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Demographic and Molecular Patterns of MMR Gene Expression in Colorectal Cancer Patients in Bangladesh

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Abstract: ***Introduction:*** Colorectal cancer (CRC) is a significant health concern in Bangladesh, with mismatch repair (MMR) gene mutations playing a crucial role in tumor development. Therefore, this study was conducted to investigate the demographic characteristics, molecular patterns, and clinicopathological associations of MMR gene expression in Bangladeshi CRC patients. ***Methods:*** This cross-sectional study was conducted in the Department of Colorectal Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from June 2023 to July 2025. This study included 63 patients who attended the colorectal surgery department of BSMMU for screening colorectal cancer during the study period. ***Result:*** The study included patients aged 18 to 77 years (mean: 49.7 years), with a male predominance (61.9%). The most common tumor sites were the rectum (30.2%) and sigmoid colon (20.6%). Adenocarcinoma was the predominant histopathological type (90.5%), with most tumors classified as moderately differentiated (71.4%). MMR gene mutations were detected in 34.9% of patients, with MLH-1 + PMS-2 (14.3%) being the most frequent. MSI-high (MSI-H) status was significantly associated with MMR mutations (p=0.025), while MSI-low (MSI-L) was exclusive to MLH-1 + PMS-2 and PMS-2-only mutations. Tumor location was also significantly correlated with MMR mutations (p=0.001). However, no significant associations were found between MMR mutations and patient age, gender, or tumor differentiation. ***Conclusion:*** This study highlights the molecular heterogeneity of CRC in Bangladesh, with MMR gene mutations influencing tumor site and MSI status. A notable correlation between MMR gene mutations and MSI status was observed, underscoring the importance of MMR testing in the diagnosis and management of CRC.

Keywords: Colorectal cancer, Microsatellite instability (MSI), MLH1, PMS2, Molecular profiling, Bangladesh.

Research Paper

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer both in the United States and worldwide. Its incidence and mortality rates vary across different ethnic groups, with the highest rates observed among Alaskan Natives (91 per 100,000 between 2010–2013) and African Americans (49 per 100,000), while the lowest rates are seen in Asian Americans (32 per 100,000) [1 ,2].

The development of CRC is influenced by multiple factors, including genetic predisposition, environmental influences, and acquired genetic mutations during tumor progression [3]. Broadly, CRC can be classified into two categories: sporadic and hereditary cases. Hereditary CRC accounts for approximately 20–25% of cases, although some estimates suggest that genetic susceptibility may contribute to up to 30% of cases [4]. The two most well-defined hereditary forms of CRC are familial adenomatous polyposis (FAP) and Lynch syndrome (LS). FAP is characterized by numerous colorectal polyps, while LS, also known as hereditary nonpolyposis colorectal cancer (HNPCC), results from defects in the

mismatch repair (MMR) genes. However, there was another category that exhibited a gathering of CRC and/or adenomas in families with recognized hereditary syndromes and is known as familial CRC. The genetic basis of familial CRC remains unknown [5, 6].

Chromosomal instability is observed in 85% of both sporadic colorectal cancer (CRC) and familial adenomatous polyposis (FAP) [7]. Another key mutational pathway in CRC is microsatellite instability (MSI), which occurs due to the inactivation, mutation, or epigenetic silencing of mismatch repair (MMR) genes [8-10]. MSI is not exclusive to hereditary non-polyposis colorectal cancer (HNPCC) but also occurs in sporadic CRC [7-10]. The genetic foundation of MSI tumors lies in inherited germline mutations in one of the five human MMR genes: MLH1, MSH2, MSH6, PMS2, and PMS1 [8-11]. Mutations in MSH2 and MLH1 are the primary cause of most HNPCC families, while mutations in MSH6 are less common, and those in PMS2 and PMS1 are rare [8]. MSI is also present in 10-15% of sporadic CRC cases. In these instances, high MSI is typically caused by the acquired hypermethylation of the MLH1 promoter, which leads to its transcriptional silencing [7-12].

