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Clinicopathologic features and prognosis of triple-negative breast cancer in patients 40 years of age and younger in Saudi Arabia

Omalkhair Abulkhair,[a] Jeelan S. Moghraby,[b] Motasim Badri,[b] Abdulmohsen Alkushi[c]

From the [a]Department of Oncology, [b]King Saud bin Abdulaziz University for Health Sciences, University Pre-Professional Programme, and [c]Department of Pathology and Lab Medicine, King Abdulaziz Medical City, National Guard Health Affairs, Riyadh, Saudi Arabia

Correspondence: Abdulmohsen Alkushi, MD · Department of Pathology and Lab Medicine, King Abdulaziz Medical City, National Guard Health Affairs, P.O. Box 22490, MC 1122, Riyadh 11426, Saudi Arabia · T: +966-507702912, F: +966-1-2520000 ext. 47235 · aalkushi@hotmail.com

BACKGROUND AND OBJECTIVES: Triple-negative breast cancer (TNBC) has a poor prognosis and overall survival (OS) compared to other types of breast cancer tumors. However, there is to date no evidence that this is also the case in Saudi Arabia.

DESIGN AND SETTING: Retrospective review of breast cancer patients who were treated from January 2001 to December 2008 (517 patients) at the King AbdulAziz Medical City, Riyadh, Saudi Arabia.

PATIENTS AND METHODS: Patients were selected as TNBC if all three markers of estrogen receptor (ER), progesterone receptor (PR) and the human epidermal growth factor (HER2) tested by immunohistochemistry as negative. They were then age- and stage-matched, and compared with non-TNBC patients to examine differences, if any, in their clinicopathologic features, prognosis and OS.

RESULTS: Twenty-six patients with a follow up time of at least three years were identified as TNBC. Thirty-three patients who were age- and stage-matched were selected as the non-TNBC controls. Clinicopathologic results illustrated significantly more grade 3 tumors (P=.02) and CK 5/6 expression (P<.001) in the TNBC group compared to the non-TNBC group. TNBC patients aged ≤40 years showed a significantly worse prognosis and OS compared to TNBC patients aged >40 years (P=.01), and when compared to the non-TNBC group (P=.04).

CONCLUSION: The incidence of TNBC in our cohort is similar to what has been illustrated in previous studies in Western population. There was no significant difference in 3-year survival between TNBC and non-TNBC groups. However, the aggressiveness of this type of tumor and OS is significantly higher in younger patients aged ≤40 years, compared to those over 40 years of age.

Breast cancer remains a clinically challenging disease, both from the therapeutic and observational points of view. It is still the most common malignancy in women and is increasing in incidence worldwide, including in Saudi Arabia.[1-3] However, the mortality rate has seen a dramatic decline over the years mainly due to development of targeted therapy as well as improvement of early breast cancer detection.[4-8] Despite this, a significant subgroup of patients derive little benefit from treatment. This subpopulation reflects the fact that breast cancers are a heterogeneous group of tumors characterized by a wide spectrum of clinical, pathological and molecular features.[9-11] This variation of factors accounts for differences in response to therapy and outcomes among women diagnosed with breast cancers.[12-14]

Gene expression profiling and immunohistochemical expression have shown that breast cancer can be classified into biologically distinct subtypes.[9,11,15] Triple-negative breast cancer (TNBC) has drawn particular attention since it lacks targeted therapies and patients do not benefit from anti-estrogen hormonal therapy or trastuzumab.[16] Some groups have shown limited response of TNBC patients with non-adjuvant therapy.[17] More recent studies have shown that TNBC patients, that are also node-negative, have a greater benefit with chemotherapy than with no chemotherapy at all.[18] As these studies only show benefit for a small subset of patients, TNBC still remains a clinical challenge.

