Chuah Kee Huat (Orcid ID: 0000-0001-9811-7546) Beh Keng Hau (Orcid ID: 0000-0003-3001-4051)

Impact of Small Intestinal Bacterial Overgrowth on Symptoms and Quality

of Life in Irritable Bowel Syndrome

Running title: Impact of SIBO on IBS

Kee Huat Chuah, Wen Xuan Hian, Sze Zee Lim, Keng Hau Beh, Sanjiv Mahadeva

Gastroenterology and Hepatology Unit

Department of Medicine

Faculty of Medicine

University of Malaya

Kuala Lumpur, Malaysia

The content of the manuscript has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of Asian Pacific Digestive Week 2021 and Annual Scientific Meeting of Malaysian Society of Gastroenterology & Hepatology GUT 2022 (oral presentation/ best paper award presentation).

Funding

This study was funded by the University Malaya Specialist Centre (UMSC) C.A.R.E Research Fund (Project No.: PV039-2019).

Author contributions: KHC was the guarantor of the study. KHC and SM designed the study; KHC, WXH, SZL and KHB participated in the acquisition,

This article is protected by copyright. All rights reserved.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1751-2980.13189

Institutional review board statement: The study was reviewed and approved by the Medical Research Ethics Committee University of Malaya Medical Centre **Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Declaration of Conflicting Interests: All authors declared that they have no competing interests.

Data sharing statement: No additional data are available.

Correspondence:

Dr Kee Huat Chuah

Gastroenterology and Hepatology Unit, Department of Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia Telephone no.: +60379492965

Fax no.: +60379604190

E-mail: chuah319@yahoo.com; chuah.kh@ummc.edu.my

Abstract

Objective

Small intestinal bacterial overgrowth (SIBO) is recognised to have an association with irritable bowel syndrome (IBS), but the impact of SIBO on symptoms and health-related quality of life (HRQOL) in IBS patients is still unknown.

Methods

A cross-sectional study of consecutive adult patients who underwent glucose hydrogen breath test was conducted. Factors associated with SIBO were evaluated. Symptom and HRQOL of IBS patients with and without SIBO were compared. The independent factors associated with severe IBS (i.e. IBS symptom severity score: IBS-SSS>300) were explored.

Results

A total of 160 patients were included (median age 40 years, males 31.3%). IBS was present among 53.8% of subjects, with 33.8% having diarrhea-predominant IBS (IBS-D). SIBO was diagnosed in 22.5% of the study population. Patients with SIBO were more commonly diagnosed with IBS-D than those without SIBO (SIBO: 50.0% vs non-SIBO: 29.0%, p=0.019). Amongst IBS patients, severe IBS was associated with SIBO (36.4% vs 15.6%, p=0.043). The presence of SIBO was associated with poorer HRQOL (EQ-5D utility score: 0.73 (0.69-0.78) vs 0.80 (0.73-1.00), p=0.024].

The presence of SIBO (44.4% vs 20.6%, p=0.043), anxiety (77.8% vs 39.7%, p=0.004) and depression (50.0% vs 19.1%, p=0.011) were associated with severe IBS at univariate analysis. However, SIBO was the only independent factor associated with severe IBS at multivariate analysis [OR: 3.83 (95% CI: 1.02-14.34), p=0.046].

Conclusions

There was a significant association between IBS-D and SIBO. The co-existence of SIBO had a significant negative impact on IBS patients.

Keywords: Dysbiosis; Gut microbiota; Pathophysiology; Functional gastrointestinal disorder; Asia

Introduction

Irritable bowel syndrome (IBS) is one of the most common form of functional gastrointestinal disorders (FGIDs). In a large-scale multinational population based study, the prevalence of IBS was reported to range from 1.5% to 10.1%.[1] The frequency of patients with IBS was similarly shown to be high in a study from primary care setting.[2] Additionally, IBS patients constituted a major proportion of patients who seek consultation in gastroenterology specialist clinic.[3] IBS does not cause mortality, but were known to contribute to the increase healthcare burden and impairment of quality of life.[2] Furthermore, because of its' poor response to standard medical treatment, the economic impact of IBS to healthcare services and society has been shown to be substantial.[4] IBS is now recognised to have a complex multifactorial pathophysiology. Genetic predisposition, psychological and cultural factors, previous gut infections, visceral hypersensitivity, increase permeability, bile acid malabsorption and dysbiosis contributed to the brain gut axis dysfunction in IBS.[5] Small intestinal bacterial overgrowth (SIBO) is one of the prominent manifestations of dysbiosis which has been reported to be associated with IBS.[6] In a previous case-control study of patients with various types of FGIDs, it was observed that SIBO was significantly more common amongst diarrhoeapredominant IBS (IBS-D) patients than healthy controls.[7]

