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Short Communication

Clinical, pathological, and adjuvant chemotherapy use differences among microsatellite unstable and microsatellite stable colon cancers

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ABSTRACT

Background: Colon cancers are categorized into mismatch repair deficient/microsatellite unstable (MSI-H) and mismatch repair proficient/microsatellite stable (MSS) cancers. This study aims to compare the disease characteristics and trends in the utilization of cancer therapies across different age groups and stages in these two groups.

Methods: MSI-H and MSS colon adenocarcinomas from 2010 to 2016 were identified using the National Cancer Database. We compared patient and disease characteristics between the two groups and evaluated the use of adjuvant chemotherapy across age groups and cancer stages. Within MSI-H and MSS groups, we conducted a landmark analysis after propensity score matching for adjuvant chemotherapy versus no chemotherapy to determine its effect on survival.

Results: Of the 542,368 patients that met inclusion criteria, 120,751 (22%) had mismatch repair results available—out of these 96,928 (80%) had MSS colon cancers while 23,823 (19.7%) had MSI-H cancers. MSI-H disease had a bimodal age distribution (<40 years = 22%; ≥75 years = 26%) and was frequent among females (22%) and non-Hispanic Whites (20%). Among those < 65 years, 15% of low-risk stage 2 MSI-H patients and 40% of high-risk stage 2 MSI-H patients received adjuvant chemotherapy. More than two-thirds of stage 3 patients <65 years received adjuvant chemotherapy in both groups. After conducting propensity-score matching for age, gender, and co-morbidities, we found that adjuvant chemotherapy use had a trend towards lower overall survival (OS) in low-risk stage 2 MSI-H (HR = 1.8 [95% CI, 0.8–4.02]) and high-risk stage 2 MSI-H (HR = 1.42 [95% CI, 0.96–2.12]) groups. Adjuvant chemotherapy significantly improved OS in stage 3 colon cancer patients irrespective of microsatellite status or risk category of disease.

Conclusions: MSI-H colon cancer had bimodal age distribution. Among stage 2 MSI-H patients <65 years, a notable proportion received adjuvant chemotherapy. Among MSI-H stage 2 patients, adjuvant chemotherapy use was associated with lower survival while it significantly improved survival for stage 3 patients, irrespective of MSI status.

1. Introduction

Colon cancer is the third most common cancer in the United States and is broadly divided into two groups based on genetic instability: DNA mismatch repair deficient (dMMR) tumors and DNA mismatch repair proficient (pMMR) tumors.[1] dMMR tumors arise due to loss of function of the mismatch repair pathway proteins (MLH1, PMS2, MSH2, MSH6). This loss triggers replication errors and mismatch mutations in DNA regions called microsatellites, leading to a phenomenon termed microsatellite instability (MSI-H). Conversely, pMMR colon cancers maintain functional mismatch repair pathways. These tumors typically exhibit chromosome copy number alterations, low tumor mutation burden, and microsatellite stability (MSS).[2] MSI-H cancers are more frequently located in the right colon, and more commonly diagnosed in

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young (<35 years) and elderly (> 75 years) populations, and while they are often linked with Lynch syndrome, they can occur sporadically.[3,4] A crucial aspect of MSI-H colon cancers is its response to immune checkpoint inhibitors, which have become first-line therapy in metastatic settings.[5-7]

Adjuvant chemotherapy plays a pivotal role in the treatment of colon cancer, yet its effectiveness varies across different patient subgroups. For stage 3 colon cancer, studies have consistently shown that adjuvant chemotherapy enhances overall survival and diminishes the likelihood of disease recurrence in both MSI-H and MSS groups.[8-12] Conversely, the advantages of adjuvant chemotherapy in stage 2 colon cancer in the setting of MSI status are less obvious. Previous studies have reported no survival advantage associated with adjuvant chemotherapy in patients with stage 2 MSI-H colon cancer.[13] However, more recent studies have reported an association between adjuvant chemotherapy with better overall survival in patients with MSI-H stage 2 colon cancer, especially in T4 tumors.[10,14] Current national clinical guidelines suggest either observation or considering the use of adjuvant chemotherapy in MSS stage 2 colon cancer with high-risk features.[15] The trends in the utilization of adjuvant chemotherapy in MSI-H and MSS colon cancer at the population level have not been studied.

We aim to provide a comprehensive comparison of clinical and pathological features between MSS and MSI-H colon cancer and describe the differences in the use of adjuvant chemotherapy for stage 2 and stage 3 colon cancer by risk and age stratification.

2. Materials and methods

2.1. Study cohort

The National Cancer Database (NCDB) is a community-oriented cancer management and outcomes database that is jointly spearheaded by the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Engaging over 1500 Commission on Cancer (CoC)-accredited facilities, the NCDB encompasses data on patient demographics, tumor characteristics, socioeconomic factors, treatments, and survival outcomes. The dataset contains more than 34 million historical records, representing more than 70% of all newly diagnosed cancer cases nationwide.

