RESEARCH ARTICLE

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Evaluation of Mismatch Repair (MMR) and Breast Cancer-1 (*BRCA-1*) Statuses in Epithelial Ovarian Cancer

Richa Singh[1], Preeti Agarwal[1]*, Shuchi Agrawal[2], Eva Raman[2], Vandana Solanki[2], Puneet Prakash[3], Malti Kumari Maurya[1], Riddhi Jaiswal[1], Sameer Gupta[3]

Abstract

Introduction: This study aims to evaluate the expression of *BRCA1* and MMR proteins using immunohistochemistry (IHC) in epithelial ovarian cancers and to explore their clinicopathological correlations. **Methodology:** IHC was performed and interpreted for *BRCA1, MLH1, MSH2, MSH6,* and *PMS2*. The results were then compared with clinical and pathological variables. **Results:** Over a period of 19 months, 508 specimens containing ovarian tissue were received, either as part of a hysterectomy or as isolated samples for various indications. Among these, 24.01% (122/508) showed invasive epithelial ovarian cancer. Of these, 49 resection specimens had sufficient tumor tissue for detailed immunohistochemistry (IHC) analysis and were included in the study. Among the evaluated cases, 51% (25/49) of invasive epithelial ovarian cancers exhibited deficient mismatch repair (dMMR). No significant correlation was observed between dMMR and pMMR with respect to grade, cellularity, and high-grade features. Patients with dMMR showed better survival, which may be due to improved response to chemotherapy in these cases. Total loss of *BRCA1* was seen in 36.7% (18/49) of cases. *BRCA1* loss was associated with poor predictive factors but had better prognosis. Loss of *BRCA1* was associated with aggressive tumors but had better response to chemotherapy. Both MMR and *BRCA1* were independent variables. The overall survival of our patient population with epithelial ovarian cancer was 86.8%. **Conclusion:** A significant number of patients displayed dMMR and *BRCA1* loss by IHC. These patients may benefit from targeted therapy, and IHC may serve as an acceptable technique for each evaluation.

Keywords: Epithelial cancers of ovary- *BRCA1*- MMR- Immunohistochemistry- ovarian cancers

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Introduction

India presents with appreciable geographic variation in the incidence of ovarian cancer, about 50% of cases occur in the age group of 45-65 years [1]. It contributes to around 5.9% of total cancer cases in the country with a mean age-adjusted rate of 5.6 per 100000 populations [2]. The tumors of the ovary are classified into- epithelial-stromal tumors, sex cord-stromal tumors, and germ-cell tumors based on the anatomic structure from which the tumor originates. Epithelial cancers in the ovary are the most common and are broadly divided into serous, mucinous, endometroid, clear cell, and brenner subtypes based on histomorphological features.

The five-year relative survival rate is approximately 30-50% cumulative of all stages [3]. As ovarian cancer does not present with specific symptoms at the disease onset, the symptoms present when the disease spreads to the abdominal cavity and peritoneum, the screening tests like transvaginal sonography and serum cancer antigen-125 (CA-125) have limited role in early detection of the cancer. The standard treatment regimen includes a combination of surgery and platinum or taxane-based adjuvant chemotherapy, which may show relapse and may result in early mortality.

Conventional chemotherapy is the main treatment for ovarian cancer. Although *BRCA1*(Breast Cancer gene 1) is a known target for treatment, it needs special molecular tests, so it is not commonly used in managing ovarian epithelial cancer [3]. A family history of ovarian, breast, or endometrial cancer can increase the risk of inheriting autosomal dominant genes. The cumulative risk of ovarian cancer is 49% in those with *BRCA1* mutations and 21% in those with BRCA2 (Breast Cancer gene 2) mutations [4]. *BRCA1* mutations can be both inherited or acquired due to epigenetic silencing [5].

Both *BRCA1* and mismatch repair (MMR) genes play key roles in DNA repair and are now widely recognized for their importance in this process [5-7]. MMR has been included in the revised WHO classification of endometrial

*[1]Department of Pathology, King George's Medical University, Lucknow, UP, India. [2]Department of Obstetrics and Gynecology, King George's Medical University, Lucknow, UP, India. [3]Department of Surgical Oncology, King George's Medical University, Lucknow, UP, India. *For Correspondence: preavn@gmail.com*

cancers. However, they have been not widely investigated for epithelial cancers in the ovary. Molecular cross-talk is a well-established phenomenon. As both of them are involved in DNA repair we expect that there must be some co-relation between both these proteins in terms of expression in tumor cells. The data from the Indian subcontinent for *BRCA1* and MMR protein expression is very scarce with no study evaluating both these markers together in ovarian epithelial cancers [6]. These have been evaluated in colorectal cancers though with suggested inter-pathway talk [7].

