TOPIC HIGHLIGHT

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Clinical characteristics and treatment of inflammatory bowel disease: A comparison of Eastern and Western perspectives

Soo Jung Park, Won Ho Kim, Jae Hee Cheon

Soo Jung Park, Won Ho Kim, Jae Hee Cheon, Department of Internal Medicine and Institute of Gastroenerology, Yonsei University College of Medicine, Seoul 120-752, South Korea
Correspondence to: Jae Hee Cheon, MD, PhD, Associate Professor, Department of Internal Medicine and Institute of Gastroenterology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 120-752,
South Korea. geniushee@yuhs.ac
Telephone: +82-2-22281990   Fax: +82-2-3936884

Abstract

Inflammatory bowel disease (IBD) is a chronic, relapsing intestinal inflammatory disorder with unidentified causes. Both environmental factors and genetic aspects are believed to be crucial to the pathogenesis of IBD. The incidence and prevalence of IBD have recently been increasing throughout Asia, presumably secondary to environmental changes. This increasing trend in IBD epidemiology necessitates specific health care planning and education in Asia. To this end, we must gain a precise understanding of the distinctive clinical and therapeutic characteristics of Asian patients with IBD. The phenotypes of IBD reportedly differ considerably between Asians and Caucasians. Thus, use of the same management strategies for these different populations may not be appropriate. Moreover, investigation of the Asian-specific clinical aspects of IBD offers the possibility of identifying causative factors in the pathogenesis of IBD in this geographical area. Accordingly, this review summarizes current knowledge of the phenotypic manifestations and management practices of patients with IBD, with a special focus on a comparison of Eastern and Western perspectives.

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Key words: Crohn's disease; Ulcerative colitis; Inflammatory bowel disease; Clinical characteristics; Treatment; Asia

Core tip: Over the past two decades, the incidence and prevalence of inflammatory bowel disease (IBD) have changed with a trend toward increasing across Asia, especially East Asia. This increasing trend in IBD epidemiology necessitates specific health care planning and education in Asia. To this end, we must gain a precise understanding of the distinctive clinical and therapeutic characteristics of Asian patients with IBD, compared to Caucasians patients with IBD. Accordingly, this review summarizes current knowledge of the phenotypic manifestations and management practices of patients with IBD, with a special focus on a comparison of Eastern and Western perspectives.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, idiopathic inflammatory disorder of the gastrointestinal tract without identifiable causes. It comprises primarily Crohn's disease (CD) and ulcerative colitis (UC). IBD was traditionally regarded as being prevalent in mainly Western countries. Over the past two decades, however, the incidence pat-

Table 1 Clinical characteristics of inflammatory bowel disease in Asian and Western countries

Differences	Asian characteristics
Peak age at disease onset	Smaller second peak
Sex distribution of CD	Male predominance
Cigarette smoking in CD	Lower prevalence
CD distribution and behavior	Ileocolonic predominance
	Similar behavior
UC distribution and behavior	Similar distribution
	Milder disease course
Familial aggregation in IBD	Lower prevalence
Extraintestinal disease	Lower prevalence
Medical treatments	Lower use of thiopurine and anti-TNF therapy
Surgical treatments	Comparable in CD
	Lower in UC
UC-associated CRC	Comparable cumulative risk

CD: Crohn's disease; UC: Ulcerative colitis; anti-TNF therapy: anti-Tumor necrosis factor therapy; CRC: Colorectal cancer.

tern of IBD has changed. The incidence in the West has remained relatively stable, while that in Asia has increased markedly[1]. This recent change in the incidence and prevalence of IBD is attributed to environmental changes.

The growing incidence of IBD in Asia has important implications for those who formulate health care policy plans; these individuals should provide specific health care planning, services, and education while balancing the health needs and social burdens of a given country. However, it also has important implications for clinicians and researchers. According to the published literature, the IBD phenotypes differ considerably between Asians and Caucasians. Nevertheless, most strategies for the prevention and treatment of IBD flare-up in Asia have followed Western guidelines. Gradual accumulation of data on IBD in Asians will facilitate the formulation of Asian-specific practice guidelines; however, direct comparisons of the clinical characteristics of IBD in Asian and Western countries are few. Formulation of appropriate strategies for Asian patients with IBD must begin with an accurate understanding of the different clinical characteristics of the two populations. These include clinical manifestations and therapeutic aspects, as well as epidemiology. To this end, this review summarizes and compares current knowledge of the phenotypic manifestations and management of patients with IBD in Eastern and Western countries. Furthermore, investigation of the Asian-specific clinical aspects of IBD offers the possibility of identifying causative factors in the pathogenesis of IBD, which will also be covered in this review.

