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Original Article

Current Status of Opportunistic Infection in Inflammatory Bowel Disease Patients in Asia: A Questionnaire-Based Multicenter Study

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Background/Aims: Opportunistic infection in inflammatory bowel disease (IBD) has become a serious problem. However, its status of doctors' opinions and test equipment in hospitals are unclear. The aim of the study was to investigate these issues to improve the prognosis of IBD patients.

Methods: This retrospective, multicenter study was conducted by 83 investigators who were members of the Asian Organization for Crohn's and Colitis. Data on opportunistic infection were collected from hospital databases between January 2017 and December 2017. The survey consisted of 11 items.

Results: Most physicians appreciated the diagnostic value of tissue cytomegalovirus (CMV) DNA, accounting for 86.1% of members in China, 37.5% in Japan, 52.9% in South Korea, and 66.7% in Southeast Asia. Only 83.1% of hospitals had the ability to test for CMV immunohistochemistry in Asia. Hepatitis B surface antigen (HBsAg) screening was recommended by all members. However, only 66.7% in China, 70.6% in South Korea, and 66.7% in Southeast Asia agreed to routinely vaccinate IBD patients when HBsAg tested negative. Most members preferred metronidazole (74.7%) as the first choice for patients with *Clostridium difficile* infection. However, the proportion of stool *C. difficile* toxin test was lower in China than in other areas (75.0% in China vs 95.8% in Japan and 100% in South Korea and Southeast Asia, $p<0.05$).

Conclusions: Opportunistic infection from CMV, hepatitis B virus, and *C. difficile* should be of high concern for IBD patients. More efforts are needed, such as understanding consensus in clinical practice and improving testing facilities in hospitals. **(Gut Liver 2022;16:726-735)**

Key Words: Inflammatory bowel disease; Opportunistic infection; Asia; Questionnaire

INTRODUCTION

Inflammatory bowel disease (IBD) has become a global disease since the beginning of the century. The incidence of IBD varies worldwide. It which appears to be stabilizing in Western countries but increasing in newly industrialized or developing countries across Asia, Africa, and South America.[1,2] The treatment of IBD with corticosteroids, immunomodulators, and biological agents provide not only clinical efficacy but also adverse effects including opportunistic infection.[3,4]

Opportunistic infection is a key safety concern with increasing use of immunosuppressive agents. Several studies have suggested that IBD patients treated with immunosuppressive drugs are prone to viral reactivation and infections from bacteria, fungi, or parasites.[5-8] These infections make the disease pattern of IBD difficult to recognize and to treat. Due to opportunistic infection, IBD patients face longer hospital stay, higher colectomy rate, and higher mortality risk. For example, McCurdy *et al.*[9] reported that colectomy-free survival at 1 year was significantly decreased in IBD patients with cytomegalovirus (CMV) infection and in IBD patients with *Clostridium difficile* infection (CDI). All these suggest that opportunistic infection is a major

concern that needs to be carefully considered in the diagnosis and treatment of IBD.

As the incidence of IBD has increased rapidly in Asia in recent years, opportunistic infection has become an obvious issue. A questionnaire survey was conducted by the Asian Organization for Crohn's and Colitis (AOCC) association group. Opportunistic infections of CMV colitis, hepatitis B virus (HBV) infection and CDI were identified. The laboratory conditions in different countries were documented, and opinions of clinicians for the diagnosis and treatment were investigated. The aim of the study was to investigate current status of opportunistic infection in different countries in Asia for contributing better prognosis.

MATERIALS AND METHODS

1. Study design and execution

This retrospective, multicenter study was conducted by the investigators who were members of the AOCC. Invitation letters along with the questionnaires were sent to all members of AOCC in September 2018. The subjects enrolled in this study were those inpatients confirmed diagnosis of ulcerative colitis or Crohn's disease, between January 2017 and December 2017. The data of opportunistic infection was collected from hospital databases. In addition, the opinions of participants for the diagnosis and treatment of IBD were documented. The study was approved by the Ethical Committee of Peking Union Medical College Hospital (approval number: S-K1142). The retrospective data are anonymous and do not involve personal privacy and commercial interests, and the requirement for informed consent was waived.

2. Participants

A total of 83 AOCC members participated in this study with one member from each hospital/institute, which included 36 members from China, 17 members from South Korea, 24 members from Japan, two members from the Philippines, three members from India, and one member from Malaysia. For statistical analysis, according to geographical location, the Philippines, India, and Malaysia were grouped into Southeast Asia.

3. Questionnaire

The questionnaire was administered in English. It consisted of 11 items, including three items for CMV infection, five items for HBV infection, and three items for CDI. Details of the items presented in this study are provided in the Supplementary Material 1. The survey comprised two parts: a report of diagnostic tests available for hospitals and a report of physicians' opinions.

4. Outcome measures

The outcome measures included comparing laboratory conditions, and identifying attitudes of clinicians for the diagnosis and treatment in CMV infection, HBV infection, and CDI. The questionnaire was validated by five IBD specialists and informatics experts for appropriateness and adequacy of items.

