Clinicopathological features and prognoses in younger and older patients with mismatch repair defects colorectal cancer: a retrospective comparative cohort study

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Background: Microsatellite instability-high (MSI-H) is an important biomarker for predicting the effects of immune checkpoint inhibitors (ICIs) in colorectal cancer (CRC) patients. However, due to the low mutation rate of MSI-H/deficient mismatch repair (dMMR) in the overall population, some doctors are of the view that testing this indicator increases the burden on patients, and consequently some patients fail to receive the most beneficial treatment methods. In order to provide testing criteria for younger patients with a higher proportion of MSI-H, we designed this retrospective controlled study.

Methods: A retrospective analysis was conducted of 1,901 patients who were admitted to the Affiliated Cancer Hospital of Zhengzhou University from January 2017 to December 2019 and underwent CRC-related gene testing. For this analysis, 100 patients aged 40 or younger are defined as the young group, and 305 patients aged 71 and older but younger than 80 are defined as the elderly group. We included patients who met the following criteria: (I) underwent preoperative colonoscopy or gastroscopy and were diagnosed with CRC; (II) received perioperative adjuvant therapy; (III) underwent curative surgery for CRC. Each patient was followed up from the time of surgery until April 30, 2023, or death, with follow-up visits scheduled every 3 months for the first 2 years after surgery, and every 6 months thereafter. Clinical characteristics such as age, gender, body mass index (BMI), tumor depth (T), number of metastatic lymph nodes (N), distant metastasis (M), tumor, node, metastasis (TNM) stage, extent of surgical resection, tumor size, tumor location, differentiation grade, and carcinoembryonic antigen (CEA) levels were collected. The microsatellite instability (MSI) status was analyzed using fluorescence in situ hybridization (FISH).

Results: In young CRC patients, the proportion of MSI-H is higher than in elderly CRC patients (33% *vs.* 10.16%, P<0.001). The proportion of poorly differentiated tumors is also higher in young CRC patients compared to elderly CRC patients (53% *vs.* 31.15%, P<0.001). However, there were no significant differences in clinical characteristics between young and elderly CRC patients. In terms of prognosis, survival analysis of the young group showed that MSI status [hazard ratio (HR) =0.26, 95% confidence interval (CI): 0.08–0.88, P=0.03], TNM staging (HR =3.84, 95% CI: 1.38–10.71, P=0.010) were associated with the prognosis of CRC patients.

Conclusions: The mutation rate of MSI-H is higher in young CRC patients compared to older. Our study further confirms that MSI-H can serve as a favorable prognostic marker for CRC patients. This finding may

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provide valuable guidance for clinicians in terms of prognosis assessment and treatment selection. If feasible, we hope that MSI testing can be performed for all CRC patients to enable targeted testing, with particular attention to monitoring the MSI status in young patients. This will aid clinicians in selecting appropriate treatment strategies for these patients.

Introduction

With 1.8 million new cases diagnosed every year and 860,000 deaths per year, colorectal cancer (CRC) is the third most common cancer and the second common cause of cancer-related death, exceeded only by lung cancer (1). CRC is a heterogeneous disease that can be classified into different subtypes with different underlying molecular alterations, such as microsatellite instability (MSI), chromosomal instability, and cytosine-phosphate-guanine (CpG)-islet methylation phenotype (2). MSI is a genomic instability in which mutations occur in nucleotide repeat sequences throughout the genome. These repeats are called microsatellites, and the differences among these sequences in tumors and germ cells are referred to as MSI. MSI arises from defects in the DNA mismatch repair system (3). In recent years, the use of immunotherapy-based drugs to treat CRCs with high MSI-high (MSI-H) or DNA deficient mismatch repair (dMMR) has been surprisingly

successful (4,5). However, we found that the proportion of MSI-H patients in CRC patients with different ages was significantly different. In this study, we focused on a large cohort of younger patients (aged ≤40 years old) and older patients (aged 71–80 years old) with colorectal tumors to explore the incidence of colorectal MSI in patients of different ages and the relationship between colorectal MSI and prognosis. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-4/rc).

Methods

Patient characteristics and data

This study was conducted at the Affiliated Cancer Hospital of Zhengzhou University. A total of 1,901 patients who underwent CRC-related genetic testing from January 2017 to December 2019, of whom 1,654 had MSI test results, were included in the study. Of these 1,654 patients, 960 (58.1%) were men and 694 (41.9%) were women. The patients' ages ranged from 17 to 90 years, with a median age of 61 years. We allocated 100 patients with CRC aged less than 41 years to the younger group, and 305 patients with CRC aged 71 and older but younger than 80 in the older group. The age distribution of these patients is shown in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of the Affiliated Cancer Hospital of Zhengzhou University (No. 2021-KY-0012-001), and the requirement of individual consent for this retrospective analysis was waived.

