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RESEARCH ARTICLE

BRCA1 in triple-negative breast cancer: A double-edged sword for prognosis and precision therapy

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ABSTRACT

Background: Triple-negative breast cancer (TNBC) is an aggressive subtype lacking estrogen receptor (ER), progesterone receptor (PR), and HER2 expression. The BRCA1 gene encodes a tumor suppressor protein critical for homologous recombination (HR) DNA repair, playing a key role in TNBC progression and treatment response. **Aim**: To assess BRCA1 protein expression in TNBC and evaluate its impact on survival status. **Material and Methods**: This study retrospectively analyzed 80 TNBC cases to assess BRCA1 protein expression through immunohistochemistry and its correlation with clinicopathologic features, recurrence patterns, and survival outcomes. Kaplan-Meier survival analysis and Cox proportional hazards regression were used for statistical evaluation. **Results**: Findings revealed that low BRCA1 expression was significantly associated with high tumor grade, lympho-vascular invasion, and poor disease-free and overall survival. Conversely, high BRCA1 expression correlated with early-stage disease, smaller tumor sizes, and improved survival outcomes. **Conclusion**: These results highlight the impact of low BRCA1 expression on TNBC aggressiveness and its potential role as a prognostic biomarker. Further research integrating multi-omics approaches may improve personalized treatment strategies for the management of BRCA1-associated TNBC.

Keywords: *BRCA1, PARP* inhibitors, Prognostic biomarker, *TNBC.*

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INTRODUCTION

Triple-negative breast cancer (TNBC) is an exceedingly aggressive subtype of breast cancer, distinguished by the absence of estrogen receptors (ER), progesterone receptors (PR), and HER2 expression. Comprising 15-20% of all breast cancer cases, TNBC is linked to an unfavorable prognosis owing to its fast progression, elevated recurrence rates, and restricted therapy alternatives (Liedtke et al., 2008) and (Foulkes et al., 2010). Among the genetic determinants of TNBC, the Breast Cancer Gene 1 (BRCA1) has surfaced as a significant factor in its pathogenesis. BRCA1 situated on chromosome 17q21, encodes a tumor suppressor protein essential for homologous recombination (HR), a method of DNA repair (Li et al., 2021). Mutations in BRCA1 impair homologous recombination, resulting in genomic instability and a markedly elevated risk of breast and ovarian malignancies (Miklikova et al., 2021). As much as 70% of breast tumors in BRCA1 mutation carriers display a triple-negative phenotype, highlighting the gene's critical significance in TNBC (Karim et al., 2023). Epidemiological studies indicate that germline BRCA1 mutations increase the risk of triple-negative breast cancer (TNBC), especially in younger women, with a peak incidence occurring prior to the age of 40 (Engel et al., 2018) and (Srivastava and Jatoi, 2021). Approximately 10-15% of patients with TNBC possess germline BRCA1 mutations, with increased prevalence among communities such as Ashkenazi Jews and those with a familial history of breast cancer.These findings underscore the significance of genetic screening in identifying individuals at high risk for early intervention (Shin et al., 2020) and (Jain et al., 2024). BRCA1-deficient triple-negative breast cancer (TNBC) is distinguished by a basal-like phenotype, featuring high-grade tumors and poor differentiation (Foulkes et al., 2010). This condition is associated with the accumulation of mutations resulting from impaired DNA repair mechanisms. Mutations in several genes, including TP53, intensify the aggressive characteristics of these malignancies (Lord and Ashworth, 2016).

The term "BRCAness" has been coined to characterize tumors exhibiting homologous recombination defects that resemble BRCA1-mutated malignancies, irrespective of BRCA1 mutation status (Foulkes et al., 2003). These cancers exhibit molecular susceptibilities, including sensitivity to DNA-damaging drugs and poly (ADP-ribose) polymerase (PARP) inhibitors (Farmer et al., 2005) and (Mweempwa and Wilson, 2019). The prognosis of BRCA1-associated triple-negative breast cancer is affected by its distinct molecular characteristics. Although BRCA1 mutations may increase sensitivity to DNA-damaging treatments such as platinum-based chemotherapy, their overall

effect on survival is still contentious (Tutt et al., 2010). such as platinum-based chemotherapy, their overall effect on survival is still contentious (Tutt et al., 2010).

