

# World Journal of *Gastroenterology*

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## Epidemiological and clinical perspectives on irritable bowel syndrome in India, Bangladesh and Malaysia: A review

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### Abstract

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder, common in clinic and in the community. It has a significant impact on both society and patients' quality of life. The epidemiology, clinical presentation, and management of IBS may vary in different geographical regions due to differences in diet, gastrointestinal infection, socio-cultural and psychosocial factors, religious and illness beliefs, symptom perception and reporting. Although previous reviews and consensus reports on IBS in Asia have been published, Asia is quite diverse socio-demographically. In this context, India, Bangladesh and Malaysia share some similarities, including: (1) large proportion of the population living in rural areas; (2) rapid development and associated lifestyle changes in urban areas; and (3) dietary, cultural and religious practices. The present review explores the clinical and epidemiological data on IBS from these three major nations in South and South-East Asia. In-depth review of the literature revealed important differences between IBS in the East, as revealed by studies from these three countries, and the West; these include a predominantly rural profile, differences in bowel habit and symptom profile, raising concern with regards to diagnostic criteria and subtyping of IBS, higher dietary fiber consumption, frequent lactose malabsorption, parasitosis, and possible overlap between post-infectious IBS and tropical sprue. Moreover, the current perception on difference in prevalence of the disorder in these countries, as compared to the West, might be related to variation in survey methods.

**Key words:** Epidemiology; Functional gastrointestinal



disorders; Irritable bowel syndrome; Asia; Symptom; Constipation; Diarrhea

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**Core tip:** The epidemiology, clinical presentation and management of irritable bowel syndrome (IBS) may vary in different geographical regions due to differences in diet, gastrointestinal infection and infestations, socio-cultural and psycho-social factors, religious and illness beliefs, symptom perception and reporting. Asia is geographically and socio-demographically diverse. In this context, India, Bangladesh and Malaysia share some similarities: (1) large population living in rural areas; (2) rapid development and associated lifestyle changes in urban areas; and (3) dietary, cultural and religious practices. The present review aims to explore clinical and epidemiological data on IBS from these three major nations in South and South-East Asia.

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## INTRODUCTION

Irritable bowel syndrome (IBS) is a bowel disorder in which chronic abdominal pain or discomfort (the latter having been removed in the Rome IV criteria) is associated with irregularity in stool form and passage in the absence of any organic cause<sup>[1]</sup>. IBS has a significant impact on patients' quality of life due to physical suffering, psychological co-morbidity, social disability and economic non-productivity<sup>[2,3]</sup>. Though the global pooled prevalence of IBS has been estimated to be 11.2%<sup>[4]</sup>, this figure has been questioned due to significant heterogeneity in published studies<sup>[5]</sup>. The prevalence, however, may be lower in the East. As the pathophysiology of IBS is poorly understood, the management generally focuses on the amelioration of symptoms and improvement in the quality of life. At present, the drugs available for the treatment of IBS have only a modest effect on symptom improvement and may not alter the natural history of the condition. The management strategy recommends a positive diagnosis, consideration of the patients' perspective, development of a good doctor patient relationship, identification of contributing factors, critical appraisal of the efficacies of various drugs according to the subtype of IBS and continuing care<sup>[6-8]</sup>.

In view of the recent and growing interest in the gut microbiome and gastrointestinal (GI) diseases, including IBS, data from Asian research (where

infection and infestations are common) may be able to offer specific epidemiological insight. Although previous reviews and consensus reports on IBS in Asia have been published<sup>[8]</sup>, Asia remains a geographically and socio-demographically diverse region. Furthermore, a significant portion of the population in Asia live in rural areas, but data from rural epidemiological studies are scant. In this context, India, Bangladesh and Malaysia, three major nations in the South and South East region of Asia, share some similarities: (1) significant proportions of their populations residing in rural areas; (2) rapid development and associated lifestyle changes in urban areas; and (3) dietary, cultural and religious practices that are somewhat similar. Another similarity between these three countries is the language used for medical education and scientific publications. Since the medical education in these three countries are in the English language and the scientific studies are also published in English, local languages were not needed for data extraction from published literature. Hence, the present review aims to explore clinical and epidemiological data on IBS from a South and South-East Asian perspective.

## EPIDEMIOLOGY

### Prevalence

Several population-based studies have been conducted to explore the epidemiology of IBS in India, Bangladesh, and Malaysia using different diagnostic criteria (Table 1 and Figure 1). In contrast to several studies from the West, most of which are either internet and telephone surveys with their inherent bias, the majority of the eastern studies were house-to-house surveys. Based on these studies, the reported prevalence of IBS varies from 4.2%-7.5%, 7.7%-12.9% and 11%-14% in India<sup>[9-12]</sup>, Bangladesh<sup>[13-15]</sup> and Malaysia<sup>[16,17]</sup>, respectively.

In addition to the studies summarized in Table 1, a few house-to-house surveys, conducted primarily on chronic constipation, provided data on constipation-predominant IBS (IBS-C) as well. In a house-to-house survey among 505 subjects aged 9-64 years from Chandigarh, India the prevalence of constipation by Rome II criteria was 16.8%<sup>[18]</sup>. In another Indian study among 925 constipated patients presenting to general physicians, 75.6% had functional constipation and 24.4% had IBS-C<sup>[19]</sup>. It has been reported that the prevalence of IBS in Asian countries is rising, with more developed nations, such as Japan and Singapore, documenting a comparable prevalence to that in western countries<sup>[20]</sup>.

