Review Article

What Are the Different Phenotypes of Inflammatory Bowel Disease in Asia?

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The burden of inflammatory bowel disease (IBD) in Asia has been increasing over the past decades. Although patients with IBD show heterogenous phenotypes depending on the individual characteristics, no significant differences have been established in the IBD phenotypes of Western and Asian populations. However, despite the much lower incidence of IBD in Asia than in Western countries, the incidence has been rapidly increasing in Asia while remaining stable in Western countries. The incidence of ulcerative colitis (UC) showed an earlier and a more marked increase than the incidence of Crohn disease (CD), but the UC-to-CD ratio has recently decreased because of a relative increase in the incidence of CD in Asia. While CD shows a significant male predominance, UC only shows a slight male predominance. A recent study reported that the incidence of IBD in Asia showed a bimodal age distribution with increasing IBD prevalence, similar to the findings of Western studies. CD in Asian patients, especially those in East Asia, is characterized by ileocolonic involvement and perianal fistula. The frequency of extraintestinal manifestations, including primary sclerosing cholangitis, appears to be lower in Asia, but this finding should be interpreted with caution due to the transient and nonspecific nature of these manifestations. Although familial aggregation is lower in East Asia, it may also be explained by the low prevalence of IBD in Asia. Thus, more studies should focus on the differences in phenotypes in Asian IBD patients versus Western patients. **(Gut Liver 2022;16:676-685)**

Key Words: Ulcerative colitis; Crohn disease; Inflammatory bowel disease; Phenotype; Asia

INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by idiopathic chronic inflammation of the gastrointestinal tract, of which the two major forms are ulcerative colitis (UC) and Crohn's disease (CD). The burden of IBD is expected to increase exponentially because of the characteristics of this disease, that is, young age of onset, low mortality, and lack of a cure.[1] Although IBD was traditionally considered as a disease of Western countries, mainly North America and Europe,[2] the IBD disease burden has recently increased in many Asian countries.[3-5] While the overall prevalence of IBD remains low in Asia, the prevalence has been steadily increasing in many Asian countries over the past two decades because of the urbanized, industrialized, and westernized lifestyles in Asia.[1] However, even with the low prevalence of IBD in Asia, the absolute number of IBD patients in Asia is expected to be greater than those in Western countries because of the larger population size of approximately 4.68 billion people in Asia (about 60% of the total global population), in comparison with the 0.6 billion people in North America and the 0.75 billion people in Europe. Although patients with IBD show heterogenous phenotypes according to individual characteristics, no significant differences have been established in the IBD phenotypes between the Western and Asian populations. Nevertheless, several studies have reported that some demographic and phenotypic characteristics of IBD at diagnosis in Asian countries differed from those in Western countries. A better understanding of the differences in the epidemiology of IBD between Asian and Western countries may provide important clues to the unknown aspects

of the etiology and mechanism of IBD, thereby facilitating the management of IBD patients.

With this perspective, the present review focused on the demographic and phenotypic characteristics of IBD at the time of diagnosis in Asia, especially from the perspective of Korean IBD patients, in comparison with the corresponding findings in Western countries.

