



# Natural history of inflammatory bowel disease: a comparison between the East and the West

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Over the past decades, there has been a rapid increase in the incidence and prevalence of inflammatory bowel disease (IBD) in Asia. The natural history of IBD in Asian patients could be different from that in Western patients due to variations in disease phenotypes and genotypes as well as the healthcare environment between the 2 populations. To adequately cope with this disease, it is important to fully understand the potential differences in its natural history among different populations. In this review, we evaluated the differences in the clinical course of IBD between Asian and Western patients with regards to phenotypic progression, hospitalization, major surgery, risk of colorectal cancer, and mortality, mainly based on the results of population-based studies. The findings of our narrative review suggest that the clinical course of Asian patients with IBD, especially ulcerative colitis, is better than that of Western patients, as indicated by the lower rates of major surgery and hospitalization. In addition, similar to Western patients, the clinical course of Asian patients with IBD has been improving as evidenced by the decreasing rates of disease behavior progression (in Crohn's disease), hospitalization, and major surgery. (**Intest Res 2022;20:418-430**)

**Key Words:** Inflammatory bowel disease; Asia; Prognosis

## INTRODUCTION

Inflammatory bowel disease (IBD) was previously considered a rare disease in Asia. However, over the past few decades, there has been a rapid increase in its incidence and prevalence, posing a substantial healthcare burden in this area.<sup>1-4</sup> Characteristics of IBD in Asian populations are known to be different from those in Western populations in many aspects.<sup>5</sup> Therefore, to adequately cope with this chronic and progressive disease, it is important to fully understand the unique clinical course of IBD in Asian populations.

The clinical course of IBD may be influenced by many factors, including disease phenotypes and genotypes, delays in

diagnosis and treatment, patient response to medications, and changes in treatment paradigms. Therefore, when comparing the outcomes of IBD between Asian and Western patients, it should be noted that the following characteristics or conditions surrounding Asian IBD may affect result interpretation. First, Asian patients have distinct phenotypic characteristics including a higher prevalence of perianal fistulas in Crohn's disease (CD) and a higher proportion of proctitis in ulcerative colitis (UC) compared with Western patients.<sup>6</sup> Regarding genotypes, *NOD2* is strongly associated with CD in Caucasians but does not demonstrate any association in Asians. In contrast, *TNFSF15* has much larger effects on CD risk in Asians than in Caucasians.<sup>7</sup> Second, the low awareness of IBD by physicians and the general population due to low disease prevalence, limited access to medical care, and high prevalence of infectious enterocolitis mimicking IBD (particularly intestinal tuberculosis)<sup>8</sup> may lead to delays in the diagnosis and treatment of IBD in many Asian countries. Previous Asian studies

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reported that 27%–45% of patients with CD received anti-tuberculosis therapy before they were finally diagnosed with CD because of the difficulty in differentiating between CD and intestinal tuberculosis, resulting in diagnostic delay and increased risk of stenotic complications.<sup>9,10</sup> In addition, the high prevalence of infectious diseases, including hepatitis B virus infection,<sup>11,12</sup> tuberculosis,<sup>13,14</sup> and cytomegalovirus colitis,<sup>15,16</sup> in Asian countries may adversely affect the treatment of IBD. Third, there may be racial differences in the medication response and the adverse events associated with medications. Thiopurine-induced acute severe leukopenia is more common in Asians than in Caucasians because of the higher prevalence

of *NUDT15* variants, limiting the use of thiopurines in Asians.<sup>17-19</sup> In contrast, previous studies have suggested that the response to biologic agents, such as infliximab,<sup>20-22</sup> adalimumab,<sup>23-25</sup> vedolizumab,<sup>26-28</sup> and ustekinumab,<sup>29</sup> does not differ between Asian and Western patients with IBD. Fourth, although the introduction of biologic agents has dramatically changed the paradigm of IBD treatment and they may be equally efficacious in Asian and Western patients, their use in Asian countries is limited because of the high cost and the generally unpermitted top-down therapy. Accordingly, a simple comparison of disease outcomes, such as surgical rates, without considering the confounding effects of the aforementioned fac-

**Table 1.** Outcomes of Patients with Ulcerative Colitis in Asian Population-Based Studies in Contrast to a Systematic Review and Meta-Analysis from Western Population-Based Studies