These data suggest that IBS might be related to economic development associated with lifestyle changes, fast living, and psychological stress associated with reduced T regulatory cell response. However, the differences in prevalence across the three countries and within the countries may be a result of variation in the

**Table 1** Prevalence of irritable bowel syndrome in India, Bangladesh and Malaysia

Ref.	Study site	Sample size	Study type	Criteria	Prevalence	Male/female ratio
Shah <i>et al</i> <sup>[9]</sup>	Mumbai, India Urban	2549	Community/healthy subjects	Manning	7.5%	1/0.87
Ghoshal <i>et al</i> <sup>[10]</sup>	Multiple sites, India	4500	Community	Clinical	4.2%	1/0.93
Makharia <i>et al</i> <sup>[11]</sup>	Haryana, India	4767	Community	Rome III	4%	1/1.5
Ghoshal <i>et al</i> <sup>[12]</sup>	Uttar Pradesh, India, rural	2876	Community	Rome III	6.8%	1/1.09
Masud <i>et al</i> <sup>[13]</sup>	Natore, Bangladesh Rural	2426	Community	Rome I	8.5%	1/1.84
Perveen <i>et al</i> <sup>[14]</sup>	Dhaka, Bangladesh, urban	1503	Community	Rome II	7.7%	1/1.28
Perveen <i>et al</i> <sup>[15]</sup>	Sylhet, Bangladesh urban and rural	3000	Community	Rome III	12.9%	1/1.09
Rajendra <i>et al</i> <sup>[16]</sup>	West coast, Malaysia, urban	1179	Community	Rome II	14%	1/1.4
Lee <i>et al</i> <sup>[17]</sup>	East coast, Malaysia rural		Community	Rome III	10.9%	1/1.18

diagnostic criteria used, socio-demographic differences in the populations studied, survey methods and the study instrument. A previous systematic review and meta-analysis of 260960 subjects from 80 studies across the globe suggested that the pooled prevalence of IBS of all studies was 11.2% (95% confidence interval (CI): 9.8%-12.8%)<sup>[4]</sup>. However, a more recent systematic review and meta-analysis demonstrated that the estimation of global prevalence of IBS may be inaccurate due to significant heterogeneity between the studies<sup>[5]</sup>.

### Urban versus rural prevalence

An urban lifestyle is reported to be associated with greater psychological stress, and thus may be associated with a higher prevalence of IBS compared to rural living. Community-based epidemiological studies on IBS have been published both from the urban and rural population in India, Bangladesh and Malaysia. Rural surveys in India have demonstrated an IBS prevalence of 4.2% (Rome III criteria) among 2774 subjects in three villages of Uttar Pradesh, the northern part of India<sup>[12]</sup>, and 4% (Rome III criteria) in another northern Indian study<sup>[11]</sup>. In Bangladesh, an IBS prevalence of 8.5% (Rome I criteria) was reported from a rural household survey among 2426 subjects<sup>[13]</sup>. In the East Coast of Peninsular Malaysia, a 10.9% prevalence of IBS (Rome III criteria) was documented among rural subjects of Malay ethnicity<sup>[17]</sup>.

Interestingly, urban surveys in these three countries did not show a significant variation in the prevalence of IBS from the rural communities. A 7.7% prevalence of IBS (using the Manning criteria) was observed among 2549 randomly selected subjects in urban Mumbai, India<sup>[9]</sup>, while an IBS prevalence of 7.7% (Rome II criteria) was reported in a survey of 1503 adult subjects in Dhaka city, Bangladesh<sup>[14]</sup>. In the West Coast of Peninsular Malaysia, investigators reported a relatively high prevalence rate of IBS at 14% (Rome II criteria) among 1179 multi-ethnic adult subjects in an urban setting, but not much higher than

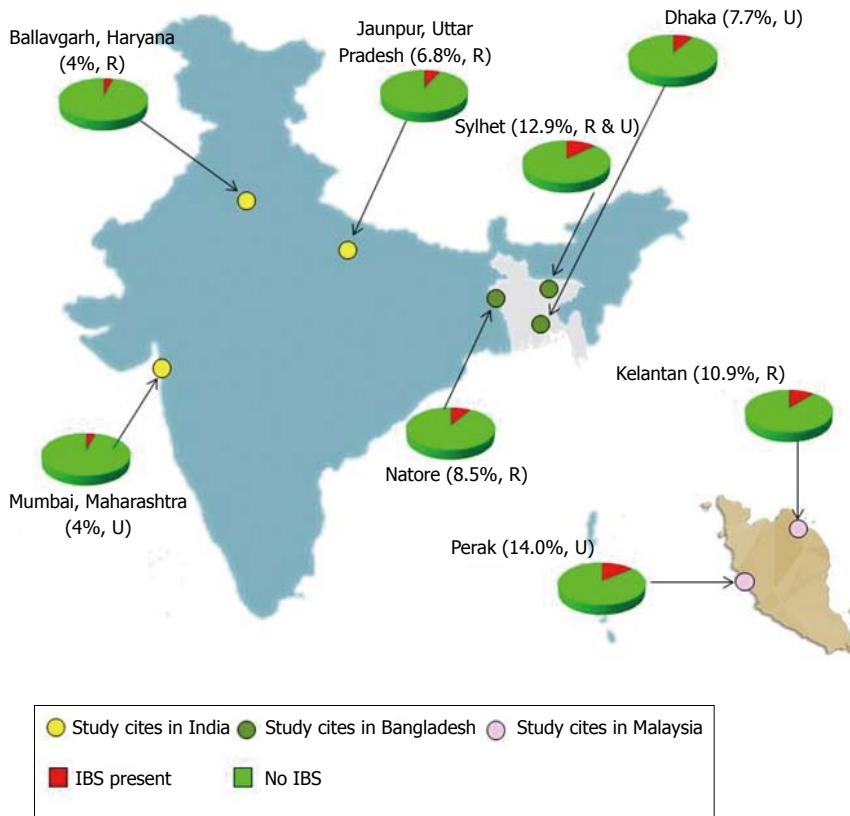
the previous rural study<sup>[17]</sup>. In this multi-ethnic study, there were no differences in prevalence among ethnic Malays, ethnic Chinese and ethnic southern Indians, who were of comparable socio-demographic status<sup>[17]</sup>.

