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# Incidence of invasive fungal diseases in inflammatory bowel disease patients: A nationwide study in South Korea

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## Abstract

**Background:** Limited reports exist regarding invasive fungal diseases (IFDs) in inflammatory bowel disease (IBD) patients.

**Objectives:** This study aims to investigate the incidence and risk factors of IFDs, specifically invasive candidiasis, aspergillosis and pneumocystosis, in IBD patients in South Korea using nationwide data.

**Patients/Methods:** A population-based retrospective cohort of 42,913 IBD patients between January 2010 and December 2018 was evaluated using the Health Insurance Review and Assessment database. The primary outcome was the incidence of IFDs, including invasive candidiasis, aspergillosis and pneumocystosis, while the secondary outcome involved analysing the risk factors associated with each specific infection.

**Results:** The study included a total of 42,913 IBD patients, with 29,909 (69.7%) diagnosed with ulcerative colitis (UC) and 13,004 (30.3%) diagnosed with Crohn's disease (CD). IFDs occurred in 166 IBD patients (0.4%), with 93 cases in UC patients and 73 cases in CD patients. The incidence rates of invasive candidiasis, aspergillosis and pneumocystosis in IBD patients were 0.71 per 1000 person-years (PYs), 0.15 per 1000 PYs and 0.12 per 1000 PYs, respectively. The cumulative incidence of invasive candidiasis (adjusted $p$-value <.001) and Pneumocystosis (adjusted $p$-value = .012) was found to be higher in CD patients than in UC patients. Each IFD had different risk factors, including IBD subtypes, age at diagnosis, anti-tumour necrotic factor agents or the Charlson comorbidity index.

**Conclusion:** Based on nationwide data in South Korea, this study shows that IFDs occur consistently in patients with IBD, albeit with a low frequency.

KEYWORDS
inflammatory bowel disease, invasive fungal diseases

## 1 | INTRODUCTION

Inflammatory bowel disease (IBD) refers to a chronic inflammatory condition affecting the gastrointestinal tract, which includes ulcerative colitis (UC) and Crohn's disease (CD). Conventional treatment approaches for IBD involve using immunosuppressive agents such as corticosteroids and immunomodulators. Additionally, various biologics and small molecules with distinct mechanisms, starting with anti-tumour necrosis factor (TNF) agents, are being used in treatment with the objective of achieving mucosal healing or even more.[1,2] However, one major concern related to these treatment regimens is the risk of opportunistic infections.[3–5] Various opportunistic

infections are primarily linked to changes in the systemic immune system caused by immunosuppressive agents.[6] The occurrence of opportunistic infections is not only detrimental to the patient's quality of life but also frequently necessitates temporary discontinuation of immunosuppressive therapy, making it a critical consideration.[5]

Reporting and guidelines regarding fungal diseases in patients with IBD are limited and have shown a low level of evidence.[4,6,7] A systematic review provided the frequency of fungal infections based on fungal species but did not differentiate them according to severity; *Candida* infections were the most common, but there was a lack of differentiation between invasive candidiasis, such as candidemia or deep-seated candidiasis, and mild infections.[8] Recent studies utilizing big data have limitations in that they either focused on hospitalized patients[9] or analysed the risk factors for overall invasive fungal diseases (IFDs) without distinguishing between fungal species.[10] Given the low frequency of IFDs and variations in their definitions across studies, there is a need for refined analyses based on nationwide data to examine the frequency of IFDs by fungal species and their associated risk factors in patients with IBD.

This study aims to investigate the incidence of IFDs, specifically categorized as invasive candidiasis, aspergillosis and pneumocystosis, and identify associated factors in IBD patients in South Korea using national data. By determining the incidence and risk factors of IFDs in IBD patients, our study aims to improve understanding of the burden of IFDs in this population and provide insights for clinical management strategies.

## 2 | METHODS

### 2.1 | Data source

For the population-based retrospective cohort study, we utilized the Health Insurance Review and Assessment (HIRA) database, which has been previously validated.[11] Diagnostic codes from the International Classification of Diseases, 10th revision (ICD-10), and the V code in the rare intractable diseases (RID) database defined IBD patients. The Institutional Review Board of Eunpyeong St. Mary's Hospital approved this study (IRB approval number: PC19ZNSE128). No ethical approval was required as the research in this article related to micro-organisms.

