PREVALENCE OF IRRITABLE BOWEL SYNDROME (IBS) AMONG HEALTHY SUBJECTS USING VALIDATED BAHASA MALAYSIA VERSION OF ROME III IBS QUESTIONNAIRE

BY

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PUM 1389

CONTENTS **Page**

CHAPTER ONE: INTRODUCTION

CHAPTER TWO: OBJECTIVES

CHAPTER THREE: METHODOLOGY

CHAPTER FOUR: RESULTS

CHAPTER SEVEN: LIMITATIONS

CHAPTER EIGHT: RECOMMENDATIONS

Abbreviations

BM	Bahasa Malaysia
CI	Confidence interval
CNS	Central Nervous System
FGIDS	Functional Gastrointestinal Diseases Syndrome
GI	Gastrointestinal
IBS	Irritable Bowel Syndrome
IBS-C	IBS with constipation
IBS-D	IBS with diarrhea
IBS-M	IBS with mixed bowel habit
IBS-U	IBS unspecified
IL	Interluekin
PI- IBS	Post infectious IBS
RM	Ringgit Malaysia
SD	Standard Deviation

List of Tables and Figures: **page**

ABSTRACT

Irritable bowel syndrome (IBS) is a very common chronic gastrointestinal disorder characterized by recurrent abdominal pain and altered bowel habits without major organic disease. ROME diagnostic criteria, based on subjective gastrointestinal (GI) complaints are the most widely used criteria for diagnosing IBS. We have developed Bahasa Malaysia version of ROME III IBS questionnaire for the study of IBS in Malaysia. This validated questionnaire was used to study the prevalence of IBS among healthy subjects.

The aims of this study were, 1) to validate the Bahasa Malaysia version of ROME III IBS questionnaire and ROME III psychosocial alarm questionnaire. 2) to determine the prevalence of IBS among normal healthy subjects in USM Health Campus, Kelantan using a validated Bahasa Malaysia version of ROME III IBS questionnaire and ROME III psychosocial questionnaire

This study was divided into two phases: 1) the validation process of the proposed translated questionnaire and 2) a cross sectional prospective studies to examine the prevalence of IBS among healthy subjects in a university campus.

The validated BM version of IBS ROME III questionnaire was shown to have good clinimetric properties. The prevalence of IBS among healthy subjects in USM Health Campus was 11.8%. Prevalence of IBS was significantly associated with age, ethnicity and level of formal education. Redflag and psychosocial alarm symptoms were higher in subjects with IBS.

This validated Bahasa Malaysia version of IBS ROME III questionnaire had good clinimetric properties suitable as a tool for research. Prevalence and characteristics of IBS among healthy subjects in USM Healthy Campus was almost similar to those reported in other Asian population.

1. INTRODUCTION

1.1 Overview of Irritable bowel syndrome (IBS)

1.1.1 Definition and disease description

IBS is defined as a functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habit, and with features of disordered defecation (Longstreth *et al.* 2006). IBS belongs to a group of functional bowel disorders, which also includes functional bloating, functional constipation, functional diarrhoea and unspecified functional bowel disorder. Functional bowel disorders are one of eight major domains in the large diagnostic group of functional gastrointestinal disorders. The main feature of IBS is recurrent abdominal pain or discomfort that is associated with disordered defecation and changes in bowel habit (Longstreth *et al.* 2006). Other characteristic symptoms for IBS and classified as supportive symptoms include: abnormal stool frequency (≤3 stools/week or >3/day), abnormal stool form, defecation straining, urgency, incomplete bowel movements, mucus and bloating. Based on these supportive symptoms, IBS is subdivided into IBS with diarrhoea (IBS-D), IBS with constipation (IBS-C) and IBS with mixed bowel habit (IBS-M) and unspecified (IBS-U).

The syndrome is chronic in nature, but it is associated with a good prognosis and has no increased mortality in long-term follow-up (Owens *et al.* 1995). Bowel habit in a patient often changes over time, and symptoms are typically fluctuating (Mearin *et al.* 2004). Extra-intestinal co-morbidity is often associated with IBS since specific disorders, such as headache, food allergy, musculoskeletal complaints, fibromyalgia and mood disorders, often overlap with IBS (Hillila *et al.* 2007). Moreover, IBS often co-exists with other functional GI disorders (Whitehead *et al.* 2007). A recent study, however, indicates that there were no specific co-morbid disorders that were associated with IBS (Whitehead et *al.* 2007). Instead, a general increase of disease incidence may be typical of IBS since the disorders that are most common in the general population (i.e. bacterial and viral infections, stroke) are the ones most common in IBS too. Excess co-morbidity may be due to hyper vigilance in noticing somatic sensations and to having a lower threshold for consulting a physician.