To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) have undergone preoperative colonoscopy and have a pathological diagnosis of CRC; (II) received perioperative adjuvant therapy; (III)

Highlight box

Key findings
- In this paper, we found that the composition of microsatellite instability (MSI) status varied among patients of different ages.
- MSI-high (MSI-H) mutations were more common in younger patients.

What is known, and what is new?
- Immunotherapy agents have had surprising efficacy in colorectal cancers (CRCs) with MSI-H mutations.
- MSI-H is presented in only about 10% of all CRCs, so testing for MSI is not widely available.

What is the implication, and what should change now?
- It could prevent physicians from not testing young CRC patients for MSI because the detection rate is too low.
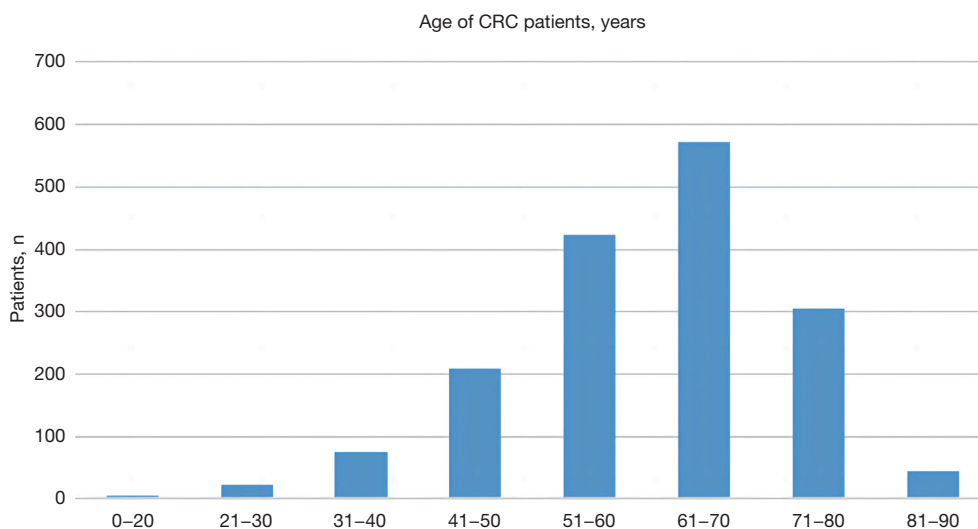

Age of CRC patients, years

Figure 1 Age distribution of the 1,654 CRC patients. CRC, colorectal cancer.

underwent curative surgery for CRC. Each patient was followed up from the time of surgery until April 30, 2023 or death (every 3 months for the first 2 years after surgery, and every 6 months thereafter).

We recorded the patients' age, sex, body mass index (BMI), tumor depth (T), number of metastatic lymph nodes (N), distant metastasis (M), the tumor, node, metastasis (TNM), the staging was based on the 8th edition of the TNM classification system of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC), radicality, tumor size, tumor site (we classified the tumors as proximal and distal, bounded by the splenic flexure of the colon), degree of differentiation, carcinoembryonic antigen (CEA) (ng/mL) level, and MSI status [fluorescence in situ hybridization (FISH) was used to determine MSI expression in CRC patients].

Statistical analysis

The data analysis was performed using SPSS 26.0 (IBM Corp, Armonk, NY, USA). A Chi-squared test was used to assess the significant differences in the clinicopathological features between the younger and older CRC patients. The survival curves were calculated by a Kaplan-Meier survival analysis, and the equivalences of the survival curves were analyzed using the log-rank test. Univariate and multivariate analyses were evaluated using the Cox proportional hazards model. A P value <0.05 was considered statistically significant.

Follow up

All patients were followed up postoperatively. Patients were followed up with postoperative imaging at an interval of 3 months for the first 3 years and at an interval of 6 months for the next 2 years, and annually thereafter. Each follow-up visit included not only a computed tomography scan of the entire body, but also quantitative testing of tumor markers, including CEA, cancer antigen 19-9, and carbohydrate antigen 72-4. The patients also underwent a colonoscopy once a year after surgery.

