RESEARCH ARTICLE

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Type I or Type II Endometrial Carcinoma? Role of *BRCA1* Immunohistochemistry

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Abstract

Objectives: Investigation of diagnostic and prognostic relevance of *BRCA1* immunohistochemistry (IHC) in endometrial carcinoma. **Methods:** Ninty four specimens of endometrial carcinomas were evaluated. Full sections stained with hematoxylin & eosin were revaluated for assessment of tumor type, grade, myometrial, & lympho-vascular invasion (LVI). Tissue microarray blocks were constructed using the pencil tip method and immunostained with Anti-*BRCA1* antibody. *BRCA1* was correlated with clinicopathological parameters as well as disease free survival and overall survival. **Results:** There was a statistically significant difference (P=0.001) between serous and endometroid carcinomas regarding *BRCA1* expression where most cases of serous carcinoma showed negative expression. No statistically significant difference was found between *BRCA1* positive and negative cases regarding disease free survival (DFS) or overall survival. Serous histotype, high grade, advanced stage, and omental deposits were the parameters significantly associated with decreased DFS. **Conclusion:** Results of this study can support inclusion of *BRCA1* IHC in a panel to differentiate both endometroid and serous carcinomas. The current study found no prognostic relevance for *BRCA1* in terms of overall survival and disease-free survival.

Keywords: Endometroid- Serous- *BRCA1*

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Introduction

Endometrial carcinoma is no longer a single entity owing to the molecular diversity that allowed its classification into 4 subtypes. However, since molecular classification is not always feasible, it is still diagnosed based on the histopathological and immunohistochemical features targeting to differentiate type 1 (endometroid) and type 2 (serous carcinoma), as type 2 is carrying worse prognosis. This always raise concern of investigating molecular markers that can help in such differentiation and can affect the therapeutic options [1].

BRCA1 is a tumor suppressor gene that is located on chromosome 17q21. The *BRCA1* gene product plays an important role in multiple biological pathways including DNA damage repair, transcriptional control, cell growth and apoptosis [2].

Data on the role of *BRCA1* in endometrial carcinoma is still controversial according to a latest systematic review done by Gasparri et al. [3]. Some studies suggest that *BRCA1* mutation carriers are at high risk for endometrial carcinoma, mostly of the uterine serous type [4, 5, 6]. Establishing a link between BRCA expression and endometrial carcinoma can raise possibility of use of target therapy like Poly (ADP-ribose) polymerase (PARP) inhibitors in such group of patients. Moreover, If such correlation has been established, hysterectomy can be added to bilateral salpingo-oophorectomy as a risk-reducing surgery [3].

BRCA1 mutational loss is well known to be detected by genetic testing, while detection by immunohistochemistry (IHC) wasn't used on a wide scale .*BRCA1*-IHC may be an inexpensive, easy to implement, and reproducible mean for detecting its mutational loss [7, 8]. Therefore, this study was carried out aiming to evaluate the immunohistochemical expression of *BRCA1* in endometrial carcinoma and investigate whether this expression has a diagnostic as well as prognostic relevance.

Materials and Methods

This is a retrospective study conducted on 94 total abdominal hysterectomy and bilateral salpingo-ophrectomy (TAH&BSO) specimens from cases diagnosed with endometrial carcinoma at University hospitals and oncology center during the period from January 2014 to December 2018. The study was performed after being approved by the Institutional Review Board

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(IRB) (proposal code "MS.18.07.221 ").

Inclusion criteria of patients

All cases diagnosed as endometrial carcinoma from hysterectomy specimen during the study period were included provided that they have complete clinical data.

Exclusion criteria of patients

Cases with incomplete clinical data, unavailable paraffin blocks, unavailable medical records, and patients with archival material insufficient for IHC processing were excluded. Carcino-sarcoma cases were excluded from the study as well.

Clinical parameters and histopathological evaluation

Patient files were retrieved and revised to obtain clinicopathological data including patient age, tumor size, presence of ascites, omental deposits, tumor extension, recurrence, distant metastases, and staging.

Follow up data were available for only 55 cases. The median follow-up duration was 30.5 months. The most recent visits were at December 2018. Hematoxylin and Eosin (H&E) stained full section slides were reexamined to determine histopathologic type, grade, myometrial invasion and lymphovascular invasion. The World Health Organization (2020) criteria were used for histologic subtype diagnosis. The International Federation of Gynecology and Obstetrics (FIGO) 2012 criteria were used for staging.

