International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Khatoon F et al. Int J Reprod Contracept Obstet Gynecol. 2024 Sep;13(9):2241-2248
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20242468

Original Research Article

Identifying the frequency of mismatch repair deficiency in endometrial carcinoma in a tertiary care hospital

Farhana Khatoon[1]*, Shirin Akter Begum[1], Bishnu Pada Dey[2], Jannatul Islam[3], Naznine Akter[1], Fatema Nihar[4], Rowson Ara[5], Babrul Alam[6]

[1]Department of Gynaecological Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[2]Department of Pathology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[3]Department of Obstetrics and Gynecology, Upazilla Health Complex, Daudkandi, Cumilla, Bangladesh
[4]Department of Gynecological Oncology, National Institute of cancer and Research Hospital (NICRH), Dhaka, Bangladesh
[5]Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh
[6]Department of Nephrology, National Institute of Kidney Diseases & Urology (NIKDU), Dhaka, Bangladesh

Received: 26 June 2024
Accepted: 05 August 2024

***Correspondence:**
Dr. Farhana Khatoon,
E-mail: farhanashimu1977@bsmmu.edu.bd

ABSTRACT

Background: Mismatch repair deficiency (MMRd) is a pivotal genetic defect that significantly contributes to the pathogenesis of various cancers, particularly colorectal and endometrial cancers. The mismatch repair (MMR) system is essential for maintaining genomic stability by correcting base-base mismatches and insertion-deletion loops that occur during DNA replication. The aim of the study was to investigate the frequency and patterns of MMR protein deficiency in endometrial cancer and their association with clinical and pathological characteristics.
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. The study included all patients admitted with histologically confirmed endometrial carcinoma, diagnosed via endometrial fractional curettage or diagnostic D&C, who were admitted for surgical management.
Results: In this study of endometrial cancer, 49 participants were analyzed for mismatch repair (MMR) protein status. MMR deficiency (MMRd) was observed in 16 cases (32.7%). Among 16 MMR deficient EC, isolated single protein loss was in 5 (31.25%) and multiple loss was in 11(68.75%) cases. Family history of malignancy often correlated with MSH2 loss. MMRd was significantly associated with higher cancer stages. Immunohistochemistry proved effective for identifying MMR status, facilitating Lynch syndrome screening and subsequent clinical management. These findings underscore the importance of MMR testing in endometrial cancer for prognosis and treatment decisions.
Conclusions: This study underscores the importance of mismatch repair (MMR) protein status in the prognosis of endometrial cancer (EC).

Keywords: Endometrial carcinoma, Immunohistochemistry, Lynch syndrome, Microsatellite instability, Mismatch repair

INTRODUCTION

Mismatch Repair Deficiency (MMRd) is a pivotal genetic defect that significantly contributes to the pathogenesis of various cancers, particularly colorectal and endometrial cancers. The mismatch repair (MMR) system is essential for maintaining genomic stability by correcting base-base mismatches and insertion-deletion loops that occur during

DNA replication. Deficiencies in this system, resulting from mutations in key MMR genes such as MLH1, MSH2, MSH6, and PMS2, lead to microsatellite instability (MSI), a hallmark of MMRd.[1,2]

MMRd has profound implications for cancer biology, influencing tumor behavior, prognosis, and treatment responsiveness. Tumors with MMRd often exhibit high levels of MSI (MSI-H) and are characterized by a distinct mutational profile and immune microenvironment. These features differentiate MMRd tumors from those with proficient mismatch repair (MMRp) systems.[3] MMRd tumors tend to accumulate mutations at a higher rate, leading to a more diverse set of neoantigens. This characteristic makes them particularly susceptible to immune surveillance, which explains the increased presence of tumor-infiltrating lymphocytes (TILs) observed in these tumors. The immune microenvironment of MMRd tumors is often inflamed, reflecting an active anti-tumor immune response that can be leveraged for therapeutic purposes.[4]

In colorectal cancer, approximately 15% of cases exhibit MMRd, with higher prevalence in hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome, where MMR gene mutations are inherited.[5] MMRd colorectal cancers are typically located in the proximal colon, present at an earlier stage, and have a better prognosis compared to MMRp tumors.[6] These tumors also show increased infiltration of TILs, correlating with improved clinical outcomes.[7]

