OPEN ACCESS

Scholars International Journal of Obstetrics and Gynecology

Abbreviated Key Title: Sch Int J Obstet Gynec
ISSN 2616-8235 (Print) | ISSN 2617-3492 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

Clinico-Pathological Characteristics of Endometrial Carcinoma with Mismatch Repair Deficiency

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DOI: https://doi.org/10.36348/sijog.2024.v07i09.004 | **Received:** 28.07.2024 | **Accepted:** 07.09.2024 | **Published:** 12.09.2024

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Abstract

Background: Endometrial carcinoma (EC) is a common gynecologic malignancy with significant implications for women's health. Mismatch repair deficiency (MMRd) has emerged as a critical factor influencing the pathogenesis and prognosis of EC. This study aims to investigate the clinicopathologic characteristics of MMRd EC in a Bangladeshi cohort. ***Methods:*** This cross-sectional observational study was conducted at the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from March 2022 to February 2023. A total of 49 patients with histologically confirmed EC were included. Data were collected through a semi-structured questionnaire and patient records. ***Results:*** Among the 49 patients, 67.35% (n=33) were MMR proficient, while 32.65% (n=16) were MMR deficient. The mean age was 55 years for MMR proficient and 55.6 years for MMR deficient patients. Hypertension was present in 69.70% of MMR proficient and 75% of MMR deficient patients, while diabetes mellitus affected 54.55% of MMR proficient and 62.50% of MMR deficient patients. MMRd patients showed higher rates of adnexal involvement (37.50% vs. 6.06%, p=0.010) and metastasis (37.50% vs. 9.09%, p=0.024). Multivariate logistic regression identified advanced FIGO stage (III & IV) as a significant predictor of MMR deficiency (adjusted OR 4.274, 95% CI: 1.691-15.515, p=0.025). ***Conclusion:*** MMRd in endometrial carcinoma is associated with more aggressive tumor features and poorer prognostic indicators. Routine evaluation of MMR status is crucial for effective prognosis and treatment planning. Addressing socioeconomic disparities and integrating targeted therapeutic strategies can improve management and outcomes for patients with MMRd endometrial carcinoma in diverse populations.

Keywords: Carcinoma, Endometrial, Mismatch Repair Deficiency, DNA Mismatch Repair System.

INTRODUCTION

Endometrial carcinoma (EC) stands as one of the most prevalent gynecologic malignancies, significantly impacting women's health globally. With an increasing incidence, particularly in low and middle-income countries, understanding the clinicopathologic characteristics of EC is crucial for improving patient outcomes and informing public health strategies [1]. This malignancy's pathogenesis is influenced by a myriad of factors, including genetic and molecular alterations. Among these, mismatch repair deficiency (MMRd) has emerged as a significant contributor to tumorigenesis in EC, necessitating a deeper investigation into its biological basis and clinical implications. MMRd results from defects in the DNA mismatch repair system, a crucial mechanism that maintains genomic stability by correcting replication errors. Deficiencies in this system, often due to mutations in genes such as MLH1, MSH2, MSH6, and PMS2, lead to microsatellite instability (MSI) and contribute to the development of cancer [2]. The biological underpinnings of MMRd involve the loss of function in these repair genes, which promotes carcinogenesis through the accumulation of mutations across the genome. This mechanism is particularly pertinent in the context of Lynch syndrome, an inherited

condition characterized by a high risk of colorectal, endometrial, and other cancers. Identifying Lynch syndrome through MMRd testing is vital for patient management and familial cancer risk assessment, emphasizing the importance of routine screening [3]. Histopathologically, MMRd ECs exhibit distinct features compared to their mismatch repair-proficient counterparts. These tumors are often high-grade and display a variety of histological subtypes, including endometrioid, undifferentiated, de-differentiated, and lymphoepithelioma-like patterns [4]. Studies have shown that MMRd tumors are more likely to present with advanced-stage disease, higher grades, and specific morphological characteristics such as deep myometrial invasion and lymphovascular space invasion. These features underscore the aggressive nature of MMRd ECs and highlight the need for precise diagnostic and therapeutic strategies [5]. The prognostic implications of MMRd in EC are significant. MMRd status has been associated with distinct survival rates and recurrence patterns. For instance, MMRd tumors often exhibit better overall survival and a higher sensitivity to adjuvant therapies, particularly in patients with probable Lynch syndrome [6]. However, the relationship between MMRd and prognosis can be complex, influenced by other genetic mutations and the broader molecular classification of the tumor. Understanding these nuances is crucial for tailoring treatment plans and improving patient outcomes [7]. Geographic and demographic factors also play a critical role in the prevalence and characteristics of MMRd ECs. There is notable variability in the frequency and presentation of these tumors across different populations. For example, studies have indicated that MMRd ECs are more common in younger patients and those with specific genetic backgrounds [8]. Despite the wealth of data from Western countries, there is a paucity of information regarding MMRd EC in Asian populations, particularly in Bangladesh. This highlights the need for region-specific studies to better understand the disease's behavior and inform local clinical practices [9]. This study aims to investigate the clinicopathologic characteristics of MMRd ECs in a cohort of Bangladeshi patients treated at Bangabandhu Sheikh Mujib Medical University (BSMMU).