TNBC is an aggressive subtype that accounts for 10% to 15% of all breast cancer cases.[19] It 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).[20] Moreover, triple-negative (TN) tumors are often positive for cytokeratin (CK) 5/6, are typically high grade, and have a higher risk of relapse within the first several years after initial diagnosis.[21-23] Aside from the established pathologic variables mentioned above, tumor size and p53 status also have specific prognostic value in TNBC. Positive staining for p53, for example, results in poor survival expectancy for these patients.[21,24] The immunohistochemical surrogates of TN tumors, the absence of ER, PR and HER2 and positivity for CK 5/6 and p53, are important breast cancer specific markers that have been commonly used to identify the TNBC.[22,24,25] This approach is applicable to standard pathology specimens and has sensitivity of 76%, and specificity up to 100%.[26] In addition, TNBC are associated with poor prognosis, younger patient age,[27] poor relapse,[11,16,28] poor Nottingham prognostic index, a high incidence of recurrence and metastasis,[29-31] poor overall survival and poor overall outcome[32-35] compared to other types of breast cancer. Furthermore, a higher percentage of visceral metastases, local relapse and cerebral metastasis occur in TNBC.[29-31,36]

The clinicopathologic features and prognostic factors of TNBC have been thoroughly studied in the Western population. However, few studies have been conducted among the non-Western ethnic groups.[37-40] We therefore decided to investigate whether the same factors are applicable to Saudi TNBC patients. Hence this present retrospective analysis was undertaken to firstly compare the clinicopathologic features and prognosis of TNBC patients versus the non-TNBC patients diagnosed in King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia, as a single institution experience. Secondly, we examined outcome differences, if any, within the TNBC and non-TNBC groups, using 40 years as a cut-off age.

PATIENTS AND METHODS

A retrospective analysis was conducted of the clinicopathologic features of TNBC patients undergoing surgery at KAMC (a single institution), Riyadh, Saudi Arabia. Data was first collected on all female patients with breast cancer diagnosed at the hospital between January 2001 and December 2008. Five hundred and seventeen pathologically proven breast cancer patients were identified with data available on tumor grade and stage, level of ER, PR and HER2 expression, patient age at diagnosis, ethnicity, site of tumor, risk factors, present-ing symptoms, clinical findings on presentation, radiological findings, and the method of treatment. Before surgery, all patients were evaluated through standard staging procedures which included complete physical examination, chest radiography as well as CT chest scan, bilateral mammography, ultrasound of the breasts, abdominal ultrasound and routine blood work. After complete staging workup, patients were treated according to standard treatment protocol after discussion of the tumor board. Follow-up information regarding tumor recurrence and survival status, including reason for death, was accomplished through the retrieval of medical records.

Data was collected from a total of 517 breast cancer patients who underwent a complete staging workup prior to final management at our institution. Patients were then categorized based on their immunohistochemical staining results for expression of the three markers ER, PR, and HER2. All patients selected had complete examination and treatment data, with a follow-up of at least three years.

The TNBC group consisted of 26 patients that tested negative for ER, PR and HER2 expression, and therefore were deemed TN. This group was further categorized into two sub-groups, those aged >40 years and those ≤40 years, to compare prognosis with age. The non-TNBC group consisted of 33 cases selected from the total breast cancer cases that were age- and stage-matched to the TNBC group, and whose immunohistochemical staining were positive for at least one of the three markers. This group was classed as the control group.

Slides for the TNBC and non-TNBC study population tumors were retrieved and reviewed again by one pathologist to collect pathological features. Tumors were regraded according to the Scarff-Bloom-Richardson grading system, and the tumor histological types and features were assessed. Immunohistochemically stained slides for ER, PR, and HER2 of the study tumors were reviewed and re-assessed to confirm the original diagnosis of either TNBC or non-TNBC. In those cases that lacked stained slides in the pathology files, serial 4 μm sections from selected paraffin blocks of the study tumors were cut and stained for ER, PR, HER2, p53 and CK 5/6 on an automated system (Ventana, Tucson, AZ, USA), as per the manufacturer's instructions. Primary antibody suppliers and dilutions for the immunohistochemical analysis were as follows: ER (Labvision, clone SP1, dilution 1:200), PR (Labvision, clone SP2, dilution 1:400), HER2 (Ventana, clone 4B5, dilution 1:200), p53 (Dako, clone DO-7, dilution 1:400), CK 5/6 (Dako, clone DS-16B4, dilution 1:100). Immunohistochemical scoring of ER, PR and HER2 followed the ASCO/CAP guidelines (www.asco.org/guidelines/erpr).

