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Epidemiology of small intestinal bacterial overgrowth

Efremova I *et al.* Epidemiology of SIBO

Abstract

Small intestinal bacterial overgrowth (SIBO) is defined as an increase in the bacterial content of the small intestine above normal values. The presence of SIBO is detected in 33.8% of patients with gastroenterological complaints who underwent a breath test, and is significantly associated with smoking, bloating, abdominal pain, and anemia. Proton pump inhibitor therapy is a significant risk factor for SIBO. The risk of SIBO increased with age and did not depend on gender or race. SIBO complicates the course of a number of diseases and may be of pathogenetic significance in the development of their symptoms. SIBO is significantly associated with functional dyspepsia, irritable bowel syndrome, functional abdominal bloating, functional constipation, functional diarrhea, short bowel syndrome, chronic intestinal pseudo-obstruction, lactase deficiency, diverticular and celiac diseases, ulcerative colitis, Crohn's disease, cirrhosis, metabolic-associated fatty liver disease (MAFLD), primary biliary cholangitis, gastroparesis, pancreatitis, cystic fibrosis, gallstone disease, diabetes, hypothyroidism, hyperlipidemia, acromegaly, multiple sclerosis, autism, Parkinson's disease, systemic sclerosis, spondylarthropathy, fibromyalgia, asthma, heart failure, and other diseases. The development of SIBO is often associated with a slowdown in orocecal transit time that decreases the normal clearance of bacteria from the small intestine. The slowdown of this transit may be due to motor dysfunction of the intestine in diseases of the gut, autonomic diabetic polyneuropathy, portal hypertension, or a decrease in the motor-stimulating influence of thyroid hormones. In a number of diseases, including cirrhosis, MAFLD, diabetes, and pancreatitis, an association was found between disease severity and the presence of SIBO. Further work on the effect of SIBO eradication on the condition and prognosis of patients with various diseases is required.

Key Words: Gut microbiota; Gut-liver axis; Breath test; Lactulose; Methane; Hydrogen

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Core Tip: Small intestinal bacterial overgrowth (SIBO) is common in functional and organic bowel diseases, liver diseases, other diseases of the digestive organs, a number of endocrine, nervous and rheumatic diseases, asthma, heart failure, and certain other diseases. In a number of diseases, including cirrhosis, metabolic-associated fatty liver disease, diabetes mellitus, pancreatitis, and cystic fibrosis, an association was found between disease severity and the presence of SIBO. Further work on the effect of SIBO eradication on the condition and prognosis of patients in various diseases is required.

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INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) is defined as an increase in the bacterial content of the small intestine above normal values (100000 cells per mL)^[1-4]. This leads to excessive gas formation in the small intestine, bloating, and pain in the umbilical region, which may be accompanied by malabsorption, malnutrition, and osmotic diarrhea. The main causes of SIBO are dysfunctional movement of contents through the small intestine [delayed orocecal transit time (OCTT)], ²⁸ reduced gastric acid secretion [for example, due to the use of proton pump inhibitors (PPI) or after gastric surgery], and reflux of the colon contents into the small intestine due to ileocecal valve dysfunction^[1-4].

Interest in SIBO is increasing, as evidenced by the continuous growth in publications on this topic indexed in PubMed (Figure 1). An important issue is the standardization of SIBO diagnosis. The main diagnostic methods are lactulose and glucose breath tests (GBTs), as well as jejunal bacterial culture quantification^[5-7]. Unfortunately, the results obtained using these different methods do not always correspond, which may explain the variation in results between different studies that use different tests. In addition, while SIBO was initially associated with hydrogen release, it is now accepted that SIBO

can also accompany the formation of methane. Methane SIBO and hydrogen SIBO are not only detected with different frequencies, but can also have different effects. It is important that the test for hydrogen SIBO does not detect methane SIBO and vice versa^[8,9].

SIBO complicates the course of a number of diseases and may be of pathogenetic significance in the development of their symptoms^[1-4]. The aim of this review is to provide up-to-date information on the association of SIBO with various diseases and their manifestations.

PATIENTS WITH GASTROENTEROLOGICAL COMPLAINTS

The presence of SIBO was detected in 33.8% of patients with gastroenterological complaints who underwent a breath test, and was significantly associated with smoking [odds ratio (OR) = 6.66], bloating (OR = 5.39), abdominal pain (OR = 4.78), and anemia (OR = 4.08)^[10]. The risk of SIBO increased with age [OR = 1.04, 95% confidence interval (CI): 1.01-1.07]^[11] and did not depend on gender or race^[11,12]. Ileocecal junction pressure was lower, small bowel, colonic and whole gut transit times were longer, and gastric and small bowel physiology was higher in patients with SIBO than those without^[13,14]. There were no significant differences in gastric emptying time and other small intestinal motility parameters (small intestinal motility index, contractions per minute, and peak amplitudes)^[13,15], or in fecal calprotectin levels^[16]. SIBO was more frequent in patients who consumed a moderate amount of alcohol than in abstainers (58% vs 39%)^[17]. SIBO was identified in 63% of children with abdominal pain^[18].

DIET

Patients with SIBO consumed lower amounts of dietary fiber and red meat than SIBO-negative individuals. Those with methane SIBO consumed more fruits, vegetables, and fish compared with those with other variants of SIBO and the control group, while individuals with hydrogen SIBO ate more poultry than those with other SIBO types and

controls^[19]. SIBO was detected more frequently in preschool children who were on a long-term dairy-free diet than in children on a regular diet (55.0% *vs* 20.0%)^[20].

PPI THERAPY

⁴ A meta-analysis of 19 studies revealed that PPI therapy is a significant risk factor for SIBO (OR = 1.71, 95%CI: 1.20-2.43)^[21]. The prevalence of SIBO increased after 1 year of continuous PPI use^[22]. Interestingly, SIBO following PPI therapy is associated with decreased OCTT, and the concomitant use of prokinetics in patients receiving PPI reduces the risk of SIBO by increasing OCTT^[23]. In older patients undergoing long-term PPI therapy, the prevalence of SIBO was higher than in patients not receiving PPI (77.1% *vs* 58.3%) and increased significantly when the administration time was longer than 6 mo^[24]. The prevalence of SIBO was also higher in older patients undergoing continuous PPI therapy (88.6%) than in those receiving on-demand PPI therapy (65.7%); no significant difference was found in the incidence of SIBO between on-demand PPI and control groups^[24].