Endometrial cancer also shows a significant incidence of MMRd, identified in approximately 20-30% of cases, making it one of the most common molecular alterations in this cancer type.[8] Similar to colorectal cancer, MMRd endometrial cancers are associated with distinct histopathological features and a better prognosis in certain subtypes.[9] The frequency of MMRd in endometrial cancer underscores the importance of genetic testing in this patient population to identify those who may benefit from targeted therapies.[10]

The identification of MMRd has significant therapeutic implications. The presence of MMRd/MSI-H tumors has been shown to predict responsiveness to immune checkpoint inhibitors, such as pembrolizumab, which has been approved for the treatment of MMRd/MSI-H solid tumors regardless of their primary site.[11] This breakthrough highlights the importance of routine MMR status testing in clinical practice to guide personalized treatment strategies.[12] Immune checkpoint inhibitors work by unleashing the immune system's ability to recognize and attack tumor cells, which is particularly effective in tumors with high mutational burdens like those with MMRd.[13]

Beyond colorectal and endometrial cancers, MMRd is also found in other malignancies, including gastric, ovarian, and urothelial cancers, although the prevalence is generally lower.[14] The presence of MMRd in these cancers also carries prognostic and therapeutic implications, supporting the broader application of MMR status testing across different tumor types.[15] In gastric cancer, for instance, MMRd tumors tend to be associated with a better prognosis and may also respond to immunotherapies, although further research is needed to fully understand the therapeutic potential.[16]

The objective of this study was to determine the frequency of MMRd among patients diagnosed with cancers associated with this deficiency in a tertiary care hospital.

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.

Inclusion criteria

The study included all patients admitted with histologically confirmed endometrial carcinoma, diagnosed via endometrial fractional curettage or diagnostic D&C, who were admitted for surgical management.

Exclusion criteria

Exclusion criteria included a history of preoperative chemotherapy or radiation therapy and recurrent endometrial carcinoma.

A total sample size of 49 was obtained using purposive sampling. Data collection involved a semi-structured questionnaire that gathered demographic information, medical history, and family history of cancer. Patients underwent surgical treatment, including total hysterectomy and bilateral salpingo-oophorectomy, with lymphadenectomy performed based on surgical risk and disease stage. Pathological examinations and immunohistochemistry (IHC) were conducted in the Pathology Department of BSMMU. IHC was used to assess the expression of MMR proteins (MLH1, MSH2, MSH6, PMS2), with a ≥10% positive staining in tumor cells indicating MMR proficiency (MMRp) and 0% staining indicating MMR deficiency (MMRd).

Statistical analysis

Data were analyzed using SPSS version 23.0, with descriptive statistics summarizing patient characteristics. Associations between MMR status and clinicopathological parameters were assessed using Chi-square tests, Fisher's exact tests, and unpaired t-tests, with odds ratios (OR) and 95% confidence intervals (CI) calculated. P-values <0.05 were considered statistically significant. The study adhered to ethical standards, with approval obtained from the Institutional Review Board (IRB) of BSMMU, and

informed consent obtained from all participants. The study ensured confidentiality and minimized risks, aligning with the Helsinki Declaration for Medical Research involving Human Subjects.

RESULTS

Figure 1 shows MMR protein status of the study participants. 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%).

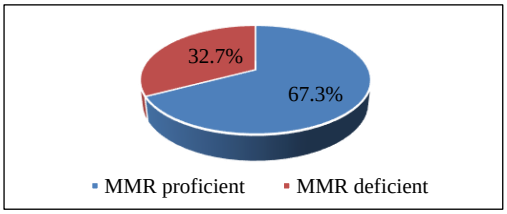

Figure 1: MMR protein status of the study participants (n=49).

Table 1 shows the characteristics of the respondents stratified by MMR status. 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%). The distribution of the respondents in respect of age, socioeconomic status, BMI, parity use of OCP and menopausal status in MMR deficient and MMR proficient EC were not statistically significant (p>0.05).