Country	Data source	Study period	No. of patients	Follow-up duration (mo), median (IQR)	Proximal disease extension rate	Colectomy rate	Hospitalization rate	Standardized mortality ratio (95% CI)
Korea <sup>30</sup>	SK-IBD cohort	1986–2015	1,013	105 (60–170)	5.4% at 1 yr	1.0% at 1 yr	10.6% at 1 yr	0.725 (0.508–1.004)
					20.5% at 5 yr	1.9% at 5 yr	15.1% at 5 yr	
					30.2% at 10 yr	2.2% at 10 yr	18.4% at 10 yr	
					46.7% at 20 yr	5.1% at 20 yr	22.0% at 20 yr	
					54.0% at 30 yr	6.4% at 30 yr		
	1986–1999	152	261 (230–289)	4.5% at 1 yr	4.6% at 1 yr	16.4% at 1 yr	-	
				21.6% at 5 yr	4.6% at 5 yr	25.3% at 5 yr		
				31.3% at 10 yr	5.3% at 10 yr	29.7% at 10 yr		
				49.5% at 20 yr	8.5% at 20 yr	33.6% at 20 yr		
				56.4% at 30 yr	9.8% at 30 yr			
2000–2009	445	141 (110–175)	6.1% at 1 yr	0.7% at 1 yr	9.7% at 1 yr	-		
			19.8% at 5 yr	1.9% at 5 yr	14.0% at 5 yr			
			29.6% at 10 yr	2.2% at 10 yr	16.5% at 10 yr			
2010–2015	416	65 (45–86)	4.9% at 1 yr	0.0% at 1 yr	9.5% at 1 yr	-		
			21.3% at 5 yr	0.8% at 5 yr	12.5% at 5 yr			
8 Asian countries <sup>31</sup>	ACCESS cohort	2011–2013	192	19 (13–24)	15.3% at 2–3 yr	1.1% at 1 yr	-	-
Hong Kong <sup>32</sup>	Territory-wide registry	1981–2014	1,541	117 (55–184)	-	1.8% at 1 yr 2.1% at 5 yr	-	1.5 (0.9–2.3)
Europe <sup>33</sup>	Review of studies from Europe	Studies published in 2010–2020	-	-	25% during the course	1%–5% at 1 yr 3%–8% at 5 yr	9%–33% at 1 yr 18%–54% at 5 yr	1.1 (0.9–1.2)
Global <sup>34</sup>	Meta-analysis of 26 studies	1962–2016	-	-	-	4.0% at 1 yr 8.8% at 5 yr 13.3% at 10 yr	-	-
		2000–2016	-	-	-	2.8% at 1 yr 7.0% at 5 yr 9.6% at 10 yr	-	-

IQR, interquartile range; CI, confidence interval; SK-IBD, Songpa-Kangdong Inflammatory Bowel Disease; ACCESS, Asia-Pacific Crohn's and Colitis Epidemiology Study.

tors, may lead to false conclusions on the prognosis of Asian patients with IBD.

In this review, we aimed to evaluate how the clinical course of IBD in Asian patients differs from that in Western patients and investigate whether there are temporal trends toward improvement in the clinical course of Asian patients with IBD.

## METHODS

### 1. Outcomes of Interest

To describe the natural history of IBD in Asian patients, we evaluated several IBD-related outcomes including phenotypic progression, hospitalization, major surgery, risk of colorectal

**Table 2.** Outcomes of Patients with Crohn's Disease in Asian Population-Based Studies in Contrast to a Systematic Review and Meta-Analysis from Western Population-Based Studies

Country	Data source	Study period	No. of patients	Follow-up duration (mo), median (IQR)	Disease behavior progression	Intestinal resection rate	Hospitalization rate	Standardized mortality ratio (95% CI)	
Korea <sup>35</sup>	SK-IBD cohort	1986–2015	418	124 (79–181)	9.2% at 1 yr	12.7% at 1 yr	31.2% at 1 yr	1.36 (0.59–2.68)	
					19.3% at 5 yr	16.5% at 5 yr	40.7% at 5 yr		
					32.5% at 10 yr	23.8% at 10 yr	51.9% at 10 yr		
					54.5% at 20 yr	45.1% at 20 yr	67.9% at 20 yr		
					54.5% at 25 yr	51.2% at 25 yr			
		1986–2003	110	223 (200–256)	15.4% at 1 yr	16.4% at 1 yr	42.8% at 1 yr		-
					26.5% at 5 yr	20.1% at 5 yr	52.2% at 5 yr		
					49.1% at 10 yr	32.5% at 10 yr	68.7% at 10 yr		
					67.7% at 20 yr	54.6% at 20 yr	77.0% at 15 yr		
2004–2015	308	101 (70–136)	67.7% at 25 yr	59.6% at 25 yr	80.6% at 20 yr	-			
			6.9% at 1 yr	11.4% at 1 yr	27.0% at 1 yr				
			16.4% at 5 yr	15.1% at 5 yr	36.6% at 5 yr				
			23.2% at 10 yr	18.7% at 10 yr	43.7% at 10 yr				
					53.1% at 15 yr				
8 Asian countries <sup>31</sup>	ACCESS cohort	2011–2013	138	19 (13–24)	20.4% at 2–3 yr	8.0% at 1 yr	-	-	
Hong Kong <sup>32</sup>	Territory-wide registry	1981–2014	983	84 (39–158)	-	20.3% at 1 yr	-	2.0 (0.9–4.0)	
						25.7% at 5 yr			
Singapore <sup>36</sup>	Multi-center	1970–2013	430	7.3 (2.9–13.0) <sup>a</sup>	-	14.9% at 90 day	-	-	
						21.2% at 5 yr			
						28.8% at 10 yr			
						38.3% at 20 yr			
						50.6% at 30 yr			
Europe <sup>33</sup>	Review of studies from Europe	Studies published in 2010–2020	-	-	25% at 5 yr	6%–14% at 1 yr	23%–49% at 1 yr	1.39 (1.30–1.49)	
					33% at 10 yr	12%–27% at 5 yr	44%–54% at 5 yr		
Global <sup>34</sup>	Meta-analysis of 22 studies	1955–2015	-	-	-	18.7% at 1 yr	-	-	
						28.0% at 5 yr			
						39.5% at 10 yr			
		2000–2015	-	-	-	12.3% at 1 yr	-	-	
						18.0% at 5 yr			
						26.2% at 10 yr			

