



## 310例结肠癌患者组织MutS同系物和绒毛蛋白的表达与临床病理特征的相关性\*

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**【摘要】目的** 探究结肠癌患者错配修复蛋白MutS同系物(MutS homolog, MSH)2、MSH6、绒毛蛋白(villin)表达及与病理特征的关系。**方法** 选取我院2017年1月–2021年9月经病理确诊的310例结肠癌患者,采用免疫组化法检测MSH2、MSH6和villin表达,分析MSH2、MSH6、villin表达与结肠癌患者临床病理特征的相关性。应用多因素logistic回归分析MSH2、MSH6、villin表达与结肠癌临床病理参数的相关性,用Kaplan-Meier生存曲线比较不同蛋白表达情况的结肠癌患者2年生存率。**结果** 患者癌组织中的MSH2、MSH6和villin蛋白阴性表达率分别为8.71%(27/310)、9.35%(29/310)和46.13%(143/310);癌旁组织中的3种蛋白阴性表达率分别为3.23%(10/310)、4.19%(13/310)和9.68%(30/310),3种蛋白在癌组织中的阴性率均高于癌旁组织( $P<0.05$ )。回归分析显示:癌组织中MSH2及MSH6的表达与结肠癌患者年龄、肿瘤病灶位置、肿瘤分化程度和淋巴结转移相关( $P<0.05$ );癌组织中villin表达与结肠癌患者肿瘤浸润深度、淋巴结转移、远处转移、临床分期相关( $P<0.05$ )。MSH2、MSH6阴性表达患者2年生存率分别为51.85%、44.83%,低于MSH2、MSH6阳性表达的患者(79.51%、80.43%, $P<0.05$ );癌组织中villin阴性表达的患者2年生存率为67.83%,低于villin阳性表达患者(85.03%, $P<0.05$ )。癌组织中的MSH2、MSH6、villin均阴性表达(简称“三阴表达”)的患者有13例(4.1%),其2年生存率为30.77%(4/13),低于不符合三阴表达的结肠癌患者[79.12%(235/297), $P<0.05$ ]。**结论** MSH2、MSH6、villin表达与结肠癌患者临床病理特征相关,检测这3种蛋白表达可能有利于辅助临床进行结肠癌诊治及预后评估。

**【关键词】** 结肠癌 错配修复蛋白MutS同系物2 错配修复蛋白MutS同系物6 绒毛蛋白 病理特征

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**【Abstract】Objective** To examine the relationship between the expressions of mismatch repair proteins, MutS homolog 2 (MSH2) and MutS homolog 6 (MSH6), and villin and the pathological features in patients with colon cancer. **Methods** A total of 310 cases of colon cancer patients who were treated at our hospital between January 2017 and September 2021 were selected. The diagnosis of colon cancer of all patients was verified by pathological evaluation. Immunohistochemistry was used to determine the protein expressions of MSH2, MSH6, and villin. The correlation between the expressions of MSH2, MSH6, and villin and the clinicopathological parameters in patients with colon cancer was analyzed accordingly. Multivariate logistic regression was used to analyze the correlation between the expressions of MSH2, MSH6, and villin and the clinicopathological parameters of colon cancer. Kaplan-Meier survival curve was used to compare the 2-year survival rates of colon cancer patients with different expression levels of the proteins. **Results** Among the 310 patients with colon cancer, the negative expression rates of MSH2, MSH6, and villin proteins in cancer tissues were 8.71% (27/310), 9.35% (29/310), and 46.13% (143/310), respectively. The negative expression rates of the three proteins in tissues adjacent to cancer were 3.23% (10/310), 4.19% (13/310), and 9.68% (30/310), respectively. The negative expression rates of the three proteins in cancer tissues were all higher than those in adjacent tissues ( $P<0.05$ ). Regression analysis showed that the expression of MSH2 and MSH6 in cancer tissues was correlated with the age, the location of tumor lesions, tumor differentiation degree, and lymph node metastasis in colon cancer patients ( $P<0.05$ ). The expression of villin in the cancer tissue is correlated with the depth of tumor infiltration, lymph node metastasis, distant metastasis, and clinical staging status in colon cancer patients ( $P<0.05$ ). The 2-year survival rates of patients with negative expressions of MSH2 and MSH6 were 51.85% and 44.83%, respectively, which were lower than those of patients with positive expression of MSH2 and MSH6 (79.51% and 80.43%,  $P<0.05$ ). Thirteen patients (4.1%) had negative expression

