STATEMENT

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Predicting outcomes to optimize disease management in inflammatory bowel disease in Japan: their differences and similarities to Western countries

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Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disease of the gastrointestinal tract, with increasing prevalence worldwide. IBD Ahead is an international educational program that aims to explore questions commonly raised by clinicians about various areas of IBD care and to consolidate available published evidence and expert opinion into a consensus for the optimization of IBD management. Given differences in the epidemiology, clinical and genetic characteristics, management, and prognosis of IBD between patients in Japan and the rest of the world, this statement was formulated as the result of literature reviews and discussions among Japanese experts as part of the IBD Ahead program to consolidate statements of factors for disease prognosis in IBD. Evidence levels were assigned to summary statements in the following categories: disease progression in CD and UC; surgery, hospitalization, intestinal failure, and permanent stoma in CD; acute severe UC; colectomy in UC; and colorectal carcinoma and dysplasia in IBD. The goal is that this statement can aid in the optimization of the treatment strategy for Japanese patients with IBD and help identify high-risk patients that require early intervention, to provide a better long-term prognosis in these patients. **(Intest Res 2018;16:168-177)**

Key Words: Crohn disease; Colitis, ulcerative; Prognosis; Colorectal neoplasms; Consensus

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INTRODUCTION

Optimization of the treatment strategy for patients with IBD or identifying high-risk patients who require early or intensive therapy is necessary to prevent progression that may

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lead to a poor long-term outcome and to avoid unnecessary or potentially harmful treatments in patients with less severe disease. This includes being able to predict specific disease complications, including extension of disease in UC, change of disease behavior and/or location in CD, the need for surgery, and the development of colorectal cancer (CRC).

IBD Ahead is an international educational program that aims to explore questions commonly raised by clinicians regarding various aspects of IBD care and to consolidate available published evidence and expert opinion into a consensus for the optimization of IBD management. Gastroenterologists from 32 countries participated at both national and international meetings. The program's goal was to provide practical answers to questions raised in daily clinical practice based on available evidence and the participants' clinical experience. Recommendations by the participants were discussed and integrated based on national meetings held in the participating countries. Recently, an international statement was published by the IBD Ahead program on adverse prognostic factors in IBD.[1]

Discussions among Japanese experts in the management of IBD suggested that there were differences in prognostic factors in Japanese patients with IBD from those reported by the international statement. The epidemiology, clinical characteristics, risk factors, management, and prognosis of IBD differ between Western countries and East Asian countries, as well as within East Asia, including Japan.[2-4] Genetic characteristics also differ between Japanese and Western patients with IBD,[5,6] underscoring the importance of country and population-specific guidelines for the management of IBD. Consequently, this article consolidates statements of factors for disease prognosis in IBD approved by Japanese IBD experts as part of the IBD Ahead program, and suggests their effective use in IBD management.

METHODS

As previously described for the international consensus statement,[1] the Global Steering Committee (GSC) of the IBD Ahead 2014 educational program identified key topics of interest or uncertainty in understanding prognostic factors in IBD; clinical questions relating to these topics were then developed. A literature search was conducted by the IBD Ahead GSC, and draft statements were developed. National meetings were then held in 32 countries to produce the international consensus statement. Participants reviewed, voted, and provided expert opinion and local perspectives on the statements; this feedback was used by the GSC to produce a consolidated set of statements, which has been published.[1] The national advisory board meeting consisting of 23 Japanese experts in the management of IBD was held in Japan in August 2014. Expert opinion from this meeting was integrated with the international results of the global plan to create the consensus statements. The Japanese IBD experts reviewed this response draft and combined their results with the literature search results of the IBD Ahead GSC and Japanese expert opinion, with a focus on clinical applications relating to predictive factors in IBD management in the Japanese setting. An updated literature search of IBD prognostic factors, including those specific to Japanese patients, was also performed. These findings were subsequently incorporated into this document to report Japanese-specific results related to the consensus statements and to report information that was not captured by the initial literature review of the IBD Ahead GSC.

Evidence levels (ELs) were assigned based on this updated literature search using University of Oxford Centre for evidence-based medicine 2011 criteria (http://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf). The Japanese experts also scored each statement by voting according to their level of agreement, with 1 indicating strong disagreement and 9 indicating strong agreement. If ≥75% of participants scored the statement within the 7 to 9 range, the statement was deemed to be agreed upon. If <75% of participants scored within this range, the statement was debated and revised, and a second vote was taken. Again, if ≥75% of participants scored the statement within the 7 to 9 range, the statement was deemed to be agreed upon. The degree of agreement (%) reflects the ratio of doctors who assigned a score of 7 to 9. The average score is the average of the Japanese experts' scores.