DIFFERENCES IN CD BETWEEN THE EAST AND WEST

Clinical characteristics of CD
Peak age of disease onset: Early studies from Western countries reported that CD was characteristically associated with a bimodal age distribution pattern, peaking at

the ages of 20 to 39 years and showing a second smaller peak at the ages of 50 to 79 years[2-4]. Various peak ages of CD onset have been reported in Asia. A Korean study reported a smaller second peak in the incidence of CD[5]. There was also a trend toward a second peak in the Hong Kong population[6]. A recent prospective, population-based study from the Asia-Pacific region also indicated a smaller second peak in the incidence of CD, albeit at a younger age (40-44 years) than that in Western countries[7]. However, this bimodal presentation has not been uniformly identified in other Asian studies[8,9]. The reason for the bimodal distribution remains unclear, but some environmental factors are known to be associated with this phenomenon. One hypothesis is that it may be due to certain age-specific environmental factors, such as passive smoking in childhood and active smoking in adulthood. It may also be caused by the different sensitivities of different age groups to certain infectious factors[10]. We speculate that Asian people with genetic susceptibilities could develop CD at the early peak ages of 20-39 years; however, the later second peak might be smaller than that in the West because environmental factors are less prevalent in Asia. Accordingly, it is expected that the second peak in the incidence of CD in Asia will increase as the region becomes increasingly westernized over time (Table 1).

Male predominance in Asians
European and North American studies have consistently revealed that the incidence of CD in females is equal to or greater than that in males[2,4,11,12]. In striking contrast, a male predominance in Asian patients with CD has been reported. In all recent studies from Korea, China, and Japan, the male-to-female ratios ranged from 1.67:1 to 2.9:1[9,13,14]. A recent prospective, population-based study from the Asia-Pacific region also demonstrated a male predominance[7]. Interestingly, a recent European study indicated a slight male predominance (60%) in adult Eastern European patients with CD[15]. Smoking, vaccination, or other factors (*e.g.*, geographic, ethnic, and social) might account for this sex difference[10]. Some Western researchers have suggested that the smoking rates, exposure of social life, or Westernized lifestyles were more prevalent in males than in females in Asia and that males might have more opportunities to receive medical services, including endoscopy, than females in Asia. However, if male predominance is in fact present in Asia, it is possible that changes in susceptible genes in sex chromosomes or changes in sex hormones might be involved in the pathogenesis of CD.

Cigarette smoking
Smoking represents one of the most consistently observed environmental risk factors for CD. Studies in Western countries have shown that smoking is a strong risk factor for the development of CD, but that it protects against the development of UC[16-20].

Based on recent prospective, population-based cohort

studies, the proportion of current or ex-smokers among Asian patients with CD (11.8%-28.0%)[7,21] is substantially lower than that among Western (57%) and Eastern European patients (62%)[15]. A study comparing patients between Melbourne and Hong Kong also reported that fewer patients were current or ex-smokers in Hong Kong (8%) than in Melbourne (50%)[22].

Western patients with CD who smoke have a worse disease course and are more likely to relapse after medically and surgically induced remission[23-25]. In terms of flare-up rates and therapeutic needs, disease severity is similar in patients who have never smoked and those who have stopped smoking, and both have a better course than continuing smokers[23]. Progression to stricturing or penetrating disease and subsequent surgery rates are reduced by smoking cessation[26]. However, smoking may not have the same effect in CD in different ethnic groups or geographic regions as in Western populations. For example, studies among Israeli Jews showed that smoking is not associated with the risk of CD[27-29]. More studies on Asian patients with CD are warranted to determine the impact of smoking on the development and progression of disease and its association with the disease phenotype in this population. Our hypothesis is that the lower rate of cigarette smoking among Asians may be one of the factors related to their better prognosis, as indicated by the lower rate of surgery in Asian than in Western patients with CD.

Familial aggregation

Previous studies have suggested that patients with IBD have less family clustering in East Asia. Studies from Asia have collectively reported that familial aggregation rates range from 0.0% to 3.0%[6,30-35], which is clearly lower than that in the Western population (13.4%)[36]. However, familial aggregation rates appear to be higher in West Asia, ranging from 12.9% to 19.0%[1,37]. Recent studies from Korea have suggested that the familial aggregation rate of IBD may increase with time, in parallel with the increase in the prevalence of IBD within the country[1,5,31]. Data on the familial clustering rates in other Asian countries must be validated by a longitudinal prospective cohort study. Moreover, it should be tested whether patients with family history of IBD would have a worse disease outcome than those without. Our own study showed no difference in clinical characteristics and outcomes between them[38]. We speculate that both environmental and genetic factors contribute to the low familial aggregation rates among Asian patients with CD. It might be valuable to elucidate the Asian-specific pathogenesis and establish prevention methods by investigating Asia-specific lifestyles or environmental factors, including breast feeding, tonsillectomy, childhood vaccination, infectious disease, or dietary intake of fiber and sugar.

Disease location

In the West, CD has been found to occur in the ileum, colon, and both the ileum and colon in equal proportions of patients[15,39]. However, a number of studies from the West have reported isolated colonic disease to be the most common type of CD[11,40,41]. A study comparing patients in China and the US also reported that American white patients have more colorectal involvement[32]. However, ileocolonic disease appears to be the most common type of CD in Asia[5,7,21,33,34,42,43]. CD confined to the small bowel is also common in Asia. Western guidelines suggest a follow-up colonoscopy to assess mucosal healing or recurrence after biologic therapy or surgery. However, routine ileocolonoscopy for therapeutic monitoring or after surgery might be less useful in Asian patients. Instead, radiological evaluation might play a role in such cases because isolated ileal or ileocolonic disease is not entirely visible by ileocolonoscopy.

