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Original Research Article

CLINICO-PATHOLOGICAL CORRELATION OF MMR (MISMATCH REPAIR) DEFICIENCY IN COLORECTAL CANCER PATIENTS

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ABSTRACT

Background: There is an increase in the incidence of Colorectal cancer (CRC), especially among young adults. Lynch syndrome is the most common genetic type with predominance of right side cancer and an early age of onset. There is dearth of literature regarding the prevalence of MMR deficiency in colorectal cancers and it's association with outcome in Indian populations. Screening patients using IHC for MMR protein expression offers an economical alternative to select patients requiring genetic testing. **Aim:** The aim of the present study was to determine the incidence of Mismatch repair deficiency in colorectal cancer patients.

Material and Methods: This prospective, cohort study was conducted in the Department of Surgical Gastroenterology, Nizams Institute of Medical Sciences, Hyderabad from October 2019 to November 2021. All patients diagnosed with colorectal cancer were included. Immunohistochemistry for MLH1, MSH2, MSH6, and PMS2 was performed to check MMR gene expression at the protein level.

Results: A total of 77 patients with a diagnosis of colorectal cancers were included in the study. The median (range) age of the study group was 52.5 years (17-73 years) with a male preponderance. There were 11 (14%) patients with MMR protein loss. There were 5 (10.4%) patients with deficient MMR above 50 years age. The comparison between patients with deficient MMR and patients with non-deficient MMR showed that the clinical and demographic profile were similar between the groups except, right sided colonic tumours were significantly higher in the MMR deficient group (p =0.011). The patients with deficient MMR had significantly early-stage tumours than patients with non-deficient MMR (p=0.032).

Sixteen (20.7%) and 50(64.9%) patients of the study group received neoadjuvant, and adjuvant therapy respectively. On median (IQR) follow up of 20 months (6-27 months), 4 patients (liver, n=2; Nodal, n=1; Anastomotic site, n=1) had a recurrence of the disease, and 6 patients were expired. All deaths were observed in the nondeficient MMR group.

Conclusion: The incidence of the MMR deficiency in CRC patients is 14%. The patients with MMR deficiency had significantly more right sided and early stage I & II malignancy. The two year overall survival was similar between two groups

Keywords: MMR (Mismatch Repair), Colorectal cancer (CRC).

INTRODUCTION

The incidence of colorectal cancer (CRC) is increasing worldwide. Although there is a high incidence of CRC in developed countries, there is a decline in mortality due to early detection and better management. However in resource limited countries with limited infrastructure the mortality remains higher.[1] Five-year survival of CRC in India is one of the lowest in the world at less than 40%.[2] The age standardized rate for CRC in India is low at 7.2 per 100,000 population in males and 5.1 per 100,000 population in women.[2]

The cause of CRC is multifactorial, involving genetic and environmental factors. Two pathways contribute to majority of CRC namely chromosomal instability (CIN) and micro-satellite instability (MSI).[3] CIN contributes to 70-80% of sporadic colorectal cancer which start with a mutation in APC gene.[3] After that KRAS and P53 mutations occur sequentially causing transition of an adenoma to carcinoma. The MSI pathway contributes to about 15% of sporadic CRC patients. Inactivation of the mismatch repair (MMR) gene MLH1 contributes to sporadic CRC.[4]

Apart from the common Sporadic form there are known genetic and familial associations. Lynch syndrome is the most common genetic type. It is caused by mutations in the mismatch repair (MMR) genes, which is characterised by autosomal dominant inheritance, predominance for right side cancer and early age of onset5. The NCCN2019 recommends universal screening of all CRC tumours to maximize sensitivity for identifying individuals with Lynch syndrome and to inform prognosis and care processes in patients with and without Lynch syndrome.

The NCCN 2019 recommends tumor testing with immunohistochemical (IHC) and/or MSI be used as the primary approach for pathology-lab–based universal screening and to guide treatment decisions. While cost constraints limit genetic testing to be performed, screening patients using IHC for MMR protein expression offers an economical alternative to select patients requiring genetic testing6. There is dearth of literature regarding the prevalence of MMR deficiency in colorectal cancers and it's association with outcome in Indian populations.

Aim

The aim of the present study was to determine the incidence of Mismatch repair deficiency in colorectal cancer patients.

