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## Observational Study

## Nested case-control study on risk factors for opportunistic infections in patients with inflammatory bowel disease

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**Author contributions:** Gong SS conducted clinical observation, analyzed the data, and wrote the paper; Fan YH designed the research and revised the paper; Han QQ collected the data; Xu Y and Lv B conducted literature search and provided valuable suggestions for this study; all authors have read and approved the final manuscript.

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**Abstract****BACKGROUND**

When opportunistic infections occur, patients with inflammatory bowel disease (IBD) commonly display a significantly increased rate of morbidity and mortality. With increasing use of immunosuppressive agents and biological agents, opportunistic infections are becoming a hot topic in the perspective of drug safety in IBD patients. Despite the well-established role of opportunistic infections in the prognosis of IBD patients, there are few epidemiological data investigating the incidence of opportunistic infections in IBD patients in China. Besides, the risk factors for opportunistic infection in Chinese IBD patients remain unclear.

**AIM**

To predict the incidence of opportunistic infections related to IBD in China, and explore the risk factors for opportunistic infections.

**METHODS**

A single-center, prospective study of IBD patients was conducted. The patients were followed for up to 12 mo to calculate the incidence of infections. For each infected IBD patient, two non-infected IBD patients were selected as controls. A conditional logistic regression analysis was used to assess associations between putative risk factors and opportunistic infections, which are represented as odds ratios (OR) and 95% confidence intervals (CIs).

**RESULTS**

Seventy (28.11%) out of 249 IBD patients developed opportunistic infections. *Clostridium difficile* infections and respiratory syncytial virus infections were found in 24 and 16 patients, respectively. In a univariate analysis, factors such as the severity of IBD, use of an immunosuppressant or immunosuppressants, high levels of fecal calprotectin, and C-reactive protein or erythrocyte sedimentation

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rate were individually related to a significantly increased risk of opportunistic infection. Multivariate analysis indicated that the use of any immunosuppressant yielded an OR of 3.247 (95% CI: 1.128-9.341), whereas the use of any two immunosuppressants yielded an OR of 6.457 (95% CI: 1.726-24.152) for opportunistic infection. Interestingly, when immunosuppressants were used in combination with infliximab (IFX) or 5-aminosalicylic acid, a significantly increased risk of opportunistic infection was also observed. The relative risk of opportunistic infection was greatest in IBD patients with severe disease activity (OR = 9.090; 95% CI: 1.532-53.941, relative to the remission stage). However, the use of IFX alone did not increase the risk of opportunistic infection.

### CONCLUSION

Factors such as severe IBD, elevated levels of fecal calprotectin, and the use of immunosuppressive medications, especially when used in combination, are major risk factors for opportunistic infections in IBD patients. The use of IFX alone does not increase the risk of opportunistic infection.

**Key words:** Nested case-control study; Opportunistic infections; Inflammatory bowel disease

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**Core tip:** When opportunistic infections occur, patients with inflammatory bowel disease (IBD) commonly display a significantly increased rate of morbidity and mortality. With increasing use of immunosuppressive agents and biological agents, opportunistic infections are becoming a hot topic in the perspective of drug safety in IBD patients. Despite the well-established role of opportunistic infections in the prognosis of IBD patients, there are few epidemiological data investigating the incidence of opportunistic infections in IBD patients in China. Besides, the risk factors for opportunistic infections in Chinese IBD patients remain unclear.

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## INTRODUCTION

Opportunistic infection refers to any infection caused by a weakened immune system and typically does not occur in people with normal immune function<sup>[1]</sup>. When they occur, patients presenting with opportunistic infections commonly display a significantly increased rate of morbidity and mortality. With increasing use of immunosuppressive agents and biological agents, opportunistic infections are becoming a hot topic in the perspective of drug safety in patients with inflammatory bowel disease (IBD). Studies have shown that opportunistic infections are closely related to the recurrence of IBD<sup>[2,3]</sup>. Severe opportunistic infection was observed in 3% of IBD patients, significantly increasing their mortality<sup>[4]</sup>. According to the consensus of The European Crohn's and Colitis Organization on opportunistic infections in IBD, IBD patients taking glucocorticoids, immunomodulators, and biologic therapies are all at an increased risk of opportunistic infection. Malnutrition and old age are also key risk factors for opportunistic infections<sup>[5]</sup>. A multicenter prospective study conducted in Japan followed 570 patients with IBD for one year and observed 52 (9.1%) cases of opportunistic infection. Further analysis found that being over 50 years of age and the use of immunosuppressive agents are contributing risk factors for opportunistic infections in patients with IBD<sup>[6]</sup>. A study conducted by Tourner *et al*<sup>[7]</sup> also concluded that immunosuppressive medications and increased patient age are related with an increased risk of opportunistic infections in IBD patients. On the other hand, positive prevention, early diagnosis, and timely control of opportunistic infections are the current focuses for improving the prognosis of IBD patients.