Accepted Articl

In SIBO, abdominal distension, pain, bloating and flatulence were caused by the formation of gases, including hydrogen, methane and carbon dioxide from the fermentation of diet by bacteria in the small intestines. In addition, the symptoms of diarrhoea and malabsorption in SIBO were postulated to be due to the enterotoxic effect of bacterial metabolites, low grade inflammation in the small intestinal mucosa, increase small bowel permeability and bile salts deconjugation.[8]

Despite the increased recognition of the role of SIBO in the development of IBS, the impact of SIBO on the symptoms and quality of life in patients with IBS is still unknown. In this study, we aimed to explore the factors associated with SIBO amongst all subjects who had a glucose hydrogen breath test (HBT) and then to further evaluate the impact of SIBO on IBS patients, in terms of symptom severity and health-related quality of life (HRQOL). The predictive factors for severe form of IBS were additionally explored.

Methodology

This was a cross-sectional study of consecutive adult patients above the age of 18 years who had a glucose HBT from University Malaya Medical Centre (UMMC), Kuala Lumpur. Subjects with FGIDs, including IBS, functional dyspepsia and functional constipation were diagnosed using the Rome III diagnostic criteria.[9] All subjects with FGIDs who attended UMMC gastroenterology specialist clinic were investigated with laboratory investigations and endoscopic examination.[10] All of them were offered to undergo glucose HBT during the study period. Non-FGID subjects were those who attended a primary care clinic for non-gastrointestinal related conditions and had no chronic gastrointestinal symptoms, from a previous case-control study.[7]

Subjects who were pregnant or had any confirmed organic cause for the gastrointestinal symptoms, were excluded from the study. Informed consent was obtained from all participants included in the study. The study conformed to the ethical guidelines and the ethical approval was obtained from our Institutional Ethics Review Board (Reference No.: 2019727-7692) before the start of the study.

Procedures

Demographic information, clinical parameters, presence of diabetes mellitus, the use of proton pump inhibitors (PPI) and anthropometric measurements were recorded. PPI usage was defined as taking a PPI at least twice a week for the past 3 months.[7] Underweight, normal weight, overweight and obesity were defined as body mass index (BMI) <18.5kg/m², 18.5 to 22.9 kg/m², 23.0 to 24.9 kg/m², \geq 25 kg/m² respectively.[11]

Three questionnaires, i.e. IBS symptom severity scale (IBS-SSS), hospital anxiety and depression scale (HADS) and EuroQol five-dimensional (EQ-5D) were administered to all IBS patients. IBS-SSS consists of five questions and records responses using a 100-point visual analogue scale. Symptom severity is categorised into mild (<175), moderate (175-300), and severe (>300).[12] HADS is a questionnaire comprising a total of 14 questions to assess for both anxiety and depression, on a scale of 0 to 21 respectively. A score of \geq 8 for each scale is suggestive of significant anxiety or depression.[13] The locally validated EQ-5D instrument is used to measure HRQOL with one question for each of the five domains (mobility, self-care, pain, usual activities and psychological status), and 3 response levels (no problem, moderate problems and severe problems). Based on the responses, a mean utility score on a scale of 0 to 1.0 is calculated, with 1.0

being the best health scenario. The instrument also includes a visual analogue scale (1-100) for assessment of self-perceived general health status with a higher score indicating better health status. [14]

Glucose hydrogen breath testing

SIBO was diagnosed using glucose HBT. All participants were requested to avoid complex carbohydrate food one day before and fast for 12 hours prior to the breath test. They were asked to brush teeth two hours before the test and to refrain from smoking on the day of the procedure. Patients were required to drink 250ml of glucose solution containing 75g of glucose after collection of end expiratory breath sample at baseline. Subsequent samples were collected every 15 minutes for over two hours. The Alveosampler bag (Quintron, Milwaukee, US) was used to collect all breath samples and a gas chromatograph (Quintron, Milwaukee, US) was then used to analyse for Hydrogen and Methane levels. A rise of \geq 20 parts per million (ppm) hydrogen from baseline by 90 minutes or \geq 10 ppm methane at any point were considered as a positive test.[15] Participants who took prokinetic agents or laxatives within one week prior to the test or any antibiotics within the last one month were required to postpone the procedure.

Sample size calculation

Based on an estimated difference of 16% in the prevalence of SIBO amongst IBS versus non-IBS subjects using glucose HBT,[16] a minimum of 132 subjects (including 66 IBS subjects) is needed to achieve a 90% statistical power at 5% level of significance.

