

IBD barriers across the continents – East Asia

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Abstract: Inflammatory bowel diseases (IBDs) are chronic illnesses with significant morbidities and impact on patients' quality of life. There has been a rapid increase in the incidence of IBD in East Asia in recent decades. However, there is a huge unmet need in the diagnosis and management of IBD in this region. With the increasing awareness of IBD in East Asia and a persistently high rate of tuberculosis in this region, this poses a significant challenge in the diagnosis and management of IBD. In this review, we will explore the barriers to the diagnosis and management of IBD in the East Asia, hoping to provide an insight on how to improve the healthcare system in the management of this complex disease.

Keywords: barriers, Crohn's disease, inflammatory bowel disease, ulcerative colitis

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Inflammatory bowel diseases (IBDs) are chronic illnesses with significant morbidities and impact on patients' quality of life due to an unpredictable relapsing and remitting course, development of complications, and use of costly therapies. In the 21st century, newly industrialized countries in Asia, South America, and Africa are witnessing a rapidly rising incidence of IBD.¹ With urbanization and industrialization, and accompanying lifestyle changes, these lead to the increasing prevalence of IBD in Asia. It is estimated that the burden of IBD will overtake that of high-income countries in the near future given the large population in Asia. The predicted disease burden is estimated to be 1.3 million in China if the prevalence is 0.1%.²

Similar to other newly industrialized countries, East Asia, which consists of China, Hong Kong and Macau Specialist Administrative Regions, Japan, North Korea and South Korea, and Taiwan,³ also experience a rapid increase in prevalence of IBD. It has been reported that the prevalence of IBD in different countries and regions of Asia ranged from 16.1 to 134.6 per 100,000 population.⁴ However, resources are generally limited in Asia. This poses unique challenges to the diagnosis and management of IBD. In this article, we will review the barriers in IBD management in East Asia. The barriers in IBD

management can be divided into diagnostic and therapeutic challenges.

Diagnostic challenges

High prevalence of infectious diseases which mimic IBD

Tuberculosis is highly prevalent in East Asia, accounting for 43% of cases worldwide.⁵ Intestinal tuberculosis, which mainly affects the ileocecal area in 50–70% of the cases, is the main differential diagnosis of Crohn's disease (CD) in the endemic regions of tuberculosis and is difficult to differentiate from CD.⁶ The diagnostic difficulty in differentiating CD and intestinal tuberculosis creates challenges in the management of IBD in East Asia. The use of immunosuppressants will make underlying tuberculosis worse and might turn it into disseminated tuberculosis while the use of anti-tuberculosis treatment will delay the diagnosis of CD and worsen the prognosis of underlying CD. There is no gold standard test to differentiate the two diseases. Symptoms of intestinal tuberculosis can be very similar to those of CD, including lower abdominal pain, weight loss, and chronic diarrhea.⁷ Besides, active pulmonary tuberculosis on chest X-ray is only found in 20–25% of patients with intestinal tuberculosis.⁷ Tuberculin skin test (TST) has limited value in