Upper gastrointestinal tract involvement, which is significantly associated with disease prognosis such as changes in behavior[44] or the need for early surgery or hospitalization[45], has been rarely reported in Asia. This might be due to the lack of consensus regarding the performance of routine gastroduodenoscopy in patients with newly diagnosed CD in real practice. A study from China found that 23.5% of patients had upper gastrointestinal tract involvement at the time of diagnosis[14], but other studies[3,7,11,46,47] from both the Asia-Pacific region and the West have reported lower proportions. In a recent Korean study, jejunal involvement was observed in 14.1% of patients with CD at the time of diagnosis[48]. This markedly different result compared to China might be an overestimation. Thus, further larger studies are needed to determine the proportion of upper gastrointestinal involvement in patients with CD in Asia.

Disease behavior and course

Studies from the West have shown that the rates of inflammation, stricture, penetration, and perianal fistulas in CD at the time of diagnosis are 62%-81%, 5%-27%, 8%-14%, and 10%-27%, respectively[11,44,47,49,50]. Similarly, Asian studies have reported inflammatory disease in 40% to 69%, stricturing disease in 20%-29%, and penetrating disease in 10%-31% of patients with CD[13,21,33,34,45,51,52]. Interestingly, several studies documenting the disease behavior at the time of diagnosis have reported higher proportions of perianal fistula at the time of diagnosis in Hong Kong (33.3%)[33], Korea (36.7%)[34], and China (58.8%)[14] than in the West. Perianal fistula is known to be a poor prognostic factor in patients with CD[44,47]. In general, however, the prognosis of Asian patients with CD patients is reportedly better than that of Western patients with CD. Whether the presence of perianal fistula is actually a poor prognostic factor of CD remains to be determined and warrants further study. Actually, perianal fistula is described as independent from the penetrating type in the Montreal classification.

The evolution from inflammatory behavior to a more complicated disease behavior (stricturing or penetrating) is well demonstrated in the Western literature[46,47,53], and has also been shown in Asian studies from Hong Kong[33]

and Korea[54].

Based on long-term follow-up studies from Japan, it appears that Japanese patients with CD have a long-term prognosis similar to that of their Western counterparts regarding cumulative operation rates[43]. However, compared with Western patients with CD[55], a recent study from Korea showed a better prognosis with respect to the incidence of surgery[13,34]. This can be partly explained by the conservative attitude regarding bowel surgery among Korean physicians and patients or the smaller numbers of patients with a severe phenotype because of the short history of CD in the Asian region, including Korea.

Extraintestinal manifestations

Extraintestinal manifestations (EIM) have been reported in Asian patients with CD with widely variable rates: 19.0%-58.8% in China[14,52,56] and 25.0% in Hong Kong[6]. Among EIM, a high rate of ankylosing spondylitis (9%) among patients with CD has been reported[6]. A study comparing patients between the US and China reported that American white patients developed more EIM (40% *vs* 20%; OR = 2.63; *P* = 0.013)[32], especially chronic arthralgia (32% *vs* 4%; OR = 13.07; *P* < 0.001). However, it is difficult to directly compare the prevalence of EIM between Asian and Western patients with CD because most Asian reports were hospital-based (not population-based) retrospective studies or prospective cohort studies involving small numbers of patients (*n* = 17, 58.8%)[14]. Moreover, they were performed under different diagnostic criteria for EIM. Generally, the prevalence of EIM in Asia is accepted to be similar or slightly lower than that in the West (19%-25% *vs* 21%-41%, respectively)[57-60]. Less frequent EIM may be associated with the relatively better prognosis among Asian patients than in Western patients because EIM, especially ankylosing spondylitis, is known to be associated with a poorer prognosis in patients with IBD.

TREATMENT OF CD: COMPARISN BETWEEN THE EAST AND WEST

Medical treatments

Conventional therapy: The use of corticosteroids for CD is variable in studies from Asia. In one study, Asian specialists used corticosteroids as the first-line treatment in 50% of patients with mild CD and 84% of patients with moderate CD[61]. Moreover, they used corticosteroids as a maintenance therapy in approximately 25% of patients with CD[61], which might appear to be inappropriately high because corticosteroids have more side effects than placebo or low-dose 5-aminosalicylic acids (5-ASA)[62]. In a recent prospective European study, 54%-55% of patients with CD received corticosteroid therapy as an initial treatment during the first 3 mo of disease in Eastern and Western European centers, but did not during the maintenance phase[15].

Among patients with CD, the overall response rates to corticosteroids in Asia were similar to or better than those in the West. The short-term response rates at 1 mo were > 80% in both Asia and the West (Figure 1A), and 56.6% and 32.0% of patients, respectively, were corticosteroid-free without the need for surgery at 1 year (Figure 1B)[63,64].