There were distinct clinicopathological characteristics of CRC with MSI. These include poor differentiation, excess mucin and signet ring component, proximal colon, medullary feature, Crohn-like reaction, and lymphocytic infiltration [7]. It is noted that the survival rate of CRC with high MSI is better when it is compared with MSS tumors evidenced by tumoral lymphocytosis of MSI tumors [7-13]. However, it is sometimes associated with metachronous cancer and resistant to traditional chemotherapeutic agents [14, 15]. Recognition of MSI phenotype can be done by histopathology and IHC. This fact allows the pathologist to dispense on PCR which remains the gold standard for recognition of MSI phenotype as it is not practicable and expensive in routine pathology lab [7-16]. Investigation for the presence of MSI in CRC is important due to many factors. It decides the extent of surgical treatment, the prophylactic surgery of hysterectomy and oophorectomy, screening of the family member for the presence of the same mutation and in some cases the choice of chemotherapy [7-17].

However, in this study, we aimed to investigate the demographic characteristics, molecular patterns, and clinicopathological associations of MMR gene expression in Bangladeshi CRC patients.

METHODOLOGY & MATERIALS

This cross-sectional study was conducted in the Department of Colorectal Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from *June 2023 to July 2025*. This study included 63 patients who attended the colorectal surgery department of BSMMU for screening colorectal cancer during the study period.

These are the following criteria to be eligible for enrollment as our study participants: a) Patients aged between 19 to 70 years; b) Patients diagnosed with Histologically adenocarcinoma of Colon & Rectum; c) Patients who were willing to participate were included in the study And a) Patients with stage IV carcinoma rectum, b) Patients with carcinoma rectum but did not have any proctectomy; c) Patients with obstructed or perforated cases of carcinoma rectum ; d) Patients with recurrent carcinoma rectum were excluded from our study.

Data Collection:

Patients who were attained in the Department of Colorectal Surgery BSMMU for screening colorectal cancer during the study period were approached for participation in the study. All patients received an explanation of the nature of the study and written informed consent was obtained from all the participants for the collection and analysis of their data for scientific purposes. The procedure of the MMR test and its importance was explained. MMR is now a well-established test for colorectal cancer patients to obtain a better management plan and the need for family screening. After the operation, MMR was tested from the pathological specimen. According to MMR results, the patient was counseled again about the prognosis of the patient, and in some cases, there was a change of treatment plan.

Statistical Analysis:

All data were recorded systematically in preformed data collection form. Quantitative data was expressed as mean and standard deviation; qualitative data was expressed as frequency distribution and percentage. The data were analyzed using the chi-square (X^2) test and ANOVA test. A p-value <0.05 was considered as significant. Statistical analysis was performed by using SPSS 25 (Statistical Package for Social Sciences) for Windows version 10. This study was approved by the ethical review committee of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

RESULTS

Table 1: Distribution of the study patients by age and gender (n=63)

Age (years)	N	P(%)
≤20	3	4.8
21-30	2	3.2
31-40	10	15.9
41-50	14	22.2
51-60	25	39.7
61.70	7	11.1
>70	2	3.2
Mean ±SD	49.7	±12.6
Range (min-max)	18.0	-77.0
Gender		
Male	39	61.9
Female	24	38.1

Table 1 shows that the patients range from 18 to 77 years old, with a mean age of 49.7 years and a standard deviation of 12.6. The largest age group falls between 51-60 years, making up 39.7% of the patients, followed by patients aged 41-50 (22.2%). Patients aged 31-40 years old account for 15.9%, while smaller proportions were seen in younger (≤20 years: 4.8%, 21-30 years: 3.2%) and older (>70 years: 3.2%) age groups. Regarding gender distribution, there were more male patients (61.9%) than female patients (38.1%). The male and female ratio was 1.63:1 in this study.

