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ORIGINAL ARTICLE

Small Intestinal Bacterial Overgrowth In Various Functional Gastrointestinal Disorders: A Case–Control Study

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Abstract

Introduction Small intestinal bacterial overgrowth (SIBO) is prevalent in irritable bowel syndrome (IBS), but its' association with other functional gastrointestinal disorders (FGIDs) is less certain. This study aimed to explore SIBO in a multi-racial Asian population with various FGIDs compared to non-FGID controls.

Methodology Consecutive Asian adults with Rome III diagnosed common FGIDs (functional dyspepsia/FD, IBS and functional constipation/FC) and non-FGID controls were subjected to glucose breath testing, with hydrogen (H2) and methane (CH4) levels determined.

Results A total of 244 participants (FGIDs $n=186$, controls $n=58$, median age 45 years, males 36%, Malay ethnicity 76%) were recruited. FGIDs had a higher prevalence trend of SIBO compared to controls (16% FGIDs vs. 10% controls, $p=0.278$) with 14% in FD, 18% in IBS and 17% in FC. Compared to controls, SIBO was associated with diarrhoea-predominant IBS (IBS-D) (24% vs. 10%, $P=0.050$) but not with other types of FGIDs**.** IBS-D remained an independent predictor of SIBO (OR = 2.864, 95% CI 1.160–7.071, $p=0.023$) but not PPI usage nor history of diabetes (both $p>0.050$) at multivariate analysis. Compared to controls, SIBO in IBS-D was associated with an elevated H_2 level (≥ 20 ppm from baseline) (18% vs. 3%, $p=0.017$), but not CH4 levels (≥ 10 ppm) (9% vs. 7%, $p=0.493$). In addition, no difference was found in the prevalence of methane-positive SIBO between chronic constipation (constipation-predominant IBS and FC) compared to controls (9% vs. 7%, $P=0.466$).

Conclusion SIBO is prevalent amongst multi-ethnic Asian adults with and without FGIDs. Amongst various FGIDs, only IBS-D is significantly associated with SIBO.

Keywords SIBO · Functional dyspepsia · Irritable bowel syndrome · Functional constipation · Diarrhoea · Breath test

Abbreviations

CH4	Methane
FC	Functional constipation
FD	Functional dyspepsia
FGIDs	Functional gastrointestinal disorders
GI	Gastrointestinal
H2	Hydrogen
HBT	Hydrogen breath test
IBS	Irritable bowel syndrome
IBS-C	Constipation-predominant Irritable bowel syndrome
IBS-D	Diarrhoea-predominant irritable bowel syndrome
PPI	Proton pump inhibitor
PPM	Parts per million
SIBO	Small intestine bacteria overgrowth

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Introduction

Functional gastrointestinal disorders (FGIDs) are common, and from the most recent global epidemiology study, an estimated 40% of the world population suffer from the condition [1]. Gut dysbiosis, including small intestinal bacterial overgrowth (SIBO), is thought to play a major role in the pathophysiology of FGID [2]. A recent systematic review estimated a 35.5% prevalence of SIBO in irritable bowel syndrome (IBS) [3]. However, the prevalence of SIBO in other FGIDs apart from IBS is largely unknown. This is further compounded by considerable heterogeneity in the methods utilized to diagnose SIBO [4]. The latest North American consensus [5] and the ACG guideline on SIBO [6] have recommended hydrogen breath test (HBT) as the non-invasive diagnostic tool comparable to duodenal culture, the gold standard. Glucose is the preferred test substrate over lactulose with a sensitivity and specificity of 20–93% and 30–86%, respectively [7].

Despite a number of SIBO studies in Western populations, there has been a dearth of reports on SIBO in Asian adults with and without FGIDs. We believe there is a difference in the prevalence of SIBO in Asian adults with and without FGIDs compared to the West. Rapid urbanization in many Asian populations, a greater fibre content amongst Asian diets, together with a higher prevalence of tropical enteric infections in Asia, e.g. acute gastroenteritis [8], Helicobacter pylori infection [9], tuberculosis [10] and giardiasis [11], are all factors which may potentially influence the prevalence of SIBO in Asians. Furthermore, patients with post-infectious chronic GI symptoms, such as IBS and tropical sprue, have been reported to have causal links with SIBO [12–14].

