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Multivariate analyses of triple-negative breast cancer compare with non-triple-negative breast cancer: A multicenter retrospective study

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Abstract

Breast cancer is a heterogeneous disease of multiple subtypes with distinct morphologies and clinical implications. Triple negative breast cancer is associated with aggressive behavior and high risk of local and regional failure. The purpose of this study is to compare outcome of breast cancer for triple negative versus non-triple negative breast cancer.

Population-based retrospective analysis was performed using the Surveillance, Epidemiology, and End Results (SEER) database. Female patients who had breast cancer from 2015 to 2021 were included in two centers and excluded patients' files with incomplete data. Patients were divided into two group, triple negative breast cancer (TNBC) and non-TNBC. Clinical outcome, stages, types of treatment and its adverse events were compared. Also, and overall survival was calculated. A total of 105 patients with TNBC and 566 with non-TNBC were included in this retrospective study. The multivariate analysis showed that the tumor size and nodal involvement were independent predictors of negative events. While age at presentation, family history, grade had significant difference (p=0.005). Moreover, the number of locoregional failures, 5-year locoregional recurrence free, and mortalities were not significantly different (p=0.2).

In conclusions: Our findings showed that the outcome of triple negative has worse survival than patients with non-TNBC and non-triple negative breast cancers and more aggressive at late stage.

Keywords: Breast cancer; Triple negative breast cancer; Non-triple-negative breast cancer

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Introduction

Breast cancer is a heterogeneous disease of multiple subtypes with distinct morphologies and clinical implications, and it is the one of the most frequently diagnosed cancers among women Worldwide [1]. The progress in the therapy including surgery, radiation therapy, hormonal therapy, chemotherapy, and targeted therapy has greatly improved the survival of patients with BC [2]. However, approximately 15-20% of BCs belong to the triple-negative BC (TNBC), which is defined by the absent expression of estrogen receptor (ER) and progesterone receptor (PR)

and the lack pf amplification/overexpression of the human epidermal growth factor 2 receptor (HER2) [3].

Currently, HER2 status is routinely assessed in all patients with breast cancer, by immunohistochemistry (IHC) and/or in situ hybridization (ISH). According to the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) 2018 recommendations [2], tumors are HER2-positive (HER2+) when HER2 overexpression is observed by IHC (score 3+, strong expression), or when ERBB2 gene amplification is detected by fluorescence in situ hybridization (FISH) [4]. Tumors with a score of 0 and 1+ (weak expression) are HER2-negative, and tumors with a score of 2+ (moderate expression) need to be assessed by FISH for confirmation. HER2 1+ and HER2 2+ tumors with negative FISH are now classified as HER2-low tumors (~45–55% of breast cancers) [5]. In TNBC, HER2 levels can vary from absent (score of 0) to moderate expression without ERBB2 gene amplification (score of 2+ ISH−) [6].

The efficacy of anti-HER2 agents in HER2-low tumors has not been demonstrated yet [7], and this breast cancer subgroup is thought to have a poorer prognosis compared with HER2 0 tumors, based on retrospective studies [8]. However, the published evidence shows conflicting results from one clinical setting to another one and depending on hormone receptor status [9]. New anti-HER2 antibody–drug conjugates (ADC), which combine an anti-HER2 antibody and a cytotoxic agent, seem to be effective in some HER2-low tumors; for instance, trastuzumab deruxtecan, a new anti-HER2 ADC that combines trastuzumab and a topoisomerase 1 inhibitor, showed promising results in heavily pretreated patients with metastatic HER2-low breast cancer (HER 1+/2+) [10].

However, the biology of breast cancers expressing low HER2 levels remains poorly investigated, especially in the TNBC group. The term “triple-positive” breast cancer was first introduced by Vici et al. [11] to describe a distinctive subtype. It is defined as a luminal HER2 tumor that expresses both the ER and PR. This type of tumor also expresses high HER2 levels and exhibits a biologically distinct phenotype and specific clinical behavior [12].