The use of thiopurines in Asia also varies among countries. A Korean single-center study reported that thiopurines were used in 63% of patients with CD[34]. A separate Korean study showed that 42% of patients received thiopurines and that the cumulative thiopurine requirement was 9.1% at 1 year, 32.2% at 5 years, and 51.6% at 10 years[65]. Another cross-sectional study from Hong Kong noted that thiopurines were used in 63.6% of patients[22]. The authors of this study stated that the use of thiopurines was significantly less frequent in Hong Kong patients than in Melbourne patients (63.6% *vs* 82.1%, respectively, *P* < 0.001). A single-center review from East China found that 61 of 227 (26.9%) patients had indications for immunomodulator use. However, such agents were prescribed to only 34.0% of the patients, and of these 34.0%, 38.0% received a subtherapeutic dose with no attempt to increase the dose[66]. A recent prospective, population-based study from the Asia-Pacific region reported that only 35% of patients with CD received immunomodulator therapy[7]. Taken together, these results indicate that Asian physicians have a tendency to inappropriately use large amounts of corticosteroids and insufficient amounts of thiopurines. It is important to educate physicians regarding these medications.

There appears to be a higher rate of adverse events, particularly leukopenia, in Asians than in Caucasians when taking thiopurines. Up to 40%-56% of Asian patients may reach the criterion for leucopenia, namely a white blood cell count of < 4000/mm[3][67,68]. The cumulative incidence of myelotoxicity in the Western population was reported to be about 7%[69]. In Asia, however, thiopurine methyltransferase genotyping itself may not be as helpful in identifying patients who are expected to develop myelotoxicity as in Western countries[70], and the metabolites of thiopurines are not widely measured in real practice in many Asian countries. In Korea, therefore, physicians usually start a thiopurine at a smaller dose (*e.g.,* 25 or 50 mg of azathioprine) and gradually increase the dose with regular evaluations of the white blood cell count instead of determining the metabolite concentration. Alternatively, they may maintain lower doses of thiopurines than recommended in the Western guidelines[71].

Biologics: In a recent prospective, population-based cohort study from Europe, the rates of biologics use as an initial treatment during the first 3 mo of disease were reportedly 7% and 2% in Western and Eastern European centers, respectively[15]. This approach was interpreted as top-down therapy or rapid accelerating therapy. However, the economic burden or the reimbursement system can be obstacles to the use of biologics in the very early phase after diagnosis of CD in many Asian countries. An
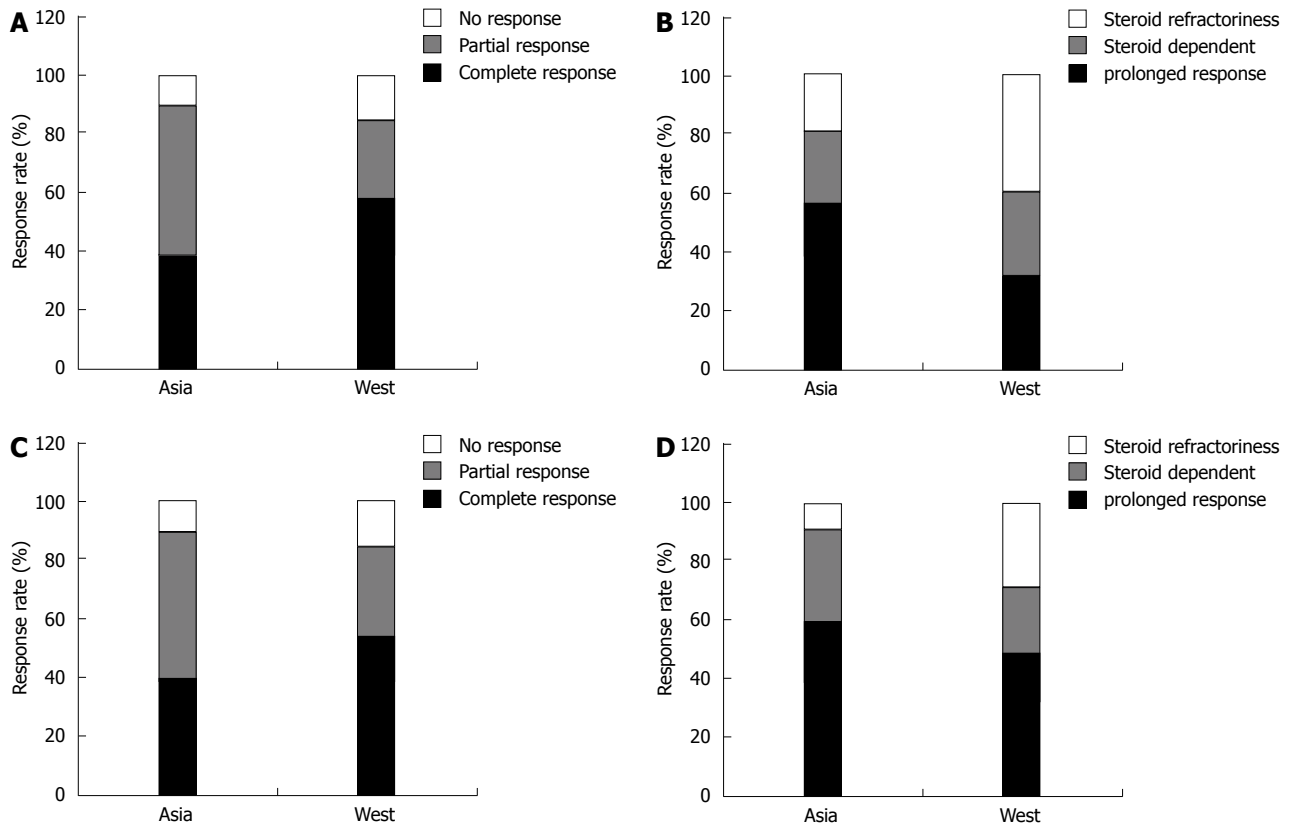
Figure 1 Comparison of the response to corticosteroids between Asia and the West[63,64,112]. A: Crohn's disease, 1 mo; B: Crohn's disease, 1 year; C: Ulcerative colitis, 1 mo; D: Ulcerative colitis, 1 year.