Objectives

1. The Clinico-pathological correlation of MMR deficiency was analyzed.
2. The role of MMR deficiency as prognostic and predictive marker was studied.

MATERIAL AND METHODS

This prospective, cohort study was conducted in the Department of Surgical Gastroenterology, Nizams Institute of Medical Sciences, Hyderabad from October 2019 to November 2021. All patients diagnosed with colorectal cancer were included. Patients known to have Familial Adenomatous Polyposis (FAP) and cancer arising in the background of inflammatory bowel disease (IBD) were excluded. The patient characteristics, presentation, outcome, in- hospital morbidity or mortality were studied.

A detailed history including comorbidities were noted. In patients with age lesser than 50 years screening for other malignancy associated with Lynch Syndrome was also done. Family history for similar disease or other malignancy seen in LYNCH syndrome [e.g. ovarian, gastric, urinary tract (kidney, renal pelvis, ureter, bladder, and prostate], pancreaticobiliary, small intestinal, and brain cancers, as well as sebaceous neoplasms of the skin and possibly slightly increased risks of female breast cancer and prostate cancer) were documented.

Complete colonoscopic evaluation was done either pre-operatively in non-obstructed patients or post-operatively in obstructed patients. Patients presenting with acute abdomen in form of obstruction or intestinal perforation were resuscitated and underwent surgery. Patients with tumors up to sigmoid colon underwent a definitive surgery in acute abdomen. Patients with rectal cancer and intestinal obstruction underwent staged therapy. Rectal cancer patients with local invasion up to muscularis propria or beyond (T stage >/= T2) and node positive disease received neoadjuvant chemoradiotherapy (NACT-RT) and later underwent surgery. After 6 weeks of completion of long course or one week after short course NACT-RT patients underwent surgery.

Resected specimen sent in formalin for histopathological examination and immunohistochemistry. Depending upon pathological report, patients of stage 2 colorectal cancer with high-risk features (presenting with obstruction or tumor perforation, T4 disease, high grade tumor, perineural or lymphovascular invasion), fewer than 12 lymph nodes resected or rare histology as mucinious or signet cell histology, stage 3 and stage 4 disease after curative resection received adjuvant chemotherapy. Patients were regularly followed up, evaluated with clinical examination, carcino embryonic antigen blood level and CECT abdomen.

Histopathological Analysis

4µm thick sections were made from normal and tumor CRC FFPE blocks using Leica microtome (RM2125RT, Leica, Germany) and stained with hematoxylin and eosin (H&E) using Leica ST5020 (slide stainer, Leica Biosystems) as per the manufacturer's instructions. Histopathological

classification and identification of epithelial cells on H& E slides were done by two experienced pathologists independently. Images were taken using the Nikon Eclipse 80i (Nikon corporations, Tokyo, Japan) at 10X and 20X magnification.

MMR gene expression at the protein level

Immunohistochemistry for MLH1, MSH2, MSH6, and PMS2 was performed to check MMR gene expression at the protein level. Four-micron sections from CRC tumor FFPE blocks were generated with the help of microtome (RM2125RT, Leica, Germany). These sections were deparaffinised by incubating the slides at 60°C for one hour and washed twice with xylene for 10 minutes each.

The slides were then hydrated by concomitantly incubating in a series of alcohol solutions with decreasing concentration (100%, 95 %, 70%, 50%). Pressure cooker method with citrate buffer (pH 6.0) / Tris- EDTA (pH 9) was used for antigen retrieval. After cooling down to ambient temperature slides were incubated with 0.3% hydrogen peroxide for 15 minutes to break the crosslinks formed by formalin. Then slides were washed with wash buffer (1X Tris Buffered Saline Tween (TBST)) thrice for 5 minutes each. Further these sections were incubated with the primary antibodies (anti-MLH1 (1:99 dilution), anti-MSH2 (ready-to-use), anti-MSH6 (ready-to-use) and anti-PMS2 (ready-to-use)) for one hour.