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

Socio-demographic characteristics	MMR proficient (n=33)		MMR deficient (n=16)		P value
	N	Percentage	N	Percentage	
Age (years)					
≤30	1	3	0	0	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	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	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		
Parity					
Nulli	4	12.1	1	6.3	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	0.553 ns
No	22	66.7	12	75	
Menopause					
Yes	28	84.8	12	75	0.449 ns
No	5	15.2	4	25	

ns = not significant

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 2 illustrates, among 16 MMR deficient EC, isolated single protein loss was in 5 (31.25%) and multiple loss was in 11 (68.75%) cases. Among them most frequent loss of MMR protein was isolated MSH2 and combined loss of MLH1/PMS2. Only one case (6.3%) shows loss of expression in all markers.

Table 3 shows that hypertension, diabetes mellitus, and both DM/HTN were the most frequently observed associated medical condition in both MMR proficient and MMR deficient EC cases. There was no statistically significant difference in the distribution of the respondents according to hypertension, diabetes mellitus, hypothyroidism, chronic liver disease ($p>0.05$) between two groups.

Table 4 shows that family history of malignancy was more in 5 (31.3%) in MMR deficient group compared to MMR proficient group 5 (15.2%). But the difference were not statistically significant ($p>0.05$) between two groups.

Table 3: Co-morbidities of the study participants stratified by MMR status (n=49).

Co-morbidities	MMR proficient (n=33) (%)	MMR deficient (n=16) (%)	P value
Hypertension	23 (69.7)	12 (75.0)	0.488 ns
Diabetes mellitus	18 (54.5)	10 (62.5)	0.415 ns
Hypothyroidism	9 (27.3)	4 (25.0)	0.577 ns
Chronic liver diseases	4 (12.1)	1 (6.3)	0.497 ns
Hyperthyroidism	0 (0.0)	2 (12.5)	0.102 ns
DM+ HTN	16 (48.5)	7 (43.8)	0.498 ns

ns = not significant, P value reached from chi square test

Table 4: Family history of malignancy of the study patients stratified by MMR status (n=49).

Family history of malignancy	MMR proficient (n=33) (%)	MMR deficient (n=16) (%)	P value
Yes	5 (15.2)	5 (31.3)	0.190 ns
No	28 (84.8)	11 (68.8)	

ns = not significant, P value reached from chi square test

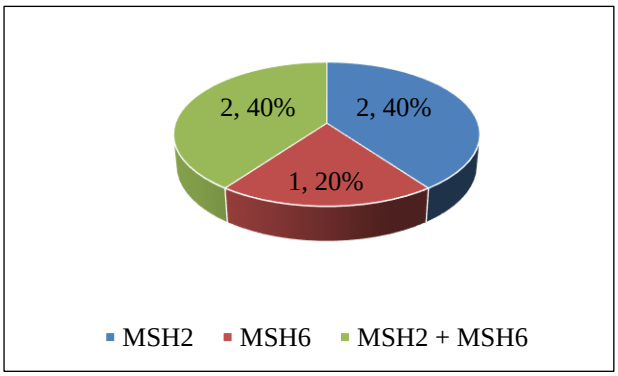

Figure 2: Pattern of MMR protein deficiency in patients having family history of malignancy (n=5).

Figure 2 shows isolated loss of MSH2, and paired loss of MSH2/MSH6 was the most common pattern of loss of expression in patient having family history of other malignancy.

Table 5 illustrate that, among 16 MMR deficient EC, 8 (50%) were grade III tumor. Loss of MSH6 and all protein markers was observed only in grade III tumor.

Table 5: Pattern of mismatch repair deficiency in relation to histopathological grading of endometrial cancer (n=16).

Mismatch repair protein deficiency	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

Table 6: Tumor grading in relation to single protein loss and multiple protein loss.

Mismatch repair protein deficiency	Grade I (%)	Grade II (%)	Grade III (%)	P value
Single	2 (40.0)	0 (0.0)	3 (37.5)	0.430 ns
Multiple	3 (60.0)	3 (100.0)	5 (62.5)	

ns = not significant

Table 7: Pattern of mismatch repair deficiency in relation to FIGO staging (2009) of endometrial cancer.

Mismatch repair protein deficiency	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 8: Tumor staging in relation to single protein loss and multiple protein loss.