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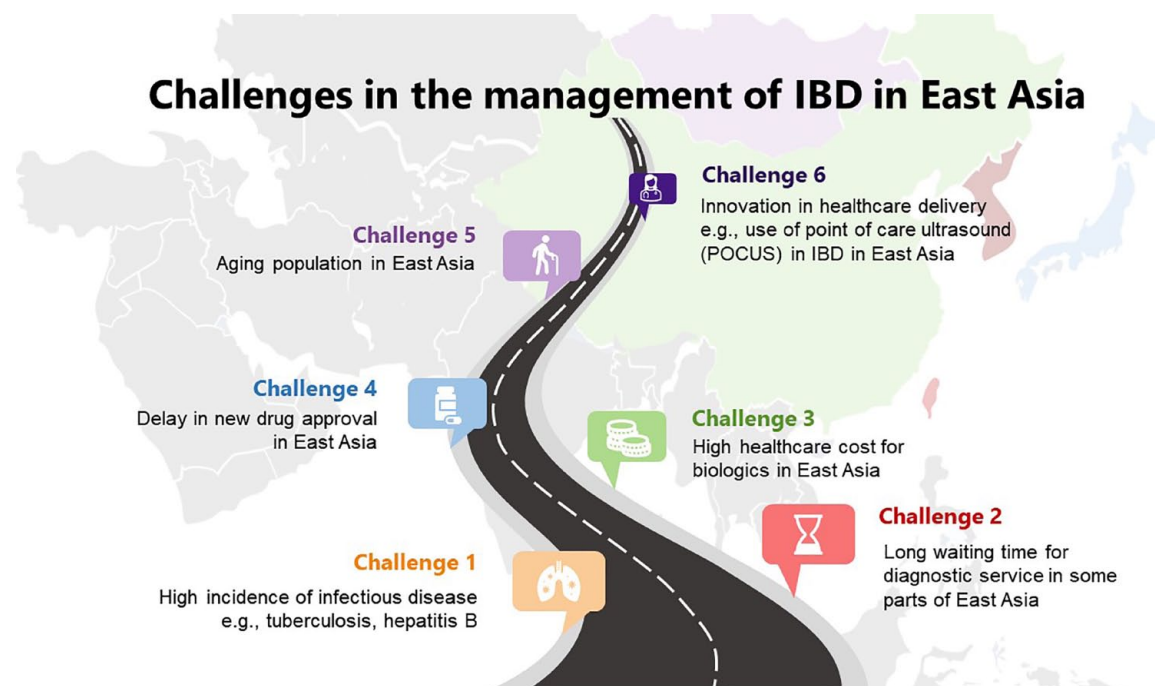


Figure 1. Challenges in the management of IBD in East Asia. IBD, inflammatory bowel disease.

the diagnosis of intestinal tuberculosis, especially in bacille Calmette-Guerin (BCG)-vaccinated populations due to a high false-positive rate.⁸ Interferon- γ release assay (IGRA), which does not cross-react with BCG vaccination or non-tuberculous mycobacteria, can be clinically useful for differentiating intestinal TB and CD. However, its sensitivity is as low as 67% in detecting intestinal TB.⁹ Classical endoscopic features of intestinal tuberculosis (presence of transverse ulcers, pronounced scarring, patulous ileocecal valves)¹⁰ and CD (presence of skip lesions, superficial and aphthous ulcerations, left colonic involvement)¹¹ might be of value in differentiating the two diseases. However, certain endoscopic features, for example, diffuse ulcerations and nodularity can be a feature of both and classical findings are not often present. The presence of caseating granulomas (in contrast to non-caseating granulomas in CD) and acid-fast bacilli under Ziehl-Neelsen stain are diagnostic of intestinal tuberculosis.¹² However, caseating granulomas and acid-fast bacilli were only found in 18–33% of cases of intestinal tuberculosis. Culture of *Mycobacterium tuberculosis* from biopsy is time-consuming (3–8 weeks) with low accuracy (25–35%).¹³ The sensitivity of *M. tuberculosis* polymerase chain reaction (PCR) testing for

extrapulmonary involvement is as low as 47%.¹⁴ Combining clinical, endoscopic and histological features helps improve the diagnostic accuracy of intestinal tuberculosis.¹⁵ However, its application to clinical practice is still limited owing to high rate of misdiagnosis.

Infectious diseases, including bacterial, protozoal, and helminth infestations are highly prevalent in Asia.¹⁶ Infectious colitis is the most common cause of diarrhea in Asia. Certain infections, including yersiniasis, actinomycosis, histoplasmosis, strongyloidiasis, and amebiasis, can also affect the gastrointestinal tract and mimic IBD. Besides, certain sexually transmitted infections, for example, chlamydia, gonorrhoea, herpes simplex virus, and syphilis, also commonly present with symptoms of proctitis among men who have sex with men. These should be considered as a differential diagnosis of IBD in at-risk groups.

