RESEARCH ARTICLE

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Mismatch Repair Gene Deficiency in Ovarian Cancer: A Clinicopathological Analysis of *MLH1, PMS2, MSH2,* and *MSH6* Mutations Across Histological Subtypes

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Abstract

Aim: Mismatch repair (MMR) deficiency is a prognostic biomarker in multiple malignancies, but its clinical significance in ovarian cancer (OC) remains poorly defined. This study investigates the prevalence of MMR gene defects (*MLH1, PMS2, MSH2, MSH6*) across OC histotypes and their clinicopathological associations. **Methods:** A retrospective cohort of 38 OC patients treated at Azerbaijan Medical University (2018–2023) underwent immunohistochemical (IHC) analysis of MMR protein expression. Clinicopathological data, including survival, recurrence, tumor characteristics, and biomarker status (Ki67, p53), were analyzed using SPSS v26.0. MMR deficiency was defined as loss of nuclear expression in ≥1 protein. **Results:** MMR deficiency was identified in 5.2% of cases (2/38), restricted to endometrioid carcinomas (33.3% of endometrioid cases, 2/6). No deficiencies occurred in serous (n=27), clear cell (n=2), or mixed subtypes (n=3). Endometrioid tumors exhibited larger mean tumor size (13.7 ±5.2 cm vs. 10.0 ±3.7 cm in serous; p=0.01) and distinct Ki67/*p53* expression patterns (p<0.05). Despite 55.3% overall mortality (21/38), MMR-deficient cases showed no recurrence or mortality. Serous carcinomas had the highest recurrence (37.0%, 10/27) and mortality rates (70.4%, 19/27). Five-year survival was 81.6%, with no significant association between MMR status and survival (p>0.05). **Conclusion:** MMR deficiency in OC is histotype-dependent, occurring exclusively in endometrioid carcinomas. While not prognostic in this cohort, dMMR screening may guide surveillance for synchronous malignancies and identify candidates for immunotherapy. Multicenter studies with expanded cohorts are needed to validate clinical utility.

Keywords: Ovarian cancer- mismatch repair deficiency- immunohistochemistry- endometrioid carcinoma

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Introduction

Ovarian cancer remains the most lethal gynecologic malignancy, with a marked rise in incidence observed over the past five decades. According to projections by the American Cancer Society (2024), an estimated 19,680 new cases will be diagnosed in the United States, with 12,740 anticipated fatalities [1]. Prognosis varies significantly by disease stage; the five-year overall survival (OS) rate approaches 93% for localized tumors but decreases to 31% in cases with distant metastases, contributing to an average OS of 30-40%. Late-stage detection persists as a principal barrier to improved outcomes, as over 70% of patients present with advanced disease [2]. As a result, the survival rates for ovarian cancer continue to be unacceptably low. Disease recurrence within six months after platinum-based chemotherapy is indicative of chemoresistance, observed in nearly 70% of ovarian cancer patients. Key independent clinical predictors of recurrence include patient age, disease stage, histological tumor grade, presence of ascites, and surface involvement of the ovary. Additionally, advanced-stage cancer, residual tumor volume following cytoreductive surgery, use of neoadjuvant chemotherapy, and BRCA mutation status have been established as significant risk factors linked to both progression of disease and increased mortality rates [3]. There is a considerable lack of accessible and reliable molecular biomarkers for prevention, diagnosis, individualized treatment, and prognosis prediction. Despite variations in histology, the clinical management approach for ovarian cancers has remained systematic.