Statistical analysis

The IBM[®] SPSS[®] Statistics Version 25 (SPSS Inc., Chicago, IL, USA) software was used to analyse the data. Categorical variables were recorded as percentage

Accepted Articl

and the differences were compared using the Pearson chi-square test or Fisher's exact test, whichever appropriate. Continuous variables were expressed as median and interquartile range. The differences were evaluated using the Mann-Whitney U test. Binary logistic regression analysis was used to identify the independent factors associated with severe IBS (i.e. IBS-SSS>300). The multivariate analysis includes all variables with a p-value < 0.2 at univariate analysis. Results were reported as odds ratio with 95% confidence interval. P-value of less than 0.05 was considered statistically significant.

Results

Overall Study Population

A total of 160 subjects were recruited from July 2017 to December 2021 (Figure 1). The median age was 40 years with 50 (31.3%) being male. As for their ethnic background, there were 92 Malays (57.5%), 43 Chinese (26.9%), 23 Indians (14.4%) and 2 others (1.3%). 67 (41.9%) of them had tertiary education. Most of them were obese (n=84, 52.5%) and non-smoker (n=153, 95.6%). Twenty-four (15.0%) had diabetes mellitus, 28 (17.6%) were frequent proton-pump inhibitor users and 43 (26.9%) had a history of abdominal pelvic surgery.

Amongst the study population, the frequency of various diagnoses were as follows: IBS n=86 (53.8%), IBS-D n=54 (33.8%), FD n=36 (22.5%), FC n=33 (20.6%), FD/ IBS overlap n=15 (9.4%) and non-FGID n=23 (14.4%).

SIBO was diagnosed in 36 (22.5%) of the study population. Twenty-one (13.1%) and seventeen (10.6%) of them were tested positive for elevated level of hydrogen and methane. Patients with hydrogen positive SIBO were more frequently found to have IBS-D (hydrogen positive SIBO: 71.4%, n=15 vs non-hydrogen positive SIBO/ non-SIBO: 28.1%, n=39; p<0.001). Amongst patients

Accepted Articl

with methane positive SIBO, co-existence of chronic constipation (IBS-C and FC, n=47) were more prevalent, but it was not statistical significant (methane positive SIBO: 35.3%, n=6 vs non-methane positive SIBO/ non-SIBO: 28.7%, n= 41; p=0.571).

Patients with SIBO were more commonly diagnosed with IBS-D than those without SIBO (SIBO: 50.0%, n=18 vs non-SIBO: 29.0%, n=35, p=0.019). Otherwise, there were no statistically significant association of sociodemographic factors and other FGID diagnosis with SIBO (**Table 1**).

IBS Patients

Of 86 IBS patients, 31 (36.0%) were male, 33 (38.4%) were Malay and the median age was 57 years with 40 (46.5%) of them had tertiary education (**Table 2**).

Forty-one (47.7%) of them had anxiety, while twenty-two (25.6%) had depression.

SIBO was present in 22 (25.5%) of them. Seventeen (19.8%) patients with IBS were tested positive for elevated hydrogen level, while seven (8.1%) of them had elevated methane level.

IBS patients with SIBO were more likely to have IBS-D than those without SIBO (SIBO: 81.8%, n=18 vs non-SIBO: 56.3%, n=36, p=0.032). No other factors were found to be associated with SIBO.

Impact of SIBO on IBS Patients

Eighteen patients (20.9%) had a severe form of IBS (i.e. IBS-SSS>300). Patients with severe IBS were associated with the presence of SIBO (SIBO: 36.4%, n=8 vs non-SIBO: 15.6%, n=10, p=0.043) (Figure 2).

IBS patients with SIBO had a higher IBS-SSS score compared to those without SIBO [245 (125-330) vs 200 (140-268), p=0.280], but they were not statistically significant.

The presence of SIBO was associated with poorer HRQOL, measured by EQ-5D utility score [SIBO: 0.73 (0.69-0.78) vs non-SIBO: 0.80 (0.73-1.00), p=0.024]. The EQ-VAS score however was not different between patients with and without SIBO [SIBO: 70 (50-80) vs non-SIBO: 75 (60-90), p=0.137].

Predictors of Severe IBS

In univariate analysis, the presence of SIBO (severe IBS: 44.4%, n=8 vs non-severe IBS: 20.6%, n=14, p=0.043), anxiety (severe IBS: 77.8%, n=14 vs non-severe IBS: 39.7%, n=27, p=0.004) and depression (severe IBS: 50.0%, n=9 vs non-severe IBS: 19.1%, n=13, p=0.011) were found to be associated with severe IBS (Table 3) (Figure 3).

However, SIBO was the only independent predicting factors associated with severe IBS on multivariate analysis [OR: 3.83 (95% CI: 1.02-14.34), p=0.046] (Table 4).