Despite the well-established role of opportunistic infections in the prognosis of IBD

patients, there are few epidemiological data investigating the incidence of opportunistic infections in IBD patients in China. The level of fecal calprotectin (FC) is a commonly used diagnostic measure for patients with IBD as its levels generally increase in patients with IBD. It is generally accepted that FC levels are a stable and reliable measure of IBD severity with a high sensitivity and specificity. However, the relationship between FC levels and the incidence of opportunistic infections in IBD has never been studied.

Therefore, this study sought to investigate the relationship between IBD and opportunistic infections from a cohort of patients with IBD using a nested case-control method. Specifically, we sought to predict the incidence of opportunistic infections in patients with IBD in China, and determine the relationship between FC and opportunistic infection, with an aim to provide a scientific basis for the effective prevention and control of opportunistic infections in patients with IBD.

## MATERIALS AND METHODS

### Research design and patient groups

This study involving 301 IBD patients [139 with ulcerative colitis (UC) and 162 with Crohn's disease (CD)] enrolled from January to December 2017. The probability of an opportunistic infection was calculated during a one-year follow-up period. Common opportunistic infections in patients with IBD include viral infections (herpes viruses, human papillomavirus, influenza virus, and JC virus), bacterial infections (tuberculosis, nocardia, *Clostridium difficile*, pneumococcus, legionella, and listeriosis), fungal infections (histoplasmosis, cryptococcosis, *Pneumocystis jirovecii* infection, aspergillosis, and candidiasis), and parasite infections (*Strongyloides stercoralis*)<sup>[8]</sup>. Patients were screened for opportunistic infection before enrollment to exclude those currently infected. Infection was based on laboratory results, in which viral IgM positivity and DNA copy were diagnosed as viral infection. The diagnosis of tuberculosis was based on the detection of *Tubercle bacillus*. *Clostridium difficile* was detected by PCR. Positive fecal cultures of mold and candida were diagnosed as fungal infections. Clinical visits were conducted once a month. Clinical follow-up and laboratory examinations [including routine blood examination, C-reactive protein (CRP), hepatic and renal function, FC, infection indicators, *etc.*] were conducted once a month. In addition, disease activity was assessed at each follow-up. Truelove and Witts disease severity classification criteria<sup>[9]</sup> and CD activity index (CDAI)<sup>[10]</sup> were used to evaluate the disease activity of patients with UC and CD, respectively. These diagnoses and disease activity index were admitted by the attending physician.

This study was approved by the ethics committee of First Affiliated Hospital of Zhejiang Chinese Medical University, and patients under the age of 16 were admitted to our study with the consent from their parents or guardians.

### Case-control study

IBD patients with opportunistic infections were selected as the case group. For each case, two uninfected patients were chosen as controls and were matched according to age (at an interval of 10 years;  $\leq 19$ , 20-29, 30-39, 40-49, and  $\geq 50$  years).

### Data collection

The demographic characteristics of patients were collected, including age, gender, course of the disease, current smoking habits, previous bowel surgery, comorbidity, disease activity, the type of IBD, and current medications. All patients were diagnosed with UC or CD based on the previously criteria<sup>[11]</sup>.

### Statistical analysis

Demographic characteristics were analyzed by the *t*-test. The univariate and multivariate analyses were performed with SPSS version 23 (SPSS, Tokyo, Japan).