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of MSH2, MSH6, and villin (referred to as "triple negative expressions") in the cancer tissues, and their 2-year survival rate was 30.77%, which was lower than that of colon cancer patients who did not meet the criteria for triple negative expressions (79.12% [235/297],  $P < 0.05$ ). **Conclusion** The expressions of MSH2, MSH6, and villin are closely correlated with the pathological features of colon cancer patients. Evaluating the expression of the three proteins may assist in the clinical diagnosis, treatment, and prognosis evaluation of colon cancer.

**【Key words】** Colon cancer Mismatch repair protein MutS homolog 2 Mismatch repair protein MutS homolog 6 Villin Pathological characteristics

结肠癌的疾病进展、预后与相关基因及其表达产物密切相关, DNA错配修复缺陷导致的微卫星不稳定性在结肠癌诊治及预后评估方面有重要提示意义, 错配修复缺陷蛋白具有维持人基因组稳定性和降低自身突变的作用, MutS同系物2(MutS homolog 2, MSH2)及MutS同系物6(MutS homolog 6, MSH6)是关键错配修复蛋白, MSH2、MSH6可识别并修复DNA在复制中的错配现象, 若二者阴性表达会造成肿瘤基因组微卫星不稳定<sup>[1-2]</sup>。绒毛蛋白(villin)属于钙调节的肌动蛋白结合蛋白, 表达于正常成人的小肠黏膜、胰管、肝胆管、胆囊上皮等组织中, 其被认为是重要的肠道分化标志物之一<sup>[3]</sup>。目前, 错配修复蛋白和villin表达在结肠癌风险评估、诊断和预后评估中的价值已多有报道, 错配修复蛋白与约85%遗传性非息肉病性结直肠癌存在明显联系, 证实了villin参与结直肠癌的发生发展过程, 但MSH2、MSH6、villin与临床病理特征的相关性仍存在争议<sup>[4-6]</sup>。基于此, 本研究通过检测行外科手术治疗结肠癌患者的MSH2、MSH6和villin表达情况, 分析上述蛋白与结肠癌患者病理特征的关系, 以期结肠癌临床诊治提供参考依据。

## 1 资料与方法

### 1.1 研究对象

选择2017年1月-2021年9月在我院诊治的结肠癌患者310例作为研究对象。纳入标准: ①按诊断标准<sup>[7]</sup>, 经病理切片确诊为原发性结肠癌; ②均接受结肠癌根治术治疗且术后进行免疫组化检测MSH2、MSH6及villin表达; ③病例资料详细、病理记录完整; ④患者及家属均知情并签署同意书。排除标准: ①结肠恶性间质瘤及淋巴瘤; ②家族性腺瘤性息肉病; ③合并其他恶性肿瘤; ④术前已行化疗、放疗或其他免疫抑制剂治疗; ⑤伴有精神认知障碍; ⑥随访资料缺失。本研究经院伦理委员会批准(批准号HNYZLLWYH-2021-013)。收集入组患者年龄、病理分型、组织学类型、病灶大小、部位、分化程度、浸润深度、转移情况及临床分期等。