Recent clinical trials indicate that PARP inhibitors, which utilize synthetic lethality in HR-deficient cells, present intriguing therapeutic alternatives (Fostira et al., 2012 and Zhu et al., 2016). The advent of resistance mechanisms, including secondary mutations that restore HR, presents considerable hurdles (Maksimenko et al., 2014). Therapeutic approaches for BRCA1-associated triple-negative breast cancer (TNBC) encompass platinum-based chemotherapy and PARP inhibitors, while current investigations are examining combinations with immune checkpoint inhibitors and further targeted therapies (Bayraktar and Arun, 2017) and (Xie et al., 2024). Notwithstanding initial success, opposition to these medicines continues to be a significant impediment (Alaklabi et al., 2024). Progress in genomics and proteomics has revealed more targets, including the PI3K/AKT/mTOR pathway and androgen receptor, presenting novel therapeutic opportunities (Akashi-Tanakaat al., 2015 and Hahnen et al., 2017). This study sought to investigate the function of BRCA1 in pathogenesis, prognosis, and therapeutic susceptibilities in triple-negative breast cancer.

Patients and Methods

Study Design and Ethical Approval

This retrospective analysis examined 80 female patients of triple-negative breast cancer diagnosed at the National Cancer Institute, Cairo University, from January 2016 to December 2019. Ethical approval was obtained from the Institutional Review Board (IRB) of the National Cancer Institute, Cairo University (Approval No. PA2502-501-093-197), guaranteeing compliance with the Declaration of Helsinki and national rules for research involving human participants. The retrospective design of the study resulted in the waiver of informed permission, and all patient data were anonymized to ensure confidentiality.

Patient Selection and Clinicopathological Data

Patient eligibility was established based on the availability of complete clinicopathologic data and formalin-fixed, paraffin-embedded (FFPE) tissue specimens. The inclusion criteria included a confirmed diagnosis of TNBC, no metastatic illness at first time of diagnosis (stages I-III), and the availability of comprehensive clinicopathologic as well as follow-up data. Clinicopathologic characteristics, such as age, tumor laterality, size, histological subtype, nodal status, and therapy specifics as well as data regarding survival outcomes, encompassing disease-free survival (DFS) and overall survival (OS), all were obtained from medical records.

Immunohistochemical Analysis

BRCA1 immunohistochemistry was conducted on 4-µm FFPE tissue sections utilizing the Ventana BenchMark ULTRA automated immunostainer (Ventana Medical Systems, Tucson, AZ, USA) in accordance with the manufacturer's guidelines. Pre-diluted primary rabbit monoclonal antibodies targeting BRCA1 (clone 287.17, Cat. No. SC-135732, Santa Cruz Biotechnology, USA) were utilized. Antigen retrieval was conducted using the ULTRA CC1 solution (Ventana), and staining detection was accomplished utilizing the ultraView Universal DAB Detection Kit.

Evaluation of BRCA1 Protein Expression

The slides were initially examined at 10× magnification to gain an overall impression of tumor cell distribution. This was followed by a semi-quantitative assessment of positively stained cells at higher magnifications (400×), leading to the final scoring. BRCA1 staining was evaluated using the H-scoring method, with three independent, blind observers who had no prior knowledge of the patients' clinical or pathological data. BRCA1 expression in breast tumor specimens was quantified by assessing both staining intensity and the percentage of positive tumor cells. Staining intensity was categorized as negative (0), weak (1), moderate (2), or strong (3). The H-score was calculated by multiplying staining intensity by the percentage of positive cells, generating a continuous scale from 0 to 300. The expected BRCA1 expression pattern was nuclear staining, regardless of cytoplasmic staining. Based on H-score values, cases were classified into three groups: low expression (≤99), moderate expression (100–199), and high expression (200–300) (Madjd et al., 2011) and (Rashed et al., 2022).