1.1.2 Epidemiology

Irritable bowel syndrome was the seventh most prevalent diagnosis amongst all physicians in the US based on data collected in the 1970s and 80s (Everhart and Renault 1991). Similarly, more recent data from the US show that IBS accounts for 19% of diagnoses made by GI specialists, and is therefore the most common diagnosis in the field of gastroenterology (Russo *et al.* 1999). The worldwide prevalence of IBS among

adults is estimated to be 10-20% (Hungin *et al.* 2005). Though the majority of prevalence figures are from Western populations, increasing data reveal that the syndrome is at least as prevalent in such non-Western societies as China, South Korea, India and Malaysia (Jain *et al.* 1991; Tan *et al.* 2003; Xiong *et al.* 2004; Park *et al.* 2007). It should, on the other hand, be taken into account that at least the urban areas are rapidly Westernising.

A prevalence study from Malaysia (Tan *et al.* 2003) found the prevalence of IBS in our multi-racial population approached the published Western figures. This study was done among healthy young subjects and used the ROME I criteria. Symptoms supportive of the diagnosis of IBS were common among young Malaysians, with a prevalence rate of 15.8%. There were significantly more women with IBS than men. Within the IBS population, the majority (77.4%) was of the IBS-C subgroup. A significantly higher prevalence of psychological and psychosomatic symptoms was found in individuals with IBS. Only a minority sought medical advice for their symptoms. There is yet any IBS study using the new Rome III criteria in Malaysia.

It is obvious that the definitions, diagnostic criteria and questionnaires employed influence the prevalence rates of IBS, and some studies have consequently shown prevalence figures below 10% (Kay *et al.* 1994; Andrews *et al.* 2005). When various set of diagnostic criteria were compared in a random adult population in Finland, the

prevalence of IBS by Manning 2 or Manning 3 (Manning *et al.* 1978), Rome I (Thompson *et al.* 1992) and Rome II (Thompson *et al.* 1999) criteria was 16.2%, 9.7%, 5.6% and 5.1%, respectively (Hillila and Farkkila 2004).

The precise incidence of IBS unknown, but the approximate incidence of the clinical diagnosis is estimated at 0.2% per year for each decade between 20 and 94 years (Camilleri *et al.* 2002). This may, on the other hand, be an underestimate of the true incidence, since only one in four IBS patients consults a physician (Talley *et al.* 1995). In general, there is a clear female predominance among IBS patients (Osterberg *et al.* 2000; Thompson *et al.* 2002; Hungin *et al.* 2003; Hungin *et al.* 2005). Even though there are few studies, which shows no gender difference such as done in U.S, Taiwan and India. Among those seeking health care services, women lead men in IBS diagnoses by a ratio of 2-4:1, whereas the distribution seems to be less than 2:1 in prevalence data that based on community surveys (Chang 2002). Possible explanations for the gender differences include social and cultural issues, such as health care seeking behaviour, and sex-related physiological differences in bowel function and pain sensitivity. In contrast to Western societies, IBS seems to be noticeably more predominant among men than women in India (Jain *et al.* 1991). This has been suggested to reflect cultural differences in health care seeking and accessibility (Chang 2002). IBS can affect people at any age, but the condition is most commonly diagnosed between ages 20 and 40, whereas organic GI diseases predominate in those over 60 (Talley 2002). IBS may also appear in childhood,

but data on prevalence are scarce. In some reports, IBS has been diagnosed in 6-14% of schoolchildren (Hyams *et al.* 1996) and 22%-45% of children aged 4-18 years presenting to tertiary care clinics (Walker *et al.* 2004).

1.1.3 Social and economic impact

Although IBS is non-life threatening, it is a painful, bothersome and distressing condition that interferes with daily life. IBS creates considerable direct and indirect costs to the society. Health related quality of life (HRQOL) is significantly lower in subjects with IBS compared to healthy controls (Amouretti *et al.* 2006). Overall, it appears that the more severe the IBS, especially symptom of abdominal pain, the more impaired the quality of life (Coffin *et al.* 2004; Amouretti *et al.* 2006). Non-consulting IBS patients have better quality of life than health care consulting patients, even though the former group also has slightly impaired HRQOL compared to healthy controls (Koloski *et al.* 2000). In comparison with other GI conditions, quality of life in IBS is significantly poorer than in those with reflux disease (Frank *et al.* 2002). Scores are also lower in selected domains compared to patients with diabetes, renal failure, asthma and migraine. In general, compromised HRQOL appears to be a common observation in patients with GI complaints, and data from the Medical Outcomes Study show that this group of patients scored amongst the lowest of all conditions studied, including conditions with high mortality such as heart failure (Stewart *et al.* 1989). It should, nevertheless, be kept

in mind that symptom severity is a strong predictor of HRQOL in IBS, and patients with mild IBS are thus not likely to score as low as subjects with serious diseases.