2.2. Cohort selection

We extracted data from the NCDB for patients aged 18 years and above diagnosed with colon cancer (ICD-O-3/WHO 2008 site recode "C18-C19, C26") from 2010 to 2016. These patients were stratified by age groups (<40, 40–55, 56–65, 66–75, 76–85, and >85 years) and microsatellite mismatch repair (MMR) status. In NCDB, microsatellite instability is reported by immunological (IHC) or a genetic method (PCR testing). Using IHC, it categorizes it as MSI-negative (equal to pMMR) or MSI-unstable (equal to dMMR), and using the PCR testing method, where it is characterized as either MSI-L (equal to MSS) or MSI-H. For our analysis, we combined pMMR and MSS into one group (MSS) and dMMR and MSI-H into another group (MSI-H). Patients for whom MMR status was reported as 'unknown' were excluded from the analysis (n = 3,196).

2.3. Baseline characteristics and treatment stratification

We reported baseline patient and disease characteristics for all patients among whom MSI testing was performed. We compared various clinical or pathological characteristics between MSI-H and MSS groups. Patient-specific variables including age groups (<40, 40–55, 56–65, 66–75, 76–85, and 85+ years), race/ethnicity (Hispanics, non-Hispanic White, non-Hispanic Black, and others), sex (male, female), Charlson Comorbidity Index Score (0–3), clinical stage (1–4), pathological stage (1–4), laterality (right-sided, left-sided), travel distance to treatment facility (<12.5, 12.5–49.9, ≥50 miles), insurance status (insured, uninsured), education (rates of patients without high school level ≥17.6%, 10.9–17.5%, 6.3–10.8%, <6.3%), and median income quartiles (<$40,227, $40,227-$50,353, $50,354-$63,332, and $63,333+) as well as disease-specific (tumor deposits, lymphovascular infiltration [LVI] status, and perineural deposits) and treatment specific variables (chemotherapy [adjuvant, none]) were compared. Right-sided tumors were defined as tumors originating from the cecum, ascending colon, hepatic flexure, and transverse colon while left-sided tumors were defined as tumors originating from splenic flexure, descending colon, sigmoid colon, and rectosigmoid junction. Travel distance was determined by the great circle distance method, which measures the distance between a patient's home and the reporting healthcare facility, using the geographic centroid of zip codes.[16]

We evaluated the proportion of patients receiving adjuvant chemotherapy in MSI-H and MSS groups among patients with low and high-risk stage 2 and 3 diseases, across various age categories. For stage 2 disease, the tumor was considered high-risk if it met one of the following criteria: pT4, lympho-vascular or perineural invasion, poorly differentiated histology (only for MSS group), and fewer than 12 lymph nodes resected.[14] For stage 3 disease, the tumor was considered high-risk if it met one of the following criteria: pT4 and/or N2 disease.[12,17]

The effect of adjuvant chemotherapy on survival was assessed for each group based on the pathological stage and the risk category for each stage. We stratified the population into the following groups: MSI-H (stage 2 low-risk, stage 2 high-risk, stage 3 low-risk, and stage 3 high-risk) and MSS (stage 2 low-risk, stage 2 high-risk, stage 3 low-risk, and stage 3 high-risk). For each group, we conducted propensity score matching to compare patients receiving adjuvant chemotherapy with those who did not, matched for age, gender, and Charlson Comorbidity Index Score due to their influence on clinical decision-making regarding adjuvant chemotherapy use.[18] For our survival analysis, we excluded patients who received neoadjuvant (or unknown) therapy, had multiple primary tumors, did not receive their first treatment at the reporting center, and had unknown follow-up information. Moreover, for the survival analysis, patients who died within the first year of surgical resection were excluded to control for immortal time bias or landmark analysis (the landmark time as determined a priori).

2.4. Statistical analysis

Comparisons between MSS and MSI-H groups were performed using the two-sample T-test or Wilcoxon rank-sum test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. All tests were reported with a two-sided P-value ($P < 0.05$ was considered statistical significance) using R version 4.3.2. For the survival analysis, we first performed propensity score matching between patients receiving adjuvant chemotherapy versus no chemotherapy in each group. Propensity score matching was performed using a 1:1 nearest neighbor matching algorithm with Match-It package using R version 4.3.2 (Nonparametric Preprocessing for Parametric Causal Inference),[19,20] adjusting for age, gender, and Charlson Comorbidity Index Score for patients with low and high-risk stage 2 and 3 colon cancer. Kaplan-Meier was performed to calculate the overall survival (OS) and Cox regression analysis was used to calculate the hazard ratio with 95% confidence interval (CI). Survival endpoints were measured from an index date of diagnosis until the date of death. Patients who did not meet the endpoint of interest were censored at the date of last contact.

