fortune Journals

Research Article

FORTUNE JOURNAL OF HEALTH SCIENCES

ISSN: 2644-2906

Relation of Mismatch Repair Deficiency in Endometrial Carcinoma and Its Clinical Implication

Dr. Farhana Khatoon*[,1], Dr. Rowson Ara[2], Dr. Subrina Meher[3], Dr. Nasrin Akter[4], Dr. Moushume Akther[5], Dr. Sunzia Sayed[6], Prof Jannatul Ferdous[7]

Abstract

Introduction: The identification of MMR deficiency allows screening for Lynch syndrome-associated endometrial carcinoma from sporadic ECs. Therefore, identification of MMRd tumors has become critical for patients with EC for therapeutic management, clinical decision making, and prognosis.

Aim of the study: The aim of the study was to evaluate the relationship between mismatch repair (MMR) deficiency and endometrial carcinoma, and to explore its clinical implications.

Methods: This cross-sectional study was conducted at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from March 2022 to February 2023 and included 49 consecutive endometrial carcinoma patients undergoing surgical management. Eligibility was based on histopathological confirmation. Surgical treatment included total hysterectomy and bilateral salpingo-oophorectomy and pelvic and para aortic Lymphdenectomy in eligible cases.. Data on clinicopathological parameters were collected from histopathological reports. Statistical analyses were conducted using SPSS version 23.0.

Result: In the study cohort, the most common age group among endometrial cancer patients was 51-60 years, irrespective of MMR status. Among the 16 MMR deficient cases, isolated single protein loss was observed in 5 (31.25%), with MSH2 being the most frequently lost protein. Notably, 16 (32.70%) of the study participants exhibited loss of MMR protein expression, indicative of MMR deficiency. Furthermore, MMR deficient endometrial cancer demonstrated a higher prevalence of grade III tumors 8 (50.00%) and an increased risk of advanced FIGO stage (III & IV) by 4.274 times compared to MMR proficient cases.

Conclusion: The study underscores a significant 33% prevalence of MMR deficiency in endometrial cancer, emphasizing the critical role of immunohistochemical detection for Lynch Syndrome screening and prognosis.

Keywords: Endometrial carcinoma, Mismatch repair deficiency (MMR), Lynch Syndrome (LS), Immunohistochemistry (IHC), Clinical implications

Introduction

Endometrial cancer is the 4th most commonly diagnosed gynecologic malignancy in the world. It is the 11th most common cancer in Bangladesh among the female population [1]. Endometrial carcinomas have been

Affiliation:

[1]Associate Professor, Department of Gynaecological Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

[2]Medical Officer, Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

[3]Junior Consultant, Directorate General of Health Services, Dhaka, Bangladesh.

[4]OSD, Department of Gynaecological Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

[5]Resident, Department of Gynaecological Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

[6]Resident, Department of Gynaecological Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

[7]Professor, Department of Gynaecological Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

***Corresponding author:**
Dr. Farhana Khatoon, Associate Professor, Department of Gynaecological Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

Citation: Khatoon F, Ara R, Meher S, Akter N, Akter M, Sayed S, Ferdous J. Relation of Mismatch Repair Deficiency in Endometrial Carcinoma and Its Clinical Implication. Fortune Journal of Health Sciences. 7 (2024): 372-381.

Received: June 03, 2024
Accepted: June 10, 2024
Published: July 03, 2024

Dr. Khatoon F, et al., Fortune J Health Sci 2024
DOI:10.26502/fjhs.198

historically grouped into Bokhman type 1 and Bokhman type 2. Bokhman type 1 endometrial carcinomas are of the endometrioid subtype and arise in a background of endometrial hyperplasia. This type of EC expresses hormone receptors for estrogen and progesterone. Type 2 endometrial carcinomas are of the serous subtype. This subtype arises in the background of endometrial atrophy and expresses p53. They are often high grade, warrant the use of chemotherapy, and carry an unfavorable [2-5]. The limitations of these two types are that about 10 to 19% of endometrial carcinomas do not fit into either of the two types by histopathology or molecular features [2-4]. Especially in the high-grade tumors, these morphological subtypes have inter-observer variability and so cannot be formally incorporated for risk stratification [6] Recently, molecular characterization of EC has addressed the etiologic heterogeneity. The Cancer Genome Atlas (TCGA) research network reported four major molecular subtypes of endometrial carcinoma with potential diagnostic, prognostic, and therapeutic uses [4]. Microsatellite Instability (MSI) has emerged as one of the major pathways in endometrial carcinogenesis [6]. Mutation in DNA mismatch repair (MMR) genes can be inherited, acquired (somatic), or epigenetic. Women with Lynch syndrome have a substantial increase in risk of developing endometrial cancer along with colorectal cancer. However, the majority of patients with MMR deficiency will not have an underlying Lynch syndrome mutation. There are three ways to detect defects in the MMR system: immunohistochemistry (IHC) for MMR protein expression, polymerase chain reaction-based assays, and MLH1 promotor methylation analysis [7]. EC which have intact expression of MMR protein are termed as MMR proficient or MMR stable EC [8].