Mismatch repair protein deficiency	Grade I (%)	Grade II (%)	Grade III (%)	P value
Single	2 (33.3)	1 (25.0)	0 (0.0)	0.098 ns
Multiple	4 (66.7)	3 (75.0)	4 (100.0)	

ns = not significant

Table 6 illustrates there is no significant relation of FIGO tumor grading in respect of single protein loss and multiple MMR protein loss in MMR deficient EC.

Table 7 shows loss of MSH2 found in both early and advanced FIGO stage. Paired loss of MLH1/PMS2 was found mostly in early FIGO stage. Loss of all four protein found in advanced FIGO stage.

Table 8 shows there was no significant relation FIGO stage according isolated protein loss and multiple proteins.

DISCUSSION

This study aimed to evaluate the mismatch repair (MMR) protein status in endometrial cancer (EC) patients and its association with various clinicopathological features. The findings highlight significant differences between MMR proficient (MMRp) and MMR deficient (MMRd) groups, providing insights into the prognostic implications of MMR status in EC.

In this study, loss of MMR protein expression (MMR deficient) was observed in 16 (32.7%) patients, while intact expression (MMR proficient) was observed in 33 (67.3%) respectively. The frequency of MMRd in EC varies across different studies. The observed prevalence of MMRP-deficient cancers in this study aligns with prior research, which has reported MMR-related protein deficiency, detected using immunohistochemistry (IHC), in approximately 16% to 45% of endometrial cancer cases.[17,18]

In this study, the age distribution between MMR proficient and MMR deficient patients showed no significant difference. The mean age was 55.0 years for MMR proficient and 55.6 years for MMR deficient groups, with a P value of 0.849. This finding aligns with several studies, such as that by Gallo et al, which found that the mean age of endometrial cancer patients with MMR deficiency was not significantly different from those without the deficiency.[19] However, other studies like Buchanan et al noted a slightly younger mean age in MMR deficient patients compared to proficient ones.[20] The mean BMI was 28.3 kg/m² for MMR proficient and 28.7 kg/m² for MMR deficient patients. These results are consistent with research by Hampel et al, which found no significant association between BMI and MMR status in endometrial cancer patients.[21] However, a study by Backes et al noted a trend towards higher BMI in MMR deficient patients, suggesting that obesity could be more prevalent in this group.[22] Menopausal status was not significantly different between the two groups in this study (p=0.449). The proportion of postmenopausal women was high in both MMR proficient (84.8%) and deficient (75.0%) groups. This finding aligns with research by Nagley et al, which reported no significant difference in menopausal status between the groups.[23] Conversely, studies like those by Huang et al have suggested that postmenopausal status might be more common in MMR deficient patients, potentially due to age-related factors.[24]

The study found a higher prevalence of family history of malignancy in the MMR deficient group (31.3%) compared to the MMR proficient group (15.2%), although this difference was not statistically significant (p=0.190).

This trend aligns with previous research indicating that MMR deficiency, particularly due to germline mutations in MMR genes, is associated with hereditary cancer syndromes such as Lynch syndrome. Studies by Hampel et al similarly report a higher prevalence of family history of cancer in MMR deficient patients.[25]

In the subset of patients with a family history of malignancy, isolated loss of MSH2 and paired loss of MSH2/MSH6 were the most common patterns of MMR protein deficiency. This is consistent with literature indicating that MSH2 and MSH6 are frequently implicated in hereditary cancer syndromes, such as Lynch syndrome, which predispose individuals to multiple cancer types including EC. For example, Hampel et al reported that MSH2 and MSH6 losses were predominant in EC patients with Lynch syndrome.[25]

Regarding histopathological grading, the study revealed that among 16 MMR-deficient EC cases, 8 (50%) were grade III tumors. Notably, loss of MSH6 and all protein markers was observed exclusively in grade III tumors. This suggests that MMRd is associated with more aggressive and poorly differentiated tumors. Previous research has similarly demonstrated a correlation between MMR deficiency and higher tumor grade, indicating worse prognosis. Stelloo et al found that MMRd was significantly associated with higher tumor grades in their cohort.[26]

The relationship between tumor grading and single versus multiple protein loss was also explored. The study found no significant association between the FIGO tumor grading and the type of protein loss (single or multiple). While 40% of grade I tumors had single protein loss, 100% of grade II tumors and 62.5% of grade III tumors exhibited multiple protein losses. This is supported by other studies that have found varied impacts of single versus multiple MMR protein losses on EC prognosis. For instance, Goodfellow et al noted no significant difference in outcomes between single and multiple MMR protein losses.[22]