## RESULTS

### IBD patients' demographic and clinical features

A total of 301 IBD patients were enrolled in this study, 52 of whom were lost to follow-up. Of the remaining 249 patients, 119 had UC and 130 had CD. The patients' ages ranged from 12 to 78 years (mean age, 45.24 years). During one year of follow-up, we found 70 IBD patients who developed an opportunistic infection (Table 1). The incidence of opportunistic infections was 28.11%. *Clostridium difficile* infection was found to be the most common opportunistic infection in patients with IBD (9.64%),

followed by respiratory syncytial virus infection (6.43%). Fifteen (6.02%) and eleven (4.42%) patients were infected with Epstein-Barr virus and Fungal, respectively. One patient developed active tuberculosis.

There were 70 patients in the case group, including 33 UC patients and 37 CD patients. In contrast, the control group consisted of 140 patients, including 66 UC patients and 74 CD patients. Selected demographic and clinical characteristics of cases and controls are provided in [Table 2](#). There were no statistically significant differences between the two groups in age, gender, type of IBD, duration of IBD, duration of medication use, prior surgery or smoking history. The data of the two groups were well balanced and comparable.

### **Severe disease activity is a risk factor for opportunistic infections in IBD patients**

Patients' gender, age, type of IBD, duration of medication, course of the disease, history of prior surgery, and smoking habits were not related to increased risk of opportunistic infections, according to the univariate analysis. However, severe disease activity in IBD patients was related to an increased rate of opportunistic infections ( $P < 0.001$ , OR = 18.404; 95%CI: 3.833-88.375). Multivariate analysis also indicated that severe IBD was the greatest risk factor for opportunistic infections ( $P < 0.001$ , OR = 18.404; 95%CI: 3.833-88.375).

### **Elevated level of FC is a risk factor for opportunistic infections in IBD patients**

In our study, FC higher than normal levels ( $>200 \mu\text{g/g}$ ) was related to an increased risk of opportunistic infections both in our univariate analysis ( $P < 0.001$ , OR = 4.431; 95%CI: 2.265-8.667) and multivariate analysis ( $P = 0.023$ , OR = 2.467; 95%CI: 1.133-5.373).

### **Immunosuppressive medications, especially when used in combination, are risk factors for opportunistic infections in IBD patients**

Compared with the use of 5-aminosalicylic acid (5-ASA), the use of infliximab (IFX) or 5-ASA+ IFX was not related to the incidence of opportunistic infections in our univariate analysis ([Table 3](#)) and multivariate analysis. On the contrary, the use of any immunosuppressant (steroids, azathioprine, tacrolimus, thalidomide, or methotrexate) was related to a significantly increased odd for opportunistic infection, compared with the use of 5-ASA both in univariate analysis ( $P < 0.047$ , OR = 2.668; 95%CI: 1.012-7.033) ([Table 3](#)) and multivariate analysis ( $P = 0.029$ , OR = 3.235; 95%CI: 1.125-9.306) ([Figure 1](#)). Especially when two or more immunosuppressants were used in combination, it represented the second largest risk factor for opportunistic infections in both univariate analysis ( $P < 0.001$ , OR = 10.375; 95%CI: 2.948-36.508) ([Table 3](#)) and multivariate analysis ( $P = 0.006$ , OR = 6.462; 95%CI: 1.727-24.172) ([Figure 1](#)). In addition, the use of 5-ASA and any immunosuppressant(s) or IFX with any immunosuppressant(s) was related to significantly increased infection rates both in univariate analysis ( $P < 0.01$ ) ([Table 3](#)) and multivariate analysis ( $P < 0.05$ ) ([Figure 1](#)).

### **High levels of CRP and erythrocyte sedimentation rate (ESR) are not related to a significantly increased risk of opportunistic infection**

Our univariate analysis showed that high levels of CRP (OR = 3.98; 95%CI: 1.994-7.944) and ESR (OR = 3.744; 95%CI: 1.87-7.494) were related to an increased risk of opportunistic infections ([Table 3](#)). However, the results of multivariate analysis did not confirm this finding ([Figure 1](#)).