CONSENSUS STATEMENTS

1. Disease Progression in CD

Summary statement	Average agreement score and rate of agreement
1. At the time of diagnosis, extensive small-intestinal lesions (EL2) and significant upper gastrointestinal tract disease (EL3) are predictive factors for complicated disease behavior in CD.	7.6 (85%)

2. Young age at diagnosis, need for steroids at first flare, and perianal disease at diagnosis predict a disabling course of CD (EL3).	8.0 (100%)
3. Smoking can predict the need for therapy intensification in CD (EL3), development of complicated disease behavior (EL3), and the need for surgery (EL3).	7.6 (95%)
4. Endoscopic severity of CD predicts the formation of fistulae (EL4) and the need for surgery (EL3).	8.3 (100%)

As indicated in the international consensus statement,[1] disease location, such as ileal and ileocolonic versus colonic, and upper gastrointestinal tract or rectal involvement are predictors of disease progression in CD. Independent factors present at diagnosis and significantly associated with a disabling course at 5 years include age <40 years (OR, 2.1; 95% CI, 1.3–3.6), presence of perianal disease (OR, 1.8; 95% CI, 1.2–2.8), and an initial requirement for steroids (OR, 3.1; 95% CI, 2.2–4.4).[7]

A variety of studies, as reported in the international consensus statement,[1] have shown that smoking is associated with stenosing/fistulizing behavior, need for steroids or immunomodulators, need for surgery, and disease recurrence following surgery. However, in Asian populations, some studies have shown different associations of smoking with CD compared to that found in Caucasian populations. For example, the same detrimental effect has not been seen in a Chinese population.[8] In the prospective Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCESS) study, which included patients from multiple countries within Asia and Australia, smoking was associated with more than a 4-fold increased risk of CD in the Australian Caucasians, yet was not a significant risk factor for the Asians with CD.[9] In a Japanese study, smoking was identified as an independent risk factor for initial surgery in patients with CD, although the results are uncertain given that this was a single-center retrospective study.[10] Thus, the exact role of cigarette smoking in conferring susceptibility to or increasing the severity of CD in Asian populations is less well established than it is in Caucasian populations.[11,12]

2. Surgery, Hospitalization, Intestinal Failure, and Permanent Stoma in CD

Summary statement	Average agreement score and rate of agreement
1. Surgery risk increases for people less than 40 years at the time of diagnosis (EL2). Surgery risk is lower if CD is diagnosed in early childhood (EL3) and in old age (EL2).	7.0 (75%)
2. Surgery risk is higher for small-intestinal lesions (in comparison with large-intestinal lesions) (EL2).	8.5 (100%)
3. Penetrating and stricturing phenotypes at diagnosis are independent risk factors for surgery compared to inflammatory type (EL2).	8.2 (90%)
4. Severe ulcers at colonoscopy in patients with colonic CD may predict need for surgery (EL4).	7.8 (95%)
5. Compared to inflammatory type, fistulizing and stricturing phenotypes are predictive factors for hospitalization and re-hospitalization (EL2).	8.5 (95%)
6. L4 lesions are a predictor of increased hospitalization and hence might be a more serious subgroup (EL3). By contrast, large-intestinal lesions predict a decrease in the hospitalization rate (EL2).	7.5 (86%)
7. Penetrating disease and younger age at diagnosis may predict increased risk of intestinal failure; bowel-sparing surgery and cases without stoma involvement may protect against intestinal failure (EL3).	7.7 (92%)
8. Complex perianal fistulae, anal-canal stricture, perineal lesions, large perianal abscesses, fecal incontinence, and distal bowel lesions are risk factors for permanent stoma (EL3).	8.3 (100%)

The prognosis of CD, such as the rate of initial surgery, is similar in Japan to that in Western countries.[10] As reported by the international consensus statement[1] and supported by numerous studies conducted in Western populations, prognostic factors for surgery include younger age at diagnosis (except in pediatric patients), ileal/ileocolonic or jejunal disease location, and penetrating and stricturing disease. A Japanese hospital-based cohort study of patients with CD found that B2 or B3 behavior at diagnosis, adjusted for age,

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sex, smoking, and drinking, entailed a higher risk of initial surgery compared with patients with B1 behavior.[10] Patients with L4 at the time of diagnosis had more B2 behavior and moderate to severe jejunal stenosis. Japanese patients with L4 at the time of diagnosis may thus be a high-risk group for initial surgery. In Western patients with CD, factors associated with time to first hospitalization include ileocolonic, ileal, and upper gastrointestinal disease relative to colonic extent alone.[13]

As reported by the international consensus statement,[1] factors associated with permanent stoma include anal-canal stenosis, perineum involvement, perianal fistulae and sepsis, fecal incontinence, and distal colonic CD.

