Characteristics of colorectal carcinoma patients with PMS2 defects detected by immunohistochemistry

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Lynch syndrome is the most prevalent form of familial colorectal cancer (CRC) and is caused by pathogenic germline mismatch repair (MMR) gene mutations. MLH1, MSH2 and MSH6 mutations have been well studied, but the rate and characteristics of PMS2 mutations are rare, especially in China. This study enrolled 1706 unselected patients with CRC who underwent colorectal resection from June 2016 to November 2018, the MMR status and clinicopathological features were analysed. A total of 11.8% of patients with CRC had defects in at least one MMR-related protein. Among them, 8.3% were identified with PMS2 defects, and 3.1% of patients had isolated PMS2 defects. Compared with MMR-proficient CRC, PMS2-defect CRC occurred more frequently in the right colon and less frequently in the rectum, had more poorly differentiated and mucinous carcinoma cases, and had fewer perineural invasions and a lower pN stage but a more advanced pT stage and a larger tumour size. In the cases with PMS2 defect, there were fewer tumours in the right colon, fewer poorly differentiated cases and smaller tumour sizes than in the cases with both MLH1 and PMS2 defects. In addition, in cases with isolated PMS2 defects, there were more tumours in the right colon and, more mucinous carcinoma cases than in cases with MMR-proficient CRCs, but had a similar cancer onset age. This study identified the rate, clinicopathological and age characteristics of PMS2 defects in CRCs in China and highlighted the importance of universal screening and germline detection of PMS2 in CRC. *European Journal of Cancer Prevention* 30: 251–257 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Colorectal cancer (CRC) is one of the most prevalent and lethal cancers worldwide, and approximately 20–30% of CRCs are familial (Herzig *et al*., 2017; Bray *et al*., 2018). Lynch syndrome is the most prevalent form of inherited CRC and is caused by germline mismatch repair (MMR) gene (*MLH1*, *MSH2*, *MSH6* or *PMS2*) mutations (Hendriks *et al*., 2006; Boland *et al*., 2018). The general characteristics of Lynch syndrome include a predilection for the right colon poor tumour differentiation with a mucinous component, and extracolonic cancers, especially early age of cancer onset (Sinicrope, 2018). The clinical characteristics, cancer risk, onset age and genetic penetrance of CRC with *MLH1*, *MSH2* and *MSH6* mutation have already been well studied (Hendriks *et al*., 2006; Daniels and Lu, 2015). These three MMR genes account for almost all of the mutations according to previous studies (Lynch and de la Chapelle, 2003). However, although *PMS2* is considered a classical MMR gene in Lynch syndrome, initial studies reported that the mutation rate of *PMS2* was low (0.03–0.4% of unselected CRCs) worldwide as well as in China, and the cancer risk and characteristics of *PMS2*-mutated CRC are poorly known (Sheng *et al*., 2010; Ten Broeke *et al*., 2015; Zheng *et al*., 2017). Therefore, further research focusing on the role of *PMS2* in CRC with Lynch syndrome is urgently needed.

MMR germline mutation can result in MMR protein expression deficiency (deficient MMR, dMMR) and DNA microsatellite instability (MSI). Thus, although the diagnosis of Lynch syndrome is always confirmed by germline genetic testing, methods such as immunohistochemistry staining for MMR proteins and MSI detection are also generally used to prescreen patients for MMR mutations (Hendriks *et al*., 2006). immunohistochemistry detection is not only sensitive in predicting MMR defects (dMMR) but also indicates which MMR protein is defective; in addition, it is more economical and

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practical than other methods. Thus, immunohistochemistry for detecting dMMR is advocated by almost all of the guidelines for Lynch syndrome screening (Stoffel *et al*., 2015; Provenzale *et al*., 2016; Rex *et al*., 2017). In published literature, defects in *MLH1*, *MSH2* and *MSH6* were common, but PMS2 defects were rare in CRC (de Jong *et al*., 2004). However, our recent unpublished study found that PMS2 defects were very common in unselected CRCs, and isolated PMS2 defect rate was as high as 30% in all dMMR CRCs. A recent review indicated that PMS2 mutation was the most common mutation type in Lynch syndrome (Hendriks *et al*., 2006). These findings overturn previous studies of PMS2 and thus attract attention to PMS2 defects in CRC.