Slides were washed again wash buffer 5 times for 5 minutes each. Subsequently, the sections were treated with HRP-conjugated anti-mouse/rabbit secondary antibody (Dako REAL Envision Detection System, Dako, Glostrup, Denmark) for 30 minutes and then subjected to chromogen detection for three minutes. Sections were counterstained with hematoxylin and mounted with DPX mounting media. The nuclear expression for MMR genes was scored by two experienced pathologists' independently (blinded for the study). Samples exhibiting > 30% nuclear staining were classified as positive and <30% as negative for the particular MMR protein. Images were taken using Nikon Eclipse 80i (Nikon corporations, Tokyo, Japan) at 20X magnification

Overall survival (OS) was defined as interval between date of surgery and date of death due to any cause. Recurrence free survival (RFS) was defined as the interval from surgery to the time of documented recurrence (radiologically/pathologically) or date of death secondary to non-malignant causes or date of last visit without recurrence.

Sample size calculation

The reported incidence rates of MSI in population is approximately 20%7. With 95% Confidence level and desired precision of estimate of 0.10, the sample size was estimated to be 62. A 10% attrition of the study population was anticipated and added to the required sample size. Hence the required sample size was 68. (Sergeant, ESG, 2018. Epitools Epidemiological Calculators. Ausvet. Available at: http://epitools.ausvet.com.au.)

Statistical Analysis

Statistical analysis was done by using SPSS 28.0version (IBM, NY) software. Categorical data were represented in number (percentage). Continuous data were represented in Mean (± standard deviation) [normal distribution] or Median (interquartile range) [non-normal distribution]. Chi-square test/Fischer's exact test were used to compare categorical data (Table 1, Table 2). Kaplan-Meir survival curves were obtained for survival data and were compared with log-rank test. P – value < 0.05(two sided) was considered significant.

The project was approved by the Institute Research Council and Ethical Committee of the Institute.

RESULTS

In the present study of 77 patients of colorectal cancer (CRC) were included. There were 52 male and 25 female (M:F = 2.08:1) of colorectal cancer who underwent resection.MMR protein loss was found in 11 (14.3%) patients. The clinical and demographic profile was summarized in Table 1. [Table 1]

Median age of the patient was 52.5 years (range 17–73 years). Twenty nine (37.6%) patients were younger than 50 years and 4 (5.1%) patients were younger than 30 years. The most common presenting symptom was abdominal pain [n = 59 (76.6%)] followed by weight loss [n= 47 (61%)] and gastrointestinal bleed [n = 27 (35%)].

The tumor characteristics in MMR deficient and nondeficient population was summarized in Table 2. [Table 2]

In the cohort of 77 patients, the frequency of colon cancer was higher 59 (76.6%) than rectal cancer 18 (23%). Sigmoid colon was the most common site [24 (31%)] among the colonic cancers. Left sided colonic malignancy (distal to splenic flexure) [42 (54.5%)] was non significantly more common than right sided colonic malignancy. Eighteen (23.4%) patients had rectal cancer and none of them had MMR deficiency. Six (7.7%) patients presented with synchronous tumors. Oncolonoscopic evaluation the most common finding was ulceroproliferative lesion [58 (75.3%)] followed by stenotic [12 (15.5%)] and polypoidal lesion [7 (9%)]. The site of tumor was summarized in Fig 1. [Figure 1]

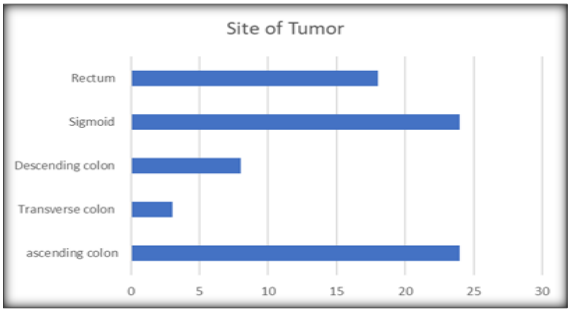

Figure 1

In the present study, patients with AJCC TNM stage II or stage III disease constituted 84.4% (n=65), and 10.3% (n=8) patients had metastatic disease(Fig 2). The most common histological type was adenocarcinoma (84.4%, n=65) followed by signet cell variant (12.9%, n=10) and mucinous variant (2.6%, n=2). Most of the tumors were well differentiated[60 (77.9%)]. [Figure 3]