Long waiting time for medical care and diagnostic services in certain regions in East Asia

Diagnosis of IBD requires a multidisciplinary approach. This might not be readily available in certain parts in East Asia, especially in rural areas,

resulting in suboptimal care and delay in diagnosis. Besides, there is a huge diversity of healthcare quality in the different regions in Asia due to the economic imbalance. There is a gross disparity between population size and health expenditure in Asian countries, resulting in a very low health expenditure per capita in the entire region, compared with high-income countries.¹⁷ National social health insurance systems are available in China, South Korea, Japan, and Taiwan, which allow universal access to medical care in these regions.¹⁸ However, in some areas, like certain provinces in China, patients are still required to pay 20% of the charges for endoscopy¹⁹ and the capacity for colonoscopy is limited in certain regions in China.²⁰ This limits patients' access to endoscopy service, leading to delayed diagnosis. Instead of social health insurance, Hong Kong is running a two-tiered health system where the public sector is financed by general tax revenue by the government and the private sector is financed primarily by out-of-pocket payments and limited private insurance. There is universal access to care; free or subsidized, good-quality public-sector services are available in Hong Kong. However, there is inequitable access to private care service in Hong Kong due to cost concern. The public system in Hong Kong provides 90% of inpatient services and 30% of outpatient services.²¹ In fact, more than 90% of the IBD patients in Hong Kong are being managed in the public sector.²² However, this creates a huge burden and long queue for colonoscopy and radiology service in the public sector, causing delay in diagnosis. It was reported that the waiting time for colonoscopy in Hong Kong is more than 1 year.²³ Thus, long waiting time for medical care is a challenge for IBD diagnosis in some parts of East Asia, especially in Hong Kong and some parts of China.

Challenges in making a correct diagnosis of IBD

With the changing epidemiology of tuberculosis and CD, together with the rising awareness of IBD in East Asia, general practitioners and gastrointestinal specialists in Asia have an increasing awareness of CD rather than intestinal TB. In addition, with the decreasing incidence of TB, cases of intestinal tuberculosis may be misdiagnosed as CD. In fact, a recent Korean study has shown that the rate of misdiagnosing CD as intestinal TB has been decreasing, whereas the rate of misdiagnosing intestinal TB as CD has been increasing over the past two decades. In 1996, a

total of 34.3% of CD patients were misdiagnosed initially as intestinal tuberculosis, but the proportion of misdiagnosed cases decreased to 8.1% in 2014. The rate of misdiagnosing CD as intestinal tuberculosis showed a significant decrease over the last two decades. No patient with intestinal tuberculosis was misdiagnosed initially as having CD in 1996, but 15.6% were misdiagnosed initially as having CD in 2014, revealing a significant increase in the rate of misdiagnosing intestinal tuberculosis as CD over the last two decades.²⁴ The misdiagnosis between CD and intestinal tuberculosis and inappropriate treatments based on the misdiagnosis could cause serious harm to patients. The inappropriate use of corticosteroids and immunosuppressants in intestinal tuberculosis misdiagnosed as having CD could have led to disseminated tuberculosis, which is potentially life-threatening. In another series from Japan, 10 out of 66 intestinal tuberculosis patients were initially misdiagnosed as having IBD, of which two received intestinal resection and one died of respiratory failure due to tuberculosis due to inappropriate use of corticosteroids.²⁵ In another single center study in Korea, 13.8% of the patients who were initially diagnosed with IBD had a change in diagnosis to non-IBD disease, with the most common updated diagnosis being acute self-limited colitis and 46.2% of these misdiagnosed patients received IBD-related medications.²⁶ Therefore, physicians should have a careful assessment of patients and patients with a questionable diagnosis of IBD should be carefully observed at follow-up, and caution should be exercised by physicians during the administration of any medications.

