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REVIEW ARTICLES

Survival of colorectal cancer patients based on mismatch repair gene mutation status

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ABSTRACT

Background: Global Cancer Observatory 2020, colorectal cancer caused 19.3 million new cases and 10 million deaths worldwide. The one of pathogenesis of colorectal cancer involves the presence of mismatch repair (MMR) gene mutations. Therefore, guidelines recommend adjusting the treatment for colorectal cancer based on the MMR gene mutation status. This approach combines targeted therapy with conventional chemotherapy regimens.

Methods: Method focuses on research from the past five years. Retrospective cohort studies were chosen due to their high level of evidence in prognostic research. The literature search was conducted using the keywords colorectal cancer and microsatellite instability or mismatch repair, gene mutation and survival or prognosis in three electronic databases, PubMed, ScienceDirect, and Scopus.

Results: Colorectal cancer showed that deficient MMR (dMMR) status was associated with better survival outcomes compared to proficient MMR (pMMR) in stage II and III colorectal cancer in

the context of treatment. Adjuvant chemotherapy was more effective in the survival of stage III colorectal cancer with dMMR status. Adjuvant chemotherapy and targeted therapy significantly improved the survival of colorectal cancer patients with dMMR status. Colorectal cancer with dMMR has a lower risk of distant metastatic but stage IV colorectal cancer with dMMR/MSI, did not show any prognostic advantage.

Conclusion: Colorectal cancer with pMMR status showed lower survival rates compared to those with dMMR status. Neoadjuvant chemotherapy and targeted therapy to stage II and III patients with dMMR/MSI status was associated with improved disease-free survival compared to pMMR/MSS patients.

Keywords: survival, mismatch repair gene mutation, colorectal cancer

Abbreviations:

dMMR: Deficient Mismatch Repair

MMR: Mismatch Repair,

MSI: Microsatellite Instability

pMMR: Proficient Mismatch Repair

INTRODUCTION

Colorectal cancer, a malignancy affecting the colon, has an etiology that is still not fully understood. It arises from the accumulation of genetic and epigenetic instability, which transforms normal colonic mucosal epithelial cells into malignant cells [1]. Global Cancer Observatory (GLOBOCAN) 2020 report, there were approximately 19.3 million new cancer cases and 10 million cancer related deaths globally, with colorectal cancer accounting for 1.93 million new cases (10.7%) and 0.94 million deaths (9.4%). In Indonesia, the incidence of colorectal cancer is estimated to reach 34,189 new cases (8.6%), with around 61% of patients coming in advanced stages (stages III and IV), thus requiring complex therapeutic modalities such as chemotherapy, targeted therapy, or immunotherapy [2,3]. Regarding genetic classification, The Cancer Genome Atlas (TCGA) categorizes colorectal cancer into two groups, namely tumors with microsatellite instability (MSI) due to mismatch repair (MMR) gene defects (16%) and non-hypermutated

microsatellite stable (MSS) tumors (84%), which often contain mutations in the adenomatous polyposis coli (APC) and Kirsten Ras (KRAS) genes [4,5]. In line with this classification, guidelines from the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) recommend that colorectal cancer treatment be adjusted to genetic mutation status, including MMR gene mutations. This approach combines targeted therapies, such as nivolumab, ipilimumab, or pembrolizumab, with conventional chemotherapy regimens such as FOLFOX, XELOX, or FOLFIRI. However, the application of MMR mutation status testing and appropriate therapy selection have not been fully optimized. This raises critical questions about the relationship between MMR gene mutation status and colorectal cancer patient survival, as well as the need for appropriate genetic testing to improve treatment efficacy. Therefore, this article aims to review patient survival in relation to MMR gene mutation status, providing deeper insights to improve the standard of colorectal cancer management in line with international guidelines [6,7].

METHODS

We conducted a literature review focusing on studies from the past five years, with a specific emphasis on the prognostic impact of mismatch repair (MMR) gene mutations in colorectal cancer patients. For this review, retrospective cohort studies were chosen due to their high level of evidence in prognostic research.

The inclusion criteria for this review were as follows: (a) studies published within the last five years, (b) inclusion of clinical studies, systematic reviews, or meta-analyses, (c) studies involving a sample population of colorectal cancer patients, (d) exploration of patient survival outcomes, and (e) analysis of mismatch repair genes. Conversely, exclusion criteria included (a) studies lacking full-text availability and (b) studies published in languages other than English or Indonesian.

