Original Article

Mismatch repair deficiency confers worse survival in stage IV colon cancer

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Background: Metastatic colon cancer (MCC) is a debilitating condition with a poor prognosis. Currently, there is limited data that investigates MCC in relation to mismatch repair (MMR) status. The aims of this study are to compare sociodemographic and clinicopathologic features and mortality between patients with MMR-proficient (MMR-P) and MMR-deficient (MMR-D) MCC.

Methods: We performed an 8-year retrospective review of the National Cancer Database (NCDB) to identify patients age ≥18 years with MCC and reported MMR status. Data collection included sociodemographic characteristics, primary tumor sites and histopathologic features, and treatment modalities. Outcomes included 90-day, 180-day, 1-year, and 2-year overall mortality. Bivariate logistic regression and multivariate Cox regression identified differences between MMR-P and MMR-D and identified predictors of mortality, respectively.

Results: A total of 10,922 MCC cases were identified; 8,796 (80.53%) were MMR-P and 2,126 (19.47%) were MMR-D. MMR-D was independently associated with older age at diagnosis, female sex, mucinous adenocarcinoma, medullary carcinoma, and lymph-vascular invasion. MMR-P was independently associated with perineural invasion and left-sided colonic primary tumor predominance. When adjusted for demographics, histology, and treatment modalities, MMR-D was associated with mortality at 180 days, 1 year, and 2 years.

Conclusions: Our study identified several key sociodemographic and clinicopathologic features of MMR-D MCC. MMR-D appears to confer increased overall mortality at 180 days, 1 year, and 2 years after diagnosis in MCC.

Keywords: Metastatic colon cancer (MCC); mismatch repair (MMR); clinical outcomes

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Introduction

Colon cancer (CC) is a common and lethal disease with an estimated 106,590 cases diagnosed annually in the United States whose mortality is strongly correlated with metastatic disease (1-3). The pathogenesis of CC can be outlined according to two distinct pathways: chromosomal instability (CIN), and microsatellite instability (MSI), which differ according to the functionality of their mismatch repair (MMR) systems. During normal DNA replication, MMR genes such as *MSH2*, *MLH1*, *MSH6*, and *PMS2* detect and repair DNA mismatch errors to form corrected DNA strands. CCs that exhibit CIN possess functional MMR systems and are referred to as MMR-proficient (MMR-P), while MSI tumors characteristically exhibit deficits in their MMR systems and are referred to as MMR-deficient (MMR-D).

MMR-P/CIN accounts for approximately 85% of all CCs and is caused by mutations in specific tumor suppressor genes and oncogenes, translating to aneuploidy, loss of heterozygosity, and structural chromosomal changes (4,5). Meanwhile, MMR-D/MSI CCs account for approximately 15% of all CCs; their MSI arises consequent to defective MMR systems rendered unable to repair single nucleotide mismatches (4-6). MMR-D/MSI CCs can manifest via mutations in the germline, as seen in Lynch Syndrome, or as sporadic epigenetic modifications of MMR genes (4,6). Lynch Syndrome comprises roughly 20% of all MMR-D CCs (and roughly 3–5% of all CCs), while the majority (roughly 80%) of MMR-D CCs arise via sporadic epigenetic inactivation of the MMR gene promoters (most commonly, *MLH1*) via DNA hypermethylation in CpG islands via the CpG Island Methylator Phenotype (CIMP) pathway (5,6). Almost 50% of MMR-D CCs are known to harbor v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) mutations (5,7,8).

MMR-D CCs, irrespective of whether in the setting of CIMP or Lynch Syndrome, exhibit distinct pathologic and epidemiologic features. Specifically, MMR-D has been associated with predominance in the proximal colon, poor differentiation, and mucinous histology (5,6). MMR-D is considered a favorable prognostic factor among patients with non-metastatic CC (stages I–III) (8-12), however, its prognostic role in patients with metastatic (stage IV) colon cancer (MCC) remains relatively unknown, and few studies have examined this relationship (8). This consideration is crucial, given that at the earliest diagnosis, distant metastatic disease exists in typically 25% of patients with CC (2,3).