Both *BRCA1* and MMR offer added therapeutic advantages in terms of available targeted chemo and immunotherapeutic options. Hence in the present study, aims to study the expression of *BRCA1* and MMR at the protein level by using immunohistochemistry (*BRCA1*, MLH1, MSH2, MSH6, and PMS2) in epithelial cancers of the ovary and their clinical and pathological co-relation.

Materials and Methods

Tertiary care hospital and lab based prospective cohort study was undertaken with interdepartmental collaboration for a duration of 19 months. Sample size was calculated using modified version of Cochran's formula, N= 4 Z2 P (1-P) / d2, where n = Sample size, P = Prevalence, d = Degree of freedom (10%); Z= Differentiation coefficient (1.96 or 2); P = 5.6% = 0.056: N= 81, which was further modified as approximately 60% of malignant ovarian tumors are epithelial by diagnosis [8]. The study was approved by institutional ethics committee via letter number 2112/Ethics/2023 dated 27.02.2023.

Inclusion and Exclusion Criteria: All the surgically resected specimens with histological diagnosis of epithelial ovarian cancer with adequate tumor tissue for further immunohistochemistry were enrolled in the study. Patients who denied to enroll or where histological diagnosis was of non-epithelial ovarian cancer were excluded.

Detailed demographic data along with histopathological findings were documented. After informed consent, tissue block with maximum tumor area with epithelial cancer of the ovary was subjected to an IHC panel of *BRCA1*, *MLH1, MSH2, MSH6,* and *PMS2.* Immunohistochemistry was performed via indirect method using peroxidase-labeled secondary antibody. Biocare decloaking chamber was used for antigen retrieval for 20 minutes at 110 degrees with TRIS-EDTA buffer (pH-9). Internal peroxidase blocking was performed by peroxidase quencher (PathnSitu). Primary antibodies used were 1) *BRCA1*- polyclonal, RTU (BioGenex Fremont CA 94538 USA) 2) MLH1- Mouse monoclonal, RTU (PathnSitu 1257, Pleasaton, CA-94566, USA) 3) *MSH2*- Rabbit monoclonal, RTU (PathnSitu 1257, Pleasaton, CA-94566, USA) 4) *MSH6*- Rabbit monoclonal, RTU (PathnSitu 1257, Pleasaton, CA-94566, USA) 5) PMS2- Rabbit monoclonal, RTU (PathnSitu 1257, Pleasaton, CA-94566, USA). Tonsillar tissue was used for control of *MLH1, MSH6* and *PMS2* respectively, and intestinal tissue for *MSH2*.

The stained sections were examined under high power (x400). Nuclear expression was then studied in terms of the percentage and intensity of expression. For *MLH1, MSH2, MSH6*, and *PMS2*: total loss of nuclear expression was considered as the loss of that marker [9]. For *BRCA1* nuclear, cytoplasmic and total expression was recorded separately and when >75% tumor cells did not show any immunoexpression only then they were considered as negative.

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 21.0 Statistical Analysis Software. The values were represented in number (%) and mean ± SD. Statistical formulas used were: Mean, Standard Deviation, Chi-square test, and Kappa test.

Results

Over a span of 19 months, a total of 508 resected specimens were received with ovarian tissue with or without being a part of hysterectomy procedure for several indications. Distribution of these cases is summarized in Figure 1. According to our dataset, the average age of patients diagnosed with benign epithelial tumors was 38.57 years, while for borderline tumors, it was 37.87 years. Patients with malignant tumors had a slightly higher average age of 46.87 years.

Out of the 508 ovarian tissue samples received, approximately 50% (253 cases; 49.8%) were identified as epithelial tumors. Nearly half of these epithelial tumors (122/253; 48.2%) showed invasive cancer, regardless of subtype. Among the 122 invasive cases, 42 were biopsy samples, taken either for staging or diagnostic purposes and 80 were resection specimens. Twenty-two ovarian resection specimens came from patients who had undergone chemotherapy, showing extensive tumor necrosis and only scant residual tumor. Immunohistochemistry (IHC) was attempted in 58 cases, but in 9 cases, the tumor tissue floated during processing even after two attempts making them unsuitable for further work-up. As a result, 49 invasive epithelial ovarian cancer cases with resection specimens were successfully evaluated using the full IHC panel. Demographic details of the studied 49 cases have been shown in Table 1. 32.7% (16/49) females harbored bilateral cancers. Most patients had stage III cancers at the time of surgery (61.2%; 30/49) with high grade morphology (85.7%; 42/49).