Results

Study cohort

Of the 1,901 patients, 247 were excluded due to poor sample conditions or inadequate clinical information. *Figure 1* shows the age distribution of the patients in the remaining sample of 1,654. In relation to age, the frequency of MSI-H was significantly higher in patients younger than or equal to 40 years old (33%) than those aged 51–60 years (10.3%, P<0.0001) (*Figure 2*). The staging was based on the 8th edition of the TNM classification system of the Union for International Cancer Control (UICC)/AJCC.

Clinicopathological features of the younger and older CRC patients

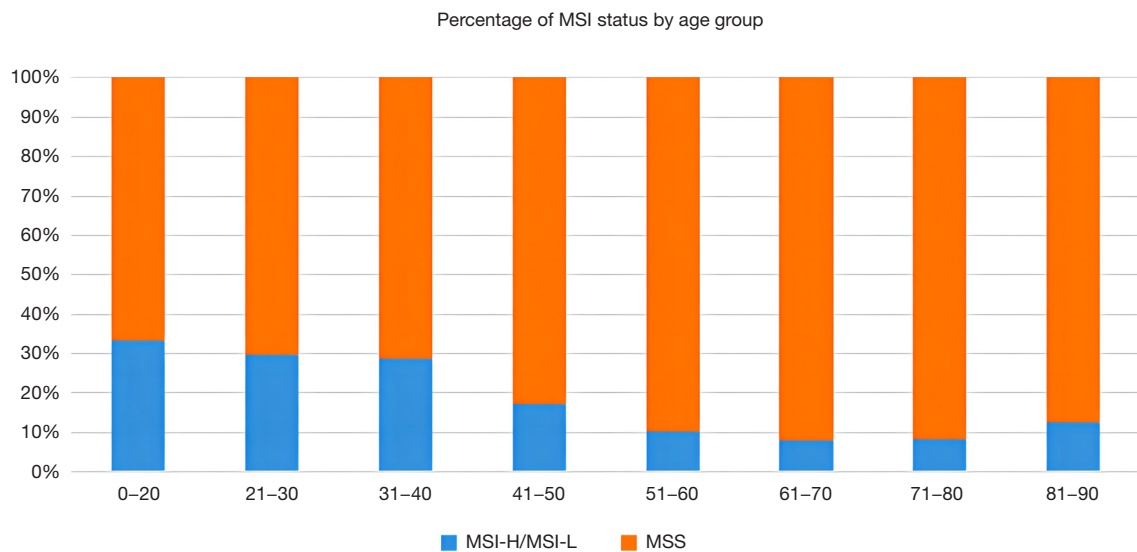The clinicopathological characteristics of the 100 younger

Figure 2 Frequency of MSI-H tumors in each generation of CRC patients. The frequency of MSI-H was significantly higher in patients aged less than or equal to 40 years (33%) than patients aged between 71 and 80 years old (10.16%; P<0.001). MSI, microsatellite instability; MSI-H, MSI-high; MSI-L, MSI-low; MSS, microsatellite stability; CRC, colorectal cancer.

CRC patients and 305 older CRC patients are shown in *Table 1*. There were more women in the older CRC patient group than the younger CRC patient group (47.2% *vs.* 36.3%, P=0.108). The proportion of MSI-H was significantly higher in the younger CRC patients than the older CRC patients (33% *vs.* 10.16%, P<0.001). The proportion of undifferentiated adenocarcinoma was significantly higher in the younger CRC patients than the older CRC patients (53% *vs.* 31.15%, P<0.001). The younger patients had a lower BMI than the older patients (P=0.019). In terms of tumor size, tumor diameter was significantly larger in the younger CRC patients than the older CRC patients. Moreover, tumor differentiation was worse in the younger patients than the older patients (P<0.001). However, in relation to the other characteristics, such as surgical eradication, tumor location, vascular invasion, and nerve invasion, there were no significant differences between the younger and older CRC patients.