High prevalence of Behcet's in Asia which mimic IBD

Another minor issue in diagnostic challenge of IBD in East Asia is the presence of Behcet's syndrome. Behcet's syndrome is a primary vasculitis that can involve vessels of all size and is most prevalent along the Mediterranean basin, an area referred to as the 'Silk Road'²⁷ which links up the West and China. It is diagnosed clinically by the International Study Group for Behcet's Disease: the presence of recurrent oral ulcers plus two of the followings: recurrent genital ulcers, eye lesions (e.g. uveitis), skin lesions, and a positive pathergy test.²⁸ The gastrointestinal tract is also commonly involved in Behcet's disease. In fact, both Intestinal Behcet's and CD have a young age of

onset, similar extraintestinal manifestations, and a chronic, relapsing and remitting course, making it difficult for physicians to differentiate the two diseases. Intestinal Behcet's typically affects the ileocecal region and is characterized by presence of solitary large ulcers (>2 cm) and punched-out ulcers.²⁷ On histology, the surrounding tissue is not inflamed in patients with intestinal Behcet's, aiding the differential diagnosis.

Therapeutic challenges

High prevalence of opportunistic infections

It is well recognized that the use of immunomodulators, particularly in combination, increases the risk of opportunistic infection.^{29,30} Advanced age also increases risk of serious infection. It was shown that risk of serious infection in patients over 65 years old was two- to threefolds greater than younger patients.³¹ Anti-tumor necrosis factor alpha (anti-TNF- α), which is most commonly available and used in East Asia, was reported to be associated with 0.9% of opportunistic infections, as compared with 0.3% in patients given placebo.³²

Tuberculosis and hepatitis B are highly prevalent in East Asia.^{5,33} Patients with tuberculosis in East Asia account for 43% of cases worldwide,⁵ in which, a significant portion of patients have latent tuberculosis. Anti-TNF agents are associated with two- to eightfold increased risk of active tuberculosis.^{34,35} The risk varies among different underlying disease and the anti-TNF agents used.^{36,37} According to a Korean national database,³⁸ the incidence of tuberculosis is highest in IBD patients, followed by rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Higher risk was found with use of monoclonal antibodies such as infliximab and adalimumab than soluble TNF receptor antagonist etanercept.^{36,37} The risk further increases when anti-TNF agents were used in combination with methotrexate or azathioprine.³⁹ Relatively, other biologics such as ustekinumab and vedolizumab, have lower rates of latent tuberculosis reactivation.⁴⁰ Tuberculosis infection can be disseminated and fatal.³⁶ Therefore, with the high popularity of anti-TNF agents in East Asia, reactivation of latent tuberculosis is a main concern before biologics initiation.

Thorough screening for latent tuberculosis is thus, highly recommended in Asia before

commencing biologics therapy. There is no gold standard for the diagnosis of latent tuberculosis. In general, the evaluation is based on epidemiological risk factor, history, physical examination, and investigations such as chest radiography, TST, and/or IGRA. According to a survey study performed by the Asian Crohn's and Colitis Organization in 2017, most Asian countries performed well in testing for latent tuberculosis before initiation of anti-TNF therapy and the documentation of IBD.⁴¹ Biologics are delayed until latent or active tuberculosis is treated.⁴²

Hepatitis B virus (HBV) prevalence is generally declining over the years. In 2019, HBV in South-East Asia was still prevalent at 3.1%.⁴³ This trend was also observed in IBD patients.⁴⁴ The disease course of IBD in patients with HBV infection is however unknown. Current guidelines recommend screening for HBV at the time of IBD diagnosis by testing hepatitis B surface antibody, hepatitis B surface antigen, and hepatitis B core antibody.⁴⁵ Patients with chronic hepatitis B infection should receive antiviral therapy at least 2 weeks before biologics. Immunosuppressants are to be withheld in case of HBV reactivation.⁴⁶