As per our institutional protocol, neoadjuvant chemotherapy (NACT) is administered to ovarian cancer patients presenting with disseminated intra-abdominal disease, including omental or peritoneal involvement, bulky locoregional lymph nodes, or gross ascites. These patients receive four cycles of Paclitaxel- and Carboplatin-based chemotherapy every three weeks. After completing four cycles, they are reassessed using contrast-enhanced CT (CECT) of the abdomen and tumor marker levels to evaluate suitability for interval cytoreductive surgery. Following surgery, four additional cycles of adjuvant chemotherapy are given. Patients who do not present with the above features undergo upfront surgery, followed by chemotherapy with the same Paclitaxel-Carboplatin regimen as required. Majority of patients studied received post operative chemotherapy (87.8%; 43/49).

Table 1. Clinico-pathological Parameters of Study Sample

S.No.	Characteristic	No. of cases	Percentage
1	Laterality		
	Bilateral	16	32.7
	Left	8	16.3
	Right	12	24.5
	NA	13	26.5
2	Capsule		
	Breached	4	8.2
	Intact	45	91.8
3	LVI	2	4.1
4	PNI	1	2
5	Lymph node		
	Not submitted	42	85.7
	Positive	1	2
	Negative	6	12.2
6	Necrosis	19	38.8
7	FIGO Stage		
	I	10	20.4
	Ia	2	
	Ib	5	
	Ic	1	
	Ic3	2	
	II	6	12.2
	IIa	2	
	IIb	4	
	III	30	61.2
	IIIa	1	
	IIIa1	1	
	IIIb	7	
	IIIc	19	
	IIIc3	2	
	IV	3	6.1
	IVa	3	
8	Grade of tumor		
	High Grade	42	85.7
	Low Grade	7	14.3
9	Chemotherapy		
	Post-operative paclitaxel and carboplatin	43	87.8
	Both pre-operative and post operative paclitaxel and carboplatin	6	12.2

The immunohistochemistry was applied on 49 cases of epithelial cancers of ovary (Figure 2), and 32 cases showed nuclear loss of *BRCA1*, 21 cases showed cytoplasmic loss whereas 18 cases displayed total loss of *BRCA1* (Table 2, Figure 3). The proportion of *BRCA-1* nuclear loss was higher in low grade (15.6% vs. 11.8%) but this difference was not found to be significant statistically. Lymph vascular invasion (n=2) and perineural invasion (n=1) were rare high-grade features in the present study and did not show any significant association with *BRCA-1* nuclear loss. Cases with *BRCA-1* nuclear loss had significantly lower tumor cellularity as compared to cancer with *BRCA-1* expression (63.75±19.13 vs. 76.76±19.76) (Table 3).

Table 2. Immunohistochemical Results of Studied Population

S.No.	Statuses	No.	%
1	*BRCA-1* nuclear loss	32	65.9
2	*BRCA-1* cytoplasmic loss	21	42.9
3	*BRCA-1* total loss	18	36.7
4	MMR deficient	25	51.1
5	MMR proficient	24	48.9

Mismatch repair gene evaluation by IHC was reported as per the recent guidelines by the College of American Pathologists (CAP) considering any positive tumor nuclei as the presence of the marker. Table 2 shows the distribution of cases according to it.

Out of 3 clear cell carcinoma cases, 2 (66.7%) were dMMR (deficient mismatch repair) and 1 (33.3%) pMMR (mismatch repair proficient). The lone case of endometrioid adenocarcinoma was dMMR. Out of 6 cases of mucinous adenocarcinoma 4 (66.7.0%) were dMMR and the rest 33.3% were pMMR. The proportion of dMMR [Figure 4] and pMMR (Figure 5) for serous carcinoma were 56.2% (18/39) and 53.8% (21/39). MMR status of the cases did not significantly correlate with high-grade features including lymph vascular invasion, necrosis and tumor cellularity (Table 4) No significant co-relation was seen between MMR status and *BRCA1* loss in the study as well.

Out of 49 cases of epithelial cancer in the ovary, 11 patients were lost to follow-up. The follow up computation of the studied variables was conducted for 38 patients. The cases were followed up for a mean duration of 8.4 months. Five patients passed away within 1-8 months of diagnosis. Four patients were currently undergoing chemotherapy. One patient who was diagnosed with high-grade serous carcinoma underwent repeat surgery after 6 months for the excision of a positive left iliac lymph node and has been planned for chemotherapy. The remaining 28 patients were doing well and are on regular follow-up (Table 5).