METHODS

This cross-sectional observational study investigated the clinico-pathologic characteristics of endometrial carcinoma with mismatch repair deficiency at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from March 2022 to February 2023. The study included all patients with histologically confirmed endometrial carcinoma admitted to the Gynecological Oncology Department during the study period. A purposive sampling technique resulted in a sample size of 49 patients. Inclusion criteria were histopathologically confirmed endometrial carcinoma diagnosed through endometrial fractional curettage or diagnostic dilation and curettage (D&C), with patients admitted for surgical management. Exclusion criteria included a history of preoperative chemotherapy or radiation therapy and recurrent endometrial carcinoma. Data were collected using a semi-structured questionnaire, refined and finalized before use. After obtaining informed written consent, data were gathered through face-to-face interviews, ensuring privacy and confidentiality, and from patients' medical histories and investigation records. The collected data were compiled and analyzed using SPSS version 23.0. Mean values were calculated for continuous variables, and qualitative observations were indicated by frequencies and percentages. The association between MMR protein status and clinico-pathological parameters was assessed using Chi-square tests, Fisher's exact test, and unpaired t-tests. Odds ratios (OR) and their 95% confidence intervals (CI) were estimated to determine the strength of associations, with statistical significance set at a two-sided p-value of less than 0.05.

RESULTS

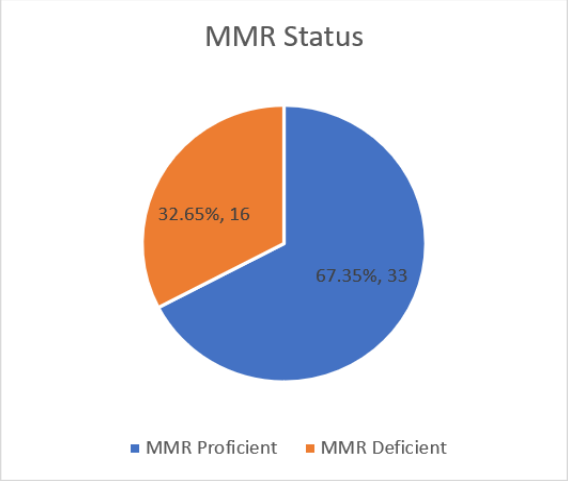

Figure 1: Distribution of participants by mismatch repair (MMR) status (N=49)

Among the study population, 33 patients (67.35%) were identified as MMR proficient, whereas 16 patients (32.65%) were found to be MMR deficient.

Table 1: Baseline Characteristics of the Respondents Stratified by MMR Status (N=49)

Variables	MMR Proficient (n=33)		MMR Deficient (n=16)	
	n	%	n	%
Age (years)				
≤30	1	3.03%	0	0.00%
31-40	3	9.09%	1	6.25%
41-50	4	12.12%	3	18.75%
51-60	18	54.55%	7	43.75%
61-70	6	18.18%	5	31.25%
Mean±SD	55±10.1		55.6±10.6	
Range (min-max)	24-70		32-70	
Monthly income (Taka)				
Low (≤8,585 Tk)	4	12.12%	4	25.00%
Middle (8,586-1,04,391 Tk)	16	48.48%	8	50.00%
High (>1,04,391 Tk)	13	39.39%	4	25.00%
BMI (kg/m^2)				
18.5-24.9	12	36.36%	4	25.00%
25.0-29.9	2	6.06%	2	12.50%
≥30.0	19	57.58%	10	62.50%
Mean±SD	28.3±4.5		28.7±3.8	
Range (min-max)	21.7-36		22.9-33	
Parity				
Nulli	4	12.12%	1	6.25%
Primi	13	39.39%	5	31.25%
Multi	13	39.39%	7	43.75%
Grand-multi	3	9.09%	3	18.75%
Oral contraceptive pill				
Yes	11	33.33%	4	25.00%
No	22	66.67%	12	75.00%
Menopause				
Yes	28	84.85%	12	75.00%
No	5	15.15%	4	25.00%