Literature search was conducted using the keywords Colorectal Cancer, Microsatellite Instability or Mismatch repair, Gene Mutation and Survival or prognosis in three electronic databases, namely, PubMed, ScienceDirect, and Scopus.

RESULTS

In Table 1, an analysis of various retrospective cohort studies from the past five years examines the relationship between MMR protein expression and clinical outcomes in colorectal cancer. These studies consistently demonstrate that deficient MMR (dMMR) status is associated with improved survival outcomes compared to proficient MMR (pMMR) in stages II and III colorectal cancer in terms of treatment. Heide et al, reported a significant survival, average of 9 months longer survival for dMMR patients compared to pMMR patients with metastatic colorectal cancer. Shaib et al, found that adjuvant chemotherapy was more effective in prolonging overall survival for stage III colorectal cancer patients with dMMR status, supporting the prognostic value of MMR status in tailoring treatment plans. Additionally, Kang et al, observed that patients with MSI high status in stage II colorectal cancer had better prognosis with adjuvant chemotherapy, emphasizing the importance of MMR status consideration in intermediate risk cases [8-10].

Table 1. Survival of Colorectal Cancer patient based on Mismatch Repair (MMR) Gene Mutation Status

Author	Location and Year	Type of Study	Type and Stage of Cancer	Sample Size	Predictive Biomarker	Analysis Method	Outcome
Heide et al [8]	United States (2023)	Retrospective cohort	CRC, Stage IV	124,587	dMMR and pMMR	IHC	The average survival is 8.9 months shorter for patients with dMMR compared to pMMR in young adults with metastatic colorectal cancer.
Shaib et al [9]	United States (2020)	Retrospective cohort	CRC, Stage III	2,384	MSI and dMMR	IHC and PCR	The adjuvant chemotherapy is associated with improved overall survival in stage III colorectal cancer patients with dMMR/MSI-H.
Kang et al [10]	South Korea (2021)	Retrospective cohort	CRC, Stage II	5774	MSI-H and dMMR	IHC and PCR	In stage II colorectal cancer patients with MSI-L/MSS or pMMR, adjuvant chemotherapy

							correlates with better disease-free survival but does not impact overall survival.
Wu et al [11]	China (2022)	Retrospective cohort	CRC, Stage II/ III	854	dMMR (MLH1, MSH2, MSH6, and PMS2) and MSI	IHC and PCR	Patients with dMMR exhibit a poorer response to chemotherapy compared to those with pMMR, in terms of tumor regression. Additionally, dMMR serves as a good prognostic marker for disease free survival in stage II and III patients following neoadjuvant therapy.
Saberzadeh-Ardestani [12]	United States (2023)	Retrospective cohort	mCRC, Not mentioned of stage	41	dMMR and MSI-H	IHC and PCR	This cohort study found a clinically significant extension of survival in elderly patients with metastatic colorectal cancer and dMMR status treated with first-line pembrolizumab in clinical practice.
Zwart et al [13]	Denmark (2023)	Retrospective cohort	mCRC, Stage I-IV	1183	pMMR, dMMR, and MSI	IHC and PCR	Patients dMMR demonstrate better recurrence-free survival than those with pMMR colorectal cancer, with an overall survival of 33.3 months for dMMR in metastatic colorectal cancer, compared to 43.5 months for pMMR, primarily due to survival duration.

Ye et al [14]	China (2020)	Retrospective cohort	CRC, Stage I-IV	1015	pMMR and dMMR	IHC	Rectal cancer patients with dMMR tumors have a better prognosis when treated with neoadjuvant chemotherapy, while neoadjuvant chemotherapy and radiotherapy benefit patients with stage III disease and pMMR tumors.
Zhang et al [15]	China (2022)	Retrospective cohort	CRC, Stage III	1365	dMMR and pMMR	IHC	Patients with dMMR status, prognosis does not differ significantly from those with pMMR during the first postoperative year. Additionally, elderly patients aged ≥ 75 years do not gain significant survival benefits from postoperative chemotherapy.