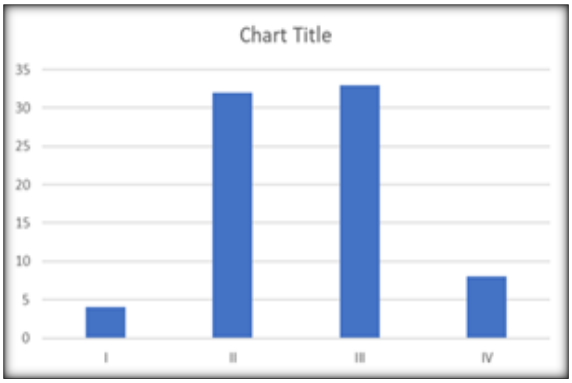

Figure 2: Stage distribution

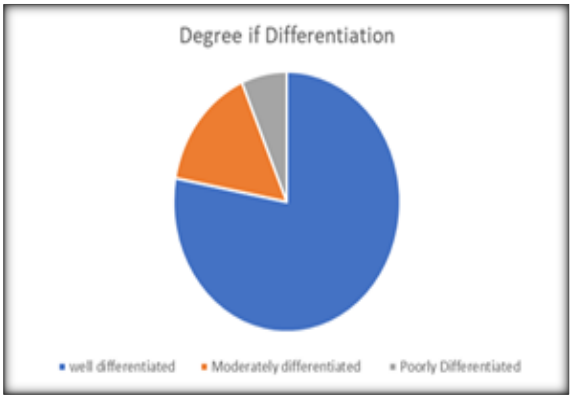

Figure 3

Rate of complications were more in stage III patients(Table 3). Most of the complications (94%) were of grade I and grade II.

MMR protein loss was found in 11 (14.3%) patients. Six (7.8%) patients were younger than 50 years. In a population of less than 30 years age 25% were deficient in MMR protein. Among the MMR deficient group 5 (45.5%) patient belong to more than 50 years age group. MMR protein loss was seen significantly more in patients with right side colon cancer [9 (81.8%)] as compared to left [2 (18.2%)] (p = 0.011). MMR protein loss was seen significantly more with early-stage tumor Stage I - II [9 (81.8%)] as compared to late stage III - IV [2 (18.2 %)] tumours (p=0.032). Proportion of well differentiated malignancy was non significantly more in stage 2 colon cancer than stage 3 colon cancer.

The most common MMR protein loss was combined loss of MLH1 + PMS2 (54.5%, n=6 patients) followed by combined loss of MSH2 + MSH6 (36.4%, n=4 patients) (Table 4). The isolated loss of MMR protein was present in one patient as loss of PMS2 (9.1 %). [Table 3]

Adjuvant Therapy

A total 50 (64.9%) patients of cohort received capecitabine and oxaliplatin based chemotherapy. Among stage II disease patients 14 received adjuvant chemotherapy because of high risk features (T4 tumor, poorly differentiated, obstruction or perforation, with lymphovascular or perineural invasion). Thirty two of 33 patients of stage III disease received adjuvant therapy while one died secondary to post operative complications. In view of curative resection of metastatic disease, as liver deposit and pelvic deposit, adjuvant therapy was given in 4 patients. Three of them are in follow-up and doing fine whereas one died after 2 months of surgery secondary to aggressive nature of disease.

Neoadjuvant therapy

Among the 77 patients of cohort 16 of 18 rectal cancer patient received long course NACT-RT and underwent subsequent definitive surgery. Two of 18 rectal cancer patient of cohort underwent upfront surgery in view of preoperative biopsy report suggesting low to moderate grade dysplasia and having symptoms of bleeding. [Table 4]