Multiple meta-analyses have established MMR-D's apparent survival-protective effect when compared to MMR-P, however, the vast majority of patients included in these pooled studies had non-metastatic CC, and the relationship between MMR-D and mortality among patients with MCC remains poorly understood (13-15). While the relatively sparse reporting on MMR-D MCC may be explained by the decreased tendency of MMR-D to exhibit lymph node and distant organ metastasis, as noted by Malesci *et al.* (16), targeted analysis of MMR status among patients with MCC is warranted to further understand the disease process and course (16). Thus, the aims of this study are to compare sociodemographic and clinicopathologic features and mortality between MMR-P and MMR-D in patients with MCC. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-387/rc).

Highlight box

Key findings

- Mismatch repair deficiency (MMR-D) manifests with distinct sociodemographic and clinicopathological characteristics in patients with stage IV colon cancer (CC), including older age, female sex, non-Black race, and higher rates of lymph-vascular invasion.
- MMR-D is independent predictor of mortality in patients with stage IV CC.

What is known and what is new?

- MMR-D is a positive prognostic factor in patients with stage I–III CC.
- This study found that MMR-D is an independent predictor of mortality in stage IV CC.

What is the implication, and what should change now?

- MMR-D patients with stage IV CC have distinct sociodemographic characteristics and may disproportionately experience CC screening barriers.
- The higher rates of lymph-vascular invasion seen in patients with MMR-D should be considered when formulating post-operative adjuvant therapeutic approaches for these patients.
- The recent emergence of immune checkpoint inhibitors may improve outcomes for patients with MMR-D.

Methods

Database description

We performed an 8-year [2010–2017] retrospective analysis of the National Cancer Database (NCDB). The NCDB

is jointly sponsored by the American College of Surgeons and the American Cancer Society; it collects data from more than 1,500 Commission on Cancer (CoC) accredited facilities across the United States and Puerto Rico (11). The NCDB is updated with 72% of all new types of cancer diagnoses at the national level with a total of over 40 million records (17). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was exempted from the Institutional Review Board as the NCDB contains no patient-identifying information. The NCDB is publicly available, and acquisition of consent to participate in the study is not applicable.

Patient selection and stratification

We included adult (age ≥18 years) patients diagnosed with stage IV CC between the years 2010-2017 with reported MMR status. The International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) was used to identify patients with stage IV CC. ICD-O-3 histology codes 8140-8263 (adenocarcinoma), 8480-8481 (mucinous adenocarcinoma), 8490 (signet ring cell carcinoma), 8510-8513 (medullary carcinoma), and remaining codes (other) were reported as tumor characteristics. Patients were then stratified into two groups based on MMR status.

Of the 1,088,765 patients with reported CC in the NCDB from 2010–2017, 255,280 were found to have stage IV disease at the time of diagnosis. MSI testing was ordered and reported for 34,438 of these patients. Patients with reported stage IV CC and MMR status were further excluded from the study population if there was missing data regarding patient sociodemographic characteristics, primary tumor locations and characteristics, treatment modalities, and mortality. There were 23,516 patients that did not have reported information regarding one or more of the aforementioned categories, and were excluded from our analysis, yielding 10,922 patients who met inclusion criteria.

Although all 10,922 patients included had confirmed metastatic disease, data on specific metastatic sites was only made available beginning in 2016 in the NCDB which equated to 2,363 patients in our population.

Parameters assessed and outcomes

The following variables were collected from the patient population: sex, age at MCC diagnosis, race, ethnicity, facility location, primary tumor site, distant lymph node involvement, metastatic sites (when applicable), and treatment modalities. Outcomes included 90-day, 180-day, 1-year, and 2-year overall mortality after MCC diagnosis.

Primary tumor sites were encoded as "right colon" if occurring in either the cecum, ascending colon, or hepatic flexure, and as "left colon" if occurring in the splenic flexure, descending colon, sigmoid colon, or rectosigmoid junction.

Statistical analysis

Our results are reported as percentages for categorical variables and as mean ± standard deviation for continuous variables. We used a Chi-squared test to analyze differences between categorical variables and an independent *t*-test for differences between the continuous variables.