## **DISCUSSION**

In our study, we prospectively predicted the occurrence of opportunistic infections in IBD patients. A total of 70 (28.11%) of the 249 patients developed opportunistic infections. Currently, there are few epidemiological data on the rate of opportunistic infection in IBD patients in China. In a study performed at Ruijin Hospital affiliated to Shanghai Jiao Tong University, of 130 patients with IBD, 12.3% developed CD infection<sup>[12]</sup>. In another study, positive serum IgG for cytomegalovirus (CMV) was found in 73% of UC patients in Wuhan, China and 89% of CD patients, and the rate in the healthy population was 50.69%<sup>[13]</sup>. Data from Peking Union Medical College Hospital indicated that the CMV infection rate in UC patients undergoing surgical operations was 46.2%<sup>[14]</sup>, compared to 36.7% among refractory UC patients in Tianjin<sup>[15]</sup>. A multicenter prospective study conducted in Japan included 570 IBD patients who were followed for one year, and the authors observed 52 cases (9.1%) of opportunistic infection<sup>[7]</sup>. Separately, a national study in France found that the

**Table 1 Opportunistic infections in inflammatory bowel disease patients evaluated between January 1, 2017 and December 31, 2018**

Organism	Number of UC patients	Number of CD patients
Mycobacterium tuberculosis	1	0
Epstein-Barr virus	10	5
Cytomegalovirus	3	1
Hepatotropic virus	0	1
Clostridium difficile	11	13
Adenovirus	0	3
Syncytial virus	5	11
Coxsackie virus	1	2
Herpes simplex virus	3	2
Herpes zoster	0	1
Mold	6	3
Candida albicans	2	0
Streptococcus	1	2

Three patients were co-infected with Epstein-Barr virus (EBV) and respiratory syncytial virus (S virus). Two patients were co-infected with EBV and mold. One patient was co-infected with EBV and *Clostridium difficile* (CDI). One patient was co-infected with EBV and cytomegalovirus (CMV). One patient was co-infected with EBV and herpes simplex virus (HSV). One patient was co-infected with EBV, S virus, and Coxsackie virus (C virus). One patient was co-infected with mold and CDI. One patient was co-infected with adenovirus and S virus. One patient was co-infected with adenovirus and C virus. One patient was co-infected with CDI and C virus. One patient was co-infected with CDI and S virus. One patient was co-infected with CDI, mold, and Streptococcus. UC: Ulcerative colitis; CD: Crohn's disease.

incidence of opportunistic infections in IBD patients was 7.9% after five years of follow-up<sup>[16]</sup>. The high incidence of opportunistic infection in IBD patients in China may be related to the level of economic development and the abuse of antibiotics. In most regions of China, expensive biological agents are not covered by medical insurance, which limits their extensive use in China. However, most immunosuppressants, such as steroids and azathioprine, are cheap and are accepted by the majority of IBD patients. China is known to be one of the countries with the worst rates of antibiotic abuse in the world. It is estimated that China produced 248000 tons of antibiotics in 2013<sup>[17]</sup>, and the per capita consumption of antibiotics was 10 times that of the United States<sup>[18]</sup>. The direct consequence of abuse of antibiotics is widespread bacterial drug resistance, which results in an increased rate and severity of opportunistic infections.

Infection with *Clostridium difficile*, an anaerobic, gram-positive bacillus, is the most common nosocomial infection which was most commonly observed in the IBD patients in our study (9.64%). IBD patients are at an increased risk for infection with *Clostridium difficile*<sup>[19-23]</sup>. Compared with those with IBD alone, patients with *Clostridium difficile* and IBD had longer hospital stay, requiring colon surgery intervention<sup>[24,25]</sup>. The use of antibiotics is closely related to *Clostridium difficile* associated diarrhea. Antimicrobials may disrupt the normal gastrointestinal flora, leading decreased colonization resistance and allowing toxigenic strains of *Clostridium difficile* to cause diseases. The abuse of antibiotics in China is serious. In addition, IBD patients are often treated with antibiotics for IBD deterioration or immunosuppressive complications, so *Clostridium difficile* infection can easily occur. *Clostridium difficile* is an increasing problem in immunocompromised patients, which can lead to higher rates of colectomy and mortality<sup>[26]</sup>. *Clostridium difficile* infection initiates with disruption of normal colonic microbiota, for which IBD patients are at high risk, conferring them an additional risk of *Clostridium difficile* infection<sup>[27,28]</sup>. In our pooled analysis, *Clostridium difficile* has the highest infection rate among opportunistic infections in IBD patients due to the extensive use of antibiotics and immunosuppressive agents.