In terms of FIGO staging, the study showed that loss of MSH2 was found in both early and advanced stages, while paired loss of MLH1/PMS2 was mostly observed in early stages. The loss of all four proteins was found in advanced stages. These patterns indicate that while some MMR protein deficiencies can occur early in disease progression, extensive protein loss is more common in advanced stages. This is corroborated by findings from other studies, which have highlighted the progressive nature of MMR deficiencies in relation to EC stage. Zhao et al observed that advanced stage ECs more frequently exhibited multiple MMR protein losses compared to early-stage tumors.[27]

Finally, the analysis of tumor staging in relation to single versus multiple protein losses revealed no significant difference. Although isolated protein loss was more common in early stages and multiple protein losses were prevalent in advanced stages, the association was not statistically significant. This indicates that the presence of multiple MMR deficiencies does not necessarily correlate with a more advanced stage, but may reflect the overall complexity and heterogeneity of the tumor's genetic profile. Nelson et al similarly reported no significant association between single versus multiple MMR protein losses and FIGO stage.[28]

This study reinforces the significant role of MMR deficiencies in endometrial cancer prognosis. The association of MMRd with higher tumor grades, advanced FIGO stages, and specific patterns of protein loss provides valuable insights into the aggressive nature of MMR-deficient EC. These findings underscore the importance of MMR status in the clinical management and therapeutic stratification of endometrial cancer patients.

Limitations

This study has few limitations. The relatively small sample size of 49 patients limits the generalizability of the findings. A larger cohort would provide more robust data and potentially reveal additional significant associations. Conducting the study at a single center may introduce selection bias. Multicenter studies involving diverse populations would enhance the external validity of the results. Endometrial cancer is a heterogeneous disease with various subtypes. The study did not differentiate between these subtypes, which might have different etiologies and responses to MMR deficiencies. A longer follow-up period is necessary to determine the true prognostic impact of MMR deficiencies on survival and recurrence rates.

CONCLUSION

This study underscores the importance of mismatch repair (MMR) protein status in the prognosis of endometrial cancer (EC). Our findings reveal that MMR deficiency (MMRd) is present in 32.7% of the patients. Importantly, MMRd was significantly associated with higher tumor grades, advanced FIGO stages, adnexal involvement, and metastasis, indicating its critical role in disease progression. The identification of MMRd in a significant portion of EC patients offers valuable insights for clinical practice. It highlights the need for routine screening for MMR status in EC patients, which can aid in stratifying patients based on their risk and tailoring treatment strategies accordingly. The presence of MMRd suggests a more aggressive disease course, and recognizing this can lead to earlier and more aggressive interventions, potentially improving patient outcomes.