Asian survey of IBD management practices in different countries found that no IBD specialists would consider anti-tumor necrosis factor (anti-TNF) agents as the first choice for the treatment of CD. Moreover, only 20% considered anti-TNF agents as the second choice[61]. In a cross-sectional study comparing the management of CD between Melbourne and Hong Kong, a significantly higher number of patients in Melbourne had been on anti-TNF agents than in Hong Kong (40% *vs* 11%)[22]. A retrospective study from Korea reported that 8.6% of patients with CD used infliximab[34].

The response rates to infliximab in Asia are similar to or higher than those in the West. Although it is difficult to directly compare the results of responses to infliximab in Asia and the West because of their different designs, the response rates at 2 wk after beginning induction therapy were 72% and 62% in Korea (unpublished retrospective data) and the West[72], respectively. Moreover, the response rates at 30 and 54 wk after beginning maintenance therapy were 91.7% *vs* 50.0% and 74.7% *vs* 39.0% in Korea (unpublished retrospective data) and the West[72], respectively. A similar pattern was reported in patients with fistulizing CD between Korea and Western countries. In Asia, anti-TNF agents are used less frequently because of the limited, strict indications under insurance coverage rules, and because of the social economic burden. Moreover, many Asian physicians have not accepted the latest treatment trends, such as rapid accelerated step-up or top-down therapeutic approaches. Again, it is nec-

essary to educate Asian physicians regarding the adequate use of the latest medical treatments for IBD.

Complementary and alternative medicines: There are diverse rates of use of complementary and alternative medicines (CAMs) across Asia. One study from China reported that 90% of patients used concomitant traditional Chinese medications[73]. Moreover, various proportions of Western patients with IBD use CAM, ranging from 23% to 49% in recent studies[74-77]. In seven randomized controlled trials of patients with CD, *Artemisia absinthium* (wormwood) and *Tripterygium wilfordii* were superior to placebo in terms of inducing remission and preventing clinical recurrence of postoperative CD, respectively[78]. In two systematic reviews, omega-3 fatty acids did not appear to be effective for the maintenance of CD remission[79,80]. Effective anti-inflammatory moieties have yet to be defined.

Another problem is the indiscriminate use of various CAMs without sufficient evidence in patients with IBD. More studies are needed to determine the efficacy and safety of CAM in such patients. In addition, the development of new CAMs from natural products would be helpful in situations in which few drugs are available for patients with IBD.

Surgical treatments

The cumulative operation rates for CD in Japanese studies are comparable to those of Western cohorts, ranging

from 25.9% to 44.4% at 5 years and 46.3% to 80.1% at 10 years, respectively[43,81]. The surgical resection rate for patients with CD in Hong Kong (29% at 10 years)[6] is similar to that in a population-based study from Norway, which reported a 10-year cumulative surgical rate of 37.9%[55]. In a cross-sectional study, there was also no significant difference in the proportion of patients with CD who underwent surgery in Melbourne compared with in Hong Kong (55.1% *vs* 46.0%, respectively, *P* = 0.065)[22]. Similarly, the cumulative probability of intestinal resection in Korea was reported to be 15.5% after 1 year, 25.0% after 5 years, and 32.8% after 10-15 years. Asian patients with CD are currently considered to have a similar or slightly lower rate of surgery than that among their Western counterparts[34]. The lack of long-term follow-up studies in Asia makes it difficult to draw a concrete conclusion regarding the cumulative surgical resection rates between Asia and the West.

DIFFERENCES IN UC BETWEEN THE EAST AND WEST

Clinical characteristics of UC

Age and sex: The median age at the time of diagnosis of UC among patients in Asia is similar to or slightly older than that among patients in the West (35-44 years in Asia[5,9,51,82-85] and 30-40 years in the West[39,86,87]). In a cross-sectional study, patients with UC in Hong Kong were diagnosed at an older age than Caucasians in Melbourne (median age, 38 years *vs* 30 years, respectively). The authors suggested that this may be partly explained by a delay in diagnosis in Hong Kong[22]. Another possible explanation would be a weaker influence of genetic factors in Asian patients, which delays disease occurrence (Table 1).

The majority of studies from the West have shown an equal sex distribution for UC, although some reported a male predominance[86,88]. A growing number of studies in Asia have shown an equal sex distribution[5,84,85,87,89] or slight male predominance[9,35,52,82,90]. Collectively, the age and sex distributions of patients with UC are not largely different between the East and West.