Table 2: Distribution of the study patients according to site of lesion (n=63)

Site of lesion	N	P(%)
Rectum	19	30.2
Sigmoid colon	13	20.6
Ascending colon	12	19.0
Caecum	7	11.1
Descending colon	3	4.8
Hepatic flexure	1	1.6
Splenic flexure	1	1.6
Transverse colon	1	1.6
Ascending colon+ Descending colon	1	1.6
Ascending colon+ Hepatic flexure	1	1.6
Caecum+ Descending colon	1	1.6
Caecum+ Rectum	1	1.6
Caecum+ Sigmoid colon	1	1.6
Sigmoid colon+ Rectum	1	1.6

Table 2 shows the most common site of lesions was the rectum, affecting 30.2% of patients, followed by the sigmoid colon (20.6%) and the ascending colon (19.0%). The caecum was involved in 11.1% of cases, while the descending colon accounts for 4.8%. Less frequently, lesions were found in the hepatic flexure, splenic flexure, and transverse colon, each representing 1.6% of cases. Some patients had lesions affecting multiple sites. These combinations include the ascending colon and descending colon, ascending colon and hepatic flexure, caecum and descending colon, caecum and rectum, caecum and sigmoid colon, and sigmoid colon and rectum each occurring in 1.6% of patients.

Table 3: Distribution of the study patients according to histopathological type and grading (n=63)

Histopathological type	N	P(%)
Adenocarcinoma	57	90.5
Mucinous adenocarcinoma	3	4.8
HGD	2	3.2
LGD	1	1.6
Histopathological grading		
G-I	6	9.5
G-II	45	71.4

Histopathological type	N	P(%)
G-III	10	15.9
Anaplastic	2	3.2

This table shows that the most common histopathological type was adenocarcinomas (90.5%). Mucinous adenocarcinoma accounts for 4.8% of cases, while high-grade dysplasia (HGD) and low-grade dysplasia (LGD) were less common, representing 3.2% and 1.6% of cases, respectively. Most patients (71.4%) had Grade II (moderately differentiated) tumors. Grade I (well-differentiated) tumors were seen in 9.5% of cases, while Grade III (poorly differentiated) tumors account for 15.9%. Anaplastic tumors were found in 3.2% of patients.

Table 4: Distribution of the study patients according to MMR gene mutation and MSI status (n=63)

MMR gene mutation	N	P(%)
MLH-1	3	4.8
MLH-1+ MSH-2	1	1.6
MLH-1+ MSH-2+ PMS-2	2	3.2
MLH-1+ MSH-6	1	1.6
MLH-1+ PMS-2	9	14.3
MSH-2+ MSH-6	2	3.2
MSH-2+ MSH-6+ PMS-2	1	1.6
PMS-2	3	4.8
No mutation	41	65.1
MSI status		
Low	4	6.3
High	18	28.6
MSS	41	65.1

Table 4 found that the majority of patients (65.1%) had no detected mutations. Among those with mutations, the most common alteration was MLH-1 + PMS-2, found in 14.3% of cases. Isolated mutations in MLH-1 or PMS-2 occur in 4.8% of patients each. Other combinations, such as MLH-1 + MSH-2 + PMS-2 (3.2%) and MSH-2 + MSH-6 (3.2%), were less frequent. Several rarer mutation patterns, each observed in 1.6% of cases, involve different combinations of MLH-1, MSH-2, MSH-6, and PMS-2. For MSI status, 65.1% of patients were MSS (microsatellite stable), 28.6% had high MSI (MSI-H), and a small proportion (6.3%) had low MSI (MSI-L).

Table 5: Association between MMR gene mutation with age and gender (n=63)

Age (years)	MMR gene mutation									p-value
	MLH-1 (n=3)	MLH-1+ MSH-2 (n=1)	MLH-1+ MSH-2+ PMS-2 (n=2)	MLH-1+ MSH-6 (n=1)	MLH-1+ PMS-2 (n=9)	MSH-2+ MSH-6 (n=2)	MSH-2+ MSH-6+ PMS-2 (n=1)	PMS-2 (n=3)	No mutation (n=41)	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
≤20	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.9)	
21-30	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.9)	
31-40	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	9 (22.0)	
41-50	1 (33.3)	1 (100.0)	0 (0.0)	0 (0.0)	4 (44.4)	0 (0.0)	0 (0.0)	1 (33.3)	7 (17.1)	
51-60	2 (66.7)	0 (0.0)	2 (100.0)	0 (0.0)	4 (44.4)	1 (50.0)	1 (100.0)	1 (33.3)	14 (34.1)	
61.70	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (50.0)	0 (0.0)	0 (0.0)	5 (12.2)	
>70	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.9)	
Mean ±SD	54.0±7.9	42.0±0.0	53.0±2.8	18.0±0.0	54.1±6.7	61.5±4.9	51.0±0.0	46.3±9.7	48.8±13.7	0.233
Range (min-max)	45.0-60.0	42.0-42.0	51.0-55.0	18.0-18.0	45.0-65.0	58.0-65.0	51.0-51.0	38.0-57.0	19.0-77.0	
Gender										
Male	3 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)	6 (66.7)	1 (50.0)	0 (0.0)	1 (33.3)	26 (63.4)	0.323
Female	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	3 (33.3)	1 (50.0)	1 (100.0)	2 (66.7)	15 (36.6)	