### 1.2 免疫组化染色检测MSH2、MSH6和villin表达

结肠癌根治术后, 取入组患者结肠癌组织及距癌组

织边缘2 cm的癌旁组织, 于-80 °C冷冻保存待检。将标本固定、脱水、石蜡包埋后切片, 厚度约4 μm, 经脱蜡、抗原修复后, 脱蜡水化, 冲洗、浸泡, 消除内源性过氧化酶活性, 室温孵育。一抗为来源于北京艾柏森公司的兔抗人MSH2、MSH6和villin单克隆抗体, 稀释浓度1 : 100。4 °C冰箱保存过夜之后冲洗, 滴加二抗并孵育, 再次冲洗、显色、苏木精复染、脱水、封片后, 以PBS为阴性对照, 在400高倍显微镜下观察切片, 每张随机选取5个视野。

MSH2、MSH6以细胞核内有棕黄色颗粒为阳性, 细胞核内无着色为阴性; villin以细胞浆内有棕黄色着色为阳性, 以细胞浆内无着色为阴性。以每个视野下的染色情况和阳性细胞占比进行评价, 染色从无、浅黄色到棕黄/褐色, 分别计0分、1分、2分; 阳性细胞从1% ~ 25%、26% ~ 50%、51% ~ 75%、> 75%, 分别计1分、2分、3分、4分。检测结果 = 染色评分 × 阳性细胞占比评分, 总分0 ~ 2分为阴性表达, ≥ 3分为阳性表达<sup>[8]</sup>。结果均由经验丰富的2名病理科医师行双盲法阅片。计算MSH2、MSH6和villin的阴性表达率。

### 1.3 随访患者生存情况

入组患者术后均进行2年门诊或电话形式随访, 前6个月每月随访1次, 之后为每3个月随访1次, 统计患者生存率及总生存期。总生存期为从随机分组开始到患者死亡时间。

### 1.4 统计学方法

采用SPSS 24.0整合分析资料数据, 计数资料蛋白缺失率、阳性率以例数(%)表示, 行 $\chi^2$ 检验; 应用多因素logistic回归分析MSH2、MSH6、villin表达与结肠癌临床病理参数的相关性,  $\alpha_{\text{纳入}} = 0.05$ ,  $\alpha_{\text{排除}} = 0.10$ ; 用Kaplan-Meier法绘制结肠癌患者生存曲线, 行log rank  $\chi^2$ 检验比较不同蛋白表达情况的结肠癌患者2年生存率。  $P < 0.05$ 为差异有统计学意义。

## 2 结果

### 2.1 MSH2、MSH6和villin在结肠癌中的表达

310例结肠癌患者, 癌组织中的MSH2、MSH6和villin阴性表达率分别为8.71%(27/310)、9.35%(29/310)和

46.13%(143/310); 癌旁组织中的MSH2、MSH6和Villin阴性表达率分别为3.23%(10/310)、4.19%(13/310)和9.68%(30/310)。MSH2、MSH6和villin在癌组织中的阴性率均高于癌旁组织( $\chi^2=8.307、6.538、102.375, P<0.05$ ), 见图1。