INCIDENCE OF IBD

The Asia-Pacific Crohn's and Colitis Epidemiologic Study (ACCESS),[4] a population-based inception cohort covering eight Asian regions and Australia, reported that the crude overall incidences of IBD, UC, and CD were 1.37, 0.76, and 0.54 per 100,000 persons, respectively (Supplementary Table 1). In this study, the incidence of IBD was the highest (3.4/100,000) in mainland China (Guangzhou), followed by 3.1/100,000 in Hong Kong and 2.2/100,000 in Macau. In Hong Kong, the incidence of IBD tripled from 1.0/100,000 to 3.1/100,000 over the last two decades.[4] An extension study of ACCESS, which covered 13 countries or regions in Asia, updated the crude overall incidences of IBD, UC, and CD to 1.14, 0.76, and 0.35 per 100,000 persons, respectively, between 2011 and 2012 and 1.89, 1.20, and 0.66 per 100,000 persons, respectively, between 2012 and 2013.[5] A population-based study from Korea showed that the incidence of IBD has been increasing over the past three decades.[6] In Korea, the adjusted incidence of UC increased 20.1-fold from 0.29/100,000 to 5.82/100,000 during 1986–2015, and adjusted incidence of CD increased 40.7-fold from 0.06/100,000 to 2.44/100,000 during the same period.[6] The incidence of UC and CD began to increase in the late 1980s and late 1990s, respectively, in Korea. A population-based study from Wuhan, China in 2010, showed that the adjusted incidence rates of UC and CD were 1.45/100,000 and 0.51/100,000, respectively.[7] Another population-based study from Zhongshan, China, during 2011–2012 also reported that the adjusted incidence rates of UC and CD were 2.05/100,000 and 1.09/100,000, respectively.[8] The pooled incidence of UC in China tripled over the past 10 years,[9] while nationwide data from Taiwan reported an increasing incidence of IBD from 1998.[10,11] The crude incidence of UC increased 1.8-fold from 0.54/100,000 to 0.95/100,000 during 2001–2015 and that of CD also increased 2.8-fold from 0.17/100,000 to 0.47/100,000 during the same period, respectively.[12] In Lebanon, the mean incidence rates of UC and CD were 4.1/100,000 and 1.4/100,000 person-years, respectively,[13] while the incidence rates of UC in Kuwait and Israel were 2.8/100,000 and 5.0/100,000, respectively.[14,15]

The incidence of IBD in Asia is much lower than those in Western countries, where the highest annual incidence rates of UC and CD were 24.3/100,000 and 12.7/100,000 person-years in Europe and 19.2/100,000 and 20.2/100,000 in North America, respectively.[2] However, while the incidence of IBD is high but stable in Western countries, it is low but rapidly increasing in Asian countries.[3,6] Moreover, the incidence of IBD varies within and between Asian countries, indicating the need for more population-based studies from Asia.

PREVALENCE OF IBD

In Korea, the overall age- and sex-adjusted prevalence rate of IBD was 76.66/100,000 for UC and 31.59/100,000 for CD on December 31, 2015 (Table 1).[6] In Japan, the estimated annual prevalence rate of IBD was 172.9/100,000 for UC and 55.6/100,000 for CD on a mail-based survey targeting hospitals in 2014.[16] It was limited data as it was based on mail-based survey using a stratified random sampling method. In Taiwan, the mean annual prevalence was 4.59/100,000 for UC and 1.05/100,000 for CD during 1998–2010.[11] In a cross-sectional study from Kazakhstan, the adjusted prevalences of IBD, UC, and CD were 113.9/100,000, 84.4/100,000, and 29.5/100,000, respectively.[17] In Western Asia, the prevalence of IBD in Turkey[18] and Israel[15] was 4.9/100,000 and 167.2/100,000, respectively. In a global review, the highest prevalence of IBD was 505/100,000 for UC and 322/100,000 for CD in Europe and 249/100,000 for UC and 319/100,000 for CD in North America, which were much higher than the prevalences of 168/100,000 for UC and 68/100,000 for CD in Asia and the Middle East.[2] Although the prevalence of IBD in Asia is lower than those in Western countries, the prevalence has been continuously increasing in many Asian countries.[19-21] In Korea, the prevalence of UC increased 4.1-fold from 7.57/100,000 to 30.87/100,000 during 1997–2005.[19] In Japan, the prevalence of CD increased 4.6-fold from 2.9/100,000 to 13.5/100,000 during 1986–1998.[20] In Singapore, the prevalence of CD increased 5.5-fold from 1.3/100,000 to 7.2/100,000 during 1992–2004.[21] In Taiwan, the prevalence of UC increased 6.1-fold from 2.1/100,000 to 12.8/100,000 during 2001–2015, and the prevalence of CD also increased 6.5-fold from 0.6/100,000 to 3.9/100,000 during the same period.[12] In Hong Kong, the prevalence of UC increased 2.8-fold from 2.26/100,000 to 6.30/100,000 during 1997–2006.[22] In Israel, the prevalence of IBD increased from 121/100,000 to 167.2/100,000 during 1987–1997.[15]

The increasing prevalence of IBD in Asia may reflect an actual increase in the population with IBD, increased

Table 1. Summary of Different Phenotypes of Inflammatory Bowel Disease in the Asian and Western Population