Univariate and multivariate analyses

In the Kaplan-Meier survival analyses, the overall survival (OS) time of the 100 younger CRC patients was much better than that of the 305 older CRC patients [*Figure 2*, P=0.111, hazard ratio (HR), 0.725, 95% confidence interval (CI): 0.488–1.076]. We conducted univariate and multivariate analyses to assess the risk factors for prognosis in the 405 CRC patients (*Table 2*). The univariate analysis of patient survival in both cohorts showed that the prognosis of CRC patients was associated with MSI status (P<0.001, HR, 0.297, 95% CI: 0.157–0.565), tumor site (proximal to distal and rectum; P=0.034, HR, 1.406 and 1.846, 95% CI: 0.92–2.147, 1.162–2.931), TNM stage (P<0.001, HR, 1.972, 95% CI: 1.432–2.714), vascular invasion (P=0.007, HR, 1.581, 95% CI: 1.135–2.204), and perineural invasion (P=0.003, HR, 1.751, 95% CI: 1.217–2.519). However, in the multivariate analysis, only MSI status (P<0.001, HR, 0.183, 95% CI: 0.088–0.381), tumor location (P<0.001, HR, 1.25, 2.604, 95% CI: 0.797–1.96, 1.599–4.241) and TNM stage (P=0.005, HR, 1.853, 95% CI: 1.208–2.84) were independent risk factors.

Subgroup analysis

We then independently analyzed the risk factors for prognosis in the 100 younger patients and the 305 older patients. In the younger patients, MSI status, AJCC TNM stage, and vascular invasion were all associated with OS in the univariate analysis, but only MSI status and AJCC TNM stage were independent risk factors for OS in the multivariate analysis (*Table 3*). Among the 305 elderly CRC patients, MSI status, tumor site, tumor size, AJCC TNM

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Table 1 Baseline characteristics of the study population in the younger and older groups

Characteristic	Younger group (n=100)	Older group (n=305)	P value
Sex			0.108
Male	62	161	
Female	38	144	
MSI status			<0.001
MSS	67	274	
MSI-H or MSI-L	33	31	
Tumor location			0.064
Proximal colon	17	84	
Distal colon	59	144	
Rectum	24	77	
BMI			0.019
<24 kg/m^2	81	210	
≥24 kg/m^2	19	95	
Differentiation			<0.001
Poor	53	95	
Well and moderate	47	210	
Tumor size			0.047
<5 cm	44	169	
≥5 cm	56	136	
TNM stage			0.067
I	14	41	
II	38	155	
III	41	84	
IV	7	25	
Vascular invasion			0.594
No	58	173	
Yes	40	105	
Perineural invasion			0.535
No	74	216	
Yes	24	59	
CEA (ng/mL)			0.307
Negative	67	187	
Positive	33	118	

Patients aged 40 or younger are defined as the young group, and patients aged 71 and older but younger than 80 are defined as the elderly group. MSI, microsatellite instability; MSS, microsatellite stability; MSI-H, MSI-high; MSI-L, MSI-low; BMI, body mass index; TNM, tumor, node, metastasis; CEA, carcinoembryonic antigen.

stage, and neurological invasion were all associated with OS in the univariate analysis; however, only MSI status, tumor site, and AJCC TNM stage were independent risk factors for OS in the multivariate analysis (*Table 4*).

Discussion

In the digestive system, MSI-H tumors are commonly found in CRC, pancreatic and gastric cancers (6). No previous studies had been conducted on the relationship between MSI-H tumors and age. A large sample study of unresectable or metastatic solid tumors in Japan examined the proportion of MSI-H in all tumors and found that the proportion was higher in patients aged less than 40 years than those aged over 80 years (7) The reason for the high proportion of MSI-H in patients aged over 80 years may be related to the occurrence of MLH1 promoter methylation (8). The high proportion of MSI-H in young patients may be related to genetic factors, and it is possible that these patients have Lynch syndrome or dMMR syndrome (9,10).

The proportion of MSI-H in the younger patients in this study was as high as 33%, while in the older group of patients, it was only 10.16% (P<0.001). The clinicopathological characteristics of the 100 younger and 305 older CRC patients are set out in *Table 1*. We found that more patients in the younger CRC group had a poorly differentiation of tumors than patients in the older CRC group (53% *vs.* 31.15%, P<0.001). However, in terms of the other characteristics, such as the tumor depth, CEA positive rate, distant metastasis, AJCC TNM stage, tumor size, and tumor depth, there were no significant differences between the younger and older CRC patients.