A bivariate logistic regression was performed to identify factors independently associated with MMR-D. Variables with a P value <0.1 in the univariate analysis were incorporated into the multivariate model. The model fit was assessed using the Hosme-Lemeshow test, which exceeded 0.05. The tolerance was above 0.1 for all independent variables with a variance inflation factor less than 10.0.

Survival and mortality were assessed using Kaplan-Meier and univariate Cox regression analysis for categorical and continuous variables, respectively. Variables with a P value of <0.1 in the univariate analyses were incorporated in a multivariate Cox regression analysis, including baseline sociodemographic and histopathological features regardless of statistical significance. A P value of less than 0.05 was considered statistically significant. All statistical analyses were performed on the Statistical Package for the Social Sciences software (SPSS, version 26; SPSS, Inc.).

Results

A total of 10,922 MCC cases were identified; 8,796 (80.53%) were MMR-P and 2,126 (19.47%) were MMR-D. The overall mean age at MCC diagnosis was 63.25±12.621 years, 49.7% (n=5,435) were female, and 81.7% (8,928) were White. Patients with MMR-P were more likely to have private insurance (45.4% *vs.* 38.6%, P<0.001) and patients with MMR-D were more likely to have Medicare (48.6% *vs.* 41.2%, P<0.001). The full breakdown of individual sociodemographic and clinicopathologic characteristics associated with MMR-P and MMR-D are summarized in *Tables 1-3*.

For 2,363 patients for whom data on metastatic sites was available, MMR-P was associated with higher rates

Table 1 Patient characteristics

Domain	MMR-P (n=8,796)	MMR-D (n=2,126)	P value
Sex			0.001
Male	4,489 (51.0)	998 (46.9)	
Female	4,307 (49.0)	1,128 (53.1)	
Age of diagnosis (years)	62.79±12.48	65.16±13.01	<0.001
Race			
White	7,155 (81.3)	1,773 (83.4)	0.03
Black	1,250 (14.2)	263 (12.4)	0.03
American Indian	36 (0.4)	10 (0.5)	0.70
Asian & Pacific Islander	289 (3.3)	60 (2.8)	0.28
Other	66 (0.8)	20 (0.9)	0.37
Facility location			
New England	547 (6.2)	103 (4.8)	0.02
Middle Atlantic	1,348 (15.3)	362 (17.1)	0.053
South Atlantic	1,894 (21.5)	447 (21.0)	0.61
East North Central	1,525 (17.3)	475 (22.3)	<0.001
East South Central	552 (6.3)	117 (5.5)	0.18
West North Central	702 (8.0)	138 (6.5)	0.02
West South Central	589 (6.7)	179 (8.4)	0.005
Mountain	530 (6.0)	107 (5.0)	0.08
Pacific	1,109 (12.7)	198 (9.3)	<0.001
Insurance status			
Not insured	340 (3.9)	80 (3.8)	0.83
Private insurance	3,992 (45.4)	820 (38.6)	<0.001
Medicaid	733 (8.3)	175 (8.2)	0.88
Medicare	3,626 (41.2)	1,034 (48.6)	<0.001
Other government insurance	105 (1.2)	17 (0.8)	0.12

Data are presented as n (%) or mean ± SD. MMR-P, mismatch repair proficient; MMR-D, mismatch repair deficient; SD, standard deviation.

of liver metastasis (73.0% *vs.* 60.8%, P<0.001). MMR-D was associated with higher rates of distant lymph node metastasis (15.5% *vs.* 10.2%, P=0.003) and involvement of other unspecified metastatic sites (35.5% *vs.* 28.2%, P<0.001) as seen in *Table 4*.

As shown in *Table 5*, patients with MMR-P were more likely to undergo chemotherapy (78.9% *vs.* 71.8%, P<0.001) and immunotherapy (23.0% *vs.* 16.3%, P<0.001) treatment, but both groups received surgical resection of the primary tumor at comparable rates (99.2% *vs.* 99.4%, P=0.29) and had no significant difference in the timing from MCC diagnosis to initiation of treatment with any intervention (15.82±30.40 *vs.* 15.27±26.47 days, P=0.44). MMR-D was associated with decreased mean survival after MCC diagnosis (23.96±21.53 *vs.* 26.44±20.41 months, P<0.001).