Different phenotype	Asia	West
Incidence of IBD	Still low, but rapidly increasing.	High, but stable.
Prevalence of IBD	Rapidly increasing and their gap between Asia and West is narrowing.	Much higher.
Environmental and dietary factors		
Brest feeding, physical activity	Both protective effect on IBD development in Asia and West.	
Smoking	No association for the risk of CD.	Increased risk of CD.
Appendectomy	Inconsistent effect on the risk of UC (no association[23] vs decreased risk[24-26]).	Decreased risk of UC.
Diet	Sugar, fat, meat, oil has increased risk of IBD. But, lower fiber has no association with the risk of IBD. Daily tea and coffee have decreased risk of IBD.	Sugar, fast food, red meat has increased risk of IBD, and lower fiber has increased risk of IBD.
UC/CD ratio	UC/CD ratio is high, but has been reduced.	UC/CD ratio is low.
Sex	Male predominance in both CD and UC, but it is significantly higher for CD and slightly higher for UC.	Female predominance for CD. No sex predominance for UC.
Age	Bimodal age distribution is noted in recent studies, but single peak is noted in the past studies.	Bimodal age distribution.
	Age at diagnosis is 5–10 years earlier for CD than that of UC in Asia and West.	
Disease extent of UC	No significant difference for the disease extent of UC between Asia and West.	
Disease location of CD	More L3 location and higher proportion of L4 for the disease location of CD.	More L2 location for the disease location of CD.
Disease behavior of CD	Disease behavior is more complicated with more perianal fistulas.	70%–80% of CD has B1 behavior.
Extraintestinal manifestation	Variable, but lower than those in West.	Variable.
Family aggregation	Lower frequency.	Higher frequency.

IBD, inflammatory bowel disease; CD, Crohn disease; UC, ulcerative colitis.

awareness of this condition among physicians, and the improved healthcare utilization and diagnostic methods for IBD. Thus, the IBD burden in Asian countries is expected to be a major threat to global public health.

ENVIRONMENTAL AND DIETARY FACTORS

The evolution of IBD in many Asian countries appears to associate with recent changes of environmental and dietary factors, which may affect the intestinal microbiota and develop IBD in genetically susceptible patients.[27] Brest feeding and physical activity exerts same protective effect for the IBD development in the Asian population as well as Western population.[23,28,29] Breast feeding, which may influence the intestinal microbiota, showed a protective effect against IBD development in Asian population than Western population.[28] Physical activity also had a protective effect against CD development in Asian and Western population.[23,29] Active smoking is associated with an increased risk of CD, and appendectomy is associated with a decreased risk of UC in the Western population.[30] Active smoking was not significantly associated with development of CD in a recent Japanese case-control study (odds ratio [OR], 1.82; 95% confidence interval [CI], 0.85 to 3.92).[31] Cigarette smoking is not associated with the development

of CD in a single-center Korean study, either.[32] In the ACCESS cohort, appendectomy was not associated with the risk of UC in the Asian population (OR, 0.437; 95% CI, 0.129 to 1.474) as well as in the Australian population.[23] However, appendectomy was protective against UC in other Asian studies from Japan,[24] China,[25] and Iran,[26] like Western studies. The role appendectomy for the risk of UC should be further evaluated for the age and indication (appendicitis vs lymphadenitis) of appendectomy as their role remains inconsistent in Asian population.

Western diet, particularly increased consumption of sugar, fast food, fatty acids, red meat as well as decreased consumption of dietary fiber, has been suspected to develop IBD,[33] as they can change intestinal microbiota. While, increased consumption of fiber, fruit, and vegetable reduced the risk of IBD development.[34] In the ACCESS cohort, however, no association was found between consumption of fiber, fruits or vegetables and the risk of development of IBD in Asia.[23] In this cohort, the consumption of tea and coffee which may contain antioxidants was associated with the lower risk of IBD development.[23] Two Japanese studies[35,36] also reported that consumption of sugar, fat, fatty acids, meat and oil increased the risk of IBD development, which were consistent findings with Western studies. Dietary studies need to be interpreted with caution as many of dietary studies are difficult to classify and inter-

pret complex dietary data. However, it is important to keep in mind that environmental and dietary factors may have different effect in the Asian population compared with the Western population, and future studies should be focused on these issues. It is important to increase our insight into the role of environmental and dietary factors for the development of IBD in Asian population to prevent the surge of the Asian IBD.