The 5-year OS rate obtained in our CRC patient cohort (59.3%) was similar to those reported in studies in Brazil (63.5%), Australia (63.0%), and Taiwan (68.7%) (11-13). In our study, the survival analysis showed that the patients in the younger group had a better prognosis than those in the older group. The multivariate analysis showed that MSI status was a significant prognostic factor for survival. The subgroup analysis revealed that MSI-H/MSI-low (MSI-L) status had an independent factor affecting on good prognosis both in the overall CRC cohort and in the younger and older patients, which may be related to the use of immunotherapy in patients (14). In terms of the relationship between tumor site and prognosis, this factor was not statistically significant in the younger group of patients (P=0.435), but was statistically significant

Table 2 Univariate and multivariate analyses of prognostic factors for all CRC patients

Characteristic	Univariate analysis			Multivariate analyses		
	HR	95% CI	P	HR	95% CI	P
Age			0.111			
Older	1					
Younger	0.725	0.488–1.076				
Gender			0.447			
Male	1					
Female	1.132	0.822–1.558				
MSI status			<0.001			<0.001
MSS	1			1		
MSI-H or MSI-L	0.297	0.157–0.565		0.183	0.088–0.381	
Tumor location			0.034			<0.001
Proximal colon	1			1		
Distal colon	1.406	0.920–2.147		1.250	0.797–1.960	
Rectum	1.846	1.162–2.931		2.604	1.599–4.241	
BMI			0.232			
<24 kg/m^2	1					
≥24 kg/m^2	0.797	0.550–1.156				
Differentiation			0.495			
Poor	1					
Well and moderate	1.121	0.807–1.559				
Tumor size			0.293			
<5 cm	1					
≥5 cm	1.187	0.862–1.633				
TNM stage			<0.001			0.005
I and II	1			1		
III and IV	1.972	1.432–2.714		1.853	1.208–2.840	
Vascular invasion			0.007			0.905
No	1			1		
Yes	1.581	1.135–2.204		0.973	0.617–1.532	
Perineural invasion			0.003			0.091
No	1			1		
Yes	1.751	1.217–2.519		1.407	0.947–2.091	
CEA (ng/mL)			0.141			
Negative	1					
Positive	1.276	0.922–1.764				

Patients aged 40 or younger are defined as the young group, and patients aged 71 and older but younger than 80 are defined as the elderly group. CRC, colorectal cancer; HR, hazard ratio; CI, confidence interval; MSI, microsatellite instability; MSS, microsatellite stability; MSI-H, MSI-high; MSI-L, MSI-low; BMI, body mass index; TNM, tumor, node, metastasis; CEA, carcinoembryonic antigen.

Table 3 Univariate and multivariate analyses of prognostic factors for the younger CRC patients

Characteristic	Univariate analysis			Multivariate analyses		
	HR	95% CI	P	HR	95% CI	P
Gender			0.380			
Male	1					
Female	1.373	0.676–2.790				
MSI status			0.003			0.030
MSS	1			1		
MSI-H or MSI-L	0.169	0.051–0.557		0.258	0.076–0.880	
Tumor location			0.435			
Proximal colon	1					
Distal colon	1.912	0.654–5.594				
Rectum	1.363	0.384–4.837				
BMI			0.648			
<24 kg/m^2	1					
≥24 kg/m^2	0.812	0.332–1.985				
Differentiation			0.539			
Poor	1					
Well and moderate	1.247	0.616–2.524				
Tumor size			0.169			
<5 cm	1					
≥5 cm	0.609	0.301–1.234				
TNM stage			<0.001			0.010
I and II	1			1		
III and IV	5.656	2.317–13.810		3.837	1.375–10.707	
Vascular invasion			0.030			0.935
No	1			1		
Yes	2.191	1.077–4.458		1.034	0.465–2.295	
Perineural invasion			0.072			
No	1					
Yes	1.970	0.941–4.124				
CEA (ng/mL)			0.913			
Negative	1					
Positive	0.959	0.451–2.038				

CRC, colorectal cancer; HR, hazard ratio; CI, confidence interval; MSI, microsatellite instability; MSS, microsatellite stability; MSI-H, MSI-high; MSI-L, MSI-low; BMI, body mass index; TNM, tumor, node, metastasis; CEA, carcinoembryonic antigen.

Table 4 Univariate and multivariate analyses of prognostic factors for the older CRC patients

Characteristic	Univariate analysis			Multivariate analyses		
	HR	95% CI	P	HR	95% CI	P
Gender			0.810			
Male	1					
Female	1.045	0.730–1.495				
MSI status			0.036			<0.001
MSS	1			1		
MSI-H or MSI-L	0.442	0.206–0.949		0.171	0.067–0.436	
Tumor location			0.018			<0.001
Proximal colon	1			1		
Distal colon	1.343	0.842–2.143		1.136	0.687–1.877	
Rectum	2.008	1.222–3.299		2.686	1.575–4.578	
BMI			0.210			
<24 kg/m^2	1					
≥24 kg/m^2	0.770	0.511–1.159				
Differentiation			0.447			
Poor	1					
Well and moderate	1.158	0.794–1.689				
Tumor size			0.033			0.115
<5 cm	1			1		
≥5 cm	1.477	1.032–2.113		1.375	0.926–2.043	
TNM stage			0.008			0.023
I and II	1			1		
III and IV	1.625	1.133–2.331		1.599	1.067–2.398	
Vascular invasion			0.058			
No	1					
Yes	1.440	0.987–2.101				
Perineural invasion			0.013			0.212
No	1			1		
Yes	1.698	1.117–2.581		1.321	0.853–2.046	
CEA (ng/mL)			0.095			
Negative	1					
Positive	1.361	0.948–1.953				