The identification of MMR deficiency allows screening for Lynch syndrome-associated endometrial carcinoma from sporadic ECs. Identification of patients with LS is important as it provides an opportunity for surveillance testing, genetic counseling, and risk-reducing measures to prevent LS-associated cancers [9, 10]. Microscopic features associated with MMR deficiency due to genetic mutation include poor differentiation, mucinous features, signet ring cell differentiation, mixed tumor histology, tumor cells growing in a medullary-type pattern, increased tumor-infiltrating lymphocytes, and a Crohn-like inflammatory infiltrate at the tumor invasion front or periphery. With the recent advent of molecular profiling, more patients are undergoing MMR testing, and there is a growing population of patients found to have abnormal MMR testing but negative germline testing for Lynch syndrome. This group is referred to as MMR-deficient or Lynch-like syndrome [11]. Clinicopathological characteristics of MMR deficient EC are variable and have implications for treatment [12, 13]. Improved survival is also observed in non-endometrioid MMR deficient EC after adjuvant radiation.

MMR deficient EC is associated with high neoantigen loads and an increase in the number of tumor infiltrating lymphocytes. Pembrolizumab has been approved by the Food and Drug Administration (FDA) for use in recurrent or metastatic EC with MMR deficiency, irrespective of tumor site or organ involved [14]. So MMR status can be considered as a predictive biomarker to predict treatment efficacy of immune checkpoint inhibitors. Therefore, identification of MMRd tumors has become critical for patients with EC for therapeutic management, clinical decision making, and prognosis. This study aims to evaluate the relationship between mismatch repair (MMR) deficiency and endometrial carcinoma, and to explore its clinical implications in our population.

Objectives

- The aim of the study was to evaluate the relationship between mismatch repair (MMR) deficiency and endometrial carcinoma, and to explore its clinical implications.

Methodology & Materials

This cross-sectional observational study was conducted at the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, over a 12-month period from March 1, 2022, to February 28, 2023. The study population comprised 49 consecutive patients with histologically confirmed endometrial carcinoma who were admitted for surgical management.

Inclusion Criteria

- Patients with histopathologically confirmed endometrial carcinoma diagnosed by endometrial fractional curettage or diagnostic D&C.
- Patients admitted for surgical management in the Gynecological Oncology department at BSMMU.

Exclusion Criteria

- Patients with a history of preoperative chemotherapy or radiotherapy.
- Patients with recurrent endometrial carcinoma.

Institutional approval was obtained from the Institutional Review Board (IRB) of BSMMU, and ethical issues were addressed according to the Helsinki Declaration. Informed written consent was obtained from all participants after explaining the study's purpose, objectives, and the right to withdraw at any time. Baseline demographic information (including age, occupation, and socioeconomic condition) and medical history (personal and family history of cancers suggestive of inherited cancer susceptibility) were recorded through face-to-face interviews ensuring privacy and confidentiality. All patients underwent surgical treatment,

Dr. Khatoon F, et al., Fortune J Health Sci 2024
DOI:10.26502/fjhs.198

which included total hysterectomy and bilateral salpingo-oophorectomy. Pelvic and/or para-aortic lymphadenectomy were performed based on surgical risk factors such as tumor grade, histology, cervical involvement, lymph node enlargement, and depth of myometrial invasion as assessed by pre-operative endometrial sampling, MRI, and intra-operative examination. Pathological examination and immunohistochemistry (IHC) were performed in the Pathology department of BSMMU. MMR protein expression was evaluated through IHC, and pathological data including tumor size, grade, lymphovascular space invasion, myometrial invasion, cervical invasion, pelvic and para-aortic lymph node involvement, adnexal involvement, and extent of metastasis were obtained from histopathological reports. Data were collected from patient files, marked with special identification stickers, and recorded in a register. Statistical analyses were carried out using SPSS version 23.0. The association of MMR protein status with clinicopathological parameters was assessed using Chi-square test, Fisher's exact test, and unpaired t-test. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated to determine the strength of associations. A p-value of <0.05 was considered statistically significant.

Results

Figure 1 shows that the majority of endometrial cancer patients were above 40 years of age. Among them, the 51-60 years age group was the most common in both MMR proficient and MMR deficient endometrial cancer (EC).