<sup>a</sup>7.3 yr (2.9–13.0).

IQR, interquartile range; CI, confidence interval; SK-IBD, Songpa-Kangdong Inflammatory Bowel Disease; ACCESS, Asia-Pacific Crohn's and Colitis Epidemiology Study.

cancers, and mortality. Moreover, when data is available, the temporal trends of IBD-related clinical outcomes in Asian patients with IBD were assessed. The outcomes of these Asian studies were compared with those of Western population-based cohort studies (Tables 1-3). If necessary, results from hospital-based studies were mentioned.

**2. Literature Search**

We conducted a systematic literature search in MEDLINE using the PubMed database to identify mainly population-based studies and, in case of lacking population-based studies, hospital-based studies from Asian countries which reported the natural history of IBD patients. We searched for the following terms: (“inflammatory bowel disease” OR “ulcerative colitis” OR “Crohn’s disease”) AND (“population-based” OR “nation-wide”) AND (“natural history” OR “natural course” OR “long-term outcome” OR “long-term follow-up” OR “temporal trend” OR “temporal change” OR “phenotype” OR “progression” OR “extension” OR “surgery” OR “resection” OR “colectomy” OR “perianal” OR “fistula” OR “hospitalization” OR “cancer” OR “malignancy” OR “mortality”). Studies from Asian population-based cohorts, including the Songpa-Kangdong Inflammatory Bowel Disease (SK-IBD) cohort,<sup>1,30,35</sup> the Asia-Pacific Crohn’s and Colitis Epidemiology Study (ACCESS) cohort,<sup>31</sup> and the Hong Kong IBD Registry<sup>32,37,38</sup> investigated various outcomes of both UC and CD, and were included in this review. In addition, several population-based studies from Asia evaluating a single-parameter outcome were included.<sup>36,39-42</sup>

**RESULTS**

**1. Phenotypic Progression**

**1) UC**

The extent of disease upon UC diagnosis is known to be different between Western and Asian patients. In a systematic review of 17 population-based cohorts,<sup>43</sup> the most common disease presentation at diagnosis was left-sided colitis (median, 40.1%; interquartile range [IQR], 32.6%–44.6%), followed by extensive colitis (30.5%; IQR, 29.8%–32.6%) and proctitis (29.4%; IQR, 25.3%–34.7%). In contrast, in the SK-IBD cohort, the most common disease presentation at diagnosis was proctitis (54.3%), followed by extensive colitis (23.2%) and left-sided colitis (22.5%).<sup>1</sup> Similarly, in the ACCESS cohort with patients from 8 Asian countries, disease presentation at diagnosis was proctitis (36.5%), extensive colitis (32.8%), and left-sided colitis (30.7%) in decreasing order of proportion.<sup>31</sup>

During the disease course, patients with UC experience proximal progression of the disease. Proximal disease extension appeared to carry a more severe disease course and was associated with an increased need for immunosuppressive treatment and an increased risk of hospitalization and colectomy.<sup>44</sup> In a population-based cohort study from Veszprem Province, Hungary, the cumulative risks of proximal disease extension at 1, 3, 5 years after the diagnosis of ulcerative proctitis or left-sided colitis were 2.9%, 9.4%, and 12.7%, respectively.<sup>45</sup> In a European population-based inception cohort (the Epi-IBD cohort), 90 (20.7%) of 435 patients with proctitis or

**Table 3.** Comparison of Outcomes of Patients with Inflammatory Bowel Disease between the East and the West along with the Temporal Trends

	Ulcerative colitis		Crohn’s disease	
	East vs. West	Temporal trends	East vs. West	Temporal trends
Phenotypic progression <sup>a</sup>	Similar	East: not decreasing West: not decreasing	Similar	East: decreasing West: conflicting
Hospitalization	East: lower	East: decreasing West: decreasing	Similar or East: lower	East: decreasing West: decreasing
Major surgery	East: lower	East: decreasing West: decreasing	Similar or East: lower	East: decreasing West: decreasing
Colorectal cancer	East: insufficient data West: SIR of 2.4 (95% CI, 2.1–2.7)	East: no data West: decreasing RR	East: insufficient data West: SIR of 1.9 (95% CI, 1.4–2.5)	East: no data West: not decreasing RR
Mortality	East: insufficient data West: SMR of 1.1 (95% CI, 0.9–1.2)	East: no data West: decreasing HR	East: insufficient data West: SMR of 1.39 (95% CI, 1.30–1.49)	East: no data West: not decreasing HR