The observations from these studies in South Asia appear to contrast with reports, which indicate that IBS is more common in urban as compared to rural populations<sup>[21-23]</sup>. Population-based studies comparing prevalence of IBS in urban and rural communities have shown differences in Chinese (urban 10.5% vs rural 6.14%)<sup>[21]</sup>, Israeli Bedouins (9.4% vs 5.8%,  $P < 0.01$ )<sup>[22]</sup> and Italians (urban 9.9% vs rural 4.4%)<sup>[23]</sup>. It is uncertain if the lack of difference in IBS prevalence between urban and rural communities highlighted in this review of Indian, Bangladeshi and Malaysian studies is related to lack of head-to-head comparison using uniform diagnostic criteria and study design. Furthermore, previous population studies in Malaysia, using similar methodologies and diagnostic criteria (Rome II) have shown significant differences in the prevalence of uninvestigated dyspepsia between urban and rural communities<sup>[24]</sup>.

### Sex-related issues

Early institution-based studies from India showed that IBS was 2-4 times more common among male adults compared to female adults<sup>[25-27]</sup> but subsequent population-based studies revealed mixed findings. The male:female ratios in relation to the prevalence of IBS in India, Bangladesh and Malaysia are highlighted in Table 1. It is important to note that among all these studies that reported female predominance from these three Asian countries, female to male ratios were not as wide as reported from the West. The lack of an obvious female predominance amongst IBS subjects appears to be common in several Asian reports<sup>[8,20,28-30]</sup>. This is in contrast to the studies from the West, which consistently reported 2-3 times greater prevalence of IBS in women than in men<sup>[3]</sup>.

Although a meta-analysis of community-based studies reported that IBS is 67% higher in females



**Figure 1** Map of India, Bangladesh and Malaysia showing sites of epidemiological studies on IBS in these countries and its prevalence. IBS: Irritable bowel syndrome; R: Rural; U: Urban.

compared to males (OR = 1.67; 95%CI: 1.53-1.82), no significant sex-related differences were observed in South Asia<sup>[4]</sup>. A recent meta-analysis on a Global prevalence of IBS found that the pooled prevalence rates were higher among females (10.2%) compared to males (8.8%). The prevalence rates of IBS were higher among females than males in each region of the globe separately<sup>[5]</sup>. However, as the authors of this meta-analysis acknowledged that due to significant heterogeneity in the number of available studies in different parts of the world and the methods, pooled estimates are expected to be biased.

## SYMPTOM PROFILE AND DIAGNOSIS OF IBS

The Rome criteria are currently the most widely accepted for establishing a diagnosis of IBS. However, studies from India and Bangladesh have reported that frequency and/or severity of abdominal pain, a cardinal symptom in the Rome criteria, may not be so common among their population with IBS. A multi-centric study involving 2785 patients visiting physicians at 30 centers across India with chronic lower GI symptoms, no 'alarm features' and negative investigations for organic causes has been published; in that study, abdominal pain and discomfort was present in only 70% of subjects<sup>[10]</sup>. Other institution-based studies on

IBS subjects from India have reported abdominal pain in a range from 33%<sup>[31]</sup> to 70%<sup>[32]</sup>. As abdominal pain is a pre-requisite for the symptom-based diagnosis of IBS by the Rome criteria, these criteria may have a low sensitivity for diagnosing IBS in India.

In another multi-center, Indian study (MIIBS) using various diagnostic criteria for IBS, the Manning criteria had the highest sensitivity (91%), followed by Asian criteria (74.5%), Rome I (68%), Rome III (52.5%) and Rome II (40%) to diagnose IBS<sup>[33]</sup>. The higher sensitivity of the Manning and Asian criteria might have been due to the fact that "abdominal pain" was not absolutely necessary for the diagnosis of IBS by both of these criteria. Furthermore, "abdominal bloating" had been included in combination with "abdominal pain or discomfort" by the Asian criteria<sup>[8]</sup>. When multiple diagnostic criteria were applied in a rural population in Bangladesh, IBS prevalence of 1.8%, 7.3%, 8.8%, and 7.7% was found using Manning  $\geq 3$ , Manning  $\geq 2$ , Rome I and Rome II criteria, respectively. The IBS prevalence varied according to the criteria applied, with rates as high as 27.9% using "Manning  $\geq 2$  without pain" and down to 1.8% using "pain with Manning  $\geq 3$ "<sup>[34]</sup>.

A systematic review previously demonstrated that the Rome II criteria had a poor sensitivity for diagnosing IBS in primary care, ranging between 31% to 65%, with the lowest sensitivity rates derived from studies in India<sup>[35]</sup>. The lack of accuracy of a



symptom-based criterion for diagnosing IBS may be more relevant for patients in India and Bangladesh for at least two reasons. Firstly, IBS patients often do not report abdominal pain as the predominant symptom in this region. Secondly, these criteria were originally developed and validated in Western populations, who are known to differ from Eastern populations with regard to socio-cultural issues, language, symptom perception and epidemiology<sup>[36]</sup>. Considering the fact that the Rome IV criteria did not include even abdominal discomfort or bloating as the essential symptom to diagnose IBS (Table 2), the sensitivity of the Rome IV criteria is expected to be lower in these three countries<sup>[37]</sup>.

A recent study by the Rome Foundation-Asian working team<sup>[38]</sup> on 1805 consecutive unselected functional gastrointestinal disorder patients presenting to the primary or secondary care centers in 11 Asian centers using a culturally adapted Rome III Diagnostic Questionnaire initially translated and validated in 9 Asian languages<sup>[39,40]</sup> identified 9 symptom clusters by principal component factor analysis with varimax rotation. Authors concluded that though IBS and chronic constipation were the dominant symptom clusters, bowel symptom cluster with meal trigger and a gas cluster were the other prominent groups that were in line with the old Asian concept that identified epigastric localization of pain, and emphasized meal- and gas-related symptoms<sup>[41]</sup>.