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The differences in pathological features, immune-marker expressions, histopathological, immunohistochemical and clinical features in the two study groups were compared using the chi-square statistics or the Fisher exact test. Overall survival (OS) between the TNBC and non-TNBC groups was calculated from the date of diagnosis of breast cancer to date of death from any cause or last follow up. The Kaplan-Meier and the log-rank test methods were used to construct and compare survival curves. Cox hazard regression models were fitted to determine factors associated with mortality. All tests were two-sided and a P-value <.05 was considered significant. SPSS (version 19) was used for data analysis.

RESULTS

Data for 517 breast cancer patients were found that were treated at KAMC and 62 patients from this cohort (12%) were identified as having TNBC, where their immunohistochemical staining tested negative for the ER, PR and HER2 markers. From these, 26 patients of Saudi origin were selected as the TNBC group since follow-up data was also available 2 years after diagnosis (mean time between diagnosis and follow up was 36 months). For the control non-TNBC group, a total of 33 patients were chosen based on age and tumor stage matching to the TNBC group, and who tested positive for at least one of the markers. This cohort therefore included 59 patients in total; 26 TNBC patients and 33 non-TNBC patients. The mean age of the total sample was 44.4 years (standard deviation 12.3, median age 42 years) and ranged from 24-84 years, and 45.8% of the sample was ≤40 years of age. The P value of the mean age between the TNBC and non-TNBC groups was not significant (45.8 and 43.2, respectively, P=.426).

When available, data was also collected for p53 over-expression and CK 5/6 expression for each group of patients. As expected, a larger proportion of TNBC patients showed p53 over-expression than the non-TNBC patients (**Table 1**), though this was not statistically significant (P=.23). In particular, statistically more CK 5/6 expression was seen in the TNBC compared to the control group (P<.0001), showing a clear difference in expression patterns between the two groups. Consistent with TNBC tumors having a more aggressive morphology, patients with TNBC had a a higher grade of tumor: 87.3% of all TNBC tumors were of grade 3, compared with 56% in non-TNBC tumors (P=.02, **Table 1**). Despite this difference in tumor morphology, there was no statistically significant difference in overall survival between the two groups.

The hazard ratio was then calculated to examine the relative risk between those TNBC patients aged ≤40

Table 1. Baseline characteristics and mortality in patients with triple-negative breast cancer (TNBC, n=26) compared with control non-triple-negative breast cancer (non-TNBC, n=33) patients.

Variable	TNBC	Non-TNBC	*P*
Age			
≤40 years	10 (38.5)	17 (51.5)	.32
>40 years	16 (61.5)	16 (48.5)	
Grade 3 tumor			
Yes	21 (87.3)	14 (56.0)	.02
No	3 (12.5)	11 (44.0)	
P53 over expression			
Yes	11 (52.4)	6 (33.3)	.23
No	10 (47.6)	12 (66.7)	
CK5/6 expression			
Yes	15 (62.5)	3 (12.0)	<.0001
No	9 (37.5)	22 (88.0)	
Died			
Yes	11 (42.3)	11 (33.3)	.48
No	15 (57.7)	22 (66.70)	

Values are number (percent). P by χ^2 test.

years against those of >40 years (**Table 2**). Patients with TNBC aged ≤40 years had a significantly higher hazard ratio of death compared with those above this age (P=.001). In addition, survival in this younger subgroup was significantly lower compared to TNBC aged >40 years (**Figure 1**). Similarly, when compared to the control-TNBC group, the TNBC aged ≤40 years also showed a lower rate of survival (P=.04, data not shown). No other factors such as tumor grade or CK5/6 expression, were associated with the hazard ratio between these two age groups (**Table 2**).

DISCUSSION

Breast cancers are known to be heterogeneous, and are characterized by a wide spectrum of clinical, pathological, and molecular characteristics that comprise a number of recognized biological subtypes.[9] TN account for 10% to 20% of breast carcinomas. The terms TNBC and basal-like breast cancer (BBC) are often used interchangeably by clinicians although they are not identical. Importantly, not all BBCs are TNBCs; TNBCs constitutes approximately 85% of all BBCs.[9-12] Thus, whereas most TNBCs are basal-like, TN and BBC are not synonymous.[41] Studies have shown that women

Table 2. Cox-regression hazard regression analysis for factors associated with death in triple-negative breast cancer patients (TNBC).

