Risk factors of cytomegalovirus infection or reactivation in ulcerative colitis patients

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Research

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Abstract

Background

To identify the risk factors for cytomegalovirus (CMV) infection or reactivation in ulcerative colitis (UC) patients.

Method

PubMed, Cochrane Library, EMBASE, Web of Science and CNKI were retrieved from the inception of electronic databases to February 2020. All analyses were performed using Stata/SE 15.1 version (StataCorp).

Result

22 papers were included. There was significant difference in severe UC (OR = 1.465, 95% CI: 1.107 to 1.939, P = 0.008), pancolitis (OR = 2.108, 95% CI: 1.586 to 2.800, P = 0.0001), age of onset (MD = 6.212, 95% CI: 2.552 to 9.971, P = 0.001), glucocorticoid (OR = 4.175, 95% CI: 3.076 to 5.666, P = 0.001), immunosuppressant (OR = 2.038, 95% CI: 1.259 to 3.301, P = 0.004), 5-ASA (OR = 0.674, 95% CI: 0.492 to 0.924, P = 0.014). However, no significant difference was detected in disease duration, infliximab.

Conclusion

Severe UC, pancolitis, glucocorticoid, immunosuppressive therapy and age of onset are the risk factors of CMV infection or reactivation in UC patients, we should closely monitor if UC patients with the above indicators and give timely symptomatic treatment to prevent the disease from worsening.

Background

The incidence of ulcerative colitis (UC) has been on the rise for the past few decades, reaching its highest level in the early 21st century according to the survey data of epidemiology in Europe and North America[1]. The highest prevalence rates in Europe, Canada and the United States were 500 per 100 000, 248 per 100 000 and 214 per 100 000, respectively[2, 3]. Although the overwhelming majority of the patients had abdominal pain, diarrhea, bloody stool as the main symptoms, a few patients had onset of oral ulcer, suppurative pyoderma, primary sclerosing cholangitis, and spinal arthritis as the first manifestations[4, 5]. The etiology of UC remains unknown. The most current hypothesis is that the pathogenesis and mechanism of UC may be related to immunity, environment, genetic susceptibility, infection, psychology and other factors[4, 5]. Patients with UC are more susceptible suffered from cytomegalovirus (CMV) infection due to decreased intestinal immune function and glucocorticoid or immunosuppressive therapy, which not only results in complicated clinical manifestations, but also increases the difficulty of diagnosis and treatment of the disease[6, 7]. The study shows that the probability of CMV infection or reactivation in UC population is between 15.8% and 34.0%[8]. CMV is an opportunistic virus, which has been biologically characterized by latency and activation[7]. CMV infection or reactivation could significantly prolong the hospitalization period, increase the Corticosteroids dependence rate, operation rate and mortality[9]. The reason may be that CMV infection or reactivation could aggravate the inflammatory response and immune process, exacerbating colon damage[10]. At present, the researchers believe that CMV infection or reactivation is an independent risk factor for UC patients[11]. European Crohn 's and Colitis Organization guidelines also recommend timely antiviral treatment

in patients with acute severe colitis with CMV infection or reactivation [12, 13]. Despite a generally favorable response to antiviral therapy, the risk of recurrent CMV colitis remained quite high and most of the recurrences developed within 8 months[11]. Therefore, it is vital to screen the high-risk groups of CMV infection or reactivation in the diagnosis and treatment of UC. In addition, it is still controversial whether the severity of the disease, the extent of the lesion, the immunosuppressive agent, and the age of onset are related to CMV infection or reactivation in patients with UC.

Materials And Methods

Literature and search strategy

The retrieved object is the research literature on the analysis of risk factors of CMV infection or reactivation in UC patients published publicly in the electronic databases including PubMed, Cochrane Library, EMBASE, Web of Science and CNKI from the inception of electronic databases to February 2020. We retrieved the following keywords in combination with Boolean logic: “ulcerative colitis” or “UC” or “inflammatory bowel disease” or “IBD” and “cytomegalovirus” or “CMV”. Beyond that, the research of the appraisal reference list was manually checked to determine other potential qualification trials. The process iterates until no more articles could be determined. The meta-analysis was based on acknowledged PRISMA guideline (the prioritized reported items for systematic review and meta-analysis).