### 2.2 | Study population

From 2010 to 2018, we screened adult patients aged 18 and older diagnosed with IBD. CD patients were those with ICD-10 code K50 and V code V130, and UC patients with ICD-10 code K51 and V code V131. We checked patients with a prior history of IBD diagnosis during the washout period of 3 years from 2007 to 2009 and excluded them. After excluding patients with a history of fungal infection before the diagnosis of IBD among the screened patients, we constructed the final cohort of eligible patients.

### 2.3 | Outcomes

The primary outcome is determining the incidence of IFDs among the study population. IFDs included specific infectious diseases: invasive candidiasis, aspergillosis and pneumocystosis.[12] The definition of each disease included the presence of ICD-10 codes and at least one dose of relevant anti-fungal agents. Invasive candidiasis encompassed both candidemia and deep-seated candidiasis (B37.1, B37.5, B37.6, B37.7, B37.82, B37.9), while mucocutaneous infections and urinary tract infections were excluded from the analysis.[13,14] Anti-fungal agents used for the treatment of invasive candidiasis were defined as fluconazole, echinocandins or amphotericin B. Aspergillosis was defined as the presence of diagnostic codes (B44.0, B44.1, B44.7, B44.8, B44.89, B44.9) in conjunction with the prescription of voriconazole or amphotericin B. Tonsillar aspergillosis (B44.2) and allergic bronchopulmonary aspergillosis (B44.81) were excluded from our analysis.[15] Isolated tonsillar aspergillosis is considered extremely rare,[16] and allergic bronchopulmonary aspergillosis primarily affects individuals with underlying conditions such as asthma. Its aetiology is an allergic or hypersensitive reaction to *Aspergillus fumigatus*.[17] Due to these distinctions, we opted to exclude them from the scope of IFDs investigated in our study. Pneumocystosis was identified based on diagnostic codes (B48.5, B59, J17.2) and the drug of either trimethoprim/sulfamethoxazole or clindamycin/primaquine. The secondary outcome involved analysing the risk factors associated with each specific infection: invasive candidiasis, aspergillosis and pneumocystosis.

### 2.4 | Covariates

The eligible patients were followed from their initial diagnosis until the last follow-up, from 2010 to 2018. In addition to IBD subtypes (UC or CD) and the occurrence of IFDs, the following variables were considered to account for potential confounders: age at IBD diagnosis, age at fungal infection, gender, disease duration only in patients with fungal infection, concomitant therapies [5-aminosalicylic acid (5-ASA), immunomodulators with methotrexate or thiopurines (IMs), steroid, and anti-TNF agents], duration of steroid (≤30 days, ≤90 days, ≤180 days, ≤1 year, and >1 year), and Charlson Comorbidity Index (CCI).

### 2.5 | Statistical analysis

Student's *t*-test analysed continuous variables, and categorical variables were analysed using the chi-squared test. The incidence of IFDs was presented as the number of events per 1000 person-years (PYs). We also plotted the annual incidence rates and the number of IFDs events yearly. The cumulative incidence of each IFD was compared between IBD subtypes using Kaplan–Meier curves with log-rank *p*-value (raw and adjusted by age, gender and CCI). Cox proportional hazards regression analysis was used to identify the

risk factors for each IFD, and variables with a *p*-value less than .1 in the univariate analysis were included in the multivariate analysis. Statistical significance was set at *p*-value <.05. Statistical analysis was performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 7.1 (SAS Institute Inc., Cary, NC).

## 3 | RESULTS

### 3.1 | Study population

Between 2010 and 2018, a total of 43,017 adult patients were newly diagnosed with IBD. After excluding 104 patients diagnosed with fungal infections before the IBD diagnosis, the final cohort consisted of 42,913 patients, including 29,909 (69.7%) with UC and 13,004 (30.3%) with CD. Among the eligible patients, 166 individuals (0.4%) experienced IFDs, with 93 cases in UC patients and 73 cases in CD patients.

Table 1 presents the baseline characteristics of IBD patients with and without IFDs. Patients in the IFDs group had an older median age at IBD diagnosis of 52.2 years than the IFDs-free group with a median age of 40.0 years. The concomitant use of IMs, steroids and anti-TNF agents was higher in the IFDs group than in the group without IFDs. The duration of steroids more than 30 days was higher across all sub-categories in the IFDs group than the group without IFDs, except for those who received steroids for below 30 days. The IFD group had a higher proportion of patients with a CCI score of 3 or higher than those without IFD (30.7% vs. 12.5%).

