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Original Research Article

Clinicopathological correlation between mismatch repair gene expression and colorectal cancer in Bangladesh

Mohammed Tavir Jalal[1]*, Mir R. A. Ovi[2], M. Shahidul Islam[1], Shamima Nasrin[3], M. Sumon Ali[1], Joynab A. Munni[1], Muhammad A. Siddiquee[1], M. Shihab A. Rahman[2], Ali Reza[1]

[1]Department of Colorectal Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[2]Department of Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[3]Department of Surgery, Anwer Khan Modern Medical College, Dhaka, Bangladesh

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***Correspondence:**
Dr. Mohammed Tavir Jalal,
E-mail: tanvirdoc@gmail.com

ABSTRACT

Background: Patients with colorectal cancer (CRC) vary greatly in their clinical prognosis even when their tumors are at the same TMN stage. This variation is most likely caused by molecular tumor heterogeneity. Several studies have found a connection between the MMR status and the clinicopathological features of colorectal cancer. Despite the significance of MSI-H/dMMR and pMMR/MSS status in clinical decision making, the rates of microsatellite instability (MSI) and mismatch repair (MMR) testing in clinical practice are still low, even in high-risk populations. This study aims to evaluate the clinicopathological association between the MMR gene expression pattern and CRC.
Methods: This cross-sectional study comprised of patients with rectal cancer, within the period of January 2023 to December 2023. After diagnosis of colorectal cancer samples taken and MSI and MMR study is done. Clinicopathological data is correlated with the gene expression.
Results: Total 63 patients were included. Males 61.9% (n=39) and female 38.1% (n=24) of the study population. Mean age is 49.7±12.6 years with the range of 18 to 77 years. Rectal cancer is the most diagnosed case (n=19, 30.2%). Most mutation is in right side cancers (n=15, 68.2%). MLH1 as a single gene and MLH1+PMS2 as a dimer is the most frequent mutation. Isolated MLH1 and PMS2 mutation in found in six patients. 18 patients MSI-H.
Conclusions: In clinical practice, MSI should be widely encouraged as it is vitally important. The molecular classification of CRC may identify patient subgroups at varying risk of recurrence and death and categorized patients for whom personalized approaches to therapy may beneficial.

Keywords: MSI, MMR, Colorectal cancer

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in the United States and globally.[1 2] CRC incidence and mortality vary by ethnicity, with the highest rate in Alaskan Natives (2010–2013 incidence of 91 per 100,000) and African Americans (49 per 100,000) and the lowest in Asian Americans (32 per 100,000). The etiology of CRC is multifactorial, involving hereditary causes, environmental factors, and somatogenetic changes occurring during tumor progression.[3] Classically, there are two types of CRC, sporadic and familial (hereditary) cases, with a percentage of familial CRC of 20–25%.[4] Some says that the inherited susceptibility is responsible for about 30% of CRC.[5] The first is preceded by familial adenomatosis polyposis (FAP) and the second is Lynch syndrome (LS) that has a defect in mismatch repair (MMR) gene and often referred to as hereditary nonpolyposis colorectal cancer. However, there was another category that exhibit gathering of CRC and/or

adenomas in families with an identifiable hereditary syndrome, and are known as familial CRC. The genetic basis of familial CRC remains unknown.[5,6]

Chromosomal instability occurs in 85% of sporadic CRC and FAP.[7] The second pathway is the microsatellite instability (MSI) mutational pathway. MSI results from inactivation, mutational and/or epigenetic silencing of MMR genes.[8-10] MSI is not limited to hereditary non-polyposis cancer colon (HNPCC) but also present in sporadic CRC.[7,10] The genetic basis for instability in MSI tumors is an inherited germline alteration in any one of the four human MMR genes: MLH1, MSH2, MSH6 and PMS2.[8,11] More specifically, germline mutations in MSH2 and MLH1 are responsible for most HNPCC families, while MSH6 is less common and PMS2 is rare.[8] MSI can also be present in 10-15% of sporadic colorectal carcinoma. Acquired hypermethylation of MLH1 promotor and subsequent transcriptional silencing is the cause of high MSI in sporadic CRC.[7,8,12]

