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ORIGINAL ARTICLE

Case Control Study

Protective effect of appendectomy against the onset of ulcerative colitis: A case-control study

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Abstract

BACKGROUND

Previous studies suggest that appendectomy has a protective effect against ulcerative colitis (UC); however, relatively few studies focusing on this topic have been reported in China.

AIM

To explore the correlation between appendectomy and the onset of UC.

METHODS

A total of 313 patients with newly diagnosed UC and 313 healthy individuals were selected for this study. According to whether their appendix was removed before the diagnosis of UC, patients were divided into appendectomized and non-appendectomized groups. Their general clinical data, appendectomy history, disease severity, extent of involvement, and blood routine test results were collected to evaluate the relationship between appendectomy and the onset of UC.

RESULTS

The study revealed that the average time interval for the diagnosis of UC after appendectomy was 14.72 ± 13.87 years. 55.81% patients were diagnosed with UC five years after appendectomy. Among them, eight patients underwent appendectomy before the age of 20 years and were diagnosed with UC five years later. In the appendectomized group, the onset age of UC was higher, and the degree of disease activity was significantly lower. This group had a higher proportion of patients in clinical remission or with mild disease and a lower proportion of

patients with severe disease. The extent of lesions in the appendectomized group was limited, with a higher proportion of E1 and E2, whereas a lower proportion of E3 lesions.

CONCLUSION
Appendectomy may delay the onset of UC, reduce disease severity, and lessen the scope of involvement.

Key Words: Appendectomy; Ulcerative colitis; Clinical features; Disease severity; Extent of lesions

Core Tip: Our study found that appendectomy may delay the onset of ulcerative colitis (UC), reduce disease severity, and lessen the scope of involvement. This study provided evidence that appendectomy plays an important role in the occurrence and development of UC. A further prospective randomized trial evaluating the improvement of appendectomy on the disease course of UC may be feasible.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic intestinal inflammatory disease with an unclear etiology and pathogenesis, mainly involving the sigmoid colon and rectum. The lesions are mostly limited to the mucosa and submucosa, and rarely involve the entire thickness of the colon[1]. The main clinical manifestations are abdominal pain, recurrent diarrhea, and the presence of mucus and blood in stools. In severe cases, UC can lead to toxic megacolon and may even progress to cancer. More than 25% of patients experience extraintestinal manifestations. The overall incidence of UC in China is about 0.0116% and shows a significant upward trend[2]. Owing to the unclear cause and the lack of a complete cure, the disease course of patients with UC is prolonged, with alternate periods of acute attacks and remission, significantly reducing their quality of life[3].

Current studies suggest that the pathogenesis of UC is a result of the combined effects of immune, environmental, and other factors[4]. Among these, abnormal immune function plays a major role[5]. The appendix is an immune organ and an important component of gut-associated lymphoid tissue. Compared with the colon, the appendix is rich in T lymphocytes and B lymphocytes, serving as a reservoir for intestinal microorganisms[6]. The intestinal flora and immune function of the appendix play an important role in the maintenance of intestinal homeostasis.

In 1958, Lumb and Protheroe[7] first found that periappendicular inflammatory lesions could act as skip lesions of UC, occurring not only in the UC of the right side or total colon, but also in patients with mild UC with lesions limited to the left colon or rectum. This finding suggests that appendicitis or periappendicular inflammatory lesions might play a certain role in the occurrence of UC. Later, Rutgeerts *et al*[8] found that compared to patients who had not undergone appendectomy, those who had undergone appendectomy in the past had a 29.4 times lower risk of developing UC. Cosnes *et al*[9] found that appendectomy can reduce disease activity in patients with UC and reduce the risk of colectomy. Mayer and Eisenhardt[10] suggested that the protective effect of appendectomy on UC may be closely related to T lymphocytes. In different mouse models of colitis, including those with T-cell receptor alpha mutation and models induced by dextran sulphate sodium salt, removal of inflamed cecum patches (akin to the human appendix) could prevent the occurrence of colitis[11]. Further research on cellular changes during appendicitis found that Paneth cells increased, goblet cells decreased, and crypt abscesses increased significantly, similar to the cellular changes observed during colonic inflammation[12]. However, the exact relationship between the appendix and the pathogenesis of UC remains unclear. Recent studies suggest that CD4+ and CD8+ regulatory T cells, natural killer T cells, and immunoglobulin A in the appendix may play a major role in the pathogenesis of UC[12,13].