Immunohistochemistry detecting dMMR of PMS2 has two potential patterns: combined MLH1 and PMS2 defects and isolated PMS2 defects. The PMS2 and MLH1 proteins form a heterodimer, and MLH1 germline mutation leads to PMS2 expression defects (Senter *et al*., 2008). Thus, *MLH1* mutations would present as MLH1-PMS2 combined defects, while isolated PMS2 defects might indicate a high probability of PMS2 germline mutations (Gill *et al*., 2005). Studies have suggested that PMS2 mutation carriers are at relatively lower risk for CRC than Lynch syndrome patients with other MMR gene mutations and that the penetrance of PMS2 mutations is lower than that of other MMR gene mutations; in addition, detection of PMS2 mutations is technically challenging because of the presence of pseudogenes (Senter *et al*., 2008; Ten Broeke *et al*., 2018). However, existing research on immunohistochemistry-based screening methods for detecting PMS2 defects is relatively sparse worldwide, and no study has specifically focused on PMS2 screening in China. Therefore, a special study to comprehend the distribution of PMS2 defects in China and summarise the associated clinical characteristics is necessary and meaningful.

In the current study, we retrospectively analysed a prospective pathological maintenance database of immunohistochemistry-detected MMR defects in 1706 unselected CRC patients with the aim of exploring the distribution of PMS2 defects and the characteristics of CRC in China.

Material and methods

Patients

From June 2016 to November 2018, 1706 consecutive patients with CRC who underwent surgical resection and underwent immunohistochemistry detection for four MMR proteins in Xiangya Hospital of Central South University (USC) and The First Affiliated Hospital of University of South China (USC) were enrolled. Detailed demographic information and clinicopathological information were collected with a specially assigned member. The information included patient age, sex, tumour location, pathological (pT) stage, lymphovascular invasion, perineural invasion, lymph metastasis (pN) stage, distant metastasis (M) stage, histological differentiation, pathological type, macroscopic type and MMR status. The family history, tumour history and colorectal polyp status were also collected for patients who were identified with dMMR. This study was approved by the ethics committee of Xiangya Hospital of CSU and The First Affiliated Hospital of USC and was in accordance with the Declaration of Helsinki.

Immunohistochemistry

The immunohistochemistry process was conducted by pathologists in the Department of Pathology of the two Hospitals. The paraffin-embedded CRC tissue was cut into 4-μm thickness sections. The paraffin sections were performed immunohistochemistry detection successively as dewaxed, antigen retrieval, block endogenous peroxidase, serum blocking, primary antibodies incubation, horseradish peroxidase (HRP)-conjugated secondary antibody incubation, 3,3N-Diaminobenzidine staining, counterstained by haematoxylin, graded dehydration and mounting as previous described (Zeng *et al*., 2018). The primary antibodies for MMR proteins were ready-to-use antibodies: MLH1 (ZM-0154, Zhongshan Goldenbridge Biotechnology Beijing, P.R. China), MSH2 (ZA-0622, Zhongshan Goldenbridge Biotechnology), MSH6 (ZA-0541, Zhongshan Goldenbridge Biotechnology) and PMS2 (ZA-0542, Zhongshan Goldenbridge Biotechnology). The polymer HRP detection system (PV-9000, Zhongshan Goldenbridge Biotechnology) was used to detect the antigen–antibody binding reaction according to the manufacturer's protocol (Zeng *et al*., 2018). The staining scoring criterion of the grading of staining intensity and the percentage of positive cells was adopted as previously mentioned (Sun *et al*., 2014). The results were evaluated by two independent pathologists with anonymous patient's information.

Statistical analysis

Continuous variables were presented as mean ± SD, categorical variables were described as frequencies (percentages). The one-way ANOVA test was used for comparisons of continuous variables. Pearson Chi-square test or Fisher's exact test was used for analysing categorical variables. The multivariate Cox regression models were employed to identify factors affected PMS2 status of CRC. $P \leq 0.05$ was considered as statistical significance. All of the statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, Illinois, USA) software.