Discussion

A mismatch repair system (MMR) targets the removal and repair of base mismatch produced in the process of DNA recombination and replication. Defect in MMR is detected by the alteration in various genes, forming the MMR complex, and is defined as deficient MMR. Microsatellite instability (MSI) is molecular alterations or mutations which lead to loss of mismatch repair proteins. This study highlights the significance of *BRCA1* and MMR protein expression in ovarian epithelial cancers, emphasizing their roles in prognosis and treatment response. The research finds that deficient

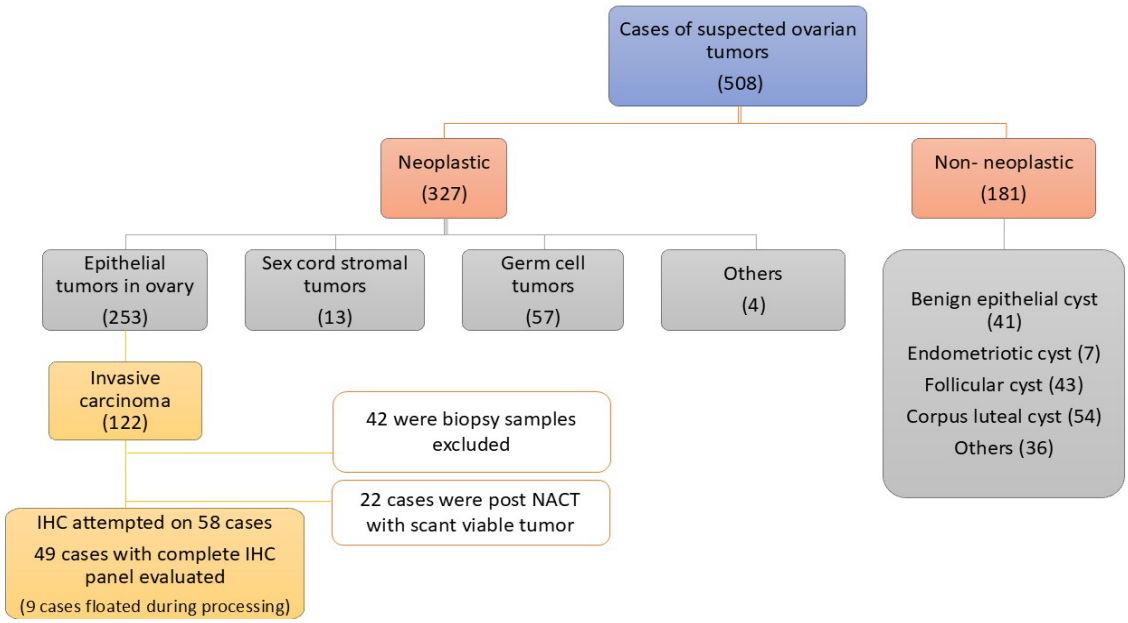

Figure 1. Flowchart Depicting the Distribution of Diagnosis among the Ovarian Tissues Received in the Studied Period.

MMR (dMMR) was found in 51% of cases, and these patients exhibited better survival rates, possibly due to increased chemotherapy sensitivity. *BRCA1* loss was present in 36.7% of cases and was associated with more aggressive tumors; however, these tumors also responded better to chemotherapy, leading to improved prognosis. Therefore, immunohistochemistry assessment of *BRCA1* and MMR proteins could serve as a valuable predictive tool for therapeutic response in ovarian epithelial cancers.