5. Statistical analysis

Data were expressed as proportions. Chi-square and Fisher exact tests were performed to determine the differences between the groups using the SPSS 11.5 software program (IBM Corp., Armonk, NY, USA). p-value <0.05 was considered to be statistically significant.

RESULTS

1. The survey of CMV infection in IBD

1) Physicians' opinions for CMV infection and CMV colitis

(1) Physicians' opinions on considering the diagnosis of CMV colitis by DNA polymerase chain reaction

Sixty-three point nine percent of member doctors agreed that tissue CMV DNA could be used as an index for the diagnosis of CMV colitis, followed by 24.1% agreed with blood CMV and 13.3% agreed with stool CMV DNA. For individual country analysis, 31 members (86.1%), nine members (37.5%), nine members (52.9%), and four members (66.7%) in China, Japan, South Korea, and Southeast Asia agreed that tissue CMV DNA could be used as diagnosis index for CMV colitis, the support rate in Japan and South Korea was lower than those in China. Very few members in China and Southeast Asia agreed with the diagnostic value of stool CMV DNA for CMV colitis, and there were significant differences among them ($p<0.05$). There was no significant difference between physicians' opinions on the diagnostic value of blood CMV DNA for CMV colitis, of which the support rates were around 25% (Table 1).

(2) Physicians' opinions on the endoscopic features of CMV colitis with UC patients

Among the endoscopic features of CMV colitis (Table 1), punched-out ulcerations (60 members, 72.3%) was the most agreed feature that indicated CMV colitis. Further analysis of individual country physicians' opinions on endoscopic features indicated that recognition of punched-out ulcerations exceeded those with mucosal defect and

Table 1. Physician's Opinion on Considering the Diagnosis of Cytomegalovirus (CMV) Colitis and the Endoscopic Features of CMV Colitis in Ulcerative Colitis Patients

Variable	Total (n=83)	China (n=36)	Japan (n=24)	South Korea (n=17)	Southeast Asia (n=6)	p-value*
Diagnosis						
Stool CMV DNA	11 (13.3)	9 (25.0)†,‡	0†,§	0‡	2 (33.3)§	<0.05
Blood CMV DNA	20 (24.1)	11 (30.6)	6 (25.0)	1 (5.9)	2 (33.3)	0.241
Tissue CMV DNA	53 (63.9)	31 (86.1)$^{\|\|,\P}$	9 (37.5)$^{\|\|}$	9 (52.9)¶	4 (66.7)	<0.01
Endoscopic features						
Longitudinal ulcers	34 (41.0)	19 (52.8)	6 (25.0)	7 (41.2)	2 (33.3)	0.191
Punched-out ulcerations	60 (72.3)	24 (66.7)	19 (79.2)	12 (70.6)	5 (83.3)	0.677
Mucosal defect	33 (39.8)	17 (47.2)	9 (37.5)	6 (35.3)	1 (16.7)	0.5

Data are presented as the number (%).
*Chi-square test or Fisher exact test was used; $^{\dagger,\ddagger,\S,\|\|,\P}$The same symbol in each row indicates that there is a significant difference between the two groups.

Table 2. Hospital Equipment for Detecting Cytomegalovirus (CMV) Infection and CMV Colitis

Variable	Total (n=83)	China (n=36)	Japan (n=24)	South Korea (n=17)	Southeast Asia (n=6)	p-value*
Blood CMV IgM	51 (61.4)	30 (83.3)†	7 (29.2)†,‡	11 (64.7)‡	3 (50.0)	<0.05
Blood CMV pp65	29 (34.9)	9 (25.0)§	16 (66.7)$^{\S,\|\|,\P}$	4 (23.5)$^{\|\|}$	0¶	<0.01
Blood CMV DNA	46 (55.4)	29 (80.6)$^{\#,**}$	5 (20.8)$^{\#,\dagger\dagger}$	10 (58.8)††	2 (33.3)**	<0.05
Tissue CMV IHC staining	69 (83.1)	28 (77.8)	19 (79.2)	17 (100)	5 (83.3)	0.216
Tissue CMV *in situ* hybridization	17 (20.5)	10 (27.8)‡‡	1 (4.2)‡‡,§§	6 (35.3)§§	0	<0.05
Tissue CMV DNA	26 (31.3)	8 (22.2)	7 (29.2)	7 (41.2)	4 (66.7)	0.128
Stool CMV DNA	8 (9.6)	7 (19.4)	0	1 (5.9)	0	0.067

Data are presented as the number (%).
IgM, immunoglobulin M; IHC, immunohistochemistry.
*Chi-square test or Fisher exact test was used; $^{\dagger,\ddagger,\S,\|\|,\P,\#,**,\dagger\dagger,\ddagger\ddagger,\S\S}$The same symbol in each row indicates that there is a significant difference between the two groups.

longitudinal ulcer appearance. There was no significant difference among different areas.