Quality Control for Immunostaining and Analysis

Stringent quality control procedures were applied throughout the immunohistochemical staining process to ensure dependability and accuracy. Every staining procedure incorporated both positive and negative controls. Positive controls were tissue samples with established BRCA1 expressions to confirm the specificity and effectiveness of the staining protocol. Negative controls were conducted by excluding the primary antibody to verify the lack of non-specific staining or background interference. The immunostaining process was standardized with an automated immunostainer, guaranteeing

constant reagent application and homogenous incubation conditions. Antigen retrieval was conducted with recognized reagents, and the staining procedure adhered to manufacturer-recommended protocols to ensure repeatability.

Stained sections were independently examined by three expert pathologists who were blinded to clinical data to mitigate observer bias. Discrepancies in interpretation were addressed by collaborative examination and consensus. The semi-quantitative H-score approach was utilized to evaluate staining intensity and the percentage of positively stained tumor cells, with all assessments performed under standardized microscopic circumstances.

Statistical Analysis

Statistical analyses were conducted utilizing SPSS software version 27.0 and R software version 4.3.3. Descriptive statistics summarized clinicopathologic characteristics, and relationships between categorical variables were examined using chi-square and Fisher's exact tests. The Kaplan-Meier method was utilized to estimate disease-free survival (DFS) and overall survival (OS), with variations in survival curves evaluated by the log-rank test. Cox proportional hazards regression analysis was employed to ascertain if BRCAness acts as an independent predictor of disease-free survival (DFS) and overall survival (OS). Statistical significance was established at $p < 0.05$.

Results

This study included 80 female patients diagnosed with triple-negative breast cancer (TNBC). The age range of the cohort was 25 to 84 years, with a median age of 53.5 years. Around 22% of patients had a family history of gynecological malignancies, and a notable proportion had a familial predisposition to BRCA1-related cancers. Tumor sizes varied from 1 cm to 8 cm, with a median size of 3 cm. Most cases (85%) were invasive carcinoma of no special type (IDC), grade 3. Tumor laterality was nearly evenly distributed, with 48% of tumors in the right breast, 50% in the left breast, and 2% presenting bilaterally. The upper outer quadrant (UOQ) was the most frequent site of tumor origin, accounting for 62% of cases.

The follow-up duration ranged from 10 to 104 months, with an average of 90.7 months (±3.15 SE). At the conclusion of the follow-up period, the overall survival (OS) rate was 80.7% (95% CI: 72.4%–90.0%), while the disease-free survival (DFS) rate was 71.0% (95% CI: 60.7%–83.0%). Recurrence occurred in 26% of patients, including 6.2% with local recurrence, 21% with metastatic recurrence, and 1 patient experiencing both local and metastatic recurrence.

Based on H-scores, tumors were classified into low (≤99), moderate (100–199), and high (200–300) BRCA1 expression groups (Figures 1-4). Low BRCA1 expression was detected in 38% of cases, moderate expression in 37%, and high expression in 25% (Table 1).

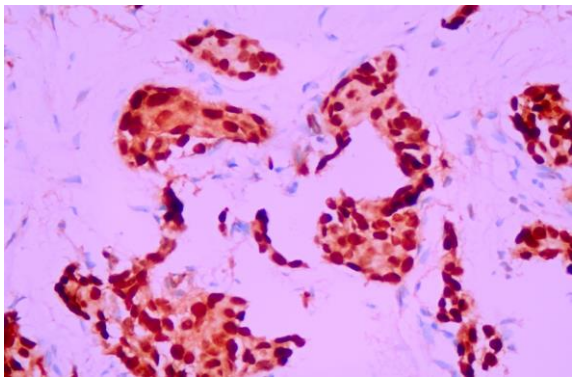

Figure 1: Immunohistochemical assessment of BRCA1 high expression, nuclear and cytoplasmic staining visualized, with DAB as the chromogen for visualization, original magnification ×400.