3. Results

3.1. Basic demographics

Among the 542,368 cases of colon cancer in NCDB from 2010 to 2016, we identified 120,751 (22%) cases with available MMR testing

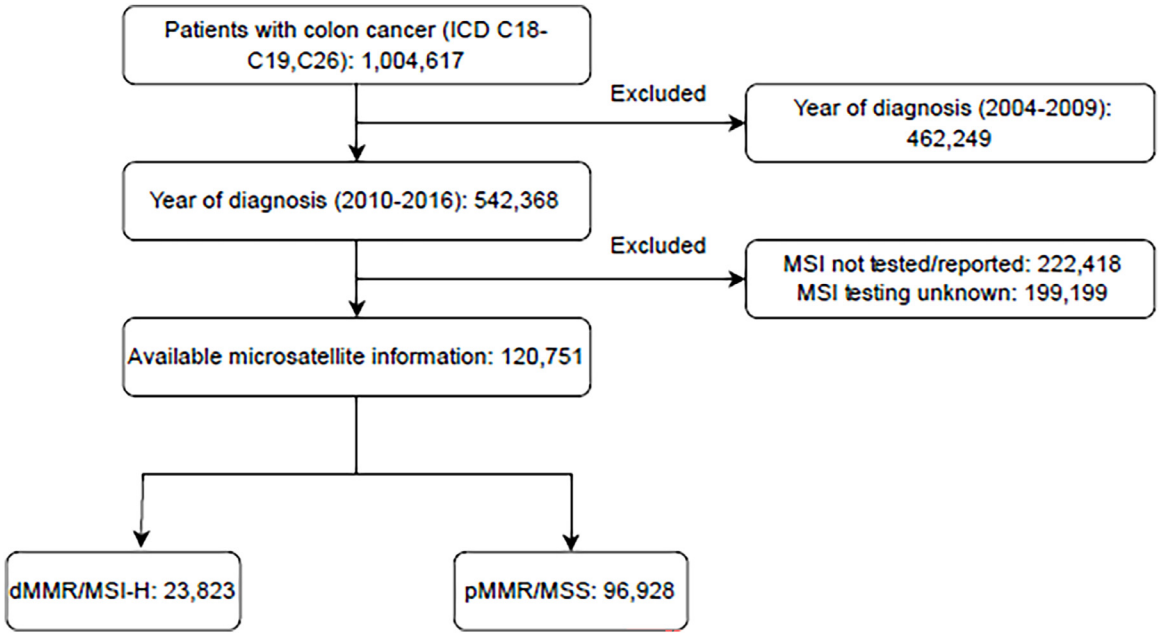

Fig. 1. CONSORT diagram depicting patient selection. dMMR, deficient mismatch repair; ICD, International Classification of Diseases; MSI-H, microsatellite instable–high; MSS, microsatellite stable; pMMR, proficient mismatch repair.

information (Fig. 1). Among these patients, 23,823 (20%) had MSI-H cancer while 96,928 (80%) had MSS cancer. MSI-H colon cancers had a bimodal age distribution occurring more frequently among those <40 years (22%) and >75 years (27%) (Table 1). Also, it was more frequent in females (22%) compared to males (17%), and among the non-Hispanic Whites (21%) compared to Hispanics (18%) and Non-Hispanic Blacks (14%). MSI-H cancers occurred more frequently in the right colon (26%) compared to left-sided colon cancer (11%) and were diagnosed at stage 2 and stage 3 more frequently compared to stage 4 disease (24%, 19%, and 13% respectively). In contrast, MSS colon cancers were more frequent in age 40–75 years, males (83%), non-Hispanic Blacks (86%), stage 4 disease (87%), and left-sided colon cancers (89%). MSI-H frequency was similar among academic and non-academic institutions and among insured and uninsured patients.

3.2. Use of adjuvant chemotherapy in stage 2 and stage 3 colon cancers

Overall, adjuvant chemotherapy use decreased with advancing age (Table 2). Adjuvant chemotherapy utilization was more common in MSS compared to MSI-H patients among stage 2 patients while it was similar in stage 3 patients. In patients <65 years, 15% of the low-risk stage 2 MSI-H cancers received adjuvant chemotherapy while approximately 40% of high-risk stage 2 MSI-H cancers received it. Similarly, in low-risk stage 2 MSS cancers approximately 30% of patients <65 years received adjuvant chemotherapy while approximately 50% for high-risk stage 2 MSS cancers received it. In stage 3 colon cancer patients <65 years, irrespective of MSI status, approximately >70% of patients received adjuvant chemotherapy. In patients >65 years with stage 2 or 3 colon cancer, adjuvant chemotherapy use declined irrespective of MSI status or risk category (Table 2).