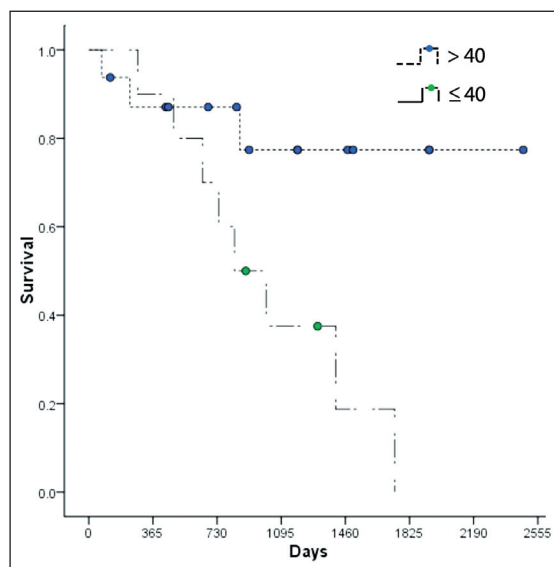| Characteristics	Hazard Ratio (95% CI)	P
Patient groups		
TNBC	1.49 (0.64-3.44)	.36
Non-TNBC	1	
Age		
≤ 40 years	5.43 (1.94-15.2)	.001
≥ 40 years	1	
Grade 3 tumor		
Yes	2.52 (0.30-21.27)	.40
No	1	
p53 over-expression		
Yes	1.81 (0.62-5.26)	.28
No	1	
CK5/6 expression		
Yes	1.74 (0.70-4.33)	.23
No	1	

P by Wald test

Figure 1. Survival in TNBC patients ≤40 vs >40 years of age (*P*<.001).

with TNBC are at a higher likelihood of relapse and have an associated overall poor survival outcome compared with women with other subtypes of breast cancer.[16,28,32,33] Based on these points and coupled with the lack of available data on non-Western countries, we embarked on this retrospective analysis to study TNBC in Saudi Arabia. We compared the prognosis and clinicopathologic features of TNBC versus non-TNBC in our patients, as well as the outcome differences within the two groups using 40 years as a cut-off age.

In the present study, we found a higher percentage of the TNBC patients expressed grade 3 tumors (87.3%) compared to the control non-TNBC group. These proportions are similar to what has been reported elsewhere (66% TNBC compared with 28% in other breast cancers),[20] and are consistent with estimates stating that TNBC tumors are of higher grade. The aggressiveness of this type of breast cancer and its highly proliferating nature, means that it also tends to be diagnosed at a later stage.[28]

Other established pathologic variables, including CK 5/6 and p53 expression status have a specific prognostic value in TNBC.[21,24,26] We have found statistically significant over-expression of CK 5/6 in our TNBC group compared to the control group. This finding supports previous studies that have shown basal-like tumors are immunohistochemically negative for ER and HER2, but positive for basal CK 5/6. Eighty percent of our TNBC patients expressed CK 5/6, a percentage that is much higher than those reported by other investigators where expression of basal cytokeratins CK5/6 and/or CK14 was detected in 55.7% of their TN tumors.[21] Though not statistically significant, our results also showed proportionally more p53 over-expression in TNBC than non-TNBC patients. A larger cohort of patients would enable us to confirm this finding. Our results, however, do provide strong evidence to support the established use of biomarker surrogates ER, PR and HER2 as clinical tools to define all TNBC, and CK 5/6 to help refine the TNBC subtypes, with high specificity;[25,26] a finding of immediate relevance to prognostication.

Our data show that there is no significant difference in the overall survival (OS) between the TNBC and the non-TNBC tumors that are age- and stage-matched. However, the evidence differs from one study to another. For instance, consistent with our data, another study showed that, regardless of stage at diagnosis, women with TNBC had a shorter OS than those with other breast cancers.[28] In addition, it has also been shown that TNBC patients have a worse prognosis,[30] and that there is shorter survival among ER and basal-like subtypes.[11,19,28] On the other hand, another study showed that there was no significant differences in 5-year survival between TNBC

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cancers and other breast cancers.[42] Further studies have shown that the difference between the TNBC and non-TNBC groups peaked at 3 years, though this difference decreased with time, suggesting that long-term survivors (beyond 10 years) in the TNBC group may have comparable survival to non-TNBC cases.[20,25] It is therefore clear that cancer-specific survival differs by subtype. Even within a group defined by high grade and expression of basal markers there is considerable heterogeneity of outcome.[43] Though we find no difference in OS between TNBC and non-TNBC patients after three years of follow up, perhaps a larger number of cases and a follow-up of at least 5 years would have yielded different results between both groups.