Tissue microarray

TMA blocks were constructed using the pencil tip method adopted from Shebl et al. [9]. The recipient block was made using a mechanical pencil tip about 0.7 mm in diameter. A cylindrical 0.9 mm core sample from the donor block was obtained and deposited onto TMA block at a suitable distance between each core. Three cores were punched from the marked area of each donor block into the recipient block to minimize the number of cases which cannot be evaluated due to tissue loss [10].

Immunohistochemistry

Tissue sections from the microarray were cut at thickness of 4μm. Then deparaffinization, rehydration and antigen retrieval were performed. Then tissue sections were incubated with Anti-*BRCA1* antibody [MS110] (GTX16780) (mouse, monoclonal, MS 110, Gene Tex at dilution rate of 1:50). Sections from breast tissue were stained as positive control. Negative control was done by omission of the primary antibody.

Evaluation of staining

Only nuclear reaction was considered positive and complete loss of nuclear staining is considered representative for protein loss. Nuclear staining in less than 20% of the tumor cells is considered also negative [11]. BRCA 1 IHC status was correlated with other clinicopathological parameters.

Outcomes

The diagnostic relevance of *BRCA1* loss in differentiating serous from endometroid carcinoma was measured as well as the prognostic relevance in correlation with disease free survival (DFS) and overall survival (OS). DFS was measured as the period of time from the operation till first occurrence of recurrence or metastases. Overall survival (OS) was defined as the duration from the date of initial surgical resection to the date of death or last contact [12].

Statistical analysis

Qualitative variable was compared using Chi-square and quntitive variable using t-test. Kaplan-Meier survival function was used to calculate overall survival and disease-free survival. Log rank to compare two survival. Cox regression model was used to calculate predictors affecting overall survival and disease-free Survival.

Results

Clinico-pathological data

This retrospective study was performed on tissue specimens for 94 cases diagnosed with endometrial carcinoma. The age of studied cases ranged from 31 to 81 years old with a mean of (62.39±9.8) years. Detailed clinico-pathological features of studied cases were illustrated in Table 1.

The standard surgical approach was total hysterectomy with bilateral salpinoophrectomy in all cases, but only in 48 cases (51.06%) this was accompanied by pelvic lymph node dissection. Out of them, only 12 cases had positive pelvic nodes (25%). Nine cases were accompanied by paraaortic lymph node dissection, of which only two were infiltrated by tumor tissue.

Immunohistochemical data

Sixty-five cases showed positive *BRCA1* nuclear expression, of which 59 cases (90.8%) were of endometrioid type, while 29 cases showed negative expression of which 10 cases were serous carcinoma and 17 cases were endometrioid carcinoma Table 2.

Correlation between BRCA1 expression and clinico-pathological parameters

Regarding age of cases, there was a statistically significant relationship between *BRCA1* expression and age (P=0.025). The mean age at diagnosis was slightly lower for the *BRCA1*- positive cases compared to *BRCA1*-negative cases (60.86± 9.68) vs (65.75± 9.36) respectively (P=0.025) Table 2.

When cases with negative *BRCA1* nuclear expression were compared to cases with positive BRCA 1 nuclear expression, only statistically significant difference (P=0.001) was found regarding the histologic subtype where positive expression was a feature of endometroid carcinoma (Figure 1) while negative expression was seen in most cases of serous carcinoma (Figure 2).

It is worth to mention that cases with Negative *BRCA1* were more likely correlated with high grade since 45% of grade III endometrioid carcinoma show negative *BRCA1* expression, however only 21% and 18% of cases with grade 1 and grade 2 respectively were *BRCA1* negative,