3.3. Effects of adjuvant chemotherapy on survival

To evaluate if the use of adjuvant chemotherapy affected OS, we performed propensity score-matched analysis as described in the Methods section. In stage 2 MSI-H patients, adjuvant chemotherapy use had a trend towards decreased survival in low-risk (5 years OS: 86% vs 94%; HR, 1.8 [95% CI, 0.8–4.02], $P = 0.2$) and high-risk group (5 years OS: 83% vs 89%; HR, 1.42 [95% CI, 0.96–2.12], $P = 0.08$). In stage 2 MSS patients, adjuvant chemotherapy use had no significant impact on survival for both low-risk (5 years OS: 91% vs 88%; HR, 0.83 [95% CI, 0.62–1.11], $P = 0.2$) and high-risk groups (5 years OS: 82% vs 79%; HR, 0.94 [95% CI, 0.79–1.11], $P = 0.4$) (Fig. 2). In stage 3 low-risk patients, the use of adjuvant chemotherapy significantly improved survival for both MSI-H (5 years OS: 90% vs 63%; HR, 0.19 [95% CI, 0.13 – 0.29], $P < 0.001$) and MSS patients (5 years OS: 88% vs 53%; HR, 0.18 [95% CI, 0.15–0.22], $P < 0.001$). Similarly, in high-risk stage 3 patients, adjuvant chemotherapy significantly improved overall survival for both MSI-H (5 years OS: 67% vs 49%; HR, 0.52 [95% CI, 0.39–0.7], $P < 0.001$) and MSS patients (5 years OS: 69% vs 36%; HR, 0.34 [95% CI, 0.29–0.4], $P < 0.001$) (Fig. 3).

4. Discussion

MSI-H colon cancer presents unique molecular, histologic, and clinical features, including response to systemic therapy. Testing for mismatch repair pathway alterations is recommended by national guidelines for all newly diagnosed colon cancer patients due to implications for outcomes and choice of treatment.[21-23] In this study, using a large patient database, we demonstrated that there are patient and disease level differences between MSS and MSI-H colon cancers. We showed that adjuvant chemotherapy use varied by age, stage, tumor risk features, and MSI status, and that adjuvant chemotherapy use had survival impact in subgroups. The most important conclusion from this study was to show the lack of advantage of adjuvant chemotherapy use among MSI-H stage 2 patients while demonstrating a significant improvement in stage 3 patients.

First, we confirmed previous findings that MSI-H colon cancers had bimodal age distribution, occurring more frequently among <40 years and >75 years.[24] Younger colon cancer patients have a higher likelihood of Lynch syndrome, which occurs due to a mutation in one of the mismatch repair pathway genes leading to early onset of colorectal, endometrial, gastric, and other cancers. Among the elderly patients, the high MSI-H disease proportion is due to an increased incidence of hypermethylation of the hMLH1 promoter region, which is characterized by sporadic MSI-H disease with BRAF mutations.[25-27] Apricio et al. also reported an increased prevalence of MSI-H disease associated with

Table 1
Baseline characteristics.

Variables	MSI-H (n = 23,823)	MSS (n = 96,928)
Age-groups at diagnosis, No. (%)		
< 40 years	1088 (22)	3808 (78)
40–55 years	3956 (15)	22,420 (85)
56–65 years	4298 (16)	22,623 (84)
66–75 years	5891 (20)	23,802 (80)
76–85 years	6051 (25)	17,873 (75)
> 85 years	2539 (28)	6402 (72)
Gender, No. (%)		
Male	10,191 (17)	49,844 (83)
Female	13,632 (22)	47,084 (78)
Ethnicity, No. (%)		
Hispanic	1201 (18)	5498 (82)
Non-Hispanic Black	1976 (14)	11,735 (86)
Non-Hispanic White	19,015 (21)	72,433 (79)
Others	882 (16)	4808 (85)
Pathological stage, No. (%)		
Stage 1	4294 (20)	17,134 (80)
Stage 2	9076 (24)	28,343 (76)
Stage 3	7015 (19)	30,223 (81)
Stage 4	2129 (13)	13,659 (87)
Unknown	1309 (15)	7569 (85)
Clinical stage, No. (%)		
Stage 1	2774 (19)	12,206 (81)
Stage 2	2629 (21)	9674 (79)
Stage 3	1738 (21)	6557 (79)
Stage 4	1980 (13)	13,348 (87)
Unknown	14,702 (21)	55,143 (79)
Risk profile for stage 2[α], No. (%)		
High	1590 (25)	4808 (75)
Low	1039 (18)	4866 (82)
Risk profile for stage 3[β], No. (%)		
High	858 (23)	2941 (77)
Low	880 (20)	3616 (80)
Laterality, No. (%)		
Left	5482 (11)	44,153 (89)
Right	17,480 (26)	48,637 (74)
Charlson Deyo, No. (%)		
0	15,907 (19)	67,563 (81)
1	5232 (21)	19,991 (79)
2	1696 (22)	5963 (78)
3	988 (22)	3411 (78)
Facility type, No. (%)		
Academic	7651 (20)	30,949 (80)
Non-academic	15,084 (20)	62,171 (80)
Travel distance, No. (%)		
Travel < 12.5 miles	14,937 (20)	61,451 (80)
Travel 12.5–49.9 miles	6792 (20)	27,210 (80)
Travel ≥ 50 miles	2058 (20)	8153 (80)
Insurance status, No. (%)		
Insured	22,894 (20)	92,813 (80)
Uninsured	714 (19)	3006 (81)
LVI Status[γ], No. (%)		
LVI absent	4750 (20)	19,362 (80)
LVI present	1866 (22)	6792 (78)
Perineural deposits[γ], No. (%)		
Absent	19,345 (20)	75,449 (80)
Present	2702 (17)	13,022 (83)
Tumor deposits[γ], No. (%)		
Absent	19,568 (21)	75,773 (79)
Present	2967 (17)	14,419 (83)
Education[δ], No. (%)		
< 6.3%	6641 (21)	25,508 (79)
6.3%-10.8%	7022 (20)	27,416 (80)
10.9%-17.5%	5789 (19)	24,122 (81)
17.6% +	4154 (18)	18,874 (82)
Income, No. (%)		
<$40,227	3648 (18)	16,509 (82)
$40,227-$50,353	5072 (20)	19,897 (80)
$50,354-$63,332	5811 (20)	22,622 (80)
$63,333+	9041 (20)	36,753 (80)
Adjuvant chemotherapy use[γ], No. (%)	5801 (18)	27,221 (82)
Stage 2 single-agent	373 (14)	2323 (86)
Stage 2 multi-agent	795 (21)	3053 (79)
Stage 3 single-agent	815 (19)	3432 (81)
Stage 3 multi-agent	3498 (17)	16,953 (83)
None	9843(25)	29,337(75)