FUNCTIONAL DIGESTIVE DISEASES

Breath tests revealed that 68.1% of patients with functional bowel diseases also had SIBO^[25].

Functional dyspepsia

A meta-analysis of 7 studies found that the prevalence of SIBO in functional dyspepsia is 34.7% (95%CI: 24.8%-45.4%)^[26]. Another meta-analysis found SIBO prevalence in functional dyspepsia to be significantly higher using the lactulose breath test (LBT) ¹⁴ (53.4%, 95%CI: 33.9%-71.9%) compared with the GBT (17.2%, 95%CI: 8.6%-31.6%). There was no significant difference in SIBO prevalence between patients with different subtypes of functional dyspepsia. The risk of SIBO in patients with functional dyspepsia was significantly higher than in controls (OR = 4.3, 95%CI: 1.1-17.5)^[27].

Irritable bowel syndrome

A meta-analysis of 37 studies revealed that the prevalence of SIBO in irritable bowel syndrome (IBS) was 36.7% (95%CI: 24.2%-44.6%). The lactulose hydrogen breath test (LHBT) for SIBO was positive in patients with IBS no more often than in the control group [risk ratio (RR) =1.6, 95%CI: 0.9-2.8], while SIBO was detected in patients with IBS significantly more often than in controls using the glucose hydrogen breath test (RR = 4.2, 95%CI: 3.0-5.9) and upper gut aspirate culture (RR = 3.2, 95%CI: 1.4-7.3). Patients with diarrhea-predominant IBS (IBS-D) were more likely to have SIBO than patients with other subtypes (OR = 1.4, 95%CI: 1.02-1.63)^[28].

Another meta-analysis of 25 studies showed that SIBO prevalence in patients with IBS was significantly higher than in controls [31.0% (95%CI: 29.4%-32.6%) *vs* 20.9% (95%CI: 19.5%-22.2%); OR = 3.7 (95%CI: 2.3-6.0)] for all studies, OR = 4.9 (95%CI: 2.8-8.6) for studies using only healthy controls, and OR = 1.3 (95%CI: 0.6-3.3) for studies using non-IBS disease controls). Using breath testing, SIBO prevalence in patients with IBS was 35.5% (95%CI: 33.6%-37.4%) *vs* 29.7% (95%CI: 27.6%-31.8%) in controls. Culture-based studies found an SIBO incidence of 13.9% (95%CI: 11.5%-16.4%) in patients with IBS and 5.0% (95%CI: 3.9%-6.2%) in controls. SIBO prevalence as diagnosed by LBT was much greater in patients with IBS (3.6-fold) and controls (7.6-fold) than that diagnosed by GBT. Similar differences were observed when LBT was compared with the bacterial culture method of diagnosis. SIBO prevalence was greater in patients with IBS-D (35.5%, 95%CI: 32.7%-40.3%) compared with patients with constipation-predominant IBS [IBS-C; 22.5% (95%CI: 18.1%-26.9%); OR = 1.8 (95%CI: 1.2-2.8) *vs* IBS-D] and mixed IBS (25.2%, 95%CI: 22.2%-28.4%). PPI use by patients with IBS was not associated with SIBO (OR = 0.8, 95%CI: 0.5-1.5). The prevalence of SIBO both in patients with IBS and controls was greatest in the United States (54.6%, 95%CI: 51.2%-58.0%) and 37.2% (95%CI: 34.7%-39.7%), respectively, followed by Europe [23.4% (95%CI: 21.1%-26.0%) and 8.1% (95%CI: 6.6%-9.6%), respectively] and lowest in India [14.1% (95%CI: 11.5%-16.7%) and 1.1% (95%CI: 0%-2.2%), respectively]^[29].

The third meta-analysis revealed that among patients with IBS, female sex (OR = 1.5, 95%CI: 1.0-2.1), older age [standard mean difference 3.1 years (95%CI: 0.9-5.4)], and IBS-D (OR = 1.7, 95%CI: 1.3-2.3) compared with other IBS subtypes increased the odds of SIBO^[30]. Separately, a meta-analysis of studies investigating methane SIBO in IBS was performed. It showed that the incidence of methane SIBO in patients with IBS was 25.0% (95%CI: 18.8%-32.4%), not significantly different from that in the control group (OR = 1.2, 95%CI: 0.8-1.7). In patients with IBS, LBT provided positive results for methane SIBO almost three times as often as GBT [29.0% (95%CI: 20.9%-38.6%) vs 11.5% (95%CI: 5.0%-24.3%)]. In contrast with hydrogen SIBO, the prevalence of methane SIBO in patients with IBS-C was higher than in those with IBS-D [37.7% (95%CI: 33.5%-42.1%) vs 12.4% (95%CI: 10.2%-14.9%); OR = 3.1 (95%CI: 1.7-5.6)]^[31].

Serum interleukin (IL)-1 β levels in SIBO-positive patients with IBS were higher and serum IL-10 levels were lower than in the SIBO-negative group^[32]. Another study also showed that increased IL-1 α and IL-1 β levels were associated with SIBO^[33]. A third study reported that IL-10 levels were reduced in IBS patients with SIBO compared with those without, but found no significant differences in serum tumor necrosis factor (TNF)- α , IL-6 and IL-8 concentrations^[34].

The body mass index (BMI) of patients with IBS-D and SIBO was significantly lower than of those without SIBO. IBS-D patients with SIBO had higher scores of abdominal pain than those without SIBO in this study. The proportion of dietary fat was significantly higher in IBS patients with SIBO than in those without SIBO. Breath methane peak value was positively correlated with the proportion of fat in the diet^[35]. Another study also showed that in non-constipation IBS, patients with SIBO had lower BMI and waist circumference than patients without SIBO. Moreover, multivariate analysis revealed that the OR of SIBO was 0.396 for obesity and 0.482 for abdominal obesity^[36].