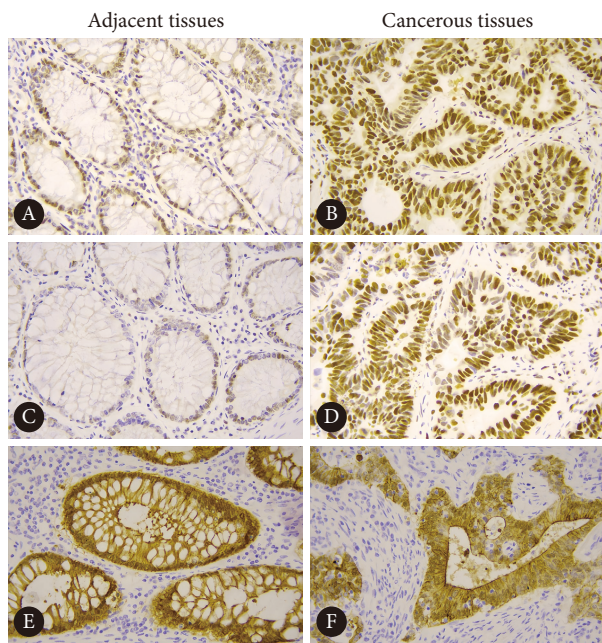


图1 结肠癌患者癌旁组织(A、C、E)及癌组织(B、D、F) MSH2(A、B)、MSH6(C、D)、villin(E、F)表达的免疫组化染色( $\times 400$ )  
Fig 1 Staining results for MSH2 (A and B), MSH6 (C and D), and villin (E and F) protein expression in the tissues adjacent to a tumor (A, C, and E) and the cancerous tissues (B, D, and F) of colon cancer patients (original magnification  $\times 400$ )

## 2.2 癌组织中MSH2、MSH6、villin表达与结肠癌临床病理参数的关系

相较于年龄 $>60$ 岁、肿瘤病灶位于左半结肠、高分化、无淋巴结转移的结肠癌患者, 年龄 $\leq 60$ 岁、肿瘤病灶位于右半结肠、中低分化、淋巴结转移患者MSH2及MSH6阴性表达率较高( $P<0.05$ ); 相较于浸润深度在T1~T2、淋巴结无转移、远处无转移及临床I期患者, 浸润深度在T3~T4、淋巴结转移、远处转移及临床II~III期的结肠癌患者villin阴性表达率较高( $P<0.05$ ), 见表1。

## 2.3 多因素logistic回归分析癌组织中MSH2、MSH6、villin表达与结肠癌临床病理参数的相关性

将单因素分析中有统计学意义的指标引入多因素logistic回归模型, 结果显示: MSH2及MSH6的阴性表达与结肠癌患者年龄、肿瘤病灶位置、肿瘤分化程度和淋巴结转移密切相关( $P<0.05$ ); villin阴性表达与结肠癌患者肿瘤浸润深度、淋巴结转移、远处转移、临床分期密切相关( $P<0.05$ ), 见表2。

## 2.4 癌组织中不同MSH2、MSH6、villin表达的结肠癌患者生存情况

整体上, 患者2年生存率为77.10%(239/310)。癌组织MSH2阴性表达者的2年生存率为51.85%(14/27), 低于MSH2表达阳性者[79.51%(225/283)]( $\log \text{rank } \chi^2=11.769, P<0.05$ ); MSH6阴性表达者的2年生存率为44.83%(13/29), 低于MSH6表达阳性者[80.43%(226/281)]( $\log \text{rank } \chi^2=16.976, P<0.05$ ); villin阴性表达的患者2年生存率为67.83%(97/143), 低于villin阳性表达者[85.03%(142/167)]( $\log \text{rank } \chi^2=4.718, P<0.05$ ), 癌组织MSH2、MSH6、villin均阴性表达患者的2年生存率为30.77%(4/13), 低于其他结肠癌患者(不符合癌组织MSH2、MSH6、villin均阴性表达)的79.12%(235/297)( $\log \text{rank } \chi^2=17.547, P<0.05$ ), 见图2。

## 3 讨论

目前我国结肠癌发病率及病死率仍处于较高水平<sup>[9-10]</sup>。研究表明, 年龄、肿瘤分期、淋巴结转移等影响结肠癌术后患者预后<sup>[11]</sup>。而对分子生物学深层次的研究, 让临床认识到分子类型可能与肿瘤病理特征、肿瘤生物学行为有关<sup>[12]</sup>。故分析不同分子生物学分型的结肠癌患者病理特征, 对临床防治结肠癌有重要意义。