Most patients were aged between 51 and 60 years, with mean ages of 55 (MMR proficient) and 55.6 years (MMR deficient). Regarding income, 25% of MMR deficient patients were low-income, compared to 12.12% of MMR proficient patients. Both groups had around 50% in the middle-income category, while 39.39% of MMR proficient and 25% of MMR deficient patients were high-income. Obesity (BMI ≥30.0) was prevalent in 57.58% of MMR proficient and 62.50% of MMR deficient patients, with mean BMIs of 28.3 and 28.7 kg/m², respectively. Most patients were primi- or multiparous, with 39.39% of MMR proficient and 43.75% of MMR deficient patients being multiparous. Grand-multiparity was more common in MMR deficient patients (18.75% vs. 9.09%). Oral contraceptive use was higher among MMR proficient patients (33.33% vs. 25%), and more MMR proficient patients were postmenopausal (84.85% vs. 75%).

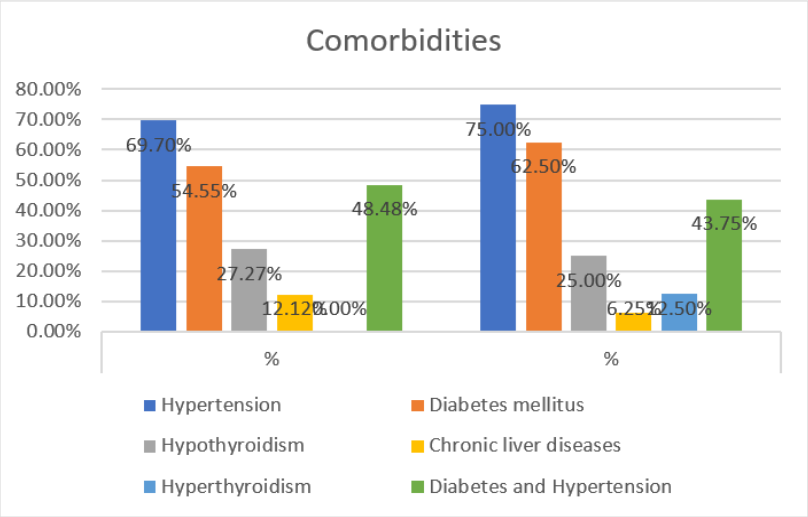

Figure 2: Comorbidities of the Respondents Stratified by MMR Status (N=49)

Hypertension was present in 69.70% of MMR proficient and 75% of MMR deficient patients. Diabetes mellitus affected 54.55% of MMR proficient and 62.50% of MMR deficient patients. Hypothyroidism was noted in 27.27% of MMR proficient and 25% of MMR deficient patients. Chronic liver diseases were present in 12.12% of MMR proficient and 6.25% of MMR deficient patients. Hyperthyroidism was seen only in MMR deficient patients (12.50%). Co-occurrence of diabetes and hypertension was observed in 48.48% of MMR proficient and 43.75% of MMR deficient patients.

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

Mismatch repair protein deficiency	Frequency	Percentage
Single loss		
MSH2	4	25.00%
MSH6	1	6.25%
Multiple loss		
MLH1+ PMS2	4	25.00%
MSH2+ MSH6	3	18.75%
MLH1+ MSH2	2	12.50%
MLH1+ MSH2+ PMS2	1	6.25%
MLH1+ MSH2+ PMS2+ MSH6	1	6.25%

In the subset of 16 MMR deficient patients, single loss of mismatch repair proteins was observed with MSH2 (25%) and MSH6 (6.25%). Multiple losses were more common, with MLH1 and PMS2 loss in 25%, MSH2 and MSH6 loss in 18.75%, MLH1 and MSH2 loss in 12.5%, MLH1, MSH2, and PMS2 loss in 6.25%, and MLH1, MSH2, PMS2, and MSH6 loss in 6.25%.

Table 3: Family History and Grading of Endometrial Cancer Stratified by MMR Status (N=49)

Variables	MMR Proficient (n=33)		MMR Deficient (n=16)		p-value
	n	%	n	%	
Family History of Malignancy					
Yes	5	15.15%	5	31.25%	0.190ns
No	28	84.85%	11	68.75%	
Histopathological Grading					
Grade I	20	60.61%	5	31.25%	0.032s
Grade II	8	24.24%	3	18.75%	
Grade III	5	15.15%	8	50.00%	
FIGO Staging					
Stage I	23	69.70%	6	37.50%	0.046s
Stage II	7	21.21%	4	25.00%	
Stage III	3	9.09%	4	25.00%	
Stage IV	0	0.00%	2	12.50%	