### **Upper abdominal symptoms and overlap with functional dyspepsia in IBS**

IBS and functional dyspepsia (FD) have common pathophysiological mechanisms, like visceral hypersensitivity, abnormal central processing of sensory perception, GI dysmotility and psychological factors; these two disorders are, therefore, expected to coexist<sup>[42]</sup>. Figure 2 shows the prevalence of IBS-FD overlap, IBS and FD in three population-based studies in India and Bangladesh<sup>[9,12,15]</sup>. These population-based studies from India and Bangladesh demonstrated that 3.5% to 4.5% of the general adult population of India and Bangladesh have dyspepsia-IBS overlap (Figure 2). In a community-based survey conducted among 3000 people in rural and urban populations in a district of Bangladesh, 42% of FD subjects had IBS and 27% IBS subjects had FD. Overall, bowel symptom frequency scores were higher in IBS-FD than IBS alone ( $10.01 \pm 4.17$  vs  $8.16 \pm 3.84$ ,  $P < 0.000$ )<sup>[15]</sup>.

In an urban survey of adults from Malaysia, subjects with IBS were more likely to report symptoms of gastroesophageal reflux disease (GERD) compared to healthy controls [56% vs 29%, odds ratio (OR) = 3.06]<sup>[16]</sup>. Environmental factors such as diet may be a contributory factor for upper GI symptoms in IBS sufferers among South Asians. In a study in Mumbai, India, > 99% of the population consumed chili in their diet and 75% of subjects consumed it in a moderate

to high quantity<sup>[9]</sup>. Chili is known to aggravate not only IBS symptoms<sup>[43]</sup> but has been shown to independently predict dyspepsia in a multi-ethnic population in Malaysia<sup>[44]</sup>. Furthermore, GERD and *H. pylori* infection are recognized to be more prevalent among ethnic Indians/South Asians compared to other ethnic groups in Asia<sup>[45,46]</sup>. It is likely that these factors may lead to a greater overlap of IBS-FD and IBS-GERD among South Asians compared to other ethnic groups in Asia.

## **SUBTYPING OF IBS**

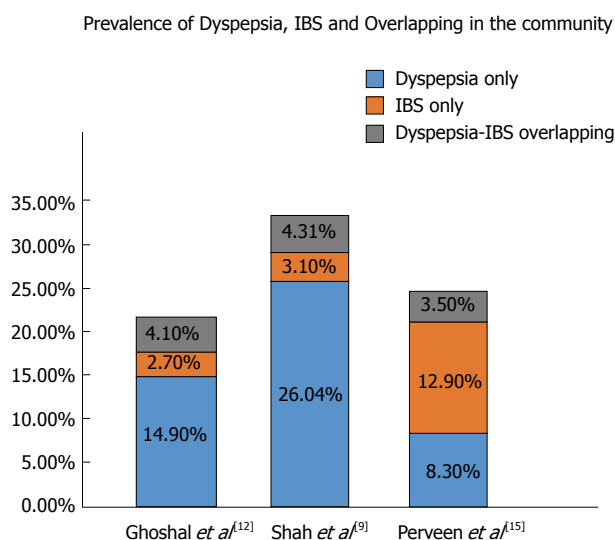
IBS sub-classification into diarrhea- and constipation-predominant (IBS-D and IBS-C, respectively) are important for determining appropriate therapeutic strategies. However, studies in India, Bangladesh and Malaysia have reported that the majority of IBS patients could not be easily classified into distinct sub-types. In a multi-centric Indian study, 53% and 47% of 2656 subjects with lower GI symptoms had subjective perceptions of constipation and diarrhea, respectively<sup>[10]</sup>. However, when stool frequency-based criteria of constipation (stool frequency < 3/wk) and diarrhea (stool frequency > 3/d) were applied to the same subjects, 19% had constipation, 4% had diarrhea and 57% had indeterminate symptoms. In that study, the median stool frequency was similar (2 times/d) in patients who had perceived themselves to have either constipation or diarrhea<sup>[10]</sup>.

In a rural community-based study at Uttar Pradesh, northern India, 83% of the IBS subjects remained unclassified using the Rome III criteria. Interestingly, the application of Asian criteria, instead of the Rome III criteria, reduced the indeterminate sub-type of IBS subjects in rural India from 83% to 12%<sup>[12]</sup>. Similarly, the MIIBS study of 1618 subjects with lower GI symptoms found that by stool frequency criteria, 78% subjects remain unclassified, whereas by patient perception and stool form (Bristol stool scale) criteria only 28% and 16% of patients remain unclassified, respectively<sup>[33]</sup>. In a rural study in Bangladesh, 64% of IBS subjects diagnosed by the Rome II criteria could not be sub-typed<sup>[13]</sup>. In Malaysia, a rural survey of ethnic Malays similarly demonstrated that the majority of IBS subjects fell into a "mixed" category with the Rome III criteria as follows: 20.8% IBS-C, 16.7% IBS-D and 58.3% mixed pattern<sup>[17]</sup>.

These studies suggest that several popularly used criteria may be poor at classifying IBS into constipation- and diarrhea-predominant types in Asia. Community-based studies in India and Bangladesh have shown that > 90% of the general population have a bowel motion of at least once per day<sup>[10,47,48]</sup>. These differences in bowel habit between South Asians and Westerners may be due to differences in dietary pattern, fiber intake, intestinal transit time and frequency of lactose malabsorption as compared to the Western population<sup>[49]</sup>. In a study from India,

**Table 2** Rome III and Rome IV criteria for diagnosis of irritable bowel syndrome<sup>[37]</sup>

Rome III criteria	Rome IV criteria
At least 3 mo, with onset at least 6 mo previous to recurrent (at least 3 d/mo) abdominal pain or discomfort associated with 2 or more of the following Improvement with defecation Onset associated with a change of frequency of stool Onset associated with a change in form of stool	Recurrent abdominal pain, on average, at least 1 d per week in the last 3 mo, associated with 2 or more of the following Related to defecation Associated with a change in frequency of stool Associated with a change in form (appearance) of stool

**Figure 2** Prevalence of IBS, dyspepsia and overlap syndromes in community studies in India and Bangladesh. IBS: Irritable bowel syndrome.

the mean fiber intake was found to be similar at 52 g in both IBS and healthy controls<sup>[50]</sup>. This is higher than the recommended daily fiber intake (20-30 g in adults) and actual daily dietary fiber intake (13.3 g) in the West<sup>[51-53]</sup>. Furthermore, the mean intestinal transit time of 39.85 h among northern Indians contrasts significantly to that of 83.4 h in Caucasian adults<sup>[54]</sup>.