### 3.2 | Incidence of invasive fungal diseases

The yearly incidence rates of invasive candidiasis ranged from 0.25% to 0.73%, the rates for aspergillosis ranged from 0.22% to 0.50%, and for pneumocystosis, the rates ranged from 0.00 to 0.16%. These findings indicate no significant variation in the incidence rates of each IFD over the years (Figure 1).

During a median follow-up period of 4 years, invasive candidiasis occurred in 125 individuals, with 67 cases identified in UC patients and 58 cases identified in CD patients (Table 2). The incidence rate for invasive candidiasis was 0.55 per 1000 PYs in UC patients and 1.07 per 1000 PYs in CD patients. The cumulative incidence of invasive candidiasis was higher in CD than in UC patients (raw *p*-value <.001 and adjusted *p*-value <.001) (Figure 2).

Aspergillosis was observed in 27 individuals among the total IBD patients, with 18 cases in UC patients and 9 cases in CD patients. The incidence rate for aspergillosis was 0.15 per 1000 PYs in UC patients and 0.17 per 1000 PYs in CD patients. There was no significant difference in the cumulative incidence of aspergillosis between UC and CD patients (raw *p*-value = .766 and adjusted *p*-value = .125).

Pneumocystosis was found in 21 of the total IBD patients, with 12 cases in UC patients and 9 cases in CD patients. The incidence rate for pneumocystosis was 0.10 per 1000 PYs in UC patients and 0.17 per 1000 PYs in CD patients. After adjusting for age, gender and CCI, the cumulative incidence of pneumocystosis was higher in CD patients than in UC patients (raw *p*-value = .231 and adjusted *p*-value = .012).

### 3.3 | Risk factors for invasive fungal diseases among IBD patients

Invasive candidiasis was found to be associated with several independent risk factors, including CD compared to UC (HR: 2.78, 95% CI: 1.91–4.04), older age at diagnosis (HR: 1.04, 95% CI: 1.03–1.05), use of anti-TNF agents (HR: 1.74, 95% CI: 1.08–2.80) and a CCI score of 3 or above (HR: 1.71, 95% CI: 1.03–2.85) (Table 3).

Aspergillosis was found to be associated with older age at diagnosis (HR: 1.05, 95% CI: 1.02–1.07) and being male (HR: 0.33, 95% CI: 0.13–0.89). CCI of 2 was significantly associated with the risk of aspergillosis (HR: 4.18, 95% CI: 1.25–13.92) compared to a CCI of 0. However, a CCI of 3 or above (HR: 2.35, 95% CI: 0.64–8.67) did not show a consistent tendency of the association.

Pneumocystosis was significantly associated with older age at diagnosis (HR: 1.06, 95% CI: 1.03–1.08) and the use of anti-TNF agents (HR: 5.56, 95% CI: 1.63–18.95) as independent risk factors.

## 4 | DISCUSSION

In this study, we observed a low yearly incidence of IFDs among newly diagnosed IBD patients, with no significant trend in incidence over time. The incidence rates per 1000 PYs for invasive candidiasis, aspergillosis and pneumocystosis were 0.71, 0.15 and 0.12, respectively, similar to previously reported low rates.[3,9,18] *Candida* species remained the most common cause of IFDs, consistent with previous findings.[8,19] Notably, CD patients showed higher incidences of invasive candidiasis and pneumocystosis than UC patients. This finding may be attributed to the higher rates of intestinal surgery and biologics use, known risk factors for IFDs, in CD compared to UC.[20–22]

This study is the first to investigate the incidence of each IFD in IBD patients, specifically UC and CD subtypes, using nationwide data. We focused on the incidence of invasive candidiasis, aspergillosis and pneumocystosis and analysed the risk factors for each fungal disease. Considering the low incidence of IFDs in previous studies, this study utilized nationwide data from HIRA and defined the diseases by combining ICD-10 codes and anti-fungal agents.

