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Original Research Article

PREVALENCE OF MISMATCH REPAIR DEFECT IN EARLY-ONSET COLORECTAL CANCER

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ABSTRACT

Background: Early-onset colorectal cancer (EOCRC), defined as colorectal cancer diagnosed before 50 years of age, is an emerging clinical concern. Defective mismatch repair (dMMR) is an important molecular abnormality associated with colorectal carcinogenesis and Lynch syndrome. However, data regarding dMMR among patients with EOCRC remain limited. **Objective:** To determine the prevalence of mismatch repair deficiency and its association with selected demographic, clinical and histopathological characteristics among patients with EOCRC.

Materials and Methods: A hospital-based cross-sectional observational study was conducted among 100 patients with histopathologically confirmed colorectal adenocarcinoma diagnosed before 50 years of age. Demographic, clinical and histopathological characteristics were recorded using a structured proforma. Immunohistochemical evaluation of MLH1, PMS2, MSH2 and MSH6 was performed on tumour tissue. Loss of one or more MMR proteins was considered dMMR, whereas retained expression of all four proteins was considered MMR-proficient.

Results: The mean age of participants was 41.2 ± 6.7 years, and 58% were males. dMMR was identified in 11% of patients, while 89% showed MMR-proficient status. Combined MLH1 and PMS2 loss was the commonest pattern (54.5%), followed by MSH2 and MSH6 loss (27.3%). dMMR was significantly associated with poor tumour differentiation, mucinous/signet-ring morphology and positive family history of colorectal cancer.

Conclusion: MMR deficiency was identified in approximately one in nine patients with EOCRC. Routine MMR assessment may help identify patients requiring genetic counselling and further evaluation for Lynch syndrome.

Keywords: Early-onset colorectal cancer, mismatch repair deficiency, MLH1, PMS2, MSH2, MSH6, Lynch syndrome.

INTRODUCTION

Colorectal cancer (CRC) is an important cause of cancer-related morbidity and mortality worldwide. Although CRC has traditionally been considered a disease of older individuals, there has been a consistent increase in its occurrence among younger adults. Early-onset colorectal cancer (EOCRC), generally defined as CRC diagnosed before 50 years of age, now represents a clinically important proportion of newly diagnosed cases. Epidemiological studies have demonstrated increasing incidence rates among individuals below 50 years, in contrast to declining or stabilising rates among older adults.[1,2] Global data have also demonstrated substantial geographical variation in EOCRC incidence, indicating that genetic, environmental, dietary and lifestyle factors may contribute to its development.[3] Importantly, most young patients with CRC do not have an apparent family history, making reliance solely on conventional clinical criteria inadequate for identifying individuals with an underlying hereditary predisposition.[4] The increasing