Worldwide literature shows a 7-22% prevalence of

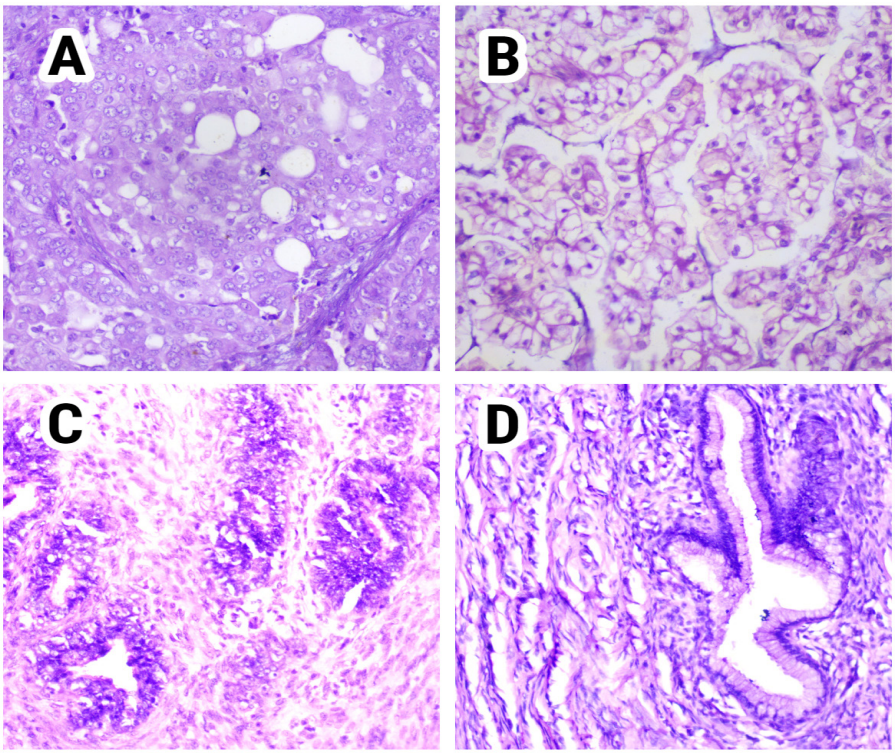

Figure 2. Section Shows Hematoxylin and Eosin-Stained Images of Epithelial Cancers in the Ovary (A) high-grade serous carcinoma is seen with tumor cells arranged in sheets displaying high nucleocytoplasmic ratio and prominent nucleoli, in B clear cell carcinoma can be seen with cytoplasmic clearing of the tumor cells. In C endometroid tumor is seen with irregular glands infiltrating the stroma. In D mucinous cancer is seen with tumor cells displaying cytoplasmic mucin. (A-D; H&E x200)

Table 3. Association of *BRCA* Nuclear Loss with Different Variables (n=49)

	Total	Nuclear loss absent (n=17)		Nuclear loss present (n=32)		Statistical significance	
		No.	%	No.	%	χ^2	'p'
Grade							
High Grade	42	15	88.2	27	84.4	0.135	0.713
Low Grade	7	2	11.8	5	15.6		
FIGO Stage							
1	10	4	23.5	6	18.8	1.774	0.621
2	6	2	11.8	4	12.5		
3	30	9	52.9	21	65.6		
4	3	2	11.8	1	3.1		
High-Grade features							
Lymphovascular invasion	2	1	5.9	1	3.1	0.216	0.642
Perineural invasion	1	0	0	1	3.1	0.542	0.461
Necrosis	19	11	64.7	8	25	7.373	0.007
Capsular invasion							
Breached	4	1	5.9	3	9.4	0.181	0.671
Intact	45	16	94.1	29	90.6		
Lymph nodes							
Negative	6	3	17.6	3	9.4	1.186	0.553
Positive	1	0	0	1	3.1		
Not submitted	42	14	82.4	28	87.5		
Chemotherapy							
CT	43	14	82.4	29	90.6	0.707	0.4
NACT	6	3	17.6	3	9.4		
Cellularity %		76.76±19.76		63.75±19.13		't'=2.241; p=0.030	

MSI in epithelial cancers of the ovary [10] whereas an Indian study by Shilpa V. et al found the prevalence to be >60%, which is in concordance with our finding of 51% MSI in epithelial cancers of the ovary [6]. The data about high MSI in the Indian population is well demonstrated in colorectal cancers as well. Worldwide prevalence of

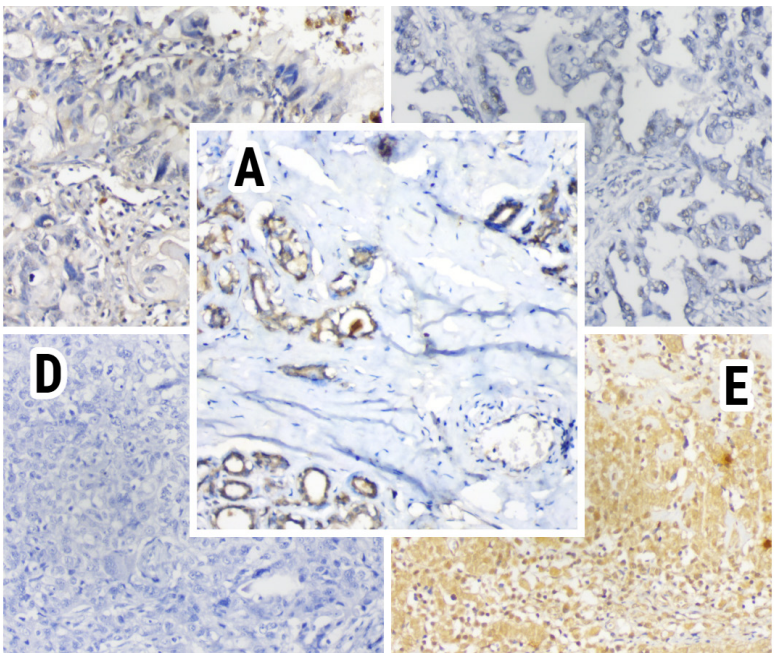

Figure 3. Section A showing positive expression of *BRCA1* in fibroadenoma (Control). Section B-E from serous carcinoma displaying nuclear loss of *BRCA1*, cytoplasmic loss of *BRCA1*, complete loss of *BRCA1* and no loss of *BRCA1* respectively. (A-E; DAB x200)