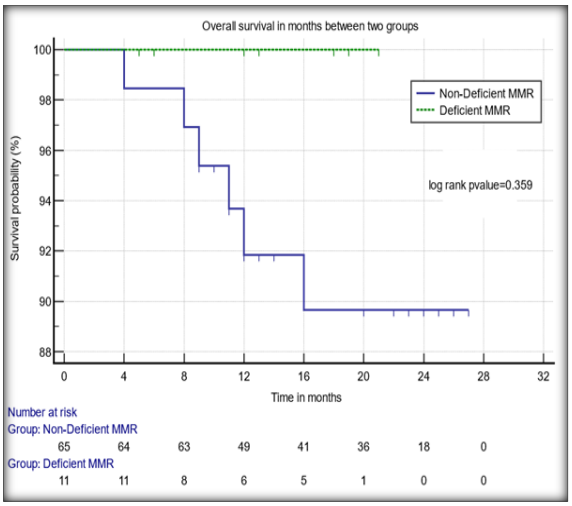

Figure 4: Survival curve

The age, gender distribution, presenting complaints, and tumor histopathological characteristics were similar between the patients with MMR protein loss and patients with stable MMR(Table 2). Of the 4 patients with recurrent disease only one had loss of MMR protein in combination of MLH1 + PMS2.

On median (IQR) follow up of 20 months (6-27 months), 4 patients (liver, n=2; Nodal, n=1; Anastomotic site, n=1) had a recurrence of the disease, and 6 patients were expired. All deaths were observed in the nondeficient MMR group. The stage wise distribution of patients and their outcome is summarized in Table 5.The survival data between both the groups was given in Fig 4 and Table 6.

Among the patients who died in follow-up didn't had loss of MMR protein.

Table 1: Clinical and demographic profile of study population (n = 77)

	MMR Deficiency, n = 11	Non Deficient MMR , n = 66	p-value*
Age			
<30 years n = 4 (%)	01(25)	03 (75)	
30-50 years n = (%)	05 (20)	20 (80)	0.443
>50 years n = 48 (%)	05 (10.4)	43 (89.6)	
Gender			
Female n = 25 (%)	02 (8)	23 (92)	0.274
Male n= 52 (%)	09 (17.3)	43 (82.7)	
Presenting complaints			
Pain n= 59 (%)	09 (11)	50 (88.9)	0.660
Bleeding 27 (%)	04 (14)	23 (86)	0.922
Obstruction 15 (%)	02 (14.5)	13 (85.5)	0.906
Altered Bowel Habits 13 (%)	01 (15.6)	12 (84.4)	0.678
Loss of weight/appetite 57 (%)	09 (10)	48 (90)	0.718
Preoperative CEA, ng/ml (%)	4.2 (2.9-12.6)	4.2 (2.7-11.1)	0.850
Site of tumor			
Ascending colon 24 (%)	08 (33.3)	16 (66.7)	
Transverse colon 3 (%)	01 (25)	02 (75)	
Descending colon 8 (%)	01 (12.5)	07 (87.5)	0.011
Sigmoid colon 24 (%)	01 (4.2)	23 (95.8)	
Rectum 18 (%) Right sided cancer 27 (%) Left sided cancer 50 (%)	00 (0) 9 (33.3) 2 (4)	18 (27.3) 18 (66.6) 48 (96%)	
Colonoscopic appearance			
Ulcero proliferative 58 (%)	09 (15.5)	49 (84.5)	
Polypoidal (%)	02 (28.6)	05 (71.4)	0.198
Stenotic (%)	00 (0)	12 (100)	
NACT/RT- Neo adjuvant chemotherapy/ radiotherapy, * - Chi square test			

Table 2: Tumor characteristics of the study population (N=77)

	MMR Deficiency, (n =11)	Non Deficient MMR, (n = 66)	p value*
T stage			
T2 n = 10 (%)	00(0)	10 (100)	
T3 n = 60 (%)	10 (16.7)	50 (83.3)	0.378
T4 n= 7 (%)	01 (14.2)	06 (85.8)	
N stage			
N0 n= 38 (%)	09 (23.7)	29 (76.3)	0.050
N1n= 23 (%)	02 (8.7)	21 (91.3)	
N2 n = 16 (%)	00(0)	16 (100)	
M stage			
M0 n= 68 (%)	10(14.7)	58 (85.3)	0.772
M1 n = 9(%)	01 (11.1)	08 (88.9)	
TNM stage			
Stage I n = 4 (%)	00 (0)	04 (100)	
Stage II n= 31 (%)	09 (28.1)	23 (71.9)	
Stage III n = 33 (%)	02 (6.1)	31 (93.9)	0.032
Stage IVn = 8 (%)	00 (0)	08(100)	
Tumor type			
Adenocarcinoma n = 65(%)	10 (15.9)	55 (84.1)	
Signet cell carcinoma n = 10 (%)	01(10)	09 (90)	0.761
Mucinous n = 2(%)	00 (0)	02 (100)	
Grade of Differentiation			
Well n = 60 (%)	08 (13.3)	52 (86.7)	
Moderate n = 12(%)	01 (8.3)	11 (91.7)	0.213
Poor n = 5 (%)	02 (40)	03 (60)	
Perineural Invasion n = 14(%)	01 (15.9)	13 (84.1)	0.678
Lymphovascular invasion n=12 (%)	01 (8.3)	11 (91.7)	0.521
* chisquar test			