As shown in *Table 6*, factors independently associated with MMR-D included older mean age at diagnosis [65.16 *vs.* 62.79 years, odds ratio (OR) 1.005, 95% confidence

Table 2 Primary tumor locations

Primary site	MMR-P (n=8,796)	MMR-D (n=2,126)	P value
Right-sided colon	3,753 (42.7)	1,119 (52.6)	<0.001
Transverse colon	708 (8.0)	198 (9.3)	0.058
Left-sided colon	4,035 (45.9)	723 (34.0)	<0.001
Colon: not otherwise specified	112 (1.3)	33 (1.6)	0.31
Overlapping lesion of colon	188 (2.1)	53 (2.5)	0.32

Data are presented as n (%). MMR-P, mismatch repair proficient; MMR-D, mismatch repair deficient.

Table 3 Primary tumor characteristics

Domain	MMR-P (n=8,796)	MMR-D (n=2,126)	P value
Histology			
Adenocarcinoma	7,716 (87.7)	1,662 (78.2)	<0.001
Mucinous adenocarcinoma	777 (8.8)	322 (15.1)	<0.001
Signet ring carcinoma	193 (2.2)	89 (4.2)	<0.001
Medullary carcinoma	12 (0.1)	29 (1.4)	<0.001
Other	98 (1.1)	24 (1.1)	0.954
Lymph-vascular invasion	5,531 (62.9)	1,433 (67.4)	<0.001
Perineural invasion	3,138 (35.7)	718 (33.8)	0.10

Data are presented as n (%). MMR-P, mismatch repair proficient; MMR-D, mismatch repair deficient.

Table 4 Metastatic sites at diagnosis*

Metastatic sites	MMR-P (n=1,983)	MMR-D (n=380)	P value
Liver	1,447 (73.0)	231 (60.8)	<0.001
Lung	295 (14.9)	45 (11.8)	0.12
Bone	41 (2.1)	14 (3.7)	0.056
Brain	13 (0.7)	2 (0.5)	0.77
Distant lymph nodes	203 (10.2)	59 (15.5)	0.003
Other metastatic sites	559 (28.2)	135 (35.5)	<0.001

Data are presented as n (%). *, data only available for patients diagnosed with MCC beginning in 2016. MMR-P, mismatch repair proficient; MMR-D, mismatch repair deficient; MCC, metastatic colon cancer.

interval (CI): 1.000–1.010, P=0.04], female sex (53.1% *vs.* 49.0%, OR 1.123, 95% CI: 1.019–1.237, P=0.02), mucinous adenocarcinoma (15.1% *vs.* 8.8%, OR 1.910, 95% CI: 1.192–3.061, P=0.007), signet ring carcinoma (4.2% *vs.* 2.2%, OR 1.962, 95% CI: 1.168–3.295, P=0.01), medullary carcinoma (1.4% *vs.* 0.1%, OR 10.243, 95% CI: 4.506–23.283, P<0.001), and lymph-vascular invasion (67.4% *vs.* 62.9%, OR 1.211, 95% CI: 1.087–1.350, P=0.001). Factors independently associated with MMR-P included perineural invasion (35.7% *vs.* 33.8%, OR 0.883, 95% CI: 0.793–0.983, P=0.02), chemotherapy treatment (78.9% *vs.* 71.8% OR 0.866, 95% CI: 0.766–0.979, P=0.02), immunotherapy treatment (23.0% *vs.* 16.3% OR 0.746, 95% CI: 0.653–0.851, P<0.001), Black race (14.2% *vs.* 12.4% OR 0.716,

Table 5 Outcomes and treatment modalities

Outcomes	MMR-P (n=8,796)	MMR-D (n=2,126)	P value
90-day mortality post diagnosis	763 (8.7)	245 (11.5)	<0.001
180-day mortality post diagnosis	1,318 (15.0)	459 (21.6)	<0.001
365-day mortality post diagnosis	2,291 (26.0)	775 (36.5)	<0.001
730-day mortality post diagnosis	4,060 (46.2)	1,164 (54.8)	<0.001
Survival (months)	26.44±20.41	23.96±21.53	<0.001
Chemotherapy			
Received	6,939 (78.9)	1,527 (71.8)	<0.001
Immunotherapy			
Received	2,025 (23.0)	346 (16.3)	<0.001
Surgery of primary site			
Received	8,727 (99.2)	2,114 (99.4)	0.29
Post-surgical inpatient length of stay (days)*	7.76±7.83	8.35±8.69	0.01
Timing from diagnosis to treatment initiation (days)	15.82±30.40	15.27±26.47	0.44