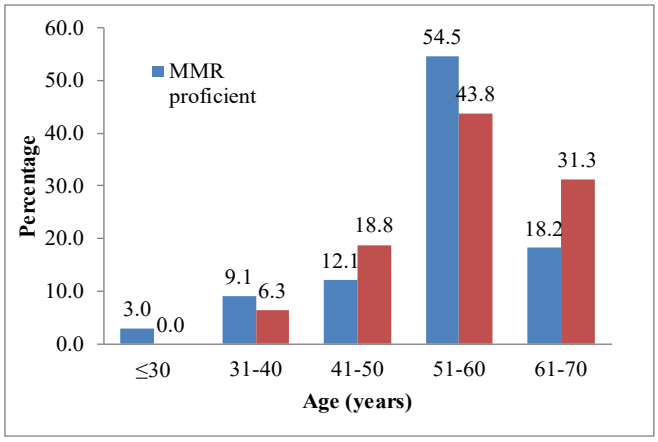

Figure 1: Age distribution of the study participants. (n=49)

Table 1: Socio-demographic characteristics of the respondents stratified by MMR status (n=49).

Socio-demographic characteristics	MMR proficient (n=33)		MMR deficient (n=16)		P value
	n	%	n	%	
Age (years)					
≤30	1	3	0	0	[a]0.849[ns]
31-40	3	9.1	1	6.3	
41-50	4	12.1	3	18.8	
51-60	18	54.5	7	43.8	
61-70	6	18.2	5	31.3	
Mean±SD	55±10.1		55.6±10.6		
Range (min-max)	24-70		32-70		
Monthly income (Taka)					
Low (≤8,585 Tk)	4	12.1	4	25	[b]0.418[ns]
Middle (8,586-1,04,391 Tk)	16	48.5	8	50	
High (>1,04,391 Tk)	13	39.4	4	25	
BMI (kg/m^2)					
18.5-24.9	12	36.4	4	25	[a]0.776[ns]
25.0-29.9	2	6.1	2	12.5	
≥30.0	19	57.6	10	62.5	
Mean±SD	28.3±4.5		28.7±3.8		
Range (min-max)	21.7-36		22.9-33		

Dr. Khatoon F, et al., Fortune J Health Sci 2024
DOI:10.26502/fjhs.198

Parity					
Nulli	4	12.1	1	6.3	[b]0.699[ns]
Primi	13	39.4	5	31.3	
Multi	13	39.4	7	43.8	
Grand-multi	3	9.1	3	18.8	
Oral contraceptive pill					
Yes	11	33.3	4	25	[b]0.553[ns]
No	22	66.7	12	75	
Menopause					
Yes	28	84.8	12	75	[b]0.449[ns]
No	5	15.2	4	25	

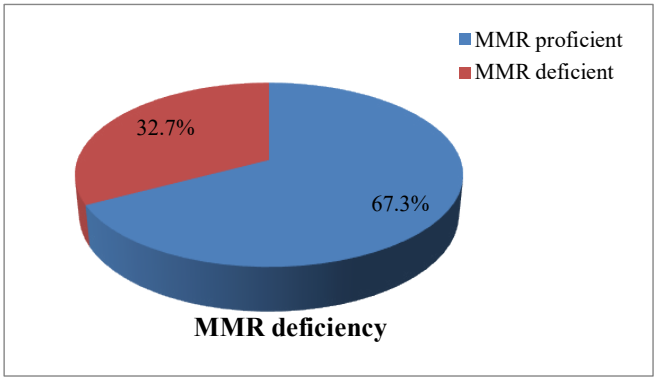

Figure 2: MMR protein status of the study participants (n=49)

Table 1 illustrates that the mean (±SD) age was almost similar in both the MMR proficient and MMR deficient groups. Nulliparity was more common in the MMR proficient endometrial cancer (EC) group compared to the MMR deficient EC group. Conversely, grand multiparity was more prevalent in the MMR deficient EC group compared to the MMR proficient EC group. The distribution of respondents with respect to age, socioeconomic status, BMI, parity, use of oral contraceptive pills (OCP), and menopausal status in both MMR deficient and MMR proficient EC groups was not statistically significant ($p > 0.05$).

Figure 2 shows that among the study participants, loss of MMR protein expression (MMR deficient) was observed in 16 (32.7%), while intact expression (MMR proficient) was observed in 33 (67.3%).

Table 2 illustrates that among the 16 MMR deficient endometrial cancer (EC) cases, isolated single protein loss was observed in 5 (31.25%), and multiple loss was observed in 11 (68.75%). Among these, the most frequent loss of MMR protein was isolated MSH2, and the combined loss of MLH1/PMS2 was also noted. Only one case (6.3%) showed loss of expression in all markers.

Table 3 illustrates that among the 16 MMR deficient endometrial cancer (EC) cases, 8 (50%) were grade III tumors. Loss of MSH6 and all protein markers was observed only in grade III tumors.

Table 4 shows that loss of MSH2 was found in both early and advanced FIGO stages. Paired loss of MLH1/PMS2 was found mostly in the early FIGO stage. Loss of all four protein markers was found in the advanced FIGO stage.

Table 2: Distribution of the study participants according to mismatch repair protein deficiency (n=16).