Table 5 shows that the youngest patient (18 years old) had an MLH-1 + MSH-6 mutation, while the oldest patients (77 years) had no mutations. The majority of MLH-1 + PMS-2 and MLH-1 mutations were found in the 51-60 age group. There were no statistically significant differences in age between mutation groups (p-value=0.233). The majority of patients were male (63.4%) and had no mutations, while females accounted for 36.6% of the non-mutated cases. MLH-1 and MLH-1 + MSH-6 mutations were only found in males, while MLH-1 + MSH-2 + PMS-2 and MSH-2 + MSH-6 + PMS-2 mutations were only seen in females. There was also no significant association between gender and MMR gene mutations (p-value=0.323).

Table 6: Association between MMR gene mutation with site of lesion (n=63)

Site of lesion	MMR gene mutation									p-value
	MLH-1 (n=3)	MLH-1+ MSH-2 (n=1)	MLH-1+ MSH-2+ PMS-2 (n=2)	MLH-1+ MSH-6 (n=1)	MLH-1+ PMS-2 (n=9)	MSH-2+ MSH-6 (n=2)	MSH-2+ MSH-6+ PMS-2 (n=1)	PMS-2 (n=3)	No mutation (n=41)	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Rectum	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	17 (41.5)	
Ascending colon	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)	1 (50.0)	0 (0.0)	2 (66.7)	3 (7.3)	
Sigmoid colon	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	13 (31.7)	
Caecum	1 (33.3)	0 (0.0)	1 (50.0)	0 (0.0)	2 (22.2)	1 (50.0)	0 (0.0)	0 (0.0)	2 (4.9)	
Descending colon	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (2.4)	
Hepatic flexure	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.001
Splenic flexure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	
Transverse colon	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Ascending colon+ Descending colon	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Ascending colon+ Hepatic flexure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	
Caecum+ Descending colon	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Caecum+ Rectum	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	
Caecum+ Sigmoid colon	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	
Sigmoid colon+ Rectum	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	

Table 6 shows that rectal lesions were most common in patients without MMR mutations (41.5%). However, some cases were seen in patients with MLH-1 (33.3%) and PMS-2 (33.3%) mutations. Mixed-site lesions were found only in a few cases, with some patients having Caecum + Descending colon (50% MLH-1 + MSH-2 + PMS-2) or Ascending colon + Descending colon (11.1% MLH-1 + PMS-2) involvement. There is a significant (p = 0.001) correlation between lesion location and MMR gene mutation status.

Table 7: Association between MMR gene mutation with Histopathological type and grading (n=63)

Histopathological type	MMR gene mutation									p-value
	MLH-1 (n=3)	MLH-1+ MSH-2 (n=1)	MLH-1+ MSH-2+ PMS-2 (n=2)	MLH-1+ MSH-6 (n=1)	MLH-1+ PMS-2 (n=9)	MSH-2+ MSH-6 (n=2)	MSH-2+ MSH-6+ PMS-2 (n=1)	PMS-2 (n=3)	No mutation (n=41)	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Adenocarcinoma	3 (100.0)	1 (100.0)	2 (100.0)	1 (100.0)	8 (88.9)	2 (100.0)	1 (100.0)	3 (100.0)	36 (87.8)	
Mucinous adenocarcinoma HGD	0 (0.0) 0 (0.0)	0 (0.0) 0 (0.0)	0 (0.0) 0 (0.0)	0 (0.0) 0 (0.0)	1 (11.1) 0 (0.0)	0 (0.0) 0 (0.0)	0 (0.0) 0 (0.0)	0 (0.0) 0 (0.0)	2 (4.9) 2 (4.9)	1.000
LGD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	
Histopathological grading										
G-I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (14.6)	
G-II	2 (66.7)	1 (100.0)	1 (50.0)	0 (0.0)	7 (77.8)	2 (100.0)	1 (100.0)	3 (100.0)	28 (68.3)	0.425
G-III	0 (0.0)	0 (0.0)	1 (50.0)	1 (100.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	7 (17.1)	
Anaplastic	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

