DOI:10.31557/APJCB.2025.10.3.713

RESEARCH ARTICLE

Relationship Between Missmatch Repair Protein Expression and Clinicopathological Features of Colorectal Cancer Patients

Muliani[1], Syakib Bakri[1], Muhammad Luthfi Parewangi[1], Arifin Seweng[2], Andi Makbul Aman[1], Rahmawati Minhajat[1]

[1]Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. [2]Department of Biostatistic, Faculty of Public Health, Hasanuddin University, Makassar, Indonesia.

Abstract

Background: The expression of Mismatch Repair (MMR) genes is a crucial mechanism in the pathogenesis of Colorectal Cancer (CRC). Clinicopathological characteristics stratified by MMR status can guide appropriate therapeutic strategies for patients. This study aimed to systematically review the relationship between clinicopathological characteristics and MMR status in CRC patients. **Methods:** A literature review was conducted, searching the PubMed, ScienceDirect, and Google Scholar databases for retrospective studies published within the last five years. The search strategy utilized a combination of keywords: ("Microsatellite Instability" OR "Gene Mutation" OR "Mismatch Repair") AND ("Colorectal Cancer" AND "Clinicopathology"). Relevant retrospective articles were selected for analysis. **Results:** A total of eight retrospective studies were included in this review. Consistently, tumors in patients with deficient MMR (dMMR) CRC exhibited larger sizes compared to those with proficient MMR (pMMR). No significant association was found between the total number of lymph nodes and MMR status. Inconsistent findings were reported regarding the association between MMR status and histological type, differentiation grade, tumor location, lymphovascular invasion (LVI), tumor stage, and lymph node metastasis. Despite these inconsistencies, the overall profile indicates that dMMR CRC is often associated with adverse histological features (e.g., poor differentiation and LVI) yet paradoxically presents at an earlier stage with low metastatic potential. **Conclusion:** CRC with dMMR status presents a paradoxical clinicopathological profile. It is often histologically aggressive yet frequently localized, leading to a better prognosis in non-metastatic stages. A thorough understanding of these characteristics is essential for accurate risk stratification and for tailoring therapeutic strategies for patients with CRC.

Keywords: Gene expression- clinicopathology- colorectal cancer- mismatch repair

Asian Pac J Cancer Biol, **10 (3)**, 713-717

Submission Date: 07/12/2025 Acceptance Date: 08/24/2025

Introduction

Colorectal cancer (CRC) is a malignancy originating from the epithelial lining of the colon and rectum mucosa [1-3]. According to Globocan 2023 data, CRC remains the third most common cancer globally and ranks second in terms of mortality. In 2020 alone, an estimated 1.9 million new CRC cases were diagnosed, leading to over 930,000 deaths worldwide [1]. Approximately 12%–15% of CRCs exhibit mismatch repair (MMR) deficiency [4].

MMR deficiency (dMMR) is a critical mechanism of carcinogenesis, primarily responsible for microsatellite instability (MSI). MSI arises from the accumulation of small insertions or deletions that frequently occur during the replication of short, repetitive DNA sequences [5]. Tumors with dMMR typically show a loss of expression of one or more proteins essential for MMR gene function, leading to impaired DNA replication error repair and increased genomic instability [6]. While mutations in MMR genes are strongly associated with MSI and can influence chemotherapy response, CRCs with high MSI often exhibit resistance to conventional chemotherapy [7]. Conversely, dMMR CRC has demonstrated favorable responses to immune checkpoint inhibitors [4]. Therefore,

Corresponding Author:
Dr. Muliani
Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia.
Email: muliani.awal@gmail.com

understanding the MMR status of a tumor is crucial for determining appropriate therapeutic strategies in CRC patients.

Understanding the relationship between MMR gene expression status and the clinical and histopathological characteristics of tumors can provide profound insights into the pathogenetic mechanisms of CRC. Such understanding can serve as a foundational basis for developing more effective therapeutic and diagnostic strategies, ultimately improving patient prognosis through a more personalized approach to CRC management. This highlights critical questions regarding the interplay between MMR gene expression and CRC's clinicopathological features. Therefore, this article aims to review the clinicopathological characteristics of CRC in relation to its MMR gene expression status.