Data are presented as n (%) or mean ± SD. *, subgroup analysis of 9,938 patients for whom this data was available (91.7% of 10,841 patients who underwent surgical resection of the primary tumor site). MMR-P, mismatch repair proficient; MMR-D, mismatch repair deficient; SD, standard deviation.

95% CI: 0.543–0.945, P=0.02), and primary tumor site in the left side of the colon (45.9% *vs.* 34.0%, OR 0.718, 95% CI: 0.555–0.929, P=0.01).

When adjusted for demographics, histologic features, and treatment modalities, MMR-D was associated with higher overall mortality at 180 days [21.6% *vs.* 15.0%, hazard ratio (HR) 1.140, 95% CI: 1.023–1.270, P=0.02], 1 year (36.5% *vs.* 26.0%, HR 1.203, 95% CI: 1.107–1.307, P<0.001), and 2 years (54.8% *vs.* 46.2%, HR 1.120, 95% CI: 1.048–1.197, P=0.001) after MCC diagnosis. Although mortality rates were higher for MMR-D at 90 days, the difference was significant in the univariate analysis but not the multivariate analysis. The full results for the univariate and multivariate Cox regression analysis are seen in *Table* 7.

Discussion

Our study, to the best of our knowledge, is the largest to describe patients with MCC according to MMR status and shows that MMR-D is an independent risk factor for mortality. This is significant, given that MMR-D is considered a positive prognostic factor in non-metastatic CC (stages I–III) (8-12). Sociodemographic characteristics associated with MMR-D include older age at MCC diagnosis, female sex, non-Black race and decreased rates of private health insurance compared to MMR-P patients. These findings are generally consistent with prior studies showing that across patients with CC of any stage, MMR-D is associated with right-sided colonic predominance, older age at diagnosis, female sex, and White race (18,19).

MMR-D was also found to be associated with specific clinicopathologic characteristics, including increased rates of mucinous adenocarcinoma, signet ring carcinoma, and medullary carcinoma, and decreased predilection for the distal colon, which are also largely consistent with prior studies in patients with CC of any stage (5,6). Although data on specific metastatic sites was only available for a subgroup of patients in our analysis, MMR-D appears to be associated with decreased rates of metastasis to the liver, and higher rates of metastasis to distant lymph nodes and other unspecified sites not including the lung, bone, or brain. A 2007 retrospective study by Malesci *et al.* reported that MSI tumors were less likely to exhibit lymph node and distant organ metastasis; 61.8% of MSI and 43.5% of MSS cancers in their study had no lymph node or distant organ metastasis at diagnosis (16).

Although MMR-D was associated with higher mortality at all investigated time points in the univariate analysis, the multivariate analysis adjusted for age, race, treatment modalities, and histologic features found that MMR-D was

Table 6 Bivariate logistic regression comparing characteristics between MMR-D and MMR-P

Domain	Adjusted odds ratio	95% CI	P value
Age of diagnosis (years)	1.005	1.000–1.010	0.04
Sex			
Male	Ref	Ref	Ref
Female	1.123	1.019–1.237	0.02
Chemotherapy	0.866	0.766–0.979	0.02
Immunotherapy	0.746	0.653–0.851	<0.001
Race			
White	0.884	0.693–1.128	0.32
Black	0.716	0.543–0.945	0.02
Facility location			
North Atlantic	0.717	0.565–0.910	0.006
Middle Atlantic	1.106	0.950–1.287	0.19
East North Central	1.307	1.134–1.505	<0.001
West North Central	0.838	0.680–1.033	0.01
West South Central	1.352	1.113–1.641	0.002
Mountain	0.872	0.692–1.100	0.25
Pacific	0.725	0.603–0.870	0.001
Insurance status			
Private insurance	0.895	0.796–1.007	0.06
Other government	0.741	0.439–1.251	0.26
Histology			
Adenocarcinoma	1.059	0.671–1.671	0.81
Mucinous adenocarcinoma	1.910	1.192–3.061	0.007
Signet ring carcinoma	1.962	1.168–3.295	0.01
Medullary carcinoma	10.243	4.506–23.283	<0.001
Lymph-vascular invasion	1.211	1.087–1.350	0.001
Perineural invasion	0.883	0.793–0.983	0.02
Primary tumor site			
Right-sided colon	1.051	0.816–1.355	0.70
Transverse colon	0.986	0.736–1.321	0.93
Left-sided colon	0.718	0.555–0.929	0.01