UC AND CD RATIO

In the ACCESS study, the incidence and prevalence of UC were about twice those of CD in the included eight Asian countries.[4] The extension study of ACCESS also reported a UC/CD ratio of 1.9 in 13 Asian countries or regions.[5] In Korea, the UC/CD ratio was 2.4 during 2011–2015.[6] In two Chinese studies, the UC/CD ratios were 2.8 in 2010[6] and 1.9 during 2011–2012.[8] In Japan, the UC/CD ratio was 3.11 on a nationwide survey.[16] In India[37] and Iran,[38] the UC/CD ratio was 1.4 and 2.2, respectively. Another study from India reported a high UC/CD ratio of 5.1.[39] Overall, the incidence of UC is about twice that of CD in Asian countries,[2-7,37,38] indicating that the number of UC patients grew much faster than that of CD in Asian countries, which is similar to the trend in Western countries.[40]

Recently, however, the UC/CD ratio in many Asian countries has reduced because of the accelerating incidence of CD.[6,12] In Korea, the UC/CD ratio was 4.8 in 1986–1990, but it reduced to 2.4 in 2011–2015.[6] In Taiwan, the UC/CD ratio was 4.3 in 2001–2005, but it similarly decreased to 2.03 in 2011–2015.[12] In the Australia data of the ACCESS cohort, UC/CD ratio was even reversed as 0.51[4] and 0.6,[5] which means the incidence of CD excessed those of UC in Australia.

SEX

A recent systematic review of studies from 11 Asian countries reported that the male-to-female (M/F) ratio of IBD at diagnosis was 1.2 to 1.4 for UC and 1.4 to 1.6 for CD.[41] This study found a marked male predominance in both CD and UC incidence, which started in adolescence and extended past middle age to 50 years of age in CD or 65 years of age in UC.[41] In Korea, the M/F ratio of the adjusted incidence rate was 1.2 for UC and 3.3 for CD.[6] Similarly, in most East Asian countries, including Korea, Japan, and China, the overall M/F ratio of CD was approximately 2.0.[19,42-44] In Japan, the M/F ratio was 1.24 for UC and 2.40

for CD.[16] In Taiwan, the M/F ratio was 1.6 for UC and 2.2 for CD.[12] In two Indian studies, the M/F ratios were 1.9 in 3,553 IBD patients,[37] and 1.6 in 3,863 IBD patients.[39] Therefore, CD showed a significant male predominance while UC showed a slight male predominance in Asia. In contrast, pooled analysis of 17 Western population-based cohorts showed a female predominance for CD, with an M/F ratio of 0.68–0.89 after 25 years.[45] In this analysis, no sex predominance was noted for UC until 45 years of age, but a slight male predominance with an M/F ratio of 1.15 to 1.47 was noted in patients aged 55 to 69 years.[45]

No explanation is currently available for the differences in the sex distributions between Asian and Western CD patients. The precise mechanism underlying these differences is unknown because previous observational studies were not designed to elucidate the etiology or mechanism. Furthermore, direct comparison of sex differences in previous Asian and Western studies is difficult, since the participants may have had different genotypic factors or environmental exposures, which are independently responsible for IBD development. As an example, smoking is more prevalent in men than in women in Asian countries,[46] but this cannot fully explain the male predominance of CD in Asian countries. Therefore, further studies are needed to resolve the role of sex as a disease modifier for CD.

AGE

While the incidence of IBD in Western studies was characterized by a bimodal age distribution with peaks at 20 to 39 and 60 to 79 years,[47-49] previous Asian studies showed a single peak without a bimodal age distribution.[43,44,50] The appearance of a single peak in previous Asian studies may be attributable to either the small sample sizes (only 23 to 389 patients) with too few elderly patients[43,44,50] or to the analysis of only the absolute number of patients rather than the age-specific incidence rate. A recent study from Korea, however, showed a bimodal age distribution, especially with UC patients aged 60 to 69 years.[6] A Japanese study also showed a bimodal age distribution for UC with 40 to 44 years peak and 50 to 60s peak.[51] However, this study was limited by a survey-based small design (n=343). In the ACCESS study, CD was associated with a bimodal age distribution, whereas the incidence of UC showed a single peak.[4]