Among MMR proficient patients, 15.15% reported a family history of malignancy, compared to 31.25% of MMR deficient patients; however, this difference was not statistically significant (p=0.190). Histopathological grading revealed significant differences between the groups (p=0.032). In the MMR proficient group, 60.61% were classified as Grade I, 24.24% as Grade II, and 15.15% as Grade III. In contrast, the MMR deficient group had 31.25% of patients in Grade I, 18.75% in Grade II, and a notably higher 50.00% in Grade III. Regarding FIGO staging, a statistically significant difference was observed (p=0.046). Among MMR proficient patients, 69.70% were in Stage I, 21.21% in Stage II, 9.09% in Stage III, and none in Stage IV. For MMR deficient patients, 37.50% were in Stage I, 25.00% in Stage II, 25.00% in Stage III, and 12.50% in Stage IV.

Table 4: 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	90.91%	15	93.75%	0.605ns
Serous adenocarcinoma	3	9.09%	1	6.25%	
Depth of myometrial invasion					
<50%	19	57.58%	11	68.75%	0.333ns
≥50%	14	42.42%	5	31.25%	
Lymph vascular space invasion					
Positive	4	12.12%	0	0.00%	0.193ns
Negative	29	87.88%	16	100.00%	
Tumour size (cm)					
≤2.0	4	12.12%	4	25.00%	0.140ns
2.1-4.0	13	39.39%	5	31.25%	
>4.0	16	48.48%	7	43.75%	
Mean±SD	5±2.8		3.8±1.8		
Range (min-max)	1.5-12		1-6.5		
Additional Findings					
Adnexal involvement	2	6.06%	6	37.50%	0.010s
Lower uterine segment involvement	14	42.42%	5	31.25%	0.452ns
Cervical involvement	6	18.18%	5	31.25%	0.250ns
Peritoneal cytology	3	9.09%	0	0.00%	0.296ns
Metastasis	3	9.09%	6	37.50%	0.024s

The histological findings of the study participants, stratified by MMR status, revealed several key observations. The majority of patients in both groups had endometrioid adenocarcinoma, with 90.91% of MMR proficient and 93.75% of MMR deficient patients (p=0.605). Serous adenocarcinoma was less common, observed in 9.09% of MMR proficient and 6.25% of MMR deficient patients. Regarding the depth of myometrial invasion, 57.58% of MMR proficient and 68.75% of MMR deficient patients had less than 50% invasion, while 42.42% of MMR proficient and 31.25% of MMR deficient patients had 50% or more invasion (p=0.333). Lymph vascular space invasion was positive in 12.12% of MMR proficient patients and absent in all MMR deficient patients (p=0.193). Tumor size varied, with 12.12% of MMR proficient and 25% of MMR deficient patients having tumors 2.0 cm or smaller. Tumors sized 2.1-4.0 cm were found in 39.39% of MMR proficient and 31.25% of MMR deficient patients, while tumors larger than 4.0 cm were observed in 48.48% of MMR proficient and 43.75% of MMR deficient patients (p=0.140). The mean tumor size was 5 cm for MMR proficient and 3.8 cm for MMR deficient patients. Additional findings showed significant differences in adnexal involvement and metastasis. Adnexal involvement was present in 6.06% of MMR proficient patients compared to 37.50% of MMR deficient patients (p=0.010). Metastasis was observed in 9.09% of MMR proficient patients and 37.50% of MMR deficient patients (p=0.024). There were no significant differences in lower uterine segment involvement (42.42% vs. 31.25%, p=0.452), cervical involvement (18.18% vs. 31.25%, p=0.250), or peritoneal cytology (9.09% vs. 0%, p=0.296) between the two groups.

Table 5: Multi variate logistic regression analysis for MMR deficient endometrial carcinoma (n=16)

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

Multivariate logistic regression analysis was performed to identify factors associated with MMR deficient endometrial carcinoma. The analysis revealed that advanced FIGO stage (III & IV) was significantly associated with MMR deficiency, with an adjusted odds ratio (OR) of 4.274 (95% CI: 1.691-15.515, p=0.025). Although adnexal involvement showed an adjusted OR of 4.901, this association was not statistically significant (95% CI: 0.537-44.683, p=0.159). Histopathological grade III had an adjusted OR of 2.072, but this was also not statistically significant (95% CI: 0.215-19.997, p=0.529). The presence of metastasis was not significantly associated with MMR deficiency, with an adjusted OR of 0.948 (95% CI: 0.078-11.592, p=0.967).