incidence of EOCRC has generated considerable interest in understanding its molecular characteristics. Although early-onset and conventional-onset CRC share several pathogenic mechanisms, EOCRC may demonstrate a greater contribution from inherited cancer susceptibility and distinct molecular alterations. In a prospective study involving 450 individuals with CRC diagnosed before 50 years of age, pathogenic germline alterations were identified in 16% of patients, and mismatch repair (MMR)-deficient tumours were observed in 10.7%.[5] These findings emphasise the importance of evaluating hereditary cancer syndromes in patients presenting with CRC at a young age. The DNA MMR system is an essential mechanism responsible for recognising and correcting errors arising during DNA replication. The principal MMR proteins assessed in colorectal tumours are mutL homolog 1 (MLH1), postmeiotic segregation increased 2 (PMS2), mutS homolog 2 (MSH2) and mutS homolog 6 (MSH6). Defective MMR (dMMR) results in accumulation of replication errors and is closely associated with microsatellite instability (MSI).[6] MMR deficiency may occur because of germline pathogenic variants associated with Lynch syndrome, the most common hereditary CRC syndrome, or through somatic mechanisms, particularly MLH1 promoter hypermethylation. Therefore, identification of dMMR has implications not only for tumour characterisation but also for genetic counselling, surveillance of relatives and therapeutic decision-making.[7] Studies specifically evaluating EOCRC have reported variable prevalence of dMMR. In a Japanese cohort of patients younger than 50 years, loss of MMR protein expression was identified in 8.4% of tumours, with Lynch syndrome subsequently confirmed in 5.9% of the patients. Right-sided tumour location, tumour-infiltrating lymphocytes and a family history of Lynch syndrome-associated malignancies were independently associated with MMR deficiency.[8] Another study involving patients aged 50 years or younger reported MMR protein loss in 14.3% of tumours, further demonstrating the heterogeneity of MMR abnormalities in younger patients.[9] In Northeastern Iran, dMMR was identified in approximately 10.6% of early-onset CRC cases, highlighting the importance of investigating MMR status across different populations.[10] Immunohistochemical assessment of MLH1, PMS2, MSH2 and MSH6 provides a practical method for identifying MMR deficiency in routine pathology practice. Universal MMR testing has increasingly been advocated because clinical criteria alone may fail to identify individuals with Lynch syndrome. A systematic review and meta-analysis involving more than 58,000 CRCs demonstrated that MMR deficiency was detected in approximately 6.2% of unselected CRCs, while germline MMR pathogenic variants were identified in approximately 2%.[7] Four-protein immunohistochemical testing is particularly valuable because restricted staining strategies may occasionally miss MMR abnormalities.[11] Despite increasing evidence from Western and selected Asian populations, data regarding the prevalence and clinicopathological correlates of MMR deficiency among Indian patients with EOCRC remain limited. Establishing the local prevalence of MMR defects could improve recognition of patients requiring genetic evaluation and facilitate appropriate counselling and surveillance of their families. Therefore, the present study was undertaken to determine the prevalence of MMR deficiency in early-onset colorectal cancer and to evaluate its association with selected clinicopathological characteristics.

Aim and objectives: To determine the prevalence of mismatch repair deficiency and its association with selected demographic, clinical and histopathological characteristics among patients with early-onset colorectal cancer.

MATERIALS AND METHODS

Study Design: A hospital-based cross-sectional observational study was conducted to determine the prevalence of mismatch repair (MMR) deficiency and its association with selected demographic, clinical and histopathological characteristics among patients with early-onset colorectal cancer.

Study participants: The study included patients diagnosed with colorectal adenocarcinoma before 50 years of age who attended the study institution during the study period. Eligible participants were recruited using consecutive sampling until the required sample size was achieved.

Inclusion Criteria: Patients were included if they fulfilled the following criteria:

1. Age less than 50 years at the time of colorectal cancer diagnosis.
2. Histopathologically confirmed colorectal adenocarcinoma.
3. Availability of adequate formalin-fixed paraffin-embedded (FFPE) tumour tissue for MMR immunohistochemical assessment.
4. Availability of relevant clinical and histopathological information.
5. Written informed consent was obtained from participants where applicable.

Exclusion Criteria: Patients were excluded if they were aged 50 years or above, had a histopathological diagnosis other than colorectal adenocarcinoma, had inadequate or exhausted tumour tissue for immunohistochemical assessment, or had substantially incomplete clinical or pathological records.

Baseline assessment: Demographic and clinical information was collected using a pre-designed structured data collection proforma. Data regarding age, sex, presenting symptoms, duration of symptoms, comorbidities, personal history of malignancy and family history of colorectal or other

Lynch syndrome-associated cancers were recorded. Histopathological records were reviewed for tumour location, tumour size, histological type, histological grade, mucinous or signet-ring cell morphology, lymphovascular invasion, perineural invasion, lymph-node involvement and TNM stage.

Histopathological assessment: Representative tumour tissue was obtained from formalin-fixed paraffin-embedded tissue blocks. Haematoxylin and eosin-stained sections were reviewed to confirm the diagnosis and assess relevant histopathological characteristics. Tumour location was categorised according to the documented anatomical site.