In two Korean studies,[6,19] the median age (22 to 24 years) at diagnosis of CD was lower than that of Western patients (27 to 31 years),[52-54] but the median age (33 to 36 years) at diagnosis of UC was similar to that of Western patients (33 to 39 years).[52-54] In Korea, the median age at

diagnosis was lower for CD than for UC (p<0.001), similar to the findings of a study published 10 years earlier from the same cohort.[19] In Iran, the age at diagnosis for UC and CD patients was 31.4 and 27.9 years, respectively.[38] In the analysis of Chinese studies, the mean age at diagnosis of pooled UC patients was 40.7 years.[9] The ACCESS study reported that the median age at diagnosis of UC and CD patients was 43 and 33 years, respectively.[5] Taken together, these findings suggest that the median age at diagnosis of CD is about 5 to 10 years earlier than that of UC in Asian countries,[6,40] which is similar to the findings of Western studies. When compared to Korean studies,[6,19] the median age at diagnosis of IBD was higher than that in the AC-CESS study.[4,5] Asian countries may show wide variations in the threshold for colonoscopy use, which is dependent on healthcare accessibility and may influence the median age at diagnosis of IBD. Because of the affordable colonoscopy access in South Korea, the median age at diagnosis of CD may be earlier than those in other studies.

DISEASE EXTENT OF UC

With respect to the disease extent of UC, more than half of the Asian IBD patients had proctitis (E1) at the time of diagnosis.[6,9,19] In Korea, 54.3% of UC patients presented with E1 at diagnosis, while 22.5% and 23.2% showed left-sided colitis (E2) and extensive colitis (E3), respectively.[6] The higher rate of E1 at diagnosis in the Korean study may be attributed to the broad use of endoscopic examination, which resulted in a higher detection rate of mild UC with E1. During 1986–2015, the proportion of E1 cases progressively increased, from 31.3% in 1986–1990 to 62.1% in 2011–2015. In the data obtained 10 years earlier from the same cohort, 10% less (44%) UC patients presented with E1.[19] The ACCESS study reported E1, E2, and E3 in 37%, 32%, and 31% of the patients, respectively.[4] The extension study of ACCESS also reported similar results, showing E1 in 32.6%, E2 in 34.9% and E3 in 32.6% of the patients.[5] In a single-hospital study from Hong Kong between 1990 to 2006, 38.4%, 26.0%, and 35.6% of the UC patients presented with E1, E2, and E3, respectively.[22] The Australian patients in the ACCESS study showed similar disease extent of UC, with E1, E2, and E3 presenting in 32%, 27%, and 41% of the cases, respectively.[4] In Western studies, 29% to 51% of UC patients presented with E1 at diagnosis.[52,54-57] In general, there was no significant difference in the extent of UC between Asian and Western countries. However, the disease extent of UC should be interpreted with caution since it may be biased by study design.

When compared with population-based studies, hos-pital-based studies have an inherent referral bias because mild UC patients with E1 were less included in the hospi-tal-based study. In a prospective registry from India, the proportions of UC cases with E1, E2, and E3 were 17.5%, 58.6%, and 23.9%, respectively.[39] One study in Thailand also showed a lower rate of E1 (21%), and rates of 35% and 43% for E2 and E3, respectively.[58] The lower rate of E1 in these studies[39,58] may be explained by the hospital-based study design.

