3).

Five factors were statistically significant relation between 5-year OS and age 40 years versus age > 40 ( $P = 0.04$ , HR = 0.17, 95% CI = 0.03 - 0.94), grade III versus grade I of tumor ( $P = 0.0001$ , HR = 5.97, 95% CI = 2.52 - 8.42), stage III at diagnosis versus stage I ( $P = 0.04$ , HR = 3.21, 95% CI = 1.03 - 10.25), visceral recurrence versus Locoregional recurrence ( $P = 0.001$ , HR = 8.05, 95% CI = 2.29 - 28.25) and bone recurrence versus Locoregional recurrence ( $P = 0.03$ , HR = 4.43, 95% CI = 1.15 - 17.04) by multivariate analysis (Table 4).

Then the unfavorable prognostic factors were studied in multivariate analysis using by Cox regression model, age 40, grade III versus grade I of tumor, stage III at diagnosis versus stage I, visceral recurrence and bone recurrence. Based on the multivariate analysis, there were no statistically significant relationships between 5-year OS and family history of breast carcinoma, grade II versus grade I of tumor at diagnosis, positive LVI versus negative LVI, presence of lymph node positive versus lymph node negative, stage II at diagnosis versus stage I and breast conserving surgery versus modified radical mastectomy (Table 4).

## 5. Discussion

Our study conducted at cancer research center, Shahid Beheshti University of Medical Sciences, analyzed the demographics, clinical, pathological, epidemiological and therapeutic characteristics of TNBC patients. There is not any report that has evaluated these factors in the Iranian population with TNBC subtype. The current study represents a large retrospective review of 180 patients with a diagnosis of TNBC in cancer research center, Shahid Beheshti University of Medical Sciences and is to our knowledge the largest series in Iran.

Of 1910 breast cancer patients, diagnosed with available IHC data, one hundred and eighty patients with breast cancer were identified as having triple-negative breast cancer (9.4%). In the western countries, approximately 15% - 20% of breast cancers are TNBC. However, some studies have suggested that its prevalence differs between countries and races (8).

Dent et al. reported that cancer patients with TNBC have younger age at diagnosis with a mean age of 53 years old, compared to 58 year old for other subgroups (9). But until now, there has not been any definitive conclusion whether age is a main risk factor of TNBC. In our study, the median age at diagnosis (48 years) was younger than the average age mostly reported in the US (10, 11), but may be comparable to the median age in African-American triple negative breast cancer patients (12). Additionally, forty three (23.4%) patients were 40 years old suggesting that there may be factors that may predispose them to development TNBC.

Our study showed 15% of breast cancer patients had familial history of breast cancer. Unfortunately, the research of a BRCA1/2 gene mutation was not performed due to its expensive genetic tests in Iran. Gonzalez-Angulo et al. showed a 19.5% incidence of BRCA mutations in TNBC patients especially in breast cancer patients who had familial history of breast cancer (13). In our study, there were no statistically significant relationships between 5-year OS and 5-year DFS and Family history of breast carcinoma.

Pathologically, TNBC breast cancer patients have primary large tumors (66% of them have tumor size > 2 cm) and a high rate of axillary node positivity (48%) (5). Similarly, in our series, 69.5% of patients had tumor size > 2 cm and 51.7% had axillary node positivity. They are associated with a higher histological grade and more frequent ductal histology (7). Similarly, in our series, TNBCs were characterized by high grade in 90% of patients and ductal histology in 93.9% of patients.

TNBC breast cancer patients were more frequently diagnosed at advanced stage. Consequently only 23% of TNBC breast cancer patients received breast conservative

**Table 3.** Five-Year, Disease-Free Survival Rate According to Univariate and Multivariate Cox Regression Analysis of Prognostic Factors of 180 Adult Patients with triple Negative Breast Cancer

Factor	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age > 40	0.82 (0.46 - 1.46)	0.55	0.94 (0.03 - 0.25)	0.0001
Family history of breast carcinoma	1.13 (0.81 - 1.57)	0.45	0.79 (0.50 - 1.22)	0.29
Grade II / Grade I	1.40 (0.77 - 2.54)	0.27	0.89 (0.38 - 2.06)	0.78
Grade III / Grade I	3.10 (1.71 - 5.59)	0.0001	1.47 (0.62 - 3.50)	0.39
LVI invasion positive / negative	3.33 (2.43 - 4.56)	0.0001	1.95 (1.05 - 2.40)	0.03
Lymph nodes positive / negative	2.80 (2.02 - 3.87)	0.0001	1.15 (0.62 - 2.16)	0.64
Stage II / Stage I	1.94 (1.01 - 3.70)	0.04	1.88 (0.72 - 4.90)	0.20
Stage III / Stage I	5.01 (2.64 - 9.49)	0.0001	3.16 (0.98 - 10.20)	0.04
Breast conserving surgery / modified radical mastectomy	1.84 (0.91 - 3.60)	0.10	1.78 (0.62 - 4.80)	0.20

Abbreviations: CI, confidence interval; HR, hazard ratio.

surgery and 77% of them received modified radical mastectomy (14). Despite our study that 61.1% TNBC breast cancer patients received breast conservative surgery and 38.9% of them received modified radical mastectomy.