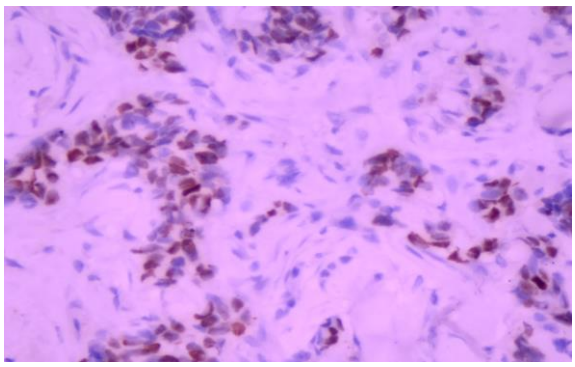

Figure 2: Immunohistochemical staining for BRCA1 showing moderate expression in the tumor cells, nuclear staining visualized, with DAB as the chromogen for visualization, original magnification ×400.

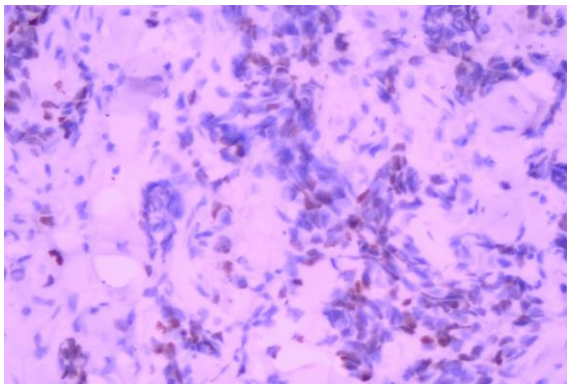

Figure 3: Immunohistochemical detection of BRCA1 low expression, with DAB as the chromogen for visualization., original magnification ×400

The analysis revealed no significant difference in BRCA1 expression based on age, with patients below and above the median age of 53.5 years showing comparable levels of expression (*P*= 0.22). Tumor size appeared to influence BRCA1 expression, as smaller tumors (<3 cm) exhibited higher expression

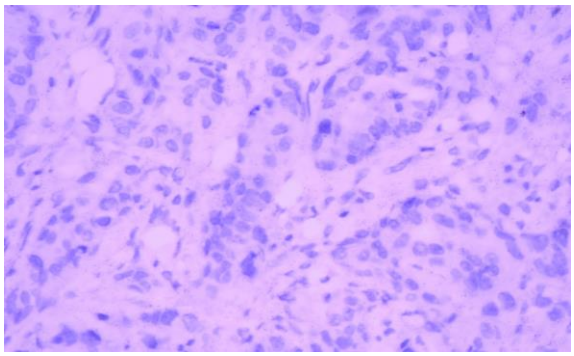

Figure 4: Immunohistochemical detection of BRCA1expression, with completely negative result, with DAB as the chromogen for visualization, original magnification ×400

more frequently than larger tumors (≥3 cm), although this difference did not achieve statistical significance (*P* = 0.071). A significant association was observed between BRCA1 expression and nodal status (*P* = 0.002), with elevated expression detected in 80% of node-negative cases, while reduced expression was more common in node-positive cases. High BRCA1 expression demonstrated a strong correlation with early TNM stages (I and II) (*C* < 0.001) and lower T-stages (T1 and T2) (*P* = 0.0146).

The analysis revealed no significant difference in BRCA1 expression based on age, with patients below and above the median age of 53.5 years showing comparable levels of expression (*P*= 0.22). Tumor size appeared to influence BRCA1 expression, as smaller tumors (<3 cm) exhibited higher expression more frequently than larger tumors (≥3 cm), although this difference did not achieve statistical significance (*P*= 0.071). A significant association was observed between BRCA1 expression and nodal status (*P*= 0.002), with elevated expression detected in 80% of node-negative cases, while reduced expression was more common in node-positive cases. High BRCA1 expression demonstrated a strong correlation with early TNM stages (I and II) (p < 0.001) and lower T-stages (T1 and T2) (*P*= 0.0146).