Materials and Methods

This literature review focused on research published within the past five years, specifically examining the clinicopathological relationship with MMR gene expression in CRC patients. A retrospective study design was chosen for this review due to its high level of evidence in prognostic studies.

A systematic literature search was conducted across three electronic databases: PubMed, ScienceDirect, and Google Scholar. The search strategy employed the following keywords: "Colorectal Cancer," "Microsatellite Instability" OR "Mismatch Repair," "Gene Expression," and "Clinicopathology."

The inclusion criteria for this review were as follows: studies published in the last five years, clinical studies, studies involving a population sample of CRC patients comparing dMMR and MMR proficient (pMMR) and studies exploring the association between clinicopathology and MMR status in CRC. Exclusion criteria included: studies that did not have full text availability and studies that did not meet the required variables in the study.

Results

These results were obtained from 8 articles with a retrospective study design that compared clinicopathological parameters between dMMR and pMMR groups (Table 1). The results of the literature review showed that tumor location was significantly associated with MMR status in 4 studies [8-11], but 2 studies reported non-significant results [12, 13]. Several lymph nodes were consistently reported to be not significantly associated with MMR status in CRC in two studies [8, 14]. Tumor size was consistently reported to be significantly associated with MMR status in 4 studies [9, 13-15]. Inconsistent results were reported for histological type, with 4 articles reporting significant results associated with MMR status [10, 13-15], however 1 article reported no significant result [12]. Tumor stage was found to be significantly associated with MMR status in 5 articles [8, 11, 13-15], but no significant results in 2 articles [9, 12]. Lymph node metastasis was significantly associated with MMR status reported in 3 studies [9, 10, 13] and 1 study stated there was no significant result [8]. Differentiation grade was reported to be significantly associated with MMR status in 4 studies [8, 9, 13, 14], but 2 studies reported non-significant results [10,12]. Lymphovascular invasion (LVI) was reported to be significantly associated with MMR status and vice versa in 1 study [9, 12].

Discussion

This literature review revealed consistent findings regarding the relationship between clinicopathological features and MMR status concerning lymph node count and tumor size. Specifically, the number of lymph nodes consistently showed no significant correlation with MMR status, whereas tumor size was consistently and significantly associated with it. However, the relationship between MMR status and other parameters including histological type, lymph node metastasis, tumor stage, differentiation grade, tumor location, and LVI yielded inconsistent results across the reviewed studies. Despite this variability, the majority of the articles indicated a significant relationship between these clinicopathological parameters and MMR status in CRC.

The study of Abadi et al. reported that the average number of lymph nodes in tumors was significantly higher in dMMR tumors compared to pMMR tumors. They also observed that LVI and angiovascular invasions were more frequent in dMMR tumors [8]. These findings align with those by Dogan et al., who similarly found that the mean number of reactive and total lymph nodes harvested was greater in CRC cases with dMMR than in those with pMMR [9]. Dogan et al. further noted that more lymph nodes were harvested from right-sided tumors compared to left-sided tumors, attributing this difference to structural variations in the anatomy of blood vessels and lymphatics [9]. This observation is supported by Rios-Valencia's study, which frequently found dMMR in right-sided colon tumors [11]. In contrast, Abadi et al. indicated that dMMR tumors are more prevalent in the proximal colon, while pMMR tumors are most frequently found in the distal colon [8].

In the study of Dogan et al. stated that mucinous histology, Crohn-like inflammatory reaction, and TIL cells were stated as strong predictors of MSI. Tumor diameter also tended to be higher in patients with dMMR [9]. Similar results were reported by Zannier et al. that CRC with dMMR was more frequently of the mucinous histotype, characterized by a higher grade (G3-G4) and by a heavier intra- and peri-tumor inflammatory infiltrate [14]. Compared with pMMR group, the proportion of mucinous adenocarcinoma, larger mean tumor diameter, mostly poor tumor differentiation was significantly higher in dMMR as well as reported in other studies [13].

The results of this review indicate that dMMR is associated with poor prognosis in CRC, especially related to larger tumor size and poor histopathology, differentiation, and LVI. This is because dMMR is associated with the main mechanism of carcinogenesis.