## **PATHOPHYSIOLOGICAL INSIGHTS**

### **Inflammation and IBS**

Current evidence suggests that the pathogenesis of IBS is multi-dimensional consisting of gut microbial dysbiosis, including small intestinal bacterial overgrowth (SIBO), visceral hypersensitivity, intestinal mucosal immune activation, dietary intolerance, increased intestinal permeability, abnormal gut-brain interaction including cognitive dysfunction, psychosocial distress and altered GI motility<sup>[55-57]</sup>. Low-grade inflammation plays a major role in the pathophysiology in a subset of patients with IBS<sup>[57]</sup>. This has been explored in several studies in India, Bangladesh and Malaysia. IBS patients in a tertiary care hospital in Bangladesh were found to have a significant increase in chronic inflammatory cells, mast cells and lymphoid follicles compared to control group of healthy subjects ( $P < 0.05$ ). Mast cells but not the number of chronic inflammatory cells, mucosal and submucosal lymphoid follicles,

were significantly increased in post-infectious (PI)-IBS compared to non-PI IBS in that study<sup>[58]</sup>. These findings are in accordance with similar reports of Western IBS patients<sup>[56,59]</sup>. Mast cell activation is associated with epithelial and neuromuscular dysfunction, visceral hypersensitivity, increased epithelial permeability and altered motility<sup>[56,59]</sup>.

In an Indian case-control study including 221 patients with IBS and 273 age- and sex-matched controls, an interleukin (IL)-1 receptor antagonist under-producer genotype was associated with IBS and its over-producer protective. Moreover, higher levels of IL-1 $\alpha$  and IL-1 $\beta$  were found in patients with SIBO, and IL-1 $\alpha$  and IL-1 $\beta$  were associated with bloating and loose stools. The findings of that study clearly show the role of inflammation in the pathogenesis of IBS in general and diarrhea-predominant IBS in particular<sup>[60]</sup>. Several case-control studies, though under-powered, on genetic polymorphisms in candidate pro-/anti-inflammatory and xenobiotic metabolizing genes support the role of inflammation in the pathogenesis of IBS<sup>[61-64]</sup>.

Imbalance in body serotonin (5HT), 95% of which is in the gut, plays a major role in the pathogenesis of IBS, with its deficiency contributing to slow gut transit and constipation, and excess causing diarrhea<sup>[65]</sup>. In an Indian case-control study, SLC6A4 was found as a potential candidate gene involved in the pathogenesis of IBS<sup>[66]</sup>. The frequency of SLC6A4 polymorphism and higher levels of 5HT were significantly associated with IBS<sup>[66]</sup>.

The association between microscopic colitis (MC) and IBS has similarly been described. In a recent systematic review and meta-analysis, the pooled prevalence of MC in Western IBS patients was 7.2% (95%CI: 1.5%-17.2%) and the prevalence varied between 2.4% to 11.5% in individual studies<sup>[67]</sup>. In the only report from Bangladesh, lymphocytic colitis (LC) was found in 37% of 60 patients with diarrhea-predominant IBS, with a complete absence of collagenous colitis. The distribution of LC was restricted in proximal colon in 68.2% patients, in the left colon in 9.1%, and diffuse in 22.7%<sup>[68]</sup>. A study of 120 subjects in a Malaysian tertiary institution found a very low (1.3% only) prevalence of collagenous colitis among 120 IBS subjects. However, IBS-D patients had a higher prevalence of moderate non-specific, microscopic inflammation compared to controls (14.9% vs 2.2%,  $P = 0.005$ ), suggesting that either occult

infection or other causes of inflammation may be contributory towards IBS-D sub-types<sup>[69]</sup>.

In an Indian case series on 29 patients with MC presenting with chronic large bowel diarrhea, of 7, 4, 7 and 11 patients with collagenous colitis, LC, minimal change colitis and microscopic colitis not otherwise specified, 28.6%, 25%, 14.3% and 33.3% had abdominal discomfort, suggesting that they would fulfill the Rome III criteria for IBS<sup>[70]</sup>. In another Indian study among 400 patients with chronic watery diarrhea, 3.7% had microscopic colitis (33% had collagenous colitis and 67% had lymphocytic colitis) and 10/15 of these patients were clinically diagnosed with IBS<sup>[71]</sup>. Data from the institutional-based studies suggest that MC is rare amongst South and South-East Asian IBS patients, perhaps in keeping with the lower prevalence of inflammatory bowel disease (IBD) in this region<sup>[72]</sup>.

### Protozoa and IBS

The presence of amoebic cysts in the stool of a patient with chronic lower GI symptoms creates confusion among physicians, and they often label such patients as suffering from chronic non-dysenteric amebic colitis. A multi-centric study on IBS from India showed that of 1237 patients reporting treatment with metronidazole in the past, 672 (24%) experienced temporary improvement<sup>[10]</sup>. Two studies in India explored this issue among IBS patients<sup>[73,74]</sup>. No significant differences were found in the proportion of amoeba in the stool (18% vs 18%), serologic evidence of infection (42% vs 41%), colonoscopic abnormalities (7% vs 3%) or histologic abnormalities among 144 IBS and 100 asymptomatic subjects. Additionally, there was no significant difference in response to therapeutic trial with metronidazole among the symptomatic patients who were cyst-positive or -negative at 6 mo<sup>[73]</sup>. In a second study of 154 inmates of a leprosy rehabilitation center, detection of amoeba among IBS and controls was found to be 50% and 19%, respectively. All strains of amoeba isolated were found to be non-pathogenic and there was no relationship between detection of amoeba and symptoms of IBS at 12 mo follow-up<sup>[74]</sup>. These studies suggest that non-pathogenic amoeba is an innocent by-stander in IBS subjects, which are inappropriately termed as "chronic amoebiasis" and often treated with anti-amoebic drugs unnecessarily.

