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Mismatch Repair (MMR) Status among Colorectal Cancer Patients in a Philippine Tertiary Hospital: A 4-Year Review

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ABSTRACT

Background. Approximately 15% of colorectal cancers exhibit deficient mismatch repair (dMMR) status, and these cases have a better prognosis and are less prone to metastasis. Moreover, dMMR is associated with an improved response to immune checkpoint inhibitors. Currently, local data on the MMR status of colorectal cancer patients remains scant.

Objective. The proponents aimed to determine the MMR status among colorectal cancer patients in a Philippine tertiary hospital.

Methodology. This is a descriptive cross-sectional study that included 42 patients with colorectal cancer seen at the Chinese General Hospital and Medical Center (CGHMC) from January 2021 to June 2024. Data was collected via retrospective review of histopathologic reports.

Results. Forty-two (42) patients were included in the study. The mean age of included patients was 61.8 years, and most were males. Half had well-differentiated tumor grade, and the most common tumor locations were rectum (38%) and sigmoid (36%). Three patients (7.14%; 95% CI:1.50-19.48%) were considered deficient. Tumor locations in dMMR patients were the cecum, descending colon, and rectum. Compared to MMR-proficient, dMMR patients had a lower mean age (63.1 vs. 45.7 years). Also, a higher proportion of males (13%) were dMMR than females (0%).

Conclusion. dMMR is uncommon among the colorectal cancer cases in this study, and was only seen at the cecum, descending colon, and rectum. Descriptive analysis revealed that patients with dMMR were younger than MMR-proficient patients. Moreover, a higher proportion of males were dMMR than females. Larger, multicenter studies are warranted to validate these preliminary findings and guide future clinical decision-making.

Key words: biomarkers, colorectal neoplasms, dMMR, DNA mismatch repair

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INTRODUCTION

According to the World Health Organization (WHO), colorectal cancer is the fourth leading cause of cancer-related death worldwide and accounts for 608,000 deaths, mainly affecting individuals over 50 years of age. There has been increasing incidence reported in young adults in Australia, Canada, and the USA. In the Philippines, colorectal cancer ranks fourth among the cancer-related deaths of Filipinos. According to the Philippine Cancer Society, Inc., almost 75 percent of the individuals affected were aged 50 and above, while only about three percent were children aged 14 years and below.[1]

Approximately 15% of colorectal cancers exhibit deficient DNA mismatch repair (dMMR), resulting in microsatellite instability.[2] These tumors are hypermutated, with an abundance of mutation-derived neoantigens that trigger a robust immune response within the tumor microenvironment. Phenotypically, dMMR colorectal cancers are characterized by a right-sided predominance, a tendency for poor differentiation, and a better prognosis in the absence of distant metastasis.[3,4] However, a worse prognosis was observed in dMMR patients with advanced stages of colorectal cancer, including those with metastasis. dMMR occurs in a small subset of advanced colorectal

cancers, leading to a high mutational burden, and the resulting neoantigens are recognized by the patient's immune system.[5] Furthermore, dMMR colorectal cancers are characterized by prominent lymphocyte infiltration, indicating an active immune response.

At the Chinese General Hospital and Medical Center (CGHMC), the chosen study setting, more than 100 colorectal cancer patients are seen annually. In 2021, mismatch repair (MMR) testing became available at CGHMC, which opened more treatment modalities for cancer patients. Currently, in the Philippines, there is limited data on the MMR status of colorectal cancer patients. One such study that touched on this topic is by Sacdalan et al., in which they showed that 12% of young-onset colorectal cancer patients are dMMR. This study, therefore, aims to determine the MMR status among colorectal cancer patients seen in a Philippine tertiary hospital from January 2021 to June 2024. Specifically, the study aims to determine the prevalence of colorectal cancer patients with dMMR. Moreover, the study aims to describe the MMR status of colorectal cancer patients by demographics, histologic grade, and tumor location.

Determining the MMR status in colorectal cancer will have significant implications for patients, clinicians, hospitals, and researchers. For patients, this information can guide treatment selection, as dMMR are more likely to respond to immune checkpoint inhibitors. Clinicians will benefit from this knowledge to make more informed treatment decisions and individual patient characteristics. Hospitals will need to establish robust testing and analysis pipelines to routinely assess MMR status in colorectal cancer patients, which can improve patient stratification and guide the use of targeted therapies. Researchers may continue to investigate the complex interplay between MMR, tumor mutational burden, and the immune landscape in colorectal cancer, to develop more effective and personalized treatment strategies.