Mismatch repair protein deficiency	Frequency(n)	Percentage (%)
Single loss		
MSH2	4	25
MSH6	1	6.3
Multiple loss		
MLH1+ PMS2	4	25
MSH2+ MSH6	3	18.8
MLH1+ MSH2	2	12.5
MLH1+ MSH2+ PMS2	1	6.3
MLH1+ MSH2+ PMS2+ MSH6	1	6.3

Table 3: Pattern of Mismatch repair deficiency in relation to Histopathological grading of endometrial cancer. (n=16).

Mismatch repair protein deficiency	Histopathological grading		
	Grade I	Grade II	Grade III
MSH2	2	0	2
MSH6	0	0	1
MLH1+ PMS2	1	2	1
MSH2+ MSH6	1	0	2
MLH1+ MSH2	0	1	1
MLH1+ MSH2+ PMS2	1	0	0
MLH1+ MSH2+ PMS2+ MSH6	0	0	1
Total	5	3	8

Dr. Khatoon F, et al., Fortune J Health Sci 2024
DOI:10.26502/fjhs.198

Table 5 showed that MMR deficient endometrial cancer (EC) was found almost entirely in Type I EC (15 out of 16), had a higher grade and advanced FIGO stage but tended to infiltrate less than 50% of the myometrium, and was absent of lymphovascular space invasion (LVSI) compared to MMR proficient EC. MMR proficient EC was found to be significantly associated with prognostic factors, including higher grade (grade III) and advanced stage (stage III/IV), with P-values of 0.032 and 0.046, respectively. However, no significant differences in LVSI and lymph node involvement were found between the MMR proficient and MMR deficient groups.

Table 6 showed that MMR deficient endometrial cancer (EC) had a reduced mean tumor size (3.8±1.8), increased involvement of adnexae in 6 (37.5%) cases, more tendency to cervical involvement in 5 (31%), and increased metastasis beyond the uterus compared to MMR proficient EC. MMR deficient EC was found to be significantly associated with adnexal involvement and metastasis, with P-values of 0.01 and 0.024, respectively. However, no significant differences were found in lower uterine segment involvement, cervical involvement, or positive peritoneal cytology between the MMR proficient and MMR deficient groups.

Table 4: Pattern of Mismatch repair deficiency in relation to FIGO staging (2009) of Endometrial cancer.

Mismatch repair protein deficiency	FIGO stage			
	Stage I	Stage II	Stage III	Stage IV
MSH2	2	0	0	2
MSH6	0	1	0	0
MLH1+ PMS2	3	0	1	0
MSH2+ MSH6	0	2	1	0
MLH1+ MSH2	0	1	1	0
MLH1+ MSH2+ PMS2	1	0	0	0
MLH1+ MSH2+ PMS2+ MSH6	0	0	1	0

Table 5: Histological findings of the study participants stratified by MMR status (n=49).

Variables	MMR proficient (n=33)		MMR deficient (n=16)		P value
	n	%	n	%	
Histological type					
Endometroid adenocarcinoma	30	90.9	15	93.8	[a]0.605[ns]
Serous adenocarcinoma	3	9.1	1	6.3	
Histopathological grading					
Grade I	20	60.6	5	31.3	[a]0.032[s]
Grade II	8	24.2	3	18.8	
Grade III	5	15.2	8	50	
Depth of myometrial invasion					
<50%	19	57.6	11	68.8	[a]0.333[ns]
≥50%	14	42.4	5	31.3	
Lymph vascular space invasion					
Positive	4	12.1	0	0	[a]0.193[ns]
Negative	29	87.9	16	100	
LN involvement	(n-24)		(n-9)		
Positive	3	12.5	2	22.2	[a]0.597[ns]
Negative	21	87.5	7	77.8	
FIGO stage					
Stage I	23	69.7	6	37.5	[a]0.046[s]
Stage II	7	21.2	4	25	
Stage III	3	9.1	4	25	
Stage IV	0	0	2	12.5	

Citation: Khatoon F, Ara R, Meher S, Akter N, Akter M, Sayed S, Ferdous J. Relation of Mismatch Repair Deficiency in Endometrial Carcinoma and Its Clinical Implication. Fortune Journal of Health Sciences. 7 (2024): 372-381.

Dr. Khatoon F, et al., Fortune J Health Sci 2024
DOI:10.26502/fjhs.198

Table 6: Histological findings of the study participants stratified by MMR status (n=49).