Drug lag

The latest adopted treat-to-target strategy for managing IBD patients suggests reaching individualized treatment targets such as endoscopic remission and mucosal healing by early introduction of optimal therapies such as biologics.⁴⁷ Multiple clinical trials showed that early biologic initiation is superior to immunomodulators in disease control.^{48,49}

In recent decades, more novel pharmacological treatments have emerged and passed the clinical phase III trials.⁵⁰ However, in Hong Kong,⁵¹ for example, only four biologics including infliximab, adalimumab, ustekinumab, and vedolizumab, are approved for the treatment of CD and ulcerative colitis (UC). Just recently, the Janus kinase inhibitor, tofacitinib, was approved for the treatment of UC in Hong Kong. Okabayashi *et al.*⁵² demonstrated the drug lag in Asia – the relative drug lag from the drug first approval for CD and UC was 13.2 and 16.5 months in South Korea, 42.1 and 53.9 months in Taiwan. The delay in drug

approval in East Asia has limited physicians' and patients' choices of the treatment regime.

High healthcare cost

The substantial cost of immunomodulators or biologics is not affordable by every patient and has imposed a heavy burden on the healthcare system in East Asia.⁵³ The COIN study showed that, the healthcare cost largely shifted from hospitalization and surgery to the use of biologics such as anti-TNF therapy in recent years.⁵⁴ These treatment costs, currently, can be up to US \$25,000 per patient-year.⁵⁵ A recent population-based study on healthcare costs by Korea⁵⁶ showed that the costs for biologics escalated over time, increasing from \$720.8 in the first year after diagnosis to \$1249.6 in the third year of diagnosis. With the increasing incidence of IBD, together with the advancement of newer generation of biologics or novel therapies, it is expected that the future treatment cost will further rise.

In Asia, the public health insurance coverage varies among countries. Unfortunately, a number of items required in the management of IBD are not covered by health insurance.⁵³ Fecal calprotectin is available in clinical practice yet remains to be a self-financed item in areas such as Hong Kong, with a cost of around US \$40–80.⁵⁵ Conventional therapies such as 5-aminosalicylic acid, steroids, and immunomodulators are paid by the public health system in Hong Kong and the national health insurance in Taiwan while patients in Japan and South Korea have to co-pay for these drugs.⁵⁷ In Taiwan and Hong Kong, biologics are covered by the government or the national health insurance if certain indications are met,^{55,57} while in China, Japan, and South Korea, patients have to co-pay for the use of biologics. The co-payment policies vary among countries, also across the provinces in China.⁵⁷ However, in Taiwan, the reimbursement policy only last for 1 year and it is mandatory for patients to stop biologics for 3 months after 1 year before they can apply for reimbursement again while in Hong Kong, the government will cover the cost of biologics indefinitely once criteria are met. This diversity in healthcare system has led to a highly variable quality of healthcare in Asia. It is essential not only to establish comprehensive measures that reduce short-term IBD costs, but also a sustainable healthcare system to support long-term management of this chronic disease.

Variable local guidelines

International diagnostic criteria and management guidelines from America and Europe are commonly used as reference in managing IBD in Asia. Despite westernization and environmental triggers in the western populations such as diet and physical activity, play a crucial role in the escalating IBD prevalence in Asia, there are marked differences in clinical manifestations, genetic risk factors, and gut microbiome in IBD patients between the East and West.^{4,58–60} CD has a male predominance and more perianal involvement in Asia. There is a lower colectomy rate in UC in Asia as compared to the West.^{61–63} The differences in genetic background between the East and West also contribute to the diversity in disease phenotype and pharmacological management of IBD. Nucleotide oligomerization domain (NOD2) variants is a strong predictor of early onset of CD.⁶⁴ However, it was not found in many Asian ethnicities.⁶¹ The enzyme nudix hydrolase 15 (NUDT15) is a better predictor than thiopurine methyltransferase to thiopurine-induced leukopenia in Asia.⁶⁵ These differences demonstrate the importance of guidelines specific for Asia IBD patients.