Our study found that disease severity was also a risk factor for opportunistic infections in IBD patients. Previously, the relationship between disease activity and the incidence of opportunistic infections was not clear. We speculate that when IBD patients progress to late-stage disease, a nonspecific inflammatory reaction is initiated in the gut mucosa, promoting pathogen invasion. The invasion of pathogens subsequently aggravates intestinal inflammation, creating a positive feedback loop. Furthermore, the increased energy consumption and low immunity state induced by

**Table 2 Demographic and clinical features of inflammatory bowel disease patients with (cases) and without (controls) opportunistic infection**

	Cases (n = 70)	Controls (n = 140)	P-value
Median age	45.67 ± 15.79	44.13 ± 14.21	0.45
Gender			0.11
Male	39	89	
Female	31	51	
Type of IBD			0.82
UC	33	66	
Proctitis	4	24	
Left-sided	7	15	
Extensive	22	27	
CD	37	74	
Ileitis (L1)	9	23	
Colitis (L2)	6	3	
Ileocolitis (L3)	17	26	
Upper gastrointestinal tract (L4)	1	4	
L1 + L4	0	5	
L2 + L4	0	2	
L3 + L4	4	11	
Duration of IBD (yr)	6.42 ± 6.01	5.12 ± 4.04	0.28
Duration of medication (yr)	2.73 ± 2.02	2.54 ± 2.11	0.71
Prior surgery	25	41	0.31
Smoking	2	13	0.11

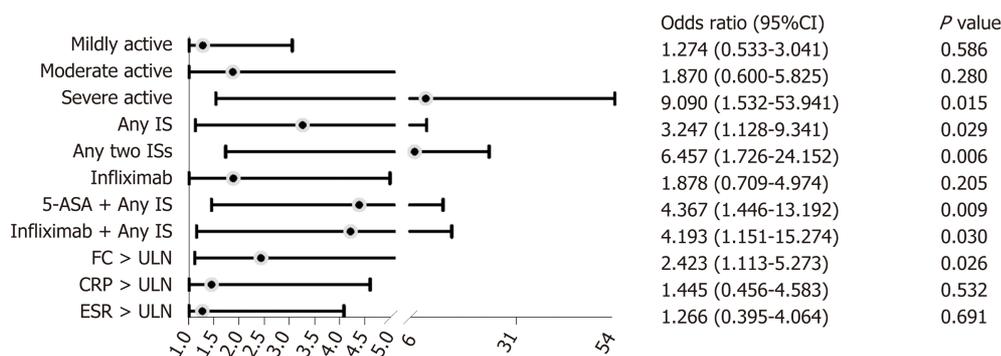
L1; Ileitis; L2: Colitis; L3: Ileocolitis; L4: Upper gastrointestinal tract; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease.

inflammation diminish IBD patients' ability to resist external pathogens, leading to further opportunistic infection.

A reliable measure of long-term outcome is paramount in predicting the course of the disease, responsiveness to treatment, potential for complications, and need for hospitalization and/or surgery<sup>[29]</sup>. Many studies have shown that mucosal healing is the best predictor of positive long-term outcomes<sup>[30-33]</sup>. Endoscopy is currently regarded as the gold standard test for the assessment of mucosal healing<sup>[34]</sup>. However, its invasive nature and high cost make it an unfeasible modality for frequent monitoring. Calprotectin is an abundant calcium-binding protein, which is derived mainly from neutrophils and a lesser extent monocytes and reactive macrophages. FC is a sensitive marker of intestinal inflammation in IBD, as its concentration reflects the migration of neutrophils into the intestinal cavity<sup>[35]</sup>. Thus, FC has emerged as a novel diagnostic tool to detect and monitor intestinal inflammation and reflect disease activity in IBD. Measurements for FC are simple, rapid, specific, sensitive, and inexpensive compared to its counterparts<sup>[36,37]</sup>. Along with CRP, ESR, and FC, our study discovered that elevated FC was a risk factor for opportunistic infections in IBD patients. One explanation for this finding may be that the level of FC serves as an indicator for intestinal inflammation and therefore, disease activity. This makes FC level a more sensitive and specific marker than CRP and ESR. When the level of FC in IBD patients is elevated, it suggests that intestinal inflammation has occurred and the disease is in an active stage, conferring the patient to opportunistic infections.