Variables	MMR proficient (n=33)		MMR deficient (n=16)		P value
	n	%	n	%	
Tumour size (cm)					
≤2.0	4	12.1	4	25	[b]0.140[ns]
2.1-4.0	13	39.4	5	31.3	
>4.0	16	48.5	7	43.8	
Mean±SD	5±2.8		3.8±1.8		
Range (min-max)	1.5-12		1-6.5		
Adnexal involvement					
Positive	2	6.1	6	37.5	[a]0.010[s]
Negative	31	93.9	10	62.5	
Lower uterine segment involvement					
Positive	14	42.4	5	31.3	[a]0.452[ns]
Negative	19	57.6	11	68.8	
Cervical involvement					
Positive	6	18.2	5	31.3	[a]0.250[ns]
Negative	27	81.8	11	68.8	
Peritoneal cytology					
Positive	3	9.1	0	0	[a]0.296[ns]
Negative	30	90.9	16	100	
Metastasis					
Yes	3	9.1	6	37.5	[a]0.024[s]
No	30	90.9	10	62.5	

Table 7: Multi variate logistic regression analysis for MMR deficient endometrial carcinoma.

	Adjusted	95% CI		P value
	OR	Lower	Upper	
Adnexal involvement	4.901	0.537	44.683	0.159[ns]
Histopathological grade III	2.072	0.215	19.997	0.529[ns]
Advance FIGO stage (III & IV)	4.274	1.691	15.515	0.025[s]
Metastasis	0.948	0.078	11.592	0.967[ns]

Table 7 showed that MMR deficient endometrial cancer (EC) had a 4.274 (95% CI 1.691 to 15.515) times increased risk of advanced FIGO stage (III & IV). However, adnexal involvement, histological grade, and metastasis were not significantly associated with MMR proficient status.

Discussion

In this study, we observed the MMRP status of endometrial cancer determined by immunohistochemistry, and the clinicopathologic characteristics of 49 patients with endometrial cancer. To our knowledge, this is the first study evaluating MMR protein status in our population. In this study, MMR deficiency (MMRd) was found in 16 (32.7%) patients and showed that MMRP deficiency status in EC significantly associated with poor prognostic factors, including stage, grade, adnexal involvement, and metastasis. Frequency of MMRd in EC is quite variable in various studies. In this current study, it was observed that the frequency of MMRP-deficient cancers is consistent with previous studies that reported MMR-related protein deficiency using IHC in approximately 16% to 45% of endometrial cancer [15, 16]. In this study, paired loss of MLH1/PMS2 4(25%) and isolated loss of MSH2 4(25.0%) were the most frequent pattern of loss of expression. A recent study by Jain et al [17] observed out of 82 cases 27(33%) were MMRd and most common pattern of MMR defect was combined loss of MLH1/ PMS2,

Dr. Khatoon F, et al., Fortune J Health Sci 2024
DOI:10.26502/fjhs.198

17(21%) cases. Similarly, other studies conducted by Sharma et al [18] and Hashmi et al [8] also shows the most common loss of MMRP were the concurrent loss of MLH1/ PMS2.

In sporadic cases hypermethylation of promotor MLH1 appears to be most important mechanism for inactivation of MMR genes rather than mutation in MMR gene. In a study it was established that 77% of MMRd EC showed MLH1 promotor hypermethylation. MLH1 promotor methylation was associated with loss of MLH1 expression with or without concurrent loss of PMS2 expression. On the other hand, loss of MSH2/MSH6 expression was found to be infrequent in sporadic case [19] Hashmi et al [8] observed the mean age of the patients in MMRd EC was 55±10 (34-70) years. Majority of the patients were above 50 years of age (65.9%) and most of the patients were post-menopausal (86.5%). In this current study consistent result was observed, mean age was 55.0±10.1 year in MMR proficient EC with and 55.6 ±10.6 year in MMR deficient EC. In both MMR proficient and MMR deficient EC, 72% and 74% were more than 50 years respectively. Like the current study some author did not observe significant difference in age in cases of EC with or without MMRD [20, 21, 22]. It has long been thought that LS-related EC occurs at younger ages than in sporadic cases. Another study observed the mean age at diagnosis for LS-related EC was 49 years compared to 60 years for EC in the general population [23]. If an age cut-off of 50 years old had been selected for LS screening, 60% of patients would have been missed [24]. As per recent NCCN guideline, 2020. MMRD testing and screening for lynch syndrome has been recommended for all patients of EC, irrespective of age. Kim et al [25] observed 88.4% of MMR deficient EC were endometroid variety and 11.6% were non endometroid variety. Other studies also agree with recent findings that MMRP deficiency occur in both type I and type II endometrial carcinoma and there is no significant relation with histologic type and MMRD status [15, 17]. In this study 93.8% of MMRD endometrial cancer were Type I endometroid variety 6.3% was type II variety (serous carcinoma). And there was no significant association with histologic type and MMRD status which is consistent with the previous studies.