In the current study, we aimed to determine the prevalence of SIBO in patients with various FGIDs and non-FGID controls, in a multi-ethnic Asian population. A secondary objective was to explore predictive factors for SIBO amongst our study population.

Methodology

Study Design and Participants

This was a case–control study of consecutive adults (> 18 year-old), recruited from two major tertiary centres in Malaysia: University Malaya Medical Centre (UMMC) situated in Kuala Lumpur, an urban metropolis, and Hospital Universiti Sains Malaysia (HUSM), situated in north-eastern Peninsular Malaysia, with a predominantly rural population-base. All patients had a clinical diagnosis of one form of FGID, i.e. FD, IBS, and FC, based on the Rome III criteria. All subjects with FGID had at least a baseline laboratory investigations that included a full blood count. Where clinically indicated, subjects underwent endoscopic examination to exclude an organic cause for symptoms. The indications for endoscopic examination were according to the Asian consensus reports on functional dyspepsia (upper endoscopy: age > 45 years or presence of any alarm symptom) and irritable bowel syndrome (colonoscopy: age > 50 year old or presence of any alarm symptom) [15, 16].

Non-FGID controls were recruited from both rural and urban communities. Non-FGID controls from the rural community were subjects who did not have any chronic GI symptoms, including abdominal pain and altered bowel habit, from a previous study conducted in a community after a flood [12]. Non-FGID controls from the urban community were subjects who consulted a primary care physician for non-GI-related conditions and did not have any chronic GI symptoms.

We excluded subjects who were pregnant or had confirmed organic gastrointestinal disease, including peptic ulcer disease, gastrointestinal malignancy, inflammatory bowel disease and coeliac disease. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and ethical approval was obtained from the University Malaya Medical Centre Medical Research Ethics Committee (Reference No: 2019727-7692) and Human Research Ethics Committee of Universiti Sains Malaysia (Reference No: USM/JEPeM/19120961) before study commencement.

Procedures

Socio-demography data, clinical symptoms, presence of diabetes mellitus and proton pump inhibitors (PPI) usage were recorded. PPI usage was defined as taking PPI at least twice a week for the past 3 months. The diagnosis of FGIDs (FD, IBS and FC) was based on the Rome III diagnostic criteria briefly described as follows: FD—bothersome postprandial fullness, early satiation, epigastric pain or burning; IBS—recurrent abdominal pain or discomfort that is improved with defecation and change in frequency/form of stool; FC—persistently difficult, infrequent or seemingly incomplete defecation. All the above criteria must be fulfilled for the last 3 months with the symptoms onset of at least 6 months prior to diagnosis [17, 18]. Non-FGID controls were subjects who did not have any GI symptoms or fulfilled a diagnosis of FGIDs, or had any known organic diseases.

Breath Testing for Small Intestinal Bacterial Overgrowth (SIBO)

A glucose-HBT was used to diagnose SIBO. One day before the test, all participants were asked to eat a low-residue carbohydrate diet and to refrain from smoking. They were requested to fast for 12 h and brush teeth 2 h prior to the

test. During the test, patients were asked to drink 75 g of glucose dissolved in 250 mls of water. End expiratory breath samples were collected at baseline followed by every 15-min interval (after glucose ingestion) for 2 h. Breath samples were collected in the Alveosampler bag (Quintron, Milwaukee, US) and then analysed for H2 (Hydrogen-H) and CH4 (Methane-M) levels using the gas chromatography machine (Quintron, Milwaukee, US). For a positive test, the following criteria were applied: a rise of ≥ 20 parts per million (ppm) H2 from baseline or ≥ 10 ppm CH4 at any point [5]. To diagnose SIBO (either hydrogen-positive SIBO: H-SIBO or methane-positive SIBO: M-SIBO), a positive breath test and reproduction of symptoms were required. History of intake of antibiotics in the past 1 month or promotility drugs/laxatives in the past 1 week were excluded from the test.