Table 1. Clinicopathological Features of CRC based on MMR gene mutation status

Author (Year)	Location	Design	Sample	Clinicopathology variable	Results
Mao et al. (2024) [13]	Bangladesh	Multicenter retrospective study	CRC patients dMMR: 237 pMMR: 1792	TNM stage, Histological type, lymph node metastasis, differentiation grade, tumor location and maximum tumor diameter.	TNM stage, Histological type, lymph node metastasis, differentiation grade, tumor location and maximum tumor diameter were significantly associated with MMR status but not tumor location.
Abadi et al. (2021) [8]	Iran	Retrospective study	153 CRC Adenocarcinoma dMMR: 25 pMMR: 128	Number of lymph nodes, Tumor location, TNM stage, differentiation grade, lymphovascular invasion (LVI).	Differentiation grade, TNM stage, and tumor location were significantly associated with MMR status but not with several lymph nodes and LVI.
Dogan et al. (2024) [9]	Turki	Retrospective study	200 CRC dMMR: 24 pMMR: 176	Tumor size, tumor stage, lymph node metastases, LVI, tumor location, differentiation grade	Tumor size, lymph node metastases, tumor location, and differentiation grade were significantly associated with MMR status but not tumor stage and LVI.
Shiraj-Um-Mahmuda et al. (2023) [12]	Bangladesh	Cross-sectional study	50 CRC dMMR: 16 pMMR: 34	Tumor location, mucinous differentiation, histological type, tumor stage, LVI.	Mucinous differentiation and LVI were significantly associated with MMR status but not with tumor location, histological type, or tumor stage.
Yu et al. (2024) [10]	China	Retrospective study	CRC patients dMMR: 136 pMMR: 341	Lymph node metastases, histological type, tumor location, and differentiation grade.	Tumor location, histological type, and lymph node metastases were significantly associated with MMR status but not differentiation grade.
Rios-Valencia et al. (2022) [11]	Mexico	Retrospective study	144 CRC dMMR: 39 pMMR: 105	Tumor location and tumor stage.	Tumor stage and tumor location were significantly associated with MMR status.
Zannier et al. (2023) [14]	Italy	Retrospective study	1037 CRC dMMR: 194 pMMR: 843	Histological type, tumor stage, number of lymph node, tumor size, and differentiation grade.	Histological type, tumor stage, differentiation grade, and tumor size were significantly associated with MMR status but not with the number of lymph nodes.
Zhang et al. (2024) [15]	USA	Retrospective study	1018 CRC dMMR: 111 pMMR: 636	Tumor size, histological type, tumor stage	Tumor size, histological type, and tumor stage are significantly related to MMR status.

MMR deficiency is responsible for MSI, which is caused by the accumulation of deletions or small insertions or small insertions that often occur during replication of short sequences [5]. In cancers with MSI-High (MSI-H), small insertions/deletions result in frameshift mutations within the repeat tract in the coding region of tumor suppressor genes or oncogenes, which further contribute to tumorigenesis. Microstellite High CRC, results in Bax inactivation and inhibition of apoptosis and leads to cancer progression [16, 17].

In relation to tumor stage, in the study of Rios-Valencia et al., it was stated that patients with dMMR tumors were more frequently found in CRC patients with stages I-III [11]. Similar results were reported in the study by Zannier et al. that dMMR was more frequently found in CRC patients with lower stages [14]. Mao et al.'s study supports these results by stating that compared with the pMMR group, the proportion of stage I and II CRC patients in the dMMR group was higher [13].

According to the American Joint Committee on Cancer, right colon cancer prognosis is unfavorable in stages III and IV, with no improvement in stages I and II. Additionally, a multicenter study indicated unchanged prognosis for patients with MSI-H metastatic CRC. While MSI-H does not affect stage III CRC prognosis, it enhances progression-free survival in stage IV CRC. MSI-H is associated with favorable outcomes in early-stage CRC [13]. The elevated incidence of dMMR in early-stage tumors indicates a potential protective effect of dMMR [18]. The improved prognosis for dMMR patients in stage II is primarily attributed to a beneficial immune response. This is linked to the correlation between the density of infiltrating CD3+ and CD8+ lymphocytes and dMMR [19].