Another common gut parasite found in the intestinal tract of humans and animals, *Blastocystis* sp, has been associated controversially with IBS, possibly as a result of irregular shedding of parasites in stool and variation in fecal detection. A recent study examining parasitic infestations using PCR techniques reported a significantly higher prevalence of *Blastocystis* sp (17% vs 5.5%), corroborated by increased cytokines for inflammation (IL-3, IL-5 and IL-10) in IBS patients compared to healthy controls in Malaysia<sup>[75]</sup>. Furthermore, IBS patients with increased stool frequency were found to have a greater quantity

of *Blastocystis* cysts, indicating that the severity of IBS symptoms correlated with the quantity of parasitic infestation<sup>[76]</sup>. These studies from Malaysia indicate that persistent chronic parasitic infection, which is often undetectable using standard culture or laboratory techniques, may be an additional contributory factor to microscopic gut inflammation in IBS in Asians.

In the light of these observations of protozoal diseases among South and South East Asian patients with IBS, it is not surprising that a multi-centric Indian study showed that 44% of the subjects with chronic lower GI symptoms took metronidazole with temporary symptom improvement among 54%<sup>[10]</sup>. Additionally, a randomized placebo controlled trial among 45 IBS subjects who were allocated to ispaghula husk (60 d), metronidazole (metronidazole 10 d and placebo 50 d) and placebo (60 d) found that metronidazole provided symptom relief in IBS compared to placebo without affecting recto-sigmoid motility<sup>[77]</sup>.

### Helminthiasis and IBS

Helminthic infestation is common in Bangladesh and India. In a report from rural Bangladesh, 70% of 252 children had been found to have soil-transmitted helminthiasis by the age of 2 years<sup>[78]</sup>. In southern India, a report suggested that 62% of all age groups had hookworm infestations<sup>[79]</sup>. Intestinal helminthiasis causes a shift in the immune system towards a T-helper 2 cell response<sup>[80,81]</sup>. This may be associated with a low-grade, protracted inflammation, which is recognized in a subset of IBS patients. Previous reviews have speculated that a high intestinal helminthic/parasitic infestation may be the cause of a low prevalence of IBS in spite of a high incidence of acute infective diarrhea in Asia<sup>[82]</sup>. Furthermore, the "hygiene hypothesis" speculates that a high childhood infection rate is responsible for the low prevalence of IBS in the developing countries.

### PI-IBS and PI-MAS

PI-IBS has been defined as an acute-onset IBS (by Rome criteria) that develops after the individual, who has not previously met the Rome criteria, experiences a GI infection with two or more of the following characteristics: fever, vomiting, diarrhea, and a stool culture positive for an infectious agent<sup>[83,84]</sup>. The pooled incidence of PI-IBS was found to be 10% in a systematic review and meta-analysis of predominantly Western studies<sup>[85]</sup>. Data on PI-IBS from Asian countries are scant, whereas acute gastroenteritis is common<sup>[86]</sup>. Studies from China and Korea have revealed that the incidence of PI-IBS is 8%-15%<sup>[87,88]</sup>. The incidence rate for acute diarrhea among those aged > 14 years in parts of India and Bangladesh have been reported as 60 per 100 person-years and between 15.2 to 135.7 per 100 person-years, respectively<sup>[89-91]</sup>.

Despite a high incidence rate of acute diarrhea

in the Indian subcontinent, there is no published study on PI-IBS. Furthermore, the relatively low prevalence of IBS in the Indian subcontinent, despite a high burden of acute diarrheal illness, appears enigmatic<sup>[83,86]</sup>. However, a condition similar to PI-IBS, post-infectious malabsorption (PI-MAS) or tropical sprue has been recognized in the Indian sub-continent for some time. A prevalence rate of 8%-20% of PI-MAS was previously reported in rural southern India following an episode of acute infectious diarrhea<sup>[92]</sup>. Both PI-IBS and PI-MAS have similar clinical features, etiopathogenesis, and potential response to treatment with antibiotics<sup>[93]</sup>. Furthermore, both PI-IBS and PI-MAS have been associated with SIBO<sup>[94,95]</sup> and abnormal small intestinal permeability<sup>[96]</sup>.

It is likely then, as IBS is a symptom-based diagnosis or that patients with mild malabsorption syndrome can be misdiagnosed as IBS, particularly of the diarrhea-predominant type, unless malabsorption is carefully excluded by appropriate investigations. In most studies on PI-IBS, PI-MAS has not been carefully excluded using tests for malabsorption. Considering the fact that PI-MAS or tropical sprue has been described recently following an attack of acute infectious diarrhea in developed countries like the United States, this issue needs consideration in developed and temperate countries as well<sup>[97]</sup>. Hence, there may be some overlap between PI-IBS and PI-MAS in the Indian sub-continent<sup>[83,86,96]</sup> and some cases of PI-MAS may be erroneously diagnosed as cases of PI-IBS. In a recent study from Dhaka, Bangladesh, 10% of 23 patients with acute gastroenteritis fulfilling Rome III criteria for IBS in the absence of previous IBS were found to have PI-MAS on investigation<sup>[98]</sup>.