ACKNOWLEDGEMENTS

Authors would like to thank the staff and participants who contributed to this study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterol. 2010;138(6):2073-87.
2. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med. 2003;348(10):919-32.
3. Coupez D, Hulo P, Touchefeu Y, Bossard C, Bennouna J. Pembrolizumab for the treatment of colorectal cancer. Expert Opinion on Biological Therapy. 2020 Mar 3;20(3):219-26.
4. Hause RJ, Pritchard CC, Shendure J, Salipante SJ. Classification and characterization of microsatellite instability across 18 cancer types. Nature Medi. 2016;22(11):1342-50.
5. Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Medi. 2005;352(18):1851-60.
6. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372(26):2509-20.
7. Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. J Clin Oncol. 2008;26(35):5783-8.
8. de Freitas D, Aguiar FN, Anton C, de Almeida DC, Bacchi CE, Carvalho JP, et al. Clinicopathological characteristics of endometrial carcinomas according to DNA mismatch repair protein status. Heliyon. 2023;9(6).
9. Shen Z, Gu L, Mao D, Chen M, Jin R. Clinicopathological and prognostic significance of PD-L1 expression in colorectal cancer: a systematic review and meta-analysis. World J Surg Oncol. 2019;17:1-9.
10. Watkins JC, Yang EJ, Muto MG, Feltmate CM, Berkowitz RS, Horowitz NS, et al. Universal screening for mismatch-repair deficiency in endometrial cancers to identify patients with Lynch syndrome and Lynch-like syndrome. Int J Gynecol Pathol. 2017;36(2):115-127.
11. Stelloo E, Nout RA, Osse EM, Jürgenliemk-Schulz IJ, Jobsen JJ, Lutgens LC, et al. Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer-combined analysis of the PORTEC cohorts. Clin Cancer Res. 2016;22(16):4215-4224.
12. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357(6349):409-13.
13. Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.
14. Salvesen HB, Haldorsen IS. Markers for individualised therapy in endometrial carcinoma. Lancet Oncol. 2018;19(12).
15. Vilar E, Gruber SB. Microsatellite instability in colorectal cancer-the stable evidence. Nat Rev Clin Oncol. 2010;7(3):153-62.
16. Boland CR, Sinicrope FA, Brenner DE, Carethers JM. Colorectal cancer prevention and treatment. Gastroenterol. 2000;118(6):1271-86.
17. Garg K, Shih K, Barakat R, Zhou Q, Iasonos A, 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. Am J Surg Pathol. 2009;33(12):1869-77.
18. Shih KK, Garg K, Levine DA, Kauff ND, Abu-Rustum NR, et al. Clinicopathologic significance of DNA mismatch repair protein defects and endometrial cancer in women 40 years of age and younger. Gynecol Oncol. 2011;123(1):88-94.
19. Gallo A, Catena U, Saccone G, Di Spiezio Sardo A. Conservative surgery in endometrial cancer. J Clin Med. 2021;11(1):183.
20. Buchanan DD, Tan YY, Walsh MD, Clendenning M, Metcalf AM, Ferguson K, et al. Tumor mismatch repair immunohistochemistry and DNA MLH1 methylation testing of patients with endometrial cancer diagnosed at age younger than 60 years optimizes triage for population-level germline mismatch repair gene mutation testing. J Clin Oncol. 2014;32(2):90-100.
21. Hampel H. Screening for Lynch syndrome in endometrial cancer. J Clin Oncol. 2006;24(18):4285-92.
22. Backes FJ, Haag J, Cosgrove CM, Suarez A, Cohn DE, Goodfellow PJ. Mismatch repair deficiency identifies patients with high-intermediate–risk (HIR) endometrioid endometrial cancer at the highest risk of recurrence: A prognostic biomarker. Cancer. 2019;125(3):398-405.
23. Nagle CM, O'mara TA, Tan Y, Buchanan DD, Obermair A, Blomfield P, et al. Endometrial cancer risk and survival by tumor MMR status. J Gynecol Oncol. 2018;29(3).
24. Huang SW, Lin H, Huang CC, Ou YC, Fu HC, Tsai CC, Changchien CC, Wu CH. Comprehensive Clinicopathologic Analysis for Mismatch Repair Protein Expression in Unselected Endometrial Carcinoma Patients With an Emphasis on the Role of MLH1 Deficiency. Int J Gynecol Pathol. 2022;41(4):407-16.
25. Hampel H, Stephens JA, Pukkala E, Sankila R, Aaltonen LA, Mecklin JP, et al. Cancer risk in hereditary nonpolyposis colorectal cancer syndrome: later age of onset. Gastroenterol. 2005;129(2):415-21.
26. Stelloo E, Jansen AM, Osse EM, Nout RA, Creutzberg CL, Ruano D, et al. Practical guidance for

mismatch repair-deficiency testing in endometrial cancer. Ann Oncol. 2017;28(1):96-102.
27. Zhao S, Chen L, Zang Y, Liu W, Liu S, Teng F, et al. Endometrial cancer in Lynch syndrome. Int J Cancer. 2022;150(1):7-17.
28. Nelson GS, Pink A, Lee S, Han G, Morris D, Ogilvie T, et al. MMR deficiency is common in high-grade endometrioid carcinomas and is associated with an unfavorable outcome. Gynecol Oncol. 2013;131(2):309-14.

Cite this article as: Khatoon F, Begum SA, Dey BP, Islam J, Akter N, Nihar F, et al. Identifying the frequency of mismatch repair deficiency in endometrial carcinoma in a tertiary care hospital. Int J Reprod Contracept Obstet Gynecol 2024;13:2241-8.