2) Variation in hospital laboratory equipment collocation for detecting CMV infection and CMV colitis

As shown in Table 2, immunohistochemistry (IHC) testing (83.1%) could be performed in more hospitals in Asia than other tests, including blood CMV immunoglobulin M, blood CMV DNA, blood CMV pp65, tissue CMV DNA, tissue CMV *in situ* hybridization, and stool CMV DNA. Stool and tissue CMV DNA analysis was carried out in fewer hospitals, including seven (19.4%) and eight (22.2%) member's hospitals in China, 0 and seven (29.2%) in Japan, one (5.9%) and seven (41.2%) in South Korea, and 0 and four (66.7%) in Southeast Asia, respectively. More hospitals had the equipment of detecting blood CMV immunoglobulin M in China and South Korea than those in Japan (83.3%, 64.7%, vs 29.2%, respectively). More hospitals had the equipment of detecting blood CMV DNA in China and South Korea than those in Japan and Southeast Asia (80.6%, 58.8%, vs 20.8%, 33.3%, respectively).

2. The survey of HBV infection in IBD

1) Comparisons of routinely selected screening items for HBV infection in IBD

Routinely selected screening items for HBV infection by physicians were shown in Table 3. Hepatitis B surface antigen (HBsAg) screening was recommended by all members. Hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb) were recommended in more than 80% of members from China, Japan and South Korea, and there was no significant difference among different areas. The proportion of recommending HBsAb was lower in Southeast Asia (33.3%) than in those in China (91.7%), Japan (91.7%), South Korea (94.1%) ($p<0.01$). Significantly more proportion of members in China recommended routine screening for hepatitis B e antibody, hepatitis B e antigen, and HBV DNA (94.4%, 97.2%, and 44.4%, respectively) than those in Japan (12.5%, 12.5%, and 16.7%, respectively), South Korea (5.9%, 11.8%, and 0%, respectively) and Southeast Asia (16.7%, 16.7%, and 0%, respectively) ($p<0.001$, $p<0.001$, and $p=0.001$).

Table 3. Comparisons of Routinely Screened Items for Hepatitis B virus (HBV) Infection and Anti-HBV Therapy in Asia

Variable	Total (n=83)	China (n=36)	Japan (n=24)	South Korea (n=17)	Southeast Asia (n=6)	p-value*
Routine screening items						
HBsAg	83 (100)	36 (100)	24 (100)	17 (100)	6 (100)	1.000
HBsAb	73 (88.0)	33 (91.7)†	22 (91.7)‡	16 (94.1)§	2 (33.3)†,‡,§	<0.01
HBcAb	75 (90.4)	35 (97.2)	20 (83.3)	16 (94.1)	4 (66.7)	0.099
HBeAb	39 (47.0)	34 (94.4)‖,¶,#	3 (12.5)‖	1 (5.9)¶	1 (16.7)#	<0.001
HBeAg	41 (49.4)	35 (97.2)**,††,‡‡	3 (12.5)**	2 (11.8)††	1 (16.7)‡‡	<0.001
HBV DNA	20 (24.1)	16 (44.4)§§,‖‖,¶¶	4 (16.7)§§	0‖‖	0¶¶	0.001
Anti-HBV therapy						
Before use of BA	72 (86.7)	31 (86.1)	20 (83.3)	17 (100)	4 (66.7)	>0.05
Before use of IM	59 (71.1)	30 (83.3)##	19 (79.2)	9 (52.9)	1 (16.7)##	0.001
First choice of hepatitis B therapy						
Lamivudine	8 (9.6)	4 (11.1)	2 (8.3)	2 (11.8)	0	>0.05
Entecavir	64 (77.1)	31 (86.1)	17 (70.8)	10 (58.8)	6 (100)	>0.05
Adefovir dipivoxil	3 (3.6)	0	1 (4.2)	2 (11.8)	0	>0.05
Tenofovir disoproxil	23 (27.7)	7 (19.4)	7 (29.1)	7 (41.2)	2 (33.3)	>0.05
Telbivudine	2 (2.4)	1 (2.8)	1 (4.2)	0	0	1.000

Data are presented as the number (%).
HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBcAb, hepatitis B core antibody; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; BA, biological agent; IM, immunomodulators.
*Chi-square test or Fisher exact test was used; †,‡,§,‖,¶,#,**,††,‡‡,§§,‖‖,¶¶,##The same symbol in each row indicates that there is a significant difference between the two groups.

2) The survey routinely recommend hepatitis B vaccination when the result of HBsAg is negative

We found that a small number of members did not recommend HBV vaccination when the HBsAg was tested negative. As shown in Fig. 1, 24 (66.7%) members in China, 12 (70.6%) members in South Korea, and four (66.7%) members in Southeast Asia routinely recommended vaccination for IBD patients when HBsAg was tested negative.