目前, 临床认为肿瘤微卫星不稳定性是癌症发病的分子生物学机制之一<sup>[13-14]</sup>。MSH2及MSH6是DNA错配修复过程的必需蛋白, 二者失活会导致微卫星不稳定<sup>[15-16]</sup>。本研究310例结肠癌患者癌组织中的MSH2、MSH6阴性表达率分别为8.71%、9.35%, 与马春涛等<sup>[17]</sup>结果类似。国外研究显示, 肿瘤患者癌组织中错配修复蛋白家族成员整体阴性表达率约15%<sup>[18]</sup>, 与国内研究有一定差异, 这可能与不同地区、种族人群遗传因素和生活方式存在差异有关<sup>[19]</sup>。本研究中癌组织MSH2、MSH6阴性率均高于癌旁组织, 这与癌组织中错配修复蛋白缺失可造成结肠癌肿瘤细胞高度微卫星不稳定性的病理过程相符。谢仲鹏等<sup>[20]</sup>发现, 癌组织中错配修复蛋白阴性与结肠癌患者年龄、肿瘤部位、肿瘤大小、分化程度、组织类型有关。潘思琼等<sup>[21]</sup>研究则表明, 出现淋巴结转移的结肠癌患者癌组织中的MSH2及MSH6阴性率较高。本研究结论与以往研究类似, 原因可能与癌组织中MSH2、MSH6的功能协同性有关, 二者结合后形成二聚体复合物发挥识别并参与完成错配修复的功能, 也与结肠癌分子生物学发病机制相一致。另外, 本研究中, 癌组织中MSH2、MSH6阴性患者2年生存率普遍较低, 说明癌组织MSH2、MSH6表达与结肠癌患者预后有关, 提示癌组织MSH2、MSH6可能为结

表 1 癌组织中MSH2、MSH6、villin蛋白阴性表达与结肠癌临床病理参数的关系

Table 1 Relationship between the negative expression of MSH2, MSH6, and villin proteins and clinical pathological parameters of colon cancer

Clinical pathological parameter	<i>n</i>	MSH2/case (%)	$\chi^2$	<i>P</i>	MSH6/case (%)	$\chi^2$	<i>P</i>	Villin/case (%)	$\chi^2$	<i>P</i>
Age			5.009	0.025		4.578	0.032		2.155	0.142
≤60 yr.	166	20 (12.05)			21 (12.65)			83 (50.00)		
>60 yr.	144	7 (4.86)			8 (5.56)			60 (41.67)		
Pathological type			0.229	0.632		0.366	0.545		2.153	0.142
Ulceration	208	17 (8.17)			18 (8.65)			102 (49.04)		
Protuberance	102	10 (9.80)			11 (10.78)			41 (40.20)		
Histological type			0.233	0.629		0.857	0.355		0.461	0.497
Mucinous adenocarcinoma	273	23 (8.42)			24 (8.79)			124 (45.42)		
Non-mucinous adenocarcinoma	37	4 (10.81)			5 (13.51)			19 (51.35)		
Diameter of the lesion			0.816	0.366		0.335	0.563		0.548	0.459
≤5 cm	197	15 (7.61)			17 (8.63)			94 (47.72)		
>5 cm	113	12 (10.62)			12 (10.62)			49 (43.36)		
Focal site			5.629	0.018		5.059	0.024		0.270	0.603
Left hemicolon	136	6 (4.41)			7 (5.15)			65 (47.79)		
Right hemicolon	174	21 (12.07)			22 (12.64)			78 (44.83)		
Degree of differentiation			5.514	0.019		6.288	0.012		0.977	0.323
Well-differentiated	82	2 (2.44)			2 (2.44)			34 (41.46)		
Medium and low levels of differentiation	228	25 (10.96)			27 (11.84)			109 (47.81)		
Infiltration depth			0.268	0.605		0.031	0.861		16.300	<0.001
T1-T2	79	8 (10.13)			7 (8.86)			21 (26.58)		
T3-T4	231	19 (8.23)			22 (9.52)			122 (52.81)		
Lymphatic metastasis			5.025	0.025		4.970	0.026		7.786	0.005
No	178	10 (5.62)			11 (6.18)			70 (39.33)		
Yes	132	17 (12.88)			18 (13.64)			73 (55.30)		
Distant metastasis			0.379	0.528		0.155	0.694		4.421	0.035
No	244	20 (8.20)			22 (9.02)			105 (43.03)		
Yes	66	7 (10.61)			7 (10.61)			38 (57.58)		
Pathological stage			3.321	0.190		3.310	0.191		18.551	<0.001
I	36	3 (8.33)			3 (8.33)			5 (13.89)		
II	151	9 (5.96)			10 (6.62)			71 (47.02)		
III	123	15 (12.20)			16 (13.01)			67 (54.47)		