DNA mismatch repair (*MMR*), an evolutionarily conserved mechanism critical for preserving genomic integrity, functions primarily by correcting DNA replication errors. In humans, the DNA mismatch repair (*MMR*) system involves seven core proteins (*MLH1*, *MLH3, MSH2, MSH3, MSH6, PMS1,* and *PMS2*), which work together in a series of interdependent steps to activate and carry out the correction of mismatched DNA base pairs [4, 5]. While emerging evidence suggests the *MMR* gene's potential utility as a prognostic biomarker in various malignancies, current findings regarding its

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clinical relevance remain inconsistent. Consequently, systematic evaluation of *MMR*-related gene expression patterns and their association with oncological outcomes is imperative to elucidate their prognostic significance in cancer progression and therapeutic response. Emerging evidence suggests that identification of the prognostic value of *MMR* genes in ovarian cancer may be useful for guiding personalized treatment and predicting prognosis.

Materials and Methods

Study contingents

A total of 38 cases were included in this study, who underwent surgery for ovarian cancer (several radical surgical procedures) between July 2018 and December 2023 at the Department of Oncology at Azerbaijan Medical University, Baku, Azerbaijan. All surgical procedures were performed by one gynecologic oncologist. Patients with OC were staged using the revised 2014 FIGO staging system. The diagnosis was confirmed post-operatively through a pathological analysis of the surgical material. Since the study was retrospective and observational, the Clinical Research Ethics Committee of Azerbaijan Medical University waived the need for written informed consent (Decision number 2023-12-06/N238). By the study, a comprehensive medical history was collected, including details such as age, pregnancy history, status of parity and menopause, histological type of ovarian cancer, presence or absence of synchronous malignancy, surgical intervention type, chemotherapeutic status, clinical stage, CA125 level, PFS, OS, status of *Ki67* and *p53*, and presenting symptoms. A family history of ovarian and breast cancer was also documented. The decision of primary cytoreductive surgery or neoadjuvant chemotherapy was based on the patient's ECOG performance, a preoperative abdominal CT scan, and peritoneal cancer index. Histologic types of the tumor were divided into high-grade serous carcinomas (27), endometrioid carcinomas (6), clear cell (2), and mixed-type carcinomas (3) groups. The clinical course (survival time from the time of diagnosis, final status, etc.) of the patients was determined from their files.

Preparation of the samples

In this investigation, formalin-fixed paraffin-embedded (FFPE) tumor tissue specimens obtained from surgical material samples were utilized. A tissue microarray (TMA) was generated to facilitate immunohistochemical analysis.

FFPE materials of patients were utilized for immunohistochemical stains. Immunohistochemical stains of *MLH1*, *PMS2, MSH2*, and *MSH6* genes were applied to all paraffin blocks. The study also assessed the status of *Ki-67* and *p53*. To determine microsatellite instability (MSI) for mismatch repair (*MMR*) genes, *MLH1*, *PMS2, MSH2*, and *MSH6* genes were analyzed. The *MMR* status was determined immunohistochemically via the assessment of four *MMR* protein expressions.

The retention or absence of nuclear expression was evaluated by the *MLH1, PMS2, MSH2*, and *MSH6* immunohistochemical stains.

Retaining nuclear expression in tumor cells was classified as microsatellite stable (MSS), whereas loss of nuclear expression in one or more markers was categorized as microsatellite instability (MSI).

Statistical analysis

In this study, all statistical analyses were conducted using IBM SPSS software, version 26.0 (IBM Corp.). Descriptive statistics were employed to summarize demographic data. The normality of variable distributions was evaluated through analytical tests (Kolmogorov-Smirnov and Shapiro-Wilk tests). The associations between qualitative variables were analyzed using the Pearson Chi-Square test. For comparing the means of all groups, the Independent Samples t-test (Student's t-test) was applied to normally distributed variables, while the Mann-Whitney U test was used for variables that deviated from normality. Survival outcomes were assessed via Kaplan-Meier curves and life tables. Due to the limited sample size, numerical variables were excluded from the Cox regression analysis to mitigate high error margins. A p-value of less than 0.05 was considered statistically significant.