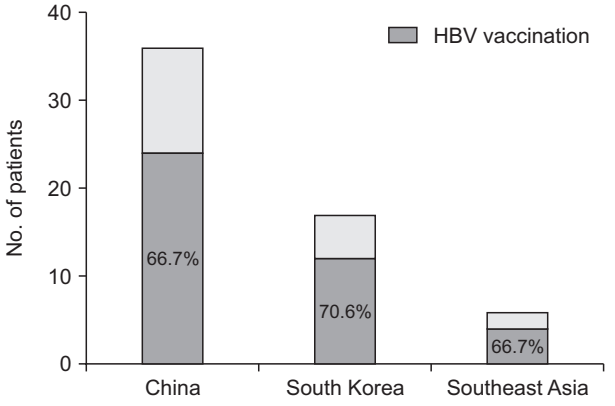

Fig. 1. Proportion of hepatitis B virus (HBV) vaccination with negative hepatitis B surface antigen (HBsAg) in inflammatory bowel disease in Asia. A total of 24 (66.7%) members in China, 12 (70.6%) members in South Korea and four (66.7%) members in Southeast Asia routinely recommended vaccination for inflammatory bowel disease patients when HBsAg tested negative.

3) The survey about antiviral treatment for those patients with positive HBsAg before the use of immunomodulators agent or a biological agent

About 86.7% and 71.1% of all members in Asia recommended anti-HBV therapy before use of immunomodulators agents or biological agent respectively when HBsAg is positive. Individual country analysis showed that 31 (86.1%) members in China, 20 members (83.3%) in Japan, 17 members (100%) in South Korea, four members (66.7%) in Southeast Asia considered antiviral treatment before the use of biological agent agents. The proportion of anti-HBV therapy before using immunomodulators agents was lower in Southeast Asia than those in China, Japan, and South Korea (16.7% vs 83.3%, 79.2%, 52.9%) (Table 3).

4) The survey of the first choice for treating HBV infection in IBD patients

For drug choices, 77.1% of all members preferred entecavir as the first choice for IBD patients, and 23 members (27.7%) for tenofovir disoproxil, eight members (9.6%) for lamivudine, three members (3.6%) for adefovir dipivoxil, two members (2.4%) for telbivudine. The proportion of choosing entecavir as first choice for HBV infection treatment was 86.1% in China, 70.8% in Japan, 58.8% in South Korea, and 100% in Southeast Asia. However, a small proportion of members (11.1% in China, 8.3% in Japan, and 11.8% in South Korea) still preferred lamivudine, which has a slow onset of action and high incidence of resistance (shown in Table 3).

Table 4. Physicians' Opinions of *Clostridium difficile* Tests in Different Countries

Variable	China (n=36)	Japan (n=24)	South Korea (n=17)	Southeast Asia (n=6)	p-value
All patients in active stage	21 (58.3)	14 (58.3)	14 (82.3)	5 (83.3)	>0.05
All IBD patients prior to use of IM	22 (61.1)*,†	5 (20.8)*	2 (11.7)†	3 (50.0)	<0.01
All IBD patients prior to use of BA	25 (69.4)‡,§	7 (29.1)‡	6 (35.2)§	4 (66.7)	<0.05
All patients in remission	1 (2.8)	1 (4.2)	2 (11.7)	0	>0.05
Glucocorticoid resistance	28 (77.8)	12 (50.0)	10 (58.8)	5 (83.3)	>0.05
Glucocorticoid dependence	24 (66.7)	13 (54.2)	8 (47.1)	1 (16.7)	>0.05

Data are presented as the number (%).
IBD, inflammatory bowel disease; IM, immunomodulators; BA, biological agent.
*,†,‡,§The same symbol in each row indicates that there is a significant difference between the two groups.

Table 5. Comparisons of Hospital Facilities and Preferences in Drug Treatment for *Clostridium difficile* Infection in Different Countries

Variable	Total (n=83)	China (n=36)	Japan (n=24)	South Korea (n=17)	Southeast Asia (n=6)	p-value*
Hospital facilities						
Stool *C. difficile* culture	45 (54.2)	19 (52.8)	16 (66.7)	9 (52.9)	1 (16.7)	>0.05
Stool *C. difficile* toxin A/B test	73 (88.0)	27 (75.0)†,‡	23 (95.8)†	17 (100)‡	6 (100)	<0.05
GDH	25 (30.1)	11 (30.6)	9 (37.5)	3 (17.6)	2 (33.3)	>0.05
Nucleotide PCR assay	21 (25.3)	14 (38.9)‡	0‡,§	7 (41.2)§	0	<0.01
Drug options						
First choice						>0.05
Metronidazole	62 (74.7)	24 (66.7)	16 (66.7)	16 (94.1)	6 (100)	
Vancomycin	22 (26.5)	15 (33.3)	6 (33.3)	1 (5.9)	0	
Second choice						>0.05
Metronidazole	18 (21.7)	9 (25.0)	7 (29.1)	2 (11.8)	0	
Vancomycin	65 (78.3)	27 (75.0)	17 (70.9)	15 (88.2)	6 (100)	
Recurrent patients						<0.05
Metronidazole	12 (14.5)	1 (2.7)‖,¶	4 (16.6)	4 (23.5)‖	3 (50.0)¶	
Vancomycin	71 (85.5)	35 (97.3)	20 (83.4)	13 (76.5)	3 (50.0)	

Data are presented as the number (%).
GDH, glutamate dehydrogenase; PCR, polymerase chain reaction.
*Chi-square test or Fisher exact test was used; †,‡,§,‖,¶The same symbol in each row indicates that there is a significant difference between the two groups.