3. Disease Progression in UC

Summary statement	Average agreement score and rate of agreement
1. Family history of IBD (EL3), nonsmoker, nonresponsiveness to treatment (frequent relapses), and need for systemic steroids or immunosuppression therapy are related to an increased risk of proximal disease extension in UC (EL4).	7.1 (78%)
2. Being young at the time of diagnosis is a predictive factor for extensive colitis (EL4).	8.0 (100%)

In UC, proximal disease extension is an important risk factor for disease progression.[14-16] A slightly higher proportion of extensive colitis is found in Western countries than in Asia, with Asian patients generally having a milder disease course compared with their Western counterparts.[3] A retrospective study showed a higher risk of proximal extension in nonsmokers, patients with >3 relapses a year, and those requiring systemic steroids or immunosuppressives.[17]

In Japanese patients, UC disease severity has been shown to be worse in patients with a family history,[18] although another Japanese study, in children with UC, did not find an association between family history and clinical symptoms.[19] A Japanese study relying upon a large nationwide registry existing since 1975 found that male sex, age <17 years, mushy stools, frequent bowel movements, extensive lesions (left-sided colitis or pancolitis), being overweight or obese, and mild or moderate-to-severe hematochezia were positively associated with UC exacerbation.[20]

In Korean patients with ulcerative proctitis, more severe disease at diagnosis predicted proximal disease extension;[16] another Korean study showed that patients with UC diagnosed at a young age had more severe disease activity.[21] The situation is similar in Japan, with disease extension being significantly higher in patients with disease onset before age 25 years.[22] Patients with UC diagnosed at a younger age have a higher risk of disease progression.[14]

4. Acute Severe UC

Summary statement	Average agreement score and rate of agreement
1. Extensive lesion(s) is a risk factor for acute severe UC (EL2).	8.3 (100%)
2. Comorbid primary sclerosing cholangitis is a protective factor for hospitalization due to UC exacerbation (EL2). Cessation of smoking is a risk factor for UC exacerbation (EL2).	8.2 (95%)
3. Extensive disease and cytomegalovirus infection are risk factors for hospitalization due to UC exacerbation (EL3).	8.4 (100%)

Acute severe UC is a potentially life-threatening condition treated by hospitalization and intravenous steroids.[23] There are few studies examining predictive factors for acute severe UC, although a U.K. study showed that a quarter of patients with UC have at least one episode of acute severe UC and that patients with more extensive lesions have a more frequent occurrence of acute severe flare.[24] Although younger age at diagnosis was shown to be a risk factor for acute severe disease (36 years vs. 39 years, P=0.049),[24] the definition of young age is vague and varies depending on the study.

A study in 139 Japanese patients found that total colonoscopic findings on sites of abnormality were the only baseline (i.e., at onset of UC) characteristics significantly related to the need for hospitalization.[25] Patients with UC with primary sclerosing cholangitis (PSC)[26] and those who smoke[27] have less hospitalizations. In Japan, physicians routinely test for cytomegalovirus infection as a factor possibly exacerbating UC flares.[28] Rates of concurrent cytomegalovirus infection in a Japanese hospital were significantly higher (by 8 times) in patients hospitalized for UC aggravation versus those not hospitalized.[29]

5. Colectomy in UC

Summary statement	Average agreement score and rate of agreement
1. Pancolitis, long disease duration (EL3), severity at the time of first hospitalization (EL3), endoscopic severity (EL1), and frequent hospitalization (EL3) are clinical predictive factors for colectomy.	8.3 (100%)
2. Physician and surgeon experience, the treatment and surveillance policy, and the patient's preference may affect the final decision to have a colectomy (EL5).	8.3 (95%)

Colectomy is a strong indicator of disease severity.[30] Because colectomy can be performed as part of acute surgery or elective surgery, rates for colectomy vary based on country and setting.[31-34] Pancolitis in children has been shown to predict colectomy.[35] European and Scandinavian studies have demonstrated a relationship between long disease duration and the extent of colitis at diagnosis with the risk of colectomy.[31,36,37] As indicated by a meta-analysis, mucosal healing is associated with long-term clinical remission and the need for colectomy.[38] Based on expert opinion, the decision to have a colectomy reflects a number of factors, including patient preferences.