The presence of SIBO did not affect IBS symptoms in another study^[37], although OCTT was significantly increased in SIBO-positive compared with SIBO-negative patients^[37]. Intestinal permeability did not differ significantly between IBS patients with

and without SIBO^[38]. The severity of anxiety, depression, and other psychological disorders was not different between patients with IBS who were positive and negative for hydrogen SIBO^[34]. Another study confirmed that the severity of IBS symptoms and associated psychological disorders did not differ between SIBO-positive and negative patients^[39]. However, it has been shown that IBS patients with SIBO who are predominant methane producers have higher urge thresholds for colon contraction and higher baseline levels of colon phasic contractions than SIBO-negative IBS patients, and report more 'hard or lumpy stools' compared with patients who are predominant hydrogen producers and those who are SIBO-negative^[39]. This is consistent with the findings that hydrogen SIBO is more prevalent in IBS-D, whereas methane SIBO is more prevalent in IBS-C^[30,31]. In children with IBS, the prevalence of SIBO was significantly higher than in control subjects [65% *vs* 7%; OR = 3.9 (95%CI: 7.3-80.1)]. Among abdominal symptoms, significant differences were observed only in bloating^[40].

Other functional digestive diseases

Tests for SIBO were positive in 43% of patients with functional abdominal bloating/distention^[41] (although this proportion reached 68% in another study^[42]), 73% of those with functional constipation^[42], and 69% of those with functional diarrhea^[42].

ORGANIC GUT DISEASES

Non-steroidal anti-inflammatory drug-induced small intestinal damage

LHBT was positive in 59% of patients with and 24% of patients without severe non-steroidal anti-inflammatory drug (NSAID)-induced small intestinal damage. Multiple regression analysis showed that SIBO was significantly associated with severe NSAID-induced small intestinal damage (OR = 6.54, 95%CI: 1.40-30.50). However, there was no significant difference in symptoms between patients with severe small intestinal damage with and without SIBO^[43].

Short bowel syndrome

SIBO was found in 50% of children with short bowel syndrome and predisposed these patients to ambulatory central line-associated bloodstream infection (RR = 1.87, 95%CI: 1.1-3.17)^[44].

Chronic intestinal pseudo-obstruction

Methane SIBO was detected more frequently in patients with chronic intestinal pseudo-obstruction than in patients with other diseases (52.6% *vs* 11.8%), while no significant difference was found in the prevalence of hydrogen SIBO between these groups (23.7% *vs* 25.7%)^[45].

Lactase deficiency and lactose malabsorption

SIBO was detected at a significantly higher rate in patients with lactase deficiency than in healthy controls (27.6% *vs* 6.7%)^[46]. SIBO was found in 90% of asymptomatic well-nourished older people with lactose malabsorption compared with 20% of those without it^[47].

Symptomatic uncomplicated diverticular disease

SIBO was found in 58.9% of patients with symptomatic uncomplicated diverticular disease (SUDD), more specifically in 93.1% of patients with diarrhea-prevalent disease and 42.6% of patients with constipation-prevalent disease^[48]. OCTT was delayed in 92.5% of SUDD patients with SIBO and 48.6% of patients without SIBO (OR = 12.9). Lactose malabsorption was identified in 92.5% of SUDD patients with SIBO and 27.0% of patients without SIBO (OR = 33.0)^[48].

Celiac disease

A meta-analysis of 14 studies showed that SIBO was more prevalent in patients with celiac disease than in controls [18.3% (95%CI: 11.4-28.1)^[1]; OR = 5.1, 95%CI: 2.1-12.4]. The prevalence of SIBO as diagnosed by breath tests was 20.8% (95%CI: 11.9%-33.7%), while that of SIBO identified by culture-based methods was 12.6% (95%CI: 5.1%-28.0%).

¹ The prevalence of SIBO in patients with celiac disease was lower in the United States [8.7% (95%CI: 6.1%-11.9%)] than in ² Asia [22.1 (95%CI: 15.4%-30.2%)] and Europe [23.3% (95%CI: 17.5%-29.9%)]. SIBO prevalence in non-responders to a gluten-free diet was similar to that in responders. Antibiotic therapy for SIBO in patients with celiac disease ³ resulted in an improvement in gastrointestinal symptoms in 95.6% (95%CI: 78.0%-99.9%) of cases. There were no ² significant differences between the degree of intestinal damage as measured by histology or celiac serology between patients with celiac disease with and without SIBO. ² Patients with celiac disease and SIBO tended to be older and have more severe signs of malabsorption (lower hemoglobin, serum beta-carotene and albumin levels, and higher fecal fat level), compared with those without SIBO^[49]. SIBO was present in 67% of celiac patients with persistence of gastrointestinal symptoms and histological response to gluten-free diet^[50].

¹⁵ *Environmental enteric dysfunction*

Environmental enteric dysfunction is an incompletely defined syndrome of inflammation, reduced absorptive capacity and barrier dysfunction in the small intestine. It is widespread in low- and middle-income countries^[51]. The prevalence of SIBO is 85.3% in children with stunted growth due to this disease^[52].

Inflammatory bowel disease

A meta-analysis of 11 studies revealed that the proportion of SIBO in patients with inflammatory bowel disease (IBD) was greater than in controls [22.3% (95%CI: 19.92%-24.68%); OR = 9.51 (95%CI: 3.39-26.68)]. The severity of abdominal symptoms (bloating, flatulence, satiety, loose stools) was also greater in patients with SIBO than in those without SIBO. Patients with SIBO had increased stool frequency, lower body weight, and prolonged OCTT compared with SIBO-negative patients^[53]. The prevalence of methane SIBO was assessed in a meta-analysis of 6 studies which did not reveal a significant difference between patients with IBD and healthy individuals^[31]. The incidence of SIBO

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was significantly higher in patients with Crohn's disease (CD) compared with patients with ulcerative colitis (UC)^[54].

CD

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A meta-analysis showed that the prevalence of SIBO in CD was higher than in controls [25.4% (95%CI: 22.5%-28.3%); OR = 10.9 (95%CI: 2.8-42.69)]. CD patients who had undergone prior surgery were more likely to test positive for SIBO than those who had not [31.8% (95%CI: 26.7%-36.9%) *vs* 19.2% (95%CI: 15.4%-23.0%); OR = 2.4 (95%CI: 1.7-3.4)]. The prevalence of SIBO in CD was highest [33% (95%CI: 19.2%-50.6%)] in patients following ileocecal valve surgery. Among different forms of the disease, fibrostenosing CD was the only one associated with an increased risk of SIBO [OR = 7.5 (95%CI: 2.5-22.2)]. No association was found between the prevalence of SIBO and CD activity index score, or thiopurine or biologic treatment^[53].