3. The survey of CDI in IBD

1) Physicians' opinion analysis

(1) The survey about recommending *C. difficile* tests in IBD patients

We found that the physicians' opinions on the screening of *C. difficile* were diverse. Fifty-five members (66.3%) agreed to test *C. difficile* in the circumstances of glucocorticoid resistance. The proportion of screening patients at active stage were higher in South Korea and Southeast Asia than that in China and Japan (82.3%, 83.3% vs 58.3%, 58.3%, respectively); for patients with steroid resistance, performing *C. difficile* tests were most common in Southeast Asia (83.3%) and China (77.8%); and in patients with steroid dependence, the proportions were 66.7% in China, 54.2% in Japan, 47.1% in South Korea and 16.7% in Southeast Asia (shown in Table 4).

(2) The survey of the first and second treatment choice for CDI, the first choice for recurrent CDI

As we could see from Table 5, most members preferred metronidazole (62 members, 74.7%) as the first choice of treatment while vancomycin was regarded by 78.3% of members as the second choice, and vancomycin (71 members, 85.5%) as the first choice for recurrent patients.

2) Variation in hospital laboratory equipment for detecting CDIF or the diagnosis of CDI

Stool *C. difficile* toxin A/B test could be performed in most hospitals (75.0% in China, 95.8% in Japan, and 100% in both South Korea and Southeast Asia, respectively). However, the proportion of having stool *C. difficile* toxin A/B test was lower in China than other areas ($p<0.05$). Stool *C. difficile* culture could be performed in over half of hospitals in China, Japan, and South Korea. Glutamate dehydrogenase antigen assay and nucleotide polymerase

chain reaction (PCR) assay were carried out in fewer hospitals less than around 40% (shown in Table 5).

DISCUSSION

The significantly rising incidence of IBD in Asia occurred along with accelerating economic development. The incidence of IBD increased from 0.09/100,000 to 5.1/100,000 in ulcerative colitis and from 0.4/100,000 to 6.0/100,000 in Crohn's disease in Asia over the last four decades.[2] With the increasing incidence of IBD in Asia and the increasing use of immunosuppressive agents, opportunistic infections have become an obvious problem. The AOCC association group conducted this study in order to attain the current status of opportunistic infections in IBD in Asia. The physicians' opinions and laboratory equipment for CMV colitis, CDI, and HBV infections in IBD were investigated and compared in different countries in Asia based on the data of inpatients with IBD hospitalization in 2017. The information obtained from this survey will help physicians in decision-making on diagnosis and treatment to minimize the impact of opportunistic infection on the prognosis of IBD.

The results of this study showed that most physicians' opinions on the diagnosis test for CMV colitis, the screening test for HBV, and the drug choice were consistent with the consensus of European Cancer Organisation (ECCO) and Chinese Medical Association.[10,11] However, different opinions appeared in a small number of members, along with shortage of testing equipment in some member's hospitals. For CMV colitis, 36.1% members did not agree with the diagnostic value of tissue CMV DNA. Only 83.1% hospitals in Asia had the test equipment. For HBV infection, only 67.8% members agreed to recommend HBV vaccination for patients with HBsAg negative. Although lamivudine is not recommended as first-line drug in ECCO consensus, 9.6% members preferred to treat HBV infection with lamivudine. For CDI, the *C. difficile* detecting appeared overtesting as some physicians chose it for patient in remission (4.8%) or with glucocorticoid dependence (55.4%). However, the variation in hospital equipment restricted the accuracy of the test for *C. difficile*.

As we know, the association between CMV infection and IBD has received increasing attention in recent years. CMV colitis was associated with IBD flare-up and severe steroid-refractory IBD, likely leading to fulminant colitis and colectomy.[12,13] The previous reports[14] have shown that the prevalence of tissue hematoxylin and eosin staining or IHC-positive CMV colitis in IBD patients ranged from 1.6% to 29%. Several studies have used blood CMV PCR assay to detect CMV infection and monitor the viral load in CMV colitis.[14-16] Our previous study showed that blood DNA PCR at more than 1,170 copies/mL had predictive value for CMV colitis.[17] However, diagnosis of CMV colitis by tissue PCR or IHC is currently considered the gold standard by ECCO consensus and PCR analysis on endoscopic biopsies had great diagnostic performance for detecting CMV.[18-20] In this study, we found the diagnostic value of tissue CMV DNA quantitative real-time polymerase chain reaction (qPCR) in CMV colitis was agreed by most members. There was a certain number of members agreed with the value of blood and stool CMV DNA qPCR for CMV colitis, which remains to be confirmed by further studies. We also found that not all hospitals were equipped with blood, stool, tissue diagnostic equipment even it is for tissue IHC and CMV DNA qPCR, which create the gap between knowledge and real world. And different member hospitals in Asia had different choices for diagnostic equipment of blood CMV immunoglobulin M, blood CMV pp65, blood CMV DNA, tissue CMV IHC staining, tissue CMV *in situ* hybridization, tissue CMV DNA, and stool CMV DNA. This finding suggests that the published prevalence data on CMV infection in IBD patients may be underestimated due to the differences in capability of hospital facilities.