Results

The demographic and clinical characteristics of the patients in the study are shown in Tables 1 and 2. The distribution of ovarian malignancies according to histological subtypes was serous in 27 cases, endometrioid in 6 cases, clear cell in 2 cases, and mixed histological types (endometrioid and serous, endometrioid and mucinous, serous and clear cell) in 3 cases (Figure 1).

The cohort exhibited a mean age of 59.6 ± 11.3 years (range: 36–92), with age variations noted across histological subtypes: serous (61.5 ± 11.3 years), endometrioid (54.7 ± 10.5 years), clear cell (47.0 ± 14.1 years), and mixed histology (61.0 ± 7.0 years). While no statistically significant age differences were observed between subtypes, serous and mixed histology cases demonstrated a trend toward older age. Postmenopausal status predominated (86.6%, n = 33), with a mean gravida of 2.2 ± 1.7 and 18.4% (n = 7) nulliparity. Germline

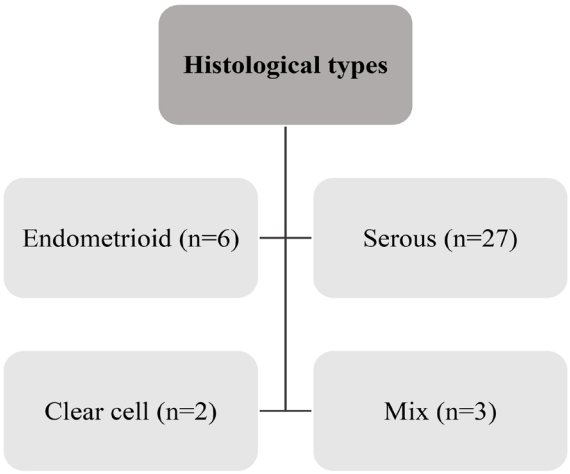

Figure 1. Flow Diagram of the Study Patients

Table 1. Demographic and Clinical Features of the Patients

Variable	All Cases (n:38)	Endometrioid (n:6)	Serous (n:27)	Clear Cell (n:2)	Mix (n:3)	p value
Age at diagnosis (avg.)	59.6±11.3	54.7±10.5	61.5±11.3	47.0±14.1	61.0±7.0	0.583
Menopause status (n, %)						0.053
Premenopausal	5 (13.2)	2 (33.3)	1 (3.7)	1 (50)	1 (33.3)	
Postmenopausal	33 (86.8)	4 (66.6)	26 (96.2)	1 (50)	2 (66.6)	
Nulliparity (n, %)	7 (18.4)	2 (33.3)	3 (11.1)	2 (100)	1 (33.3)	
Family history of cancer (n, %)						
None	25 (65.8)	6 (100)	16 (59.3)	2 (100)	1 (33.3)	0.108
Yes	13 (34.2)	-	11 (40.7)	-	2 (66.6)	
Ovarian	1	-	1	-	-	
Breast	4	-	3	-	1	
Colon	5	-	5	-	-	
Other	3	-	2	-	1	
Neoadjuvant CT						0.779
Yes	6 (15.8)	1 (16.7)	4 (14.8)	-	1 (33.3)	
None	32 (84.2)	5 (83.3)	23 (85.2)	2 (100)	2 (66.6)	
Primary surgery (n, %)	32 (84.2)	5 (83.3)	23 (85.2)	2 (100)	2 (66.6)	0.779
FIGO Stage (n, %)						0.063
Stage I	10 (26.3)	4 (66.6)	4 (14.8)	2 (100)	1 (25)	
Stage II	2 (5.3)	1 (16.7)	-	-	1 (25)	

BRCA1/2 mutations were detected in 15.8% (n = 6), and synchronous malignancies (exclusively colon cancer) were identified in 2 cases. Familial cancer history was reported in 34.2% (n = 13), predominantly involving breast and colon rather than ovarian malignancies.