OCTT was significantly longer in patients with CD with SIBO than in those without^[54]. SIBO also occurred more frequently in patients who had CD recurrence within 18 mo than in those who remained in remission (63.0% *vs* 37.0%; OR = 2.79). Relapses were more frequent in patients with SIBO than in those without (26.5% *vs* 7.7% at the 6-mo follow-up, and 50.0% *vs* 25.6% at the 18-mo follow-up)^[55].

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CD patients with and without SIBO were comparable with regard to demographics, systemic inflammatory biomarkers, and disease characteristics, except for the fibrostenosing phenotype that was more common in patients with SIBO than in those without [43.3% *vs* 19.3%; OR = 3.8 (95%CI: 1.5-6.8)]. Fecal calprotectin levels were significantly higher in SIBO-positive than in SIBO-negative patients (OR = 9.4, 95%CI: 3.0-11.3)^[56].

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Another study reported that CD patients with SIBO had increased stool frequency and significant reduction of stool solidity, were older, reported a longer history of CD, and were significantly more likely to have had prior surgery than CD patients without SIBO. An association was identified between the number of surgical procedures and the presence of SIBO (OR = 2.83, 95%CI: 1.15-6.96)^[57].

In CD patients in remission, the prevalence of SIBO was 16.8%. No associations were observed between SIBO in these remission patients and the use of thiopurine or biological drugs.³ Multivariate analysis revealed that the presence of meteorism and a fistulizing phenotype were associated with the presence of SIBO in patients in remission for CD^[58].

UC

¹⁰ A meta-analysis showed that the prevalence of SIBO in patients with UC was greater than in controls [14.3% (95%CI: 10.52%-18.1%); OR = 8.0 (95%CI: 1.67-38.4)]^[31]; OCTT has also been shown to be significantly longer in these patients than in controls^[54]. Serum levels of lipopolysaccharide (LPS), and the expression levels of toll-like receptor (TLR)2 and TLR4 on the surface of peripheral blood mononuclear cells in UC patients with SIBO were higher than in those without SIBO. LPS levels were positively correlated with expression levels of TLR2 and TLR4^[59]. Serum levels of pro-inflammatory cytokines (IL-6, IL-8, and TNF- α), anti-inflammatory cytokines (IL-10), and lipid peroxidates (a marker of oxidative stress) were significantly higher, and levels of reduced glutathione (antioxidant) were lower in UC patients with SIBO than in those without SIBO^[60].

LIVER DISEASES

In a mixed cohort of patients with various liver diseases, SIBO prevalence was significantly higher in patients with cirrhosis than in those without (41.2% vs 13.1%). Moreover, both cirrhotic and non-cirrhotic patients had a greater SIBO prevalence than healthy controls^[61].

Cirrhosis

A meta-analysis of 21 studies revealed that the prevalence of SIBO in patients with cirrhosis was greater than in healthy controls (40.8%, 95%CI: 34.847.1%-) and OR = 6.83 (95%CI: 4.1611.21-) for all studies; 48.0% (95%CI: 27.569.1%-) and OR = 5.32 (95%CI:

1.0227.82-) for studies using culture-based methods; 52.7% (95%CI: 43.961.4%-) and OR = 3.24 (95%CI: 1.34-7.84) for studies using LBT; and 35.9% (95%CI: 30.641.6%-) and OR = 8.65 (95%CI: 4.30-14.42) for studies using GBT. The prevalence of SIBO in patients with decompensated cirrhosis (classes B and C) was higher than in those with compensated cirrhosis class A [50.5% (95%CI: 40.360.7%-) vs 31.2% (95%CI: 19.945.1%-); OR = 2.56 (95%CI: 1.604.09-)]. The prevalence of SIBO was higher in patients with cirrhosis class C than in patients with cirrhosis class B [59.2% (95%CI: 45.0%-71.7%) vs 47.6% (95%CI: 35.9%-59.5%); OR = 1.79 (95%CI: 1.18-2.71)]^[62].

Patients with cirrhosis and SIBO were more likely to have ascites, minimal hepatic encephalopathy, and spontaneous bacterial peritonitis than those without SIBO. SIBO relationship with hypocoagulation, alanine aminotransferase and glutamyl transpeptidase activity, white blood cell and platelet counts, hemoglobin and ascitic fluid albumin levels, or esophageal varices was not found^[62]. Recent meta-analyses have shown that SIBO in cirrhosis is associated with hepatic encephalopathy (OR = 4.43, 95%CI: 1.73-11.32)^[63]. Short-term treatment with rifaximin effectively reduced blood ammonia levels, improved psychometric test scores, and reduced the rate of SIBO as determined by breath testing^[64]. No significant association was found between SIBO and hepatic venous pressure gradient^[65]. SIBO in patients with cirrhosis was associated with the presence of bacterial DNA in peripheral blood^[66], higher plasma LPS levels^[67], a shift to an alkaline pH in gastric juices^[68], malnutrition^[69], prolonged OCTT^[70,71], lower systolic blood pressure and systemic vascular resistance, higher cardiac output and serum C-reactive protein levels^[72], splanchnic vasodilation and abdominal hyperdynamic circulation^[73].

In patients with cirrhosis, gut microbiota changes with SIBO (a higher abundance of *Firmicutes* and *Fusobacteria*, and a lower abundance of *Bacteroidetes*) did not correspond to cirrhosis-associated gut dysbiosis; therefore, it can be assumed that gut dysbiosis and SIBO are most likely independent disorders of gut microbiota in patients with cirrhosis^[74].

Hepatocellular carcinoma

The incidence of SIBO in patients with hepatocellular carcinoma (HCC) was higher than in cirrhosis patients without HCC (71.8% *vs* 41.1%; OR = 3.7) and healthy controls (71.8% *vs* 3.0%; OR = 81.5). The expression levels of TLR2 and TLR4 on the surface of peripheral blood mononuclear cells in patients with HCC and SIBO were higher than in patients without SIBO^[75].

Extra-hepatic portal vein obstruction

Patients with extra-hepatic portal vein obstruction had similar rates of SIBO compared with healthy controls (7.14% *vs* 1.97%)^[76].