Our previous study[17] showed that CMV colitis caused colonoscopic changes in ulcerative colitis patients, presenting as punched-out ulcers, longitudinal ulcers, and mucosal defects. Our previous study also showed that patients with punched-out ulceration presenting more inclusion bodies at the biopsy site. In this study, we surveyed physician' opinions about the endoscopic features of CMV colitis. Punched-out ulcerations had the greatest acceptability among physicians for identifying CMV colitis (66.7% of doctors in China, 79.2% in Japan, 70.6% in South Korea, and 83.3% in Southeast Asia), which suggested that most doctors agreed with the value of endoscopic features in the diagnosis of CMV colitis. The typical endoscopic features may be an alert sign of CMV colitis when no histological evidence or test was available.

It has been reported that the prevalence of HBV infection is higher in the Asia-Pacific region than in Western countries. HBV infection is always key point in the prevention and treatment of infectious disease in Asian countries, and HBV vaccines are generally nationally recommended in Asian countries.[21-23] The prevalence is also higher in IBD patients than that in general population.[24,25] The ECCO consensus and a recent Korean guideline suggested that all IBD patients should be tested for HBsAg, HBsAb and HBcAb to determine HBV status at the time of diagnosis and all IBD patients should be given an HBV vaccination if

there was no vaccination history at the time of diagnosis.[26] In addition, during immunosuppressive drug treatment, patients who are HBsAg positive should receive potent antiviral agents regardless of the degree of viremia in order to prevent hepatitis B flare.[27] The results of this study showed that HBsAg screening was accepted by all members. However, some members did not accept screening HBsAb and HBcAb, and purposely recommending vaccination for IBD patients, and did not accept prophylactic antiviral treatment for IBD patients with HBsAg positive. And the attitude to HBV vaccination was similar in our studies and previous reports. HBV vaccination is recommended in all HBV HBcAb seronegative patients with IBD. Approximately 60% to 70% members in Asian countries recommend HBV vaccination when the HBsAg was tested negative, a slightly higher than that in the United States (around 50%).[28] For treatment, entecavir and tenofovir should be the preferred antivirals for IBD patients due to their rapid onset of action. However, 11.1% of members in China, 8.3% in Japan, and 11.8% in South Korea preferred lamivudine, although it has a slow onset of action and high incidence of resistance. The difference between doctors' opinions about HBV might be related to the economic situation in different countries in Asia, which indicated that more efforts should be made in clinical practice.

Since IBD is an independent risk factor for CDI,[29,30] CDI was also considered in this study. We found that all member hospitals in South Korea and Southeast Asia had stool *C. difficile* toxin A/B testing facilities, and 75.0% and 95.8% hospitals in China and Japan had these facilities, which indicated that the method was more acceptable for detecting CDI by physicians in Asia. Few hospitals had glutamate dehydrogenase and PCR tests for detecting *C. difficile*. Regarding the treatment for CDI, metronidazole was still the primary therapeutic option for initial, non-severe patients with CDI, while vancomycin for recurrent patients, which was complied with the Chinese consensus on CDI in patients with IBD or general population.[31,32] What is noteworthy is that updated CDI guidelines published by Society for Healthcare Epidemiology of America/Infectious Diseases Society of America in 2018 until now have recommended vancomycin as the first-line treatment for patients with an initial CDI episode.[33-35] We predict our study may not fully demonstrate this transformation of first-line therapy for mild CDI patients due to our inclusion time focused on 2017. Further study of therapeutic choice for initial period of CDI beyond 2017 will help to determine whether the dominant role of metronidazole persists. But more importantly, although not recommended with priority in present guidelines, the role of metronidazole in initial therapy for CDI has always been controversial so far. Several studies revealed that there were no significant differences in therapeutic failure, CDI recurrence or mortality between initial CDI receiving metronidazole and vancomycin.[36,37] In addition, vancomycin is more expensive and inconvenient in some areas, leading to metronidazole to account for main proportion in CDI treatment yet. Likewise, some studies from Western countries after update of guidelines just exactly supported this condition.[38,39]

The strength of this study is that it is a multicenter survey in Asia. The results of this study provide an overview of the current status of opportunistic infection in IBD, which may guide future practice. However, there are several limitations of this study. Questionnaire surveys always have information bias and recall bias. Only some members of AOCC participated in this questionnaire survey, which cannot represent the whole country and Asia, causing a representational bias. In addition, data of only 1 year may not reflect the overall status of opportunistic infection in IBD in Asia. Furthermore, we did not acquire the real word data about the management for opportunistic infection and did not obtain the effect of insurance policy on the real-world management. But more satisfactorily, the knowledge awareness of detection and management for opportunistic infections in IBD patients is very high and has the high agreement rate with consensus in AOCC members institutes.