Inclusion And Exclusion Criteria

The articles will be incorporated into the present meta-analysis if the literatures meet the following principles in accordance with PICOS. Population: UC patients with definite diagnosis; Intervention: UC patients with OR without CMV infection or reactivation (Diagnostic criteria: Intestinal tissue H&E staining reveals CMV inclusion bodies; CMV-DNA is positive in intestinal tissue; CMV-DNA or pp65 is positive in blood with typical deep intestinal ulcer); Comparison: Risk factors of CMV infection or reactivation; Outcome measures: one or more adequate data of the outcomes could be conducted statistical analysis; Study design: an official published RCT or RCS. Exclusion criteria: (I) The diagnosis of CMV infection or reactivation is only based on the positive serological antibody or endoscopic performance, but the serological test is negative (II) abstracts, letters, editorials and expert opinions, case reports (III) non-comparative study (IV) The study design is not rigorous (V) inadequate raw data.

Data Extraction And Outcome Measures

Two of the reviewers (Hong-da Wang, De-jun Kong) respectively extracted data from the included studies. The following essential information was captured: first author names, publication year, samples size, study design, outcomes and other relevant data. The extracted data [median, range, mean difference, 95% confidence interval (CI) and standard deviation (SD)] is input into the designed standardized table. When there are differences of opinion, another authority author has the final decision. The outcome measurements were UC severity, intestinal lesion range, age of onset, course of UC, corticoids, immunosuppressants, azathioprine, infliximab, 5-aminosalicylic acid(5-ASA).

Quality Assessment And Statistical Analysis

Newcastle-Ottawa Scale (NOS) [14]were respectively conducted to evaluate the methodological quality of the included RCTs and RCS. The literature quality evaluation was conducted separately by two reviewers (Xiang Li, Yong-

hao Hu). Consensus was reached through consultation for divergence. The GRADEpro software was used for evidence quality assessment. We use the Stata 15.1 version (Stata Corporation, College Station, Texas, USA) for statistical analyses. When $I^2 > 50\%$, the data was considered as obvious heterogeneity. We conduct a meta-analysis using random-effect model according to Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0). Otherwise, fixed-effect model was performed. For continuous outcomes (Age of onset, Disease duration), Weighted Mean Difference (WMD) were expressed for the evaluation. For discontinuous various outcomes (UC severity, Pancolitis, Glucocorticoid, Immunosuppressants, Azathioprine, Infliximab, 5-ASA), Odds Ratio (OR) were applied for the assessment.

Publication Bias

Use Egger's linear regression for t-test to reduce publication bias.

Sensitivity Analysis

Sensitivity analysis of the effects were performed by omitting each trial in turn and recalculating the pooled effect size.

Results

Search results

A total of 495 studies were identified as potentially relevant literature reports. There were no additional studies identified through other sources. We got 405 articles when the duplicate was removed. By scanning the title and abstract, 363 studies were excluded according to the eligibility criteria. Another 22 articles were further excluded by reading the full text. Ultimately, 20[9, 15–33] articles were eligible for data extraction and meta-analysis. The searching process is shown in Fig. 1.

Characteristics Of Included Studies

The characteristics of the 20 included studies are summarized in Table 1. 2099 individuals were incorporated into our trial of whom 591 UC patients with CMV infection or reactivation and 1508 UC patients are CMV negative.

Table 1
The basic characteristics and quality evaluation of the included studies.