肠癌预后评估指标。

villin能使肠黏膜上皮管腔表面的肌动蛋白聚集形成微丝,具有捆绑、切割、戴帽和成核等功能<sup>[22-24]</sup>。该蛋白表达仅限于上皮性肿瘤而不表达于肉瘤、黑色素瘤、淋巴瘤等,具备组织特异性<sup>[25-27]</sup>。也有研究发现,villin蛋白在腺样分化的胃肠道癌、胆囊癌等癌组织呈异常表达<sup>[27-29]</sup>,本研究结果与之类似,且显示浸润深度在T3~T4、淋巴

结转移、远处转移及临床Ⅱ~Ⅲ期的结肠癌患者癌组织中villin阴性率较高,这说明癌组织villin阳性表达减少可能参与了结肠腺癌的浸润转移。本研究中,癌组织villin阴性者2年生存率低于villin阳性者,说明癌组织villin表达也与结肠癌患者生存期有关,提示临床可将癌组织中的villin作为结肠癌预后评估指标。另外,本研究癌组织中3种蛋白均阴性表达的患者2年生存率远低于非

表 2 多因素logistic回归分析癌组织中MSH2、MSH6、villin表达与结肠癌临床病理参数的相关性

Table 2 Multivariate logistic regression analysis of the correlation between MSH2, MSH6, and villin expression and clinical pathological parameters of colon cancer

Variable	$\beta$	SE	Wald $\chi^2$	OR	95% CI	P
Negative expression of MSH2						
Age $\leq$ 60 yr.	1.020	0.487	4.387	2.773	1.068-7.203	0.037
Tumor lesion located in the right colon	1.043	0.416	6.286	2.838	1.256-6.413	0.013
Moderate to low differentiation	1.486	0.518	8.230	4.419	1.601-12.198	0.004
Lymph node metastasis	0.893	0.341	6.858	2.442	1.252-4.765	0.009
Negative expression of MSH6						
Age $\leq$ 60 yr.	0.935	0.406	5.304	2.547	1.149-5.645	0.022
Tumor lesion located in the right colon	0.933	0.379	6.060	2.542	1.209-5.343	0.014
Moderate to low differentiation	1.563	0.475	10.828	4.773	1.881-12.110	0.001
Lymph node metastasis	0.542	0.246	4.854	1.719	1.062-2.785	0.028
Negative expression of villin						
Infiltration depth is between T3-T4	0.667	0.285	5.477	1.948	1.114-3.406	0.019
Lymph node metastasis	0.641	0.234	7.504	1.898	1.200-3.003	0.006
Transfer appears in the distance	0.415	0.168	6.102	1.514	1.090-2.105	0.014
Clinical stages II - III	1.739	0.543	10.257	5.692	1.963-16.499	0.001

$\beta$ : partial regression coefficient; SE: standard error; OR: odds ratio; CI: confidence interval.