Discussion

This current study highlighted the co-existence of SIBO had a significant negative impact (more severe symptoms and poorer HRQOL) on IBS patients. In addition, SIBO was also found to be associated with IBS-D. These findings support the potential benefit of screening for SIBO in IBS patients, in particular those with IBS-D and severe form of IBS. Although the association of SIBO and IBS were frequently explored in previous studies, the findings of a negative impact of SIBO amongst IBS patients' symptom severity and HRQOL is novel. In a recent systemic review of 25 studies, the prevalence of SIBO in IBS patients was significantly higher compared to healthy controls with an OR of 3.7, in particular patients with IBS-D were at higher odds (OR 1.8) of being affected with SIBO than patients with IBS-C.[16] In this present study, we only found an association between IBS-D and SIBO. Further analysis including only IBS subjects showed similar results. These observations suggest that the focus of screening for SIBO should be on patients with IBS-D.

The Rome Foundation Working Team concluded that the severity of IBS is related to and influences HRQOL, health behaviors and also guides diagnostic and therapeutic clinical decision making.[17] Severity of abdominal pain was also reported to be the primary driver of increased utilization of outpatients visits and medications for GI symptoms among patients with functional bowel syndrome.[18] Hence, identifying patients with severe IBS is essential and further establishing the factors associated with severe IBS are equally important. In this current study, we found that 20.9% of our IBS cohort had a severe form of IBS. Additionally, the patients with SIBO were more than two times more likely to have severe IBS than those without SIBO (36.4% vs. 15.6%). Moreover, SIBO remained the only independent predictive factors of severe IBS after adjusted the confounding factors with an OR of 3.83.

One may argue that IBS symptom severity, including using the scoring system of IBS-SSS may not be adequately measured the impact of IBS on the patients. A study from Maastricht, Netherlands reported that the reduction in IBS symptom severity is not parallel with the improvement in quality of life in patients with IBS.[19] In this study, the presence of SIBO amongst patients with IBS was also associated with poorer HRQOL, measured by EQ-5D utility score. Taken together, the presence of SIBO had a significant negative impact (symptom severity and HRQOL) on patients with IBS.

Rifaximin is the most well recognized treatment for SIBO.[20] On the contrary, Rifaximin was reported to be effective in treating non-constipated IBS in a previous RCT, but the absolute reduction compared to placebo was only 10%.[21] Meanwhile, an open labeled Rifaximin trial involving subjects with IBS-D had demonstrated that the optimal benefit of the antibiotic was seen in those with a positive baseline lactulose breath test.[22] Hence, screening for SIBO amongst IBS patients, especially those with severe IBS or IBS-D will be useful to identify a more effective therapeutic target.

Screening for anxiety and depression should always be part of the assessment for patients with FGIDs, also known as disorder of gut brain interaction (DGBI). These psychological comorbidity were well known to have bi-directional associations with DGBI.[23] In addition, anxiety and depression among patients with IBS were also reported to be linked to more severe gastrointestinal and non-gastrointestinal symptoms, fatigue and poorer quality of life.[24] Our study showed that anxiety (47.7%) and depression (25.6%) were common amongst patients with IBS. Although both anxiety and depression were associated with severe IBS in univariate analysis, but the association with severe IBS were not found in multivariate analysis. This could be due to the relatively small numbers of participants in this study.

There were several limitations in this study. Firstly, the participants with FGIDs were diagnosed using the older Rome III criteria. However, a previous study from primary care setting and a systemic review suggested that the latest Rome IV diagnostic criteria may not be as sensitive to diagnose IBS.[2,25] Secondly,

we used glucose HBT to diagnose SIBO, instead of the current gold standard, i.e. jejunal culture. However, the North American consensus[15] and the latest American guideline on SIBO[6] have recommended the non-invasive HBT as the non-invasive diagnostic tool comparable to small bowel culture. In addition, the performance of HBT using glucose as the substrate to diagnose SIBO was reported to be superior compared to lactulose with a sensitivity of 47.3% and a specificity of 80.9%.[26] Thirdly, non-IBS patients were recruited in our centre from the previous multi-centre case control study[7] and the psychological comorbidities of them, e.g. anxiety and depression were not collected. However, the focus of the study was to look for factors associated with SIBO, which psychological morbidities were less likely to be related. Furthermore, sub-group analysis was limited by the small sample size. Nevertheless, the data on IBS patients, which were prospectively collected, were complete to explore the other main objectives of the study, i.e. the impact of SIBO amongst IBS patients and the predictive factors of severe IBS.

In conclusion, the present study has demonstrated that IBS-D was significantly associated with SIBO. The presence of SIBO amongst patients with IBS was associated with more severe symptoms and led to poorer quality of life. Hence, screening for SIBO amongst selected IBS patients should be considered as part of the routine workout.