Family history: Studies in Asia have reported a family history in 0.0%-3.4% of patients with UC[35,82,85]. This figure is lower than the 10%-25% reported in Western countries[37]. A recent population-based cohort study conducted in the Asia-Pacific area showed a family history in 3% of patients in Asia and in 17% of patients in Australia (*P* < 0.001)[7]. Interestingly, in Korea, an increase in the prevalence of a positive family history from 1.3% in 2001 to 2.7% in 2005[5] paralleled the increased incidence of IBD. This suggests that the low prevalence of a family history may be a reflection of the low population prevalence and will probably change with time.

In terms of genetic associations, a previous Japanese genome-wide association study (GWAS) and a recent Korean GWAS showed considerable overlap of genetic

associations for UC between Asia and the West. Despite the overlap of genetic associations of Asian and Western patients with UC, as can be seen by the lower proportion of patients with a family history of UC in Asia compared with the West, we realize that UC is one of the principal forms of IBD with complex manifestations, and genetic factors that account for only a portion of the overall disease development. This indicates a need to better explore gene-environment interactions or Asia-specific environmental factors of etiological importance in the development of IBD.

Disease extent: In UC, the extent of disease is classified into three types: proctitis, left-sided colitis, and extensive colitis. In Western population-based studies, these three types comprise 30%-60% of cases, 16%-40% of cases, and 18%-35% of cases, respectively[91-93]. In Asian population-based studies, they comprise 25.0%-43.7%, 31.0%-31.4%, and 24.9%-39.0%, respectively[5,42]. Most hospital-based studies in Asia have shown a trend toward a lower proportion of proctitis (8.5%-38.4%), higher proportion of left-sided colitis (29.7%-70.2%), and similar proportion of extensive colitis (21.3%-42.4%) compared with population-based studies[35,52,84,85,94], indicating that more severe cases were recruited into the hospital-based studies.

In terms of age and disease extent, several studies have reported that the extent of UC at diagnosis differs significantly according to age at diagnosis[83,95]. In one Korean study, proctitis was more common in elderly patients (28.9% in the young group *vs* 33.8% in the elderly group) and extensive colitis was more common in younger patients (35.1% in the young group *vs* 22.5% in the elderly group), suggesting a poorer clinical outcome in younger patients (*P* < 0.05)[83].

In a recent comparative epidemiological study of IBD across Asia and the Pacific, the extent of UC was classified as proctitis in 37%, left-sided colitis in 32%, and extensive colitis in 31%. These results are not significantly different from those in a study from Australia, which classified UC as proctitis in 32%, left-sided colitis in 27%, and extensive colitis in 41% (all *P* > 0.05)[7]. A recent population-based cohort study from the West and East Europe showed that the ratios of disease extent for UC from Western and Eastern European centers were proctitis in 20% and 22%, left-sided colitis in 41% and 46%, and extensive colitis in 38% and 32%, respectively[15]. Collectively, a slightly higher proportion of extensive colitis is observed in Western countries than in Asia, suggesting a more favorable prognosis of UC in Asia.

Disease course: Although definitions of clinical relapse and measurements of disease severity vary among studies, most suggest that Asian patients with UC have a milder disease course than do patients from Western countries[82,90,96]. In Asian studies, most patients with UC had a chronic relapsing disease course rather than continuous active disease[84,97], similar to Western data[98]. In a Malay-

sian study, the rate of maintaining remission was reported as 64.3% of patients with UC at 10 years after diagnosis, the rate of a chronic relapsing disease course as 25%, and the rate of chronic persistent disease with low or high activity as 3% after 10 years[97]. In a Norwegian study, the rate of maintaining remission was reported to be 55% of patients with UC at 10 years after diagnosis, which are slightly lower than the Malaysian data[98], and the rate of a chronic relapsing disease course to be 37%. In a Korean study, the cumulative relapse rate at 10 years after diagnosis (88.4%) was similar to that of a Western study (83%). However, the cumulative probabilities of colectomy (2.0% after 1 year, 2.8% after 3 years, and 3.3% after 5-15 years)[96] were lower than those in a Western study (3.5% after 1 year, 7.6% after 5 years, and 9.8% after 10 years)[98].

Based on the larger numbers of patients with a remission status, lower numbers of patients with a chronic relapsing or persistent active disease course, and lower cumulative operation rates, Asian patients with UC appear to have a milder disease course than that of Western patients with UC. However, the above-mentioned lower cumulative surgical rates may also be associated with diversity in management strategies or different levels of acceptance of colectomy by physicians and/or patients between Asia and the West in addition to disease severity.

Incidence of colorectal cancer

The overall prevalence of colorectal cancer (CRC) associated with UC is reportedly 3%-5% in the West[99] and 0.0% to 2.2% in Asia[35,52,85,90,96,100-103]. In a previous meta-analysis from the West, the cumulative risk of CRC associated with UC was reportedly 1.6%, 8.3%, and 18.4% at 10, 20, and 30 years, respectively[104]. In Asian studies, the cumulative risk of CRC in patients with UC was reportedly 0.70% to 1.15% at 10 years, 3.56%-7.90% at 20 years, and 14.4%-33.2% at 30 years[100,103], which is comparable with Western cohorts. However, considering the hospital-based design of most Asian studies, the actual corresponding risks might be lower than estimated.