Author	Year	Country	Study design	Study Group		Gender		Age	
				CMV+	CMV-	CMV+ (M/F)	CMV- (M/F)	CMV+	CMV-
Matsuoka	2007	Japan	Retrospective	25	23	12/13	17/6	40.0(15–73)	33.0(19–64)
Omiya	2010	Japan	Prospective	7	13	NA	NA	NA	NA
Suzuki	2010	Japan	Retrospective	15	58	8/7	26/32	42 (17–65)	34 (14–81)
Criscuoli	2011	Italy	Prospective	28	57	19/9	31/26	NA	NA
Kim	2012	Korea	Prospective	31	41	20/11	28/13	43.1 ± 15.4	43.4 ± 14.1
Inokuchi	2014	Japan	Retrospective	40	78	26/14	31/47	45 (14–79)	36 (12–87)
Chun	2015	Korea	Retrospective	12	31	6/6	14/17	NA	NA
McCurdy	2015	USA	Retrospective	45	139	NA	NA	NA	NA
Pillet	2015	France	Prospective	39	70	28/11	44/26	51.2 ± 17.0	46.5 ± 18.0
Hirayama	2016	Japan	Retrospective	34	115	19/15	64/51	42.3 ± 14.4	29.0 ± 14.4
Lee	2016	Korea	Retrospective	50	99	30/20	50/49	45 ± 14.75	42 ± 10.33
ORMECI	2016	Turkey	Retrospective	8	35	6/2	17/18	NA	NA
Zagórowicz	2016	Poland	Retrospective	33	62	22/11	39/23	NA	NA
Henmi	2018	Japan	Retrospective	26	60	15/11	38/22	55.0 ± 13.2	41.8 ± 16.2
Levin	2017	USA	Retrospective	13	15	6/7	12/3	38 ± 19	41 ± 19
Nowacki	2018	Germany	Retrospective	34	205	25/9	108/97	37 ± 17.8	36 ± 18.9
Feng	2016	China	Retrospective	31	60	18/13	39/21	NA	NA
Xu	2016	China	Retrospective	49	143	28/21	82/61	39.15 ± 2.84	38.32 ± 2.94
Li	2019	China	Retrospective	34	91	21/13	49/42	43.08 ± 3.07	42.41 ± 2.36
Zhang	2018	China	Retrospective	37	113	23/14	61/52	43.17 ± 3.08	42.45 ± 2.55

Study Quality And Risk Of Bias

The quality of the included studies was evaluated by the scale of NOS. NOS scores for all studies were greater than or equal to 7 (Table 2).

Table 2
The Newcastle-Ottawa Scale (NOS) assessment of the included studies

Study	Year	Selection	Comparability	Exposure	Total
Matsuoka	2007	4	3	2	9
Omiya	2010	4	2	2	8
Suzuki	2010	4	2	3	9
Criscuoli	2011	4	2	2	8
Kim	2012	4	2	3	9
Inokuchi	2014	3	3	2	8
Chun	2015	4	2	3	9
McCurdy	2015	4	2	3	9
Pillet	2015	4	2	3	9
Hirayama	2016	3	2	3	8
Lee	2016	4	2	3	9
ORMECI	2016	4	2	2	8
Zagórowicz	2016	3	2	2	7
Henmi	2018	3	2	3	8
Levin	2017	4	2	3	9
Nowacki	2018	4	1	3	8
Feng	2016	4	1	3	8
Xu	2016	4	2	2	8
Li	2019	3	2	2	7
Zhang	2018	4	1	3	8

Publication Bias

The details of Egger tests were presented in Table 3. The Egger tests did not indicate publication bias in all the outcomes.

Table 3
Results of Egger test for outcomes

	Number of Studies	Std_Eff	t	P> t	95%CI	
Severe UC	10	Slope	-0.24	0.813	-1.521	1.231
		Bias	0.88	0.404	-1.866	4.172
Pancolitis	14	Slope	1.66	0.123	-0.206	-1.442
		Bias	0.17	0.868	-1.442	1.686
Age of onset	8	Slope	0.87	0.419	-22.170	9.180
		Bias	-0.42	0.690	-12.965	9.180
Disease duration	9	Slope	-2.27	0.057	-10.227	0.201
		Bias	1.71	0.130	-1.252	7.857
Glucocorticoid	14	Slope	1.28	0.224	-0.477	1.841
		Bias	1.40	0.186	-0.688	3.184
Immunosuppressant	15	Slope	0.48	0.642	-1.186	1.854
		Bias	0.50	0.623	-2.391	3.598
Azathioprine	5	Slope	0.41	0.706	-2.628	3.415
		Bias	-0.09	0.937	-5.430	5.144
Infliximab	7	Slope	0.87	0.423	-1.860	3.770
		Bias	-0.24	0.821	-5.632	4.675
5-ASA	9	Slope	-1.66	0.140	-2.285	0.399
		Bias	0.99	0.354	-1.554	3.803

Methodological Quality Assessment

The total qualities of the evidence were low for the severe UC, glucocorticoid, immunosuppressant as well as very low for pancolitis and age of onset (Table 4).