CRC, colorectal cancer; HR, hazard ratio; CI, confidence interval; MSI, microsatellite instability; MSS, microsatellite stability; MSI-H, MSI-high; MSI-L, MSI-low; BMI, body mass index; TNM, tumor, node, metastasis; CEA, carcinoembryonic antigen.

in the older group, which may be related to the small sample size of the younger group. Further large-scale and multicenter studies need to be conducted to understand the potential reasons for the differences in outcomes, such as progression-free survival.

After analyzing the data from our unit, we believe that the detection of MSI status is essential for young CRC patients, as it can guide clinical treatment plans. In earlier studies, we found that MSI-H tumors may be insensitive to basic chemotherapy with 5-fluorouracil (10). However, with the introduction of immunotherapy and the advent of immunosuppressive agents [e.g., immune checkpoint inhibitors (ICIs)], ICIs have been shown to have surprising efficacy in the treatment of MSI-H tumors. In the KEYNOTE-164 study, researchers proposed that anti-programmed death-1 therapy has a controlled safety profile for MSI-H/dMMR CRC patients (15). A follow-up KEYNOTE-158 study concluded that ICIs have clinical benefits in patients with unresectable or metastatic MSI-H/dMMR non-CRC (16). The CheckMate 142 trial used a different type of ICIs, but similarly concluded that ICIs could provide a durable response and disease control in patients with dMMR/MSI-H metastatic CRC (17). Moreover, this is not limited to CRC, as similar results have been shown in gastric cancer, indicating that patients with MSI-H can benefit from immunotherapy (18). Thus MSI-H is an important biomarker for predicting the efficacy of ICIs on tumors. However, as CRCs exhibiting MSI-H represent only 10–15% of all CRCs (2), most clinicians do not test for MSI status in CRC patients, despite the availability of more convenient liquid biopsies for clinical implementation (19). Furthermore, high tumor mutational burden (high-TMB), which often co-occurs with MSI-H, can also serve as a prognostic factor for evaluating patient overall survival (20). As a result, patients may not receive the most appropriate treatments, which in turn may affect their prognosis. To our knowledge, this is the first time that MSI data from younger patients in Asia have been compared to the data of older patients. The data and results obtained from this study are informative given the testing protocols and treatment options.

This study had some limitations. First, it was a retrospective study conducted at a single hospital, which may have led to some errors. Second, and perhaps most importantly, while we advised all of the patients who needed adjuvant chemotherapy to attend follow-up appointments at our hospital or other hospitals, not all of them received the follow-up standard treatment. We intend to further validate our findings in a multicenter, large sample study conducted in conjunction with additional units.

Conclusions

MSI-H mutations occur more frequently in younger patients than older patients. This finding provides an important reference basis for clinicians to more accurately conduct targeted testing for patients and to select the most appropriate treatment regimen. By understanding the status of MSI-H mutations, doctors can better evaluate each patient's condition and develop a more personalized treatment plan to improve the treatment effects and patient survival. Physicians should consider MSI-H mutations in young CRC patients. However, in elderly patients, physicians should pay more attention to their physical condition and drug tolerance due to their decreased physical function. When formulating a treatment plan, physicians should fully consider each patient's age, physical condition, and the severity of the disease to select the most appropriate treatment plan. In addition, doctors should pay close attention to the nutritional status and psychological state of elderly patients and provide them with necessary support and nursing. By understanding the occurrence of MSI-H mutations in young CRC patients, physicians can better develop personalized treatment plans for patients, improve treatment efficacy, and patient survival. Doctors should also pay attention to the ages of patients and provide targeted diagnosis and treatment plans for patients of different ages.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-4/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-4/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-4/coif). The authors have no conflicts of interest to declare.

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). The study was approved by the ethics board of the Affiliated Cancer Hospital of Zhengzhou University (No. 2021-KY-0012-001), and the requirement of individual consent for this retrospective analysis was waived.

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