With rising incidence of IBD in Asia, we are facing increasing challenges in managing opportunistic infection. Awareness, screening, prevention and timely therapy for opportunistic infection should be seriously considerable before and during immunosuppressive treatment. From our study, knowledge of current status of opportunistic infection in Asian IBD patients and whether adheres to guidelines, and the underlying affecting factors will help healthcare institutions and doctors to adjust the surveillance and treatment strategies to ensure that all patients receive optimal medical care. Additionally, it provides some help for optimization of the guidelines to be more suitable for Asian patients, development priorities of health facilities and adjustment of medical insurance policies. For example, the development of stool *C. difficile* toxin A/B test in China requires more investment. The effects of preventing hepatitis B, CMV colitis and CDI on prognosis in IBD are worthy of further study.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: H.Y., J.M.Q. Methodology: H.Y., J.M.Q. Data analysis: H.Y. Data collection support: Z.R., M.J. Data analysis support: Z.R., M.J. Project administration: J.M.Q. Writing - original draft: H.Y. Writing - review and editing: Z.R., J.M.Q. Funding acquisition: J.M.Q. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

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REFERENCES

1. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2017;390:2769-2778.
2. Prideaux L, Kamm MA, De Cruz PP, Chan FK, Ng SC. Inflammatory bowel disease in Asia: a systematic review. J Gastroenterol Hepatol 2012;27:1266-1280.
3. Li Y, Xu H, Xu T, et al. Case-control study of inflammatory bowel disease patients with and without Clostridium difficile infection and poor outcomes in patients coinfected with C. difficile and cytomegalovirus. Dig Dis Sci 2018;63:3074-3083.
4. Xu H, Tang H, Xu T, et al. Retrospective analysis of Clostridium difficile infection in patients with ulcerative colitis in a tertiary hospital in China. BMC Gastroenterol 2019;19:3.
5. Sagami S, Kobayashi T, Hibi T. Prevention of infectious diseases due to immunosuppression and vaccinations in Asian patients with inflammatory bowel disease. Inflamm Intest Dis 2018;3:1-10.
6. Schneeweiss S, Korzenik J, Solomon DH, Canning C, Lee J, Bressler B. Infliximab and other immunomodulating drugs in patients with inflammatory bowel disease and the risk of serious bacterial infections. Aliment Pharmacol Ther 2009;30:253-264.
7. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol 2006;4:621-630.
8. Ng SC, Tang W, Ching JY, et al. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-Pacific Crohn's and colitis epidemiology study. Gastroenterology 2013;145:158-165.
9. McCurdy JD, Enders FT, Khanna S, et al. Increased rates of Clostridium difficile infection and poor outcomes in patients with IBD with cytomegalovirus. Inflamm Bowel Dis 2016;22:2688-2693.
10. Kucharzik T, Ellul P, Greuter T, et al. ECCO guidelines on the prevention, diagnosis, and management of infections in inflammatory bowel disease. J Crohns Colitis 2021;15:879-913.
11. Inflammatory Bowel Disease Group, Chinese Society of Gastroenterology, Chinese Medical Association. Evidence-based consensus on opportunistic infections in inflammatory bowel disease (republication). Intest Res 2018;16:178-193.
12. Papadakis KA, Tung JK, Binder SW, et al. Outcome of cytomegalovirus infections in patients with inflammatory bowel disease. Am J Gastroenterol 2001;96:2137-2142.
13. Oh SJ, Lee CK, Kim YW, et al. True cytomegalovirus colitis is a poor prognostic indicator in patients with ulcerative colitis flares: the 10-year experience of an academic referral inflammatory bowel disease center. Scand J Gastroenterol 2019;54:976-983.
14. Römkens TE, Bulte GJ, Nissen LH, Drenth JP. Cytomegalovirus in inflammatory bowel disease: a systematic review. World J Gastroenterol 2016;22:1321-1330.
15. Dave M, Purohit T, Razonable R, Loftus EV Jr. Opportunistic infections due to inflammatory bowel disease therapy. Inflamm Bowel Dis 2014;20:196-212.
16. Nakase H, Honzawa Y, Toyonaga T, et al. Diagnosis and treatment of ulcerative colitis with cytomegalovirus infection: importance of controlling mucosal inflammation to prevent cytomegalovirus reactivation. Intest Res 2014;12:5-11.
17. Yang H, Zhou W, Lv H, et al. The association between CMV viremia or endoscopic features and histopathological characteristics of CMV colitis in patients with underlying ulcerative colitis. Inflamm Bowel Dis 2017;23:814-821.
18. Tsuchido Y, Nagao M, Matsuura M, et al. Real-time quantitative PCR analysis of endoscopic biopsies for diagnosing CMV gastrointestinal disease in non-HIV immunocompromised patients: a diagnostic accuracy study. Eur J Clin Microbiol Infect Dis 2018;37:2389-2396.
19. Kredel LI, Mundt P, van Riesen L, et al. Accuracy of diagnostic tests and a new algorithm for diagnosing cytomegalovirus colitis in inflammatory bowel diseases: a diagnostic study. Int J Colorectal Dis 2019;34:229-237.
20. Tandon P, James P, Cordeiro E, Mallick R, Shukla T, McCurdy JD. Diagnostic accuracy of blood-based tests and histopathology for cytomegalovirus reactivation in inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis 2017;23:551-560.
21. Liao X, Liang Z. Strategy vaccination against hepatitis B in China. Hum Vaccin Immunother 2015;11:1534-1539.
22. Nishimura K, Yamana K, Fukushima S, et al. Comparison of two hepatitis B vaccination strategies targeting vertical transmission: a 10-year Japanese multicenter prospective cohort study. Vaccines (Basel) 2021;9:58.
23. Cho EJ, Kim SE, Suk KT, et al. Current status and strategies for hepatitis B control in Korea. Clin Mol Hepatol 2017;23:205-211.
24. Huang ML, Xu XT, Shen J, Qiao YQ, Dai ZH, Ran ZH. Prevalence and factors related to hepatitis B and C infection in inflammatory bowel disease patients in China: a retrospec-