Mean CA125 and CA19-9 levels were 1207.3 ± 1708.1 U/ml (p = 0.48) and 138.5 ± 415.7 U/ml, respectively, with no significant variation across histological subtypes. Surgical management included primary cytoreduction in 84.2% (n = 32) and NACT with interval debulking in 15.8% (n = 6). FIGO 2014 staging revealed 26.3% (n = 10) at stage 1, 5.3% (n = 2) at stage 2, 44.7% (n = 17) at stage 3, and 23.7% (n = 9) at stage 4. Serous tumors were predominantly stage 3 (55.5%, n = 15), whereas endometrioid tumors were primarily stage 1 (66.6%, n = 4).

The histopathological and dimensional attributes of tumors in the cohort are summarized in Table 3. The mean tumor diameter across all cases measured 10.4 ± 4.3 cm. Stratified by histological subtype, distinct variations emerged: serous (10.0 ± 3.7 cm), endometrioid (13.7 ± 5.2 cm), clear cell (16.0 ± 1.4 cm), and mixed (5.3 ± 1.5 cm). Inter-subtype comparisons revealed statistically significant differences in tumor size (p=0.01), with clear cell tumors demonstrating the largest dimensions (16.0 cm) and mixed histology the smallest (5.3 cm).

Immunohistochemical evaluation of *Ki67* and *p53* expression demonstrated *Ki67* positivity in 97.4% (n=37) of cases, with a single negative case (2.6%). *p53* positivity was observed in 73.7% (n=28) of cases, while 26.3% (n=10) were negative. Mean expression levels were quantified as 65.5% ± 25.2 for *Ki67* and 43.3% ± 36.6 for p53. Subtype-specific staining patterns were significant (p=0.045 for *Ki67*; p=0.039 for *p53*). *Ki67* exhibited intense staining in serous and mixed subtypes, moderate in endometrioid, and weak in clear cells. *p53* staining intensity inversely correlated with *Ki67*, showing moderate expression in serous and mixed types, weak in endometrioid, and absence in clear cells.

Tumor grading analysis indicated a predominance of

Table 2. Clinical and Laboratory Features of the Patients

Variable	All Cases (n:38)	Endometrioid (n:6)	Serous (n:27)	Clear Cell (n:2)	Mix (n:3)	p value
Synchronous cancer (n, %)						0.835
Yes	2 (5.3)	-	2 (7.4)	-	-	
None	36 (94.7)	6 (100)	25 (92.6)	2 (100)	3 (100)	
BRCA1/2 (n, %)						0.779
Positive	6 (15.8)	1 (16,7)	5 (18.5)	-	-	
Negative	32 (84.2)	5 (83.7)	22 (81.5)	2 (100)	3 (100)	
Tumour markers (U/ml, avg.)						
CA 125	1207.3	1413	1372.7	30	92.3	0.48
CA 19-9	138.5	538	27.9	48	395.5	0.6