Sample Size Calculation

Based on estimated differences of 19%, 58% and 21% in SIBO prevalence of IBS, FD and FC, respectively, versus non-FGID controls [19–21], a minimum of 109 subjects with FGIDs (57 IBS, 11 FD, 41 FC) and 57 non-FGID controls would be required to achieve a 90% statistical power at the 0.05 significance level.

Statistical Analysis

Data were analysed using the IBM® SPSS® Statistics Version 25 (SPSS Inc., Chicago, IL, USA) software. Continuous variables were expressed as median and interquartile range. Different groups were compared using the Mann–Whitney *U* test. Categorical variables were expressed as frequency and percentage and differences evaluated using the Pearson chi-square or Fisher's exact test, whichever appropriate. Binary regression analysis was used to determine factors associated with SIBO. All variables with a p value < 0.4 at univariate analysis were included into the multivariate model. Results were expressed as odds ratio with 95% confidence interval. *P* value of less than 0.05 was considered statistically significant.

Results

A total of 244 subjects (FGID $n = 186$, control $n = 58$) were recruited between July 2015 and August 2020 (Fig. 1). The median age of the study population was 45 years, 88 (36%) were male and their ethnic background were as follows: 185 Malay (76%), 36 Chinese (15%), 18 Indian (7%) and 5 others (2%). 17 (7%) had diabetes mellitus and 42 (17%) were frequent proton pump inhibitor users.

Amongst the study population, 58 (24%) were non-FGID controls and 186 (76%) had at least one type of FGIDs, i.e. 59 (24%), 80 (33%), 45 (18%) and 63 (26%) of them were diagnosed with FD, IBS, diarrhoea-predominant IBS (IBS-D) and FC, respectively (Tables 1 and 2).

SIBO was present in thirty-six (15%) of the study population. Nineteen (8%) subjects had a raised H2 level, eighteen (7%) subjects had a raised CH4 level whilst one subject (0.4%) had both raised H2 and CH4 levels.

There were no differences in age and diabetes mellitus frequency between FGIDs subjects and non-FGID controls. There were more males (FGIDs: 40.3%, $n = 74$ vs non-FGID: 22.4%, $n = 13$, $p = 0.013$) and fewer ethnic Malays (FGIDs: 69.9%, $n = 130$ vs. non-FGID: 94.8%, $n = 55$, $p = 0.001$) amongst FGIDs subjects compared to controls (Table 1).