Results

Of the 1706 patients with CRC, 201 patients (11.8%) had at least one MMR protein defect. Among them, 141 patients (8.3%) were identified with loss of PMS2 expression. Overall, 53 patients showed isolated PMS2 defects;

76 patients showed defects in both MLH1 and PMS2; 4 patients showed defects in both MSH6 and PMS2; 1 patient showed defects in MSH2, MSH6 and PMS2; 2 patients showed defects in MLH1, MSH6 and PMS2; and 5 patients showed defects in MLH1, MSH2, MSH6 and PMS3. Because the isolated PMS2 and MLH1-PMS2 subtypes were overwhelmingly more common than the other subtypes, we chose these 129 patients with PMS2-defect CRC for further study, and representative immunohistochemistry images are shown in Fig. 1.

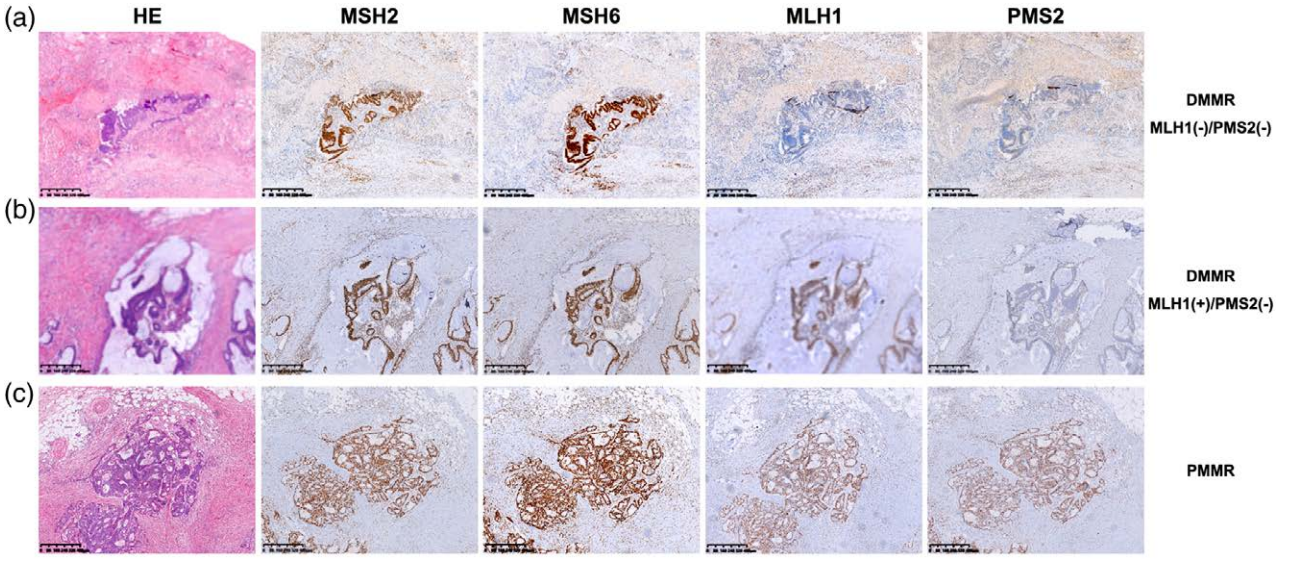
Demographic and clinicopathological characteristics of patients with PMS2 defects and mismatch repair proficiency

We analysed the association of demographic and clinicopathological characteristics with PMS2 expression status, and the results are shown in Table 1. The results showed that compared with MMR-proficient CRC, PMS2-defect CRC occurred more frequently in the right colon and less frequently in the rectum ($P<0.001$), was more likely to be poorly differentiated and more likely to be of the mucinous carcinoma subtype (both $P<0.001$), and had less perineural invasion ($P=0.001$) and lower pN stage ($P=0.006$) but advanced pT stage ($P=0.012$) and larger tumour size ($P<0.001$). However, though diagnostic age is one of the most important factors for Lynch syndrome, it showed no significant difference between the two groups (57.57 ± 13.43 years vs. 59.39 ± 11.81 years, $P>0.05$), even after stratification of the PMS2 group into isolated PMS2 (58.66 ± 13.60 years) and MLH1-PMS2 (56.80 ± 13.34 years) groups ($P>0.05$, not shown in Table 1). These results indicated that PMS2-defective CRC patients were not uncommon in our cohort, and they had previously reported classical characteristics of Lynch syndrome. However, the diagnostic age of patients with PMS2-defective CRCs was similar to that of unselected patients with CRCs, challenging the view that Lynch syndrome-associated CRC usually occurs before the age of 50 years.