Additionally, lymphovascular invasion (LVI), present in 62% of cases, was less frequently associated with high BRCA1 expression (40%) compared to moderate (59%) and low (80%) expression groups, with the difference reaching statistical significance (*P*= 0.0152). BRCA1 expression was significantly linked to recurrence patterns. Metastatic recurrence was observed in 17 patients, predominantly among those with low BRCA1 expression (50%, *P*< 0.001). Local recurrence occurred in 6.2% of cases, with the significantly better DFS and OS. Cox proportional hazards regression identified low BRCA1 expression as an independent prognostic highest incidence observed in the low-expression group (17%, *P*= 0.0183). Kaplan-Meier analysis revealed that high BRCA1 expression was associated factor for poorer DFS (*P*= 0.014) and OS (*P*= 0.017), (figure 5). Adjuvant chemotherapy was administered to 89% of patients, with no statistically significant differences in BRCA1 expression among different chemotherapy regimens (*P*= 0.34). Radiotherapy was received by 85% of the cohort, and high BRCA1 expression was significantly associated with the administration of adjuvant radiotherapy (*P*< 0.001), particularly in the adjuvant-only treatment group compared to those receiving palliative regimens.

Discussion

TNBC is a particularly formidable subtype of breast cancer, characterized by its aggressive clinical behavior, restricted treatment alternatives, and unfavorable prognosis. Characterized by the absence of ER, PR, and HER2 expression, TNBC is linked to a greater incidence of distant metastases and reduced survival rates relative to other breast cancer subtypes (Liedtke et al., 2008 and Foulkes et al., 2010).

BRCA1 functions as a tumor suppressor gene and is essential in homologous recombination DNA repair, playing a crucial role in the pathogenesis and treatment response of TNBC. This study's findings highlight the prognostic importance of BRCA1 protein expression. Reduced BRCA1 expression was substantially correlated with advanced tumor stage, increased lymphovascular invasion rates, and reduced survival outcomes.

This corresponds with previous research demonstrating that low BRCA1 expression corresponds to genomic instability and a more aggressive tumor phenotype (Wooster et al., 1995) and (Karim et al., 2023). Foulkes et al. established a robust association between germline mutations in BRCA1 and the onset of TNBC, which is correlated with certain clinicopathologic features, such as elevated tumor grade and a basal-like molecular profile (Foulkes et al., 2010). Likewise, tumors with diminished BRCA1 expression display characteristics of "BRCAness," a phenotype akin to BRCA-mutant malignancies, marked by impaired DNA repair pathways (Lord and Ashworth, 2016).

The identified link between BRCA1 expression and nodal involvement, tumor size, and lympho-vascular invasion underscores its significance in assessing TNBC aggressiveness. Elevated BRCA1 expression was more prevalent in early-stage illness and smaller tumors, reinforcing its role in preserving genomic stability and inhibiting tumor growth (Foulkes et al., 2010) and (Lord and Ashworth, 2016).