Metabolic-associated fatty liver disease

A meta-analysis of 18 studies revealed that, among patients with metabolic-associated fatty liver disease (MAFLD), the rate of SIBO was 35.0% (95%CI: 24.4%-47.2%); in patients with metabolic-associated steatohepatitis (MASH), the rate of SIBO was 41.1% (95%CI: 21.9%-63.4%)^[77]. The prevalence of SIBO in MAFLD was a higher than in controls (OR = 3.82, 95%CI: 1.93-7.59) in another meta-analysis that included 10 studies^[78].

Patients with MAFLD and SIBO had increased OCTT; echomarkers of liver steatosis and fibrosis; severity of liver steatosis, fibrosis, lobular and portal inflammation, and ballooning by liver biopsy; levels of hepatic *CD14* mRNA, nuclear factor kappa beta mRNA, and TLR4 protein expression; homeostatic model assessment for insulin resistance scores; and serum LPS levels compared with patients without SIBO. However, there was no significant difference in BMI, or in serum levels of TNF- α , adiponectin, glutamyl transpeptidase, triglycerides, or low-density lipoprotein between MAFLD patients with and without SIBO. SIBO was associated with significant fibrosis and MASH in MAFLD^[79-81]. However, the presence of abdominal obesity was significantly associated with the absence of SIBO (RR = 0.38; 95%CI: 0.02-0.48)^[82]. There

was no significant difference in the incidence of SIBO in MASH patients with and without signs of metabolic syndrome^[83].

A meta-analysis of 3 studies showed that children with SIBO were more likely to have MAFLD (OR = 5.27; 95%CI: 1.66-16.68) and children with MAFLD were at an increased risk of developing SIBO (RR = 2.17; 95%CI: 1.54-2.81)^[84]. Metabolic syndrome and MAFLD were risk factors for SIBO development in obese children^[85].

Primary biliary cholangitis

The prevalence of SIBO was higher in patients with primary biliary cholangitis (PBC) than in controls (32.8% vs 2.5%; OR = 18.9). Patients with PBC and SIBO were significantly more likely to have diarrhea (78.9% vs 35.9%) than those without SIBO. Age, sex, BMI, comorbidities, severity of disease, signs of portal hypertension, and the prevalence of abdominal pain and bloating were similar in PBC patients with and without SIBO^[86].

ABDOMINAL SURGERY

Bariatric surgery

SIBO was detected in 43% of patients who had undergone bariatric Roux-en-Y gastric bypass or one-anastomosis gastric bypass and was associated with a higher frequency of defecation in these patients than in those without SIBO^[87]. In a separate study, SIBO was detected in 73.4% of patients who received a Roux-en-Y gastric bypass^[88]. A third study reported that SIBO testing was negative in all pre-surgery patients and positive in 37.0% of patients 6 mo after one-anastomosis gastric bypass. SIBO in this study was associated with lower reported dietary intake and folate levels and higher vitamin A deficiency rates. No significant differences in alpha and beta diversities of gut microbiota were observed between patients with and without SIBO at 6 mo post-surgery^[89]. Among patients that underwent Roux-en-Y gastric bypass at least 1 year before, the SIBO-positive group had a higher BMI than the SIBO-negative group^[90]. SIBO prevalence does not increase after adjustable gastric banding (before, 15%; after,

10%), whereas it increased from 15% before Roux-en-Y gastric bypass to up to 40% afterwards. This study also found an association between SIBO and lower weight loss^[91].

Gastrectomy

SIBO was found in 61.6% of patients who had undergone gastrectomy. No correlation was found with any malnutrition parameter^[92]. Another study reported significant differences in SIBO prevalence between postgastrectomy patients and controls (77.6% vs 6.7%)^[93]. Abdominal fullness or borborygmus during oral glucose load were more common in patients with SIBO than in those without SIBO. The prevalence of dumping syndrome and postprandial hypoglycemia, pulse rate and hematocrit levels were not different between patients following gastrectomy with and without SIBO^[93]. A third study revealed that SIBO was more frequent in patients after gastrectomy than in controls (71.4% vs 13.3%; OR = 16.3). Specifically, 75% of patients that had undergone a Billroth I or II operation and 50% of patients that had undergone total gastrectomy were positive for SIBO^[94].

Colectomy

Patients who had undergone colectomy had a greater incidence of SIBO than healthy controls (62% vs 32%; OR = 3.47). There was a higher prevalence of aerobic organisms and a lower prevalence of anaerobic organisms in the duodenal contents in the colectomy group compared with controls^[95]. SIBO was detected in 74% of patients after right-sided hemicolectomy for colorectal cancer; no association between SIBO and bile acid malabsorption, delayed OCTT, or loose stools was found in these patients^[96].

Cholecystectomy

Patients that had undergone cholecystectomy were more likely to have SIBO than controls (46.8% vs 13.3%; OR = 5.7)^[97]. Another study reported similar results (41.1% vs 13.3%; OR = 4.5)^[94]. Cholecystectomy patients with SIBO had more severe abdominal

and chest discomfort, bloating, early satiety, nausea, and tenesmus than those without SIBO^[97].

Other abdominal surgery

The presence of asymptomatic chronic pouchitis after ileoanal anastomosis was not associated with SIBO^[98].

OTHER DIGESTIVE DISEASES

Erosive esophagitis

Patients with erosive esophagitis had SIBO more frequently than controls (65% *vs* 31%; OR = 4.0)^[99].

Helicobacter pylori infection

Among patients with abdominal symptoms, SIBO was detected more frequently in *Helicobacter pylori* (*H. pylori*)-infected patients than in uninfected ones (60.4% *vs* 30.6%; OR = 3.45). The incidence of SIBO after *H. pylori* eradication decreased to 20.8%. The remission rate of SIBO after eradication was 66.7%^[100].

Gastroparesis

SIBO was present in 60% of patients with gastroparesis, 43.8% of whom had hydrogen SIBO and 22.2% of whom had methane SIBO (6% of patients produced both gases). SIBO was associated with greater disease duration. No significant differences were noted in age, sex, gastric emptying parameters, and etiology of gastroparesis between patients with and without SIBO^[101].