Recently, however, a Western report showed that the risk of CRC decreased from 1979 to 2008 (RR = 1.34 in 1979-1988 to 0.57 in 1999-2008) and that the overall risk of CRC among patients with UC was comparable with that of the general population (RR = 1.07; 95%CI: 0.95-1.21). These findings suggest that a diagnosis of UC no longer seems to increase patients' risk of CRC. However, subgroups of patients with UC, including those diagnosed with UC in childhood or as adolescents, those with a long duration of disease, and those with concomitant primary sclerosing cholangitis, remain at increased risk[105].

Current evidence indicates that the risk of CRC in Asian patients with UC is slightly lower than that in Western patients. There is a chance that the prevalence of CRC will increase with the rising incidence and increasing proportion of patients with a longer follow-up in Asian countries. A very recent single-center study in Korea showed a substantial increase in CRC among patients with long-standing UC, which is comparable to Western data (unpublished data). Long-term prospective follow-up studies are warranted to estimate the actual risk of CRC in Asian patients with UC.

Extraintestinal manifestations

Although there are limited numbers of long-term prospective cohort studies and variations in the definition of EIM in Asian studies, the prevalence of EIM in UC seems to be lower in Asian than in Western countries[58,59,73]. The most commonly involved sites of EIM differ between Asia and the West. The most commonly involved site of EIM is the joints in Asian patients with UC (2.0%-19.5%). Next, eye and skin involvement accounts for 0.0%-4.2% and 0.0%-4.2%, respectively[35,52,82,90,97]. In contrast, eye involvement (iritis/uveitis) in females (3.8%) and primary sclerosing cholangitis (PSC) in males (3.0%) were the most commonly involved sites in a Western population-based study[58].

PSC associated with UC is less prevalent in Asia (0.0%-1.7%)[52,84,96,97,106] than in the West (1.6%-7.0%)[59,107]. Because PSC is associated with a risk of CRC in patients with UC, a diagnosis of PSC should not be neglected in real practice despite the low prevalence of PSC in Asia.

TREATMENT OF UC: COMPARISN BETWEEN THE EAST AND WEST

Medical treatments

Conventional therapy: In a recent population-based cohort study in the Asia-Pacific area that compared UC treatments in the first year between Asia and Australia[7], treatment with antibiotics (22% *vs* 14%, P = 0.15) and immunomodulators (thiopurine or methotrexate) (18% *vs* 9%, P = 0.05) did not differ between Asia and Australia. Mesalazine (79% *vs* 62%, P = 0.012) and corticosteroids (62% *vs* 28%, P < 0.0001) were more commonly prescribed for IBD at the time of diagnosis in Australia than in Asia. Topical therapy (mesalazine or corticosteroids) for UC was also more frequently prescribed in Australia than in Asia (55% *vs* 28%, P = 0.04).

In a recent population-based European study, 69 (44%) patients with left-sided colitis and 19 (23%) with extensive colitis in Western Europe received more frequently receive combination therapy with oral and topical 5-ASA compared with 21 (42%) and 6 (22%), respectively, in Eastern Europe[15]. In this study, 26%-33% of patients with UC received corticosteroid therapy as initial treatment during the first 3 mo of disease in Eastern and Western European centers.

In an Asian survey of management practices for IBD in different countries[61], 83%, 75%, and 61% of respondents preferred 5-ASA, a combination of topical and oral 5-ASA, and corticosteroids, respectively, as induction treatment of mild-to-moderate UC. Almost all respondents agreed that maintenance therapy should be recommended for patients with IBD in remission, with most recommending the use of 5-ASA to maintain remission in UC (91%). However, they also replied that thiopurines and corticosteroids were needed to maintain the remis-
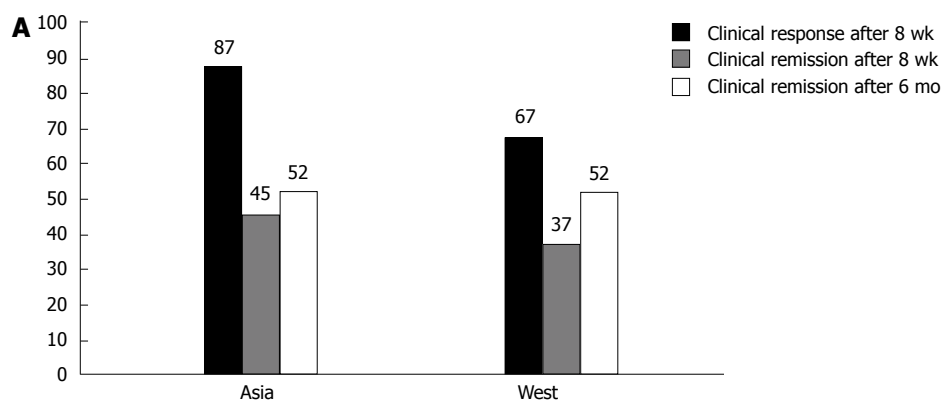
Figure 2 Comparison of the response to infliximab in patients with ulcerative colitis between Asia and the West[113-115].

sion in approximately 30% and 13% of patients with UC, respectively.