Abbreviations: LVI, lymphovascular infiltration; MSI-H, microsatellite instable–high; MSS, microsatellite stable.

[α] High risk defined if it met one of the following criteria: pT4, LVI/PNI, poor differentiation (only for MSS group), <12 lymph nodes resected.

[β] High risk defined if it met one of the following criteria: pT4, N2.

[γ] For pathological stage 2–3 patients.

[δ] Patients without high school level.

BRAF V600E mutation among older patients with colon cancers.[25] MSI-H frequency among racial groups was similar to previous reports with non-Caucasians having a higher incidence.[28] Also, MSI-H was more frequent in females and right-sided colon, confirming previously reported evidence in a larger patient population.[29] Furthermore, our analysis uncovered that approximately 13% of patients with stage 4 colon cancers exhibited MSI-H, which is a notably greater fraction compared to earlier research.[30] This elevation could stem from a selection bias within our cohort, reflecting an overrepresentation of subgroups inherently more susceptible to MSI-H malignancies.

NCCN colon cancer guidelines recommend against the routine use of adjuvant chemotherapy in stage 2 MSI-H colon cancer, but ASCO 2021 guidelines recommend a shared decision-making process to decide about adjuvant chemotherapy in stage 2 MSI-H or MSS with high-risk features.[22,23] These recommendations are derived from a limited number of studies that suggest a survival benefit only in patients with high-risk features, more specifically with T4 lesions.[31-33] This current analysis is novel as it examines the population at large, categorizing stage 2 and stage 3 patients into high-risk and low-risk groups and compares the use of adjuvant chemotherapy across various age categories in MSI-H and MSS patients. In stage 2 MSI-H colon cancer, where adjuvant chemotherapy has been linked to poor overall survival,[31] our analysis revealed that about 15% of low-risk patients <65 years and approximately 40% of high-risk patients <65 years, received adjuvant chemotherapy. Among patients ≥65 years with stage 2 colon cancers regardless of MSI status or risk category, the use of adjuvant chemotherapy was much lower, likely due to concern for toxicity or patient preferences. This is consistent with findings from a prior study that suggest intensified multi-agent adjuvant chemotherapy regimens may not be as beneficial for older patients, possibly due to a higher incidence of adverse effects and a lower overall survival rate. Therefore, it becomes crucial to balance the potential benefits against the risks when considering adjuvant chemotherapy in the older population.[34] For stage 3 colon cancer patients, we observed that patients <65 years with high-risk or low-risk disease, had significantly higher use of adjuvant chemotherapy, regardless of MSI status. For low-risk stage 3 colon cancer, the use of adjuvant chemotherapy was marginally lower than that seen in high-risk stage 3 disease, but still higher than that observed in stage 2 disease. This trend is reassuring as it is in stage 3 patients where the best data exists for benefit from the adjuvant chemotherapy.[8-12] Even though there is an opportunity to improve the acceptance of adjuvant chemotherapy, most of the relatively young and healthy population do receive it. For the remaining patients, who do not agree to adjuvant chemotherapy, we have previously demonstrated that this decision was likely due to patient-specific reasons,[35] which should be an active area for education.