CRC: Colorectal cancer; mCRC: Metastatic colorectal cancer; dMMR: deficient mismatch repair; pMMR: proficient mismatch repair; MSI: Microsatellite unstable; IHC: Immunohistochemistry; PCR: polymerase chain reaction

DISCUSSION

Diagnosis colorectal cancer in early stage through patient history may lack distinctive symptoms. Symptoms often emerge as the disease progresses to advanced stages, including changes in bowel habits, alterations in stool characteristics (such as blood or mucus in stool), abdominal pain or discomfort, and the presence of an abdominal mass. Systemic symptoms like anemia, weight loss, fatigue, and fever can also be observed in colorectal cancer patients. Genetic factors contribute to approximately 6% of colorectal cancer cases, necessitating a detailed family

history inquiry regarding Lynch syndrome and familial adenomatous polyposis. Physical examinations include an assessment of the general condition, inspection of superficial lymph nodes throughout the body (particularly the inguinal and supraclavicular nodes), abdominal examination through inspection, percussion, palpation to check for intra-abdominal masses, and auscultation to evaluate bowel sounds. A rectal examination is routinely performed to assess the size, shape, texture, extent of wall involvement, distance of the tumor's lower margin from the anus, tumor invasion into the intestine, its relationship with surrounding organs, and possible invasion of the pelvic floor, while noting any blood on the glove as a clinical sign of colorectal cancer [16].

Microsatellite instability, CpG island methylator phenotype, and chromosomal instability are the three main routes that contribute to the genomic instability that underlies the etiology of colorectal cancer [1,4]. About 85% of adenocarcinoma transitions involve chromosomal instability, which is typified by loss of heterozygosity on chromosome 18q (18q LOH), oncogene activation (K-RAS and BRAF), and tumor suppressor gene inactivation (APC and TP53). These factors can all contribute to the development of tumors. Hypermethylation of CpG island sites, frequently coupled with DNA hypomethylation associated with genomic instability and chromosomal abnormalities, is indicative of epigenetic instability in colorectal cancer. While CpG islands found in gene promoter regions are typically unmethylated, the majority of CpG sites in normal cells are substantially methylated. However, hypermethylation in promoter regions can cause tumor suppressor genes to become inactive once cancer has started, which can result in unchecked cell development [4].

Guidelines chemotherapy of National Comprehensive Cancer Network 2022 propose chemotherapy for colorectal cancer [6,7]:

- Tis, T1N0M0, T2N0M0, T3-4N0M0 (MSI-H/dMMR): Observation is recommended, or consider treatment with capecitabine (6 months) or 5-FU/leucovorin (6 months) for T4 cases with high risk.
- T3N0M0 (MSS/pMMR and not high risk): Observation is recommended, or consider treatment with capecitabine or 5-FU/leucovorin for 6 months.
- T3N0M0 with high recurrence risk or T4N0M0 (MSS/pMMR): Treatment options include capecitabine or 5-FU/leucovorin, with FOLFOX or CAPEOX as the preferred options.

- T1-3 N1 (low risk stage III): The preferred regimen is CAPEOX (3–6 months) or FOLFOX (6 months), with alternative options of capecitabine (6 months) or 5-FU (6 months).
- T4 N1-2, anyT N2 (high risk stage III): The preferred regimen is CAPEOX (3–6 months) or FOLFOX (6 months), with alternatives of capecitabine (6 months) or 5-FU (6 months).

Guidelines recommend basing treatment decisions on mutation status, including MMR gene mutations, to optimize therapy. Targeted therapies, such as nivolumab and ipilimumab or pembrolizumab, may be combined with conventional chemotherapy regimens, including FOLFOX (oxaliplatin, 5-FU, and leucovorin), XELOX (capecitabine and oxaliplatin), and FOLFIRI (oxaliplatin, 5-FU, and irinotecan), to enhance treatment efficacy [6,7].

Mismatch repair gene play an important role in cell damage, apoptosis, and recombination. MMR genes have been identified such as mutL homolog 1 (MLH1), mutS homolog 2 (MSH2), mutS homolog 6 (MSH6), and postmeiotic segregation increased 2 (PMS2). Immunohistochemical testing of MMR genes is a relatively simple and rapid method for assessing the expression of MLH1, MSH2, MSH6, and PMS2 proteins, as illustrated in Figure 1. Deficient MMR tumors typically show loss of expression of one or more of these proteins, indicating that the MMR genes are unable to repair DNA replication errors, thereby increasing the risk of developing cancer. Loss of protein expression MSH6 and MSH2 show damaged of MSH2. Thus, if one or more proteins show loss of expression, then they are classified as deficient MMR. Otherwise, they are considered proficient pMMR [16,17].