METHODOLOGY

This is a descriptive cross-sectional study which included all colorectal cancer patients with available data on MMR status seen in CGHMC from January 2021 to June 2024. CGHMC is a tertiary private hospital located in Manila City, Philippines. In CGHMC, MMR immunohistochemistry involved the use of 4 μm formalin-fixed, paraffin-embedded tissue sections that were stained for MMR proteins using the OptiView DAB IHC Detection Kit (Roche Diagnostics, Basel, Switzerland) on a Ventana Benchmark ULTRA automated stainer (Tissue Diagnostics, ADRIAMED Ltd., Skopje, Macedonia). The slides were counterstained with hematoxylin II and a bluing reagent. The following monoclonal antibodies (Ventana Medical Systems, Tucson, AZ, USA) were used as part of the Ventana MMR IHC Panel: MLH1 (clone M1), PMS2 (clone A16-4), MSH2 (clone G219-1129), and MSH6 (clone SP93). The internal positive controls which include non-neoplastic epithelial cells, stromal cells, and lymphocytes, were evaluated for each slide. In contrast, the external positive controls consisted of normal colonic mucosa with intact nuclear expression of all four MMR proteins. The interpretation criteria were as follows: Intact expression: unequivocal nuclear staining in viable tumor cells, in the presence of internal positive controls (nuclear staining in lymphocytes, fibroblasts, or normal colonic epithelium in the vicinity of the tumor; loss of expression – unequivocal loss of nuclear staining or focal weak equivocal nuclear staining in the viable tumor cells in the presence of internal positive controls. If an unequivocal nuclear stain is absent in internal positive controls and/or background staining interferes with interpretation, the test should be considered unacceptable and repeated.

The researchers included patients of all age groups, admitted as either pay or charity cases, with histopathologically-confirmed diagnosis of colorectal adenocarcinoma, and underwent biopsy and/or colorectal surgery for tumor excision, with specimens submitted to the CGHMC Institute of Pathology for MMR immunohistochemistry. Excluded were those with unavailable results for MMR status.

OpenEpi sample size calculator was used to calculate the minimum sample size requirement. A minimum of 37 patients is required, given a prevalence of dMMR of 21%,[6] a maximum tolerable error of 5%, an alpha level of 5%, and a finite population correction of 43%. Although a minimum sample size calculation was presented, the researcher opted to conduct a total enumeration, wherein all eligible cases would be included in the study. The list of colorectal cancer patients with specimens submitted for immunohistochemistry was obtained from the CGHMC Section of Histopathology.

The researcher performed data gathering from October 1 to 31, 2024. The following data were obtained from the histopathologic reports and recorded in a standardized data collection form: age, sex, tumor location, tumor histologic grade, MMR status. Data obtained from MMR results indicated intact or absent nuclear expressions for MLH1, PMS2, MSH2, and MSH6.

Data was encoded in MS Excel by the researcher. Stata MP version 17 software was used for data processing and analysis. Continuous variable (i.e., age) was presented as mean (standard deviation/SD) due to the normal data distribution based on the Shapiro-Wilk test. Categorical variables were expressed as frequencies and percentages. Missing data was neither replaced nor estimated.

Ethics approval was granted by the CGHMC Research Ethics Review Board (CGHMC RERB Protocol No. 2024-R-80).

RESULTS

A total of 42 patients with colorectal cancer were included in the study. Table 1 presents the characteristics of patients. The mean age was 61.9 years (range, 29-88 years), with the majority being males. Half had well-differentiated tumor grade, and the most common tumor locations were rectum (38%) and sigmoid (36%). Two patients had multiple tumor locations. One had tumors in both the transverse and descending colon, and the other patient had tumors in the descending colon and rectum.

Of the 42 patients with data on MMR status, 3 had dMMR, corresponding to a prevalence of 7.14 (95% CI: 1.50-19.48). Table 2 shows the MMR status by tumor location. Of the three patients with dMMR, tumors were in the cecum, descending colon, and rectum. Only one patient

Table 1. Characteristics of colorectal cancer patients (n = 42)

Characteristics	n (%); Mean ± SD
Age (in years), mean	61.8 ± 12.5
Sex	
Female	18 (43)
Male	24 (57)
Histologic grade [n=18]	
Poorly differentiated	1 (6)
Moderately differentiated	8 (44)
Well differentiated	9 (50)
Tumor location	
Cecum	1 (2)
Ascending colon	1 (2)
Transverse colon	3 (7)
Descending colon	6 (14)
Sigmoid	15 (36)
Rectum	14 (38)
Multiple location	2 (4)

Table 2. MMR status by tumor location among colorectal cancer patients (n=42) [a]

Tumor location	N	dMMR, n (%)	MMR-proficient, n (%)
Cecum	1	1 (100)	0
Ascending colon	1	0	1 (100)
Transverse colon	4	0	4 (100)
Descending colon	8	1 (13)	7 (87)
Sigmoid	15	0	15 (100)
Rectum	15	1 (7)	14 (93)

[a] Two patients had tumor in two locations; dMMR: deficient mismatch repair; MMR: mismatch repair; % presented are row percentages

Table 3. MMR status by age, sex, and histologic grade (n=42)