Many international studies suggest that undergoing an appendectomy before being diagnosed with UC can afford a protective effect against the occurrence and development of the disease. However, there is a scarcity of research on the relationship between appendectomy and UC in China. This study aims to study the correlation between a history of appendectomy and the clinical characteristics of newly diagnosed UC.

MATERIALS AND METHODS

Study subjects

Following a review and approval by the ethics committee (approval No. K202303-20), this study enrolled 626 participants,

comprising 313 patients newly diagnosed with UC and 313 healthy individuals without any underlying diseases, from the First Affiliated Hospital of Xinjiang Medical University from January 2011 to December 2021. Participants were categorized into two groups based on their UC diagnosis: The UC group (313 cases) and the non-UC group (313 cases). Within the UC group, participants were further divided based on whether they had undergone an appendectomy before being diagnosed with UC, resulting in 43 cases (13.74%) in the appendectomized group and 270 cases (86.26%) in the non-appendectomized group.

Inclusion criteria

The study included patients with UC who were newly diagnosed according to the "Consensus Opinion on the Diagnosis and Treatment of Inflammatory Bowel Disease (2018, Beijing)"[14] along with healthy individuals without any underlying diseases, while ensuring that all included cases had complete data.

Exclusion criteria

Individuals previously diagnosed with Crohn's disease or those with an unclear diagnosis; patients with UC who also had infectious colitis, ischemic colitis, or other severe intestinal diseases, as well as those who had previously undergone a colectomy; those with a history of tonsillectomy; individuals diagnosed with hypertension, diabetes, or coronary heart disease; and cases with incomplete data were excluded from the study.

Study methods

The baseline data of patients collected in this retrospective case–control study included age, sex, nationality (Han *vs* ethnic minorities), area of residence (urban *vs* rural), education level (categorized into low and middle education equivalent to high school and below, and higher education, which is beyond high school), smoking history (smokers *vs* non-smokers), drinking history (with and without a history of alcohol consumption), history of appendectomy, disease severity, extent of disease involvement, and blood routine indicators. The blood routine indicators included white blood cell (WBC) count, neutrophil count, lymphocyte count, monocyte count, red blood cell (RBC) count, hemoglobin (Hb), platelet (PLT) count, neutrophil-to-lymphocyte ratio (NLR), and PLT-to-lymphocyte ratio (PLR). The study then aimed to analyze the correlation between appendectomy and the clinical features of the onset of UC.

The modified Mayo score system[14] was used to evaluate the activity of the disease, by considering factors such as the frequency of defecation, the degree of blood in the stool, endoscopic findings, and the overall evaluation of the physician. The extent of lesions was classified according to the Montreal classification[15] into three categories: E1, E2, and E3, E1 represents involvement limited to the rectum, E2 represents involvement limited to a proportion of the colorectum distal to the splenic flexure, and E3 represents involvement extends proximal to the splenic flexure.

Statistical analysis

Data were analyzed using SPSS version 26.0 (IBM, Armonk, NY, United States). The measurement data were tested for normal distribution. Data that conformed to a normal distribution were expressed as the mean ± SD, and comparisons between groups were conducted using the two-independent sample *t*-test. Data not conforming to a normal distribution were represented by the median (lower quartile, upper quartile), with the Mann–Whitney *U* test used for between-group comparisons. Categorical data were expressed as numbers and percentages (%), and the Chi-square test was used for comparisons between groups. Blood routine factors influencing the onset of UC were analyzed using binary logistic regression analysis. The dependent variable in this analysis was the diagnosis of UC, with a score of 1 indicating UC and 0 indicating non-UC. A *P*-value of < 0.05 was considered statistically significant.

RESULTS

Comparison of clinical data between the UC and non-UC groups

A total of 626 patients were included in this study, which were divided into the UC group (313 cases) and the non-UC group (313 cases), and their clinical data were compared and analyzed. According to the baseline clinical data, no statistically significant differences were observed between the two groups in terms of age, sex, and education level. However, statistically significant differences were noted in nationality, area of residence, smoking habits, and alcohol consumption, as shown in Table 1.

Blood routine test results showed statistically significant differences in WBC count, neutrophil count, lymphocyte count, monocyte count, RBC count, Hb, PLT count, NLR, and PLR between the groups, as shown in Table 2.

