

Clinicopathological and Radiological Features of Triple Negative Breast Cancer in Bahrain

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Abstract

Background: Triple Negative Breast Cancer (TNBC) is an aggressive type of breast cancer. Hormone based treatments are not an effective choice. There are fewer treatment options for this type of breast cancer.

Objective: To determine the incidence of Triple Negative Breast Cancer (TNBC) and analyze the clinical, pathological and radiological features of this type of breast cancer.

Methods: Two hundred fifty four patients diagnosed with breast cancer over one year period (January to December 2017) were included in this study. The requested data was extracted from I-SEHA information system database

Results: Forty patients out of 254 patients were diagnosed with Triple negative breast cancer with age range from 32-70 years and an average age of 52 years. Most of these patient were female and most of them were Bahraini (34 patient, 85%).

Conclusion: Our study shows that majority of breast cancers in Bahrain were Luminal A subtype (48.8%). However, TNBC shows an aggressive behavior that warrants recognition and early diagnosis and therefore early treatment.

Keywords: Triple negative breast cancer; Hormone receptor; Estrogen; Oncogenes

Introduction

Breast Cancer (BC) is increasingly recognized as a heterogeneous disease showing substantial differences with regard to biological behavior and requiring distinct therapeutic interventions. Steroid Hormone Receptors (HR) such as Estrogen Receptor (ER) and Progesterone Receptor (PR) along with the oncogene ErbB-2/Human Epidermal Growth Factor Receptor 2 (HER-2) are critical determinants of these breast cancer subtypes [1].

Triple-Negative Breast Cancer (TNBC) refers to any breast cancer that does not express the genes for Estrogen Receptor (ER), Progesterone Receptor (PR) and HER2/neu. Using gene expression profiling, five distinct molecular subtypes of breast cancer have been identified: Luminal A, luminal B, HER2-overexpressing, basal-like and unclassified [2]. Immuno Histo Chemistry (IHC) studies in detecting Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor-2 (HER2) are routinely used to classify tumors as luminal (ER+), HER2-overexpressing (H2E) (ER-/HER2+) and Triple Negative (TN or basal-like cancers) [3]. Recent studies concluded that TNBC is an aggressive subtype with a distinct molecular profile and associated with poorer prognosis and survival rate compared to luminal tumors. The aim of this study is to determine the incidence and prevalence of Triple Negative Breast Cancer in Bahrain and to analyze the clinical, pathological and radiological features of this type of breast cancer, and compare it with other subtypes of breast cancer (Table 1 and Figure 1).

Case Description

The study was performed from January 2017 and December 2017. The following were documented: Age, Nationality, type of surgery, tumor laterality (right or left breast), tumor histological subtype, tumor grade, Hormonal status (IHC), Her 2 neu FISH results, Lymph node status, distant metastasis and radiological features (Ultrasound/mammogram/MRI) (Table 2) [4].

Diagnosis was established after clinical suspicion followed by radiological investigations and surgical interventions. Statistics were done by Office Excel 2013.

Results

Two hundred and fifty-four patients were diagnosed with breast cancer

at Salmaniya Medical Complex in the time period between January 2017 and December 2017. The patients were all female patients except for 3 who were men [5]. The age range was from 29 to 92 years with the average age of 55 years. Most of these patient were Bahraini (230 patient, 90.5%). In regards to the tumor laterality, most of breast cancer were in the left breast (55.5%). Most of these patients underwent mastectomy +/- axillary lymph nodes dissection. The tumor histology of the majority was invasive ductal carcinoma (88.1%), followed by invasive lobular carcinoma (7.1%). Majority of these tumors were grade II (59.4%) [6]. The radiological features on mammogram/ultrasound of these tumors were mostly a mass or a lump (69.2%), followed by micro calcifications (7.8%). The rates of ER (-), PR (-) and HER-2 (-) tumors were 24%, 35.4% and 66% 21 (8.3%) showed ER-/PR-/HER2+ expression (HER-2 variant) (Table 3).