Table 1. Clinic-Pathologic Features of Studied Cases

		N=94	%
Type	Endometrioid	76	80.9
	Serous	15	16.0
	Clear cell	2	2.1
	Undifferentiated	1	1.1
Grade n=76	I	28	36.4
	II	38	49.4
	III	10	14.3
Stage n=94	IA	39	41.4
	IB	21	21.3
	IC	1	1.1
	II	11	11.7
	IIIA	10	10.6
	IIIB	1	1.1
	IIIC	10	10.6
	IVA	1	1.1
	IVB	1	1.1
Size n=94	<2 cm	22	22.8
	>2 cm	72	77.2
Myometrial invasion n=94	< 1/2	52	55.3
	> 1/2	42	44.7
Lymphovascular invasion(LVI) N=94	-ve	49	52.2
	+ve	45	47.8
Pelvic LN n=94	-ve	36	75.0
	+ve	12	25.0
Para-aortic LN N=9	-ve	7	77.8
	+ve	2	22.2
Extension to adenexa (n=94)	-ve	80	85.1
	+ve	14	14.8
Extension to cervix n=94	-ve	78	83.0
	+ve	16	17.0
Extension to vagina	-ve	92	97.9
	+ve	2	2.1
Serosa N=94	-ve	92	97.9
	+ve	2	2.1
Bladder or bowel mucosa (n=94)	-ve	93	98.9
	+ve	1	1.1
Omentum N=19	-ve	16	84.2
	+ve	3	15.8
Positive Cytology N=11	-ve	8	72.7
	+ve	3	27.3

Table 2. Correlation between *BRCA* eExpression & Clinic-Pathological Parameters

	BRCA		test of significance
	Negative n=29	Positive n=65	
Pathology			P=0.001*
*Endometrioid	17 (22.4)	59 (77.6)	
*Serous	10 (66.7)	5 (33.3)	
Clear cell	1 (50.0)	1 (50.0)	
Undifferentiated	1 (100.0)	0 (0.0)	
Grade			p=0.167
I	6 (21.4)	22 (78.6)	
II	7 (18.4)	31 (81.6)	
III	4 (45.5)	6 (54.5)	
Size			p=0.197
<2 cm	4 (14.3)	18 (26.6)	
>2 cm	25 (85.7)	47 (73.4)	
Myometrial invasion			P=0.092
< 1/2	12 (41.5)	40 (60.9)	
> 1/2	17 (58.6)	25 (38.4)	
LVI			p=0.102
-ve	11 (38)	38 (57.8)	
+ve	18 (62)	27 (41.5)	
Pelvic LN			p=0.714
-ve	10 (71.4)	26 (76.5)	
+ve	4 (28.6)	8 (23.5)	
Para-aortic LN			P=1.0
-ve	4 (80)	3 (75)	
+ve	1 (20)	1 (25)	
Extension to adenexa			p=0.922
-ve	23 (85.2)	54 (84.4)	
+ve	4 (14.8)	10 (15.6)	
Extension to cervix			p=0.970
-ve	24 (82.8)	54 (83.1)	
+ve	5 (17.2)	11 (16.9)	
Extension to vagina			P=0.524
-ve	28 (96.6)	64 (98.5)	
+ve	1 (3.4)	1 (1.5)	
Serosa			P=1.0
-ve	29 (100)	63 (96.9)	
+ve	0	2 (3.1)	
Bladder or bowel mucosa			P=1.0
-ve	29 (100)	64 (98.5)	
+ve	0	1 (1.5)	
Omentum			P=1.0
-ve	6 (85.7)	10 (83.3)	
+ve	1 (14.3)	2 (16.7)	

but that was statistically insignificant (P= 0.167). Similarly, was the LVI, where LVI was present in 62% of *BRCA1* negative cases while only 41.5% of *BRCA1* positive cases showed LVI, however this difference wasn't statistically significant.

Correlation between BRCA expression and patient outcome

Of the 94 studied cases, only 55 cases were eligible for follow up. Their median follows up duration was (30.5 months), 15 cases died, 11 had local recurrence, and 7 had distant metastasis by the end of the follow up period.

Regarding the prognostic parameters, in comparison of the *BRCA1* positive and *BRCA1* negative cases,