Haftty et al. found that there was no evidence that TNBC patients are at higher risk of local recurrence after breast conservative surgery and radiation versus patients who received modified radical mastectomy (15). The findings of their study were consistent with our findings that showed TNBC patients were not at higher risk of local relapse after breast conservative surgery and radiation in univariate analyses and multivariate analyses.

Our study was a retrospective study analyzing 180 breast cancer patients from 1910 women suffering from TNBC breast cancer in Iran. Based on the univariate analysis, effective factors in 5-year DFS were grade III of tumor, positive LVI, presence of lymph node positive, stage II and stage III at diagnosis.

Multivariate analysis showed unfavorable prognostic factors in 5-year DFS were as follows: age 40, the presence of positive LVI, and stage III at diagnosis versus stage I. We also found that the most effective factor in recurrence in 5 years was stage of disease which is in line with the findings of some other studies (16, 17).

Multivariate analysis showed factors affecting death in patients with TNBC were factors such as age:  $\geq 40$ , grade III of tumor compared to those with grade I, stage III of tumors than those with stage I and recurrence site, had a significant role. Risk of death in visceral recurrence was more than loco regional recurrence and in patients with bone recurrence, it was more than loco regional recurrence but less than visceral metastasis.

Bone metastasis is the most common type of distant

recurrence in breast cancer patients (18). The findings of their study were inconsistent with our findings that showed the most common type of distant metastasis is the liver.

In the present study, 17.08% (31 patients) were involved with any recurrences with 22 patients (12.2%) with distant metastasis and 5% (9 patients) involved with loco regional recurrence. The most common type of distant metastasis is seen in the liver (40.9% of total distant metastasis).

Patients with bone metastasis generally have longer survival time as compared with the patients with other organ distant metastasis (19). The findings of their study were consistent with our findings that showed 5-year OS was longer in patients with bone metastasis than patients with visceral metastasis.

Our study was limited by two major limitations. First, lack of a comparative study of TNBC breast cancer patients with other subtypes of breast cancer patients. Second, inability to evaluate BRCA gene mutation due to the low socioeconomic level of these patients in our institution.

### 5.1. Conclusion

In conclusion our results suggested that incidence of TNBC in Iranian women is half lower than incidence of TNBC in western country women. Most clinical and pathological TNBC characteristics in Iranian patients are consistent with others findings in literature, such as younger age at diagnosis, high grade tumors, advanced stage at diagnosis, and short time of 5-year DFS and 5-year OS.

According to the findings of this study, a better understanding of invasive tumor features in breast cancer patients together with the risk factors in individual patients can lead to individual treatments not general guidelines.

**Table 4.** Five-Year Overall Survival Rate According to Multivariate Cox Regression Analysis of Prognostic Factors of 180 Adult Patients with Triple Negative Breast Cancer

Factor	Multivariate Analysis	
	HR (95% CI)	P Value
Age > 40	0.17 (0.03 - 0.94)	0.04
Family history of breast carcinoma	0.82 (0.53 - 1.25)	0.31
Grade II / Grade I	0.91 (0.41 - 2.10)	0.82
Grade III / Grade I	5.97 (2.52 - 8.42)	0.0001
LVI invasion positive / negative	0.48 (0.17 - 1.34)	0.16
Lymph nodes positive / negative	3.44 (0.90 - 13.00)	0.07
Stage II / Stage I	4.80 (0.12 - 19.13)	0.40
Stage III / Stage I	3.21 (1.03 - 10.25)	0.04
Breast conserving surgery / modified radical mastectomy	4.69 (0.05 - 18.03)	0.40
Visceral recurrence / Locoregional recurrence	8.05 (2.29 - 28.25)	0.001
Bone recurrence / Locoregional recurrence	4.43 (1.15 - 17.04)	0.03

Abbreviations: HR, hazard ratio; CI, confidence interval.

Future research can be conducted to study more patients with recurrence as well as treatment types.

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## Footnotes

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