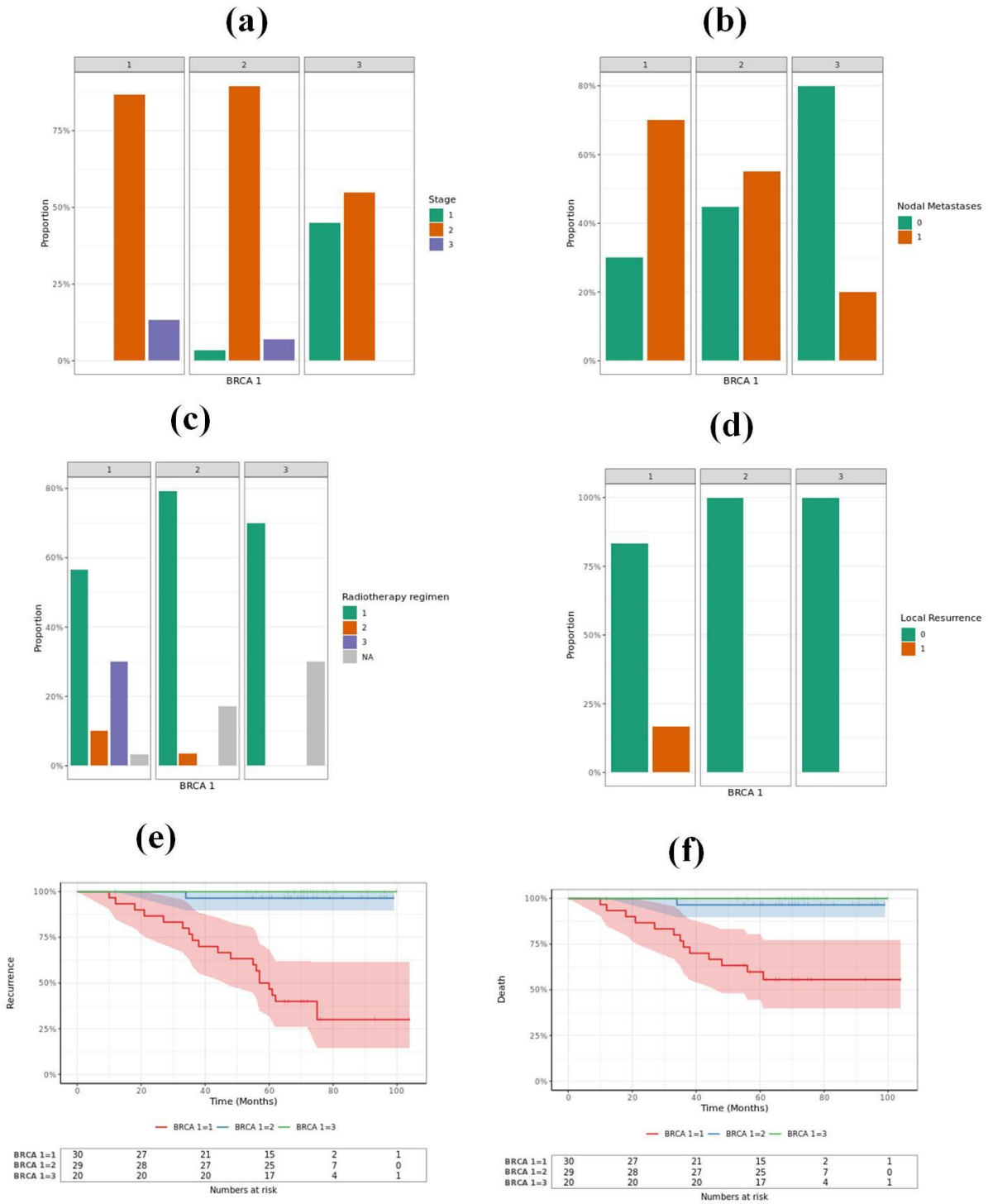

Figure 5: Statistical analysis of clinical outcomes in relation to BRCA1 expression in TNBC.
(a) Proportion of patients in each BRCA 1 expression category across different tumor stages (1, 2, and 3). Stage 1 (green), stage 2 (orange), and stage 3 (blue) are represented.
(b) Proportion of patients with positive (1) and negative (0) nodal metastases across BRCA 1 expression categories. Nodal metastases were categorized as negative (0) or positive (1).
(c) Distribution of patients across different radiotherapy regimens (1: adjuvant, 2: palliative, 3: combined, NA: not applicable)

Table (1): Clinicopathological characteristics and their association with BRCA1 H-scores in patients with TNBC.