In our study, immunosuppressive agents included methotrexate, 6-mercaptopurine, azathioprine, thalidomide, tacrolimus and steroids. From this study, we have found that the use of immunosuppressive medications alone increased the risk of an opportunistic infection about 3.247-fold. When any two immunosuppressive medications were used in conjunction, the risk was increased greatly to about 6.457-fold. This result from our study is consistent with recent results in the literature<sup>[7,8,38,39]</sup>. Additionally, it was determined that when immunosuppressive medications were combined with 5-ASA or IFX, the risk of opportunistic infection was increased greatly to about 4 to 5 folds. This conclusion is consistent with the findings reported by Tourner *et al*<sup>[7]</sup>, Lawrance *et al*<sup>[40]</sup>, and Kirchesner *et al*<sup>[16]</sup>.

The relationship between biologics and opportunistic infections has not been



**Figure 1 Risk factors for opportunistic infection in inflammatory bowel disease patients (multivariate analysis).** 5-ASA: 5-aminosalicylic acid; IS: Immunosuppressant (steroids, thiopurine, thalidomide, tacrolimus, or methotrexate); FC: Fecal calprotectin; CRP: C-reaction protein; ESR: Erythrocyte sedimentation rate; ULN: Upper limit of normal; CI: Confidence interval. *P*-values and 95% confidence intervals (CIs) for mild, moderate, and severe disease were compared with remission. *P*-values and 95%CIs for any immunosuppressant (IS), any two IS, infiximab, 5-aminosalicylic acid (5-ASA) + any IS, and infiximab + any IS were compared with 5-ASA.

clearly established. Some studies<sup>[41-44]</sup> indicated that biologics increase the incidence of opportunistic infections, while others do not support this conclusion<sup>[45,46]</sup>. In our study, we found no association between the use of IFX alone and the increased risk of opportunistic infections. One possible explanation is that IFX may not cause opportunistic infections within the one-year period of the study (shorter than the previous five-year period)<sup>[7]</sup>.

Despite the important findings, this study had several limitations. First, the sample size of our study was small. A larger sample size would have allowed for more accurate estimation of the incidence of opportunistic infections and increase in reliability of risk factors in Chinese IBD patients. Second, our study was a single-center clinical study, which cannot represent the situation of IBD patients in China as a whole.

In conclusion, severe disease activity, elevated levels of FC, and immunosuppressive medications, especially when used in combination, are risk factors for opportunistic infections in IBD patients. The use of IFX alone has nothing to do with opportunistic infections. With the increasing use of immunosuppressants in IBD and the advocacy of combination therapy, patients and physicians need to pay attention to and prevent opportunistic infections. As the genetic background, living environment, lifestyle, and diet of IBD patients in China are different from those in Western countries, our study of opportunistic infection could provide vital information for clinicians and IBD patients in China and other countries.

**Table 3 Risk factors for opportunistic infection in inflammatory bowel disease patients (univariate analysis)**

	Cases (n = 70)	Controls (n = 140)	P-value	Odds ratio	95%CI
Disease activity					
Remission	25	85		Reference	
Mildly active	20	40	0.145	1.673	0.837-3.345
Moderate	14	13	0.004	3.604	1.505-8.626
Severe	11	2	<0.001	18.404	3.833-88.375
Treatment					
5-ASA	20	83		Reference	
Any IS	8	12	0.047	2.668	1.012-7.033
Any two IS	10	4	<0.001	10.375	2.948-36.508
Infliximab	13	24	0.109	1.992	0.857-4.632
5-ASA + any IS	11	9	0.002	5.072	1.853-13.887
Infliximab + any IS	9	7	0.003	5.336	1.773-16.058
FC > ULN	57	69	<0.001	4.431	2.265-8.667
CRP > ULN	26	18	<0.001	3.98	1.994-7.944
ESR > ULN	25	18	<0.001	3.744	1.87-7.494

5-ASA: 5-aminosalicylic acid; IS: Immunosuppressant (steroids, thiopurine, thalidomide, tacrolimus, or methotrexate); FC: Fecal calprotectin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; ULN: Upper limit of normal; CI: Confidence interval.