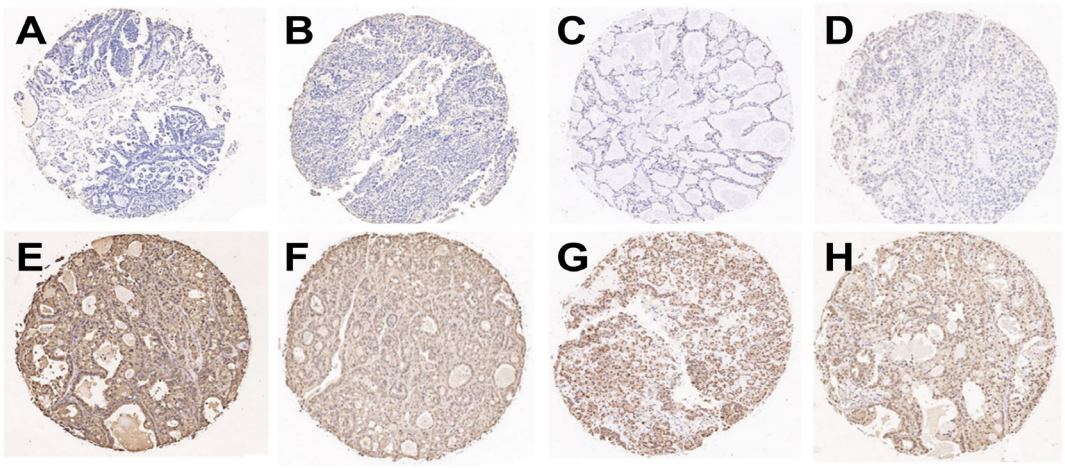

Figure 2. Images of Immunostaining of Four Principal Markers for Mismatch Repair Status (*MMR*) in Ovarian Carcinoma (OC) Patients. A) low *PMS2* expression, B) negative *MSH6* expression, C) low *MLH1* expression, D) low *MSH2* expression, E) high *PMS2* expression, F) high *MSH6* expression, G) high *MLH1* expression, H) high *MSH2* expression

Table 3. Tumor Size and Histopathological Features

Variable	All Cases (n:38)	Endometrioid (n:6)	Serous (n:27)	Clear Cell (n:2)	Mix (n:3)	p value
Tumor size (cm, avg.)	10.4 ± 4.3	13.7 ± 5.2	10.0 ± 3.7	16.0 ± 1.4	5.3 ± 1.5	0.01
Ki67 (%, avg.)	65.5±25.2	53.3±28,1	71.7±22.7	27.5±10.6	71.7±22.6	0.045
Positive	37	6	27	2	3	
Negative	1	-	-	-	-	
p53 (%, avg.)	43.3±36.6	17.8±35.8	53.3±34.5	-	33.3±28.9	0.039
Positive	28	4	22	-	2	
Negative	10	2	5	2	1	
Grade (%)						0.002
Grade 1	21.1	66.7	7.4	100	-	
Grade 2	23.6	33.3	22.2	-	33.3	
Grade 3	55.3	-	70.4	-	66.7	

Table 4. Patterns of *MMR* gene loss (*MLH1/PMS2* and *MSH2/MSH6*)

	MSS		Total	MSI
	MLH1/ PMS2	*MSH2/ MSH6*		
Histological Type				
Endometrioid	1	1	2	4
Serous	-	-	-	27
Clear cell	-	-	-	2
Mix	-	-	-	3

grade 3 serous tumors (70.4%). Conversely, 66.7% of total endometrioid subtypes were non-grade-3 tumors.

The findings of this study, as outlined in Table 4, detail the mismatch repair (*MMR*) gene deficiency profiles (specifically *MLH1*/*PMS2* and *MSH2/MSH6*) among the examined cases. Immunohistochemical evaluation of pathological specimens identified *MMR* gene loss in two instances: one involving the *MLH1*/*PMS2* gene pair and the other affecting the *MSH2/MSH6* gene pair. Notably, both cases exhibiting *MMR* deficiency were confined to the endometrioid histological subtype, with no such deficiencies detected in other histological categories Figure 2. Furthermore, clinical follow-up revealed no instances of disease recurrence or mortality in these patients.

The therapeutic and follow-up outcomes of the cohort are detailed in Table 5. Over an average follow-up duration of 45.7 months, clinical recurrence was identified in 12 patients (31.6%), with a mean survival period of 25 months following disease progression. Analysis of histological subtypes revealed the highest recurrence rates in serous carcinoma (10 cases, 37.0%), followed by endometrioid (1 case, 16.7%) and mixed-type carcinomas (1 case, 33.3%), while no recurrences were documented in clear cell carcinoma. The overall median survival duration for the cohort was 80.0 months, with a 5-year survival rate of 81.6% and a median progression-free survival of 78.5 months. Mortality was reported in 21 of 38 cases (55.3%), stratified by subtype as follows: serous carcinoma (19 cases, 70.4%), endometrioid carcinoma (1 case, 16.7%), and mixed-type carcinoma (1 case, 33.3%).