To determine if the use of adjuvant chemotherapy had an impact on survival, we performed a propensity-score-matched landmark analysis within sub-groups. This allowed us to balance the potential differences in comparable populations from a large database. We observed that low-risk and high-risk stage 2 MSI-H patients had a trend towards lower survival if they received adjuvant chemotherapy compared to no adjuvant chemotherapy. Considering that more than one-third of high-

Table 2
Adjuvant chemotherapy utilization among patients with stage 2 and stage 3 MSI-H and MSS colon cancer patients, stratified by age and risk features.

Stage	Risk category	Age at diagnosis, years	MSI-H, No. (%)		MSS, No. (%)		*P* value
			Adjuvant chemo		Adjuvant chemo		
			Yes	No	Yes	No	
Stage 2	High-risk (n = 15,999)	< 40	70 (39)	108 (61)	198 (61)	124 (39)	< 0.001
		40–55	261 (45)	321 (55)	1122 (55)	916 (45)	< 0.001
		56–65	238 (32)	505 (68)	1072 (42)	1463 (58)	< 0.001
		66–75	235 (20)	954 (80)	856 (30)	1972 (70)	< 0.001
		76–85	104 (8)	1226 (92)	324 (13)	2200 (87)	< 0.001
		> 85	10 (2)	608 (98)	20 (2)	1092 (98)	0.93
		Total	918	3722	3592	7767	
	Low-risk (n = 20,153)	< 40	28 (18)	132 (82)	156 (41)	226 (59)	< 0.001
		40–55	108 (16)	576 (84)	796 (27)	2170 (73)	< 0.001
		56–65	96 (13)	652 (87)	579 (16)	3007 (84)	0.03
		66–75	66 (6)	1012 (94)	437 (10)	3745 (90)	< 0.001
		76–85	32 (3)	1010 (97)	126 (4)	3384 (96)	0.48
		> 85	1 (0)	472 (100)	11 (1)	1331 (99)	0.28
		Total	331	3854	2105	13,863	
Stage 3	High-risk (n = 17,168)	< 40	202 (89)	26 (11)	680 (92)	63 (8)	0.23
		40–55	533 (90)	61 (10)	3125 (90)	336 (10)	0.73
		56–65	526 (84)	100 (16)	2723 (85)	484 (15)	0.62
		66–75	597 (77)	175 (23)	2379 (78)	667 (22)	0.68
		76–85	423 (50)	428 (50)	1265 (53)	1114 (47)	0.09
		> 85	46 (12)	338 (88)	128 (15)	749 (85)	0.25
		Total	2327	1128	10,300	3413	
	Low-risk (n = 18,882)	< 40	152 (90)	17 (10)	565 (90)	64 (10)	1
		40–55	504 (87)	73 (13)	3338 (90)	384 (10)	0.11
		56–65	503 (82)	112 (18)	2999 (83)	607 (17)	0.43
		66–75	604 (76)	190 (24)	2881 (75)	957 (25)	0.58
		76–85	432 (49)	456 (51)	1319 (48)	1431 (52)	0.75
		> 85	30 (9)	291 (91)	122 (13)	851 (87)	0.15
		Total	2225	1139	11,224	4294	

Abbreviations: chemo, chemotherapy; MSI-H, microsatellite instable–high; MSS, microsatellite stable.