The symptoms of IBS represent one of the most common reasons for primary care visits, and consultation with a gastroenterologist. Based upon these observations, it should come as no surprise that the annual economic consequences of IBS are substantial which include direct medical cost and indirect costs largely resulting from work absenteeism and decreased productivity. Total health care utilization and, as a result, direct health care costs are higher amongst subjects with IBS than in control populations without IBS (Akehurst *et al.* 2002), even though the majority of IBS patients do not seek medical help (Talley *et al.* 1995). A majority of the excess costs result from medical care not directly related to GI problems. A recent review estimates that the total direct costs per IBS patient per year is between USD 348 and USD 8,750, which correlates to a 1.1- to 6-fold higher cost compared to matched non-IBS control groups (Maxion Bergemann *et al.* 2006). Compared to other GI problems, the costs per patient for IBS are lower than for inflammatory bowel diseases (IBD), but of the same magnitude as in gastro oesophageal reflux disease (Levy *et al.* 2001). The economic burden of IBS is partly due to loss of productivity: the average annual number of days off work due to IBS is calculated to be between 8.5 and 21.6 in the US and UK (Maxion-Bergemann *et al.* 2006). For comparison, this corresponds to an approximately 3-fold higher risk for absence from work in a US IBS population compared to non-IBS patients (Drossman *et al.* 1993)

1.1.4 Pathophysiologic Mechanisms

IBS is seen as a complex biopsychosocial condition in which a number of major mechanisms interact at the central and peripheral level (Drossman 2006). These include altered gut motility, enhanced visceral sensation, low-grade mucosal inflammation, abnormal brain-gut communication, psychosocial factors, food intolerance, intestinal microbiota and genetics. The prominence of any particular factor may vary from patient to patient.

1.1.4.1 Abnormal motility

Varieties of motor abnormalities have been described throughout the GI tract in IBS. Several distinct patterns of motility that vary in their intensity, type and location normally occur within the human GI tract. Overall, patients and healthy controls differ in quantitative, rather than qualitative, aspects of these motility patterns. In comparison with controls, IBS patients appear to have a delayed gastric emptying (Evans *et al.* 1997). Small bowel motility is altered in IBS in several ways: typical findings include a shorter duration of postprandial motor activity combined with episodes of clustered, recurring contractions correlating with abdominal pain (Kellow *et al.* 1990). Small bowel transit time is significantly shorter in IBS-D and longer in IBS-C, compared to controls (Cann *et al.* 1983). Both in the small and large bowel, IBS patients show an exaggerated response to a range of provocative stimuli. Basal non-stimulated large-bowel motility parameters,

such as the myoelectric activity (Bueno *et al.* 1980) and sigmoid-colonic motor activity (Chey *et al.* 2001), also appear to be altered in IBS. Similarly to the small bowel transit times, the whole gut and colonic transit times are shortened in IBS-D and prolonged in IBS-C (Cann *et al.* 1983; Chey *et al.* 2001; Dunlop *et al.* 2005). Besides aberrant gut transit, an impaired transit and tolerance of intestinal gas is suggested to be typical for IBS (Serra *et al.* 2001). This may be a consequence of altered gut motor function. Although abnormal GI motor patterns are frequently observed in IBS, the mechanism behind such dysmotility is largely unknown. It has been proposed that disordered functioning of the enteric nervous system and serotonin signalling may be involved.