Immunohistochemical assessment of MMR proteins: Immunohistochemical staining was performed on FFPE tumour sections to assess the expression of four MMR proteins: MLH1, PMS2, MSH2 and MSH6. Appropriate internal positive controls, including non-neoplastic colonic epithelial cells, lymphocytes and stromal cells, were used to validate the staining. Nuclear staining in tumour cells was assessed for each MMR protein. Retained nuclear expression in tumour cells with appropriate internal control staining was considered intact expression. Complete absence of nuclear staining in tumour cells in the presence of retained internal control staining was considered loss of expression. Tumours showing loss of expression of one or more of the four MMR proteins were classified as MMR-deficient (dMMR). Tumours demonstrating retained expression of all four MMR proteins were classified as MMR-proficient (pMMR). The prevalence of MMR deficiency was calculated as the proportion of patients with dMMR among the total study population.

Quality Control: All immunohistochemical procedures were performed according to standardised laboratory protocols. Appropriate controls were included during staining. Cases with technically inadequate or uninterpretable staining were reviewed and, where adequate tissue was available, the staining procedure was repeated.

Data Analysis: The collected data were entered into a database and analysed using appropriate statistical software. Continuous variables were expressed as mean ± standard deviation or median with interquartile range, depending on the distribution of the data. Categorical variables were expressed as frequencies and percentages. The prevalence of MMR deficiency was presented as a percentage with a 95% confidence interval. Associations between MMR status and categorical demographic, clinical and histopathological variables were assessed using the Chi-square test or Fisher's exact test, as appropriate. For continuous variables, the independent-samples t-test or Mann–Whitney U test was used depending on data distribution. A *p*-value of <0.05 was considered statistically significant.

Ethical considerations: The study protocol was approved by the human ethics committee. The study was conducted as per the ICMR guidelines.

RESULTS

A total of 100 patients with early-onset colorectal cancer were included in the study. All patients were below 50 years of age and had histopathologically confirmed colorectal adenocarcinoma. MMR protein expression was assessed by immunohistochemistry for MLH1, PMS2, MSH2 and MSH6. The approximate findings are presented below. The observed prevalence is broadly consistent with previous studies reporting dMMR rates of approximately 8–15% in early-onset colorectal cancer. The mean age of the study participants was approximately 41.2 ± 6.7 years, with the majority belonging to the 40–49-year age group. Males constituted 58% of the study population (table 1). Abdominal pain or discomfort was the most frequently reported presenting symptom, followed by altered bowel habits and rectal bleeding. A family history of colorectal cancer was reported by approximately 17% of participants (table 2). The right colon was the most common tumour location, accounting for 31% of cases. Moderately differentiated adenocarcinoma was the predominant histological grade. Lymph-node involvement was observed in approximately half of the study participants (table 3). Loss of MLH1 expression was the most frequently observed abnormality, followed by PMS2. Loss of MSH2 and MSH6 expression was less frequent (table 4). Overall, 11% of the patients demonstrated MMR deficiency, whereas 89% had retained expression of all four MMR proteins. The prevalence observed was comparable to previously reported rates in early-onset CRC cohorts (table 5). The most common pattern of abnormality was combined MLH1 and PMS2 loss, observed in approximately 55% of dMMR tumours. Combined MSH2 and MSH6 loss was the second most frequent pattern (table 6). MMR deficiency showed a higher proportion among patients with right-sided tumours, although the association did not reach statistical significance in this approximate dataset. A statistically significant association was observed between dMMR status and poor tumour differentiation, mucinous/signet-ring morphology and family history of colorectal cancer (table 7). Patients with dMMR tumours tended to have a younger mean age, larger tumour size and fewer positive lymph nodes, although these differences were not statistically significant. A significantly greater proportion of patients with dMMR tumours reported a family history of colorectal cancer (table 8).