## ARTICLE HIGHLIGHTS

### Research background

Opportunistic infection refers to any infection caused by a weakened immune system and typically does not occur in people with normal immune function. When they occur, patients presenting with opportunistic infections commonly display a significantly increased rate of morbidity and mortality. A number of studies have been conducted in Western countries and Japan to investigate the incidence of and risk factors for opportunistic infection in inflammatory bowel disease (IBD) patients. Currently, there are few epidemiological data on the rate of opportunistic infection in IBD patients in China. The risk factors for opportunistic infection in Chinese IBD patients remain unclear.

### Research motivation

The main topics in our study are to predict the incidence of opportunistic infections related to IBD in China, and explore the risk factors for opportunistic infections. The key problems to be solved is to ensure compliance of enrolled IBD patients. The significance of solving these problems for future research in this field is to more accurately predict the incidence of and risk factors for opportunistic infections.

### Research objectives

The main objectives in our study were to predict the incidence of opportunistic infections related to IBD in China, and explore the risk factors for opportunistic infections. The realized objectives include that the incidence of opportunistic infection in IBD patients in China is higher than that in Western countries and factors such as severe IBD, elevated levels of fecal calprotectin, and the use of immunosuppressive medications, especially when used in combination, are major risk factors for opportunistic infections in IBD patients, according to our single-center study. The significance of realizing these objectives for future research in this field is to alert patients and physicians to pay attention to and prevent opportunistic infections. Meanwhile, our study can provide important information for clinicians and IBD patients in China and other countries.

### Research methods

The research design that was adopted to realize the objectives is observational study and nested case-control study. Observational study is to observe and record the characteristics of research objects in a natural state, and describe and compare the results. In our study, the patients were followed for up to 12 mo to identify the incidence of infections. In nested case-control studies, cases and controls come from the same cohort, so the selection bias in effect estimation is reduced and comparability is good. For each infected IBD patient, two non-infected IBD patients were selected as controls in our study.

### Research results

Our study found that the incidence of opportunistic infection in IBD patients in China is higher than that in Western countries and factors such as severe IBD, elevated levels of fecal calprotectin, and the use of immunosuppressive medications, especially when used in combination, are major risk factors for opportunistic infections in IBD patients. Meanwhile, the

use of infliximab alone does not increase the risk of opportunistic infection. Our findings remind patients and physicians to pay attention to and prevent opportunistic infections. As the genetic background, living environment, lifestyle, and diet of IBD patients in China are different from patients in Western countries, our study of opportunistic infection could provide important information for clinicians and IBD patients in China and other countries. The following problems remain to be solved: (1) Our study was a single-center clinical study, which cannot represent the situation of IBD patients in China as a whole; and (2) the sample size of this study for both ulcerative colitis and Crohn's disease patients was small. A larger sample size would have allowed for more precise estimation of the incidence of opportunistic infections and increase in reliability of risk factors in Chinese IBD patients.

### Research conclusions

The new findings of this study are that the incidence of opportunistic infection in IBD patients in China is higher than that in Western countries, according to our single-center study, and factors such as severe IBD, elevated levels of fecal calprotectin, and the use of immunosuppressive medications, especially when used in combination, are major risk factors for opportunistic infections in IBD patients. Meanwhile, the use of infliximab alone does not increase the risk of opportunistic infection. The original insights into the current knowledge that this study offered is when opportunistic infection occurs, patients commonly display a significantly increased rate of morbidity and mortality. Therefore, prevention and identification of opportunistic infections are critical. The implications of this study for clinical practice in the future is patients and physicians need to pay attention to and prevent opportunistic infections.

### Research perspectives

From this study, we can conclude that the incidence of opportunistic infection in IBD patients in China is higher than that in Western countries, and doctors should pay attention to and prevent the incidence of opportunistic infections. The future research direction is to conduct a multi-center study to evaluate the incidence of opportunistic infection in Chinese IBD patients, and more accurately screen out the risk factors leading to the occurrence of opportunistic infection in Chinese IBD patients, so as to effectively prevent the occurrence of opportunistic infection.

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