Demographic and clinicopathological characteristics of patients with isolated PMS2 and MLH1-PMS2 defects

Because PMS2 expression deficiency had two main types, we next compared the demographic and clinicopathological characteristics, as well as tumour history, family history and colorectal polyp history, between patients with isolated PMS2 defects and patients with MLH1-PMS2 defects, which we also partly explored in a previous study, and the results are shown in Table 2. The results showed that the isolated PMS2 subtype had fewer tumours in the right colon ($P=0.001$), fewer poorly differentiated tumours ($P=0.002$) and smaller tumours ($P<0.001$) than the MLH1-PMS2 subtype. Other factors, such as age, sex, lymphovascular and perineural invasion, pN stage, pT stage, distant metastasis, pathological type, macroscopic type, family history, tumour history and colorectal polyp history, were not different between the two subtypes (all $P>0.05$, Table 2). These results

Fig. 1



Typical immunohistochemical staining for PMS2 in colorectal carcinoma (CRC). (a) This panel shows representative images of CRC samples with loss of both PMS2 and MLH1 expression. (b) This panel shows representative images of CRC samples with isolated expression PMS2 loss. (c) This panel shows representative images of CRC samples with proficient MMR. The scale is shown on the bottom left of each image. MMR, mismatch repair.

Table 1 Demographic and clinicopathological features of mismatch repair proficient and PMS2 defect colorectal cancer patients

Variables	pMMR patients (1505)	PMS2 defect patients (129)	*P* value
Age (years)			
Average	59.39±11.81	57.57±13.43	0.096
<50	315 (20.9%)	35 (27.1%)	0.099
≥50	1190 (79.1%)	94 (72.9%)	
Sex			0.884
Female	640 (42.5%)	54 (41.9%)	
Male	865 (57.5%)	75 (58.1%)	
Location			<0.001
Right colon	324 (21.5%)	71 (55.0%)	
Left colon	437 (29.0%)	45 (34.9%)	
Rectum	744 (49.4%)	13 (10.1%)	
Lymphovascular invasion			0.919
No	1149 (76.3%)	99 (76.7%)	
Yes	356 (23.7%)	30 (23.3%)	
Perineural invasion			0.001
No	1172 (84.5%)	123 (95.3%)	
Yes	233 (15.5%)	6 (4.7%)	
pN stage			0.006
N0	869 (57.7%)	90 (69.8%)	
N1	387 (25.7%)	30 (23.3%)	
N2	249 (16.5%)	9 (7.0%)	
pT stage			0.012
T1	65 (4.3%)	2 (1.6%)	
T2	276 (18.3%)	12 (9.3%)	
T3	984 (65.4%)	93 (72.1%)	
T4	180 (12.0%)	22 (17.1%)	
Distant metastasis			0.591
M0	1396 (92.8%)	118 (91.5%)	
M1	109 (7.2%)	11 (8.5%)	
Differentiation			<0.001
Well differentiated	210 (14.0%)	13 (10.1%)	
Moderately differentiated	1096 (72.8%)	73 (56.6%)	
Poorly differentiated	199 (13.2%)	43 (33.3%)	
Pathological type			<0.001
Adenocarcinoma	1319 (87.6%)	93 (72.1%)	
Mucinous carcinoma	186 (12.4%)	36 (27.9%)	
Macroscopic type			0.213
Massive	424 (28.2%)	43 (33.3%)	
Ulcerous	1081 (71.8%)	86 (66.7%)	
Size (cm)			
Average	4.38±1.95	5.97±3.01	<0.001
<5 cm	940 (62.5%)	47 (36.4%)	<0.001
≥5 cm	565 (37.5%)	82 (63.6%)	

pMMR, MMR proficient; pN, lymph node classification; pT, T classification.

indicated that isolated PMS2-defective CRC might be a special type of Lynch syndrome without typical characteristics and might be more similar to sporadic CRC than Lynch syndrome.