6. Colorectal Carcinoma and Dysplasia in IBD

Summary statement	Average agreement score and rate of agreement
1. Longer disease duration and extensive disease are related to a higher risk of CRC development in IBD (EL2). There is a need for surveillance for colitis-associated dysplasia/cancer in patients with macroscopically or microscopically active inflammation.	8.0 (91%)
2. PSC is related to the development of dysplasia and CRC in UC. At the time of diagnosis of the complication, surveillance with colonoscopy is necessary (EL2). In Japan, there are much fewer UC cases with comorbid PSC compared with Western countries (EL3). However, surveillance and caution towards the development of CRC still seem necessary.	7.7 (90%)
3. Histological inflammation score is related to dysplasia and CRC occurring in UC (EL3). Therefore, surveillance should now be considered based on past disease activity.	7.8 (90%)
4. Family history of sporadic CRC in immediate family members is related to the onset of CRC in IBD (EL3). However, there are no data confirming this for Japan.	7.6 (85%)
5. Surveillance is required for rectal cancer and fistula cancer with regards to CD patients with intractable anal lesions (EL3).	8.6 (100%)

Japan currently has no consensus for a cancer surveillance program in patients with CD,[39] yet a need for consensus exists. The importance of surveillance colonoscopy in patients with long-standing UC in Japan has been well recognized.[40,41]

As reported in the international consensus statement,[1] longer duration of IBD and greater extent of colonic involvement at diagnosis were found to be independent risk factors for the development of CRC or high-grade dysplasia. A retrospective study of Japanese patients with CD found an increased risk of cancer, particularly CRC,[42] confirming findings from Western patients. The risk of CRC in Japanese patients with long-standing CD has been reported to be similar to that of Western patients with CD.[43]

Proximal disease extension in Japanese patients with UC with proctitis may be associated with an increased CRC risk.[22] As previously reported in Western populations, a single-center study of Japanese patients with UC confirmed that development of CRC occurred more often in patients with long-standing UC and with UC more extensive than left-sided colitis.[44] Compared to an age- and sex-matched healthy population, at a tertiary referral center for IBD in Japan, significant risk factors for the development of CRC in patients with CD included female sex, positive history of surgery, observation period >20 years, onset of CD at <25 years of age, mixed small and large bowel type, and presence of anal disease.[43]

Numerous studies, as reported in the international consensus statement,[1] have shown that comorbid PSC strongly predicts dysplasia or CRC development, warranting surveillance. Although the prevalence of comorbid PSC was estimated to be <1% in Japan,[45] surveillance and caution towards the development of CRC is warranted.

Histologic inflammation is a risk factor for progression to CRC in patients with UC.[46,47] A meta-analysis includ-

ing 31,287 Asian patients with UC found a 0.02% (95% CI, 0.00–0.04) risk of CRC at 10 years, 4.81% (3.26–6.36) at 20 years, and 13.91% (7.09–20.72) at 30 years, similar to that of North America and Europe.[48] In Japan, the number of patients with UC-associated CRC diagnosed by surveillance colonoscopy has increased, with many detected in the very early stages.[41] Surveillance colonoscopy in Japanese patients with UC has thus proved efficient by detecting CRC in the earlier stages. In Japan, a targeted biopsy strategy is more common than conventional random biopsies for surveillance of UC-associated CRC, as recently reported by a randomized controlled trial.[49]

In Japanese patients with CD, perianal diseases were the most frequent complications;[50] 15% of Japanese patients with CD had an anal fistula[10] and 55% of Japanese patients with CD with lower gastrointestinal cancer had cancer in their anorectal regions.[51] Because rectal and fistula cancer could occur in patients with CD with intractable anal lesions,[52] further investigation to develop the surveillance program is needed. In Japan, cancer associated with CD more often occurs on the left side of the colon and particularly in the rectum and anal canal.[53] Screening for perianal cancer, such as with anal canal biopsy,[53] may be recommended based on the higher incidence of perianal lesions and cancers associated with CD in Japanese patients[51] compared with patients in Western countries.[54]