Acknowledgement

The authors would like to thank Associate Professor Dr Reena Rajasuriar, Dr

Khoo Xin Hui and Madam Talvant Kaur for their assistance in the research project.

References:

- 1 Sperber AD, Bangdiwala SI, Drossman DAet al. . Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study *Gastroenterology*. 2021;160:99-114.e113.
- 2 Chuah KH, Beh KH, Mahamad Rappek NA, Mahadeva S. The epidemiology and quality of life of functional gastrointestinal disorders according to Rome III vs Rome IV criteria: A cross-sectional study in primary care J Dig Dis. 2021;22:159-166.
- 3 Chuah KH, Cheong SY, Lim SZ, Mahadeva S. Functional dyspepsia leads to more healthcare utilization in secondary care compared with other functional gastrointestinal disorders *J Dig Dis*. 2022;23:111-117.
- 4 Canavan C, West J, Card T. Review article: the economic impact of the irritable bowel syndrome *Alimentary pharmacology & therapeutics*. 2014;40:1023-1034.
- Chuah KH, Mahadeva S. Cultural factors influencing Functional Gastrointestinal Disorders in the East *Journal of neurogastroenterology* and motility. 2018; Lacy BE, Mearin F, Chang Let al. . Bowel Disorders *Gastroenterology*. 2016;150:1393-1407.e1395.
- 6 Pimentel M, Saad RJ, Long MD, Rao SSC. ACG Clinical Guideline: Small Intestinal Bacterial Overgrowth *Official journal of the American College* of Gastroenterology | ACG. 2020;115.
- 7 Chuah KH, Wong MS, Tan POet al. . Small Intestinal Bacterial Overgrowth In Various Functional Gastrointestinal Disorders: A Case-Control Study *Digestive diseases and sciences*. 2021.
- 8 Ghoshal UC, Shukla R, Ghoshal U. Small Intestinal Bacterial Overgrowth and Irritable Bowel Syndrome: A Bridge between Functional Organic Dichotomy *Gut and liver*. 2017;11:196-208.
- Tack J, Talley NJ, Camilleri Met al. . Functional gastroduodenal disorders *Gastroenterology*. 2006;130:1466-1479; Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders *Gastroenterology*. 2006;130:1480-1491.
- Miwa H, Ghoshal UC, Fock KMet al. . Asian consensus report on functional dyspepsia *Journal of gastroenterology and hepatology*. 2012;27:626-641; Gwee KA, Bak YT, Ghoshal UCet al. . Asian consensus on irritable bowel syndrome *Journal of gastroenterology and hepatology*. 2010;25:1189-1205.

- 11 Anuurad E, Shiwaku K, Nogi Aet al. . The new BMI criteria for asians by the regional office for the western pacific region of WHO are suitable for screening of overweight to prevent metabolic syndrome in elder Japanese workers *Journal of occupational health*. 2003;45:335-343.
- 12 Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress *Alimentary pharmacology & therapeutics*. 1997;11:395-402.
- 13 Yusoff N, Low WY, Yip CH. Psychometric properties of the Malay Version of the hospital anxiety and depression scale: a study of husbands of breast cancer patients in Kuala Lumpur, Malaysia Asian Pacific journal of cancer prevention : APJCP. 2011;12:915-917.
- 14 Mahadeva S, Wee H-L, Goh K-L, Thumboo J. The EQ-5D (Euroqol) is a valid generic instrument for measuring quality of life in patients with dyspepsia *BMC gastroenterology*. 2009;9:20-20.
- 15 Rezaie A, Buresi M, Lembo Aet al. . Hydrogen and Methane-Based Breath Testing in Gastrointestinal Disorders: The North American Consensus *The American journal of gastroenterology*. 2017;112:775-784.
- 16 Shah A, Talley NJ, Jones Met al. . Small Intestinal Bacterial Overgrowth in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis of Case-Control Studies *The American journal of gastroenterology*. 2020;115:190-201.
- 17 Drossman DA, Chang L, Bellamy Net al. . Severity in Irritable Bowel Syndrome: A Rome Foundation Working Team Report *Official journal* of the American College of Gastroenterology | ACG. 2011;106.
- 18 Yu V, Ballou S, Hassan Ret al. . Abdominal Pain and Depression, Not Bowel Habits, Predict Health Care Utilization in Patients With Functional Bowel Disorders *Official journal of the American College of Gastroenterology | ACG*. 2021;116.
- 19 Weerts Z, Vork L, Mujagic Zet al. . Reduction in IBS symptom severity is not paralleled by improvement in quality of life in patients with irritable bowel syndrome *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society.* 2019;31:e13629.
- Quigley EM, Murray JA, Pimentel M. AGA Clinical Practice Update on
 Small Intestinal Bacterial Overgrowth: Expert Review *Gastroenterology*.
 2020.
- 21 Pimentel M, Lembo A, Chey WDet al. . Rifaximin therapy for patients with irritable bowel syndrome without constipation *The New England journal of medicine*. 2011;364:22-32.
- 22 Rezaie A, Heimanson Z, McCallum R, Pimentel M. Lactulose Breath Testing as a Predictor of Response to Rifaximin in Patients With Irritable Bowel Syndrome With Diarrhea *Official journal of the American College of Gastroenterology | ACG.* 2019;114.