Demographic and clinicopathological characteristics of patients with isolated PMS2-deficient and patients with mismatch repair-proficient colorectal cancer

Because the data showed that patients with isolated PMS2 defects had few common characteristics with patients with MLH1-PMS2 defects, we next compared the demographic and clinicopathological characteristics of patients with isolated PMS2 defects and patients with MMR-proficient CRCs, and the results are shown in Table 3. The results showed that patients with isolated PMS2 defects had more tumours in the colon, especially the right colon ($P<0.001$), and more mucinous carcinoma cases ($P=0.009$) than patients with MMR-proficient CRCs. Other demographic and clinicopathological factors, such as age, sex, lymphovascular and perineural invasion, pN stage, pT stage, distant metastasis, pathological type, differentiation and macroscopic type, were not significantly different between the two groups (all $P>0.05$, Table 3). These findings showed that CRCs with isolated PMS2 defects had some common Lynch syndrome features, such as a predilection for the right colon and a mucinous carcinoma pathological appearance, but other general Lynch syndrome characteristics were not prominent, these were the unique characteristics of patients with isolated PMS2-defect CRC.

Table 2 Demographic and clinicopathological characteristics of isolated PMS2 and MLH1/PMS2 defect

Variables	MLH1/ PMS2 (76)	Isolated PMS2 (53)	*P* value
Age (years)			
Average	56.80±13.34	58.66±13.60	0.442
<50 (47)	23 (30.3%)	12 (22.6%)	0.338
≥50 (112)	53 (69.7%)	41 (77.4%)	
Sex			0.667
Female (64)	33 (43.4%)	21 (39.6%)	
Male (95)	43 (56.6%)	32 (60.4%)	
Location			0.001
Right colon (83)	51 (67.1%)	20 (37.7%)	
Left colon (54)	22 (28.9%)	23 (43.4%)	
Rectum (22)	3 (3.9%)	10 (18.9%)	
Lymphovascular invasion			0.159
No	55 (72.4%)	44 (83.0%)	
Yes	21 (27.6%)	9 (17.0%)	
Perineural invasion			0.689
No	73 (96.1%)	50 (94.3%)	
Yes	3 (3.9%)	3 (5.7%)	
pN stage			0.103
N0	58 (76.3%)	32 (60.4%)	
N1	15 (19.7%)	15 (28.3%)	
N2	3 (3.9%)	6 (11.3%)	
pT stage			0.839
T1	1 (1.3%)	1 (1.9%)	
T2	7 (9.2%)	5 (9.4%)	
T3	54 (71.1%)	34 (64.2%)	
T4	14 (18.4%)	13 (24.5%)	
Distant metastasis			0.640
M0	68 (89.5%)	46 (86.8%)	
M1	8 (10.5%)	7 (13.2%)	
Differentiation			0.002
Well differentiated	4 (5.3%)	9 (17.0%)	
Moderately differentiated	38 (50.0%)	35 (66.0%)	
Poorly differentiated	34 (44.7%)	9 (17.0%)	
Pathological type			0.476
Adenocarcinoma	53 (69.7%)	40 (75.5%)	
Mucinous carcinoma	23 (30.3%)	13 (24.5%)	
Macroscopic type			0.613
Massive	24 (31.6%)	19 (35.8%)	
Ulcerous	52 (68.4%)	34 (64.2%)	
Size			
Average	6.79±3.20	4.80±2.26	<0.001
<5 cm	18 (23.7%)	29 (54.7%)	<0.001
≥5 cm	58 (76.3%)	24 (45.3%)	
Family history			0.699
No	65 (85.5%)	44 (83.0%)	
Yes	11 (14.5%)	9 (17.0%)	
Other tumour history			0.332
No	61 (80.3%)	46 (86.8%)	
Yes	15 (19.7%)	7 (13.2%)	
Colorectal polyp			0.475
Absent	53 (69.7%)	40 (75.5%)	
Present	23 (30.3%)	13 (24.5%)	

pN, lymph node classification; pT, T classification.