Table 7 shows that adenocarcinoma was the most common histopathological type across all groups, affecting 87.8% of mutation-free patients and 100% of most mutation-positive patients except for one case in the MLH-1 + PMS-2 (88.9%) group. Mucinous adenocarcinoma and high-grade dysplasia (HGD) were found only in mutation-free patients (4.9%) and one case in the MLH-1 + PMS-2 (11.1%) group. There was no significant (p = 1.000) association between histopathological type and MMR gene mutation status. Moderately differentiated tumors (G-II) were the most frequent, appearing in 68.3% of mutation-free cases and 100% of some mutation groups (MLH-1 + MSH-2, MSH-2 + MSH-6, MSH-2 + MSH-6 + PMS-2, PMS-2). Histopathological grading was not significantly associated with MMR gene mutation status (p-value=0.425).

Table 8: Association between MMR gene mutation with MSI status (n=22)

MSI status	MMR gene mutation								p-value
	MLH-1 (n=3)	MLH-1+ MSH-2 (n=1)	MLH-1+ MSH-2+ PMS-2 (n=2)	MLH-1+ MSH-6 (n=1)	MLH-1+ PMS-2 (n=9)	MSH-2+ MSH-6 (n=2)	MSH-2+ MSH-6+ PMS-2 (n=1)	PMS-2 (n=3)	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	3(100.0)	0.025
High	3 (100.0)	1 (100.0)	2 (100.0)	1 (100.0)	8 (88.9)	2 (100.0)	1 (100.0)	0 (0.0)	

Table 8 shows that MSI-H was present in 100% of patients with MLH-1, MLH-1 + MSH-2, MLH-1 + MSH-2 + PMS-2, MLH-1 + MSH-6, MSH-2 + MSH-6, and MSH-2 + MSH-6 + PMS-2 mutations. MSI-L was found only in the MLH-1 + PMS-2 group (11.1%) and PMS-2-only group (100%). There was a statistically significant (p-value=0.025) association between MSI status and MMR mutations.

DISCUSSION

In the present study, the majority of the patients (n=25, 39.7%) belonged to the 51–60 age range. The mean age was 49.7 ± 12.6 years. Both MLH1 and PMS2 mutations were present in nine individuals. No significant relation between age and mutation IDs was found in our study. Findings from multiple studies suggest that dMMR status is associated with early-onset disease among patients with CRC, as dMMR CRCs are more frequent in younger patients than in older patients. A retrospective analysis of 133 patients with CRC showed that mutations in MLH1, MSH2, MSH6, and PMS2 were significantly associated with age [18]. A subsequent retrospective study of 61 patients with stage I–III CRC confirmed a significant association between dMMR status and patient age [19]. A recent real-world study revealed that among patients with dMMR CRC, dMMR tumors were observed in both older (≥60 years) and younger (<50 years) patients. The frequency of

MSH6/ MSH2, MSH6, and PMS2 loss was higher in younger patients than in older patients [20]. Among patients with Lynch syndrome, the median age at CRC diagnosis was ten years higher for carriers of MSH6 mutations than for those carrying MLH1 and MSH2 mutations [21].

Males made up 61.9% (n=39) of our study population. Thirteen of the 22 dMMR patients were men and nine female patients had dMMR. No relation was found between MMR status and sex. However, similar associations have been reported for dMMR status and sex in most studies. A large-scale study of 535 patients with CRC showed that tumors from women had a higher frequency of MLH1/PMS2 loss than tumors from men [22]. Consistently, Viñal *et al*., reported that the percentage of women was significantly higher among patients with dMMR CRC than among those with pMMR CRC (55% [n = 55/100] vs. 38% [n = 351/914]; P = 0.001) [23].