### SIBO and IBS

SIBO and IBS have similar clinical features. Routine investigations conducted to exclude organic diseases in IBS, such as colonoscopy and blood tests, do not rule out SIBO. Several studies have reported the presence of SIBO in IBS patients in India, as shown in Table 3<sup>[95,99-101]</sup>. Ghoshal *et al.*<sup>[99]</sup> reported that 19% of 80 IBS patients had SIBO, diagnosed by upper gut aspirate culture with a colony count  $> 10^5$  CFU/mL. In a case-control study among 225 Indian IBS patients, 11% had SIBO by glucose hydrogen breath test (GHBT), whereas 1% of 100 healthy subjects had SIBO<sup>[100]</sup>. In the third study, 9 (13%) of 69 IBS patients had SIBO by GHBT. There was no significant difference in the frequency of SIBO among subjects with and without lactose intolerance and IBS<sup>[101]</sup>. In the fourth study, 11 (8.5%) of 129 IBS subjects had SIBO compared to 1 (2%) of 51 healthy subjects<sup>[95]</sup>.

An evidence-based review documented that the prevalence of SIBO in patients with IBS varies widely due to different criteria for defining a positive breath test and the methodology employed. It is 28%-84% with lactose hydrogen breath test (LHBT), 2%-31%

with GHBT and 2%-6% based on culture<sup>[102]</sup>. Most of the studies used GHBT to diagnose SIBO in India. GHBT had a sensitivity and specificity of 44% and 82%, respectively, when the culture of the upper gut aspirate was taken as the gold standard in a study on patients with malabsorption syndrome in India<sup>[103]</sup>. However, in a recent study on 80 patients with IBS (Rome III criteria), GHBT had a sensitivity of 27% and specificity of 100% considering quantitative jejunal aspirate culture as the gold standard<sup>[99]</sup>. The lower sensitivity of GHBT among patients with IBS as compared to malabsorption syndrome might be related to lower bacterial colony counts in proximal small bowel among the former rather than the latter group of patients.

Further evidence for the association between SIBO and IBS was provided by a randomized, placebo controlled trial from India, of norfloxacin in IBS cases with SIBO compared to those without SIBO. In this study, the response rate (negativity of Rome III criteria at 1 mo) of norfloxacin and placebo among IBS patients with and without SIBO was 87.5% (7/8) and 0% (0/7), 25% (8/32) and 0/33 (0%), respectively. Overall, 37.5% of 40 IBS patients responded to norfloxacin<sup>[99]</sup>.

### Food intolerance including lactose malabsorption and IBS

In recent years, dietary fermentable oligo, di, monosaccharide, and polyols (FODMAP) have been incriminated in contributing to the symptoms of IBS<sup>[104]</sup>. However, studies on dietary FODMAP in the pathogenesis of IBS symptoms and their exclusion in its treatment have been scant from India, Bangladesh and Malaysia, except for lactose as an isolated FODMAP. In a multi-centric Indian study, self-reported milk intolerance was present among 32% of 2785 subjects with lower GI symptoms. Patients with IBS-D reported milk intolerance more often than those with IBS-C<sup>[10]</sup>. In a rural community-based study in Bangladesh, a regular dairy intake was present in 61.7% of 2542 subjects, but 13.8% reported milk intolerance. Among 593 subjects with IBS, 12.6% reported milk intolerance and they showed a higher frequency of frequent bowel motion and loose or watery stool ( $P < 0.025$ )<sup>[13]</sup>.

However, the diagnostic accuracy of self-reported milk intolerance to diagnose lactose malabsorption was reported as having a sensitivity, specificity, positive predictive value and negative predictive value of 53%, 61%, 26% and 55%, respectively, in a case-control study in India among 112 IBS patients and 53 healthy controls<sup>[101]</sup>. In the same study, the frequency of lactose malabsorption diagnosed either by LHBT or lactose tolerance test was similar among IBS (82%) and healthy controls (77%). Nevertheless, symptoms of lactose intolerance were more frequent among IBS (55%) compared to healthy subjects (34%).



**Table 3** Studies on small intestinal bacterial overgrowth in India

Ref.	Number of IBS patients	Diagnostic criteria of IBS	Number of controls	Method of diagnosis of SIBO	% of SIBO in IBS	% of SIBO in controls
Ghoshal <i>et al</i> <sup>[99]</sup>	80	Rome III	-	Culture of upper jejunal aspirate	19	-
Rana <i>et al</i> <sup>[100]</sup>	225	Rome II	100	GHBT	11.1	1
Gupta <i>et al</i> <sup>[101]</sup>	69	Rome II	-	GHBT	13	-
Ghoshal <i>et al</i> <sup>[95]</sup>	129	Manning	51	GHBT	8.5	2

GHBT: Glucose hydrogen breath test; IBS: Irritable bowel syndrome; SIBO: Small intestinal bacterial overgrowth.

In an Indian study, the researchers demonstrated that lactose malabsorption diagnosed using 25-g lactose dose is clinically more meaningful than that diagnosed using the conventional 50-g lactose dose, which is quite a non-physiological dose; in fact, lactose malabsorption diagnosed using 25-g lactose dose was associated with 10 times higher rate of clinical improvement following milk withdrawal than that diagnosed using 50-g dose<sup>[105]</sup>.

More recently, investigators were able to demonstrate a similar frequency of C/T -13910 and G/A-22018 lactase gene polymorphism between Indian IBS patients and healthy controls<sup>[106]</sup>. These studies indicate that the prevalence of lactose malabsorption is high in South Asians, with no difference between IBS and non-IBS adults. However, the clinical consequences of lactose malabsorption are likely to be exaggerated in patients with IBS who often have underlying abnormalities in motility and visceral sensation and a reduced pain threshold.

Of the other FODMAP agents, a northern Indian study showed that 14.4% patients with IBS, particularly IBS-D, as compared to 2.4% of healthy controls had fructose malabsorption as demonstrated by fructose hydrogen breath test<sup>[107]</sup>. Importance of dietary factors in occurrence of IBS in the third world countries has been shown in a Brazilian study as well<sup>[108]</sup>. More studies on FODMAP diet and IBS, and their elimination in its treatment are needed from South Asia.