Blood routine factors influencing the onset of UC

The variables from the blood routine tests mentioned above were incorporated into a binary logistic regression analysis, and the fit of the regression equation was evaluated ($P = 0.651$), indicating that the equation fitted well. The results showed that monocyte count and Hb levels were the factors influencing the onset of UC ($P < 0.05$). Specifically, monocyte count was a risk factor for the development of UC [odds ratio (OR) = 16.039, 95%CI: 4.312–59.653, $P < 0.001$], whereas Hb level served as a protective factor (OR = 0.975, 95%CI: 0.961–1.005, $P < 0.001$), as shown in Table 3.

Table 1 General clinical data of patients, *n* (%)/mean ± SD

	UC (*n* = 313)	Non-UC (*n* = 313)	t/χ^2	*P* value
Age	42.50 ± 13.94	41.84 ± 13.71	0.590	0.556
Sex			0.058	0.810
Male	176 (56.23)	173 (55.27)		
Female	137 (43.77)	140 (44.73)		
Nationality			29.344	< 0.001
Han	159 (50.8)	225 (71.88)		
Ethnic minorities	154 (49.2)	88 (28.12)		
Education level			2.334	0.127
Low and middle education	183 (58.47)	164 (52.40)		
Higher education	130 (41.53)	149 (47.60)		
Region of residence			8.395	0.004
Urban	214 (68.37)	246 (78.59)		
Rural	99 (31.63)	67 (21.41)		
Smoking history			6.157	0.013
Smoking	58 (18.53)	84 (26.84)		
No smoking	255 (81.47)	229 (73.16)		
Drinking history			10.102	0.001
Drinking	43 (13.74)	74 (23.64)		
No drinking	270 (86.26)	239 (76.36)		
History of appendectomy			37.541	< 0.001
Appendectomized	43 (13.74)	3 (0.96)		
Nonappendectomized	270 (86.26)	310 (99.04)		

UC: Ulcerative colitis.

Comparison of onset age, scope of lesions, and degree of disease activity between male and female in the UC group

Among 313 patients with UC, 176 (56.23%) were male and 137 (43.77%) were female. There was no significant difference in age of onset, scope of lesions and degree of disease activity between male and female patients, as shown in Table 4.

Age analysis of patients with UC in the appendectomized and non-appendectomized groups

Patients with UC were divided into the appendectomized group (43 cases, 13.74%) and the non-appendectomized group (270 cases, 86.26%). The average age at onset of UC in the appendectomized group was 49.51 ± 14.16 years, which was higher than the average age of 41.38 ± 13.61 years observed in the non-appendectomized group ($P < 0.05$). Among men diagnosed with incipient UC, the average age in the appendectomized group was 50.52 ± 13.95 years, and that in the non-appendectomized group was 41.37 ± 13.40 years ($P < 0.05$). Among women diagnosed with incipient UC, the average age in the appendectomized group was 48.55 ± 14.62 years, and that in the non-appendectomized group was 41.39 ± 13.94 ($P < 0.05$; Table 5).

After stratification based on age, it was found that the most frequent age range for the diagnosis of UC in the appendectomized group was 50–59 years (30.23%), whereas in the non-appendectomized group, it was 40–49 years (30.37%), as shown in Figure 1. There was a significant difference in the incidence of onset of UC between the non-appendectomized and appendectomized groups in the age range of 50–59 years ($\chi^2 = 4.837$, $P = 0.028$), as shown in Table 6.

The average interval between appendectomy and the onset of UC was 14.72 ± 13.87 years. Eight patients (18.60%) with UC had undergone appendectomy before the age of 20 years, and all were diagnosed with UC five years later. Among the patients who underwent appendectomy after the age of 20 years, 8 (18.60%) were diagnosed with UC within a year after surgery, 11 (25.58%) were diagnosed with UC two to five years after surgery, and 16 (37.21%) were diagnosed with UC more than five years after surgery. Overall, more than half of the patients (55.81%) were diagnosed with UC more than five years after undergoing appendectomy.