In current clinical settings, systemic therapeutic approaches for triple-positive breast cancer comprise hormone receptor (HR)-specific hormonal therapies, HER2-directed therapy, and systemic chemotherapy; these may include other therapeutic approaches and may be applied in all cases, except in patients with early-stage breast cancer who have good prognostic factors [13]. Previous clinical data of patients with HER2-positive breast cancer have demonstrated better prognostic outcomes with HR-positive than HR-negative disease [14].

Additionally, previous clinical and experimental data have revealed that HER2-directed therapy is less effective for HR-positive/HER2-positive breast cancer but may prolong survival. This outcome may be supported by the finding that crosstalk between the ER and HER2 pathways plays a role in resistance to endocrine therapy [15].

Despite these earlier findings, previous clinical data obtained from patients with HER2-positive breast cancer have been limited owing to their focus on HR positivity [16]. Previous results

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suggest that only a subset of HR-positive/HER2-positive breast cancers do not undergo significant reduction due to HER2-directed therapy [17]. Therefore, a more detailed analysis is needed to identify the distinct characteristics of triple-positive breast cancer.

The objective of this study is to investigate the clinical outcomes of triple-positive breast cancer versus triple-negative breast cancer.

Methods and patients

A population-based retrospective analysis was performed using the Surveillance, Epidemiology, and End Results (SEER) database. Patients included in the analysis were divided into 2 groups according to hormonal status.

A total of 105 patients with TNBC and 566 with non-TNBC were included in this retrospective study. Female patients who had breast cancer from 2015 to 2021 were included in two centers and excluded patients' files with incomplete data. Patients were divided into two group, triple negative breast cancer (TNBC) and non-TNBC.

Clinical outcome, stages, types of treatment and its adverse events were compared. Also, and overall survival was calculated. The multivariate analysis showed that the tumor size and nodal involvement were independent predictors of negative events. While age at presentation, family history, grade had significant difference (p=0.005). Moreover, the number of locoregional failures, 5-year locoregional recurrence free, and mortalities were not significantly different (p=0.2).

Neoadjuvant chemotherapy was used in patients with locally advanced and node positive tumors. Adjuvant chemotherapy was used in patients with pathologically staged T2 tumors or above, positive nodes and poor differentiation. Hormonal therapy was used in estrogen and progesterone receptor positive tumors. Receptor status was confirmed using Immunohistochemical staining (IHC) and equivocal Her2/neu (2+) results were subjected to Florescent in Situ Hybridization (FISH). Staining of 1% or above on IHC was considered positive for estrogen and progesterone receptors. Patients were followed 3 monthly for 1 year, 6 monthly for 2 years and yearly thereafter with regular bilateral mammograms. Patients in the current study were divided into 2 groups.

Tumors that were Estrogen receptor (ER), Progesterone receptor (PR) and Her2neu negative were grouped as Triple negative breast cancer (TNBC). If anyone, two or three receptors were positive; patients were considered as non-TNBC. Patient characteristics including age at presentation, family history and clinicopathological variables were assessed. Actual number of observed adverse events was compared between two groups. Adverse events included locoregional failures, distant failures and. Local failure was defined as a recurrence in operated breast. Regional failure was defined as recurrence in ipsilateral axillary, supraclavicular or internal mammary lymph nodes. Any other site of recurrence was defined as distant metastasis.

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Overall Survival (OS) was calculated by determining time duration between death of patient irrespective of cause or date of last follow up from date of surgery.

Statistical analysis

Chi square test or Fishers exact test was used for patient characteristics, medical treatments, and adverse events. Tumor size was grouped as early (T1/T2) and advanced (T3/T4) for statistical analysis. Kaplan Meier curves were used to calculate expected 5-year LRRFS, DFS and OS and Log rank test was used to determine significant differences between TNBC and Non-TNBC groups. Cox proportional hazard regression model was used for univariate and multivariate analysis. Variables that were found significant on univariate analysis were included in multivariate analysis and 95% confidence intervals and hazard ratios were calculated. A P value 0.05was considered significant for all analysis. SPSS version 20 was used for statistical analysis.