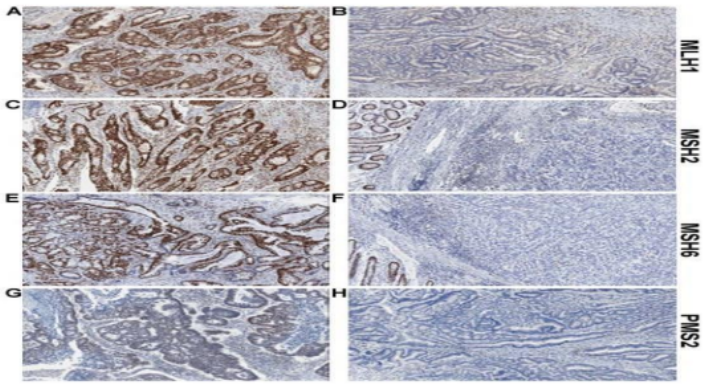

Figure 1. (A) Immunohistochemistry examples for MLH1 proteins show positive staining (B) shows the negative staining of MLH1, but positive staining control in stromal lymphocytes (C) shows positive staining for MSH2, while (D) depicts the absence of MSH2 in tumor epithelium,

with normal colonic epithelium shows positive staining (E) shows positive staining for MSH6, while (F) in tumor epithelium loss of MSH6 with positive staining in adjacent normal colonic epithelium (G) depicts positive staining for PMS2 (H) shows the negative of PMS2 in tumor epithelium, with positive internal control staining in stromal [16].

The above studies indicate a correlation between MMR gene mutation status and survival. Several studies and systematic reviews suggest that MMR status is linked to prognosis. Adjuvant chemotherapy and targeted therapies significantly enhance survival in colorectal cancer patients with dMMR/MSI status. Incidence of 20% in stage II, 11% in stage III, and 3.5% in metastatic disease, commonly seen in disease colorectal cancer with dMMR/MSI status. This pattern suggests that colorectal cancers with deficient MMR or microsatellite instability (MSI) have a reduced tendency for distant metastasis. The prognostic value of dMMR/MSI depends on the immunologic response associated with dMMR/MSI tumors. Increased lymphocytic infiltration with an immune reaction is detected in dMMR/MSI colorectal cancers, enhancing the host's anti-tumor immunity to suppress tumor metastasis. In stage IV colorectal cancer with dMMR/MSI, no prognostic advantage is observed. One study found that the proportion of tumors with MSI instability varied significantly based on primary location: 179 out of 695 (26%) in the right colon, 22 out of 685 (3%) in the left colon, and 3 out of 407 (1%) elsewhere. Disease-free survival is significantly better in dMMR tumors in the proximal colon compared to the distal colon [18,19].

Wang et al. demonstrated that, in early to intermediate stages, patients with MSI-H status generally have a better prognosis than those with microsatellite stable (MSS) or proficient MMR (pMMR) status. This benefit is attributed to a stronger immune response in MSI-H patients, characterized by higher lymphocytic infiltration within the tumor microenvironment [19]. However, in advanced stages (stages III and IV), the favorable impact of MSI-H on survival becomes less clear. While some previous studies support the benefit of MSI-H in prolonging disease free survival (DFS), no significant impact of MSI-H on overall survival (OS) was found in advanced-stage colorectal cancer patients. The researchers speculate that this may be due to the overexpression of immune checkpoint proteins, such as PD-1 and CTLA-4, in advanced-stage MSI-H tumors, which could inhibit an effective immune response against cancer cells [19,20].

CONCLUSIONS

Colorectal cancer patients with proficient MMR (pMMR) gene status show lower survival rates compared to those with deficient MMR (dMMR) status. However, the administration of neoadjuvant chemotherapy and targeted therapy in stage II and III patients with dMMR/MSI mutation status is associated with improved disease-free survival (DFS) compared to pMMR/MSS patients. The authors recommend that colorectal cancer stages III and IV should adhere to the guidelines, where testing for MMR gene mutation status is essential to determine the appropriate chemotherapy regimen.

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Conflict of interest: The author declares no conflict of interest.

Authors' contributions:

TIPA (Concept, Design, Sources, Materials, Data Collection and Processing, Literature Search, Manuscript Writing). SB (Concept, Design, Sources, Supervision, Literature Search), AMA (Concept, Design, Sources, Supervision, Literature Search), RM (Concept, Design, Sources, Supervision, Literature Search), AMLP (Concept, Design, Sources, Supervision, Literature Search), AAZ (Concept, Design, Sources, Supervision, Literature Search).

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TABLES AND FIGURES

NOTE:

Table 1: Survival of Colorectal Cancer patient based on Mismatch Repair (MMR) Gene Mutation Status.

Figure 1 : Examples positive and negative staining of immunohistochemistry for MLH1, MSH2, MSH6, and PMS2 proteins.