Table 3: Comparison of post-operative complications in various stages of cancer (n=12)

Stage	Complication
I	1 (8%)
II	4 (33.3%)
III	6 (50 %)
IV	1 (8 %)

Table 4: Pattern of MMR

MMR deficiency	Patients
MLH1 + PMS2	6 (54.5%)
MSH2 + MSH 6	4 (36.4%)
PMS2	1(9.1%)

Table 5: Stage wise distribution of patients and their outcome

Stage	No. of patients	MMR protein deficiency	Well differentiated histology	Disease recurrence	Died
I	4	0	0	0	0
II	32	9	7	0	0
III	33	2	1	4	3
V	8	0	0	0	3

Table 6: Survival table

	Mean Survival in months (SE)	2 -year survival %	P value
Deficient MMR	21 (0)	100	0.359
Non Deficient MMR	25.2 (0.67)	89.7	

DISCUSSION

Demography

The prevalence of CRC in India is low with estimated five-year prevalence is 87 per 100,000 population.[8] However, the prevalence was more in Indian immigrants in USA and Singapore but it is still lower than the native population.[9] This shows that environmental factors may play an etiological role in addition to genetic factors.

CRC incidence rates are higher for men in most regions of the world1. The male to female distribution was 2:1 in the present study. There are lot of regional variations in India with reported ratio of 3:1 in North India 1, 2.4:12in South India and 1.7:1 in West India1.Thirty seven percent of our patients were under 50 years compared to only 10% in USA.[10]

In studies from India 20 to 50% of cases were in less than 50 yrs of age with some regional variations.[11-14] In India the incidence of colorectal cancer in young population is increasing. [Table 7]

In our study, most of the tumors were left-sided, the commonest primary site being sigmoid (31%) followed by rectum (23%). Left-sided tumors are more likely to present with overt bleeding per rectum and pain and therefore are more likely to become symptomatic earlier.

The present study represents one of the first few studies from South India to determine the loss of MMR protein expression in colorectal cancer. IHC was used because of its high sensitivity and specificity in detecting microsatellite instability.

The sensitivity of IHC to detect MMR loss is 65–70% with the use of 2 antibodies (MLH1, MSH2) which is further increased to 90–92% with use of all four antibodies (MLH1, MSH2, MSH6, PMS2)6. This may be because of different environmental factors or may represent a different genetic predisposition.

MMR protein loss of 14% in the present study is lesser than previously reported from North Indian study.[18] A study from the UK reported MMR protein loss of 21% while another from Memorial Sloan-Kettering Cancer Centre reported it as 19%; other studies from the west have reported MMR protein loss from 15–21%.[6] Dubey et al. reported MSI- high in 22% patients.[16] The reported MMR protein loss was 17.8 to 19.9% by Pandey et al19and Malhotra et al.20. Table 7 shows that MSI loss is between 15% to 41.9% in Indian studies.

Out of all the cases with MMR loss, 54.5% showed loss of MLH1 and PMS2, 36.4% showed loss of MSH2 and MSH6, 9.1% showed isolated loss of PMS2. The loss of MLH1 and PMS2 was the predominant pattern followed by loss of MSH2, MSH6 18.However, isolated loss of PMS2 was a rare finding in our study. In this study, MSI tumours did not show any age or sex predilection similar to studies by Kaur et al.[15]

Unlike various studies where MSI tumours had poorly differentiated/mucinous/medullary type morphology, in our study, the most common histologic type (72 %) of tumour in MSI cases was well differentiated tumors; poorly differentiated/mucinous morphology constituted only a minor group. Intratumoural lymphocytic infiltrate was absent in majority of the cases and marked only in one case. In study by Gandhi etal18 peritumoural lymphocytic infiltrate was mild to moderate in most of the cases (26.9%) and marked Crohn's-like infiltrate was seen in only 7.6% cases

Isolated loss of MLH1 is usually the result of promoter hypermethylation preventing its expression and hence is usually sporadic. The present study has no isolated MLH1 loss which may suggest a high proportion of Lynch syndrome amongst patients with MMR protein loss.