This study found that MMRP-deficient status was significantly associated with unfavorable prognostic factors, including histologic grade, advanced FIGO stage, adnexal involvement, and metastasis in univariate analysis. However, in multivariate analysis, only a significant relation was found with advanced FIGO stage. This study observed that high-grade (grade III) tumors were predominant (50%) in MMR-deficient tumors, while low-grade (grades I and II) tumors were predominant (84.8%) in MMR-proficient groups. The difference was significant in univariate analysis. Among all study populations, FIGO stage I was the most represented stage (59.1%), whereas MMR-deficient tumors tended to have more advanced stages (III, IV) compared to the other group ($p = 0.04$). For good reason, both metastasis (37.5% vs. 9.1%) and adnexal involvement (37.5% vs. 6.1%) were higher in MMR-deficient tumors compared to MMR-proficient groups ($p = 0.024$ and 0.010, respectively). However, in multivariate analysis, the association between MMR defect and advanced FIGO stage was significant ($p = 0.025$) with an odds ratio of 4.274 (95% CI 1.69-15.51) for MMRd. Other studies have reported mixed findings.

The NRG Oncology/Gynecologic Oncology Group 210 study also showed a significant association between MMRP deficiency and advanced stage, higher grade, and LVSI. Still, subgroup analysis revealed that the association with higher-stage disease was limited to women whose tumors had epigenetic MMR defects. McMeekin et al [6] and Kim et al [26] reported that the MMRd cohort was older in age (61 vs. 59; $p = 0.001$) and had a higher proportion of grade 3 disease (17% vs. 9%; $p<0.001$) and was associated with lymphovascular space invasion (LVSI) (28% vs. 18%; $p=0.024$) and lymph node involvement (7% vs. 5%; $p<0.001$) compared to MMR-proficient EC. On the other hand, other studies found that MMRP deficiency was associated with lower tumor grade and localized stage, and superficial myometrial invasion [27, 28]. Two large series showed no significant relation in LVSI status and MMRD status [29, 30]. In this study, no significant relation with LVSI and lymph node involvement in MMRd status was found. Underreporting of LVSI status by pathologists and the inclusion of only endometrioid variety and differences in MMR typing may explain the difference between our study and what was reported previously. To our knowledge, it is still unclear why MMRP deficiency is associated with a poor prognosis in endometrial cancer. The different methodologies used to assess MMR abnormalities and the histological variants of EC may account for the discordant findings [31].

Among other pathological characteristics in this study, a smaller tumor size and less predominant involvement of the lower uterine segment were characteristics of MMRd EC. Whereas various other studies showed larger tumor size and a significant predilection for LUS as characteristics of MMRd EC [13, 22, 32]. On the other hand, in this study, a higher tendency for cervical involvement (31.3% vs. 18.2%) and adnexal involvement (37.5% vs. 6.1%) was observed in MMRd EC compared to MMRp EC (31.3% vs. 18.2%), which is supported by other authors [8, 32]. Both Kim et al [25] and McMeekin et al [6] show a significant association between MMRP-deficient cancers and poor prognosis, but the differences in OS and DFS with MMR status were not statistically significant; rather, MMRP-deficient status tended to favor OS compared to MMRP-proficient status. In a subgroup analysis, Kim et al [25] observed that a trend toward better OS in MMRP-deficient cancers was more prominent at advanced stages (III/IV) and in patients who received adjuvant treatment. Adjuvant therapy shows a four-fold advantage in MMR-deficient tumors compared to

Dr. Khatoon F, et al., Fortune J Health Sci 2024
DOI:10.26502/fjhs.198

normal tumors [6] Reijnen et al [33] suggested that MMRP deficiency may serve as a useful prognostic marker for evaluating patient response to adjuvant radiation therapy. MMRP-deficient tumors have a highly immunogenic environment with upregulated immune checkpoints, including the programmed death-1 pathway [34]. So, another significance of MMR testing is the therapeutic benefit of anti-PDL therapy in MSI-associated endometrial cancers. It has been suggested that MSI-associated endometrial cancers have a better response to anti-PDL therapy compared to microsatellite-stable endometrial cancers [35]. This study demonstrates that MMRP deficiency in endometrial cancer is significantly associated with unfavorable prognostic factors, including FIGO advanced stage, but no significant relation with LVSI and deep myometrial invasion. However, patients with MMRP-deficient tumors tend to have a better survival rate, which may result from an enhanced response to adjuvant treatment.

Limitations of the study

The study has several limitations:

- The study population was selected from a single tertiary care hospital in Dhaka city. Therefore, the results may not be generalizable to the broader population.
- The sample size was relatively small, which may limit the statistical power of the study.
- Time and financial limitations restricted the scope and scale of the research.
- The sample was taken purposively, introducing the potential for selection bias that could influence the study's outcomes.
- The study was limited by the non-availability of further confirmation of MMR protein status through genetic testing, which could have provided more comprehensive results.