	N	dMMR n (%); Mean ± SD	MMR-proficient n (%); Mean ± SD
Age (in years), mean	42	45.7 ± 17.0	63.1 ± 11.5
Sex			
Female	18	0 (0)	18 (100)
Male	24	3 (13)	21 (88)
Histologic grade [n=18]			
Poorly differentiated	1	1 (100)	0 (0)
Moderately differentiated	8	0 (0)	8 (100)
Well differentiated	9	0 (0)	9 (100)

dMMR: deficient mismatch repair; MMR: mismatch repair; % presented are row percentages

had a tumor located in the cecum, which was classified as dMMR. Meanwhile, dMMR was noted in 13% of tumors in the descending colon and 7% in the rectum. MMR status by age, sex, and histologic grade by were also explored (Table 3). The mean age of dMMR cases was lower than that of MMR-proficient cases. In terms of sex, none of the females were dMMR, compared to 13% of males. The lone patient with a poorly differentiated histologic grade was classified as dMMR. While all patients with well- and moderately differentiated histologic grades were MMR-proficient.

DISCUSSION

While MMR status is increasingly utilized in the management of colorectal cancer, most of the data available are derived from Western or East Asian populations. In the Philippines and other Southeast Asian countries, data on these biomarkers remain limited. This study aimed to determine the prevalence as well as clinicopathologic associations in a cohort of 42 Filipino colorectal cancer patients who were tested for MMR.

The dMMR rate of 7.14% in this study is lower than the rates reported in Western cohorts, where the prevalence ranges from 10% in early-stage colorectal cancer and to approximately 4-5% in metastatic cases.[7] In large, pooled studies, the overall prevalence is estimated at 11.7%.[8] This discrepancy may be attributed to the predominance of left-sided tumors in our sample and a potentially lower burden of hereditary syndromes such as Lynch syndrome in Filipinos. In clinical practice, the low rate of dMMR implies that immunotherapy based on this biomarker may apply only to a small population of Filipino colorectal cancer patients. This necessitates the use of broader biomarker panels, such as BRAF and KRAS, to identify additional candidates for immune checkpoint inhibitors.

Consistent with findings in the literature, the 3 dMMR in this study was identified in tumors located in the cecum, descending colon, and rectum. No cases were observed in the sigmoid, transverse, or ascending colon. This supports the established pattern that dMMR and MSI-H are more common in right-sided tumors due to unique molecular pathways involving hypermethylation and BRAF mutations.[9,10] The low prevalence of dMMR in our study may also be due to the small sample size for right-sided cases, since only two patients in the cohort have cecal or ascending tumors.

All three dMMR cases are seen among male patients, and dMMR patients were relatively younger than MMR-proficient cases (mean age 45.7 vs. 63.1 years). This is consistent with the data showing that dMMR is more common in early-onset colorectal cancer and that male sex may be associated with certain MSI-H subtypes.[11] The only poorly differentiated tumor in our cohort was also dMMR, which is consistent with studies that exhibit strong associations between MSI-H and poorly differentiated histology, mucinous features, and increased immune cell infiltration.[12–14] Although histologic data were limited, the trend supports the use of histomorphologic features as a basis for MMR testing in low-resource settings.

The study has some limitations. First, the characteristics of patients included in this study may differ from those presenting in other institutions, which limits the generalizability of the results. Moreover, not all colorectal cancer cases seen in our institution undergo MMR testing since this was based on the physician's discretion and the patient's decision. Due to the high cost of MMR testing, not all patients can afford this procedure, which may potentially introduce selection bias. Second, due to the low sample size, the prevalence of dMMR is imprecise as evidenced by the wide 95% CI. Third, due to the retrospective nature of this study, completeness of information cannot be ascertained, leading to information bias. In this study, not all patients had data on histologic grade, particularly those who underwent biopsy only. Fourth, right-sided tumors were underrepresented, possibly underestimating the true prevalence of dMMR.

Despite these limitations, the study represents one of the few Filipino colorectal cancer cohorts with biomarker data and lays the foundation for future multicenter studies with expanded molecular testing.

CONCLUSION

This study provides one of the first local analyses of MMR status in colorectal cancer patients in the Philippines. The local data shows that dMMR is relatively uncommon in this population, and with a predominance of left-sided tumors. This implies potential benefit from immunotherapy even in MMR-proficient cases. Tumor location and histologic grade are the key features that influence the expression of these biomarkers. These findings further highlight the need for broader molecular profiling and biomarker testing as part of routine care, especially in low- to middle-income settings where funds and treatment access may be limited. Larger, multicenter studies are warranted to validate these preliminary findings and guide future clinical decision-making.

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STATEMENT OF AUTHORSHIP

Both authors certified fulfillment of ICMJE authorship criteria.

DATA AVAILABILITY STATEMENT

No datasets were generated or analyzed for this study.

AUTHOR DISCLOSURE

Both authors declared no conflict of interest.

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