Our most intriguing result was the effect of age on the prognosis of our TNBC patients. When we closely analyzed and segregated our patients based on age, we found that TNBC patients aged ≤40 years had a statistically worse prognosis and OS compared to TNBC patients >40 years. In addition, a similar result was seen when these younger patients were compared to all of the non-TNBC patients. Other studies have suggested that, among TNBC patients, disease-free survival was significantly correlated with the menopausal status, where premenopausal status might reflect an unfavorable prognosis in TNBC.[44] Our finding of poor survival in patients aged ≤40 years, coupled with the previous data highlights the direct relation between age and OS of the patients. In addition, we uncovered a new association between the age in TNBC patients and unfavorable prognosis. Our results have an important implication, indicating that young women with TNBC tumors may be an ideal cohort to target in clinical trials and therefore may be an important avenue for future research. The extent to which the menopausal status contributes to the behavior of TNBC in Saudi patients and the natural history of the TNBC subtype in the identified age group (≤40 years) are areas of active research.

We acknowledge that our study has a number of limitations inherent to most retrospective studies. Potential limitations include a relatively small sample size, lack of data on the menopausal status of our cases and our comparison of prognosis between both groups at 3 years of follow up only. These limitations, however, are balanced by the strengths of providing unique data to Saudi Arabia, a data extraction review and re-assessment of tumors by a single pathologist, and therefore a consistent and single-institution approach to pathological diagnosis and patient care, and finally inclusion of a wide range of ages. These strengths contributed to our database, confirming many previously established comparisons between TNBC and non-TNBC tumors.

Few studies have been conducted among a non-Western population. Having said that, our study stands on the strength of the fact that the observations we report from this database provide new insights into the Saudi population. Our findings illustrate that our TNBC patients showed a similar trend to that described in others studying those patients in Western countries, where the incidence of TNBC is 12% in our cohort in Saudi Arabia (single institution). In other studies, a similar percentage of 11.2% (20) and 12.5% (28) were identified as having TNBC using a larger cohort of patients (1601 and over 50 000 women, respectively).

In conclusion, the incidence of TBNC in our institution in Saudi Arabia is similar to that described in other countries. These TNBC tumors expressed a significantly higher grade of tumors, with higher expression of CK 5/6 compared to the non-TNBC control group. These tumors were distributed over a wide range of ages, but showed no survival difference when compared with other tumors that are age- and stage-matched. However, we have identified that not all TNBC patients had a similar prognosis. Of the TNBC patients, only the younger aged patients were associated with poor prognosis and OS compared to those TNBC patients >40 years, as well as all non-TNBC patients. Indeed this subset of TNBC that are aged ≤40 years, and whose tumor showed p53 over-expression and expressed basal CK 5/6, had aggressive outcomes and were more likely to develop brain metastasis ($P<.001$ and $P<.01$, respectively). Our cohort provided us with the unique opportunity of defining the effect of young age on the worsening of prognosis and OS of the TNBC patients. It would be worth conducting further analyses in Saudi Arabia to compare TNBC patients, covering different age groups and different menopausal statuses to get a better understanding of the genetic and epigenetic alterations that are responsible for the biologically aggressive phenotype of these tumors. Long-term studies are needed to examine whether the prognosis and overall survival of TNBC becomes comparable to that of other tumors.

Conflict of Interest

The authors have no conflicting interests.

Author Contributions

OK provided patients visiting breast cancer clinic and collected patient data; AK performed the clinical pathological analysis and overall supervision of the project; JSM provided scientific advice and analysis of data; MB performed statistical analysis. OK and JSM wrote the initial draft of the manuscript, and all authors contributed to the final version. All authors read and approved the final manuscript.

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