DISCUSSION

Optimization of the treatment strategy for patients with IBD or identifying high-risk patients that require early intervention is important to prevent long-term poor outcomes. Earlier recognition of risks for exacerbation in patients with UC could enable precautious optimal care.[20] Similarly, identification of factors predictive of a disabling course of CD could point to the need for earlier "top-down" intensive therapy.[7]

This Japanese consensus statement was created because a variety of factors related to prognosis differ between the Japanese setting and Western settings. These include socioeconomic factors such as access to medical treatment and insurance coverage. Because of regulatory requirements, Japan has been conducting a variety of trials specifically in Japanese patients with IBD. In Japan, IBD diagnosis and treatment also differ from that in the West and other countries in East Asia.[2,28] For example, because of economic and geographic factors, access to specialist centers in Japan is easier compared with other countries, both in the East and in the West, which may influence differences in diagnosis and treatment. In Japan, upper gastrointestinal endoscopy is more likely to be actively performed in patients with CD, with characteristic gastric and duodenal lesions secondary features of the diagnostic criteria. Leukocyte apheresis is approved in Japan, whereas it is not commonly used in other countries; budesonide was not approved in Japan at the time of the meeting; and anti–tumor necrosis factor therapy for postoperative patients with CD with a high risk of recurrence is actively performed in Japan. Because of Japan's public health system, a patient's economic considerations do not affect the use of anti-tumor necrosis factor drugs.

Genetic and other patient-related factors also differ between Japanese patients with IBD and those in the West. Consequently, some statements included in the international statement were not included here for lack of relevance. For example, NOD2/CARD15 polymorphism and positive anti-*Saccharomyces cerevisiae* antibodies increase the risk of surgery:[55,56] this does not apply to patients in Japan because of the absence of these polymorphisms[6] and the lack of evidence in Japanese patients with CD. Thus, it was not included as a statement. Also, although serum immune responses, such as circulating antibodies against bacterial antigens, are associated with complicated CD[57] and predict rapid disease progression,[58] this testing has not been proven to be useful among Japanese patients and is therefore rarely done in clinical practice in Japan. With respect to UC, unlike the international consensus statement, the Japanese experts did not feel that a delay in diagnosis of >6 months merited inclusion as a factor related to an increase in the risk of proximal disease extension because the study upon which it was based was in a pediatric population.[15] Comorbid PSC is reported to be associated with an increased risk of proximal disease extension,[14] may be a protective factor for hospitalization,[26] and is also a risk factor for colectomy, primarily because of the associated risk of colorectal neoplasia in the Western population.[59] However, the prevalence of comorbid PSC was estimated to be <1% in Japan, which is significantly lower than the rates in North American and European countries.[45] Also, unique features of Japanese patients with PSC compared with those in the West include 2 peaks in age distribution at diagnosis and less comorbid IBD.[45] Approximately 3 quarters of Western patients with PSC have been reported as also having UC, with the prevalence being over 90% in some studies,[59] whereas in Japan, only 34% of patients with PSC also have UC.[45] In addition to such epidemiological differences, no relationship was found between the documented colonic manifestations of chronic UC and the presence of

PSC in Japanese patients.[60] However, the Japanese experts still believed that caution towards the development of CRC for patients with UC comorbid with PSC is necessary.

This statement was created by consolidating expert opinions based on literature evidence. It is meant to extend the previously published international consensus statement,[1] contextualized for Japanese patients with IBD and within the Japanese setting. Thus, it may not be applicable to other settings or to other patients. IBD prognostic factors are clinical and have been mostly based on retrospective studies, many conducted over a decade ago. ELs were based on the literature reviews, and in general, reflect the reporting and study design of the studies cited as opposed to the quality of the results. However, combining the literature review with expert opinion, as well as further identification of Japanese patient-specific studies, allowed for contextualization of the results and suggests potential strategies for implementation into clinical practice in Japan. Nonetheless, the dearth of studies on prognostic factors specifically in Japanese patients with IBD merits caution when applying these statements to clinical practice because most of the studies were performed in Western patients under Western treatment paradigms. Future studies, specifically conducted in Japanese patients, will be more effective in uncovering prognostic factors for patients with IBD.

In conclusion, while there were many similarities in specialists' agreement on prognostic factors between Western patients with IBD and Japanese patients with IBD, certain differences exist, of which clinicians caring for Japanese patients with IBD should be aware.

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AUTHOR CONTRIBUTION

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