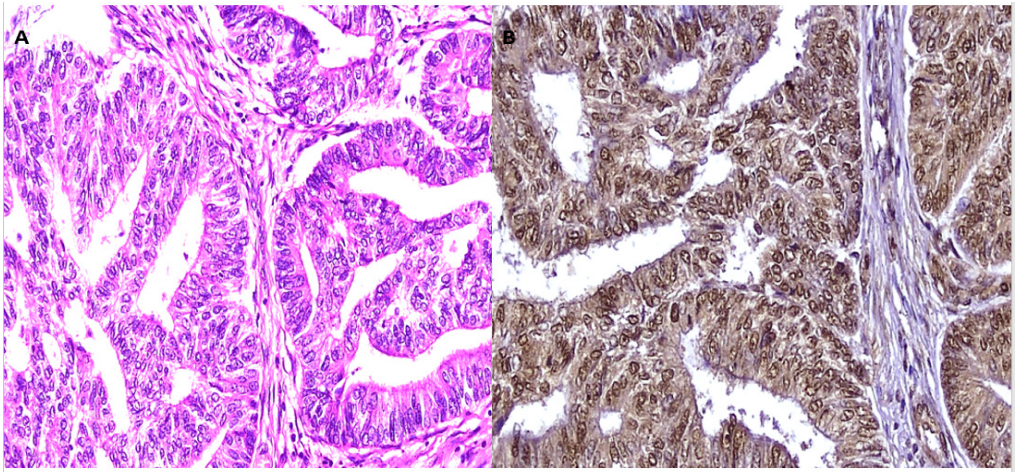

Figure 1. A Case of GI Endometrioid Carcinoma. (A) Predominantly glandular structures more than 50% of the tumor with tumor cells showing mild atypia (H&E X400). (B) Positive nuclear& cytoplasmic *BRCA1* expression (IHC for *BRCA1* X400).

Table 3. Association between *BRCA 1* Expression and Patient Outcome

		BRCA1		test of significance
		Negative n=17	positive n=38	
Metastasis	-ve	16 (94.1)	32 (84.2	p=0.308
	+ve	1 (5.9)	6 (15.8)	
Recurrence	-ve	14 (82.4)	30 (78.4)	p=0.736
	+ve	3 (17.6)	8 (21.6)	
Death	Alive	13 (76.4)	27 (69.4)	p=0.989
	Died	4 (23.5)	11(30.6)	

no statistically significant difference was encountered between both groups regarding the recurrence, metastasis and number of deaths (Table 3).

Survival analysis

Disease free survival

The median duration for C survival (DFS) was 26.0 months and it ranged from 18.3 to 33.7 months. Although Cases with positive *BRCA1* expression had median DFS period 29 months, while cases with negative *BRCA1* expression had shorter median DFS of 18 months, a statistically significant difference was not achieved between the two groups as shown in Table 4.

In univariate regression analysis for highlighting factors affecting DFS, only microscopic type, grade, FIGO stage, and omental deposits were statistically significant Table 4. Serous carcinoma was associated with decreased DFS compared to endometrioid type (P=0.04). Additionally, grade II and grade III tumors showed reduced DFS median (19 and 20 months respectively)

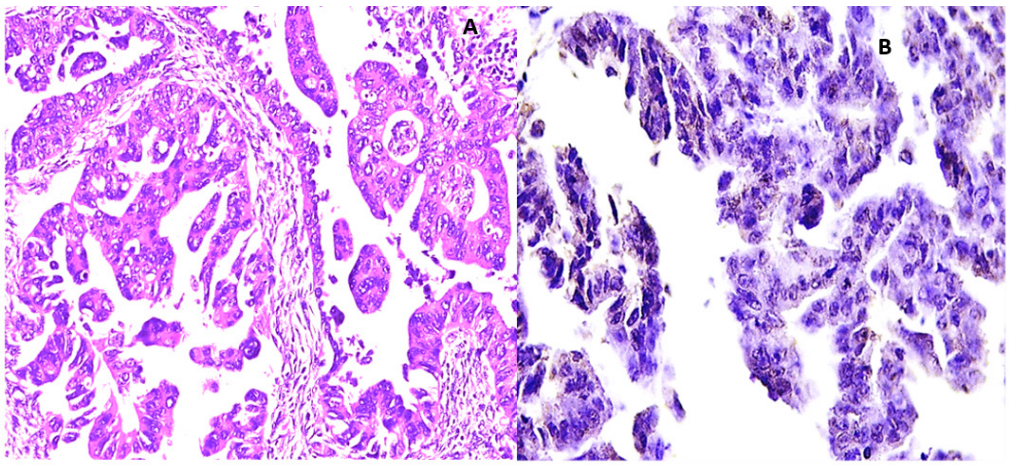

Figure 2. A Case of Serous Carcinoma. (A): Papillae and glandular structures with intra-luminal tufting .Tumor cells showing high degree of atypia and pleomorphism (H&E X400). (B): Negative nuclear B*RCA1* expression (IHC for *BRCA1* X400)