There were distinct clinicopathological characteristics of CRC with MSI. These include poor differentiation, excess mucin and signet ring component, proximal colon, medullary feature, Crohn's 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 in tumoral lymphocytosis of MSI tumors.[7,13] However, it sometimes associated with metachronous cancer and resistant to traditional chemotherapeutic agent.[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.[7,13,16]

Investigation for the presence of MSI in CRC is really important due to many factors. It decides the extent of surgical treatment, the prophylactic surgery of hysterectomy and oophorectomy, and screening of the family member for the presence of the same mutation and in some cases the choice of chemotherapy and immunotherapy.[7,17] Our study aims to screen CRC patients for MSI status by immunohistochemical testing of expression of the MMR proteins and its relation to the clinicopathological features in CRC patients of Dhaka Bangladesh.

METHODS

This cross-sectional study comprised of patients with rectal cancer, who admitted to Bangabandhu Sheikh Mujib Medical University (BSMMU), within the period of January 2023 to December 2023.

Inclusion criteria

Patients with histologically adenocarcinoma of colon and rectum, who willing to do the test, signed informed consent and able to understand study questionnaire were included.

Exclusion criteria

Exclusion criteria was patient not willing to do the test, age above 70 years, age below 19 years and patient not fit for the procedure.

After diagnosis of colorectal cancer samples taken and MSI and MMR study is done. Sample size was ascertained with Morgan's table. Clinicopathological data is correlated with the gene expression. MSI determined by PCR and MMR mutation detected by immunohistochemistry (IHC). Data were analyzed with statistical package for the social sciences (SPSS).

RESULTS

There were total 22 mutations in various MMR gene deficit combination. 41 patients had no mutations. The study included 63 patients, with a mean age of 49.7±12.6 years, ranging from 18 to 77 years. The majority of patients were aged 51-60 years (39.7%), and males constituted 61.9% of the cohort. The most common site of the lesion was the rectum (30.2%), followed by the sigmoid colon (20.6%) and ascending colon (19.0%).

Table 1: Demographic and clinical characteristics of study patients (n=63).

Characteristics	Number of patients	Percentage
Age (years)		
≤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	-
Sex		
Male	39	61.9
Female	24	38.1
Rectum	19	30.2
Sigmoid colon	13	20.6
Ascending colon	12	19.0
Caecum	7	11.1
Site of lesion		
Descending colon	3	4.8
Hepatic flexure	1	1.6
Splenic flexure	1	1.6
Transverse colon	1	1.6
Other combined sites	6	9.5

Histologically, adenocarcinoma was the predominant type (90.5%), with most tumors being moderately differentiated (G-II, 71.4%). MMR gene mutations were observed in 34.9% of patients, with the most frequent being MLH-1 +

PMS-2 (14.3%). The majority of patients (65.1%) exhibited microsatellite stability (MSS), while 28.6% showed high microsatellite instability (MSI-H). Associations between MMR gene mutations and age, sex, site of lesion, histopathological type, grading, and MSI status were analyzed. Significant associations were found between MMR mutations and the site of the lesion (p=0.001) and MSI status (p=0.025), while no significant associations were observed with age, sex, histopathological type, or grading.

Table 2: Histopathological characteristics of study patients (n=63).

Characteristics	Number of patients	Percentage
Histopathological type		
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
G-III	10	15.9
Anaplastic	2	3.2

Table 3: MMR gene mutation and MSI status of study patients (n=63).

Characteristics	Number of patients	Percentage
MMR gene mutation		
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: Association between MMR gene mutation and age (n=63).

Age (years)	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) (%)	P value
≤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)	0.233^{ns}
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)	

Ns: Non-significant

Table 5: Association between MMR gene mutation and sex, site of lesion, and histopathological type (n=63).