Forty patients out of 254 patients were diagnosed with Triple negative breast cancer with age range from 32-70 years and an average age of 52 years. Most of these patient were female and most of them Bahraini (34 patient, 85%). In regards to the tumor laterality, most of breast cancer were in the left breast (60%) followed by right breast (40%). Most of these patients underwent mastectomy +/- axillary lymph nodes dissection. The tumor histology of the majority was invasive ductal carcinoma (90%), followed by invasive lobular carcinoma (7.1%). Majority of these tumors were grade III (70%). Majority of these patients presented with radiological features of a mass (67.5%). No significant variations were noted when comparing age, tumor laterality, tumor type, tumor size and lymph node status in Triple negative breast cancer and the rest of the studied subtype. Although our data revealed a difference in tumor grade and histology type (Table 4 and Figure 2).

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Received: March 01, 2021; **Accepted:** March 15, 2021; **Published:** March 22, 2021

Citation: Hammad MF, Alkhatay R (2021) Clinicopathological and Radiological Features of Triple Negative Breast Cancer in Bahrain. J Cancer Diagn 5: 126.

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Type	Estrogen receptor (ER)	Progesterone receptor (PR)	HER2 expression	Phenotype	Total no. of cases	% of total
1 Triple negative	ER –	PR-	HER2-	ER-/PR-/HER2-	40	15.7
2 Luminal B/triple positive	ER+	PR+	HER2+	ER+/PR+/HER2+	29	11.5
3 Luminal A	E+	P+	HER2-	ER+/PR+/HER2-	124	48.8
4 Her2	ER-	PR-	HER2+	ER-/PR-/HER2+	21	8.3
5	ER+	PR-	HER2+	ER+/PR-/HER2+	2	0.8
6	ER+	PR-	HER2-	ER+/PR-/HER2-	36	14.1
7	ER-	PR+	HER2-	ER-/PR+/HER2-	1	0.4
8	ER-	PR+	HER2+	ER-/PR+/HER2+	1	0.4
Total (%)	ER+= 193, (76%) ER-= 61, (24%)	PR+= 164, (64.5%) PR-= 90, (35.4%)	HER2+= 53, 20.8% HER2-= 168, (66%)		254	(100)

Table 1: Distribution of the studied cases according to IHC profile expressions.

HER2	Negative (ihc) (0 and 1+)	Equivoal(ihc) (2+)	Positive (ihc)(3+)	Negative (fish)	Positive (fish)	Borderline (fish)	Total her2 negative (ihc+fish)
(NO.) OUT OF 254	113 (71+42)	83	43	55	10	3	168
(%)	44.4	32.6	16.9	21.6	3.9	1.1	66.1

Table 2: HER2-neu profile in studied cases (IHC and FISH).

	Negative (no) (%)	Positive (no) (%)	Total
ER	61 (24%)	193(76%)	254, 100%
PR	90 (35.4%)	164 (64.5%)	
HER 2	168 (66%)	53 (20.8%)	

Table 3: Tumor hormonal receptors profile in total cases.

Clinical and tumor characteristics	Triple negative subtype (NO.)	Triple negative subtype (%)
Age		
<30	0	0%
30-39	2	5%
40-49	12	30%
50-59	17	42.5%
>60	9	22.5%
Tumor laterality		
Left	24	60%
Right	16	40%
Bilateral	0	0%
Type of specimen		
Mastectomy	20	50%
Lumpectomy	2	5%
Core biopsy	12	30%
Review slides and blocks	6	15%
Tumor type		
Ductal	36	HER 2
Lobular	1	
Metaplastic	2	
Mucinous	0	
Tubular	1	
Micropapillary	0	
Tumor grade		
Grade I	2	5%
Grade II	10	25%
Grade III	28	70%
Tumor size		
T0-Tis	0	0%
T1	5	12.5%
T2	17	42.5%
T3	2	5%
T4	4	10%
Tx	12	30%
LN Status		
N0	12	30%
N1	13	32.5%
N2	3	7.5%
NX	11	27.5%
Radiological Feature		
Mass	27	67.5%
Micro calcifications	6	15%
Cyst	1	2.5%
Not known	6	15%
Distant metastasis		
Yes	15	37.5%
No	19	47.5%
Not known	6	15%

Table 4: TNBC Patient and tumor characteristics.