1.1.4.2 Enhanced visceral perception

Visceral hypersensitivity, defined, as an increased sensation in response to intestinal stimuli, is one of the most commonly found hallmarks of IBS and other functional gastrointestinal disorders (Delvaux 2002). The phenomenon is a frequent, but not constant, finding in IBS patients. Evidence of visceral hypersensitivity in humans is principally based on barostat tests that measure the pain sensation caused by gastrointestinal balloon distension. In these study settings, IBS patients perceive the first sensation of pain at lower volumes or pressures than healthy controls or display increased pain scores for a specific stimulus (Whitehead *et al.* 1990; Kilkens *et al.* 2005). Furthermore, visceral hypersensitivity in IBS patients and controls is different with

regard to external stimuli (Posserud *et al.* 2004). As in the case of dysmotility, visceral hypersensitivity in IBS is not limited to the colon, and it should rather be considered as a generalised sensitisation of the GI tract (Trimble *et al.* 1995). Sensory thresholds may be interrelated with bowel habits, and evidence suggests that diarrhoea-predominant patients are more sensitive to distension compared with healthy controls, while patients with constipation tendency are equally or less sensitive compared with controls (Prior *et al.* 1990). Symptom types and intensity do not distinct hypersensitive and normosensitive IBS patients: subjects with enhanced visceral perception present comparable symptoms to those with normal sensitivity level (Kuiken *et al.* 2005). The threshold for somatic pain in IBS patients has been considered similar or even higher compared to healthy controls (Whitehead *et al.* 1990). The exact cause behind the enhanced visceral pain perception in IBS remains unknown, but studies point out that defects at both the peripheral and central level contribute to the phenomenon. Atypical gut parietal mechanoreceptors, possibly sensitised due to low-grade inflammation, may be some of the key players.

1.1.4.3 Gastroenteritis and low-grade inflammation

The term "post-dysenteric irritable bowel syndrome" was introduced nearly 50 years ago by Chaudhary and Truelove (1962), who described a subset of patients with "irritable colon syndrome" dated the onset of their symptoms to an attack of GI infection. Today, prospective studies showed a 4%-31% incidence of post-infectious IBS (PI-IBS)

following bacterial gastroenteritis (Spiller 2007). The relative risk for developing PI-IBS after acute gastroenteritis is estimated to be approximately 12 (Rodriguez and Ruigomez 1999). Most patients do not, however, develop PI-IBS, and the prevalence of IBS is not elevated in countries with high rates of enteric infection, which indicates that a range of risk factors are associated with PI-IBS. Factors associated with increased vulnerability for post-infectious IBS include a longer duration of the initial diarrheal disease (Neal *et al.* 1997), female gender (Neal *et al.* 1997; Gwee *et al.* 1999) and psychological factors, *e.g.* depression and the presence of adverse life events in the previous three months (Gwee *et al.* 1999; Dunlop *et al.* 2003). An age of over 60 years, in contrast, correlates with a protective effect against developing PI-IBS (Neal *et al.* 1997). Besides gastroenteritis, the use of antimicrobials for GI infection or other conditions also serves as an independent risk factor for developing functional bowel symptoms (Maxwell *et al.* 2002). Even though IBS patients have no identifiable inflammation on routine inspection of intestinal biopsies, there is an increasing amount of data showing that both post-infectious and unspecified IBS patients display a low-grade mucosal inflammation. Arrays of immunological cells and markers have been examined, and the levels of lymphocytes, mast cells and enterochromaffin cells are repeatedly found to be altered in the mucosa of IBS patients. Moreover, evidence of systemic immune activation is accumulating, as elevated levels of plasma pro-inflammatory interleukin (IL)-6 and IL-8 have been observed in IBS (Dinan *et al.* 2006). Peripheral blood mononuclear cells (PBMCs) of IBS patients also produce higher amounts of tumour necrosis factor-α, IL-1s, IL-6 and IL-12

in vitro than cells from healthy controls (O'Mahony *et al.* 2005). These findings are supported by genotyping studies indicating that IBS patients are predisposed towards a pro-inflammatory cytokine profile (van der Veek *et al.* 2005). Gut barrier function is tightly interlinked with inflammation since permeability is increased both by inflammatory cytokines and by bacterial gastroenteritis (Chavez *et al.* 1999; Spiller *et al.* 2000). In parallel with studies on cytokine imbalance in IBS, evidence is mounting that there may be an IBS subgroup with increased mucosal permeability (Spiller *et al.* 2000; Marshall *et al.* 2004; Dunlop *et al.* 2006). The involvement of inflammation in neuromotor function is also supported by the finding that, both in normal and in inflamed mucosa, immunocytes lie in intimate contact with nerve fibres, providing an anatomical basis for a functional interplay between immune cells and the enteric nervous system (Stead *et al.* 1987).