<sup>a</sup>Proximal disease extension in ulcerative colitis and disease behavior progression in Crohn’s disease. SIR, standardized incidence ratio; SMR, standardized mortality ratio; CI, confidence interval; RR, relative risk; HR, hazard ratio.

left-sided colitis at diagnosis experienced proximal disease extension during the first 5 years of follow-up.<sup>46</sup> In a Danish population-based inception cohort, 72 (32.7%) of 220 patients with proctitis or left-sided colitis at diagnosis experienced proximal disease extension during the median follow-up of 7.5 years.<sup>47</sup> Additionally, in a population-based inception cohort of South-Eastern Norway (the IBSEN cohort), 100 (34.7%) of 288 patients with proctitis or left-sided colitis at diagnosis experienced proximal disease extension during the first 10 years of follow-up.<sup>48</sup> Meanwhile, in a meta-analysis of 30 studies including both population-based and hospital-based studies and both Western and Asian studies, the cumulative risk of proximal disease extension was 17.8% (95% confidence interval [CI], 12.3–25.1) at 5 years and 31.0% (95% CI, 23.5–39.7) at 10 years.<sup>49</sup> In a population-based cohort study from Orebro, Sweden, between 1963 and 2010, there was no difference in the risk of proximal disease extension among the 3 temporal cohorts.<sup>50</sup>

In the SK-IBD cohort, the cumulative risks of proximal disease extension at 5, 10, 20, and 30 years after the diagnosis of ulcerative proctitis or left-sided colitis were 20.5%, 30.2%, 46.7%, and 54.0%, respectively.<sup>30</sup> The risks of proximal disease extension were significantly higher in patients with proctitis than in those with left-sided colitis at diagnosis and did not differ among the 3 temporal cohorts.<sup>30</sup> In the ACCESS cohort, the cumulative risk of proximal disease extension in Asian patients was 15.3% at 2–3 years after diagnosis.<sup>31</sup> Taken together, the risk of proximal disease extension in Asian patients is comparable with that in Western patients. However, it remains unknown whether any treatment can reduce the risk of proximal disease extension. The results of the SK-IBD cohort study showing no change in the risk of proximal disease extension between 1986 and 2015 raise questions about the role of any treatment in reducing the risk of proximal disease extension. Further studies using standardized approaches are required to investigate proximal disease extension.

## 2) CD

Although the most common disease behavior at CD diagnosis is inflammatory behavior, Western population-based cohort studies have demonstrated that 15%–35% of patients with CD already had stricturing or penetrating behavior at the time of CD diagnosis.<sup>45,51–57</sup> In the SK-IBD cohort, disease behavior at CD diagnosis was inflammatory in 81.1%, stricturing in 8.1%, and penetrating in 10.8%.<sup>1</sup> In a population-based cohort study from Singapore, disease behavior at CD diagnosis was inflammatory in 78.1%, stricturing in 14.0%, and penetrating in 7.9%.<sup>36</sup>

In the ACCESS cohort, disease behavior at CD diagnosis was inflammatory in 68.1%, stricturing in 18.8%, and penetrating in 13.0%.<sup>31</sup> Perianal fistulas are common manifestations of CD and are known to be a predictor of poor prognosis. Perianal fistulas are considered more common in Asian patients with CD than in Western patients with CD.<sup>58</sup> In Western population-based cohort studies, 8.1%–16.7% of patients with CD developed a perianal fistula before or at CD diagnosis.<sup>59–64</sup> In contrast, 43.3% and 33.3% of patients with CD developed a perianal fistula before or at CD diagnosis in the SK-IBD cohort<sup>1</sup> and a Korean nationwide population-based cohort study using the National Health Insurance claims data,<sup>39</sup> respectively. In addition, in the Hong Kong IBD Registry, 20.9% of patients with CD had perianal CD before or at CD diagnosis.<sup>38</sup>

In population-based cohort studies from Europe, 14%–22% of patients with CD who had an inflammatory behavior at diagnosis experienced disease behavior progression during the first 5 years after diagnosis.<sup>51,52,65</sup> In a population-based cohort study from Olmsted County, the cumulative risks of disease behavior progression at 1, 5, 10, 20, and 30 years after the diagnosis of CD with inflammatory behavior were 4.1%, 18.5%, 24.7%, 39.5%, and 43.9%, respectively.<sup>60</sup> Regarding the temporal trends of disease behavior progression, the Dutch IBD South Limburg cohort failed to show any changes between 1991 and 2011.<sup>65</sup> However, in a population-based inception cohort from Western Hungary, the 5-year cumulative risk of disease behavior progression significantly decreased from 35.5% in the 1977–1989 cohort to 15.2% in the 1999–2008 cohort.<sup>66</sup> Regarding perianal fistulas, in Western population-based cohort studies, 13.9%–28.1% of patients with CD developed perianal fistulas during the median follow-up of 8.4–16.2 years after CD diagnosis.<sup>59–62,67,68</sup> In the Dutch IBD South Limburg cohort, the cumulative risks of developing a perianal fistula at 1, 5, and 10 years after CD diagnosis were 8.3%, 11.6%, and 15.8%, respectively.<sup>67</sup> In a population-based cohort study from Olmsted County, the cumulative risks of developing a perianal fistula at 1, 5, 10, 20, and 30–40 years after CD diagnosis were 11%, 15%, 18%, 23%, and 24%, respectively.<sup>61</sup>