Table 4a. Factors Affecting Disease Free Survival

	Disease free survival time median (95% CI)	P-Value
Overall	26.0 (18.29-33.71)	
1-year	80.00%	
3-years	32.00%	
Pathology		
Endometrioid	28 (17.94-38.05)	
Serous	19 (11-41.31)	p=0.119
Clear cell carcinoma	12 (9.25-50)	
Endometrioid	28 (17.94-38.06)	p=0.04*
Serous	19 (4.11-41.31)	
Grade		
I	39 (32.95-45.05)	
II	19 (11.78-26.22)	p=0.012*
III	20 (14.16-25.84)	
Size		p=0.165
<2cm	33 (24.68-41.32)	
>2cm	19 (16.86-21.14)	
stage		
IA	34.0 (26.2-41.8)	
IB	15.0 (6.24-23.76)	p=0.01*
II	29.0 (13.44-55.33)	
III A	7.0 (6-37.9)	
III B	34.0 (34-34)	
III C	19.0 (10.24-27.77)	
IV A	34.0 (34-34)	
IV B	8.0 (8-8)	
Myometrial invasion		p=0.064
< 1/2	29 (12.12-45.88)	
>1/2	21 (14.52-27.48)	
LVI		p=0.092
-VE	29 (19.77-38.23)	
+VE	21 (14.07-27.93)	
Pelvic LN		
-VE	28 (16.58-39.42)	p=0.167
+VE	20 (14.13-25.87)	
Para-aortic LN		p=0.462
-VE	19 (9.61-28.39)	
+VE	7 (1.25-26.24)	

Table 4b. Factors Affecting Disease Free Survival

	Disease free survival time median (95% CI)	P-Value
Extension to adenexa		p=0.406
-ve	27 (16.25-37.75)	
+ve	18 (15-49.17)	
Extension to cervix		
-ve	24 (14.86-33.15)	p=0.675
+ve	29 (20.19-37.81)	
Extension to vagina		p=0.263
-ve	26 (17.15-34.85)	
+ve	5 (2.0-8.0)	
serosa		
-ve	24 (15.14-32.86)	p=0.937
+ve	28 (25.12-36.88)	
Bladder or bowel mucosa		p=0.930
-ve	26 (18.4-33.65)	
+ve	34 (34-34)	
Omentum		
-ve	20 (11.51-28.49)	p=0.04*
+ve	7.0 (3.08-10.92)	
BRCA1		p=0.189
-ve	18 (8.59-27.4)	
+ve	29 (21.1-36.9)	

compared to 39 months for grade I (P=0.012). Regarding the FIGO stage, cases with stages I &II tended to have increased DFS compared to those with stages III&IV (P=0.01) .Cases with omental deposit had greatly reduced DFS (P=0.04) .

On the other hand, in multivariate Cox regression analysis for these factors, none of which was proved to be independent prognostic factor affecting the DFS.

Overall survival

The median overall survival (OS) in our study was 60 (38.59-81.40) months. By univariate regression analysis, *BRCA1* expression was not found to significantly affect the overall survival (P=0.890). Similarly were all other studied factors

Discussion

A main target in pathological evaluation of endometrial carcinoma is differentiating both endometroid and serous subtypes. Immunohistochemistry is a useful tool in this regard. Aiming to assess the diagnostic and prognostic utility of *BRCA1* IHC staining, the current study evaluated the expression of *BRCA1* in 94 cases of endometrial carcinoma. Additionally this study proposed that *BRCA1* IHC staining could be a rapid, relatively inexpensive, and easily applicable way for detecting *BRCA1* mutational protein loss. This hypothesis was coped with previous studies which assessed the reliability of *BRCA1* IHC staining on *BRCA1* mutant ovarian and breast cancers and reported that IHC staining is an effective method for evaluation *BRCA1* status [2, 5,13].

As an answer for our research question, we recorded a significant diagnostic difference in *BRCA1* expression between endometrioid and serous cases (P=0.001). Most of the serous cases in the current study (66.7%) lost *BRCA1* expression while most of the endometrioid cases (77.6%) retained *BRCA1* expression. This was concordant to the study of Hecht et al. [5] in which there was a statistical significant association between loss of *BRCA1* IHC expression and serous cases. The IHC staining showed a great concordance with the mutational status in the studied cases, which is considered a good point of

reassurance [5].