Chronic pancreatitis

A meta-analysis of 13 studies showed that ¹² the prevalence of SIBO in patients with chronic pancreatitis (CP) was higher than in controls in all patients [38.6% (95%CI: 25.5%-53.5%); OR = 5.58 (95%CI: 2.26-13.75)], nonsurgical cases [34.6% (95%CI: 20.7%-

51.8%); OR = 4.61 (95%CI: 1.67-12.73)] and cases that needed surgical intervention [54.2% (95%CI: 23.3%-82.2%); OR = 10.86 (95%CI: 0.90-131.72)]. Diabetes mellitus (OR = 2.1; 95%CI: 1.2-3.5) and pancreatic exocrine insufficiency (OR = 2.5; 95%CI: 1.3-4.8), but not narcotic drug or PPI use were associated with SIBO in patients with CP^[102]. SIBO was more prevalent in patients with alcohol-induced CP than in patients with other forms of this disease^[103]. A separate study showed no association between the severity of CP symptoms and the presence of SIBO^[104].

Acute pancreatitis

SIBO was found in 17.8% of patients with acute pancreatitis (AP) and was associated with disease severity, as it was detected in 8.42%, 25.58%, and 25.92% of patients with mild, moderate, and severe AP, respectively. The production of hydrogen by gut microbiota was significantly lower in the late than in the early stage, and SIBO mainly developed within 72 h of AP onset. The incidence of organ failure was significantly higher in patients with SIBO than in those without. However, the incidence of infectious or local complications was not associated with SIBO, and neither was systemic inflammatory response syndrome^[105]. Another study reported that SIBO incidence in AP was 12.0%, similar to the results of historic healthy controls, and that glucose tolerance was lower in AP patients with SIBO than in those without^[106].

Cystic fibrosis

The prevalence of SIBO in cystic fibrosis was 31.6%. SIBO was associated with pancreas insufficiency, and independently associated with lower BMI and serum albumin levels^[107]. Another study reported the prevalence of SIBO in cystic fibrosis as 40.0%; fecal calprotectin levels did not differ between patients with and without SIBO^[108].

Gallstone disease

SIBO prevalence in patients with gallstones was higher than in controls and those who had undergone cholecystectomy (40.5% vs 20.5% and 24.6%; OR = 2.23)^[109]. Another

study also reported that SIBO was more frequent in patients with gallstones than in controls (14.8% vs 0.7%; OR = 26.9)^[110]. OCTT and serum bile acid levels were increased in patients with SIBO compared with patients without SIBO, and there was a positive correlation between OCTT and serum bile acid levels in SIBO-positive patients^[110].

Children with encopresis

Hydrogen SIBO was detected in 42% of children with encopresis and 23% of controls (OR = 2.4). Methane was produced by 56% of children with encopresis and 23.1% of controls^[111].

ENDOCRINE AND METABOLIC DISEASES

Obesity and metabolic syndrome

A meta-analysis of 5 studies revealed that the increased risk of SIBO in obese individuals did not reach statistical significance (OR = 2.08; 95%CI: 0.82-5.31) but was significant when including only studies from Western countries (OR = 3.41; 95%CI: 1.21-9.59)^[112]. However, SIBO was not related to BMI. Small intestinal manometry showed a marked increase of clustered contractions in obese individuals with SIBO compared with those without SIBO; no other differences were observed in parameters of fasting cyclic activity^[113]. Patients with SIBO have higher visceral to subcutaneous fat ratios than the general population. Metabolic syndrome (OR = 2.5; 95%CI: 1.1-5.7) and higher visceral to subcutaneous fat ratio (OR = 3.3; 95%CI: 1.6-7.2) were independently associated with SIBO in the general population^[114]. Obese individuals with SIBO ingested more carbohydrates and refined sugars and less total and insoluble fibers than those without SIBO. There were no significant differences in lipid and protein intake between the two groups^[115].

The prevalence of SIBO in obese children was greater than in controls (37.6% vs 3.3%; OR = 17.5). Obese children with SIBO had higher rates of MAFLD, hypertension, and metabolic syndrome, and higher alanine transaminase and aspartate transaminase levels than those without SIBO^[116].

Diabetes mellitus

A meta-analysis of 14 studies showed that SIBO is detected in patients with diabetes mellitus more frequently than in controls [29% (95%CI: 20%-39%); OR = 4.18 (95%CI: 1.34-13.05)]. The rate of SIBO was 35% (95%CI: 21%-49%) in Western countries and 24% (95%CI: 14%-34%) in Eastern countries. The prevalence of SIBO in type 2 diabetes was similar to that in type 1 diabetes [30% (95%CI: 13%-47%) vs 25% (95%CI: 14%-36%)]^[117].

Serum levels of biomarkers of oxidative stress (lipid peroxidates, catalase, and superoxide dismutase) and systemic inflammation (TNF- α , IL-6 and IL-10) were higher and serum levels of the antioxidant glutathione were lower in type 2 diabetic patients with SIBO than those without^[118]. SIBO was associated with lower fasting insulin levels, lower insulin release after glucose load, and poorer glucose tolerance and long-term glycemic control (higher glycated hemoglobin) in patients with type 2 diabetes. At the same time, insulin resistance and BMI were lower in patients with SIBO than in those without^[119]. In type 2 diabetics, OCTT was more delayed, urinary d-xylose levels was more reduced, and lactose intolerance was more severe in patients with SIBO than those without SIBO^[120].

In type 1 diabetes mellitus, OCTT was more delayed and a history of uncontrolled diabetes was more likely in patients with SIBO than those without. SIBO was significantly higher in patients who had had type 1 diabetes for ≥ 5 years than in those who were diagnosed < 5 years previously^[121]. Patients with autonomic neuropathy in type 1 diabetes have a higher prevalence of SIBO, which was associated with higher daily insulin requirements^[122].

The rate of SIBO in patients with gestational diabetes mellitus was greater than in those without SIBO (54.6% vs 27.5%; OR = 3.16). Patients with SIBO had higher levels of fasting blood glucose, glycated hemoglobin, and C-reactive protein, and lower levels vitamin D than those without; neonates from these patients with SIBO had higher weights and lower levels of blood glucose than those from patients without SIBO^[123].

Hypothyroidism

SIBO prevalence in patients with hypothyroidism was higher than in controls [54% vs 5%; OR = 22.3 (95%CI: 4.8-102.7)]. Abdominal discomfort, flatulence, and bloating were more prevalent in the patients with SIBO^[124].