Table 4
Risk factors of cytomegalovirus infection or reactivation in UC patients

Patient or population: UC patients with definite diagnosis						
Settings: Risk factors of cytomegalovirus infection or reactivation						
Intervention: UC patients with OR without CMV infection or reactivation						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk	(95% CI)			
	Control	New Comparison				
Severe UC	Study population		OR 1.46	1169	⊕⊕⊕⊕	
	533 per 1000	625 per 1000 (557 to 688)	(1.1 to 1.93)	(10 studies)	low	
	Moderate					
	531 per 1000	623 per 1000 (555 to 686)				
Pancolitis	Study population		OR 1.77	1516	⊕⊕⊕⊕	
	625 per 1000	747 per 1000 (693 to 795)	(1.35 to 2.32)	(14 studies)	very low ¹	
	Moderate					
	657 per 1000	772 per 1000 (721 to 816)				
Glucocorticoid	Study population		OR 3.75	1488	⊕⊕⊕⊕	
	497 per 1000	787 per 1000 (734 to 832)	(2.79 to 5.03)	(14 studies)	low	
	Moderate					
	514 per 1000	799 per 1000 (747 to 842)				
Immunosuppressant	Study population		OR 1.92	1662	⊕⊕⊕⊕	
	229 per 1000	363 per 1000 (307 to 423)	(1.49 to 2.47)	(15 studies)	low	
	Moderate					
	175 per 1000	289 per 1000 (240 to 344)				

Patient or population: UC patients with definite diagnosis			
Settings: Risk factors of cytomegalovirus infection or reactivation			
Intervention: UC patients with OR without CMV infection or reactivation			
Age of onset	The mean age of onset in the intervention groups was	965 (8 studies)	⊕⊕⊕⊕ very low
	6.21 higher (2.55 to 9.87 higher)		
<p>*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: Confidence interval; OR: Odds ratio;</p>			
<p>GRADE Working Group grades of evidence</p> <p>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</p> <p>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</p> <p>Very low quality: We are very uncertain about the estimate.</p>			
¹ The statistical test for heterogeneity shows a low P value.			

Outcomes Of The Meta-analysis

Severe UC

All the UC patients were evaluated by modified Mayo scoring system and modified Truelove and Witts scoring system. We extracted the data of amount of severe UC and mild to moderate UC patients from 10 included articles. The results show that the risk of CMV infection or reactivation in severe UC patients was 1.465 times higher than that in mild to moderate UC patients. (heterogeneity $P = 0.858$, $I^2 = 0.0\%$, OR = 1.465, 95% CI: 1.107 to 1.939, $P = 0.008$; Fig. 2).

Pancolitis

14 articles reported on colonoscopy in patients with UC to determine the extent of intestinal lesions. There is no significant heterogeneity in the statistical results of the pooled literature ($I^2 = 0.0\%$, $P = 0.507$). The result of the fixed effect model showed that the pancolitis could increase the risk of CMV infection or reactivation (OR = 2.108, 95% CI: 1.586 to 2.800, $P = 0.0001$; Fig. 3).

Age of onset

8 publications focused on the age of UC patients with CMV infection or reactivation. The heterogeneity test of the included studies demonstrated significant heterogeneity ($I^2 = 64.6\%$, $P = 0.006$). The result of the random effect model

showed that the older the age of onset of UC, the more likely to suffer from be CMV infection or reactivation. (MD = 6.212, 95% CI: 2.552 to 9.971, P = 0.001; Fig. 4).

Disease duration

9 articles described the relationship between the disease duration and the risk of CMV infection or reactivation. The heterogeneity test of the included articles indicated that there was heterogeneity among the studies. The results of random effect model analysis suggested that there was no statistical significance between the different course of UC patients and the risk of CMV infection or reactivation (heterogeneity P = 0.000, $I^2 = 72.4\%$, MD=-0.921, 95% CI: -2.423 to 0.582, P = 0.23; Fig. 5).

Glucocorticoid

14 articles described the risk of CMV infection or reactivation in UC patients treated with glucocorticoid. The heterogeneity test indicated that there was no heterogeneity ($I^2 = 38.1\%$, P = 0.073). The results of fixed analysis indicated that glucocorticoid treatment could significantly increase the risk of CMV infection or reactivation in UC patients, which was 4.175 times higher than that without glucocorticoid treatment (OR = 4.175, 95% CI: 3.076 to 5.666, P = 0.001; Fig. 6).