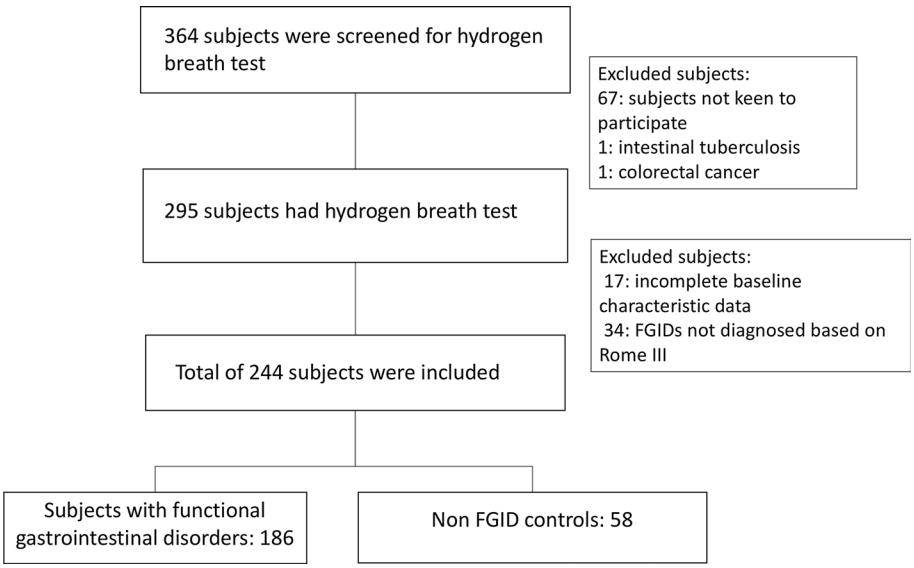


Fig. 1 Flow chart of study population

Table 1 Basic demography of FGIDs subjects and non-FGID controls

	Overall $N=244$	FGID ($n=186$)	Non-FGID controls ($n=58$)	p value
Age	45 (32–59)	41 (31–57)	51 (39–64)	0.056
Gender, male	88 (36)	75 (40.3)	13 (22.4)	0.013
Ethnicity				0.001
Malay	185 (76)	130 (69.9)	55 (94.8)	
Chinese	36 (15)	33 (17.7)	3 (5.2)	
Indian	18 (7)	18 (9.7)	0	
Others	5 (2)	5 (2.7)	0	
Diabetes mellitus	17 (7)	11 (5.9)	6 (10.3)	0.191

FGID functional gastrointestinal disorder

Table 2 Univariate analysis of the parameters with and without SIBO

	Overall $N=244$	SIBO $N=36$	Non-SIBO $N=208$	p value
Age	45 (32–59)	40 (31–61)	46 (32–59)	0.844
Male n, (%)	88 (36)	11 (31)	77 (37)	0.292
Ethnicity				0.811
Malay	185 (76)	31 (76)	182 (77)	
Chinese	36 (15)	6 (15)	34 (14)	
Indian	18 (7)	4 (10)	16 (7)	
Others	5 (2)	0	5 (2)	
PPI usage	42 (17)	5 (14)	37 (18)	0.383
Diabetes mellitus	17 (7)	5 (14)	12 (6)	0.086
Non-FGID	58 (24)	6 (17)	52 (25)	
FGIDs	186 (76)	30 (83)	156 (75)	0.278
FD	59 (24)	8 (22)	51 (25)	0.476
IBS	80 (33)	14 (39)	66 (32)	0.254
IBS-D	45 (18)	11 (31)	34 (16)	0.041
FC	63 (26)	11 (31)	52 (25)	0.304

SIBO small intestinal bacterial overgrowth, *PPI* proton pump inhibitors, *FGID* functional gastrointestinal disorder, *FD* functional dyspepsia, *IBS* irritable bowel syndrome, *IBS-D* diarrhoea-predominant irritable bowel syndrome, *FC* functional constipation

SIBO in FGIDs and Non-FGID Controls

Participants with FGIDs (FD, IBS and FC) had a trend towards a higher frequency of SIBO compared to controls (16%, $n=30$ FGID vs. 10%, $n=6$ controls, $p=0.278$). The frequency of SIBO amongst the various FGIDs were as follows: 8 FD (14%); 14 IBS (18%); 11 FC (17%). However, the difference of frequency of SIBO amongst FGIDs, FD, IBS and FC compared to controls was not statistically significant (Fig. 2).

When analysed according to the type of breath test, the following were observed: (i) For H-SIBO, there was a stronger association between FGIDs and IBS with H-SIBO, compared to controls (9%, $n=17$, $P=0.125$ in FGIDs; 11%, $n=9$, $P=0.085$ in IBS vs. 3%, $n=2$ in controls), but this was not statistically significant. (ii) For M-SIBO**,** no strong association was observed between FGIDs, IBS compared to controls (8%, $n=14$, $P=0.568$ in FGIDs; 8%, $n=6$, $P=0.584$ in IBS vs. 7%, $n=4$ in controls) (Fig. 3).

SIBO in IBS Subtypes

The proportion of IBS-D subjects with SIBO was higher compared to controls (24%, $n=11$ vs. 10%, $n=6$; $P=0.05$) (Figs. 2 and 4). This association of IBS-D compared to non-FGIDs was greater with H-SIBO (18%, $n=8$ vs. 3%, $n=2$; $P=0.017$), but not with M-SIBO (9%, $n=4$ vs. 7%, $n=4$; $P=0.493$) (Fig. 3). Subgroup analysis of the prevalence of SIBO amongst other subtypes of IBS showed no differences between constipation-predominant IBS (IBS-C), IBS-Mixed and IBS-unclassified compared to controls (Fig. 4).