tive study. J Crohns Colitis 2014;8:282-287.
25. Chen D, Luo S, Ben Q, Lu L, Wan X, Wu J. Prevalence of hepatitis B and C and factors for infection and nonimmune in inflammatory bowel disease patients in China. Eur J Gastroenterol Hepatol 2017;29:509-515.
26. Park SK, Choi CH, Chun J, et al. Prevention and management of viral hepatitis in inflammatory bowel disease: a clinical practice guideline by the Korean Association for the Study of Intestinal Diseases. Intest Res 2020;18:18-33.
27. Ooi CJ, Hilmi I, Banerjee R, et al. Best practices on immunomodulators and biologic agents for ulcerative colitis and Crohn's disease in Asia. Intest Res 2019;17:285-310.
28. Ben Musa R, Gampa A, Basu S, et al. Hepatitis B vaccination in patients with inflammatory bowel disease. World J Gastroenterol 2014;20:15358-15366.
29. Kaneko T, Matsuda R, Taguri M, et al. Clostridium difficile infection in patients with ulcerative colitis: investigations of risk factors and efficacy of antibiotics for steroid refractory patients. Clin Res Hepatol Gastroenterol 2011;35:315-320.
30. Nitzan O, Elias M, Chazan B, Raz R, Saliba W. Clostridium difficile and inflammatory bowel disease: role in pathogenesis and implications in treatment. World J Gastroenterol 2013;19:7577-7585.
31. Expert Committee of Laboratory Physicians of Infectious Disease, Chinese Medical Doctor Association. Expert consensus on diagnosis and treatment of Clostridium difficile infection in Chinese adults. Med J PUMCH 2017;8:131-138.
32. Consensus expert group of "Modern Digestive and Interventional Diagnosis and Treatment". Expert consensus on the management of inflammatory bowel disease with Clostridium difficile infection in Chinese adults. Mod Dig Intervention 2019;24:448-452.
33. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018;66:987-994.
34. Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of Clostridioides difficile infections. Am J Gastroenterol 2021;116:1124-1147.
35. Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of Clostridioides difficile infection in adults. Clin Infect Dis 2021;73:e1029-e1044.
36. Appaneal HJ, Caffrey AR, LaPlante KL. What is the role for metronidazole in the treatment of Clostridium difficile infection? Results from a national cohort study of veterans with initial mild disease. Clin Infect Dis 2019;69:1288-1295.
37. Imwattana K, Putsathit P, Leepattarakit T, Kiratisin P, Riley TV. Mild or malign: clinical characteristics and outcomes of Clostridium difficile infection in Thailand. J Clin Microbiol 2020;58:e01217-e01220.
38. Adelman MW, Goodenough D, Sefton S, et al. Changes in treatment of community-onset Clostridioides difficile infection after release of updated guidelines, Atlanta, Georgia, 2018. Anaerobe 2021;70:102364.
39. Clancy CJ, Buehrle D, Vu M, Wagener MM, Nguyen MH. Impact of revised Infectious Diseases Society of America and Society for Healthcare Epidemiology of America clinical practice guidelines on the treatment of Clostridium difficile infections in the United States. Clin Infect Dis 2021;72:1944-1949.