In agreement with our findings regarding the loss of *BRCA1* in serous carcinoma cases, De Jonge et al. [14] have reported significant association between homologeous recombination (HR) deficiency resulted from germline *BRCA1* mutation and non-endometrioid histology since 100% of HR deficient cases were of non-endometrioid histology [14]. Moreover, Pennington et al., found that *BRCA1* mutation had about 2.5-fold increased risk of developing endometrial carcinoma with a statistically significant increased risk of serous subtype [15]. On the contrary, Lee et al. [16] assessed the incidence of endometrial carcinoma in *BRCA1* mutant carriers in their prospective cohort analysis , they found that most of the developed cases were of endometrioid subtype [16].

Similary, another cohort study reported that women with a either *BRCA1* or BRCA2 mutant variant do not have a significant increased risk of endometrial carcinoma of any histopathologic type compared with the general population indicating that hysterectomy is unlikely to be of benefit if performed as a preventive measure [17].

Berine and colleagues reported that 62% of the studied serous cases had positive *BRCA1* IHC expression in contrast to our study where only 33% of the serous cases showed positive *BRCA1* expression. We thought that this difference may be because most of included patients in their study received combination of platinum and paclitaxel chemotherapy that could affect *BRCA1* protein expression. Another explanation could be related to the underlying mechanism of *BRCA1* gene mutation such as promoter methylation and absence of LOH which may lead to retained *BRCA1* expression [7].

When investigating the prognostic relevance of *BRCA1*, deficient cases did not score a statistically significant correlation regarding poor prognostic parameters as high grade, advanced stage, and LVI. Although these parameters were more frequent in *BRCA1* negative cases, the small number of cases in the current study interfered with achieving statistically significant results. In this regard De Jonge et al. [14] reported significant association between *BRCA1* neagtive cases and high grade endometrial carcinoma as well as LVI but found no difference regarding the stage [14].

Moreover, the current study didn't reveal an association between *BRCA1* expression and overall survival. On the other hand, *BRCA1* negative cases had reduced median disease-free survival period (DFS); 18 months compared to 29 months, for *BRCA1* positive cases. This finding suggested that *BRCA1* mutant cases may have worse prognosis than wild type cases, however that was statistically insignificant (P= 0.189). These results were comparable to the study of De Jonge et al. [14] in which *BRCA1* mutant cases had lower overall survival than cases without *BRCA1* mutation [14].

To the best of our knowledge, the current study is one of the few studies addressing *BRCA1* IHC expression in endometrial carcinoma. The statistically significant difference in the expression of *BRCA1* between endometroid and serous carcinoma cases encountered in this study can support its inclusion in a panel to differentiate both tumors. This can add a great help in the daily practice of problematic cases. Additionally, detecting cases with *BRCA1* loss using rapid, relatively inexpensive, daily adopted mean as IHC can help in selection of group of patients that can enefit from use of PARP inhibitors.

Unfortunately, whether *BRCA1* IHC is correlated with *BRCA1* mutational sate, still an open question that this current study was limited to answer, since the studied cases weren't referred for genetic testing. Although *BRCA1* negative expression by IHC can indicate *BRCA1* mutation, on the contrary, *BRCA1* positive IHC doesn't necessarily indicate absent mutation. In this regard, Maxwell et al., found that most cases with promoter methylation retain protein expression and this may be related to the methylation of the mutant allele as opposed to wild type one [18]. These cases may show resistance to platinum-based therapy and therefore can't get benefit from PARP inhibitors. This sheds lights upon the need to investigate the correlation between *BRCA1* IHC and mutational state on wider scale and the benefit of the costly genetic testing for *BRCA1* mutation in cases with endometrial serous carcinoma that are platinum resistant. Additionally, prognostic value of *BRCA1* need to be validated on larger scale studies since we were limited by the availability of prognostic data.

Author Contribution Statement

Sara Ahmed Ali Eldegwi: Data curation, Methodology, Writing; Maha Mohamed Amin: Supervision, Review &editing; Sylvia Albair Ashamallah: Supervision, Review &editing; Reham Alghandour: Data collection , follow up of cases; Reham Mohamed Nagib: Conceptualization, Methodology, Writing, Review &editing.

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