Results

Patient and Tumor Characteristics

We obtained breast cancer individuals' data from the SEER database that were released in from 2015 to 2021. These data include demographic, clinicopathological, and survival information. Our work followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines. The cohort included 105 patients with TNBC and 566 with non-TNBC. Patients diagnosed with HER2 status unknown, ER status unknown or borderline, PR status unknown or borderline were excluded.

Table 1 lists their main clinicopathological characteristics that were consistent with classical TNBC features. The patients' median age was 57.7 years (range: 28.5–98.6 years). Ductal carcinoma was the most common histological type (81.9%), 75.3% of the patients received adjuvant chemotherapy, and the remaining 24.7% received adjuvant radiation therapy if clinically indicated. None of the included patients received hormonal therapy, targeted therapy, or an investigational product.

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Table 1
Patient and tumor characteristics.

Variables	N = 671	
Age (years), median [min–max]	52.9	
Tumor size		
T1	310	46
T2	200	29.8
T3/T4	161	23.9
Nodal status		
N−	301	44.8
N+	365	54.3
Histological grade (missing = 6)		
1–2	106	15.7
3	565	84.3
Histology (missing = 3)		
Ductal	558	83.1
Lobular	69	10.2
Other	44	6.5
Adjuvant chemotherapy (missing = 1)		
No	111	16.5
Yes	560	83.5
HER2		
0	105	15.6
1+	44	6.6
2+	522	77.8

N−: Node negative, N+: Node positive

HER2 Expression and Pathological Associations

Among the 566 TNBC samples, 44 (6.6%) were classified as HER2 1+, and 522 (77.8%) as HER2 2+. Based on the HER2 expression level distribution, correlation analyses were performed by classifying tumors into two groups (HER2 0 vs. HER2 1+/2+).

HER2 1+/2+ tumors were significantly more frequent in older patients and displayed a lower histological grade and a molecular apocrine phenotype more frequently compared with HER2 0 tumors (Table 2).

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Table 2
Univariate correlations between TNBC features and HER2 expression level by IHC.

Variables	HER2 = 0		HER2 = 1+/2+		*p*-Value
	N	%	N	%	
Age (years), median [min–max]					
<55	106	41.1	18	33.3	0.05
≥55	112	43.2	38	61.4	
Tumor size					
T1	119	47.6	24	43.7	
T2	112	49.1	29	54.1	0.4
T3/T4	13	5.3	3	7.2	
Node status					
N−	177	53.3	41	69.6	0.6
N+	81	40.7	18	37.4	
Histological grade					
1–2	49	19.2	19	38.7	0.003
3	200	91.8	36	67.8	
Basal-like phenotype					
No	96	41.1	24	43.7	0.42
Yes	166	71.9	29	61.6	

N−: Node negative, N+: Node positive

Survival outcomes of patients with triple-positive

The results of univariate analysis Kaplan–Meier survival curves of triple-negative breast cancer (TNBC) versus non-TNBC in figure 1. The RFS of patients with triple-positive, luminal A, and HER2-enriched breast cancer was calculated using CMC data. During a mean follow-up period of 35.88±21.90 months, patients with the triple-positive subtype showed intermediate RFS between those of patients with luminal A and HER2-enriched subtypes. Although patients with triple-positive breast cancer had significantly better RFS outcomes than those with the HER2-enriched subtype (generalized Wilcoxon test, p=0.025), we observed no significant difference between patients with the triple-positive and luminal A subtypes (generalized Wilcoxon test, p=0.315).

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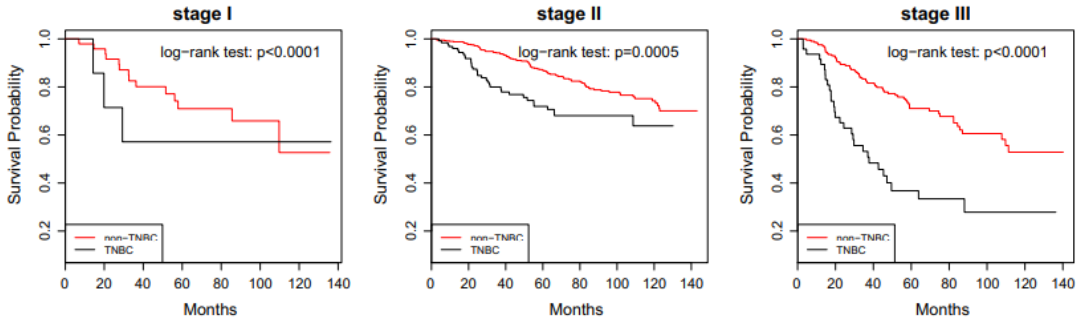

Figure 2.