The positive rates of SIBO were 56.7% and 31.6% in pregnant women with and without subclinical hypothyroidism, respectively (OR = 2.83). The incidence of abdominal distension and constipation, presence of thyroid peroxidase antibody, levels of thyroid-stimulating hormone, and BMI were higher, and the levels of thyroxine were lower in women with SIBO compared with those without SIBO^[125].

Acromegaly

Patients with acromegaly showed an increased prevalence of SIBO compared with controls (43.9% vs 3.3%; OR = 22.7)^[126].

Atherosclerosis and hyperlipidemia

SIBO was found in 78.9% of patients with hyperlipidemia and 40% of controls. The level of exhaled hydrogen at 120 min was positively correlated with serum triglyceride and low- and very-low-density lipoprotein levels, and negatively correlated with serum high-density lipoprotein levels^[127]. Among patients who did not have previous cardiovascular events and presented with gastrointestinal discomfort, asymptomatic atherosclerotic plaques were detected more often in patients with SIBO than those without SIBO. This was true for the abdominal aorta (OR = 4.18; 95%CI: 2.56-6.80), carotid arteries (OR = 1.93; 95%CI: 1.23-3.02), lower extremity arteries (OR = 1.81; 95%CI: 1.14-2.88), and any-territory plaque presence (OR = 5.42; 95%CI: 2.78-10.58)^[128]. Arterial stiffness was elevated in patients with SIBO compared with those without SIBO but carotid intima-media thickness and arterial calcifications did not differ between the two groups^[129].

NERVOUS DISEASES

Multiple sclerosis

SIBO was detected in patients with multiple sclerosis more frequently than in controls [38.1% (95%CI: 29.4%-46.9%); OR = 4.50 (95%CI: 2.38-8.50)]. SIBO was associated with more severe disease according to the Expanded Disability Status Scale and Multiple Sclerosis Severity Score^[130].

Restless legs syndrome

Patients with restless legs syndrome were more likely to have SIBO than healthy controls (69% *vs* 10%; OR = 19.8)^[131].

Alzheimer's disease

SIBO was detected in 49% of patients with Alzheimer's disease, a higher level than in controls (OR = 3.35). SIBO was not associated with fecal calprotectin and zonulin levels, degree of cognitive impairment, comorbidities or drug treatment^[132].

Autism

Children with autism had an SIBO incidence of 31.0% (95%CI: 25.8%-36.1%), which was higher than in controls (OR = 4.35). Autistic children with SIBO had higher Autism Treatment Evaluation Checklist scores than those without SIBO^[133].

Spinal cord injury

SIBO was detected in 21% of patients after spinal cord injury. SIBO was observed more frequently in the subacute than in the chronic phase (37.5% *vs* 0%), and in tetraplegia more frequently than in paraplegia (55.6% *vs* 0.5%)^[134]. Another study reported that the SIBO rate after spinal cord injury was 38.5% (95%CI: 29.9%-59.0%) and that SIBO was associated with deep vein thrombosis in these patients (OR = 3.72; 95% CI: 1.97-6.62)^[135].

Parkinson's disease

A meta-analysis of 11 studies showed that the prevalence of SIBO in patients with Parkinson's disease was 46% (95%CI: 36%-56%), which was higher than in controls (OR = 5.22; 95%CI: 3.33-8.19). This incidence was greater in Western countries than in Eastern ones [52% (95%CI: 40%-64%) vs 33% (95%CI: 22%-43%)]^[136]. Patients with SIBO used smaller doses of dopaminergic drugs and had lower serum triglyceride and total bilirubin levels. SIBO was not associated with motor or abdominal symptoms^[137] or weight loss^[138]. However, another study reported that disease duration, Hoehn and Yahr stage, unified Parkinson's disease rating-III and -IV scores, and Non-Motor Symptoms Scale score were associated with SIBO in these patients^[139].

RHEUMATIC DISEASES

Systemic sclerosis

A meta-analysis of 14 studies reported that the prevalence of SIBO in patients with systemic sclerosis was 34% (95%CI: 27%-42%), which was higher than in controls (OR = 12.51; 95%CI: 6.51-24.03). SIBO prevalence was greater in Western countries than in Asian countries [38% (95%CI: 31%-47%) vs 15% (95%CI: 10%-23%)]. Systemic sclerosis patients with SIBO were more likely to have diarrhea (OR = 8.82; 95%CI: 4.09-19) than those without. Sex, diffuse or limited disease, digital ulcer, pulmonary fibrosis, and the presence of centromere or Scl-70 antibodies were not associated with SIBO in these patients^[140,141]. Fecal calprotectin levels were higher in patients with SIBO than in those without it^[141]. The average disease duration was longer in patients with SIBO, and these patients had lower levels of hemoglobin, ferritin, total serum protein, phosphorus, calcium, and triglycerides and an elevated erythrocyte sedimentation rate compared with patients without SIBO^[142]. The duration of disease (> 5 years) was significantly associated with the presence of SIBO in systemic sclerosis (OR = 9.38; 95%CI: 1.09-80.47)^[143].

Behçet's disease

SIBO was diagnosed in 36% of patients with Behçet's disease. No significant differences in disease activity, patient age, severity of abdominal symptoms, frequency of drug use, surgery, smoking status, serum total protein, albumin, and C-reactive protein levels, and erythrocyte sedimentation rate were found between patients with and without SIBO^[144].

Spondylarthropathy

¹² The prevalence of SIBO in patients with spondylarthropathy was higher than in the control group (63% vs 5%; OR = 32.9) and did not depend on the presence of HLA-B27, or treatment with NSAID, salazopyrin or PPI^[145].

Fibromyalgia

SIBO was diagnosed in 100% of patients with fibromyalgia, compared with 20% of controls. ³ The degree of somatic pain correlated significantly with hydrogen level as measured by the breath test^[146].

ASTHMA

SIBO was detected in 67% and 43% of patients with allergic and non-allergic asthma, respectively. Patients with SIBO had higher levels of immunoglobulin E in serum and eosinophils in sputum, and more severe impairment of respiratory function^[147].