Years ago, the main challenge in formulating local guidelines is the lack of structured and large-scale population-based cohorts originating in Asia.⁵⁹ The incidence rates of traditionally prevalent areas such as the United States and Europe has reached a plateau while the incidence of IBD is still rapidly emerging in newly industrialized areas since 1990.⁴ Many Asian countries also do not have a national registry for IBD patients. This has led to scarcity and a significant variety of data resources^{66,67} which increases the bias in the small cohort or cross-sectional studies that were based on the hospital data.⁶⁷

With IBD being more recognized in East Asian countries, more guidelines and consensus are developed by the local committees, for example, the Taiwan Society of Inflammatory Bowel Disease, the Korean Association for the Study of Intestinal Diseases, the Japanese Society of Gastroenterology, to guide the diagnosis and management, with reference to the national population-based studies and current evidence.^{68–70} Recently, the Asian Organization for Crohn's and Colitis (AOCC) and Asia Pacific Association of Gastroenterology (APAGE) practice have jointly

published a consensus on medical management and monitoring for IBD in Asia as well.⁶¹

The treatment target and management of IBD in East Asia are principally in concordance with the West. Yet, there are also some unique management strategies in different countries across East Asia. For example, the clinical practice guidelines by the Japanese Society of Gastroenterology have recommended cytopheresis (CAP) for induction of remission in moderate to severe UC or colonic CD patients who fail pharmacotherapy or nutrition therapy, with acknowledgment of the heterogeneity in evidence. The two available methods of CAP – granulocyte monocyte apheresis and leukocytapheresis are accepted by the ministry of Labour and Welfare of Japan and are covered by insurance in Japan for patients with moderate to severe UC.^{71,72} Based on the primary goal of CAP to deplete effector cells of the intestinal inflammatory response, this non-pharmacological extracorporeal therapy has been gaining evidence in its efficacy in UC treatment with excellent safety profile.^{72–74}

Recently, the AOCC and APAGE practice have jointly published a consensus on medical management and monitoring for IBD in Asia as well.⁶¹ With the development on more structured recommendations, these have shed lights on management targeting the Asia IBD patients. More comprehensive epidemiological studies and high-quality clinical data will help further formulation of targeted guidelines to not only address the differences in the IBD diagnosis and management between the West and the East, but also provide more insights into the decision-making process under different medical systems.

Development of multidisciplinary management

IBD is a chronic inflammatory disorder encompassing a spectrum of manifestations requiring management from different aspects instead of mere disease activity control by medical therapy.

Despite the biologics era leading to more effective IBD management and lower rates of colectomy,⁷⁵ surgery still plays a major role in complicated phenotype, for example in stricturing or fistulating CD and complex IBD patients with suboptimal response to medical therapy and refractory disease course.^{76,77} On the other hand, malnutrition which is worsened at the time of disease

flare-up, is known to be associated with worse prognosis, increased complication rates and increased mortality.⁷⁸ Special diets such as exclusive enteral nutrition, specific carbohydrate diet, anti-inflammatory diet for IBD, fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) are proven to have positive effects on the control of IBD.⁷⁹ Apart from that, the disease course is uncertain with characteristics of relapsing and remitting and is potentially disabling. This has led to substantial socio-economic impact.⁵⁴ Controversies remain on whether psychological disorders, such as anxiety and depression, are consequences of or precede IBD.⁸⁰ But it is understood that psychological issues play a crucial role in IBD.