DISEASE LOCATION OF CD

In a Korean study, disease locations of CD were ileal (L1) in 24.9%, colonic (L2) in 9.3% and ileocolonic (L3) in 65.8% of the cases.[6] In this study, upper gastrointestinal disease modifier (L4) was present in 22.5% of the cases according to Montreal classification. The ACCESS study reported that the disease location of CD was L1, L2, L3, and L4 in 31.7%, 24.4%, 43.9%, and 6.0% of the cases, respectively.[5] In an IBD registry from India, L1, L2, L3, and L4 locations of CD were observed in 30.8%, 30.9%, 36.3%, and 2.1% of the cases, respectively.[39] Interestingly, L3 was the most common (45% to 71%) type of CD in East Asian studies,[5,6,8,59,60] while L2 was the most common type (39% to 52%) in Western studies.[56,61-64] In addition, a recent meta-analysis confirmed that the incidence of L4 in Asian CD patients was significantly higher than that in Caucasian CD patients (8% vs 4%).[65] L4 location is at risk for underestimation during work-up for the location of CD by skipping upper endoscopy or proximal small bowel imaging. The very high L4 proportion of 22.5% in Korea could be explained by affordability and easily accessibil-ity of upper endoscopy or proximal small bowel imaging in Korea.[6] Upper endoscopy is recommended only in CD patients with upper gastrointestinal symptoms in Western countries,[66] however, routine upper endoscopy should be recommended to exactly classify the disease location of CD.

DISEASE BEHAVIOR OF CD

The behavior of CD may progress with time from an inflammatory (B1) to a stricturing (B2) or penetrating (B3) phenotype. In a Korean study, disease behaviors at CD diagnosis were B1, B2, and B3 in 81.1%, 8.1%, and 10.8% of the cases, respectively.[6] In this study, the proportion of B1 cases decreased from 78.9% in 1991–1995 to 75.0% in 2011–2015, but the proportion of B3 cases increased from 10.5% in 1991–1995 to 14.9% in 2011–2015.[6] The ACCESS

study reported B1, B2, and B3 phenotypes in 66%, 17%, and 19% of the cases, respectively.[4] The extension study of ACCESS cohort also reported B1, B2, and B3 phenotypes in 71.4%, 21.3%, and 10.1% of the cases, respectively.[5] In a Japanese single-center study including 520 CD patients, stenosis or fistula were complicated in about half of patients after 5 years from diagnosis.[67]

In a population-based cohort from Olmsted County in the United States, 81% of patients had a B1 phenotype, followed by B2 and B3 phenotypes in 5% and 14% of the cases, respectively.[68] In French CD patients (n=2,002) with disease duration >5 years, 60% of patients developed B2 or B3 complications. In this cohort, 20-year actuarial rates of B1, B2, and B3 were 12%, 18%, and 70%, respectively.[69] In a population-based cohort of elderly-onset CD (n=367), 78% of patients had B1 behavior at diagnosis of CD, but, digestive extension and complicated behavior occurred in 8% and 9%, respectively.[70] In 989 pediatric CD patients, the cumulative incidence of complicated disease was 13.0%, 26.7%, and 37.9% at 1, 5, and 10 years from the time of diagnosis of CD.[71] The 10-year cumulative incidences of B2 and B3 complications were 20.5% and 24.5%, respectively.

In general, the disease behaviors of Asian CD patients were comparable to those of Western studies.[6,68] However, a meta-analysis showed a more complicated behavior in Asian CD patients than Caucasian CD patients, with fewer cases of the B1 phenotype (61% vs 69%) and more cases of the B2 (21% vs 17%) and B3 (14% vs 13%) phenotypes.[65] Further studies are required to evaluate this issue because of the lack of population-based studies with long-term follow-up from Asia. Perianal fistulas (PAFs) are very common in Asian CD patients.[5,8,65,72] In a population-based study from Korea, PAF/abscess was present in 43.3% of the patients before or at diagnosis of CD.[6] In a population-based study from China, PAF was present in 58.5% of the newly diagnosed CD patients.[8] A hospital-based study from Korea also reported PAF in 43.1% of the cases at diagnosis of CD.[72] These findings were consistent with recent meta-analysis data indicating that PAF is more common in Asian CD patients than in Caucasian CD patients.[65] Similarly, hospital-based Korean study reported that the cumulative occurrence rates of perianal lesions in CD were 37.2% at diagnosis, 45.2% and 53.0% after 5 years and 10 years, respectively.[73] In contrast, a Western study reported that only 13% to 38% of CD patients had perianal disease.[74] In addition, the ACCESS study, also reported that only 15.6% to 17.7% of the cases showed PAF at diagnosis of CD.[4,5] The frequency of perianal lesions in CD varies greatly depending on the definition, which may be a future research question for clear classification of CD.