HEART FAILURE

Among patients with heart failure (HF), 45% were positive for SIBO, including 41% of patients with reduced ejection fraction (EF) and 51% of patients with preserved EF. SIBO was associated with an increased risk of rehospitalization in patients with reduced EF and cardiovascular death in patients with preserved EF. Patients with SIBO showed higher rates ³⁴ of New York Heart Association functional class III-IV, atrial fibrillation, peripheral edema, spironolactone and intravenous diuretic use, lower use of beta-blockers, and increased left atrial diameter and pulmonary artery systolic pressure than

patients without SIBO. Among patients with reduced EF, those with SIBO had ²⁹ higher serum levels of N-terminal pro B-type natriuretic peptide (a biomarker of HF) than those without^[148]. Another study also reported higher SIBO incidence in HF than in controls (41.7% *vs* 9.1%; OR = 7.14) but found that SIBO in HF was not associated with the New York Heart Association functional class, echocardiographic data, number of supraventricular and ventricular extrasystoles, indicators of complete blood count or biochemical blood analysis. However, patients with SIBO had higher C-reactive protein levels and ventricular tachycardia incidence (OR = 6.8; 95%CI: 1.5-30.2) compared with those without SIBO^[149].

CANCER

SIBO was found in 63.3% of patients with pancreatic cancer and 46.7% of patients with cholangiocarcinoma, which was greater than in the healthy controls (OR = 11.2 and 5.7, respectively). TLR4 protein expression in pancreatic carcinoma and cholangiocarcinoma patients ⁵ was significantly higher in patients with SIBO than in those without SIBO^[150].

OTHER DISEASES

Obstructive sleep apnea

Among patients with obstructive sleep apnea, 30.8% tested positive for SIBO. ⁵ The incidence of flatulence was significantly greater in patients with SIBO than those without SIBO. Waist-to-hip ratio was independently associated with SIBO in these patients (OR = 12.9; 95%CI: 1.3-132.2)^[151].

Post coronavirus disease 2019 syndrome

SIBO was detected more frequently in patients with post coronavirus disease 2019 IBS than in those with typical IBS (93.3% *vs* 60.0%; OR = 9.3)^[152].

Deep vein thrombosis

The prevalence of SIBO in deep vein thrombosis was higher than in controls (69.8% *vs* 39.9%; OR = 3.5) and SIBO was independently associated with this disease (OR = 3.27; 95%CI: 1.70-6.32)^[153].

Rosacea and psoriasis

SIBO was detected in patients with rosacea more frequently than in controls in one study (46.0% *vs* 5.0 %; OR = 16.2)^[154] and was not more common in these patients than in controls in the other (10.0% *vs* 7.8%)^[155]. The prevalence of SIBO in psoriatic patients did not differ from the controls (10% *vs* 5%)^[156].

SIBO AND OTHER DISEASES: COMMON PATTERNS

As shown above, SIBO is often detected in functional and organic bowel diseases, liver diseases, other diseases of the digestive organs, a number of endocrine, nervous and rheumatic diseases, asthma, HF, and certain other diseases. We have summarized all the reported information on the incidence and OR for SIBO in various diseases in Table 1. An important issue in comparing data is that the presence of SIBO was determined by different tests in different studies, giving different results. In addition, we have observed pronounced heterogeneity in the frequency of SIBO detection in healthy individuals within the control groups, which ranged from fractions of a percent to several tens of percent. The reason for this is yet to be established. However, the detection of SIBO in such a large number of clinically healthy individuals shows that this disorder can be relatively harmless and often asymptomatic.

For many diseases, the development of SIBO is associated with a slowdown in OCTT that decreases the normal clearance of bacteria from the small intestine and is one of the mechanisms underlying the development of SIBO. The slowdown of this transit may be associated with motor dysfunction of the intestine in diseases of the gut, autonomic diabetic polyneuropathy, portal hypertension, or a decrease in the motor-stimulating influence of thyroid hormones.

Bariatric surgery and gastrectomy lead to a decrease in the barrier function of the stomach which prevents the colonization of the small intestine by oral microbiota. Colectomy leads to a decrease in the barrier function of the ileocecal valve, which prevents the colonization of the small intestine by the colon microbiota. This may explain the increased risk of SIBO following these surgeries.

Interestingly, the frequency of SIBO is increased in a number of nervous and rheumatic diseases, which may support the existence of the gut-brain^[157-159] and gut-joint^[160-162] axes, suggesting that the products of gut microbiota metabolism can directly or indirectly affect emotional-cognitive and immune function^[163], predisposing individuals to the development of these diseases, which is well illustrated by the example of hepatic encephalopathy^[164,165] and reactive arthritis^[166,167].

The presence of SIBO affects the course of various diseases in different ways. Some diseases, such as IBS, functional diarrhea, and functional constipation, can be mimicked by SIBO with the same symptoms. In these cases, it is not clear what disease is present: SIBO, which manifests itself as IBS and other functional bowel diseases, or these diseases, which are aggravated by the development of SIBO.

In a number of diseases, including cirrhosis, MAFLD, diabetes mellitus, pancreatitis, and cystic fibrosis, an association was found between disease severity and the presence of SIBO. This may be due to the fact that intestinal motility is more severely disturbed in more severe diseases (in cirrhosis or autonomic diabetic polyneuropathy) or that the digestive capabilities of the gut are more affected (in severe pancreatitis and cystic fibrosis) in these cases, which increases the nutrients available for bacteria of small intestine, leading to their excess growth. However, in SIBO, the overgrown bacteria themselves can, through their metabolic products, affect the metabolism of lipids and carbohydrates, aggravating the course of diabetes^[168] and MAFLD^[169], and also, through bacterial translocation and systemic inflammation, aggravate the course of portal hypertension in cirrhosis^[170-172].

Since SIBO is associated with many diseases, even those not related to the intestines, it seems useful to continue studying the association of SIBO with other diseases and

their manifestations. It is also important to clarify the pathogenetic ways in which the underlying disease can contribute to the development of SIBO, and SIBO, in turn, can have a negative effect on the course of the underlying disease. Currently, such studies are being conducted in cirrhosis^[72], MAFLD^[79-81], diabetes^[118,119], and other diseases. An important question is how the course of the underlying disease will respond to SIBO treatment. These results have already been obtained for some diseases^[49,154], but their presentation is the aim for the next review.

CONCLUSION

In conclusion, we have summarized almost all published information on the association of SIBO with various diseases and their manifestations. Almost one third of cited studies were published within the last 2 years, highlighting the recent interest in the field and the importance of our review. However, further study on SIBO in various diseases, and particularly on the effect of its eradication on the condition and prognosis of patients, is required.

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