MMR-D, mismatch repair deficient; MMR-P, mismatch repair proficient; CI, confidence interval; Ref, reference.

an independent predictor of mortality at 180 days, 1 year, and 2 years after MCC diagnosis.

One possible reason for the increased mortality associated with MMR-D may be due to the contribution of specific mutations known to be associated with MMR-D, such as *BRAF* and the type II receptor for transforming growth factor β1 (TGF-β1), which we were unable to examine in this study (7,20). Watanabe *et al*. found higher

Table 7 Cox regression analysis of key survival outcomes

Domain	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
90-day mortality						
MMR-D	1.348	1.168–1.557	<0.001	1.026	0.886–1.188	0.74
Age at diagnosis (years)	1.054	1.049–1.059	<0.001	1.006	1.001–1.012	0.02
Chemotherapy	0.043	0.036–0.051	<0.001	0.057	0.047–0.068	<0.001
Immunotherapy	0.058	0.036–0.094	<0.001	0.249	0.152–0.408	<0.001
Sex						
Male	Ref	Ref	Ref	Ref	Ref	Ref
Female	0.932	0.823–1.054	0.26	0.806	0.711–0.913	0.001
Histology						
Adenocarcinoma	0.807	0.684–0.952	0.01	0.406	0.280–0.589	<0.001
Mucinous adenocarcinoma	0.776	0.618–0.974	0.03	0.288	0.188–0.441	<0.001
Signet ring carcinoma	1.959	1.466–2.617	<0.001	0.651	0.410–1.032	0.07
Medullary carcinoma	3.254	1.796–5.894	<0.001	0.741	0.368–1.491	0.40
Other	2.818	1.948–4.077	<0.001	Ref	Ref	Ref
Race						
White	1.079	0.916–1.271	0.36	2.609	0.650–10.467	0.18
Black	1.103	0.928–1.312	0.27	2.641	0.654–10.665	0.17
American Indian	0.692	0.223–2.150	0.53	1.930	0.322–11.573	0.47
Asian	0.507	0.314–0.819	0.006	1.512	0.349–6.555	0.58
Other	0.245	0.061–0.980	0.047	Ref	Ref	Ref
180-day mortality						
MMR-D	1.483	1.334–1.650	<0.001	1.140	1.023–1.270	0.02
Age at diagnosis (years)	1.053	1.049–1.057	<0.001	1.014	1.010–1.018	<0.001
Chemotherapy	0.087	0.078–0.096	<0.001	0.116	0.104–0.130	<0.001
Immunotherapy	0.191	0.155–0.234	<0.001	0.525	0.424–0.651	<0.001
Sex						
Male	Ref	Ref	Ref	Ref	Ref	Ref
Female	1.011	0.921–1.109	0.82	0.869	0.791–0.954	0.003
Histology						
Adenocarcinoma	0.687	0.610–0.774	<0.001	0.359	0.267–0.482	<0.001
Mucinous adenocarcinoma	1.032	0.886–1.202	0.69	0.339	0.245–0.468	<0.001
Signet ring carcinoma	2.059	1.656–2.560	<0.001	0.692	0.483–0.990	0.04
Medullary carcinoma	3.569	2.271–5.609	<0.001	0.753	0.440–1.291	0.30
Other	2.742	2.046–3.674	<0.001	Ref	Ref	Ref

Table 7 (*continued*)

Table 7 (*continued*)