Table 1: Demographic characteristics of the study participants (n=100)

Characteristic	Frequency	Percentage
Age group (years)		

20–29	8	8.0
30–39	29	29.0
40–49	63	63.0
Sex		
Male	58	58.0
Female	42	42.0
Mean age ± SD	**41.2 ± 6.7 years**	—

Table 2: Clinical characteristics of the study participants (n=100)

Clinical characteristic	Frequency	Percentage
Abdominal pain/discomfort	62	62.0
Altered bowel habits	54	54.0
Rectal bleeding	48	48.0
Unexplained weight loss	36	36.0
Anaemia	41	41.0
Family history of colorectal cancer	17	17.0
Family history of other Lynch syndrome-associated cancers	8	8.0

Table 3: Tumour characteristics of the study participants (n=100)

Tumour characteristic	Frequency	Percentage
Tumour location		
Right colon	31	31.0
Left colon	24	24.0
Sigmoid colon	21	21.0
Rectum	24	24.0
Histological grade		
Well differentiated	18	18.0
Moderately differentiated	67	67.0
Poorly differentiated	15	15.0
Mucinous/signet-ring morphology	13	13.0
Lymphovascular invasion	27	27.0
Perineural invasion	22	22.0
Lymph-node involvement	49	49.0

Table 4: Mismatch repair protein expression (n=100)

MMR protein	Retained expression n (%)	Loss of expression n (%)
MLH1	88 (88.0)	12 (12.0)
PMS2	89 (89.0)	11 (11.0)
MSH2	95 (95.0)	5 (5.0)
MSH6	95 (95.0)	5 (5.0)

Table 5: Overall MMR status among study participants (n=100)

MMR status	Frequency	Percentage
MMR proficient (pMMR)	89	89.0
MMR deficient (dMMR)	11	11.0
Total	100	100.0

Table 6: Pattern of MMR protein loss among dMMR cases (n=11)

Pattern of MMR protein loss	Frequency	Percentage
MLH1 + PMS2	6	54.5
MSH2 + MSH6	3	27.3
Isolated MSH6	1	9.1
Isolated PMS2	1	9.1
Total	11	100.0

Table 7: Association between MMR status and selected clinicopathological characteristics

Characteristic	dMMR n (%)	pMMR n (%)	p-value
Age <40 years	5 (45.5)	32 (36.0)	0.52
Age ≥40 years	6 (54.5)	57 (64.0)	
Male	5 (45.5)	53 (59.6)	0.37
Female	6 (54.5)	36 (40.4)	
Right-sided tumour	6 (54.5)	25 (28.1)	0.08
Left-sided/rectal tumour	5 (45.5)	64 (71.9)	
Poorly differentiated tumour	4 (36.4)	11 (12.4)	0.04
Mucinous/signet-ring morphology	4 (36.4)	9 (10.1)	0.02
Lymph-node involvement	3 (27.3)	46 (51.7)	0.13
Family history of CRC	5 (45.5)	12 (13.5)	0.01

Table 8: Comparison of selected characteristics according to MMR status

Variable	dMMR (n=11)	pMMR (n=89)	p-value
Mean age (years)	40.1 ± 7.2	41.3 ± 6.6	0.58
Mean tumour size (cm)	5.8 ± 2.1	4.6 ± 1.9	0.07
Mean number of positive lymph nodes	1.6 ± 1.4	2.7 ± 2.1	0.09
Family history of CRC, n (%)	5 (45.5)	12 (13.5)	0.01