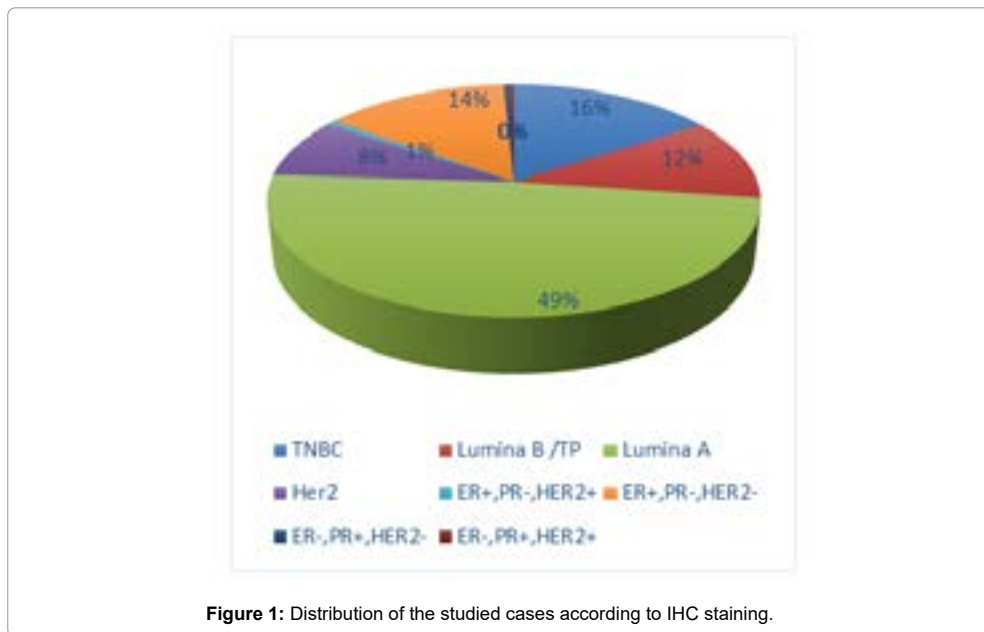


Figure 1: Distribution of the studied cases according to IHC staining.

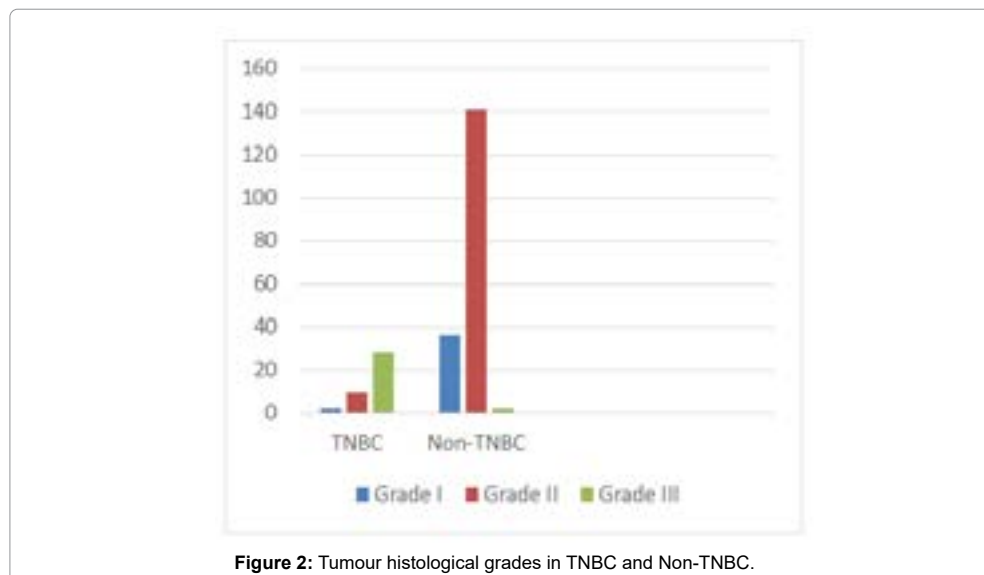


Figure 2: Tumour histological grades in TNBC and Non-TNBC.

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. TNBC lacks therapeutic options, such as molecular therapy or targeted therapy) (Endocrine or HER2-directed inhibitors); thus, the prognosis of TNBC is dismal compared with other subtypes of breast cancer. Currently, surgery plus chemotherapy or chemotherapy alone is the only systemic option for improving the prognosis of TNBC [7].

This implies that early detection of this aggressive type of breast cancer is necessary owing to the rapid progress and failed prognosis. This study described the clinical, pathological, and radiological characteristics of patients with TNBC in comparison with non-TNBC in Bahrain as well as in compare to TNBC studies done in the region and the world.