Immunosuppressant

15 articles described the risk of CMV infection or reactivation following immunosuppressive agents (azathioprine, cyclosporine A, methotrexate) in UC patients. Heterogeneity testing of the included literature indicated that there is heterogeneity among the literatures ($I^2 = 65.9\%$, P = 0.000). The results of the random effect model analysis showed that the use of immunosuppressive therapy would increase the risk of CMV infection or reactivation in patients in UC patients (OR = 2.038, 95% CI: 1.259 to 3.301, P = 0.004; Fig. 7).

Azathioprine

5 included articles reported on the use of azathioprine in UC patients. Heterogeneity test of included studies suggested no obvious heterogeneity ($I^2 = 0.0\%$, P = 0.501). There is no statistical difference on the Azathioprine (OR = 1.357, 95% CI: 0.831 to 2.217, P = 0.222; Fig. 8).

Infliximab

7 studies concentrated on whether the infliximab had side-effects on CMV infection or reactivation in UC patients. There was no obvious heterogeneity ($I^2 = 68.3\%$, P = 0.004); therefore, a random effect model was applied. Pooling the results demonstrated that infliximab treatment was not a risk factor for CMV infection or reactivation (OR = 1.915, 95% CI: 0.870 to 4.217, P = 0.107; Fig. 9).

5-ASA

9 articles described the risk of CMV infection or reactivation in UC patients treated with 5-ASA. Interestingly, the results of the fixed-effect model showed that 5-ASA could reduce the risk of CMV infection or reactivation (heterogeneity P = 0.283, $I^2 = 18.0\%$, OR = 0.674, 95% CI: 0.492 to 0.924, P = 0.014; Fig. 10).

Sensitivity Analysis

Results of sensitivity analysis demonstrated that the effects of all the outcomes (severe UC, pancolitis, age of onset, disease duration, glucocorticoid, immunosuppressant, azathioprine, infliximab, 5-ASA) on CMV infection or reactivation in UC patients remained consistent after removing the trials one by one, as shown in Fig. 11.

Discussion

The relationship between UC and CMV has been reported for nearly 60 years. Many studies have shown that UC accompanied with CMV infection or reactivation may increase mortality and surgical risk[34].

In UC patients, a large number of proinflammatory cytokines, such as TNF- α , IFN- γ and IL-2, are expressed locally in the intestinal mucosa. These proinflammatory cytokines activate the expression of transcription factor AP-1 and NF- κ B, thus promoting the expression of more chemical factors (IL-8, MIP-1, RANTES, MCP-1) and adhesion molecules (ICAM-1, VCAM-1)[35, 36]. Stimulated by these cytokines, monocytes and dendritic cells phagocytosing CMV chemotaxis to the intestinal mucosal injured area, then the proinflammatory factors TNF- α and IFN- γ mediate the activation of CMV in monocytes and dendritic cells, respectively. Macrophages with the role of “saving cells”, especially CD14⁺ and CD34⁺ macrophages, support CMV from latent to active state[37–39]. The research of Phillip D et al [40] on the mechanism of CMV enhancing inflammatory response proved that monocytes with latent CMV entered tissues and differentiated into macrophages and specifically expressed CD14, TLR4 and TLR5. On the one hand, CMV promotes inflammatory cytokine mRNA expression. on the other hand, CMV infection or reactivation promotes the MyD88 expression and enhances the phosphorylation effects of IKBA and NF- κ B[41]. Notably, IL-6 promotes Th17 differentiation and aggravates the intestinal inflammatory response, which is consistent with the experimental results in humans and mice[42]. Another reason is that IL-6 promotes the reactivation and replication of CMV[43]. Moreover, CMV is more likely to enter the lamina propria and induce abnormal mucosal immune response following intestinal mucosal injury, exacerbating the intestinal and systemic response[44].

The more severe UC is, the higher the risk of CMV infection or reactivation increases. In this study, we found that the risk of CMV infection or reactivation in patients with severe UC was 1.465 times higher than that in patients with mild to moderate UC, and the risk of CMV infection or reactivation in UC patients with lesions of the whole colon was 2.108 times higher than that in patients with left colon or rectum only. A study of 149 UC patients showed a higher Mayo score in patients accompanied with CMV infection or reactivation. We consider that patients with severe lesions are often accompanied by more extensive intestinal mucosal barrier disruption and increased intestinal mucosal permeability, which facilitates the entry of CMV into the lamina propria.