Considering disease severity, invasive candidiasis was defined to include candidemia or deep-seated infection, excluding mucocutaneous and urinary tract infections. Risk factors for invasive candidiasis were identified as CD, older age at diagnosis, anti-TNF agents and a high CCI. In a registry following CD patients for more than 5 years, among a total of four patients with invasive candidiasis, three received infliximab treatment.[3] These risk factors align relatively with well-known predisposing factors for invasive candidiasis,[23,24] and

**TABLE 1** Baseline characteristics of the study population.

| Variable | Total patients (*N* = 42,913) | Patients with IFDs (*N* = 166) | Patients without IFDs (*N* = 42,747) | *p*-Value |
|---|---|---|---|---|
| Disease type | | | | |
| UC | 29,909 (69.7) | 93 (56.0) | 29,816 (69.7) | .009 |
| CD | 13,004 (30.3) | 73 (44.0) | 12,931 (30.3) | |
| Age at diagnosis, years | 40.1 ± 16.8 | 52.2 ± 16.8 | 40.0 ± 16.8 | <.001 |
| Age at fungal infection, years | | 54.1 ± 16.7 | | |
| Gender | | | | |
| Male | 27,454 (64.0) | 111 (66.9) | 27,343 (64.0) | .486 |
| Female | 15,459 (36.0) | 55 (33.1) | 15,404 (36.0) | |
| Disease duration, years | | 2.0 ± 1.9 | | |
| Concomitant medication | | | | |
| 5-ASA | 35,831 (83.5) | 135 (81.3) | 35,696 (83.5) | .515 |
| IMs | 14,677 (34.2) | 70 (42.2) | 14,607 (34.2) | .037 |
| Steroid | 33,677 (78.5) | 146 (88.0) | 33,531 (78.4) | .004 |
| Anti-TNF agents | 6175 (14.4) | 40 (24.1) | 6135 (14.4) | .001 |
| Duration of steroid | | | | |
| ≤30 days | 13,838 (32.2) | 35 (21.1) | 13,803 (32.3) | <.001 |
| ≤90 days | 9285 (21.6) | 43 (25.9) | 9242 (21.6) | |
| ≤180 days | 5356 (12.5) | 29 (17.5) | 5327 (12.5) | |
| ≤1 year | 3071 (7.2) | 19 (11.4) | 3052 (7.1) | |
| >1 year | 2127 (5.0) | 20 (12.0) | 2107 (4.9) | |
| CCI | | | | |
| 0 | 18,764 (43.7) | 51 (30.7) | 18,713 (43.8) | <.001 |
| 1 | 12,642 (29.5) | 36 (21.7) | 12,606 (29.5) | |
| 2 | 6133 (14.3) | 28 (16.9) | 6105 (14.3) | |
| 3 or above | 5374 (12.5) | 51 (30.7) | 5323 (12.5) | |
| Follow-up duration, years | 4.1 ± 2.6 | 2.0 ± 1.9 | 4.1 ± 2.6 | <.001 |

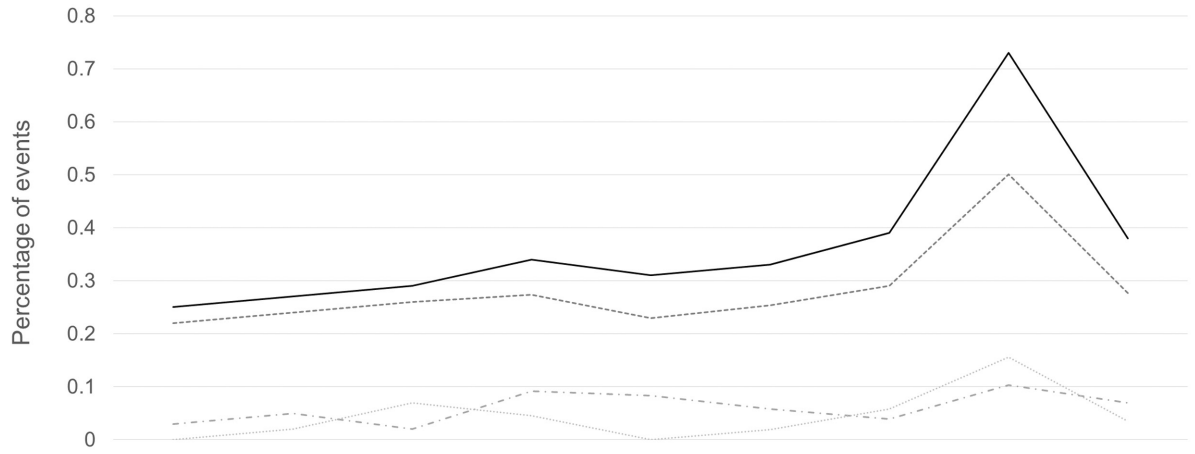
*Note*: Variables are expressed as mean ± standard deviation or number (%). *p*-Value was compared between the patients with fungal infection and without fungal infection.