Table 5. Analyses of Recurrence, Mortality, and Survival Outcomes

Variable	All Cases (n:38)	Endometrioid (n:6)	Serous (n:27)	Clear Cell (n:2)	Mix (n:3)	p value
Recurrence (n, %)						0.59
Yes	12 (31.6)	1 (16.7)	10 (37.0)	-	1 (33.3)	
No	26 (68.4)	5 (83.7)	17 (63.0)	2 (100)	2 (66.7)	
Mortality	21 (55.3)	1 (16.7)	19 (70.4)	-	1 (33.3)	0.027
Survival (5 year)	81.6	100	77.8	100	66.7	-
PFS (month avg.)	78.5	66.7	78.7	-	48	-
OS (month avg.)	80	-	80	-	-	-

PFS, Progression-free survival; OS, overall survival

Discussion

While the clinicopathological features of mismatch repair-deficient (*dMMR*) tumors are well-established in endometrial carcinoma, their manifestation in ovarian cancer (OC) remains poorly characterized and inconsistent [4, 5]. Notably, in this investigation, we evaluated a panel of four established biomarkers for determining mismatch repair (*MMR*) status in ovarian cancer (OC) tissue microarrays (TMAs), identifying loss of *MMR* gene expression in two cases. Prior to the advent of genetic testing for microsatellite instability (MSI), molecular analyses and immunohistochemistry (IHC) were the predominant methodologies for assessing *MMR* gene status in tumor tissue research. From an economic perspective, immunohistochemistry (IHC) presents a cost-effective and practical alternative for assessing mismatch repair (*MMR*) gene defects, demonstrating high concordance with microsatellite instability (MSI) genetic testing [6]. Existing literature reports variable frequencies of deficient *MMR* (*dMMR*) in ovarian cancer (OC) [7]. The relationship between mismatch repair (*MMR*) status and clinicopathological characteristics has yielded conflicting findings across studies. Prior research indicates that deficient *MMR* (*dMMR*) status is associated with an enhanced response to immunotherapy in colorectal carcinoma and potential resistance to 5-fluorouracil-based chemotherapy in pancreatic adenocarcinoma. However, retrospective cohort studies evaluating *dMMR* in ovarian cancer (OC) remain limited. In this study, we aimed to assess the prognostic significance of *dMMR* in ovarian cancer patients. The association between *MMR* (mismatch repair) status and its impact on survival outcomes remains inconclusive in prior research. Existing literature in gynecologic oncology has predominantly focused on endometrial carcinomas when examining *MMR* profiles. While certain investigations have reported reduced survival rates in endometrial carcinoma patients with deficient *MMR* (*dMMR*) tumors [8], others have conversely observed improved survival outcomes in this subgroup, highlighting heterogeneous findings across studies [9]. Some studies have indicated that ovarian carcinomas exhibiting microsatellite instability (MSI) are associated with an unfavorable prognosis [10]. The underlying mechanism through which deficient mismatch repair (*dMMR*) status impacts clinical outcomes may involve mutations in specific genetic targets implicated in ovarian carcinogenesis. Investigating the prognostic relevance of *dMMR* status, particularly in early-stage ovarian cancer patients, could enhance clinical counseling by providing critical insights into survival outcomes and guiding the selection of adjuvant therapeutic regimens. The research conducted by Le et al. presents compelling evidence supporting the potential efficacy of immune checkpoint blockade as a therapeutic intervention for mismatch repair-deficient (*dMMR*) tumors, irrespective of their tissue of origin [11]. Concurrently, recent studies indicate that elevated *PD-L1* expression levels may be a predictive biomarker for improved clinical response to anti-*PD-1*/*PD-L1* therapeutic regimens across diverse cancer types [12].