Table 2 Comparison of blood routine results between ulcerative colitis and non-ulcerative colitis, median (25th-75th percentiles)

	UC (*n* = 313)	Non-UC (*n* = 313)	*Z*	*P* value
WBC ($\times 10^9$/L)	6.96 (5.41-9.08)	5.81 (4.91-7.19)	-5.980	< 0.001
Neutrophile granulocyte ($\times 10^9$/L)	4.15 (3.04-5.97)	3.16 (2.51-4.12)	-7.319	< 0.001
Lymphocyte ($\times 10^9$/L)	1.77 (1.37-5.97)	2.01 (1.66-2.45)	4.778	< 0.001
Monocytes ($\times 10^9$/L)	0.52 (0.38-0.69)	0.40 (0.32-0.52)	-7.385	< 0.001
RBC ($\times 10^{12}$/L)	4.42 (3.93-4.80)	4.53 (4.16-4.95)	3.449	< 0.001
Hb (g/L)	128.00 (108.75-143.00)	138.00 (125.00-152.00)	6.348	< 0.001
PLT ($\times 10^9$/L)	277.50 (211.75-350.25)	230.00 (193.00-264.00)	-6.733	< 0.001
NLR	2.38 (1.62-3.68)	1.55 (1.20-2.07)	-9.520	< 0.001
PLR	154.00 (120.64-219.67)	111.91 (91.11-143.25)	-9.251	< 0.001

UC: Ulcerative colitis; WBC: White blood cell; RBC: Red blood cell; Hb: Hemoglobin; PLT: Platelet; NLR: Neutrophil-to-lymphocyte; ratio; PLR: Platelet-to-lymphocyte ratio.

Table 3 Blood routine factors influencing incipient ulcerative colitis

	β	SE	Wald	*P* value	OR	95%CI	
						Lower limit	Upper limit
WBC	0.121	0.104	1.361	0.243	1.129	0.921	1.383
Neutrophile Granulocyte	-0.043	0.112	0.148	0.701	0.958	0.769	1.193
Lymphocyte	-0.452	0.317	2.026	0.155	0.637	0.342	1.186
Monocytes	2.775	0.670	17.146	0.000	16.039	4.312	59.653
RBC	0.296	0.252	1.384	0.239	1.345	0.821	2.204
Hb	-0.026	0.007	12.238	0.001	0.975	0.961	0.989
PLT	0.001	0.002	0.056	0.812	1.001	0.996	1.005
NLR	0.260	0.238	1.196	0.274	1.297	0.814	2.066
PLR	0.003	0.003	0.764	0.382	1.003	0.996	1.010
Constant	-0.154	0.879	0.031	0.861	0.858		

WBC: White blood cell; RBC: Red blood cell; Hb: Hemoglobin; PLT: Platelet; NLR: Neutrophil-to-lymphocyte; ratio; PLR: Platelet-to-lymphocyte ratio.

Comparison of clinical data between the appendectomized and non-appendectomized groups

No significant differences were found in sex, education level, smoking habits, and alcohol consumption between the two groups. Compared with the non-appendectomized group, the onset age of UC in the appendectomized group was higher, with a greater proportion of Han patients and patients residing in cities for a long time. In addition, in the appendectomized group, the degree of disease activity of UC was significantly lower; the proportion of patients in clinical remission and mild disease was higher, and that of patients with severe disease was lower. The scope of UC lesions in the appendectomized group was limited, with a higher proportion of E1 and E2, whereas a lower proportion of E3 Lesions, as shown in Table 7.

DISCUSSION

UC is a chronic intestinal inflammatory disease characterized by repeated attacks that seriously affect patients' quality of life. According to previous studies, as an immune organ, the appendix contains abundant immune cells, which are activated during inflammation and can produce immunoglobulins, cytokines, and chemokines, participating in immune response and playing an important role in maintaining intestinal microecological stability and modulating the immune system[12]. Current studies suggest that the pathogenesis of UC is closely related to the interaction between immune factors and intestinal microbes. An appendectomy may affect the course of UC by preventing the recolonization of harmful bacteria and reducing the production of immunoglobulins and cytokines[16].

Table 4 Comparison of onset age, scope of lesions, and degree of disease activity between male and female with ulcerative colitis, *n* (%)/mean ± SD

	Male (*n* = 176)	Female (*n* = 137)	t/χ^2	*P* value
Onset age	42.46 ± 13.75	42.54 ± 14.24	-0.50	0.96
Scope of lesions			4.90	0.09
E1	17 (9.66)	25 (18.25)		
E2	66 (37.50)	46 (33.57)		
E3	93 (52.84)	66 (48.18)		
Degree of disease activity			2.29	0.52
Clinical remission	6 (3.41)	2 (1.46)		
Mild	29 (16.48)	29 (21.17)		
Moderate	112 (63.64)	82 (59.85)		
Severe	29 (16.48)	24 (17.52)		