The TNBC incidence in this study is in accordance with the literature (10%-20%), as it accounts for 15.7% of all breast cancers diagnosed in Salmaniya Medical Complex in 2017. Although TNBC is frequently diagnosed in younger patients, the mean age at diagnosis in our study was 52 years, which may partly reflect late diagnosis or difficult access to health care services [8]. The higher percentage of TNBC was in Bahraini women with left breast tumor laterality and the tumor histology of grade III invasive ductal carcinoma. Majority of these patients presented with radiological features of a mass. The variables such as age, tumor laterality, tumor type, tumor size and lymph node status did not seem to differ in the 2 groups (TNBC and non-TNBC) (Table 5).

Hormonal class	Molecular sub-type (tumor phenotype)	ER and PR expression	Her2-neu expression
Hormone positive "luminal class"	Luminal A	ER/PR positive	Her2 negative
Hormone positive "luminal class"	Luminal B Triple positive	ER/PR positive	Her2 positive

Hormone negative "non-luminal class"	Her-2	ER/PR negative	Her2 positive
Hormone negative "non-luminal class"	Triple Negative	ER/PR negative	Her2 negative

Table 5: Molecular tumor subtypes according to the IHC Profile expressions of invasive breast carcinomas.

Similar to findings in other studies, Our study also found a higher prevalence of perimenopausal breast cancer, grade 3 disease, and larger tumor size, all of which are associated with triple-negative disease. Because TNBC is known to be more aggressive than other breast cancer subtypes, higher prevalence of TNBC could be a contributing factor to the high fatality rate of patients with breast cancer in Bahrain. Multiple factors may account for higher prevalence of TNBC reported by studies conducted in the region among patients with breast cancer. The early age of onset of breast cancer; lifestyle factors, such as diet and obesity; reproductive factors, such as multiparity; socioeconomic status; and screening behaviors may be hypothesized as probable etiology that were not measured or assessed in our study. Another important factor could be a potential genetic susceptibility of Bahraini to TNBC. More focused research into these factors will help clarify underlying determinants of TNBC in Bahrain.

In addition, this study did not show any difference in tumor size and in the axillary lymph nodal status between TNBC and non-TNBC, although there was a trend for more axillary lymph nodal metastases in TNBC. Previous studies show that the patients with TNBC were significantly more likely to have larger tumor sizes and positive axillary lymph

nodes than the patients with non-TNBC [9]. Pathologically, this study showed that the most common histological type of TNBC was invasive ductal carcinoma, although there was no statistically significant difference between the two groups (Table 6). Consistent with other studies, our results showed that the majority of the patients with TNBC were of histological Grade 3.

Radio logically, there have been few studies describing mammography findings of TNBC. This study showed that approximately 67.5% of TNBC patients had a visible tumor mass on mammography/ultrasound, and the masses were less frequently associated with micro calcification. This finding is consistent with previous studies that observed TNBC was most commonly presented as a mass and the mass was less frequently associated with micro calcifications [10]. The small sample size, its retrospective design, and performing this study in only one hospital were major limitations. However, the standardized method of data collection, the use of stratified multivariate models, and the analysis of data from public sectors probably resulted in less likely bias. The statistical analysis showed that data losses were random, partially overcoming the missing data limitation. Finally, the miscegenation of the Bahraini population needs to be considered when comparing the results with other populations. It is noteworthy that despite this factor, patients with TNBC and non-TNBC patients still presented markedly different characteristics, which were generally similar to other population groups. The heterogeneity of TNBC is inter- and intratumoral. And different population studies have yet to provide a common factor that could be used in the therapy of this disease (Figure 3).