Abbreviations: 5-ASA, 5-aminosalicylic acid; anti-TNF, anti-tumour necrosis factor; CCI, Charlson comorbidity index; CD, Crohn's disease; IFD, invasive fungal diseases; IMs, immunomodulators; UC, ulcerative colitis.

IBD patients could be exposed to these risk factors. Firstly, there is a predisposition to the repetitive use of broad-spectrum antibiotics. In cases of acute exacerbation of symptoms in IBD patients, it is essential to differentiate from infectious colitis, potentially leading to exposure to empirical antibiotic therapy based on the severity of that condition. Moreover, there is a possibility of exposure to antibiotic treatment for various reasons, such as anal complications or extraintestinal manifestations. Secondly, chronic inflammation of the intestinal lining can lead to mucosal barrier disruption. In cases where disease activity is poorly controlled, complications such as perforation or abscess may occur, ultimately requiring intestinal surgery. Lastly, commonly used treatments such as steroids, immunomodulators (thiopurines or methotrexate), biological therapy or small molecules can create an environment vulnerable to deep-seated infections associated with candidemia due to their association with systemic immunosuppression. Therefore, caution for invasive candidiasis should be exercised in IBD patients with these risk factors.

Few reports exist on the frequency of aspergillosis in IBD patients.[9] The main risk factors for aspergillosis include structural lung disease, cancer, steroid use for conditions such as chronic obstructive pulmonary disease or acute respiratory distress syndrome, and severe respiratory viral infections. Although there have been case reports linking infliximab to *Aspergillus* infection, the causality of this association is limited by the concurrent use of other immunosuppressive agents in these cases.[25–28] Our study also did not establish a relationship between anti-TNF agents and aspergillosis. In comparison, the comorbidities (high CCI) tended to be associated with aspergillosis, similar to existing risk factors. This suggests underlying comorbidities may be more significant factors for aspergillosis in IBD patients. Further research and surveillance are needed to understand better the frequency and clinical significance of aspergillosis in IBD patients.

Our study revealed a low incidence of pneumocystosis in IBD with an incidence rate of 0.1–0.17 per 1000 PYs, similar to previous




| | 2010 (N = 3,568) | 2011 (N = 4,119) | 2012 (N = 4,169) | 2013 (N = 4,380) | 2014 (N = 4,798) | 2015 (N = 5,133) | 2016 (N = 5,171) | 2017 (N = 5,791) | 2018 (N = 5,784) |
|---|---|---|---|---|---|---|---|---|---|
| Invasive fungal diseases | 0.25 (9) | 0.27 (11) | 0.29 (12) | 0.34 (15) | 0.31 (15) | 0.33 (17) | 0.39 (20) | 0.73 (42) | 0.38 (22) |
| Invasive candidiasis | 0.22 (8) | 0.24 (10) | 0.26 (11) | 0.27 (12) | 0.23 (11) | 0.25 (13) | 0.29 (15) | 0.50 (29) | 0.28 (16) |
| Aspergillosis | 0.03 (1) | 0.05 (2) | 0.02 (1) | 0.09 (4) | 0.08 (4) | 0.06 (3) | 0.04 (2) | 0.10 (6) | 0.07 (4) |
| Pneumocystosis | 0.00 (0) | 0.02 (1) | 0.07 (3) | 0.05 (2) | 0.00 (0) | 0.02 (1) | 0.06 (3) | 0.16 (9) | 0.03 (2) |



**FIGURE 1** The yearly trend of invasive fungal diseases in inflammatory bowel disease patients. Data are presented as a percentage (number of events).