### Psychological comorbidity and IBS

With rapid development and urbanization in many of the South Asian countries, including India, Malaysia and Bangladesh, it is anticipated that an increase in urban-related psychopathology may contribute to IBS symptoms, severity and clinic visit in these nations. In a cross-sectional study of 248 adult patients in a referral center in Malaysia, a higher prevalence of anxiety and depression was observed in FD, non-erosive reflux disease and IBS patients compared to a healthy control group (43.5%, 45.2% and 67.7% vs 14.5%,  $P < 0.001$ ; and 22.6%, 33.9% and 38.7% vs 6.5%,  $P < 0.0001$ ). IBS patients had a higher rate of anxiety than FD patients ( $P = 0.01$ ) and non-erosive reflux disease patients ( $P = 0.02$ ), while no significant differences in depression rates were observed among all three groups of functional GI disorders<sup>[109]</sup>.

In a similar study from India, a greater prevalence of major depressive (47.3% vs 5.1%,  $P < 0.001$ ), somatoform (50% vs 14.6%,  $P < 0.001$ ) and panic disorder (44% vs 11.6%,  $P < 0.001$ ) were identified in IBS patients compared to healthy controls<sup>[110]</sup>. Whilst these studies in Malaysia and India have indicated an association between psychological disorders and IBS, a causal relationship could not be considered from these studies as patients with any chronic disorder are expected to have more psychological issues than healthy subjects. Furthermore, data on the efficacy of psychopharmacological therapy among Indian subjects with IBS have not been convincing. A prospective double-blind randomized controlled study among 90 IBS patients showed that oxyphenonium bromide and imipramine was not superior to placebo in improving symptoms nor the health-related quality of life ( $P > 0.05$ )<sup>[111]</sup>. Nevertheless, about one-third of patients with lower GI symptoms in India were reported to be on tricyclic antidepressants in a previous survey<sup>[10]</sup>.

### Healthcare seeking/consultation behavior

Several community-based studies in India and Bangladesh have investigated healthcare seeking behavior among IBS subjects in both rural and urban areas. Table 4 shows the consultation rates of IBS patients in India and Bangladesh. Physician consultation rates were 34.9%<sup>[13]</sup> and 65.5%<sup>[14]</sup> of IBS subjects in rural and urban Bangladesh, respectively, with no significant sex differences (68.6% vs 61.2%,  $P > 0.05$ ). The main predictor of consultation was the presence of multiple dyspeptic symptoms. The studies from India have alluded to a similarly high consultation rate (Table 4), with higher consultation rates for male IBS subjects (70% vs 44%,  $P = 0.00001$ )<sup>[9]</sup>. The types of healthcare practitioners consulted were explored in one study and found to include physician of modern medicine (MBBS and above) 3.1%, homeopathic physicians 5%, ayurvedic physicians 8.3% and Unani practitioners 0.8%<sup>[12]</sup>. These studies from India and Bangladesh suggest that availability, accessibility, and cost of the consulting physician may be important determinants of the consultation behavior of the IBS patients.

## CONCLUSION

This review has highlighted several unique aspects



**Table 4 Consultation rate of IBS patients in different population-based studies in India and Bangladesh**

Ref.	Study areas/ country	Number of IBS patients	Diagnostic criteria of IBS	Consultation Rate	Reason of consultation	Nature of consulting doctors
Shah <i>et al</i> <sup>[9]</sup>	Urban/India	190	Manning	28.94%	-	-
Ghoshal <i>et al</i> <sup>[12]</sup>	Rural/India	FGIDs	Rome III	17.20%	-	MBBS and above (3.1%) Homeopathic (5%) Ayuervadic (8.3%) Unani (0.8%)
Masud <i>et al</i> <sup>[13]</sup>	Rural/Bangladesh	593	Manning	39.0%	Altered stool passage Sense of incomplete evacuation Mucus in stool	
Perveen <i>et al</i> <sup>[14]</sup>	Urban/Bangladesh	116	Rome II	65.50%	Multiple dyspeptic symptoms	

IBS: Irritable bowel syndrome; FGIDs: Functional gastrointestinal disorders.

of IBS in the populations of India, Bangladesh and Malaysia. The prevalence of IBS is comparable in urban and rural areas of these three countries. A male predominance has been reported in institution-based studies in India, but a sex-based disparity has not been observed in community studies. Upper abdominal symptoms and FD are common among IBS subjects in the community. The sensitivity of the Rome criteria to diagnose IBS is lower in India. Many patients with IBS cannot be subtyped into constipation- and diarrhea-predominant sub-types based on popularly used criteria developed in the West, and a stool subtype and the Asian criteria appear to be more sensitive.

From a pathophysiological perspective, chronic gut infections, gut microbial dysbiosis, and SIBO appear to have important roles in IBS in South Asia. In spite of the high incidence of acute infective gastroenteritis, the low prevalence of IBS in India and Bangladesh remains somewhat enigmatic. PI-IBS, PI-MAS and SIBO may have a great degree of overlap in adults and may need specific investigations to differentiate them. Therefore, a role of the gut-specific antibiotics, such as rifaximin, cannot be over-estimated. Healthcare consultation by IBS subjects in India and Bangladesh are high in both rural and urban areas.

### Future direction

Further epidemiological studies using the same instruments and survey method are needed for valid comparison of the prevalence of IBS in the East and the West, as well as a head-to-head comparison in the rural and urban areas in Asian countries. Further studies are also needed on the symptom profile and subtyping of IBS in Asian countries using clinical, Rome and Asian-based criteria. Considering the high burden of acute infectious diarrhea in the Indian Subcontinent and frequently reported cases of tropical sprue, more studies are needed on the pathophysiology of PI-IBS and PI-MAS.

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