Conclusion

The results of the study suggest a considerable frequency of MMR deficiency (33%) in endometrial cancer within our population. The most frequent patterns of MMR protein loss were the combined loss of MLH1/PMS2 and isolated MSH2. Immunohistochemical (IHC) detection of MMR protein expression proves to be a simple, economical, and rapid method that can significantly aid in the screening of Lynch Syndrome (LS). This screening enables further surveillance testing, genetic counseling, and risk-reducing measures to prevent LS-associated cancers. This study also demonstrates that MMR deficiency in endometrial cancer is significantly associated with higher stages of the disease. Identifying MMR-deficient tumors is crucial for therapeutic management, clinical decision-making, and prognosis in patients with endometrial carcinoma.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians* 68 (2018): 394-424.
2. Hanley KZ, Birdsong GG and Mosunjac MB. Recent developments in surgical pathology of the uterine corpus. *Archives of Pathology & Laboratory Medicine* 141 (2017): 528-541.
3. Siegel R, Jemal A, Xu J, Ward E, Cancer Statistics. CA: *A Cancer Journal for Clinicians* 62 (2010): 10-29.
4. Kandoth C, Schultz N, Cherniack AD, Akbani R. Integrated Genomic Characterization of Endometrial Carcinoma. *Nature* 497 (2013): 67-73.
5. Lax SF and Kurman RJ. A dualistic model for endometrial carcinogenesis based on immunohistochemical and molecular genetic analyses. *Verhandlungen der Deutschen Gesellschaft fur Pathologie* 81 (1997): 228-232.
6. McMeekin DS, Tritchler DL, Cohn DE, Mutch DG, Lankes HA, Geller MA, et al. Clinicopathologic significance of mismatch repair defects in endometrial cancer: an NRG oncology/gynecologic oncology group study. *Journal of Clinical Oncology* 34 (2016): 3062.
7. Bruegl AS, Djordjevic B, Batte B, Daniels M, Fellman B, Urbauer D, et al. Evaluation of clinical criteria for the identification of Lynch syndrome among unselected patients with endometrial cancer. *Cancer Prevention Research* 7 (2014): 686-697.
8. Hashmi AA, Hussain ZF, Qadri A, Irfan M, Ramzan S, Faridi N, et al. Androgen receptor expression in endometrial carcinoma and its correlation with clinicopathologic features. *BMC research notes* 11 (2018): 1-5.
9. Halvarsson B, Lindblom A, Rambech, E, Lagerstedt, K and Nilbert M. Microsatellite instability analysis and/or immunostaining for the diagnosis of hereditary nonpolyposis colorectal cancer?. *VirchowsArchiv* 444 (2004): 135-141.
10. Lynch HT and De la Chapelle A. Hereditary colorectal cancer. *New England Journal of Medicine* 348 (2003): 919-932.
11. Kahn RM, Gordhandas S, Maddy BP, Baltich Nelson B, Askin G, Christos PJ, et al. Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population? *Cancer* 125 (2019): 3172-3183.

Citation: Khatoon F, Ara R, Meher S, Akter N, Akter M, Sayed S, Ferdous J. Relation of Mismatch Repair Deficiency in Endometrial Carcinoma and Its Clinical Implication. Fortune Journal of Health Sciences. 7 (2024): 372-381.

Dr. Khatoon F, et al., Fortune J Health Sci 2024
DOI:10.26502/fjhs.198

12. Garg K and Soslow RA. Endometrial carcinoma in women aged 40 years and younger. *Archives of pathology and laboratory medicine* 138 (2014): 335-342.

13. Pasanen A, Loukovaara M and Bützow R. Clinicopathological significance of deficient DNA mismatch repair and MLH1 promoter methylation in endometrioid endometrial carcinoma. *Modern Pathology* 33 (2020): 1443-1452.

14. Lemery S, Keegan P and Pazdur R. First FDA approval agnostic of cancer site-when a biomarker defines the indication. *The New England journal of medicine* 377 (2017): 1409-1412.

15. Garg K, Shih K, Barakat R, Zhou Q, Iasonos A and Soslow RA. Endometrial carcinomas in women aged 40 years and younger: tumors associated with loss of DNA mismatch repair proteins comprise a distinct clinicopathologic subset. *The American journal of surgical pathology* 33 (2009): 1869-1877.

16. Shih KK, Garg K, Levine DA, Kauff ND, Abu-Rustum NR, Soslow RA and Barakat RR. Clinicopathologic significance of DNA mismatch repair protein defects and endometrial cancer in women 40 years of age and younger. *Gynecologic oncology* 123 (2011): 88-94.

17. Jain E, Prasad S, Dhar A, Kini L, Sharma S and Dewan A. The utility of evaluating mismatch repair proteins in endometrial carcinoma: an experience from a tertiary referral centre in North India. *Pathologica* 113 (2021): 115.

18. Sharma A, Kamboj M, Panaych A, Gupta G, Pasricha S, Jain V, et al. Assessment of mismatch repair protein expression by immunohistochemistry in endometrial carcinomas with clinicopathological correlation: A study from Indian Tertiary Cancer Care Centre. *International Journal of Molecular and Immuno Oncology* 5 (2020): 101-107.