**TABLE 2** Incidence of invasive fungal diseases in inflammatory bowel disease patients.

| | *N* of patients | *N* of events | Person-years | Incidence/1000 PYs |
|---|---|---|---|---|
| Invasive candidiasis | | | | |
| Total | 42,913 | 125 | 177,371 | 0.71 (0.59–0.84) |
| UC | 29,909 | 67 | 122,993 | 0.55 (0.42–0.69) |
| CD | 13,004 | 58 | 54,377 | 1.07 (0.81–1.38) |
| Aspergillosis | | | | |
| Total | 42,913 | 27 | 177,736 | 0.15 (0.10–0.22) |
| UC | 29,909 | 18 | 123,162 | 0.15 (0.09–0.23) |
| CD | 13,004 | 9 | 54,573 | 0.17 (0.08–0.31) |
| Pneumocystosis | | | | |
| Total | 42,913 | 21 | 177,768 | 0.12 (0.07–0.18) |
| UC | 29,909 | 12 | 123,192 | 0.10 (0.05–0.17) |
| CD | 13,004 | 9 | 54,576 | 0.17 (0.08–0.31) |

Abbreviations: CD, Crohn's disease; PYs, person-years; UC, ulcerative colitis.

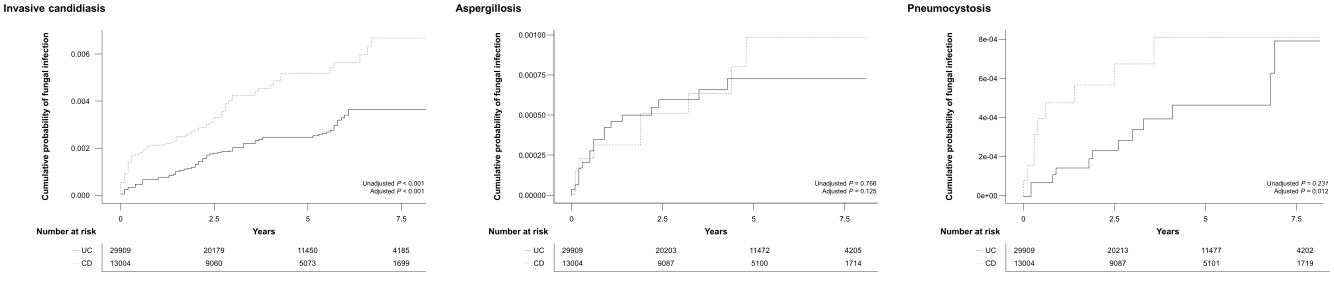



**FIGURE 2** Comparison for the cumulative incidence of invasive fungal diseases between ulcerative colitis and Crohn's disease.

**TABLE 3** Risk factors associated with invasive fungal diseases.

| | Invasive candidiasis | | | | Aspergillosis | | | | Pneumocystosis | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Univariable | Multivariable | | | Univariable | Multivariable | | | Univariable | Multivariable | | |
| | *p*-Value | HR | 95% CI | *p*-Value | *p*-Value | HR | 95% CI | *p*-Value | *p*-Value | HR | 95% CI | *p*-Value |
| UC[a]/CD | <.001 | 2.78 | 1.91–4.04 | <.001 | .766 | | | | .231 | | | |
| Age at diagnosis | <.001 | 1.04 | 1.03–1.05 | <.001 | <.001 | 1.05 | 1.02–1.07 | <.001 | <.001 | 1.06 | 1.03–1.08 | <.001 |
| Male[a]/Female | .642 | | | | .064 | 0.33 | 0.13–0.89 | .028 | .110 | | | |
| 5-ASA No[a]/Yes | .080 | 0.75 | 0.48–1.16 | .193 | .490 | | | | .838 | | | |
| IMs No[a]/Yes | .519 | | | | .603 | | | | .002 | 3.04 | 0.09–9.78 | .063 |
| Steroid duration | | | | | | | | | | | | |
| No[a] | | | | | | | | | | | | |
| ≤90 days | .864 | 0.92 | 0.54–1.56 | .759 | .353 | 1.89 | 0.42–8.40 | .404 | .735 | 1.13 | 0.13–9.72 | .915 |
| ≤1 year | .594 | 1.12 | 0.61–2.05 | .725 | .145 | 2.99 | 0.64–14.16 | .167 | .031 | 3.81 | 0.46–31.91 | .217 |
| >1 year | <.001 | 1.39 | 0.67–2.88 | .374 | .042 | 4.27 | 0.77–23.54 | .096 | .184 | 1.36 | 0.11–16.65 | .810 |
| Anti-TNF agents No[a]/Yes | .062 | 1.74 | 1.08-2.80 | .023 | .323 | | | | <.001 | 5.56 | 1.63–18.95 | .020 |
| CCI | | | | | | | | | | | | |
| 0[a] | | | | | | | | | | | | |
| 1 | .645 | 0.94 | 0.57–1.54 | .797 | .129 | 2.10 | 0.61–7.20 | .239 | .164 | | | |
| 2 | .066 | 1.14 | 0.65–1.99 | .652 | .001 | 4.18 | 1.25–13.92 | .020 | .222 | | | |
| 3 or above | <.001 | 1.71 | 1.03–2.85 | .039 | .004 | 2.35 | 0.64–8.67 | .199 | .201 | | | |