Clinicopathologic Factors		BRCA1 H score				p value
		Total	Low ≤99	Moderate 100-199	High 200-300	
			30 (38%)	29 (37%)	20 (25%)	
Age	<53.5	39 (49%)	13 (43%)	18 (62%)	8 (40%)	0.22
	>53.5	41 (51%)	17 (57%)	11 (38%)	12 (60%)	
Laterality	Rt	38 (48%)	14 (47%)	11 (38%)	13 (65%)	0.15
	Lt	40 (50%)	14 (47%)	18 (62%)	7 (35%)	
	Bilateral	2 (2.5%)	2 (6.7%)	0 (0%)	0 (0%)	
Site	UOQ	50 (62%)	18 (60%)	20 (69%)	11 (55%)	0.83
	UIQ	2 (2.5%)	2 (6.7%)	0 (0%)	0 (0%)	
	LOQ	4 (5%)	1 (3.3%)	2 (6.9%)	1 (5%)	
	LIQ	14 (18%)	6 (20%)	4 (14%)	4 (20%)	
	Retro-areolar	10 (12%)	3 (10%)	3 (10%)	4 (20%)	
Type of surgery	CBS	49 (61%)	20 (67%)	16 (55%)	13 (65%)	0.63
	MRM	31 (39%)	10 (33%)	13 (45%)	7 (35%)	
Tumor Size	<3cm	34 (42%)	11 (37%)	10 (34%)	13 (65%)	0.071
	≥3cm	46 (57%)	19 (63%)	19 (66%)	7 (35%)	
Tumor Type	IDC	68 (85%)	27 (90%)	23 (79%)	17 (85%)	0.48
	Other types	12 (15%)	3 (10%)	6 (21%)	3 (15%)	
DCIS	Absent	18 (22%)	5 (17%)	8 (28%)	5 (25%)	0.59
	Present	62 (78%)	25 (83%)	21 (72%)	15 (75%)	
Nodal Status	Negative	38 (48%)	9 (30%)	13 (45%)	16 (80%)	0.00223
	Positive	42 (52%)	21 (70%)	16 (55%)	4 (20%)	
Capsular invasion	Absent	17 (40%)	9 (43%)	7 (44%)	1 (25%)	0.81
	Present	25 (60%)	12 (57%)	9 (56%)	3 (75%)	
Lympho-vascular emboli	Absent	30 (38%)	6 (20%)	12 (41%)	12 (60%)	0.0152
	Present	50 (62%)	24 (80%)	17 (59%)	8 (40%)	
TNM stage	I	10 (12%)	0 (0%)	1 (3.4%)	9 (45%)	<0.001
	II	64 (80%)	26 (87%)	26 (90%)	11 (55%)	
	III	6 (7.5%)	4 (13%)	2 (6.9%)	0 (0%)	
T Stage	T1	18 (22%)	3 (10%)	5 (17%)	10 (50%)	0.0146
	T2	50 (62%)	22 (73%)	18 (62%)	9 (45%)	
	T3	10 (12%)	3 (10%)	6 (21%)	1 (5%)	
	T4	2 (2.5%)	2 (6.7%)	0 (0%)	0 (0%)	
LN stage	N0	38 (48%)	9 (30%)	13 (45%)	16 (80%)	0.00386
	N1	39 (49%)	18 (60%)	16 (55%)	4 (20%)	
	N2	2 (2.5%)	2 (6.7%)	0 (0%)	0 (0%)	
	N3	1 (1.2%)	1 (3.3%)	0 (0%)	0 (0%)	
Type of chemotherapy	Neoadjuvant	2 (2.5%)	1 (3.3%)	0 (0%)	1 (5%)	0.34
	Adjuvant	71 (89%)	26 (87%)	25 (86%)	19 (95%)	

	Both	7 (8.8%)	3 (10%)	4 (14%)	0 (0%)	
Radiotherapy	No	12 (15%)	1 (3.3%)	5 (17%)	6 (30%)	0.0266
	Yes	68 (85%)	29 (97%)	24 (83%)	14 (70%)	
Radiotherapy Regimen	Adjuvant	54 (79%)	17 (59%)	23 (96%)	14 (100%)	<0.001
	Palliative	4 (5.9%)	3 (10%)	1 (4.2%)	0 (0%)	
	Both	10 (15%)	9 (31%)	0 (0%)	0 (0%)	
Recurrence	No	59 (74%)	11 (37%)	28 (97%)	20 (100%)	<0.001
	Yes	21 (26%)	19 (63%)	1 (3.4%)	0 (0%)	
Local Recurrence	No	75 (94%)	25 (83%)	29 (100%)	20 (100%)	0.0183
	Yes	5 (6.2%)	5 (17%)	0 (0%)	0 (0%)	
Metastatic Recurrence	Absent	63 (79%)	15 (50%)	28 (97%)	20 (100%)	<0.001
	Present	17 (21%)	15 (50%)	1 (3.4%)	0 (0%)	
Death	No	65 (81%)	17 (57%)	28 (97%)	20 (100%)	<0.001
	Yes	15 (19%)	13 (43%)	1 (3.4%)	0 (0%)	