- 23 Beh KH, Chuah KH, Rappek NAM, Mahadeva S. The association of body mass index with functional dyspepsia is independent of psychological morbidity: A cross-sectional study *PLoS One*. 2021;16:e0245511.
- 24 Midenfjord I, Polster A, Sjövall H, Törnblom H, Simrén M. Anxiety and depression in irritable bowel syndrome: Exploring the interaction with other symptoms and pathophysiology using multivariate analyses *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society.* 2019;31:e13619.
- 25 Oka P, Parr H, Barberio B, Black CJ, Savarino EV, Ford AC. Global prevalence of irritable bowel syndrome according to Rome III or IV criteria: a systematic review and meta-analysis *Lancet Gastroenterol Hepatol*. 2020;5:908-917.
- 26 Losurdo G, Leandro G, Ierardi Eet al. . Breath Tests for the Non-invasive Diagnosis of Small Intestinal Bacterial Overgrowth: A Systematic Review With Meta-analysis *Journal of neurogastroenterology and motility*. 2020;26:16-28.

	Overall	SIBO	Non-SIBO	P-value
	(n=160)	(n=36)	(n=124)	
	(11 100)	(11 0 0)	(
$M_{a1a} = m(0/)$	50 (21.2)	11(20.6)	20(21.5)	0.010
Male, n (%)	50 (31.3)	11 (30.6)	39 (31.5)	0.919
Age, y	40 (30-62)	43 (31-66)	40 (31-60)	0.411
		, , ,	× /	
Ethnicity, n (%)				
Etimetty, II (70)				
				0.000
-Malay	92 (57.5)	25 (69.4)	67 (54.0)	0.230
-Chinese	43 (26.9)	9 (25.0)	34 (27.4)	
- Indian	23 (14.4)	2(5.6)	21 (16.9)	
- Illulall	23 (14.4)	2 (5.6)	21 (10.9)	
-Others	2 (1.3)	0	2 (1.6)	
Education, n (%)				
2				
Duine a ma	((2,0))	1 (2 0)	F(1,0)	0.252
-Primary	6 (3.8)	1 (2.8)	5 (4.0)	0.252

Table 1. Characteristics of overall study populations with and without SIBO

-Secondary	50 (31.3)	10 (27.8)	40 (32.3)	
-Vocational/College	37 (23.1)	5 (13.9)	32 (25.8)	
-Tertiary	67 (41.9)	20 (55.6)	47 (37.9)	
Body mass index,				
kg/m ²	11 (6.9)	3 (8.3)	8 (6.5)	0.981
<18.5	42 (26.3)	9 (25.0)	33 (26.6)	
18.5-22.9	23 (14.4)	5 (13.9)	18 (14.5)	
23-24.9	84 (52.5)	19 (52.8)	65 (52.4)	
>25				
Smoker, n (%)	7 (4.4)	0	7 (5.6)	0.161
Diabetes, n (%)	24 (15.0)	7 (19.4)	17 (13.7)	0.396
Taking proton pump	28 (17.6)	3 (8.3)	25 (20.3)	0.097
inhibitor, n (%)				
History of	43 (26.9)	10 (27.8)	33 (26.6)	0.890
abdominal pelvic				
surgery, n (%)				
IBS, n (%)	86 (53.8)	22 (61.1)	64 (51.6)	0.314
IBS-D, n (%)	54 (33.8)	18 (50.0)	35 (29.0)	0.019
Functional	36 (22.5)	9 (25.0)	27 (21.8)	0.683
dyspepsia, n (%)				
Functional	33 (20.6)	8 (22.2)	25 (20.2)	0.788
constipation, n (%)				
Non-FGIDs, n (%)	23 (14.4)	3 (8.3)	20 (16.1)	0.241

Overlap	15 (9.4)	5 (13.9)	10 (8.1)	0.226
IBS/Functional				
dyspepsia, n (%)				