In the SK-IBD cohort, the cumulative risks of disease behavior progression at 1, 5, 10, and 20 years after the diagnosis of CD with inflammatory behavior were 9.2%, 19.3%, 32.5%, and 54.5%, respectively.<sup>35</sup> Compared with the 1986–2003 cohort, the 2004–2015 cohort had significantly lower cumulative risks of progression: 6.9%, 16.4%, and 23.2% at 1, 5, and 10 years, respectively.<sup>35</sup> In the ACCESS cohort, the cumulative risk of behavioral progression in Asian patients was 20.4% at 2–3 years

after diagnosis.<sup>31</sup> Taken together, there appears to be no difference in the risk of disease behavior progression between Asian and Western patients with CD. As for perianal fistulas, in a population-based cohort study using the National Health Insurance claims data, 39.2% of patients with CD developed a perianal fistula during the median follow-up of 4.2 years after CD diagnosis.<sup>39</sup> The cumulative risks of developing a perianal fistula at 1 and 5 years after CD diagnosis were 35.2% and 40.0%, respectively. In addition, in the Hong Kong IBD Registry, 28.8% of patients with CD had perianal disease during the median follow-up of 8.8 years after CD diagnosis.<sup>38</sup>

## 2. Hospitalization

### 1) UC

In a recent review of European population-based cohort studies, the 1- and 5-year hospitalization rates in patients with UC were 9%–33% and 18%–54%, respectively.<sup>33</sup> Hospitalization rates varied substantially among different European countries.<sup>33</sup> In the Olmsted County cohort, the cumulative risk of hospitalization at 5, 10, 20, and 30 years after UC diagnosis was 29.4%, 38.7%, 49.2%, and 52.3%, respectively.<sup>69</sup> In addition, the rate of hospitalization in the Olmsted County cohort decreased from 134/1,000 patient-years in 1970–1979 to 88/1,000 patient-years in 2000–2004.<sup>69</sup>

In the SK-IBD cohort, the cumulative risks of hospitalization at 1, 5, and 10 years after UC diagnosis were 10.6%, 15.1%, and 18.4%, respectively.<sup>30</sup> The cumulative risk of hospitalization was significantly lower in the recent cohort than in the older cohort, with the 5-year cumulative risk of hospitalization being 25.3% in the 1986–1999 cohort and 12.5% in the 2010–2015 cohort. This temporal trend of decreasing hospitalization rate was also observed in a hospital-based cohort study from Thailand, where the cumulative risks of hospitalization at 1 and 5 years after diagnosis were 18% and 30%, respectively, in the 2000–2009 cohort and 5% and 21%, respectively, in the 2010–2018 cohort.<sup>70</sup> Furthermore, considering the absolute risks of hospitalization, it appears that Asian patients with UC have lower risks compared with Western patients. However, this does not necessarily mean that Asian patients experience a less severe disease form because the hospitalization rate is influenced by many factors other than disease severity, such as accessibility to healthcare services.

### 2) CD

In a recent review of European population-based cohort studies, the 1- and 5-year hospitalization rates in patients with CD

were 23%–49% and 44%–54%, respectively.<sup>33</sup> In the Olmsted County cohort, 120 (57%) of 211 patients with CD had at least 1 CD-related hospitalization during the total observation period of 2,247 patient-years.<sup>71</sup> In the Dutch IBD South Limburg cohort, the risk of hospitalization in patients with CD significantly decreased over time, with the 5-year cumulative risk of hospitalization being 65.9% in the 1991–1998 cohort and 44.2% in the 2006–2011 cohort.<sup>65</sup> In a population-based study from Ontario, Canada, CD-related hospitalizations decreased by 32% from 154/1,000 patients in 2003 to 104/1,000 patients in 2014.<sup>72</sup>

In the SK-IBD cohort, the cumulative risks of hospitalization at 1, 5, 10, and 20 years after CD diagnosis were 31.2%, 40.7%, 51.9%, and 67.9%, respectively.<sup>30</sup> The cumulative risk of hospitalization was significantly lower in the recent cohort than in the older cohort, with the 5-year cumulative risk of hospitalization being 52.2% in the 1986–2003 cohort and 36.6% in the 2004–2015 cohort. The cumulative risks of hospitalization in the SK-IBD cohort were similar to or slightly lower than those in Western population-based cohort studies.<sup>33,65,71,72</sup>