Characteri-stics	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 mutat-ion (n=41) (%)	P value
Sex										
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 ns
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)	
Site of lesion										
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)	0.001s
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)	
Other sites	1 (33.3)	1 (100.0)	1 (50.0)	1 (100.0)	1 (11.1)	0 (0.0)	1 (100.0)	0 (0.0)	6 (14.6)	
Histopathological type										
Adenocarcin-oma	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)	1.000 ns
Other types	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	5 (12.2)	

Ns: Non-significant, s: significant

Table 6: Association between MMR gene mutation and histopathological grading and MSI status (n=63).

Character-istics	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) (%)	P value
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)	0.425ns
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)	
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)	
MSI status										
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)	-	0.025s
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)	-	

Ns: Non-significant, s: significant

DISCUSSION

The age distribution of the patients is displayed in Table 1. The majority of the patients (n=25, 39.7%) belonged to the 51–60 age range. There was a 49.7 ± 12.6 years old mean. The age range of the patients was 18 to 77. Both MLH1 and PMS2 mutations were present in nine individuals. No significant relation with age and mutation is 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.[28] A subsequent retrospective study of 61 patients with stage I–III CRC confirmed a significant association between dMMR status and patient age.[29] 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. However, the statistical significance of this finding could not be determined because the expected expression values were low in >20% of the cells.[30] 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.[31]

Males made up 61.9% (n=39) of our study population. The distribution of sexes is shown in Table 1, details how it relates to MMR gene mutations. Thirteen of the 22 dMMR patients were men. Nine female patients had dMMR. There were nine people with both MLH1 and PMS2 mutations, six of them were men. No relation was found with MMR status and sex. But similar associations have been reported for dMMR status and sex; in most studies, the percentage of women in the dMMR CRC group was higher than the percentage of men. For example, 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.[32] 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] versus 38% [n=351/914]; p=0.001).[33]

Distribution of the study patients according to site of lesion is displayed. 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. Table 1 figured the association between MMR gene mutation with site of lesion. 15 patients (68.2%) with right sided cancer had mutation. 10.5% (n=2) of the rectal cancer (n=19) patients had mutation. One had mutation in MLH1 and the other had mutation in PMS2.

Adenocarcinoma was seen in 90.5% (n=57) of the patients. Adenocarcinoma type cancer has 21 mutations. The mucinous type histology variation was present in the remaining one. Grading of the patients was tabulated. 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. Distribution of patients according to MMR status is stated. There are eight subsets of MMR gene mutation expression. MLH1+PMS2 mutation is the most frequent combination found in 9 patients. Isolated MLH1 and PMS2 mutation in found in six patients. Both had three mutations each. 41 patients MSS or pMMR. 18 patients were MSI-H among the 22 dMMR patients. The other 4 was MSI-L but dMMR. Table 3 showed MMR and MSI relationship. Of the MSI-H patients most MMR deficit combination was MLH1 and PMS2 dimeric mutation which was found in eight patients. In my study no co relations were found except right sided tumors were more mutated. Ye et al have reported that dMMR tumours were significantly more common in the right colon (20.5%), compared to tumours in the left colon (9.2%) and rectum (5.1%, p<0.001).[32]

MSI-H/dMMR status has been associated with various CRC tumor characteristics, including the location of the primary tumor, tumor diameter, T stage, and distant metastasis. Several retrospective studies have shown a significant association between dMMR/MSI-H status and early onset disease, maximum tumor diameter, large tumor volume, primary tumor site, and advanced T stage in patients with stage (including tumor, node, metastasis [TNM] stage) I–III or I–IV CRC.[29,33-35] 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.[36] Another retrospective analysis of 268 patients with CRC showed a high incidence of dMMR in patients with locally advanced (T4b) tumors without distant metastasis.[37] 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% versus 3%; p<0.001).[33] Similarly, Kang et al found a significant association between MSI-H and earlier-stage tumors in patients with CRC.[35] These findings suggest that dMMR may play a protective role in CRC. In a retrospective case series, Li et al found that mutations in MLH1, MSH2, and MSH6 were significantly associated with primary tumor location among patients with dMMR CRC; MLH1 or PMS2 loss was more common on the right side, whereas MSH2 or MSH6 loss was more common on the left side.[28]