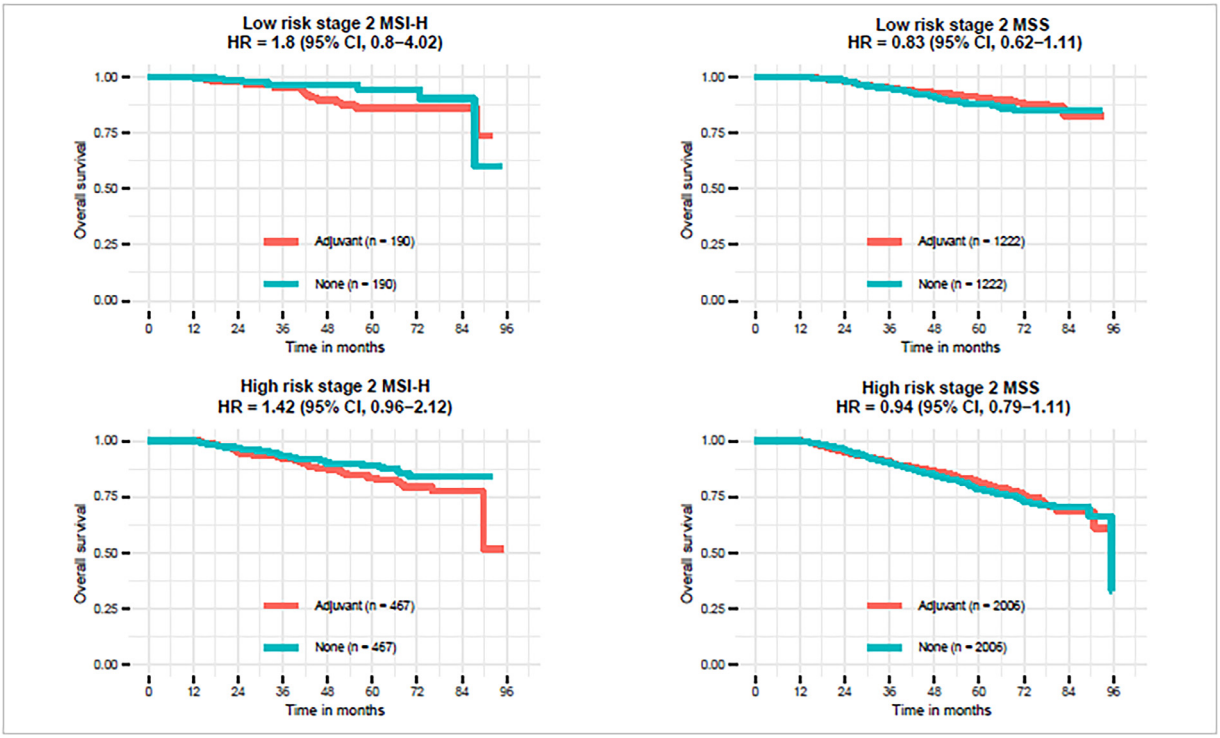

Fig. 2. Overall survival in patients with stage 2 MSI-H and MSS colon cancer after propensity score matching between adjuvant chemotherapy and no chemotherapy receipt. Patients were matched for age, gender, and comorbidity score, and survival was analyzed. CI, confidential interval; HR, hazard ratio; MSI-H, microsatellite instable–high; MSS, microsatellite stable.

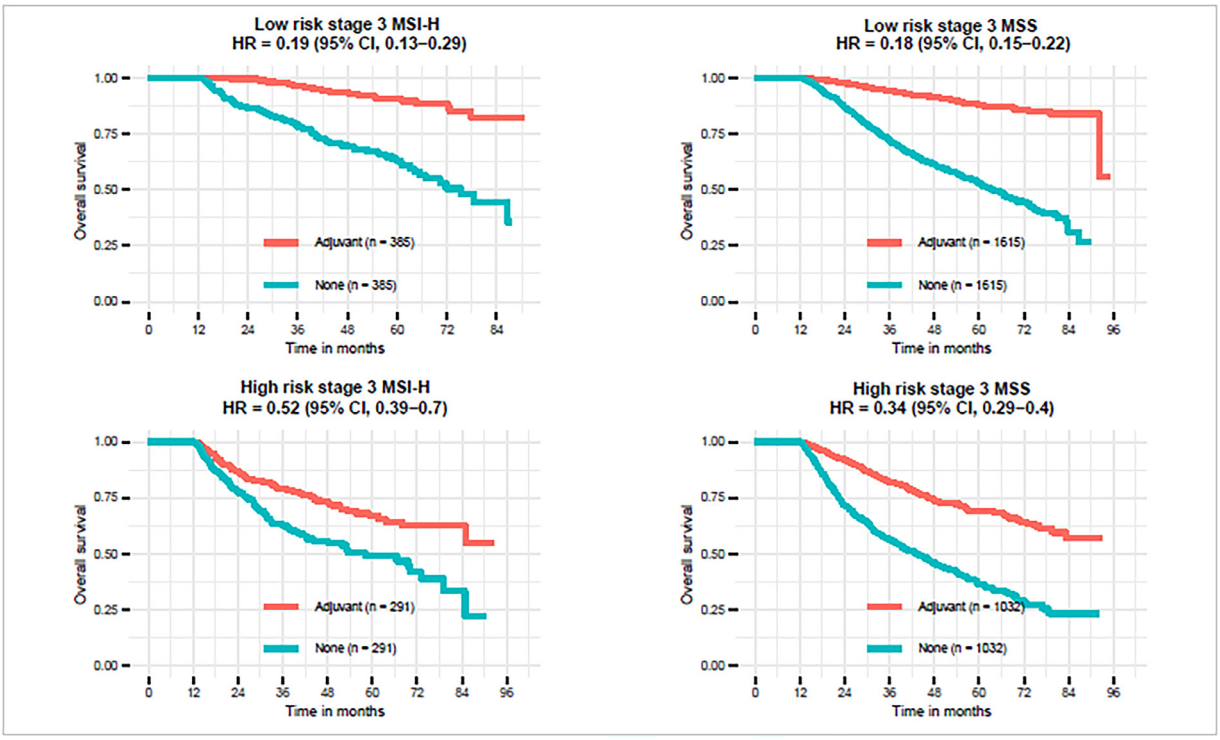

Fig. 3. Overall survival in stage 3 patients with MSI-H and MSS colon cancer after propensity score matching between adjuvant chemotherapy and no chemotherapy receipt. Patients were matched for age, gender, and comorbidity score, and the survival was analyzed. CI, confidential interval; HR, hazard ratio; MSI-H, microsatellite instable–high; MSS, microsatellite stable.