Table 5 Comparison of onset age of different sexes between appendectomized group and nonappendectomized group, mean ± SD

	Appendectomized	Non-appendectomized	*t* value	*P* value
Onset age	49.51 ± 14.16	41.38 ± 13.61	-3.621	<0.001
Onset age of male	50.52 ± 13.95	41.37 ± 13.40	-2.903	0.004
Onset age of female	48.55 ± 14.62	41.39 ± 13.94	-2.188	0.029

Table 6 Age comparison of confirmed ulcerative colitis between two groups, *n* (%)

Onset age	Appendectomized	Non-appendectomized	χ^2	*P* value
10-19	0 (0.00)	15 (5.56)	2.509	0.113
20-29	3 (6.98)	49 (18.15)	3.342	0.068
30-39	7 (16.28)	54 (20.00)	0.327	0.567
40-49	12 (27.91)	82 (30.37)	0.107	0.743
50-59	13 (30.23)	44 (16.30)	4.837	0.028
≥ 60	8 (18.60)	26 (9.63)	3.086	0.079

Among the 313 UC patients, the UC patients in urban areas were more than those in rural areas, which is consistent with the findings of most studies[17]. It may be related to the difference in lifestyle between urban and rural residents. Current research has shown that patients in cities experienced more psychological stress and fatigue[18]. Meanwhile, a western diet with high red meat, fatty foods and refined sugars in city can also closely related to UC.

In this study, compared with the non-appendectomized group, the appendectomized group of patients with newly diagnosed UC showed significantly lower disease activity. There was a higher proportion of patients in clinical remission or with mild disease and a lower proportion of patients with severe UC. In addition, the range of lesions was limited, with a higher proportion of E2 and E1, whereas a lower proportion of E3 lesions, which is consistent with the results of Radford–Smith and other studies conducted in China. The study conducted by Radford–Smith in Australia[19], which involved 307 UC patients, showed that among 21 patients with UC in the appendectomized group, 20 had mild disease and did not require immunosuppressants or colectomy, 3 of these did not receive maintenance treatment, and 17 were treated only with oral 5-aminosalicylic acid; while 71 patients in the non-appendectomized group required continuous immunotherapy. No patient in the appendectomized group underwent colectomy for severe colitis, while 60 (21.4%) patients in the non-appendectomized group underwent colectomy, indicating a negative association between appendectomy and UC and suggesting that the clinical condition of patients who have undergone an appendectomy tends to be milder.

A study conducted on 402 patients with UC in Shanghai found that compared with the non-appendectomized group, the disease severity in the appendectomized group was lower, with a higher proportion of patients with mild disease (45.45% *vs* 32.23%). In addition, more patients had lesions limited to the rectum (36.36% *vs* 9.21%), and fewer cases had extensive colon involvement (18.18% *vs* 48.59%). This study supports the hypothesis that a prior appendectomy can

Table 7 Comparison of clinical data between two groups, *n* (%)/mean ± SD

	Appendectomized (*n* = 43)	Non-appendectomized (*n* = 270)	t/χ^2	*P* value
Age	49.51 ± 14.16	41.38 ± 13.61	-3.621	< 0.001
Sex			1.107	0.293
Male	21 (48.84)	155 (57.41)		
Female	22 (51.16)	115 (42.59)		
Nationality			7.716	0.007
Han	30 (69.77)	129 (47.78)		
Ethnic minorities	13 (30.23)	141 (52.22)		
Region of residence			7.202	0.007
Urban	37 (86.05)	177 (65.56)		
Rural	6 (13.95)	93 (34.44)		
Education level			0.509	0.476
Low and middle education	23 (53.49)	160 (59.26%)		
Higher education	20 (46.51)	110 (40.74%)		
Smoking history			0.167	0.682
Smoking	7 (16.28)	51 (18.89)		
No smoking	36 (83.72)	219 (81.11)		
Drinking history			1.923	0.166
Drinking	3 (6.98)	40 (14.81)		
No drinking	40 (93.02)	230 (85.19)		
Degree of disease activity			48.739	< 0.001
Clinical remission	4 (9.3)	4 (1.48)	9.109	0.003
Mild	22 (51.16)	36 (13.33)	35.162	< 0.001
Moderate	16 (37.21)	178 (65.93)	12.981	< 0.001
Severe	1 (2.33)	52 (19.26)	7.562	0.006
Scope of lesions			21.631	< 0.001
E1	13 (30.23)	29 (10.74)	12.130	< 0.001
E2	21 (48.84)	91 (33.70)	3.697	0.055
E3	9 (20.93)	150 (55.56)	17.793	< 0.001

reduce the disease activity of UC and result in a relatively limited range of lesions[20].