We additionally explored the association between M-SIBO and chronic constipation (IBS-C and FC) and found no difference in prevalence between constipation compared to controls (9%, $n=7$ vs. 7%, $n=4$; $P=0.466$). (Online Resource 1).

Risk Factors for SIBO

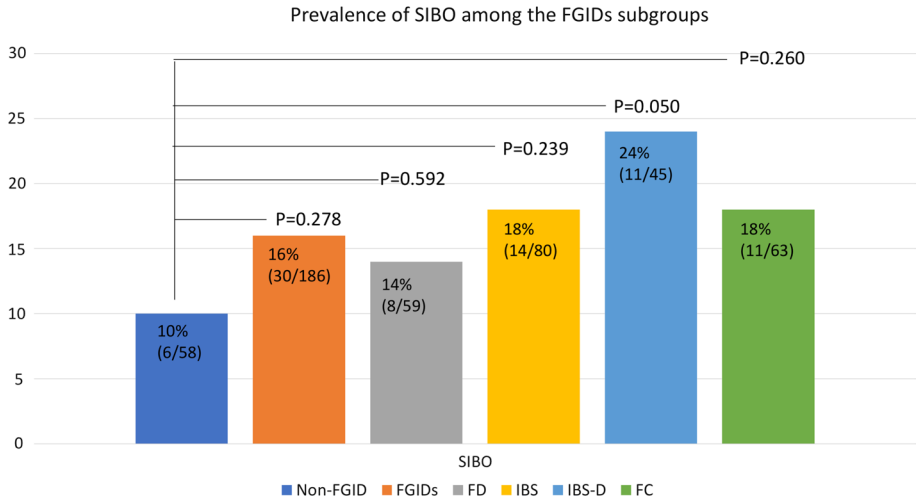
Predictive factors for SIBO were explored by univariate and multivariate analysis. There was no statistical significant difference on age, gender and ethnicity between subjects with and without SIBO (Table 2).

Only IBS-D was found to be associated with SIBO compared to subjects without SIBO (31%, $n=11$ vs. 16%, $n=34$, $P=0.041$) (Table 2). On multivariate analysis, IBS-D remained independently associated with SIBO (OR = 2.864, 95% CI 1.160–7.071, $p=0.023$) (Table 3).

A trend between the presence of diabetes mellitus and SIBO was observed (14%, $n=5$ in SIBO vs. 6%, $n=12$ in non-SIBO; $P=0.086$), but this was not statistically significant. Of note, no association between frequent PPI usage and SIBO was observed in our study cohort (14%, $n=5$ in SIBO vs. 18%, $n=37$ in non-SIBO; $P=0.383$) (Table 2).

Discussion

The association of SIBO with FGIDs, aside from IBS, has not been studied much. In this case–control study, we have shown that the prevalence of SIBO was 16% in FGIDs, but this was not significantly different from controls. It should not come as a surprise that SIBO is present in both FGIDs and controls since we have shown similar findings in a post-flood community-based study [12]. However, SIBO may