risk MSI-H stage 2 patients in our cohort (predominantly younger population) received adjuvant chemotherapy, the findings underscore the need for guidelines to emphasize and disseminate knowledge against the use of adjuvant chemotherapy in these patients. Therefore, for stage 2 MSI-H patients, we agree with NCCN guidelines over ASCO guidelines about avoiding adjuvant chemotherapy use in such patients.[22,23] In addition, we found that the stage 2 low-risk or high-risk MSS groups also did not benefit from adjuvant chemotherapy, and better biomarkers for residual disease assessment are needed in this setting such as circulating tumor DNA-based assays. For stage 3 patients, there was a significant survival benefit observed in this study, in all sub-groups. Therefore, we recommend the use of adjuvant chemotherapy for stage 3 colon cancer irrespective of MSI status and risk stratification. There are ongoing clinical trials about the use of circulating tumor DNA as a predictive biomarker of the benefit of chemotherapy in stage 2 and 3 patients and whether such a biomarker can help identify patients where we can avoid adjuvant chemotherapy is yet to be determined (CIRCULATE US-NCT05174169, COBRA trial [now closed]-NRG-GI005). We found a stronger survival benefit from adjuvant chemotherapy in patients with high-risk MSS stage 3 colon cancer compared to those with high-risk MSI-H stage 3 colon cancers (HR: 0.34 vs 0.52). This suggests that MSS status may get more benefit from the adjuvant chemotherapy in the high-risk stage 3 colon cancer group. The differential response warrants further investigation into the molecular mechanisms driving the varied therapeutic outcomes and may have significant implications for tailoring treatment strategies according to MSI status in this group.

We observed a sharp decline in the use of adjuvant chemotherapy among patients >75 years. This age group is an important population frequently overlooked in clinical trials. Lack of use of adjuvant chemotherapy is generally due to concerns about toxicity from chemotherapy or other competing medical co-morbidities. This concern is substantiated by the ADAGE-PRODIGE 34 study[36] which observed that older patients, especially those categorized as frail exhibited more severe toxicities when treated with oxaliplatin-based regimens. Given this, the trial emphasizes the necessity to tailor chemotherapy regimens according to patient fitness and tolerance levels, particularly in the older population. Since immunotherapy works well in metastatic MSI-H cancers, the ATOMIC trial (NCT02912559) has compared FOLFOX chemotherapy with or without PD-L1 immune checkpoint inhibitor, atezolizumab, in adjuvant setting for stage 3 colon cancer patients. Enrollment is completed, but the percentage of elderly MSI-H patients enrolled in this study is unknown. It also does not address the question of whether single-agent immunotherapy alone could offer survival benefits. This gap in research demonstrates a need to focus future trials on adjuvant, neoadjuvant, or peri-operative single-agent immunotherapy trials for elderly stage 3 MSI-H colon cancer patients. This may be important since immunotherapy typically results in fewer grade 3/4 adverse events compared to chemotherapy and might show a survival advantage.

Our study has several limitations due to the type of data collected in the NCDB. First, it does not include information about the duration of chemotherapy, specific chemotherapy agents used for various stages, and compliance during chemotherapy sessions. Secondly, MSI status data were only available for a limited subset of the overall cohort of colon cancer patients, potentially introducing a selection bias. However, the absolute number of patients with available MSI data remains significant, lending credibility and robustness to our analysis. Lastly, it does not mention tumor recurrence rate and disease-free survival for MSI-H and MSS stage 2 and stage 3 colon cancers. At the same time, however, there are several advantages of our study. Firstly, we reported 120,751 patients, an extensive cohort of MSI-H and MSS colon cancer patients reported to date in the medical literature. Secondly, we used a multicenter, audited, national database that provides generalizable and reliable information.[37] Lastly, it extensively categorizes stage 2 and 3 colon cancer into cohorts based on age groups, MMR status, and risk categories, enabling a detailed evaluation of the adjuvant chemotherapy use and, after accounting for immortal time bias, determined its impact on survival outcomes in each distinct group.

5. Conclusions

This study identified useful clinical and pathological differences between MSI-H and MSS patients relevant to clinical practice. Adjuvant chemotherapy should be avoided in stage 2 patients, especially in the MSI-H population, while it should be strongly encouraged in all stage 3 colon cancer patients regardless of MSI status. For elderly patients, who had a higher proportion of MSI-H disease, novel trials should be designed using immune checkpoint inhibitors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

S.K., B.J., M.B. and A.M. conducted the study conceptualization and design. B.J. and S.K. acquired and interpreted the data. B.J. conducted the statistical analysis. S.K. administrated the project. S.K. and B.J. conducted the investigation and methodology. S.K., B.J., M.B. and A.M. drafted the original manuscript. All of the authors conducted the critical revision of the manuscript for important intellectual content.

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