Table 4. Association of MMR Status with Studied Variables (n=49)

	Total	dMMR(n=25)		pMMR(n=24)		Statistical significance	
		No.	%	No.	%	χ^2	'p'
Grade							
High Grade	42	20	80	22	91.7	1.361	0.243
Low Grade	7	5	20	2	8.3		
FIGO Stage							
1	10	6	24	4	16.7	1.914	0.591
2	6	4	16	2	8.3		
3	30	13	52	17	70.8		
4	3	2	8	1	4.2		
High-Grade features							
Lymphovascular invasion	2	0	0	2	8.3	2.172	0.141
Perineural invasion	1	1	4	0	0	0.99	0.322
Necrosis	19	9	36	10	41.7	0.166	0.684
Capsular invasion							
Breached	4	3	12	1	4.2	1.002	0.317
Intact	45	22	88	23	95.8		
Lymph nodes							
Negative	6	4	16	2	8.3	1.742	0.418
Positive	1	1	4	0	0		
Not submitted	42	20	80	22	91.7		
Chemotherapy							
CT	43	14	82.4	29	90.6	0.707	0.4
NACT	6	3	17.6	3	9.4		
Cellularity %		67.80 ±18.71		68.75±21.93		't'=0.163; p=0.871	

MSI in colorectal cancers is 10-15% whereas the Indian population harbors 27-40% MSI [7, 11-13]. Significant co-relation between evaluation of MSI by molecular methods and dMMR immunohistochemical profile has been seen, still about 5–11% patients with MSI are not deficient MMR on immunohistochemistry. This may be due to the fact that rare missense mutations may lead to functional inactivation of the resultant protein which does not lose its antigenicity [14].

As per our observation, there was no significant correlation in the grade of ovarian cancers according to MMR status. However, as most of our cases belonged to

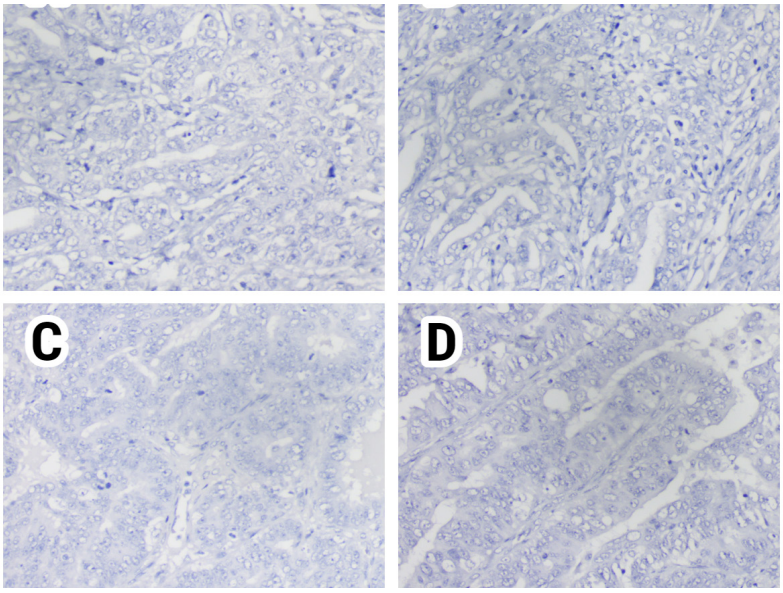

Figure 4. Section from a High-Grade Serous Carcinoma Displaying Loss of Nuclear Expression of All Markers in A-D; MLH1, MSH2, MSH6, and PMS 2 respectively. (A-D; DAB x200)

Table 5. Association of Outcome with Different Variables (n=38)

	Total	Expired (n=5)		Alive (n=33)		Statistical significance	
		No.	%	No.	%	c^2	'p'
Grade							
High Grade	31	4	80	27	81.8	0.01	0.922
Low Grade	7	1	20	6	18.2		
FIGO Stage							
1	9	1	20	8	24.2	3.015	0.389
2	4	0	0	4	12.1		
3	23	3	60	20	60.6		
4	2	1	20	1	3		
High Grade features							
Lymph vascular invasion	2	0	0	2	6.1	0.32	0.572
Perineural invasion	1	0	0	1	3	0.156	0.693
Necrosis	16	3	60	13	39.4	0.756	0.384
Capsular invasion							
Breached	3	0	0.00%	3	9.10%	0.482	0.494
Intact	35	5	100.00%	30	90.90%		
Lymph nodes							
Negative	4	2	40.00%	2	6.10%	5.381	0.068
Positive	1	0	0.00%	1	3.00%		
Not submitted	33	3	60.00%	30	90.90%		
BRCA-1 Nuclear loss							
Absent	14	3	60	11	33.3	1.327	0.249
Present	24	2	40	22	66.7		
BRCA-1 Cytoplasmic loss							
Absent	22	5	100	17	51.5	4.187	0.041
Present	16	0	0	16	48.5		
BRCA-1 Total loss							
Absent	24	5	100	19	57.6	3.359	0.067
Present	14	0	0	14	42.4		
MMR status							
dMMR	23	2	40	21	63.6	1.015	0.314
pMMR	15	3	60	12	36.4		
Chemotherapy							
CT	34	5	100	29	87.9	0.677	0.41
NACT	4	0	0	4	12.1		
Cellularity %		80.00±17.32		67.73±19.96		't'=1.299; p=0.202	