DISCUSSION

The current study aimed to elucidate the clinicopathologic characteristics of endometrial carcinoma (EC) with mismatch repair deficiency (MMRd) in a Bangladeshi population. Our findings reveal significant insights into the prevalence and implications of MMRd in EC, aligning with and expanding upon the existing body of literature. Among the 49 patients studied, 32.65% were MMR deficient (n=16), a prevalence consistent with other reports that document MMRd in approximately 30% of endometrial cancers (5,8). The age distribution was similar between MMR proficient and deficient patients, with mean ages of 55 and 55.6 years, respectively, suggesting that age may not be a distinguishing factor for MMR status in EC. Socioeconomic factors, such as monthly income, also showed notable patterns. A higher percentage of MMR deficient patients fell into the low-income bracket (25%) compared to MMR proficient patients (12.12%). This socioeconomic disparity highlights the potential for differential access to healthcare and early detection services, echoing findings from previous studies that underscore the role of socioeconomic status in cancer outcomes (14). Obesity was prevalent among both groups, with 57.58% of MMR proficient and 62.50% of MMR deficient patients having a BMI ≥30.0. This aligns with the broader literature that identifies obesity as a significant risk factor for endometrial cancer, influencing tumor biology and patient prognosis (9). Postmenopausal status was observed in a higher proportion of MMR proficient patients (84.85%) compared to MMR deficient patients (75%). This difference may reflect underlying hormonal influences on tumor development and progression, consistent with the findings of Wong and Ngeow (2015), who discuss the interplay between hormonal factors and endometrial carcinoma (3). Hypertension and diabetes mellitus were prevalent comorbidities, affecting 69.70% and 54.55% of MMR proficient patients, and 75% and 62.50% of MMR deficient patients, respectively. These comorbidities are common in EC patients and have been linked to worse outcomes, underscoring the need for integrated management approaches (15). Histopathological analysis revealed that Grade III tumors were significantly more common in MMR deficient patients (50%) compared to MMR proficient patients (15.15%). This finding is consistent with the literature that suggests MMRd is associated with higher grade, more aggressive tumors (4,8). Additionally, advanced FIGO stages (III & IV) were more prevalent among MMR deficient patients, which further supports the association between MMR deficiency and advanced disease stages (16). Depth of myometrial invasion was less than 50% in 68.75% of MMR deficient patients, compared to 57.58% of MMR proficient patients. While lymphovascular space invasion (LVSI) was absent in MMR deficient patients, it was present in 12.12% of MMR proficient patients, indicating a possible inverse relationship between MMR deficiency and LVSI, as previously suggested (17). Tumor sizes larger than 4.0 cm were found in 48.48% of MMR proficient and 43.75% of MMR deficient patients. This finding suggests that tumor size alone may not be a reliable marker for MMR status, echoing earlier reports that emphasize the complexity of tumor biology in EC (18). Adnexal involvement was significantly higher in MMR deficient patients (37.50%) compared to MMR proficient patients (6.06%). This finding highlights the aggressive nature of MMRd tumors, aligning with studies that report higher rates of adnexal and distant metastases in MMRd EC (8,19). Multivariate logistic regression analysis identified advanced FIGO stage as a significant predictor of MMR deficiency (adjusted OR 4.274, 95% CI: 1.691-15.515, p=0.025). This association underscores the prognostic value of FIGO staging in MMRd EC, reinforcing the importance of comprehensive staging in clinical management (14,16). In conclusion, this study provides valuable insights into the clinicopathologic characteristics of MMR deficient endometrial carcinoma in a Bangladeshi cohort. Our findings are consistent with the global literature, emphasizing the aggressive nature of MMRd tumors and the critical role of advanced FIGO stage as a prognostic marker. These results underscore the need for targeted diagnostic and therapeutic strategies to improve

outcomes for patients with MMRd endometrial carcinoma.

Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

This study provides significant insights into the clinicopathologic characteristics of endometrial carcinoma with mismatch repair deficiency in a Bangladeshi population. The findings indicate that MMRd is prevalent in a substantial proportion of endometrial carcinoma cases and is associated with higher tumor grades, advanced FIGO stages, and more aggressive clinical features, such as increased adnexal involvement and metastasis. The study highlights the importance of routine MMR evaluation in endometrial carcinoma for guiding prognosis and therapeutic decisions. Addressing the socioeconomic disparities observed in MMRd patients could improve early detection and treatment outcomes. These results underscore the need for targeted diagnostic and therapeutic strategies to manage MMRd endometrial carcinoma effectively, ultimately aiming to enhance patient outcomes in diverse demographic settings.

Funding: No funding sources.

Conflict of interest: None declared.

Ethical approval: The study was approved by the Institutional Ethics Committee

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