Based on metastasis, the presence of metastatic lymph nodes was found to be more common in pMMR patients compared to dMMR [9]. Mao et al.'s study supports these results by stating that vascular invasion and lymph node metastasis are less frequent in dMMR compared to pMMR [13]. pMMR is more likely to develop early metastasis, the underlying mechanism of which is still unclear. Nevertheless, downregulated miR-6511b-5p emerges as a potential biomarker for diagnosing pMMR CRC, particularly in metastatic instances, and is associated with unfavorable prognoses in CRC patients, though this assertion lacks robust empirical support [20].

Some research results obtained inconsistent results that may be related to differences in the number of research samples. In addition, the theory of tumor heterogeneity explains that there are other factors such as genetics and the environment also affect the MMR mutation status.

In conclusion, dMMR CRC presents a distinct clinicopathological profile from its pMMR counterpart, stemming from its unique molecular biology. Although generally associated with a better prognosis, certain parameters including tumor size, histological type, differentiation, LVI, stage, and metastasis can indicate a poor prognosis within the dMMR subgroup. Understanding these characteristics is clinically crucial for guiding therapeutic decisions. Further research is necessary to resolve inconsistencies regarding the correlation between MMR status and the clinicopathological features of CRC.

Acknowledgments

None

Conflict of interest statement

No ethical approval and patient consent are required because all analyses were based on previous published studies.

Ethics approval and consent to participate

Not applicable.