The correlation between age of onset and risk of CMV infection or reactivation remains controversial. Valeria Criscuoli [45] evaluated the natural history of CMV infection or reactivation in a series of 28 UC patients and founded that there was no significant difference in the risk of CMV infection or reactivation between the age ≥ 50 and < 50 years old ($\chi^2 = 0.39$, $P = 0.53$). However, Sylvie Pillet [7] believed that UC age over 30 is a risk factor for CMV infection or reactivation. The result of present meta-analysis indicated older the age of onset of UC is, the more likely to suffer from CMV infection or reactivation they are. A careful analysis of the included literatures showed the age span of the included population was relatively small, with the majority of patients between 42 and 46 years old. The results of meta-analysis suggested that the duration of UC was not related to the risk of CMV infection or reactivation. Further analysis of the included literature found that in the studies that considered the disease duration to be a risk factor for CMV infection or reactivation, the mean disease duration was longer.

In addition to the disease characteristics of UC patients, the relationship between the therapeutic drugs of UC and CMV infection or reactivation should also be noted. The meta-analysis results of this topic also suggest that

corticosteroids therapy is a risk factor for CMV infection or reactivation, which will increase the risk by 4.175 times[46]. Lee et al. [7]believed that the average glucocorticoid usage > 40 mg/d within 1 month is a risk factor for CMV infection or reactivation, and some scholars believe that the total glucocorticoid usage > 400 mg within 4 weeks is a risk factor. However, there were few studies on glucocorticoid dosage and CMV infection or reactivation. The result showed that immunosuppressive therapy was also a risk factor for CMV infection or reactivation, which increased the risk by 2.038 times, among which azathioprine and infliximab therapy could not increase the risk, but there were few literatures on cyclosporine and methotrexate, which could not be further analyzed. Interestingly, we found that 5-ASA could reduce the risk of CMV infection or reactivation. This index needs to be verified by larger sample literatures.

Infliximab is increasingly used as a biological agent in the treatment of UC. This study demonstrated showed that infliximab was not a risk factor for CMV infection or reactivation in UC patients. TNF- α promotes the reactivation of CMV in monocytes and dendritic cell. Infliximab, as a TNF- α antagonist, has been shown to block inflammatory response, clear CMV of infection, and enhance resistance[47, 48]. More large sample studies are needed to confirm this result. 5-ASA did not increase the risk of CMV infection or reactivation in UC patients. The trials included in this research are all high-quality studies, and the conclusions of the research are relatively reliable. But some studies have heterogeneity. Therefore, the validity of the conclusion needs to be confirmed by more relevant studies.

Conclusion

Severe UC, pancolitis, glucocorticoid, immunosuppressive therapy and age of onset are the risk factors of CMV infection or reactivation in UC patients, we should monitor if UC patients with the above indicators closely and give timely symptomatic treatment to prevent the disease from worsening.

Abbreviations

RCT: Randomized controlled trial; RCS: retrospective controlled trial; OR: Odds Ratio; WMD: Weighted Mean Difference; CI: Confidence interval; CMV: cytomegalovirus; UC: Ulcerative Colitis; 5-ASA: 5-aminosalicylic acid; SD: Standard Deviation.

Declarations

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Authors' contributions

YFQ, DJK and HDW conceived of the design of the study. JPH, YHH, YMZ, WJ, XL, BRZ and DDY performed and collected the data and contributed to the design of the study. GML and HW prepared and revised the manuscript. All authors read and approved the final content of the manuscript.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Flowchart of the study selection process

Figure 2

Forest plot diagram showing the severe UC

Figure 3

Forest plot diagram showing the pancolitis

Figure 4

Forest plot diagram showing the age of onset

Figure 5

Forest plot diagram showing the disease duration

Figure 6

Forest plot diagram showing the glucocorticoid

Figure 7

Forest plot diagram showing the immunosuppressant

Figure 8

Forest plot diagram showing the azathioprine

Figure 9

Forest plot diagram showing the infliximab

Figure 10

Forest plot diagram showing the 5-ASA

Figure 11

Sensitivity analysis of all the outcomes on CMV infection or reactivation in UC patients. (A) Severe UC (B) Pancolitis (C) Age of onset (D) Disease duration (E) Glucocorticoid (F) Immunosuppressant (G) Azathioprine (H) Infliximab (I) 5-ASA

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