Domain	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Race						
White	1.115	0.984–1.263	0.09	2.075	0.861–4.997	0.10
Black	1.045	0.914–1.193	0.52	2.114	0.872–5.126	0.098
American Indian	0.913	0.435–1.918	0.81	2.014	0.638–6.350	0.23
Asian	0.535	0.377–0.759	<0.001	1.233	0.480–3.166	0.66
Other	0.338	0.141–0.814	0.02	Ref	Ref	Ref
1-year mortality						
MMR-D	1.495	1.378–1.622	<0.001	1.203	1.107–1.307	<0.001
Age at diagnosis (years)	1.046	1.043–1.049	<0.001	1.021	1.018–1.024	<0.001
Chemotherapy	0.164	0.152–0.176	<0.001	0.217	0.200–0.235	<0.001
Immunotherapy	0.426	0.382–0.475	<0.001	0.815	0.725 -0.915	0.001
Sex						
Male	Ref	Ref	Ref	Ref	Ref	Ref
Female	1.012	0.943–1.086	0.74	0.898	0.837–0.965	0.003
Histology						
Adenocarcinoma	0.643	0.588–0.704	<0.001	0.344	0.271–0.438	<0.001
Mucinous adenocarcinoma	1.151	1.030–1.287	0.01	0.374	0.289–0.485	<0.001
Signet ring carcinoma	2.273	1.928–2.680	<0.001	0.823	0.618–1.095	0.18
Medullary carcinoma	3.168	2.137–4.697	<0.001	0.715	0.451–1.133	0.15
Other	2.685	2.114–3.409	<0.001	Ref	Ref	Ref
Race						
White	1.127	1.025–1.240	0.01	2.147	1.153–3.997	0.02
Black	0.996	0.898–1.104	0.94	2.211	1.181–4.141	0.01
American Indian	0.909	0.516–1.603	0.74	2.192	0.947–5.076	0.07
Asian	0.663	0.522–0.841	0.001	1.533	0.790–2.977	0.21
Other	0.376	0.202–0.700	0.002	Ref	Ref	Ref
2-year mortality						
MMR-D	1.320	1.237–1.409	<0.001	1.120	1.048–1.197	0.001
Age at diagnosis (years)	1.037	1.035–1.039	<0.001	1.022	1.019–1.024	<0.001
Chemotherapy	0.249	0.235–0.263	<0.001	0.316	0.297–0.337	<0.001
Immunotherapy	0.621	0.577–0.667	<0.001	0.934	0.866–1.008	0.08
Sex						
Male	Ref	Ref	Ref	Ref	Ref	Ref
Female	0.994	0.941–1.049	0.83	0.928	0.879–0.980	0.007

Table 7 (*continued*)

Table 7 (*continued*)

Domain	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Histology						
Adenocarcinoma	0.684	0.636–0.734	<0.001	0.416	0.336–0.514	<0.001
Mucinous adenocarcinoma	1.141	1.047–1.245	0.003	0.458	0.365–0.574	<0.001
Signet ring carcinoma	2.267	1.979–2.598	<0.001	1.002	0.781–1.285	0.99
Medullary carcinoma	2.580	1.802–3.694	<0.001	0.776	0.511–1.177	0.23
Other	2.338	1.891–2.890	<0.001	Ref	Ref	Ref
Race						
White	1.139	1.059–1.224	<0.001	2.204	1.420–3.421	<0.001
Black	0.971	0.897–1.051	0.46	2.207	1.415–3.444	<0.001
American Indian	0.797	0.502–1.266	0.34	1.987	1.051–3.757	0.04
Asian	0.732	0.617–0.870	<0.001	1.701	1.063–2.722	0.03
Other	0.409	0.264–0.634	<0.001	Ref	Ref	Ref

MMR-D, mismatch repair deficient; CI, confidence interval; Ref, reference.

5-year survival in patients with early-stage CC and MSI was higher among those with a mutated gene for the type II receptor for TGF-β1 compared to those with MSI tumors that did not have this mutation (20). A pooled analysis by Venderbosch *et al*. found that *BRAF* mutations were present in 34.6% of patients with MMR-D MCC compared to 6.8% of patients with MMR-P and conferred an inferior prognosis regardless of MMR status (21). Since data on these specific mutations were not available in the NCDB, it was not possible to reach a conclusion in this regard.