Kaplan–Meier survival curves of triple-negative breast cancer (TNBC) versus non-TNBC

Discussion

The current consensus is that adjuvant and neoadjuvant anti-HER2 therapies are effective for patients with HER2-positive breast cancer, irrespective of the HR status [17-23]. Therefore, the National Comprehensive Cancer Network Guidelines, Version 1.2017 [24], state that endocrine therapy is recommended as an initial treatment for patients with HR-positive/HER2-positive breast cancer whereas adjuvant chemotherapy with trastuzumab is strongly recommended for patients with tumors of >1 cm in size or node-positive disease.

Additionally, the European School of Oncology-the European Society for Medical Oncology second international consensus guidelines [25] suggest that for patients with ER-positive/HER2-positive advanced breast cancer for whom endocrine therapy is selected over chemotherapy, the addition of anti-HER2 therapy should be considered when initiating endocrine therapy [26-30]. Nonetheless, the paradigm of chemotherapy plus anti-HER2 therapy remains the mainstay of treatment for advanced HER2-positive breast cancer, regardless of the HR status.

Recent evidence, however, suggests an inverse correlation between the HER2 positive status and HR-positive status, which consequently reduces the efficacies of both hormonal and anti-HER2 therapies [31-34]. These results demonstrate the low efficacy of anti-HER2 therapy for HR-positive/HER2-enriched breast cancer.

A growing body of data suggests that because of the role of BRCA1 in DNA damage response and cell cycle checkpoint control, TNBCs associated with BRCA1 mutations, such as the high-grade serous ovarian cancers associated with this mutation, may display greater sensitivity to platinum-based chemotherapy regimens [35-37]. The androgen receptor is another area of interest. There are some early data to suggest that positive expression of the androgen receptor in TNBC may represent a distinct subgroup of TNBCs, which might respond to androgen receptor blockade [38]. The recently identified claudinlow subtype, including metaplastic carcinoma, shows breast cancer stem cell signatures and may be resistant to conventional chemotherapies [39].

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Finally, high levels of tumor-infiltrating lymphocytes (TILs) have been shown to be both predictive of improved response to neoadjuvant chemotherapy and prognostic for improved survival in TNBC [40]. TNBC with prominent TILs may be more responsive to immunotherapy. A more detailed staging system may be needed as our understanding of the various subtypes of TNBC grows. Lehmann et al. identified 6 defined subtypes of TNBC and an unstable subtype based on different gene expression profiles [41]. These different subtypes may respond differently to therapies and have different prognoses [42-44]. We have targeted therapies for non-TNBC breast cancers that improve their prognosis.

There is still much research that needs to be done in TNBC in order to refine the multiple subtypes of this disease entity and to better understand which subtypes are likely to respond best to specific treatments. We need to continue to better understand the so-called ‘‘TNBCs’’ to find their specific targets and improve their treatment and prognosis.

Conclusion

In the current study, we found that patients with TNBC had significantly worse disease cause-specific survival and overall survival times compared to patients with non TNBC breast cancers even when adjusted for patient age, race, tumor grade, and surgery and radiation treatments.

Study limitation

The present study had many limitations. The limitation was the SEER-based retrospective nature of the study. The other limitation, data on potential prognostic parameters, such as the Eastern Cooperative Oncology Group performance status score, other tumor metastatic sites, detailed systemic therapy strategies, and the intrinsic subtypes of triple-positive breast cancer, were not included in the SEER database. Furthermore, datasets did not incorporate chemotherapy information.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

Both shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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