Clinical and tumor characteristics	Triple negative subtype (NO.)	Triple negative subtype (%)	All other subtypes (NO.)	All other subtypes (%)
Age				
<30	0	0%	2	0.9%
30-39	2	5%	24	11.2%
40-49	12	30%	64	29.9%
50-59	17	42.5%	90	42%
>60	9	22.5%	74	34.5%
Tumor laterality				
Left	24	60%	141	65.8%
Right	16	40%	105	49%
Bilateral	0	0%	8	3.7%
Type of specimen				
Mastectomy	20	50%	121	56.5%
Lumpectomy	2	5%	30	14%
Core biopsy	12	30%	83	38.7%
Review slides and blocks	6	15%	19	8.8%
Tumor type				
Ductal	36	90%	188	87.8%
Lobular	1	2.5%	17	7.9%
Metaplastic	2	5%	2	0.9%
Mucinous	0	0%	2	0.9%
Tubular	1	2.5%	2	0.9%
Micropapillary	0	0%	3	1.4%
Tumor grade				
Grade I	2	5%	36	16.8%
Grade II	10	25%	141	65.8%
Grade III	28	70%	37	17.2%
Tumor size				
T0-Tis	0	0%	2	0.9%
T1	5	12.5%	43	20%
T2	17	42.5%	89	41.5%
T3	2	5%	31	14.4%
T4	4	10%	11	5.1%
Tx	12	30%	86	40.1%
Total=254 100%	40 15.7%		214 84.2%	

Table 6: Clinico-pathological characteristics of TNBC compared to the other subtypes.

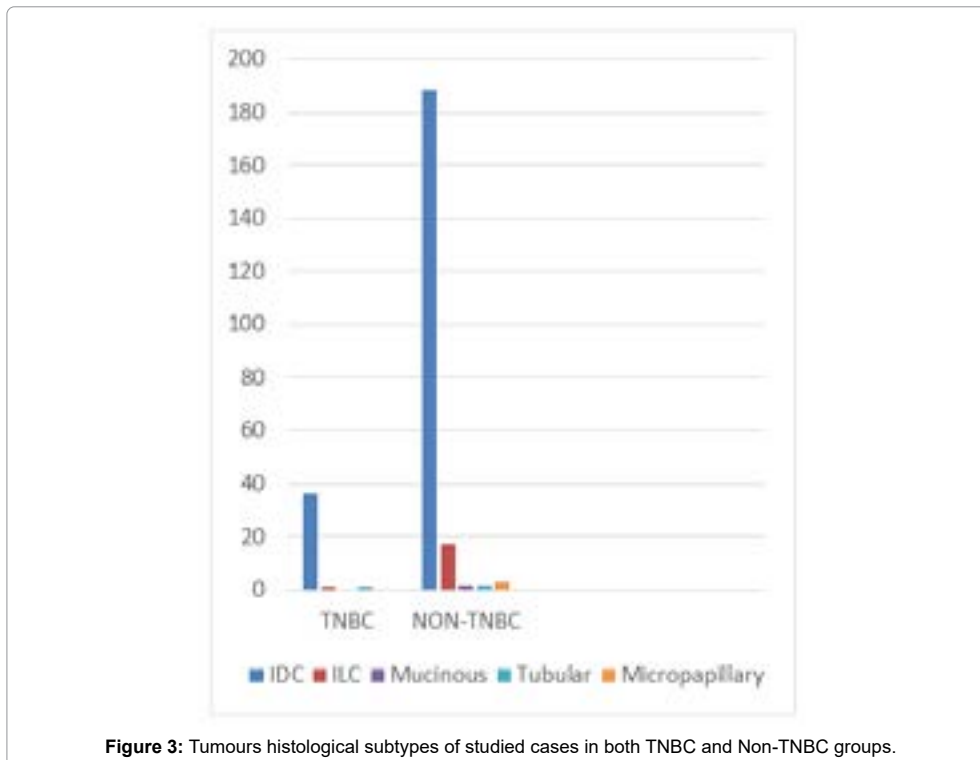


Figure 3: Tumours histological subtypes of studied cases in both TNBC and Non-TNBC groups.

Conclusion

Our study shows that majority of breast cancers in Bahrain were Luminal A subtype (48.8%). However, TNBC shows an aggressive behavior that warrants recognition and early diagnosis and therefore early treatment. TNBC lacks therapeutic options, such as molecular therapy or targeted therapy (endocrine or HER2-directed inhibitors); thus, the prognosis of TNBC is dismal compared with other subtypes of breast cancer. Currently, surgery plus chemotherapy or chemotherapy alone is the only systemic option for improving the prognosis of TNBC. This implies that early detection of this aggressive type of breast cancer is necessary owing to the rapid progress and failed prognosis. More focused research into demographic and genetic factors will help clarify underlying determinants of TNBC in Bahrain.

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