19. Simpkins SB, Bocker T, Swisher EM, Mutch DG, Gersell DJ, Kovatich AJ, et al. MLH1 promoter methylation and gene silencing is the primary cause of microsatellite instability in sporadic endometrial cancers. *Human molecular genetics* 8 (1999): 661-666.

20. Tangjitgamol S, Kittisiam T and Tanvanich S. Prevalence and prognostic role of mismatch repair gene defect in endometrial cancer patients. *Tumor Biology* 39 (2017): 1010428317725834.

21. Woo YL, Cheah PL, Shahruddin SI, Omar SZ and Arends M. The immunohistochemistry signature of mismatch repair (MMR) proteins in a multiethnic Asian cohort with endometrial carcinoma. *International Journal of Gynecological Pathology* 33 (2014): 554-559.

22. Rekhi B, Menon S, Deodhar KK, Ghosh J, Chopra S and Maheshwari A, Clinicopathological features of 50 mismatch repair (MMR)-deficient endometrial carcinomas, tested by immunohistochemistry: A single institutional feasibility study, India. *Annals of Diagnostic Pathology* 47 (2020): 151558.

23. Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la Chapelle A, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. *International journal of cancer* 81 (1999): 214-218.

24. Ryan P, Mulligan AM, Aronson M, Ferguson SE, Bapat B, Semotiuk K, et al. Comparison of clinical schemas and morphologic features in predicting Lynch syndrome in mutation-positive patients with endometrial cancer encountered in the context of familial gastrointestinal cancer registries. *Cancer* 118 (2012): 681-688.

25. Kim JH, Kwon BS, Kim H, Suh DH, Kim K, Kim YB and No JH. Clinicopathologic significance of DNA mismatch repair protein status in endometrial cancer. *Taiwanese Journal of Obstetrics and Gynecology* 61 (2022): 415-421.

26. Kim SR, Tone A, Kim RH, Cesari M, Clarke BA, Eiriksson L, et al. Understanding the clinical implication of mismatch repair deficiency in endometrioid endometrial cancer through a prospective study. *Gynecologic Oncology* 161 (2021): 221-227.

27. Doghri R, Houcine Y, Boujelbène N, Driss M, Charfi L, Abbes I, et al. Mismatch repair deficiency in endometrial cancer: immunohistochemistry staining and clinical implications. *Applied Immunohistochemistry & Molecular Morphology* 27 (2019): 678-682.

28. Gordhandas S, Kahn RM, Gamble C, Talukdar N, Maddy B, Nelson BB, et al. Clinicopathologic features of endometrial cancer with mismatch repair deficiency. *Ecancermedicalscience* 14 (2020).

29. Peiro G, Lohse P, Mayr D and Diebold J. Insulin-like growth factor-i receptor and PTEN protein expression in endometrial carcinoma: correlation with Bax and Bcl-2 expression, microsatellite instability status, and outcome. *American journal of clinical pathology* 120 (2003): 78-85.

30. Pijnenborg JMA, Dam-de Veen GC, De Haan J, Van Engeland M and Groothuis PG. Defective mismatch repair and the development of recurrent endometrial carcinoma. *Gynecologic oncology* 94 (2004): 550-559.

31. Zighelboim I, Goodfellow PJ, Gao F, Gibb RK, Powell MA, Rader JS et al. Microsatellite instability and epigenetic inactivation of MLH1 and outcome of patients with endometrial carcinomas of the endometrioid type. *Journal of Clinical Oncology* 25 (2007): 2042-2048.

Dr. Khatoon F, et al., Fortune J Health Sci 2024
DOI:10.26502/fjhs.198

32. Loukovaara M, Pasanen A and Bützow R. Mismatch repair deficiency as a predictive and prognostic biomarker in molecularly classified endometrial carcinoma. *Cancers* 13 (2021): 3124.

33. Reijnen C, Küsters-Vandevelde HV, Prinsen CF, Massuger LF, Snijders MP, Kommoss S, et al. Mismatch repair deficiency as a predictive marker for response to adjuvant radiotherapy in endometrial cancer. *Gynecologic oncology* 154 (2019): 124-130.

34. Westdorp H, Fennemann FL, Weren RD, Bisseling TM, Ligtenberg MJ, Figdor CG, et al. Opportunities for immunotherapy in microsatellite instable colorectal cancer. *Cancer Immunology, Immunotherapy* 65 (2016): 1249-1259.

35. Howitt BE, Shukla SA, Sholl LM, Ritterhouse LL, Watkins JC, Rodig S, et al. Association of polymerase e–mutated and microsatellite-instable endometrial cancers with neoantigen load, number of tumor-infiltrating lymphocytes, and expression of PD-1 and PD-L1. *JAMA oncology* 1 (2015): 1319-1323.