FIGO stage III, 56.6% of cases belonged to the pMMR group i.e. there was no defect in the MMR pathway, and among 10 cases in FIGO stage I, 60% of cases had dMMR. There was no significant correlation between high-grade features like lymph vascular invasion, perineural invasion, necrosis, and cellularity in both groups. Though capsule breach was more common in the dMMR group, this can be correlated to the large size of tumors exhibiting dMMR because of high erroneous replicative potential as per the published literature [13].

The literature suggests that the relationship between MMR gene inactivation in ovarian cancer and factors such as stage, grade, or pathological features lacks clarity due to a lack of large-scale data [15]. Despite our detailed literature review, we did not encounter any studies detailing the correlation between MMR defects and the pathological features or grade of the disease. However, in colorectal cancer patients, those with MSI exhibit distinct clinical and pathological characteristics, such as early onset, a higher prevalence in the right hemicolon, and a favorable prognosis. Though not significant, 63.5% of all alive and doing well females of our study population had dMMR. The dMMR in ovarian cancers has also been linked to favorable prognosis due to response to immunotherapy/ chemotherapy [16, 17].

As per our interpretation of protein expression of *BRCA1* as nuclear loss, cytoplasmic loss, and total loss, we inferred the results as total loss in 36.7% (18/49)

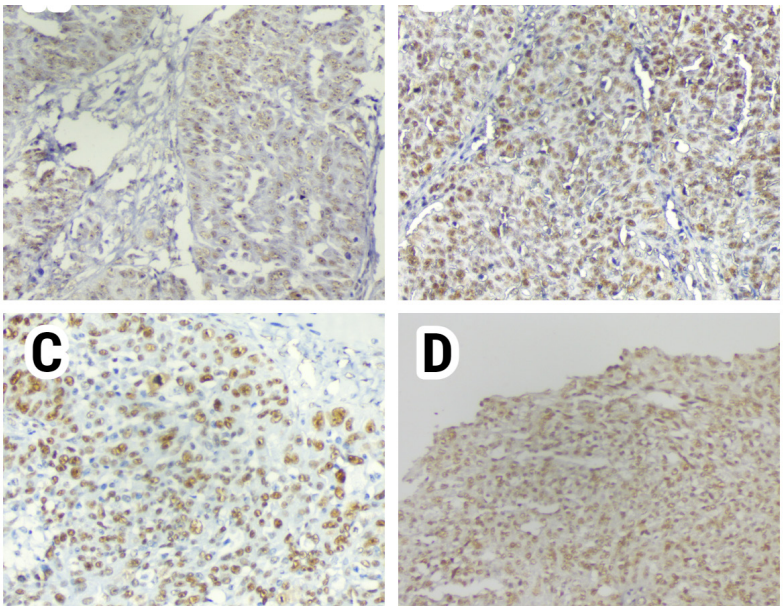

Figure 5. Section from a High-Grade Serous Carcinoma Displaying Nuclear Expression of All Markers in A-D; MLH1, MSH2, MSH6, and PMS 2 respectively. (A-D; DAB x200)

cases. When *BRCA1* was compared to the survival of the cases, we found that patients with nuclear loss of *BRCA1* had better survival as compared to the intact *BRCA1*. According to our datasets, the loss of *BRCA1* is associated with poor predictive factors, as *BRCA1* was associated with tumors with high grade morphology, 70% of FIGO stage III tumors displayed loss of *BRCA1*. Though not significant but perineural invasion, capsular breach, and lymph node metastasis was common in tumors with loss of nuclear expression of *BRCA1*.