The loss of expression of MSH2, MSH6 or PMS2 in isolation or in combination, provides reasonably strong evidence of germline mutation in respective genes and therefore highly suggestive of HNPCC 15. MMR protein loss is more commonly seen in right sided tumours compared to left sided and rectal tumours as was evident in this series as well with significance (p=0.032). This is similar to studies from other parts of the world.

Treatment and prognosis

Several meta-analyses have shown that MSI CRC cases have good prognosis in terms of disease-free survival, and overall survival regardless of the stage, whereas others have shown the benefit of knowledge of MSI status only in stage 2 and 3 CRCs.[21] Data also highlight that in a recurrent or metastatic setting the MSI tumors tends to have negative prognostic role with reduced OS as compared to the MSS CRC21. Our study didn't show higher recurrence-free survival and mean overall survival in MMR deficient group.

Multiple retrospective and population-based studies have shown that patients with MSI-H CRCs have a more favourable stage-adjusted prognosis than those with MSS tumors.[22] In our study there was no survival advantage. MMR protein testing using IHC is a less costly, rapid method compared to MSI testing, having similar sensitivity with the use of all 4 antibodies. It also directs further germline mutational analysis. Patients having MMR protein loss may be suspected to have Lynch syndrome, and warrant genetic testing. A major hurdle in this approach is lack of facilities for genetic counselling and testing. Even at places where such facility is available, IHC testing for MMR protein is not readily available. One of the factors for non-availability of a relatively economical IHC testing is lack of data regarding the incidence of MMR protein loss in India; hence, its importance is not understood.

A 14% loss of MMR protein needs no further emphasis on the importance of MMR protein testing. Out of 11 patients having MMR protein loss, 2 (18.2%) patients had family history. Therefore, universal IHC testing is required for all colorectal cancer patients in India irrespective of family history. The strength of the study lies in its prospective nature. However, the study lacks genetic analysis which is done to actually determine the patients suffering from Lynch syndrome. A correlation with MSI testing is also missing from the study.

There were a few limitations of the study. The precision was kept 0.10 due to time constraints. Hence, the incidence might not reflect absolute estimate. Approximately one-fourth of patients were rectal cancers. The neoadjuvant radiation therapy received by these patients would have denatured the MMR protein. An IHC on pre-operative tissue biopsy would have increased the incidence. Though, the recurrences are most commonly seen in initial two years after surgery, the longer follow up may provide better information.

Thus except for right sided malignancy and early-stage disease, none of the typical clinicopathological features of MSI tumours were substantiated by our study, highlighting no correlation of specific histological features as described in literature and MMR protein loss.

Table 7: Clinicopathological comparison between different studies

Studies Variable	Kaur et al[15] 2011		Dubey et. al[16]. 2016	Patil et al[2] 2017	Kumar et. al[17]. 2018	Gandhi et al[18] 2018	Our study 2021
Mean Age (years)	59.4			48.5	52.5	60.2	52.5
Sex (M:F)	1.08:1		2.4:1	1.35:1	2.8:1	3.2:1	2.08:1
Site of tumor (Left : Right)	3.1:1		2.5:1		1.6:1	1.8:1	1.8:1
Stage	I			6.2	4.5		5.2
	II			38.2	35.6		41.5
	III			50.2	55.4		42.8
	IV			5.4	5.0		10.4
Grade (%)	Well	109	60.2	64		60	78
	Mod.	20	32.4	25.8		13	16.4
	Poor	8	7.4	5.2		18	5.6
MSI (%)	15%		22%	26%	29%	41.9%	14%

CONCLUSION

The incidence of the MMR deficiency in CRC patients is 14%. The patients with MMR deficiency had significantly more right sided and early stage I & II malignancy. The two year overall survival was similar between two groups.

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