Table 3 Demographic and clinicopathological features of isolated PMS2 defect and mismatch repair proficient colorectal cancer patients

Variables	pMMR patients (1505)	Isolated PMS2 defect patients (53)	*P* value
Age (years)			
Average	59.39±11.81	58.66±13.60	0.660
<50	315 (20.9%)	12 (22.6%)	0.764
≥50	1190 (79.1%)	41 (77.4%)	
Sex			0.674
Female	640 (42.5%)	21 (39.6%)	
Male	865 (57.5%)	32 (60.4%)	
Location			<0.001
Right colon	324 (21.5%)	20 (37.7%)	
Left colon	437 (29.0%)	23 (43.4%)	
Rectum	744 (49.4%)	10 (18.9%)	
Lymphovascular invasion			0.260
No	1149 (76.3%)	44 (83.0%)	
Yes	356 (23.7%)	9 (17.0%)	
Perineural invasion			0.051
No	1172 (84.5%)	50 (94.3%)	
Yes	233 (15.5%)	3 (5.7%)	
pN stage			0.592
N0	869 (57.7%)	32 (60.4%)	
N1	387 (25.7%)	15 (28.3%)	
N2	249 (16.5%)	6 (11.3%)	
pT stage			0.237
T1	65 (4.3%)	1 (1.9%)	
T2	276 (18.3%)	5 (9.4%)	
T3	984 (65.4%)	34 (64.2%)	
T4	180 (12.0%)	13 (24.5%)	
Distant metastasis			0.104
M0	1396 (92.8%)	46 (86.8%)	
M1	109 (7.2%)	7 (13.2%)	
Differentiation			0.549
Well differentiated	210 (14.0%)	9 (17.0%)	
Moderately differentiated	1096 (72.8%)	35 (66.0%)	
Poorly differentiated	199 (13.2%)	9 (17.0%)	
Pathological type			0.009
Adenocarcinoma	1319 (87.6%)	40 (75.5%)	
Mucinous carcinoma	186 (12.4%)	13 (24.5%)	
Macroscopic type			0.223
Massive	424 (28.2%)	19 (35.8%)	
Ulcerous	1081 (71.8%)	34 (64.2%)	
Size (cm)			
Average	4.38±1.95	4.80±2.26	0.128
<5 cm	940 (62.5%)	29 (54.7%)	0.253
≥5 cm	565 (37.5%)	24 (45.3%)	

pMMR, MMR proficient; pN, lymph node classification; pT, T classification.

Discussion

The identification of suspected Lynch syndrome-related CRC is important, as patients with this subtype of Lynch syndrome could benefit from genetic counselling, surveillance, and specific treatments, such as subtotal colectomy, prophylactic hysterectomy and immune checkpoint inhibitors (Ma and Zeng, 2014; Boland *et al.*, 2018). Moreover, the identification of this subtype of Lynch syndrome can result in early cancer detection and decreased cancer-related mortality of relatives with Lynch syndrome. A recent study showed that the true prevalence of Lynch syndrome in the overall population is obviously more than is traditionally estimated (Boland *et al.*, 2018). Detecting MMR protein expression with immunohistochemistry is a widely used method to prescreen patients with Lynch syndrome, has high sensitivity (>90%) and consistency with DNA sequencing for mutations, and indicates which MMR protein is potentially mutated. Thus, immunohistochemistry staining to detect four of the MMR proteins is advocated as a universal prescreening test for Lynch syndrome in all newly diagnosed patients with CRC by nearly all guidelines (Provenzale *et al.*, 2016; Vangala *et al.*, 2018).