Hb was found to be a protective factor against the onset of UC, whereas monocytes were found to be a risk factor. Some studies have reported that peripheral blood monocytes are related to the severity of UC[21,22], exhibiting increased expression in patients with severe disease and decreased expression in those with moderate and mild disease. However, in both instances, monocyte levels are higher compared to the normal population. Some studies have also shown that the capacity for bacterial phagocytosis by monocytes in patients with inflammatory bowel disease (IBD) significantly increases within 2 hours, suggesting that peripheral blood monocytes can be activated[23].

Anemia and fatigue are common in patients with IBD. In a retrospective analysis of 465 patients with IBD, 51.6% of patients had anemia, which was more common in women than in men ($P < 0.001$). Iron deficiency anemia was the most common, followed by anemia of chronic disease[24]. In addition, in patients with UC, Hb levels decreased as systemic inflammation increased[25]. Reinisch *et al*[26] suggested that low Hb levels were similar to high levels of inflammatory markers, which might indicate adverse outcomes in patients at an early stage of UC. These findings are consistent with the results of our study.

In this study, a total of eight patients with UC who underwent appendectomy before the age of 20 years were diagnosed with UC five years later, consistent with the findings of Lowenfels and Maisonneuve[27], Frisch *et al*[28]. Hansen *et al*[29] screened 2004 patients with UC in Denmark and found that undergoing appendectomy before the onset of UC during adolescence (age < 20 years) can reduce the incidence of UC. Kiasat *et al*[30] also confirmed that ap-

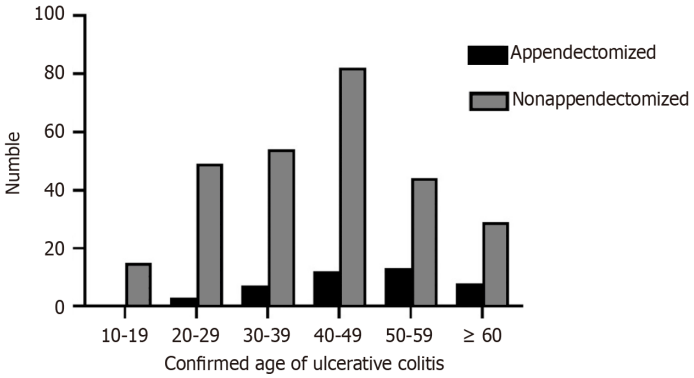

Figure 1 Age composition of confirmed ulcerative colitis between appendectomized group and nonappendectomized group.

pendicitis in children, followed by appendectomy, can significantly reduce the risk of being diagnosed with UC in adulthood. Our study revealed that more than half of the patients were diagnosed with UC five years after undergoing appendectomy. Fantodji *et al*[31] followed up patients with UC five years after undergoing appendectomy and found an enhanced protective effect of appendectomy against UC. Based on these findings, we believe that appendectomy before the diagnosis of UC can delay the onset age of the disease.

Although an increasing number of studies and experimental evidence show that appendectomy (with or without appendicitis) plays an important role in the occurrence and development of UC, the exact mechanism underlying this relationship remains unclear. Current studies have proved that the intestinal microbiome of patients with UC is disordered. However, there is a lack of studies evaluating the microbiome of the appendix in individuals with UC. Future studies can focus on the diversity of microbial composition in the appendix to identify the pathogenic bacteria associated with UC and explore the underlying mechanism.

In China, very few studies have reported on the relationship between UC and the role of appendectomy in its occurrence and development, indicating a need for more basic studies and long-term clinical follow-up studies to clarify this relationship and its mechanisms. At present, there is no consensus regarding the use of appendectomy in the treatment of UC. The limitation of this study is that our study is a small sample, single center study. Hence, multicenter, large-scale, prospective, randomized controlled studies are still needed to further clarify the indications for appendectomy in patients with UC.

CONCLUSION

In summary, we found that appendectomy may delay the onset of UC, reduce disease severity, and lessen the scope of involvement.

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FOOTNOTES

Author contributions: Cui M performed the majority of study and wrote the manuscript; Yao P designed the study and corrected the manuscript; Shi C participated to the collection of the human material and wrote the manuscript.

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