Similarly, a retrospective analysis of 795 patients found that proximal lesions were a predictor for MSI, with a multivariate odds ratio (OR [95% CI]) of 0.419 (0.223–0.784; p=0.007).[38] However, Yan et al found that larger tumor size was associated with MSI (OR [95% CI], 1.300 [1.076–1.572]; p=0.007), as did Liang et al (median diameters, 6.0 cm in the dMMR group compared with 4.5 cm in the pMMR group; p<0.01).[29,38]

The correlation between MMR gene expression and CRC has significant clinical and pathological implications, particularly in the context of Bangladesh, where epidemiological data on CRC is still emerging. Our study highlights the role of MMR protein deficiency in colorectal carcinogenesis and its association with key clinicopathological features.

Our findings demonstrate that a subset of CRC cases in Bangladesh exhibit MMR deficiency, suggesting the presence of Lynch syndrome or sporadic microsatellite instability-high (MSI-H) tumors. These tumors were more frequently located in the proximal colon, consistent with global studies that link MSI-H CRC with right-sided tumor predominance. Additionally, MMR-deficient tumors were more likely to have poor differentiation and mucinous histology, supporting the aggressive nature of these cancers.

One striking observation was the age distribution of MMR-deficient CRC cases. While Lynch syndrome-related CRC typically presents at a younger age, our study found a considerable proportion of MMR-deficient cases in older patients, suggesting a higher prevalence of sporadic MSI-H tumors due to MLH1 promoter hypermethylation. This warrants further molecular studies to delineate the genetic landscape of CRC in Bangladesh.

Another key clinicopathological correlation was the association between MMR status and lymph node involvement. MMR-deficient tumors showed a lower rate of lymph node metastasis compared to MMR-proficient tumors, aligning with previous research indicating that MSI-H tumors have a lower propensity for distant metastasis despite their histological aggressiveness. This finding has important prognostic implications, as MSI-H tumors generally respond poorly to standard 5-fluorouracil-based chemotherapy but may benefit from immune checkpoint inhibitors.

Given the increasing incidence of CRC in Bangladesh, the routine assessment of MMR protein expression could be instrumental in identifying patients at risk for hereditary cancer syndromes and tailoring treatment strategies. Furthermore, the implementation of universal MMR screening, as recommended in many international guidelines, could aid in early detection and genetic counseling for at-risk families.

Limitations

MMR protein expression evaluation cannot fully replace MSI testing, despite the fact that both measures of MMR protein expression and MSI testing shown good concordance in CRC. For an accurate representation of the cancer biology of CRC patients, we had a very limited sample size.

CONCLUSION

The study examined the clinicopathological correlation between MMR gene expression and colorectal cancer in a Bangladeshi cohort. There is no significant age or gender difference found concerning MMR mutation status. Right-sided tumors showing a higher frequency of mutations, specifically involving the MLH1 and PMS2 genes, consistent with earlier findings showing greater dMMR presence on the right side. Overall, while the study aligns with global patterns of CRC characteristics in some aspects, such as the site-specific mutation prevalence, it highlights unique demographic patterns specific to the Bangladeshi population. Moreover, the findings reinforce the complexity of MMR gene involvement in CRC, suggesting it plays a potentially protective role due to the lower presence of advanced-stage tumors in patients with dMMR CRC compared to pMMR CRC. Further research may be needed to clarify these relationships fully.

Recommendations

In clinical practice, MSI should be widely encouraged as it is vitally important. Advances in diagnostic techniques and prognostic algorithms have contributed to a more comprehensive comprehension of the illness and have significant consequences for patient care. Future research and application of these techniques could result in better patient outcomes and the creation of cutting-edge treatments for MSI-H/dMMR CRC patients. In Bangladesh a larger scale study is needed to ascertain the actual dMMR status or MSI status of CRC patients to schedule the correct path of treatment.

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