SIBO, small intestinal bacterial overgrowth; IBS, irritable bowel syndrome; IBS-

D, diarrhea-predominant IBS; FGIDs, functional gastrointestinal disorders

Table 2. Characteristics of IBS patients with and without SIBO

	All IBS	SIBO	Non-SIBO	P-value
	(n=86)	(n=22)	(n=64)	
Male, n (%)	31 (36.0)	9 (40.9)	22 (34.4)	0.582
Age, y	57 (33-70)	64 (32-72)	54 (33-70)	0.443
Ethnicity, n (%)				0.178
-Malay	33 (38.4)	12 (54.5)	21 (32.8)	
-Chinese	32 (37.2)	8 (36.4)	24 (37.5)	
-Indian	20 (23.3)	2 (9.1)	18 (28.1)	
-Others	1 (1.2)	0	1 (1.6)	

	-Primary
	-Secondary
	-Vocational/Col
0	-Tertiary
	Body mass inde
0	kg/m ²
	<18.5
	18.5-22.9
	23-24.9
	>25
	Smoker, n (%)
p	Diabetes, n (%)
	Taking proton p
t(inhibitor, n (%)
	History of
	abdominal pelv
H	surgery, n (%)
	IBS-D, n (%)
0	Overlap
	IBS/Functional
7	dyspepsia, n (%

Education, n (%)				0.572
	5 (5 9)	1 (4 5)	4 (6.2)	
-Primary	5 (5.8)	1 (4.5)	4 (6.3)	
-Secondary	34 (39.5)	7 (31.8)	27 (42.2)	
-Vocational/College	7 (8.1)	1 (4.5)	6 (9.4)	
-Tertiary	40 (46.5)	13 (59.1)	27 (42.2)	
Body mass index,				
kg/m ²	9 (10.5)	3 (13.6)	6 (9.4)	0.850
<18.5	19 (22.1)	5 (22.7)	14 (21.9)	
18.5-22.9	12 (14.0)	2 (9.1)	10 (15.6)	
23-24.9	46 (53.5)	12 (54.5)	34 (53.1)	
>25				
Smoker, n (%)	2 (2.3)	0	2 (3.1)	0.552
Diabetes, n (%)	20 (23.3)	5 (22.7)	15 (23.4)	0.946
Taking proton pump	22 (25.6)	3 (13.6)	19 (29.7)	0.137
inhibitor, n (%)				
History of	32 (37.2)	8 (36.4)	24 (37.5)	0.924
abdominal pelvic				
surgery, n (%)				
IBS-D, n (%)	54 (62.8)	18 (81.8)	36 (56.3)	0.032
Overlap	15 (17.4)	5 (22.7)	10 (15.6)	0.518
IBS/Functional				
dyspepsia, n (%)				
Anxiety, n (%)	41 (47.7)	12 (54.5)	29 (45.3)	0.454
Depression, n (%)	22 (25.6)	8 (36.4)	14 (21.9)	0.179

SIBO, small intestinal bacterial overgrowth; IBS, irritable bowel syndrome; IBS-

D, diarrhea-predominant IBS; FGIDs, functional gastrointestinal disorders

 Table 3. Univariate analysis of the parameters of severe versus non-severe IBS

 patients

	Severe IBS	Non-severe	P-value
	(n=18)	(n=68)	
Male, n (%)	4 (22.2)	27 (39.7)	0.170
Age, y	56 (33-70)	63 (33-71)	0.443
Ethnicity, n (%)			
-Malay	7 (41.2)	28 (40.0)	0.836
-Chinese	5 (29.4)	26 (37.1)	

- Indian	5 (29.4)	15 (21.4)	
-Others	0	1 (1.4)	
Education, n (%)			0.591
Education, II (70)			0.391
-Primary	0	5 (7.4)	
-Secondary	7 (38.9)	27 (39.7)	
-Vocational/College	1 (5.6)	6 (8.8)	
-Tertiary	10 (55.6)	30 (44.1)	
Body mass index,			
kg/m ²			0.617
<18.5	2 (11.1)	7 (10.3)	
18.5-22.9	6 (33.3)	13 (19.1)	
23-24.9	2 (11.1)	10 (14.7)	
>25	8 (44.4)	38 (55.9)	
Smoking, n (%)	0	2 (2.9)	0.623
Diabetes, n (%)	6 (33.3)	14 (20.6)	0.202
Taking proton pump	7 (38.9)	15 (22.1)	0.126
inhibitor, n (%)			
Abdominal pelvic	6 (33.3)	26 (38.2)	0.702
surgery, n (%)			
Anxiety, n (%)	14 (77.8)	27 (39.7)	0.004
Depression, n (%)	9 (50.0)	13 (19.1)	0.011
IBS-D, n (%)	11 (64.7)	44 (62.9)	0.887
SIBO, n (%)	8 (44.4)	14 (20.6)	0.043

SIBO, small intestinal bacterial overgrowth; IBS, irritable bowel syndrome; IBS-

D, diarrhea-predominant IBS.