## 3. Major Surgery

### 1) UC

In a meta-analysis of 26 population-based cohort studies from Europe (n = 17), North America (n = 5), Oceania (n = 2), Asia (n = 1), and Africa (n = 1), the cumulative risks of colectomy at 1, 5, and 10 years after UC diagnosis were 4.0% (95% CI, 3.3–5.0), 8.8% (95% CI, 7.7–10.0), and 13.3% (95% CI, 11.3–15.5), respectively.<sup>34</sup> Among patients diagnosed in the 21st century, the cumulative risks of colectomy at 1, 5, and 10 years after UC diagnosis were 2.8% (95% CI, 2.0–3.9), 7.0% (95% CI, 5.7–8.6), and 9.6% (95% CI, 6.3–14.2), respectively. There was no difference in the cumulative risk of colectomy between Europe and North America.<sup>34</sup>

Compared with Western studies, population-based cohort studies from Asia have reported very low colectomy rates.<sup>30-32</sup> The cumulative risk of colectomy at 1 year after UC diagnosis was only 1.1% in the ACCESS cohort,<sup>31</sup> and that at 1 and 5 years after UC diagnosis was 1.8% and 2.1%, respectively, in the Hong Kong IBD Registry.<sup>32</sup> The risk of colectomy in the SK-IBD cohort was even lower than that reported in these 2 studies. In the SK-IBD cohort, the cumulative risks of colectomy at 1, 5, 10, 20, and 30 years after UC diagnosis were 1.0%, 1.9%, 2.2%, 5.1%, and 6.4%, respectively.<sup>30</sup> Because the cumulative risks of colectomy significantly decreased over the study period of 1986–2015, they were even lower among patients diagnosed

in the 21st century: 0.4% at 1 year, 1.4% at 5 years, and 1.6% at 10 years after diagnosis. Moreover, in the 2010–2015 cohort, no patients underwent colectomy during the first year after diagnosis, and only 0.8% of patients underwent colectomy during the first 5 years after diagnosis.<sup>30</sup>

## 2) CD

In a meta-analysis of 22 population-based cohort studies from Europe (n=16), North America (n=2), Oceania (n=2), Asia (n=1), and Africa (n=1), the cumulative risks of intestinal resection at 1, 5, and 10 years after CD diagnosis were 18.7% (95% CI, 15.0–23.0), 28.0% (95% CI, 24.0–32.4), and 39.5% (95% CI, 33.3–46.2), respectively.<sup>34</sup> Among patients diagnosed in the 21st century, the cumulative risks of intestinal resection at 1, 5, and 10 years after CD diagnosis were 12.3% (95% CI, 10.8–14.0), 18.0% (95% CI, 15.4–21.0), and 26.2% (95% CI, 23.4–29.4), respectively. There was no difference in the cumulative risk of intestinal resection between Europe and North America.<sup>34</sup> Proctectomy is required in some patients with a refractory complex perianal fistula. In a population-based cohort study from Olmsted County, the cumulative risk of proctectomy was 20% at 10 years and 22% at 20–40 years after the diagnosis of a perianal fistula.<sup>61</sup>

In the SK-IBD cohort, the cumulative risks of intestinal resection at 1, 5, 10, 20, and 25 years after CD diagnosis were 12.7%, 16.5%, 23.8%, 45.1%, and 51.2%, respectively, with a trend of decreasing risk over the study period.<sup>30</sup> In the 2004–2015 cohort, the cumulative risks of intestinal resection at 1, 5, and 10 years after CD diagnosis were 11.4%, 15.1%, and 18.7%, respectively. In a population-based study from Singapore, the cumulative risks of intestinal resection at 5, 10, 20, and 30 years after CD diagnosis were 21.2%, 28.8%, 38.3%, and 50.6%, respectively.<sup>36</sup> In the Hong Kong IBD Registry, the cumulative risks of intestinal resection at 1 and 5 years after CD diagnosis were 20.3% and 25.7%, respectively.<sup>32</sup> The cumulative risk of intestinal resection at 1 year after CD diagnosis was the lowest at 8.0% in the ACCESS cohort.<sup>31</sup> Taken together, the cumulative risks of intestinal resection at 1, 5, and 10 years after CD diagnosis in Asian population-based cohort studies were 8%–20%, 17%–26%, and 24%–29%, respectively. These rates are comparable to or slightly lower than those of the aforementioned meta-analysis. In addition, the cumulative risks of intestinal resection in the 2004–2015 cohort of the SK-IBD cohort were comparable to or slightly lower than those in the contemporary cohorts of patients diagnosed with CD after 2000 in the meta-analysis. As for proctectomy due to a perianal fistula, in the