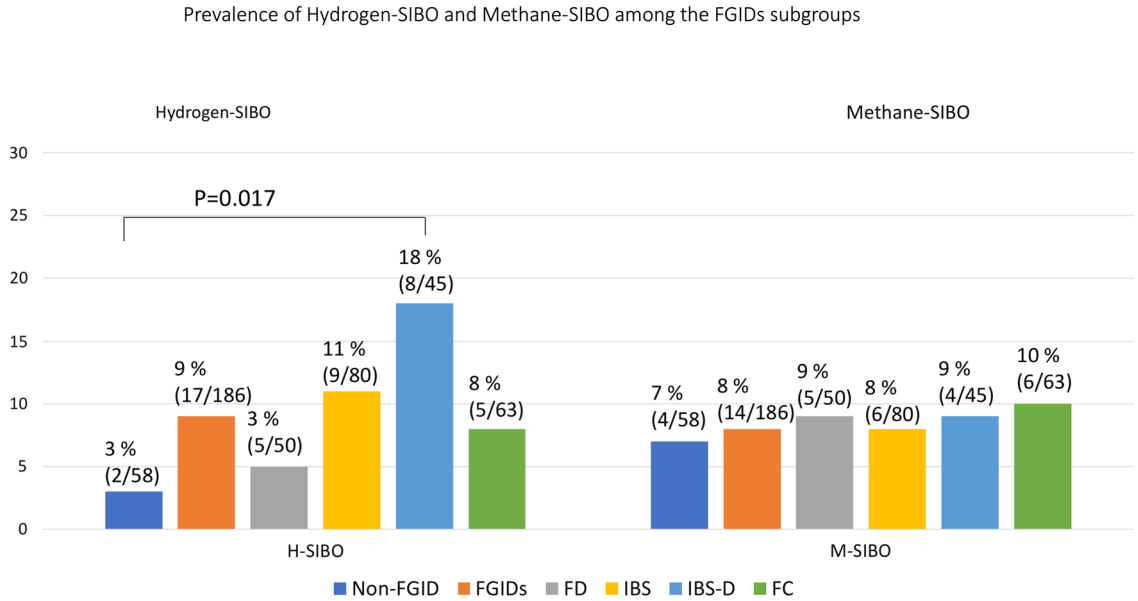


Fig. 3 Prevalence of H-SIBO and M-SIBO amongst FGIDs and non-FGID controls

cause more symptoms in FGIDs compared to non-FGID adults due to visceral hypersensitivity in the former.

Our data are in contrast to several case–control studies, in predominantly Western adults, which have demonstrated a higher prevalence of SIBO in IBS, FD and FC (diagnosed based on Rome III) compared to healthy controls (Table 3). Interestingly, a study from Japan by Shimura et al. showed that the prevalence of SIBO amongst refractory FGIDs was much lower at 5.3% but there was no control group in the study [22]. These observations suggest that the SIBO burden in Asians appears to differ from the West, for reasons alluded to beforehand.

Nevertheless, we have shown in the current study that IBS-D was significantly associated with SIBO, which is similar to other published data. Based on a recent systemic review of 25 studies (based on various diagnostic methods), SIBO was reportedly more common amongst IBS subjects compared to controls, with an odds ratio of 3.7 (95% CI 2.3–6.0). In the same review, IBS-D was at greater odds of having SIBO compared to IBS-C [3]. Our study demonstrated that IBS-D was associated with SIBO with an adjusted odds ratio of 2.864. The prevalence of SIBO was significantly higher, in particular H-SIBO, compared to non-FGID controls (SIBO: 24% vs. 10%, $p=0.05$ and H-SIBO: 17% vs. 3%, $p=0.017$, respectively). A recent open-labelled rifaximin trial on patients with IBS-D had demonstrated that the optimal benefit of rifaximin was seen in subjects with a positive baseline lactulose breath test, of whom the

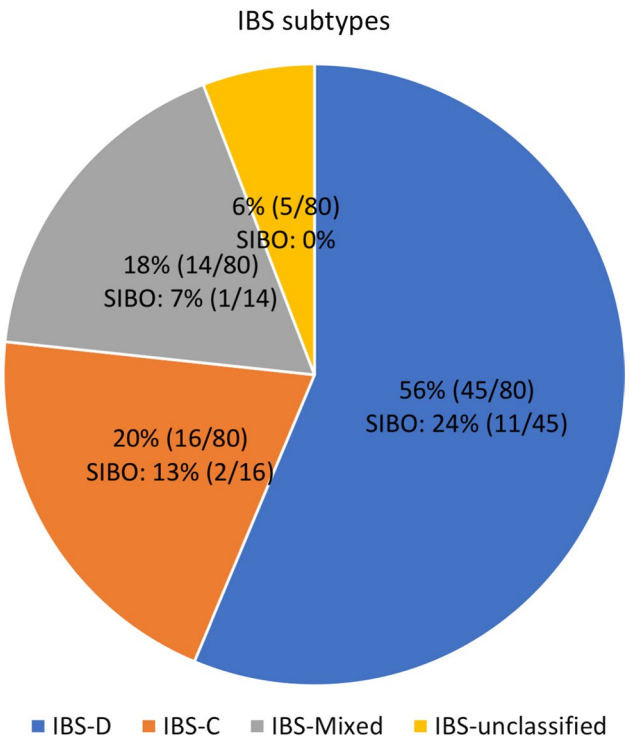


Fig. 4 IBS subtypes and SIBO

majority were H2 positive [23]. Taken together, the study further highlighted the importance of identifying SIBO and H-SIBO in IBS-D. In contrast, excessive CH4 excretion was reported to be less common in IBS-D [24], similar to the results of our study.