BRCA1 is essential for homologous recombination repair of DNA double-strand breaks, hence defective BRCA gene results in a defect in the repair pathway and produces tumor cells, resistant to apoptosis, thus the necrosis seen in these tumors can be attributed to reduced perfusion. However, this resistance to apoptosis is employed as a therapeutic mechanism against *BRCA1* mutated tumors [18]. The tumors with intact *BRCA1* had significantly higher tumor necrosis and higher percentage cellularity. [Table 3]

As per our records, the overall survival was 86.8%, which is much higher than the published literature i.e. 30-50%. This may be because our mean follow-up duration was 8.5 months and further follow-up may provide a better picture. Secondly, it might be due to the higher prevalence of *BRCA1* loss and dMMR, which is linked to better response to the chemotherapeutic agents. However, all these presumptions need confirmation by the longer duration of follow-up of these cases [6, 13].

Our findings demonstrate that *BRCA1* and MMR are independent variables, as there was no significant correlation between them. Few limitations of the present study were lack of further molecular work-up of the cases and limited follow- up. The observations need to be confirmed on larger dataset.

Strengths and limitations

Strengths: The study addresses a pertinent gap by exploring *BRCA1* and MMR status in ovarian epithelial cancers within an Indian cohort, where limited data is available. IHC was meticulously conducted, with comprehensive reporting on the expression of key markers (*MLH1, MSH2, MSH6, PMS2,* and *BRCA1*). The findings hold potential clinical relevance, suggesting that IHC profiling could aid in guiding targeted therapies.

Limitations: A limited sample of 49 cases may restrict the generalizability of findings, particularly given the study's cross-sectional nature. The mean follow-up duration of 8.4 months is relatively short for capturing long-term survival outcomes or recurrence data. The study lacks molecular confirmation of MMR status and *BRCA1* mutations, which would strengthen the reliability of the findings, as IHC alone may not fully capture the functional status of these proteins. Despite some associations between MMR/*BRCA1* status and clinical outcomes, many comparisons did not reach statistical significance, indicating the need for larger sample sizes to validate these relationships.

Clinical implications of the study

The FDA has granted approval for the use of pembrolizumab in managing patients with unresectable or metastatic MSI-H or dMMR solid tumors, regardless of the cancer's site of origin. It has also been proven effective in gynecologic cancers. Therefore, by assessing the microsatellite instability status in epithelial ovarian cancers, we can implement targeted therapy and potentially prolong patients' overall survival [19]. PARP inhibitors, such as olaparib, are a major therapeutic option for *BRCA1*/2-mutated solid tumors. Therefore, identifying the *BRCA1* status and associated morphological characteristics will help guide therapy more effectively [20]. Recent studies highlight the therapeutic efficacy of hyperthermic intraperitoneal chemotherapy in advanced cancers with dMMR. This technique holds promise for advanced ovarian cancers and has become recently

available in our center. however, further studies with a larger patient population are needed to establish its clinical significance.

In conclusion, as per our study 51% of epithelial cancers of the ovary were dMMR. No significant correlation was observed between dMMR and pMMR with respect to grade, cellularity, and high-grade features. Patients with dMMR had better survival which may be due to better response to chemotherapy seen in these cases. Total loss of *BRCA1* was seen in 36.7% of cases. The loss of *BRCA1* was associated with poor predictive factors but had better prognosis. Loss of *BRCA1* was associated with aggressive tumors but had better response to chemotherapy. Both MMR and *BRCA1* were independent variables. The overall survival of our patient population with epithelial cancer of the ovary was 86.8%.

Author Contribution Statement

Conceptualization-Preeti Agarwal; Methodology- Richa Singh, Eva Raman, Sameer Gupta and Preeti Agarwal, Software- Richa Singh, Puneet Prakash and Preeti Agarwal; Validation- Richa Singh, Puneet Prakash, Shuchi Agrawal, Riddhi Jaiswal and Preeti Agarwal; Formal analysis- Richa Singh, Eva Raman, Malti Kumari Maurya and Preeti Agarwal; Investigation- Vandana Solanki and Puneet Prakash ; Resources-Shuchi Agrawal and Puneet Prakash; Data Curation- Riddhi Jaiswal and Sameer Gupta; Writing - Original Draft- Richa Singh and Preeti Agarwal; Writing - Review & Editing- Preeti Agarwal; Visualization-Preeti Agarwal; Supervision- Preeti Agarwal; Project administration- Preeti Agarwal; Funding acquisition- Research cell, seed grant for post graduate student Letter number: 728/R-cell:23

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Scientific body approval

This is a part of intramural seed grant and was approved by departmental scientific committee after which it was also approved by institutional ethical committee.

Competing/ conflict of interests

Both Dr. Richa Singh and Dr. Preeti Agarwal have equal contribution to the manuscript

Ethical approval and consent

The study was approved by institutional ethical committee of King George's Medical University, Lucknow via letter number 1949/ethics/2023 (Ref code: XIV-PGTSC-IIA/P61). Informed consent was taken from each enrolled patient.

Data availability

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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