Hong Kong IBD Registry, the cumulative risks of defunctioning surgery and/or proctectomy at 1, 3, and 10 years after the diagnosis of a perianal fistula were 4.1%, 5.4%, and 6.8%, respectively.<sup>38</sup> In a hospital-based cohort from Korea, the cumulative risks of proctectomy at 10, 20, and 30 years after the diagnosis of a perianal fistula were 2.9%, 12.2%, and 16.2%, respectively.<sup>39</sup> Therefore, the risk of proctectomy in patients with CD who developed perianal fistulas is lower in Asian patients than in Western patients. In this Korean study, the cumulative risk of proctectomy was significantly lower in the biologic era than in the pre-biologic era.<sup>39</sup>

## 4. Risk of Colorectal Cancer

### 1) UC

In a meta-analysis of 8 Western population-based cohort studies from Europe (n=6) and North America (n=2), the cumulative risks of colorectal cancer were <1.0% at 10 years, 0.4%–2.0% at 15 years, and 1.1%–5.3% at 20 years after UC diagnosis, and the pooled standardized incidence ratio (SIR) for colorectal cancer was 2.4 (95% CI, 2.1–2.7).<sup>73</sup> In population-based cohort studies from Copenhagen and Hungary, the 30-year cumulative risks of colorectal cancer were 2.1% and 7.5%, respectively.<sup>74,75</sup> In a study involving the Uppsala and Stockholm cohorts of IBD, there was a trend toward a decrease in the risk of colorectal cancer from 1960 to 2004, but it did not reach statistical significance.<sup>76</sup> However, in a study involving a nationwide cohort of Danish patients with IBD, the relative risk of colorectal cancer in patients with UC decreased significantly from 1.34 (95% CI, 1.13–1.58) in 1979–1988 to 0.57 (95% CI, 0.41–0.80) in 1999–2008.<sup>77</sup>

Recently, 3 population-based studies from Asian countries have been published on the risk of colorectal cancer in patients with IBD. In the Hong Kong IBD Registry, during the median follow-up of 10 years, 13 of 1,603 patients with UC developed colorectal cancer, with an SIR of 0.95 (95% CI, 0.55–1.64).<sup>37</sup> Similarly, in a study from Taiwan, during the mean follow-up of 7.2 years, 18 of 2,663 patients with UC developed colorectal cancer, with an SIR of 1.39 (95% CI, 0.8–2.2).<sup>40</sup> No observed increase in the risk of colorectal cancer in these 2 studies was possibly due to the short follow-up period. In contrast, in a study from Korea utilizing the National Health Insurance claims data, during the median follow-up of 2.20 years (range, 0.00–3.99 years), 31 of 9,785 patients with UC developed colorectal cancer, with SIRs of 2.14 (95% CI, 1.31–3.30) for male patients and 2.95 (95% CI, 1.47–5.29) for female patients.<sup>41</sup> Although this Korean study demonstrated an increased risk of colorectal cancer in patients

with UC, considering the very short follow-up period, the results of this Korean study should be interpreted with caution. According to previous Danish population-based studies, there was a remarkably high risk of colorectal cancer in the first year after IBD diagnosis, probably due to coincidental detection of recent-onset or prevalent IBD in patients diagnosed with colorectal cancer and misclassification of IBD versus cancer.<sup>77,78</sup> Therefore, more population-based studies with a longer follow-up period are needed to verify these results. In hospital-based cohort studies, the 30-year cumulative risk of colorectal cancer in Asian patients with UC ranged from 5.2% to 14.4%,<sup>79-82</sup> which was similar to that in previous Western studies. In a hospital-based cohort study from Korea, the SIR for colorectal cancer in patients with UC was 1.70 (95% CI, 1.00–2.66).<sup>79</sup>

**2) CD**

In a meta-analysis of 6 population-based cohort studies from Europe (n=3), North America (n=2), and Israel (n=1), the pooled SIR for colorectal cancer was 1.9 (95% CI, 1.4–2.5).<sup>83</sup> In a study involving a nationwide cohort of Danish patients with IBD, the relative risk of colorectal cancer in patients with CD was lower than previously known (relative risk, 0.85; 95% CI, 0.67–1.07) and, in contrast to UC, did not decrease significantly from 1979 to 2008.<sup>77</sup>

In the 3 Asian population-based cohort studies, the SIRs for colorectal cancer in patients with CD were 1.64 (95% CI, 0.74–3.65) in Hong Kong,<sup>37</sup> 0.96 (95% CI, 0.1–3.5) in Taiwan,<sup>40</sup> and 3.67 (95% CI, 1.58–7.22) for males and 4.67 (1.52–10.90) for females in Korea.<sup>41</sup> These results have problems similar to that in UC. In a hospital-based cohort study from Korea, the SIR for colorectal cancer in patients with CD was 6.0 (95% CI, 3.10–10.48).<sup>79</sup> Of note, in all 6 patients who developed colorectal cancer in the Hong Kong IBD Registry, the cancer was located in the anorectum.<sup>37</sup> Similarly, in hospital-based cohort studies from Korea<sup>79</sup> and Japan,<sup>84,85</sup> the colorectal cancer was located in the rectum in 89%–100% of patients with CD and colorectal cancer, in contrast with only 40% in Western studies.<sup>86</sup> The high proportion of rectal cancer in Asian patients with CD and colorectal cancer may be partly explained by the high prevalence of perianal fistulas in this population.<sup>1,79,87</sup>