Informed consent

Not applicable

Patient consent for publication

Not applicable

Author contributions

Conceptualisation: MLN, SB, MLP, AS, RM, and AMA; Data collection and analysis: MLN and RM; Writing: MLN; Supervision: SB, MLP, AS, and AMA; Editing: MLN; All authors read and approved final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. Lancet (London, England). 2019 Oct 19;394(10207):1467-1480. https://doi.org/10.1016/S0140-6736(19)32319-0
2. Dharmaji AB, Kusuma MI, Sampetoding S, Labeda I, Uwuratuw JA, Syarifuddin E, Hendarto J, Faruk M. Analysis of colorectal cancer survival rate at a single institution. Medicina Clínica Práctica. 2021 04 01;4:100232. https://doi.org/10.1016/j.mcpsp.2021.100232
3. Minhajat R, Benyamin AF, Miskad UA. The Relationship Between Histopathological Grading and Metastasis in Colorectal Carcinoma Patients. Nusantara Medical Science Journal. 2020;:51-60. https://doi.org/10.20956/nmsj.v5i2.8786
4. Yamada A, Yamamoto Y, Minamiguchi S, Kamada M, Sunami T, Ohashi S, Seno H, Kawada K, Muto M. Clinicopathological and molecular characterization of deficient mismatch repair colorectal cancer. Human Pathology. 2022 Dec;130:1-9. https://doi.org/10.1016/j.humpath.2022.09.005
5. Ye M, Ru G, Yuan H, Qian L, He X, Li S. Concordance between microsatellite instability and mismatch repair protein expression in colorectal cancer and their clinicopathological characteristics: a retrospective analysis of 502 cases. Frontiers in Oncology. 2023;13:1178772. https://doi.org/10.3389/fonc.2023.1178772
6. Li C, Liu F, Huang D, Wu Y, Wang Z, Xu Y. The correlation between DNA mismatch repair status and the clinicopathological and molecular features of Chinese sporadic colorectal cancer. Translational Cancer Research. 2020 01;9(1):137-144. https://doi.org/10.21037/tcr.2019.11.24
7. Taieb J, Svrcek M, Cohen R, Basile D, Tougeron D, Phelip J. Deficient mismatch repair/microsatellite unstable colorectal cancer: Diagnosis, prognosis and treatment. European Journal of Cancer (Oxford, England: 1990). 2022 Nov;175:136-157. https://doi.org/10.1016/j.ejca.2022.07.020
8. Abadi ZMA, Asl DH, Rahmani B, Peimani A, Dodaran MS, Rad FSAMIEE. the Clinicopathologic Features of Colorectal Adenocarcinoma With Respect To Mismatch Repair Genes and Kras Status: a Retrospective Study. World Cancer Res J. 2021;8:1-11. https://doi.org/10.32113/wcrj_20211_1850
9. Doğan M, Kılıç M, Tatlı Doğan H. The Relationship Between DNA Mismatch Repair Status and Clinicopathologic Characteristics in Colon Cancer. The Turkish Journal of Gastroenterology: The Official Journal of Turkish Society of Gastroenterology. 2024 08 12;35(9):718-725. https://doi.org/10.5152/tjg.2024.23366
10. Jinchuan YU, Xuexue X, Weiying HE, Yanan Y, Junqiu YUE. Clinicopathological Characteristics of Colorectal Cancer Patients with Different Mismatch Repair Statuses and Their Correlation with KRAS/NRAS/BRAF Gene Mutations. Cancer Research on Prevention and Treatment. 2024 Nov 25;51(11):937-944. https://doi.org/10.3971/j.issn.1000-8578.2024.24.0156
11. Rios-Valencia J, Cruz-Reyes C, Galindo-García TA, Rosas-Camargo V, Gamboa-Domínguez A. Mismatch repair system in colorectal cancer. Frequency, cancer phenotype, and follow-up. Revista De Gastroenterologia De Mexico (English). 2022;87(4):432-438. https://doi.org/10.1016/j.rgmxen.2022.05.017
12. Shiraj-Um-Mahmuda S, Begum F, Rahman M, Islam T, Shabnam U, Afroz A, et al. DNA Mismatch Repair Deficiency in Colorectal Adenocarcinoma by a Two-Antibody Immunohistochemical Approach and its Association with Clinicopathological Features among Bangladeshi Patients. Ann Hematol Oncol. 2023;10.. https://doi.org/10.26420/annhematoloncol.2023.1426
13. Mao J, He Y, Chu J, Hu B, Yao Y, Yan Q, Han S. Analysis of clinical characteristics of mismatch repair status in colorectal cancer: a multicenter retrospective study. International Journal of Colorectal Disease. 2024 07 05;39(1):100. https://doi.org/10.1007/s00384-024-04674-z
14. Zannier F, Angerilli V, Spolverato G, Brignola S, Sandonà D, Balistreri M, Sabbadin M, et al. Impact of DNA mismatch repair proteins deficiency on number and ratio of lymph nodal metastases in colorectal adenocarcinoma. Pathology, Research and Practice. 2023 03;243:154366. https://doi.org/10.1016/j.prp.2023.154366
15. Zhang P, Bakhtar O, Wixom C, Cox B, Lee J, Sadeghi S, Clement A, Kabakibi L, Schwab M. Differences in Prevalence of Colorectal Carcinoma by Gender and Marital Status and Expression of DNA Mismatch Repair Proteins. International Journal of Translational Medicine. 2024 09;4(3):584-594. https://doi.org/10.3390/ijtm4030040
16. Bataritoja A. Hubungan Letak Tumor dan Klasifikasi TNM dengan Gambaran Histopatologi Pada Pasien Kanker Kolorektal di RS Wahidin Sudirohusodo Tahun 2018. 2020.
17. Jung J, Kang Y, Lee YJ, Kim E, Ahn B, Lee E, Kim JY, et al. Comparison of the Mismatch Repair System between Primary and Metastatic Colorectal Cancers Using Immunohistochemistry. Journal of Pathology and Translational Medicine. 2017 03;51(2):129-136. https://doi.org/10.4132/jptm.2016.12.09
18. Mei W, Mi M, Qian J, Xiao N, Yuan Y, Ding P. Clinicopathological characteristics of high microsatellite instability/mismatch repair-deficient colorectal cancer: A

narrative review. Frontiers in Immunology. 2022;13:1019582. https://doi.org/10.3389/fimmu.2022.1019582
19. Hestetun KE, Rosenlund NB, Stanisavljević L, Dahl O, Myklebust MP. Stage-dependent prognostic shift in mismatch repair-deficient tumors: Assessing patient outcomes in stage II and III colon cancer. Frontiers in Oncology. 2022;12:853545. https://doi.org/10.3389/fonc.2022.853545
20. Sun J, Ye L, Shi Y, Wang X, Zhao X, Ren S, Fan J, Shao H, Qin B. MiR-6511b-5p suppresses metastasis of pMMR colorectal cancer through methylation of CD44 by directly targeting BRG1. Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2022 Oct;24(10):1940-1953. https://doi.org/10.1007/s12094-022-02845-4