Abbreviations: 5-ASA, 5-aminosalicylic acid; anti-TNF, anti-tumour necrosis factor; CCI, Charlson comorbidity index; CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; UC, ulcerative colitis.

[a]Reference.

reports.[29,30] *Pneumocystis jiroveci* pneumonia (PJP) is known to carry an increased risk in IBD patients, particularly in CD compared to UC.[31] Our study confirmed these findings with a higher cumulative incidence of pneumocystosis in CD compared to UC after adjusting for relevant factors. We identified older age at diagnosis and anti-TNF agents as risk factors for pneumocystosis, in line with previous research.[32] Other factors reported in previous studies include lymphopenia, corticosteroid use, immunosuppressants and interstitial lung disease.[32,33]

Pneumocystosis is the only IFD for which a specific preventive measure is recommended. Recent guidelines suggest prophylaxis for pneumocystosis in IBD patients receiving triple immunosuppressants.[6,7] However, the current case series for PJP in IBD patients showed a significant proportion of patients who developed pneumocystosis were receiving below two immunosuppressants.[34] These findings emphasize the need for further individualization of PJP prophylaxis in IBD patients to account for the potential risk in patients receiving fewer immunosuppressants. For example, in patients with autoimmune and inflammatory diseases who are taking prednisolone at a dosage of 20 mg or higher for 1 month or more, PJP prophylaxis recommendations vary depending on the disease type, concurrent immunosuppressants or biological agents, and underlying interstitial lung disease,[33] based on the incidence differences depending on the specific disease and concurrent immunosuppressive therapy.[30,35,36]

This study has several limitations. Firstly, as a retrospective study, selection bias is possible. However, using nationwide data and defining IFDs by combining diagnosis codes and medication helped minimize these biases. Another limitation is related to the factor of steroid administration. Although the IFDs group had a longer duration of steroid treatment, it was not identified as a significant risk factor compared to patients who received shorter steroid treatment, which differs from findings in other studies.[23,24] The lack of data on cumulative doses of steroids may have impacted the analysis. Furthermore, this study did not specifically evaluate the impact of combinations of multiple immunosuppressants on the risk of IFDs, and the assessment of PJP prophylaxis was not conducted.[10] Finally, our data lack information on the impact of IFDs on disease activity and clinical outcomes. Typically, in cases where IFDs are present, discontinuation of immunosuppressive therapy is recommended. Therefore, understanding the prognosis of these patients remains a crucial task. These limitations are important considerations for future research to understand better the risk factors and preventive strategies associated with IFDs in IBD patients.

In conclusion, our study confirmed that IFDs occur consistently in IBD patients, albeit at a low frequency. CD patients showed higher frequencies of invasive candidiasis and pneumocystosis than UC patients. Despite their low frequency, additional research is needed for IFDs that are challenging to predict and diagnose. Based on our findings, there is a need to advance preventive measures for IFDs in IBD patients.

## AUTHOR CONTRIBUTIONS

**Ji Eun Na:** Conceptualization; methodology; investigation; writing – original draft; writing – review and editing; visualization; project administration; resources. **Sung Hoon Jung:** Supervision; methodology; conceptualization; writing – review and editing; validation; funding acquisition; resources. **Arum Choi:** Software; formal analysis; data curation; methodology. **Sukil Kim:** Software; formal analysis; data curation; methodology. **Tae-Oh Kim:** Writing – review and editing; supervision; investigation; validation; visualization.

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## CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest for all authors.

## DATA AVAILABILITY STATEMENT

Data are available on request. The data underlying this article will be shared upon reasonable request to the corresponding author.

## CONSENT FOR PUBLICATION

All authors approved this publication.

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