**5. Mortality**

**1) UC**

Most Western population-based cohort studies published after 2000 reported no increase in mortality in patients with UC compared with in the general population,<sup>88-92</sup> barring some

studies that reported a slight increase<sup>93,94</sup> or decrease.<sup>95</sup> In a meta-analysis of 10 Western population-based cohort studies from Europe (n=8), North America (n=1), and Oceania (n=1), the pooled standardized mortality ratio (SMR) was 1.1 (95% CI, 0.9–1.2).<sup>96</sup> In a study involving a Danish national cohort, the mortality in patients with UC was significantly higher than that in matched controls (hazard ratio, 1.25; 95% CI, 1.22–1.28), and it decreased gradually from 1982 to 2010.<sup>93</sup>

In the SK-IBD cohort, the cumulative survival rates at 1, 5, 10, 20, and 30 years after UC diagnosis were 99.7%, 98.7%, 96.6%, 92.2%, and 91.2%, respectively, and the SMR was 0.725 (95% CI, 0.508–1.004).<sup>30</sup> In the Hong Kong IBD Registry, the SMR was 1.5 (95% CI, 0.9–2.3).<sup>32</sup> In contrast to these 2 Asian studies and the Western meta-analysis, a population-based study from Taiwan using the National Health Insurance database showed increased mortality in patients with UC (SMR, 1.44; 95% CI, 1.26–1.65).<sup>42</sup> The SMR in the Taiwanese patients with UC decreased from 1.88 (95% CI, 1.33–2.60) in 2001–2005 to 1.36 (95% CI, 1.11–1.65) in 2011–2015. However, the mortality rate remained higher in patients with UC than in the general population even in the most recent cohort. The reason for this high mortality rate is unclear. This may be explained by inadequate treatment due to the low awareness of this rare disease, misclassification bias inherent in code-based administrative database studies, or differences in prognosis among different populations.

**2) CD**

In contrast to UC, a meta-analysis of 9 Western population-based cohort studies from Europe (n=8) and North America (n=1) demonstrated increased mortality from CD with a pooled SMR of 1.39 (95% CI, 1.30–1.49).<sup>97</sup> In addition, in a Danish national cohort, there was no improvement in the hazard ratio for mortality in patients with CD from 1982 to 2010.<sup>93</sup>

In the SK-IBD cohort, the cumulative survival rates at 1, 5, 10, 20, and 30 years after CD diagnosis were 100%, 99.0%, 98.6%, 98.6%, and 84.5%, respectively, and the SMR was 1.36 (95% CI, 0.59–2.68).<sup>30</sup> In the Hong Kong IBD Registry, the SMR was 2.0 (95% CI, 0.9–4.0).<sup>32</sup> The SMRs in these 2 Asian studies seemed comparable to those in Western studies, although the increased mortality from CD in these 2 studies did not reach statistical significance probably due to a type II error. In contrast to these 2 Asian studies, a population-based study from Taiwan showed a remarkably increased mortality from CD (SMR, 3.72; 95% CI, 3.02–4.55).<sup>42</sup> The SMR in the Taiwanese patients with CD decreased from 5.46 (95% CI, 3.38–8.43) in 2001–2005 to 2.80

(95% CI, 2.01–3.80) in 2011–2015. However, the SMR in the most recent cohort remained higher than that in the Western meta-analysis. Possible reasons for this high mortality were discussed in the section on UC mortality.

## SUMMARY AND CONCLUSION

The results of this review suggest that the clinical course of Asian patients with IBD, especially UC, is better than that of Western patients, as indicated by the lower rates of major surgery and hospitalization. In addition, as in Western patients, the clinical course of Asian patients with IBD is improving, as evidenced by decreasing rates of disease behavior progression (in CD), hospitalization, and major surgery.

However, this study had a few limitations. First, this review contains data only from East Asia and Southeast Asia, because there are no population-based studies on the clinical course of IBD in the Middle East and South Asia. Therefore, it is unclear whether the disease outcomes of this review can be generalized to all Asian populations, considering that there is genotypic and phenotypic heterogeneity among IBD patients in different Asian populations.<sup>5,7,98</sup> Second, although Asian countries have very heterogeneous medical environments, the different medical standards of each country were not considered in this review. Third, we could not reach conclusions in the case of some outcome parameters such as colorectal cancer risk and mortality rate, because these parameters need longer-term studies.

Therefore, to make a definite conclusion on the prognosis of IBD in Asian patients, more studies from different Asian countries with long-term follow-up are needed. Knowledge of the clinical course of Asian patients with IBD may help in selecting optimal treatment strategies and developing healthcare policies.

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Not applicable.

### Author Contribution

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