In one cross-sectional study, there was less use of corticosteroids (15.3% *vs* 46.5%, *P* < 0.001) and thiopurines (19.7% *vs* 55.3%, *P* < 0.001) for UC in Hong Kong than in Melbourne, which also reflects differences in practice according to region[22]. The authors suggested that Asian physicians prefer to manage UC with less intense medical treatments despite more extensive UC and that they use less thiopurines for maintenance therapy compared with the physicians in Melbourne. Again, it is important to educate Asian physicians in terms of following the adequate use of medical treatments according to the practice guidelines for IBD.

Among the UC patients who receive 5-ASA or sulfasalazine therapy, 49.6%[108] and 72.0% to 75.0%[109,110] experienced disease relapse in Asia and the West, respectively. The cumulative relapse rate was 21.5% after 1 year, 36.5% after 2 years, 46.9% after 3 years, and 59.8% after 5 years during maintenance therapy with 5-ASA/sulfasalazine, and both the disease extent at diagnosis and anemia were major predictive factors for clinical relapse after 5-ASA/sulfasalazine therapy for Korean patients with mild to moderate UC[108].

The overall response rates of Asian patients with UC to corticosteroids are similar to or better than those of patients in the West. Short-term response rates at 1 mo were more than 89.2% and 84.0% in Asia and the West (Figure 1C), and 59.4% and 49.0% showed a prolonged response at 1 year, respectively (Figure 1D)[64,111].

Biologics
A significant difference in the use of anti-TNF inhibitors between Hong Kong and Melbourne has been shown (2/203 *vs* 12/159, *P* = 0.001)[22]. An Asian survey of IBD management practices in different countries found that < 15% of Asian physicians would use anti-TNF therapy in the management of UC[61]. In many countries in Asia, the use of biologic agents is self-financed, making the high cost an obstacle to their wider use. However, a short-term population-based study showed that treatment with biological therapy in the first year after diagnosis (2.0% *vs* 0.0%, *P* = 0.21) did not dif-

fer between Asia and Australia[7]. Long-term follow-up studies are needed to show the chronological trends in the use of anti-TNF therapy in Asia. Emerging studies suggest that anti-TNF therapies are effective and safe in Asian patients with UC. The rates of clinical response and remission to infliximab were 87% and 45% in patients with UC at week 8[112], which is slightly higher than the rate of clinical response in the West (69.4%-64.5% at week 8)[113] (Figure 2). Data on long-term efficacy were obtained from 85 of 134 Korean patients who were followed up for more than 6 mo after the first dose of infliximab, and 44 of them (52%) were in remission, which is compatible with UC data in the West[114]. An another recent Korea study reported that 66.3% of patients demonstrated a clinical response at week 8, 32.6% of whom were determined to be in clinical remission[115]; this is similar to the response rates in previous Western reports. Collectively, a similar or slightly higher response rate of infliximab in patients with UC is observed in Asia than in Western countries. In the future, it is expected that other anti-TNF agents, such as adalimumab and golimumab, will be used more widely in addition to infliximab in patients with UC in Asian countries.

Complementary and alternative medicines
In 14 randomized controlled trials of patients with UC, aloe vera gel, *Triticum aestivum* (wheat grass juice), *Andrographis paniculata* extract (HMPL-004), and topical Xilei San were superior to placebo in inducing remission or response, and curcumin was superior to placebo in maintaining remission. *Boswellia serrata* gum resin and *Plantago ovata* seeds were as effective as mesalazine, whereas *Oenothera biennis* (evening primrose oil) was not effective and had relapse rates similar to those of omega-3 fatty acids in the treatment of UC[78]. Larger controlled studies with stricter endpoints and better-defined patient groups are required to obtain more conclusive findings regarding the use of CAM in IBD.

CONCLUSION
Over the past two decades, the incidence and prevalence of IBD have changed with a trend toward increasing

across Asia, especially East Asia. A younger second peak age of disease onset has been shown in Asian populations with CD compared to in Western populations. There is a predominance of male sex and ileocolonic involvement among Asian patients with CD. In patients with UC, the age and sex distribution are not different between Asia and the West. The proportion of current or ex-smokers among Asian patients with CD is lower than that among Western patients. The familial aggregation rates of patients with CD and UC are lower in Asia, but appear to be higher in the West. The disease extent in Asian patients with UC is not significantly different from, and may be slightly less severe than, that in Western populations. Asian patients with UC seem to have a milder disease course than do patients in Western countries. PSC associated with UC is less prevalent in Asia than in the West. Cumulative surgical resection rates in patients with CD do not appear to be different between Asia and the West despite the lack of large-scale, long-term follow-up studies in Asia. Whereas the cumulative surgical resection rates in Asian patients with UC are lower than those in Western patients, the cumulative risk of CRC associated with UC among Asian patients with UC is reportedly comparable with that among Western patients. The use of thiopurine or biologics in patients with IBD remains less frequent in Asia than in the West. There appears to be a higher rate of adverse events, particularly myelotoxicity, in Asians than in Caucasians prescribed thiopurines. The treatment responses for corticosteroids, thiopurines, and biologics of Asian patients with IBD are slightly better than or comparable to those of Western patients.

Several recent prospective, population-based cohort studies were conducted in Asia. Long-term follow-up results from these cohort studies are warranted to help clinicians and researchers further objectively compare the disease prognosis between Asian and Western countries, provide specific health care planning and education, and offer the possibility of identifying causative factors in a population with a rapidly increasing incidence in Asia.

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