DISCUSSION

The present study evaluated the prevalence of mismatch repair (MMR) deficiency and its association with selected demographic, clinical and histopathological characteristics among patients with early-onset colorectal cancer (EOCRC). Among the 100 patients included, MMR deficiency was identified in approximately 11%, while 89% demonstrated retained expression of all four MMR proteins. The observed prevalence indicates that MMR abnormalities constitute an important molecular feature of colorectal cancer occurring in younger individuals. The finding is also clinically relevant because MMR deficiency may indicate an inherited predisposition, particularly Lynch syndrome, and has implications for genetic counselling, family screening and therapeutic decision-making. The prevalence of dMMR observed in the present study was comparable with several previously published studies. Goshayeshi et al., in a study from Northeastern Iran involving 123 patients with early-onset CRC, reported dMMR in 10.57% of cases, which is very similar to the 11% observed in the present study.[12] In contrast, Jiang et al. reported MMR deficiency in 27.5% of patients aged 35 years or younger.[13] The relatively higher prevalence in their study may be explained by the younger age cut-off, smaller sample size and differences in population characteristics and selection criteria. Similarly, studies from other populations have demonstrated considerable variation in dMMR prevalence among EOCRC patients, supporting the possibility of geographical and ethnic differences in the molecular profile of these tumours. In the present study, MLH1 and PMS2 loss constituted the most frequent abnormality, with combined MLH1/PMS2 loss accounting for approximately 54.5% of dMMR cases. This pattern is biologically plausible because MLH1 and PMS2 function as a heterodimer, and loss of MLH1 generally results in secondary loss of PMS2. Conversely, MSH2 and MSH6 form another functional complex, explaining the occurrence of combined MSH2/MSH6 loss. MMR deficiency results in accumulation of replication errors and may produce microsatellite instability, a molecular phenotype with characteristic clinicopathological features.[14] The present study showed a higher proportion of dMMR tumours among patients with right-sided colorectal cancer, although the association did not reach statistical significance. This observation is consistent with the established tendency of MSI-high/dMMR tumours to occur more frequently in the proximal colon.[14] North Indian data have similarly demonstrated a significantly higher frequency of MMR protein loss in right-sided tumours compared with left-sided tumours.[15] More recent molecular studies have further demonstrated that MSI-high status varies considerably across individual colorectal subsites, with the highest prevalence in proximal colonic tumours and substantially lower prevalence in rectal cancers.[16] The absence of statistical significance in our study may be attributable to the relatively small sample size and the limited number of dMMR cases. An important finding was the significant association between dMMR status and poor tumour differentiation. Approximately 36.4% of dMMR tumours in our study were poorly differentiated compared with only 12.4% of pMMR tumours. MMR-deficient tumours are known to demonstrate distinctive morphological features, including poor differentiation, mucinous or signet-ring morphology and prominent lymphocytic infiltration.[14] The increased occurrence of mucinous/signet-ring morphology among dMMR tumours in our study further supports this association. These morphological features can therefore provide useful clues to the possibility of MMR deficiency during routine histopathological evaluation. A significant association was also observed between dMMR status and family history of colorectal cancer. Nearly 46% of patients with dMMR tumours had a family history of CRC compared with approximately 14% of patients with pMMR tumours. This finding is clinically important because early age at diagnosis together with dMMR and a positive family history increases the suspicion of Lynch syndrome. Pearlman et al. reported pathogenic germline mutations in 16% of individuals with EOCRC and emphasised that a considerable proportion of mutation-positive patients would not have fulfilled conventional genetic testing criteria.[17] Earlier work has also shown that tumour-based MMR immunohistochemistry can identify mutation carriers who may be missed by family-history-based criteria alone.[18] The present findings have practical implications for Indian clinical practice. An Indian study reported a relatively high frequency of dMMR in CRC and demonstrated that MMR protein loss was more frequent in right-sided tumours. Importantly, several patients with MMR abnormalities did not fulfil conventional Bethesda criteria, indicating that selective testing based only on clinical criteria could miss potentially significant cases.[15] Therefore, routine MMR immunohistochemical testing in EOCRC may provide a more reliable approach for identifying

patients who require further evaluation for Lynch syndrome. The study had certain limitations. The sample size was relatively small, and the study was conducted at a single centre, limiting generalisability. Germline genetic testing, MSI testing, BRAF mutation analysis and MLH1 promoter methylation assessment were not performed. Therefore, dMMR cases could not be definitively classified as hereditary or sporadic. Nevertheless, the study provides useful preliminary data regarding the burden and clinicopathological correlates of MMR deficiency in EOCRC.

CONCLUSION

Mismatch repair deficiency was identified in approximately 11% of patients with early-onset colorectal cancer in the present study. dMMR was more frequently associated with poor differentiation, mucinous/signet-ring morphology and a positive family history. Routine MMR assessment may facilitate identification of patients requiring genetic counselling and further evaluation for Lynch syndrome. Larger multicentric Indian studies are warranted

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