1.1.4.4 Brain-gut communication

Perturbations in the brain-gut axis are increasingly recognised as underlying pathophysiological factors in functional GI disorders. The brain-gut axis is considered a model describing the complex bidirectional neural pathways connecting the brain with the gut neuroendocrine centres, the enteric nervous system and the immune system (Aziz and Thompson 1998). Disturbed brain-gut communication is not an independent pathophysiological factor in IBS, as the brain gut axis is the key regulator of *e.g.* gut

motor activity and visceral perception, both known to be changed in IBS. Altered communication between the central nervous system (CNS) and the gut is thus tightly interlinked with other established pathophysiological phenomena in IBS. Overall, brain-gut interactions play an important role in the regulation of many vital functions both in health and in disease. Digestive functions, including motility, secretion, mucosal transport and blood flow are coordinated by the CNS in a top-down manner (for review, see Costa and Brookes 1994). Conversely, signals from the gut play a role in reflex regulation and pain perception in a bottom-up manner (Randich and Gebhart 1992). The CNS functions as a "filter" with regard to the perception of peripheral afferent signals, and the brain-gut communication is for the most part not consciously perceived: only very few of the signals reaching the brainstem and thalamus are consciously perceived in the cortex (Rosen *et al.* 1996). The brain-gut axis is stimulated by various stressors, as shown by the fact that acute intestinal inflammation is associated with central sensitisation , whereas psychological events alter gut function (Monnikes *et al.* 1993; Nakade *et al.* 2007). Symptoms of IBS are thought to be produced by primary alterations in the CNS, by primary alterations in the periphery, or by a combination of both.

Evidence for central alterations in IBS comes from studies using functional brain imaging techniques where different brain areas involved in pain processing are activated in IBS patients vs. controls following painful rectal stimuli (Silverman *et al.* 1997). Central processing may also distinguish between different bowel habits, as demonstrated by

lower parasympathetic tone and higher autonomic nervous system balance in constipation-predominant vs. diarrhoea-predominant patients (Heitkemper *et al.* 2001). The role of the central and the autonomic nervous system in IBS pathophysiology is supported by findings of sleep disturbances, and especially an enhancement of rapid eye movement sleep in IBS (Orr *et al.* 1997). Studies presenting elevated levels of corticotropin-releasing and adrenocorticotropic hormones as well as alterations of the visceral perception in IBS patients following mental stress also point towards disturbed brain-gut interaction (Posserud *et al.* 2004).

Numerous neurotransmitters are involved in the regulation of the brain-gut axis. Amongst those, serotonin is of particular interest. Serotonin effects on gut motility, secretion and sensation as well as on cognition and mood make it of paramount relevance in IBS pathophysiology (Mawe *et al.* 2006). Acute lowering of serotonin synthesis reduces the threshold for painful stimuli and induces a depression-like memory bias both in IBS patients and in control subjects, illustrating the essential role of serotonergic modulation in the brain-gut axis (Kilkens *et al.* 2004). In contrast, increased 5-HT activity induced by citalopram is associated with enhanced affective memory performance biased towards positive words (Kilkens *et al.* 2005). Several elements of serotonin signaling are altered in IBS. Another important group of molecules affecting the brain-gut is prostaglandins, which appear to exert their effects via peripheral mechanisms in the GI tract rather than via central mechanisms (Dajani *et al.* 2003).

1.1.4.5 Genetics

Aggregation of symptoms of abdominal pain or bowel disturbances has been described in relatives of IBS patients (Saito *et al.* 2005). Familial studies suggest that a modest genetic contribution is involved in IBS pathophysiology (Saito *et al.* 2005). Findings comparing monozygotic and dizygotic twin pairs are controversial as a number of studies show a genetic factor in aetiology (Bengtson *et al.* 2006), while others fail to demonstrate a hereditary component (Mohammed *et al.* 2005). It also appears that children of parents with IBS tend to use health care more frequently for GI complaints than children of parents not suffering from the condition (Levy *et al.* 2000). Genotyping studies reveal that IBS, and particularly a diarrhoea-predominant bowel habit, may be associated with different polymorphisms in the serotonin transporter gene (Park *et al.* 2006c; Saito *et al.* 2007). Moreover, a pharmacogenetic study suggests that polymorphisms of the serotonin transporter gene predict the response to 5-HT3 antagonist therapy (Camilleri *et al.* 2002a). Besides putative serotonin transporter polymorphisms, little is known about other genetic variants that may affect expression of irritable bowel syndrome. In addition to genetic inheritance, the tendency of IBS to run in families could also be due to social learning (Levy *et al.* 2000). Parental modelling and reinforcement of illness behaviour seem to contribute to the development of IBS with an effect at least as large as hereditary.