A 14% prevalence of SIBO in FD was observed in the current study. Dysbiosis has been implicated in the pathophysiology of FD [25], but the association between SIBO and FD is unclear. Using lactulose hydrogen breath test performed in 34 subjects (23 FD vs. 11 control subjects), Costa et al. reported a 56.5% prevalence of SIBO in FD compared to 0% amongst healthy controls [20]. In contrast, our current study (50 FD vs. 58 control subjects) did not demonstrate any association between SIBO and FD (14% in FD vs. 10% in controls). There may be several explanations for the different observations between our study and that of Costa et al. Firstly, environmental and cultural factors (e.g. diet) may have contributed to this difference. Epidemiological differences in FD have been recognized between Asians and Western adults [26]. Secondly, the Brazilian study utilized a lactulose breath test and we used the glucose hydrogen breath test. Unlike glucose, the lactulose breath test has a greater false positive rate due to colonic fermentation, poorer specificity compared to culture and lactulose can affect orocecal transit [7]. Both studies however have small sample sizes, and thus a larger study is needed to validate these findings. Furthermore, rifaximin, the most effective therapy for SIBO, has been shown to be useful over placebo in functional dyspepsia [27], which supports the hypothesis of SIBO playing a role in FD.

The association between SIBO and constipation remains unclear although methanogenic flora has been implicated in slow transit [28]. In a case–control study by Attaluri et al., methane positivity on breath testing was significantly associated with chronic constipation [21]. In our current study, we had grouped IBS-C and FC as chronic constipation. While we showed a trend in the association between SIBO and chronic constipation, no association was found with M-SIBO. Again, the difference of the results of meta-analysis and our study could be due to geographical and genetic variation. The prevalence of constipation is recognized to be lower in Asia compared to the West, with cultural factors such as dietary differences in fibre being a possible explanation [29].

Advanced age, female gender, diabetes mellitus and PPI usage have been reported to be predictive factors for SIBO, but the evidence is few and conflicting [6, 30, 31]. Likewise, in our study, we did not demonstrate any association of SIBO with age, gender, history of diabetes mellitus and PPI usage in FGIDs or controls. However, we cannot rule out the possibility of type 2 statistical error due to the small representation of subjects with diabetes and PPI usage in the current study (Table 4).

There are several limitations in this study. Firstly, information on several other recognized factors for SIBO, e.g. history of past abdominal surgery and smoking, was not

Table 3 Logistic regression analysis for risk factors of SIBO

	Odd ratio	95% CI	*P* value	Adjusted odd ratio	95% CI	*P* value
Male	0.75	0.35–1.61	0.457	0.65	0.30–1.44	0.289
PPI usage	0.75	0.27–2.05	0.568	0.89	0.31–2.50	0.817
Diabetes	2.63	0.87–7.99	0.087	2.36	0.76–7.40	0.139
IBS-D	2.25	1.01–5.01	0.046	2.86	1.16–7.07	0.023
FC	1.32	0.61–2.87	0.483	1.76	0.74–4.21	0.203

SIBO small intestinal bacterial overgrowth, *PPI* proton pump inhibitors, *IBS-D* diarrhoea-predominant irritable bowel syndrome, *FC* functional constipation

Table 4 Summary of case–control studies of SIBO in various FGIDs using Rome III criteria