Patients with MMR-D were less frequently treated with chemotherapy and immunotherapy compared to MMR-P patients, however, nearly all patients across both groups underwent surgical resection of the primary tumor, and no significant differences in timing from diagnosis to treatment initiation were found. One explanation for this may be that many of the patients included in our study developed MCC prior to the Food and Drug Administration approving the use of anti-programmed cell death protein 1 (anti-PD1) antibody pembrolizumab in 2017 following the 2015 KEYNOTE-016 trial (22,23). The advent of newer immune therapies such as dostarlimab in treating MMR-D cancers was also not accounted for in our study timeframe; this is likely to refine our approach to treating MMR-D tumors and highlights the importance of continued surveillance of MMR status among CC patients (24). Although the multivariate Cox regression analysis was adjusted for variables including treatment modalities, it is possible that mortality rates for MMR-D patients with MCC may trend downward in the future given these developments.

It is also possible that MMR-D patients experienced more comorbidities than MMR-P patients, given that they were older at age of diagnosis and were less likely to have private insurance. However, given that information on specific medical comorbidities was not available in the NCDB, a possible component of the increased burden of more comorbidities cannot be definitively excluded. Furthermore, in our study, the incidence of MMR-D was 19.47% among patients with MCC, which is higher than what was found in prior studies from the earlier 2000s, which describe an incidence closer to 5% among patients with MCC (9,21,25). While this may be reflective of the relatively increased incidence of right-sided CCs observed in the United States recently given MMR-D CCs right-sided colonic predominance (26,27), it is possible that MMR-D patients may exhibit disproportionate screening and surveillance barriers, as indicated by their relative lack of private insurance as well as the low percentage of patients in the NCDB with MCC who had reported MMR status (34,438 of 255,280, or 13.5%).

Our study has limitations. Since this was a retrospective study using a large, de-identified database, we were unable

to account for missing data and excluded variables. As previously mentioned, this included data on medical comorbidities, and specific mutations. Additionally, a small number of patients with MCC had reported MMR status, which may have skewed our results given the high incidence. A minority of the patient population had available information regarding specific metastatic sites, and these patients needed to be analyzed as a subgroup. Lastly, the mortality variables of 90 days, 180 days, 1 year, and 2 years after MCC diagnosis may not accurately reflect cancer-related mortality. Our study population also included predominantly White patients (81.3%), which may not optimally represent current United States demographics.

Despite these limitations, our study, to the best of our knowledge, is the largest to describe exclusively MCC patients according to MMR-D, and shows that MMR-D is an independent risk factor for overall mortality, despite being a favorable prognostic factor in non-metastatic CC.

The implications for patients given these findings are significant. The association of MMR-D with increasing age may be reflective of age-related accumulation of genomic instability, which may highlight a more aggressive tumor biology in these patients. The longer postoperative length of stay in patients with MMR-D could be indicative of more complex postoperative care needs, possibly due to the presence of multiple comorbidities often seen in older patients. The increased rates of lymph-vascular invasion seen in MMR-D patients may guide clinicians in approaching postoperative adjuvant therapy decisions. The potential for utilizing immune checkpoint inhibitors in this population could offer a promising area for future research.

Conclusions

Despite being a favorable prognostic factor in stages I–III CC, MMR-D is associated with higher mortality at 90 days, 180 days, 1 year, and 2 years from diagnosis in stage IV CC compared to MMR-P in our univariate analysis. When adjusting for age, race, treatment modalities, and histologic features, MMR-D was found to be an independent predictor of mortality at 180 days, 1 year, and 2 years from MCC diagnosis. MMR-D is associated with older age at MCC diagnosis, female sex, non-Black race, decreased rates of private health insurance, more aggressive primary tumor histologic features, increased rates of lymph-vascular invasion, decreased rates of metastasis to the liver and lung and distal colonic primary tumor sites compared to MMR-P. The reasons for observed survival differences possibly entail specific oncogenic mutations associated with MMR-D as well as the aforementioned sociodemographic comorbidities.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-387/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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