Therefore, a multidisciplinary approach consisting of not only gastroenterologists, but also colorectal surgeons, pharmacists, specialized dietitians, radiologists, IBD nurse, psychologists, and social workers is encouraged and is widely accepted worldwide^{81–83} to provide holistic and tailor-made management for IBD patients. It has been reported that IBD patients managed by multidisciplinary team approach with interdisciplinary conference has good outcome, particularly for IBD patients with complex disease.⁸²

The implementation of multidisciplinary team in Asia for IBD patients is challenging. The health-care delivery and financing are heterogeneous in Asia. Large-scale managed care is therefore scarce in certain regions in East Asia.^{53,84} In more developed regions in East Asia, like South Korea, Japan, Hong Kong, and Taiwan, there is already establishment of multidisciplinary teams that include gastroenterologists, surgeons, radiologists, histopathologists, dietitians, dedicated IBD nurses, and pediatricians in tertiary centers, although not in all hospitals.^{69,85,86} The management of IBD patients still relies heavily on gastroenterologists, with involvement of other specialties by on-demand basis only in certain parts of East Asia. Not every center has all the professionals, especially in the less developed regions of East Asia. With the increasing prevalence of IBD in Asia,² more widely available multidisciplinary teams are urgently needed to provide a more all-rounded care for IBD patients. The promotion of successful implementation of multidisciplinary team management of IBD will enhance its development in other centers, improving the quality of care to IBD patients.

Future perspectives

Most East Asian countries are now in the stage of accelerated incidence in IBD. However, it is anticipated that, in the impending future, the patient population in East Asia will pick up the trend of aging, entering into the compound prevalence stage as in the West.³ It is estimated that by 2050, one in three people in East Asia would be over the age of 65, according to the United Nations World Population Prospects.⁸⁷ Healthcare professionals in East Asia do not only have to be prepared for the rising number of cases of IBD, but also to manage IBD in an older population with multiple age-related comorbidities. In order to manage IBD efficiently and effectively, it is crucial to unwind the current diagnostic and therapeutic challenges. With IBD being more recognized in East Asia in recent years, more readily available local guidelines and more advanced therapies have been implemented in many countries of East Asia. However, the unique nature of East Asia makes the diagnosis and management of IBD remain challenging. For example, the high prevalence of tuberculosis increases the difficulty in diagnosis of IBD and delays treatment initiation.

Point of care ultrasound (POCUS) has been implemented in Europe and North America as part of the management protocol of IBD. However, this is still under-used in most parts of East Asia. Introducing POCUS in East Asia can help alleviate the burden of radiology service in East Asia. In fact, certain parts of East Asia, like Japan, has been pioneering in the use of intestinal ultrasound (IUS) in IBD¹⁸ in East Asia. However, in other parts of East Asia, there are still barriers for its regular use in clinical practice. These include the lack of experience and established centers with well-developed training programs in some parts of East Asia.²⁰ Establishment of centers for formal training and collaborative research amongst different East Asian countries would aid in raising the awareness and utility of IUS in daily clinical practice in East Asia. Prompt actions and adequate support by the healthcare policy makers in maintaining a sustainable healthcare system will undoubtedly facilitate the healthcare parties in improving the diagnosis and treatment of IBD. Along with the close collaboration between the IBD experts across East Asia, more population-based epidemiological database will guide the formulation of guidelines targeting the East Asia population.

Conclusion

The incidence of IBD has been rising rapidly in East Asia. Over the years, we have been improving awareness and care for IBD. However, significant challenges including high prevalence of tuberculosis, high healthcare cost, and the aging population in East Asia, still make the management of IBD challenging. New collaborative research on gut microbiome and environmental determinants on IBD disease prevention are now underway to decelerate the slope of increasing prevalence of IBD in East Asia.²³ Innovative healthcare delivery such as enhancement of multidisciplinary model, development of big data and artificial intelligence, should be developed in East Asia to improve monitoring and treatment of IBD. Multi-pronged efforts from healthcare policy makers, healthcare experts, local committees, and researchers will be essential for East Asia to overcome its distinctive challenges in IBD diagnosis and management.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Joyce Wing Yan Mak: Conceptualization; Writing – original draft; Writing – review & editing.

Agnes Hiu Yan Ho: Conceptualization; Writing – original draft.

Siew Chien Ng: Conceptualization; Supervision; Writing – review & editing.

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