Study	Study Year, country	FGID type, *N*	Controls, *N*	Mode of diagnosis of SIBO	
IBS					
Parodi et al. [32]	2009, Italy	IBS (Rome III): 130	70	GBT	SIBO in patients with IBS: 16.2% versus controls: 4.4% (IBS-D: 21.6%)
Lambordo et al. [19]	2010, Italy	IBS (Rome III): 200	50	GBT	SIBO in patients with IBS: 24.5% versus controls: 6%
Sachdeva et al. [33]	2011, India	IBS (Rome III): 59	37	GBT	SIBO in patients with IBS: 23.73% versus controls: 2.7% (IBS-D: 37%)
Abbasi et al. [34]	2014, Iran	IBS (Rome III): 107	107	GBT	SIBO in patients with IBS: 37.4% versus controls: 12.1% (IBS-D: 30%)
Moraru et al. [35]	2014, Romania	IBS (Rome III): 331	105	GBT	SIBO in patients with IBS: 31.7% versus controls: 6.6% (IBS-D: 18.1%)
FD					
Costa et al.[20]	2012, Brazil	FD (Rome III): 23	11	LBT	SIBO in patients with FD: 56.5% versus controls: 0%
Chronic constipation (IBS-C/FC)					
Attaluri et al. [21]	2010, United States	Chronic constipation (Rome III): 96	106	GBT	Methane on breath test in patients with chronic constipation (Slow transit: 75% versus normal transit 44%) versus controls: 28%
Our study	2021, Malaysia	FD: 59 IBS: 80 FC: 63	58	GBT	SIBO in patients with FD: 14%; IBS: 18%; FC: 14% versus controls: 10% (IBS-D: 24%)

SIBO small intestinal bacterial overgrowth, *FGID* functional gastrointestinal disorder, *FD* functional dyspepsia, *IBS* irritable bowel syndrome, *IBS-D* diarrhoea-predominant irritable bowel syndrome, *IBS-C* constipation-predominant irritable bowel syndrome, *FC* functional constipation, *GBT* glucose breath test, *LBT* lactulose breath test

collected. However, the case–control design of the study would have minimized the effect of this omission of data. Secondly, the sample size was calculated based on a higher prevalence of SIBO than we had observed, which may have influenced the findings of the present study. Thirdly, the Rome III criteria was used to diagnose FGIDs, as data were collected before the year 2015 and the Rome IV criteria was only launched in 2016. Based on the recent global FGID study using the Rome IV criteria [1], the differences between Rome III and Rome IV might not be that apparent apart from a lower prevalence of IBS and a higher frequency of constipation. Fourthly, part of the non-FGID controls were recruited from a cohort of flood-affected subjects and the controls were not gender/ethnic matched. These potential selection biases may explain the higher rate of SIBO amongst controls. However, the effects were minimized by the fact that the controls were asymptomatic and did not fulfil any FGID criteria.

In conclusion, the present case–control study has demonstrated that the prevalence of SIBO does not differ significantly between subjects with and without FGID in a multi-racial Asian population. However, amongst common FGIDs, IBS-D remains significantly associated with SIBO. The strengths of this study, which include a multi-centre, multi-ethnic and rural–urban representation of Asian adult subjects, indicate that a true difference in SIBO prevalence in FGIDs may exist between Asia and the West. Further studies in other Asian populations are required to validate the findings from our population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-021-07227-4.

Author's contribution KHC and SM contributed to conceptualization. KHC, MSW, POT, SZL, KHB, SCSC, KKZ and AMT contributed to data curation. KHC, MSW, POT, SZL, KHB, SCSC, KKZ, AMT, SM and YYL contributed to methodology. KHC, MSW, POT, SZL, KHB, SCSC, KKZ, AMT, SM and YYL contributed to project administration. KHC contributed to formal analysis and investigation. KHC contributed to writing—original draft preparation. KHC, SM, YYL and MSW contributed to writing—review and editing. KHC and YYL contributed to funding acquisition. SM and YYL contributed to supervision.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Consent to participate Written informed consent was obtained from all individual participants included in the study.

Consent to publish Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the University Malaya Medical Centre Medical Research Ethics Committee (Reference No: 2019727-7692) and Human Research Ethics Committee of Universiti Sains Malaysia (Reference No: USM/JEPeM/19120961).

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