In the present study, rectal cancer was the most diagnosed case (n=19.30.2%), followed by sigmoid (n=13, 20.6%) and ascending colon (n=12, 19%) cancer. This study found that 15 patients (68.2%) with right-sided cancer had the mutation, and 10.5% (n=2) of rectal cancer (n=19) patients had the mutation. One had a mutation in MLH1 and the other had a mutation in PMS2. The present study reported that adenocarcinoma was seen in 90.5% (n=57) of the patients and Grade II is the commonest representation (n=45, 71.4%). Among the 22 mutation patients 21 are of grade II. No grade I patients had mutations. This study also found that 18 patients were MSI-H among the 22 dMMR patients. The other 4 were MSI-L but dMMR. Of the MSI- H patients most MMR deficit combination was MLH1 and PMS2 dimeric mutation which was found in eight patients. In this study, no correlations were found except that right-sided tumors were more mutated. Ye *et al*., have reported that dMMR tumors were significantly more common in the right colon (20.5%), compared to tumors in the left colon (9.2%) and rectum (5.1%, P<0.001) [22].

MSI-H/dMMR status has been linked to various tumor characteristics in colorectal cancer (CRC), such as the location of the primary tumor, tumor diameter, T stage, and the presence of distant metastasis. Several retrospective studies have demonstrated a significant association between dMMR/MSI-H status and factors like early disease onset, larger tumor size, increased tumor volume, primary tumor site, and more advanced T stage in patients with stage I–III or I–IV CRC [19-25]. In a retrospective case series, Li *et al*., found that mutations in MLH1, MSH2, and MSH6 were significantly associated with the primary tumor's location in patients with dMMR CRC. Specifically, loss of hMLH1 or PMS2 was more common on the right side, while loss of hMSH2 or hMSH6 was more frequently seen on the left side [18]. A retrospective study of 245 patients with CRC showed that the incidence of MSI-H was higher in patients with right colon cancer and TNM stage I– II disease [26]. Another retrospective analysis of 268 patients with CRC showed a high incidence of dMMR in patients with locally advanced (T4b) tumors without distant metastasis [27]. Additionally, a recent analysis of 1,014 patients with CRC (100 [9.8%] with dMMR and 914 [90.2%] with pMMR tumors) indicated that advanced-stage tumors were significantly more common among patients with pMMR CRC than among those with dMMR CRC (stage IV: 21% vs. 3%; P < 0.001) [23]. Similarly, Kang *et al.*, found a significant association between MSI-H and earlier-stage tumors in CRC patients, suggesting that dMMR might have a protective role in CRC development. [25] In another retrospective analysis of 795 patients, proximal lesions were identified as a predictor for MSI, with a multivariate odds ratio (OR [95% CI]) of 0.419 (0.223–0.784; P = 0.007) [28]. However, Yan *et al*., observed that larger tumor size was associated with MSI (OR [95% CI], 1.300 [1.076–1.572]; P = 0.007), a finding that was corroborated by Liang *et al*., who reported median tumor diameters of 6.0 cm in the dMMR group compared to 4.5 cm in the pMMR group (P < 0.01) [19-28].

Limitations of the Study

Our study was a single-center study. We took a small sample size due to the short study period. After evaluating those patients, we did not follow up with them for the long term and did not know other possible interference that may happen in the long term with these patients.

CONCLUSION AND RECOMMENDATIONS

In conclusion, microsatellite instability (MSI) colorectal cancers (CRCs) exhibit unique clinicopathological and molecular features compared to microsatellite stable (MSS) CRCs. Advances in testing technologies, including next-generation sequencing (NGS), AI-based histology algorithms, and image-based radiomic analysis, have further clarified and defined this subset of CRCs. Identifying patients with MSI-high or deficient mismatch repair (dMMR) CRC can be enhanced by integrating histological and clinicopathological data. Immunohistochemistry (IHC) staining should be the initial test for MMR protein expression in CRC patients. If feasible, both IHC and NGS can be conducted simultaneously to ensure comprehensive testing. Moreover, NGS can serve as a validation tool when immunotherapy is considered, helping predict treatment efficacy and guide personalized prognosis.

Further study with a prospective and longitudinal study design including a larger sample size needs to be done to validate the findings of our study.

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