A more detailed analysis explored the relationship between mismatch repair (*MMR*) genes and distinct histological subtypes of ovarian cancer. Notably, the findings revealed that deficiencies in the *MLH1/PMS2* and *MSH2/MSH6* gene pairs were exclusively observed in the endometrioid subtype, with no comparable aberrations identified in other histological classifications. These outcomes underscore that the prognostic implications of *MMR* gene alterations in ovarian cancer are not uniform and instead exhibit significant variation depending on tumor subtype.

The present investigation exhibits several methodological merits, notably its population-based approach, the length of the follow-up, and the systematic compilation of clinical and demographic variables across the participant cohort.

In our investigation, the absence of mismatch repair (*MMR*) gene expression was identified in 5.2% of epithelial ovarian cancer cases. Notably, this deficiency was exclusively observed in the endometrioid subtype, accounting for 33.3% of endometrioid ovarian carcinomas. These findings align with prior studies of unselected ovarian cancer cohorts (lacking subtype stratification), which report *MMR* loss frequencies ranging from 2.1% to 10% [13]. According to the some study, documented somatic *MMR* loss in 12% of cases, with the highest prevalence in clear cell (35%), endometrioid (34%), and mucinous (26%) subtypes [14, 15]. Concordant with our results, no *MMR* deficiency was detected in serous carcinomas. These observations are reinforced by a Creighton University series identifying endometrioid carcinomas as the predominant gynecological malignancies in hereditary *MMR* germline mutation carriers [14].

In serous ovarian carcinomas, our study detected no

MMR loss-consistent with earlier reports. Additionally, variations in study populations may influence observed *MMR* deficiency rates [14].

No correlation between *MMR* loss and clinical outcomes was established in our cohort. Given the predominance of serous carcinomas (devoid of *MMR* loss) in ovarian cancer, the observed *MMR* deficiency in endometrioid subtypes may imply an elevated risk for synchronous colorectal or endometrial malignancies, as typified by *MMR*-deficient tumors. While hereditary *MMR* mutation carriers exhibit heightened susceptibility to synchronous uterine cancers, the limited sample size of *MMR*-deficient cases in our study precluded robust prognostic evaluation.

Conclusion

The elevated incidence of *MMR* loss in endometrioid ovarian carcinomas necessitates heightened clinical awareness of associated extracolonic malignancies. To conclusively delineate the prognostic and survival implications of *MMR* deficiency in ovarian cancer, multicenter studies with expanded cohorts are imperative.

While these advantages underscore the study's rigor, certain limitations warrant consideration, such as the database only including 38 patients, particularly its retrospective design, which introduces the potential for selection bias. However, it should be noted that the MMR gene mRNA was isolated from heterogeneous cancer tissues consisting of several cellular populations. Consequently, the cell type-specific expression profiles of *MMR* gene mRNA remain uncharacterized and may exhibit variability. This knowledge gap underscores the necessity for further investigation to delineate the functional roles and clinical relevance of individual *MMR* genes within distinct cellular subtypes.

Future research could incorporate quantitative molecular methodologies to augment the immunohistochemical findings. Nevertheless, executing comprehensive laboratory evaluations across the entire patient population remains resource-intensive and logistically complex.

MMR deficiency in ovarian cancer is histotype-dependent, occurring predominantly in endometrioid carcinomas. While not prognostic here, *dMMR* screening may identify patients at risk for synchronous malignancies or eligible for immunotherapy. Validation in larger cohorts is critical to clarify its clinical utility.

Author Contribution Statement

Conceptualization: [AI]; Methodology: [AI], [FN]; Formal analysis and investigation: [AI], [FN]; Writing - original draft preparation: [AI], [FN]; Writing - review and editing: [AI]; Supervision: [AI].

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Ethics approval and informed consent statement

Since the study was retrospective and observational, the Clinical Research Ethics Committee of Azerbaijan Medical University waived the need for written informed consent (Decision number 2023-12-06/N238). All procedures followed the Declaration of Helsinki.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors have no conflicts of interest in this study.

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