Table 4. Multivariate analysis for risk factors of severe IBS using logistic regression

	OR (95% CI)	P-value	AOR (95% CI)	P-value
Male	2.31 (0.69-	0.177	2.82 (0.73-	0.132
	7.75)		10.82)	
Taking proton	2.25 (0.74-	0.152	2.20 (0.58-	0.248
pump inhibitor	6.81)		8.28)	
SIBO	3.09 (1.03-	0.045	3.83 (1.02-	0.046
	9.27)		14.34)	

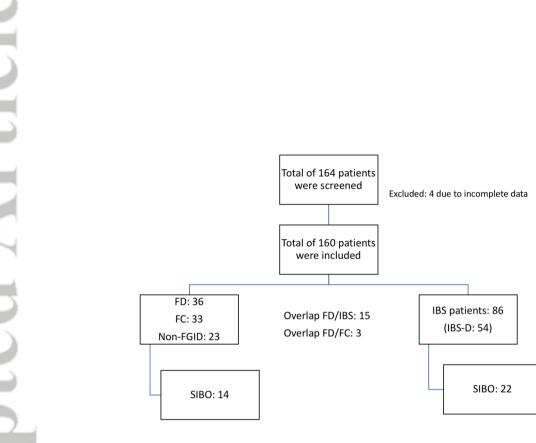
Anxiety	5.32 (1.58-	0.007	3.54 (0.87-	0.078
	17.87)		14.42)	
Depression	4.23 (1.40-	0.010	2.09 (0.57-	0.270
	12.76)		7.70)	

IBS, irritable bowel syndrome; OR, odd ratio, AOR; adjusted odd ratio; SIBO, small intestinal bacterial overgrowth

Figure Legends:

Figure 1 Flow chart of study population

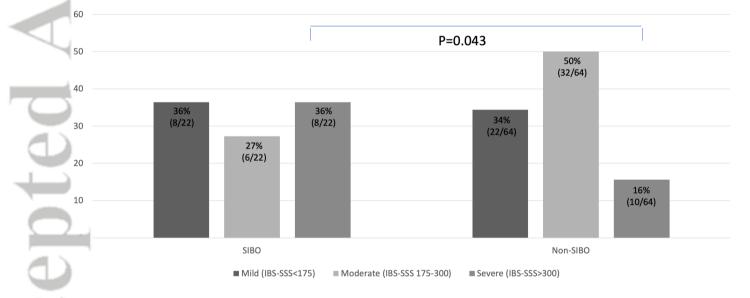
Figure 2 Frequency of SIBO amongst patients in different IBS categories Figure 3 Frequency of anxiety and depression amongst patients in different IBS categories



FD functional dyspepsia; FC, functional constipation; FGID, functional gastrointestinal disorder; IBS, irritable bowel syndrome; SIBO, small intestinal bacterial overgrowth

Figure 1 Impact SIBO IBS.tiff

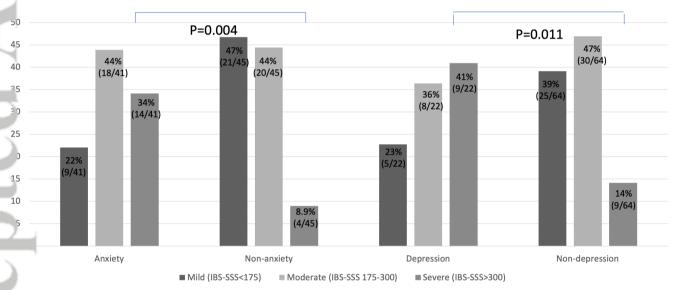
Frequency of SIBO amongst patients in different IBS categories



^s 3O, small intestinal bacterial overgrowth; IBS, irritable bowel syndrome; IBS-SSS, IBS symptom severity scale

Figure 2 Impact SIBO IBS.tiff

Frequency of anxiety and depression amongst patients in different IBS categories



" S, irritable bowel syndrome; IBS-SSS, IBS symptom severity scale

p

Figure 3 Impact SIBO IBS.tiff

Impact of Small Intestinal Bacterial Overgrowth in Patients with Irritable Bowel Syndrome on Symptoms and Quality of Life



Small intestinal bacterial overgrowth (SIBO) was the only independent factor associated with severe irritable bowel syndrome (IBS) at multivariate analysis.

The presence of SIBO was associated with poorer health-related quality of life.

JDD graphical abstract Image Impact SIBO IBS.tiff

The impact of small intestinal bacterial overgrowth (SIBO) on the symptoms and health-related quality of life (HRQOL) in irritable bowel syndrome (IBS) patients has not been studied before. This present study has demonstrated that diarrhoea-predominant IBS was significantly associated with SIBO. The presence of SIBO amongst patients with IBS was associated with more severe symptoms and a lower HRQOL.