The found inverse relationship between BRCA1 expression and lympho-vascular invasion in our investigation indicates that BRCA1 expression may reduce metastatic potential, aligning with previous findings (Lord and Ashworth, 2016) and (Fostira et al., 2012). Survival investigation indicated that patients exhibiting elevated BRCA1 expression demonstrated markedly improved overall survival (OS) and disease-free survival (DFS). Reduced BRCA1 expression was recognized as an independent predictive indicator of worse survival outcomes. These findings align with the increasing evidence indicating that functional BRCA1 is associated with less aggressive tumor biology (Foulkes et al., 2010) and (Zhu et al., 2016). Moreover, patients exhibiting elevated BRCA1 expression showed reduced recurrence rates, encompassing both local and metastatic recurrence, so underscoring its prognostic significance (Fostira et al., 2012) and (Maksimenko et al., 2014). Genetic predisposition is a significant element in the management of TNBC.

Germline mutations in BRCA1 and BRCA2 are recognized risk factors for triple-negative breast cancer (TNBC), and genetic screening has become a fundamental component of clinical practice. Multi-gene panel testing, as articulated by Shin et al., facilitates the detection of supplementary hereditary cancer-associated mutations, hence enhancing patient classification and individualized treatment strategies (Li et al., 2021 and Miklikova et al., 2021). This study advocates the integration of BRCA1 expression analysis into standard diagnostic procedures to improve prognostic assessments and inform treatment choices. This work underscores the pivotal significance of BRCA1 expression in influencing the prognosis and treatment response of TNBC. Elevated BRCA1 expression is associated with advantageous clinicopathologic characteristics and enhanced survival rates, highlighting its significance as a prognostic biomarker and a therapeutic target.

Nonetheless, tackling the obstacles of treatment resistance in TNBC research continues to be a priority for enhancing patient outcomes (Mweempwa &Wilson, 2019) and (Karim et al., 2023). Future goals in BRCA1-associated TNBC research encompass tackling therapeutic resistance, utilizing multi-omics strategies for precision medicine, and creating non-invasive biomarkers for tracking disease progression (Havel et al., 2019), (Imyanitov &Sokolenko,2021) and (Dilmac & Ozpolat, 2023). Liquid biopsy technologies, including circulating tumor DNA sequencing, offer potential for real-time evaluation of genetic modifications and therapeutic response (Mazzeo et al., 2024).

Conclusion

This study revealed a substantial association between BRCA1 expression and critical clinicopathologic characteristics, recurrence patterns, and survival outcomes in TNBC. Elevated BRCA1 expression was associated with favorable prognostic indicators, including early-stage illness, lack of nodal involvement, and enhanced disease-free and overall survival rates. Conversely, diminished BRCA1 expressions were identified as an autonomous predictor of unfavorable prognosis, associated with elevated recurrence rates, especially metastatic recurrence. These findings underscore the predictive importance of BRCA1 expression in TNBC and its prospective function in informing risk

evaluation and therapeutic approaches. Further research is required to validate these results and investigate their therapeutic implications.

Declaration

Author Contribution

All authors contributed to the study design, data collection, and statistical analysis. Noura A. A. Ebrahim spearheaded the document composition, while Nancy H. Amin and Mustafa A. Hussein contributed essential modifications. All authors examined and endorsed the final paper and assumed responsibility for the integrity and accuracy of the study.

Ethics Approval and Consent to Participate

To maintain confidentiality and adhere to ethical guidelines, all identifying information was removed. Ethical approval for the study was granted by the Institutional Review Board (IRB) of the National Cancer Institute, Cairo University (Approval No. PA2502-501-093-197).

Consent for Publication

This original research study was approved by the Institutional Review Board of the National Cancer Institute, Egypt. Conducted retrospectively with fully anonymized data, the study does not involve identifiable individual information or images; therefore, consent for publication is not applicable.

Availability of Data and Materials

Data and materials related to the study are available upon reasonable request .

Conflict of Interest

The authors declare no conflicts of interest or financial relationships that could have influenced the study's design, execution, or interpretation .

Funding

This research was conducted without external financial support or funding

Human Rights Statement

This study was conducted in compliance with the Declaration of Helsinki, ensuring the dignity, privacy, and confidentiality of all patients. Personal identifiers were excluded, and the research was performed with the goal of advancing medical knowledge.

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