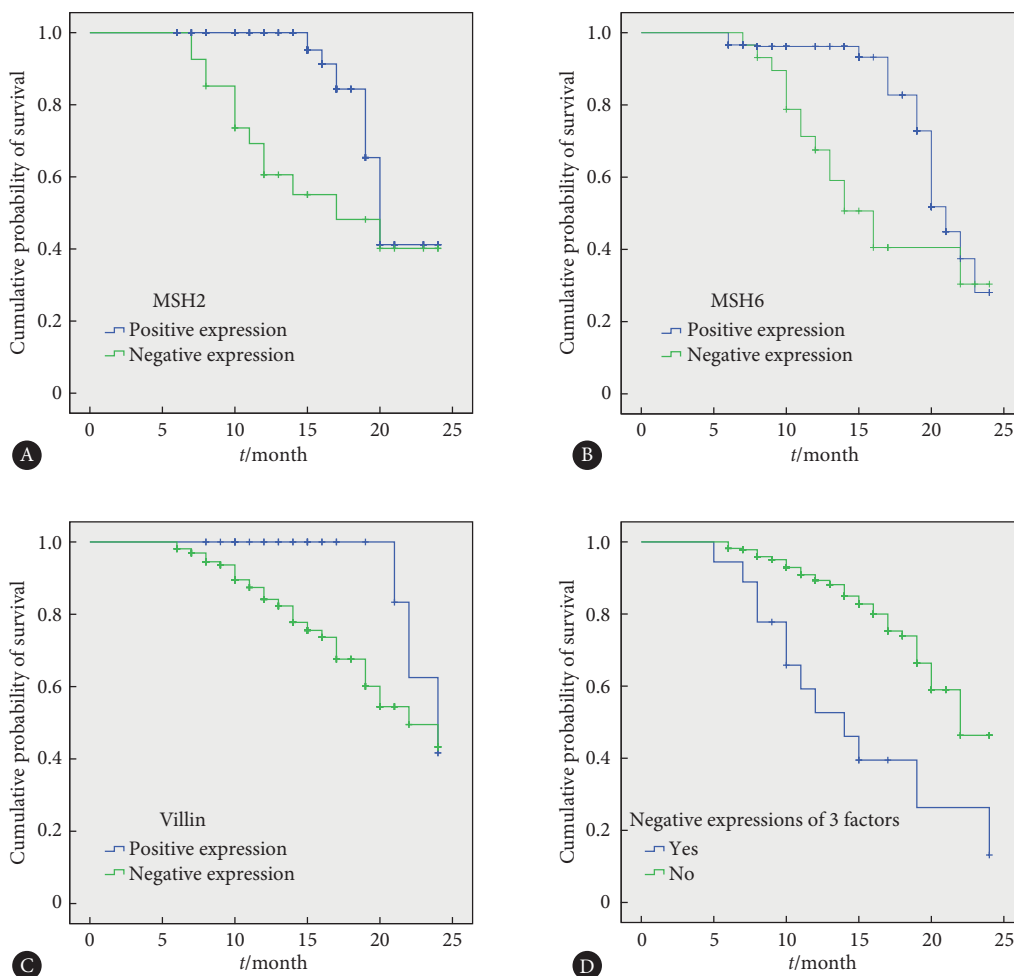


图 2 癌组织中不同MSH2、MSH6和villin蛋白表达状态影响结肠癌患者总生存的Kaplan-Meier曲线

Fig 2 Different expressions of MSH2, MSH6, and villin proteins in cancer tissues affect Kaplan-Meier curve of overall survival of patients with colon cancer

A: MSH2 expression; B: MSH6 expression; C: villin expression; D: combination of three factors (MSH2, MSH6, and villin).

三者均阴性患者,说明在结肠组织从正常-腺瘤-腺癌的演变过程中,癌组织中MSH2、MSH6和villin的表达均呈逐渐下降趋势,虽然MSH2、MSH6与villin作用机制不同,但作用结果类似,联合检测三者表达可提高结肠癌预后评估准确性。

综上所述,结肠癌组织MSH2、MSH6、villin表达与部分病理特征具有相关性,检测癌组织中的这三种蛋白表达可能有利于辅助临床进行结肠癌诊治及预后评估。但由于本研究结论来自单一中心的小样本,未来仍需多中心大样本进行进一步验证。

\*                    \*                    \*

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