EXTRAINTESTINAL MANIFESTATION

In an Asian multinational study, extraintestinal manifestations (EIMs) were reported in 11.3% of IBD patients and noted in 8% of the patients before IBD diagnosis.[75] In the ACCESS cohort, 19% of Asian IBD patients had EIMs.[76] In a Chinese study, 6.1% of pooled UC patients had EIMs.[9] In an IBD registry from India, EIMs were recorded among 13% and 20% of the patients with UC and CD, respectively.[39] The prevalence of EIMs in the West was also variable, ranging between 6% and 47%.[77] The frequencies of EIMs in Asian countries have been lower than those in Western studies.[39,44,75,76,78-80] However, the rate of EIM in IBD studies should be interpreted with caution because symptoms associated with EIM are transient and nonspecific and show a wide variety. Although primary sclerosing cholangitis (PSC) is the most reliable EIM, the prevalence of PSC is also variable because of differences in definition or diagnostic modalities. PSC was reported in 1.1% of UC and 0% of CD patients in a Korean study.[81] PSC has also been reported in 2% to 8% of UC patients[82,83] and 1% to 3% of CD patients[84,85] in Western studies. Therefore, additional prospective studies are required on this issue.

FAMILY AGGREGATION

A positive family history of IBD was reported in 1.9% to 6.6% of the cases in Korean studies.[86-88] In a hospital-based IBD registry from Korea, first- and second-degree family history of IBD was recorded in 2.4% of IBD patients, including 2.5% of CD patients and 2.4% of UC patients.[86] In a single hospital-based study, a first-, second-, and/or third-degree family history of IBD was reported in 6.6% of the patients, including 6.8% of CD patients and 6.5% of UC patients.[87] In a university and community hospital-based study, a first-degree family history of IBD was observed in 1.9% of IBD patients, including 1.5% of CD patients and 2.0% of UC patients.[88] The crude prevalence of IBD in first-degree relatives of probands with IBD was 0.31%. The lifetime risk of IBD was 0.54% in all first-degree relatives of IBD probands, 0.52% in UC probands, and 0.67% in CD probands, with overall lifetime relative risks of 0.12% in parents, 0.79% in siblings, and 1.43% in offspring.[88]

In a nationwide IBD registry from Japan, first-degree family history was reported in 2.5% of IBD patients, including 2.6% of CD patients and 2.7% of UC patients.[89] In China, 1.5% of the pooled UC patients had a positive family history.[9] In an IBD registry from India, family histories of IBD, UC, and CD were reported in 3.1%, 3.1%, and 3.2% of the cases, respectively.[39] In another study from India,

first- and second-degree family histories of IBD, UC, and CD were reported in 4.25%, 4.34%, and 4.13% of the cases, respectively.[37] In a nationwide IBD registry from Iran, 11.8% of the participants showed positive results for first-degree family history and 6.87% showed positive results for second-degree family history.[38] In general, IBD patients in the Middle East had a higher rate of family history compared to those in East Asia. Considering the 5% to 18% incidence of positive family histories in the Western countries,[89,90] Asian IBD patients showed a much lower frequency of family history. Nevertheless, the population relative risk in the Korean study was 13.8,[86] which is comparable to the risk reported in Western studies,[91,92] which means that the positive family history in Korea may become similar to those in Western countries as the prevalence of IBD approaches that in Western countries.[46] Therefore, the low rate of familial aggregation in Asian IBD patients may be explained by the presently lower prevalence of IBD in Asia than in the West.[46] The data for familial aggregation may be variable because of different definitions of familial aggregation ranging from a first-degree to first–third-degree family history in previous studies.[86-88] In addition, a positive family history in IBD patients may have been underestimated in observational studies due to incomplete history-taking.

CONCLUSION

Asian IBD patients may show different epidemiologic characteristics with real heterogeneity of phenotypes in comparison with Western IBD patients. Table 1 summarizes the different phenotypes of IBD in the Asian and Western populations. However, the findings of Asian studies may be biased due to delays in diagnosis by lack of medical awareness and insufficient medical logistics. Even within Asia, there were some differences in the epidemiologic characteristics of IBD, especially between East Asia and the Middle East. Thus, more rigorous studies are needed to identify the epidemiologic differences within Asia considering the impact of both genetic and environmental factors between Asian countries.

CONFLICTS OF INTEREST

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

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SUPPLEMENTARY MATERIALS

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