PMS2 was first cloned and linked to Lynch syndrome by Nicolaides, *et al.* (1994). However, compared with the other MMR proteins, PMS2 has not been as well studied, and the exact incidence and characteristics of PMS2 defect-related Lynch syndrome, especially concurrent with CRC, are still controversial and mysterious (Ten Broeke *et al.*, 2015; Goodenberger *et al.*, 2016). Previous studies have reported that PMS2 mutations account for 1–6% of all identified Lynch syndrome mutations and are associated with a lower risk for Lynch syndrome-related cancer than the other mutations, but the clinicopathological features associated with PMS2 defects are not very clear (Gill *et al.*, 2005; Borràs *et al.*, 2013). However, immunohistochemistry to detect PMS2 defects produces several types, mainly combined MLH1-PMS2 expression loss and isolated PMS2 expression loss. Previous immunohistochemistry studies have consistently shown PMS2 defects in the form of combined MLH1-PMS2 expression loss, which reflects the dysregulation of protein heterodimer formation caused by MLH1 mutation. However, isolated loss of PMS2 expression is typically caused by a PMS2 germline mutation (Sinicrope, 2018). Thus, immunohistochemistry detecting isolated PMS2 expression loss has vital value for the diagnosis of PMS2 germline mutations, but few studies have been conducted worldwide, especially in China (Gill *et al.*, 2005; Senter *et al.*, 2008).

The present study provides the first report of PMS2 expression defect patterns in China. The immunohistochemistry results showed that 11.8% (201/1706) of total CRCs had dMMR; among them, 70.1% (141/201) had PMS2 defects. Strikingly, CRCs with isolated PMS2 defects accounted for 26.4% (53/201) of all dMMR CRCs, which was far beyond the estimated incidence and reported values. PMS2-defective cases were more frequent in the right colon, more poorly differentiated and more likely to be mucinous carcinomas, and had less perineural invasion and lower pN stage but higher pT stage and larger tumour size than MMR-proficient CRCs. However, age was not different between patients with PMS2-defective CRC and unselected patients with CRC. These findings indicate that PMS2-defective CRCs have the classical characteristics of Lynch syndrome, but they likely have later CRC onset than other MMR-related CRCs. In addition, compared with MMR-proficient CRCs, CRCs with isolated PMS2 defects were more often found in the right colon, more likely to be mucinous carcinomas, and more likely to have an advanced pT stage. Furthermore, compared with CRCs with MLH1-PMS2 defects, CRCs with isolated PMS2 defects

were less likely to be in the right colon, were less likely to be poorly differentiated and were smaller tumours. Age was not different between the groups. These findings indicate that CRC with isolated PMS2 defects is atypical for Lynch syndrome-related cancer with only some classical Lynch syndrome features (fewer than those seen in CRCs with MLH1-PMS2 defects).

More importantly, the prevalence of isolated PMS2 defects in our study was obviously higher than that in any former study. Although some studies assumed that the appearance of an isolated PMS2 defect was caused by MLH1 mutation or that no PMS2 mutations occurred, most studies support that isolated PMS2 defects mainly reflect PMS2 mutation (Dudley *et al*., 2015; Ten Broeke*et al*., 2015; Silva *et al*., 2017). Thus, the data presented in our study indicate a high incidence of PMS2 mutations and require further study. Our study findings were also consistent with those from a recent critical review indicating that PMS2 mutations were most common in the general population (Boland *et al*., 2018). The older diagnosis age in this study was also concordant with previous studies, which indicated that colonoscopy surveillance should begin at 35 years of age (Sinicrope, 2018).

Conclusion

Taken together, our results suggest that although the demographic, clinicopathological and age characteristics of CRC patients with isolated PMS2 defects in China were somewhat different from those seen in patients with MMR-proficient CRCs, they were also not typical of Lynch syndrome, increasing the difficulty of differentiating these patients from patients with sporadic CRCs. Thus, further prognostic studies of PMS2-defect CRCs are necessary to update the guidelines and determine whether extended resection or prophylactic operation is appropriate. These findings also highlight the importance of universal screening and germline mutation detection for MMR defects in unselected CRCs.

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Z.Z.J. and X.S. conceived the study and wrote the manuscript; Z.Z.J., Y.Q.J., C.G.D., Z.X.L., P.X.D., H.J., K.F. and X.S. conducted the experiments and contributed to the analysis of data. X.S., Z.Z.J., Y.Q.J., C.G.D. and Z.X.L. collected clinical sample data. X.S., K.F. and P.X.D. revised the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

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