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Small-intestinal bacterial overgrowth in cirrhosis is related to the severity of liver disease

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SUMMARY

Background
Small-intestinal bacterial overgrowth (SIBO) is known to be present in patients with cirrhosis, predisposing to various complications.

Aim
To determine the frequency of SIBO in cirrhotics and correlate with severity of cirrhosis.

Methods
Small-intestinal bacterial overgrowth was determined by glucose–hydrogen breath test (GHBT). A basal breath-hydrogen >20 ppm or a rise by ≥12 ppm above baseline following glucose administration was taken as positive test. Prevalence of SIBO in cirrhotics was compared with healthy controls and correlated with severity of cirrhosis.

Results
Of the 53 cirrhotics, 26 (49%) had SIBO, compared to one (8%) control ($P = 0.010$). The prevalence of SIBO increased with severity of cirrhosis (Child–Pugh A 20%, B 52% and C 73%; $P = 0.013$). On multivariate analysis, SIBO was independently associated with serum bilirubin and ascites. The best cut-off of serum bilirubin was ≥2 mg/dL [AUROC 0.77 (95% CI 0.64–0.90)] predicting SIBO with sensitivity 65%, specificity 81%, positive predictive value 77%, negative predictive value 71% and accuracy 74%. Patients having combination of ascites and serum bilirubin ≥2 mg/dL had 82% chance, while patients having neither had only 10% chance of having SIBO.

Conclusions
Small-intestinal bacterial overgrowth was prevalent in about half of cirrhotics. Its frequency increased with increase in severity of cirrhosis. Ascites and raised serum bilirubin reliably predicted presence of SIBO.

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INTRODUCTION

Derangement of gut flora, in particular, small-intestinal bacterial overgrowth (SIBO) is highly prevalent in patients with cirrhosis.[1–3] Significantly increased counts of both Gram-positive and -negative bacterial species have been recovered from faeces of cirrhotic patients.[4] This has been attributed, at least in part, to a decrease in small intestinal motility and increased adrenergic activity due to cirrhosis.[2, 3, 5–7]

In addition to the range of symptoms and consequences of SIBO *per se*, increasing evidence suggests that derangement of gut flora is of substantial clinical relevance to patients with cirrhosis. SIBO and increased bacterial translocation of gut flora from the intestinal lumen, in combination with failure of immune defence mechanisms to remove efficiently these translocating microorganisms, predispose to an increased potential for bacterial infections like spontaneous bacterial peritonitis (SBP) and sepsis in this group.[3, 8] Recent studies also suggest that gut flora, both in the colon and small intestine, may contribute to the proinflammatory state of cirrhosis even in the absence of overt infection.[9] Furthermore, manipulation of gut flora, to augment the intestinal content of lactic acid-type bacteria at the expense of other gut flora species with more pathogenic potential, may favourably influence liver function in cirrhotic patients.[10]

There are scanty data in literature about the prevalence of SIBO in cirrhotics and its relationship to severity of liver disease. A relationship has been reported between the severity of liver failure and the intensity of small intestinal motility disturbances.[11] Such disturbances could play a role in the pathogenesis of SIBO and even lead to complications of cirrhosis, such as SBP and encephalopathy. A high prevalence of SIBO has been observed in patients with liver cirrhosis with SBP.[3]

We hypothesized that severity of liver disease and hepatic decompensation can have a pathogenic role in altering the small intestinal bacterial contents in cirrhotic patients; we tested this hypothesis by comparing presence of SIBO in subjects with and without cirrhosis and among patients with varying severity of cirrhosis. We used glucose–hydrogen breath test (GHBT), the most commonly used non-invasive test, to diagnose SIBO. We also tried to associate various clinical and laboratory parameters with presence of SIBO. We believe that this information would help in prevention of some of the serious complications of cirrhosis by identifying patients with SIBO by simple clinical and laboratory parameters and targeting therapy against bacterial overgrowth in this high-risk population.

PATIENTS AND METHODS

Patients

Inclusion criteria. All consecutive patients of cirrhosis, attending the out-patient or in-patient departments of our hospital were included in the study. Controls were healthy subjects who were not on any probiotic supplements.

Exclusion criteria. Patients with gastro-intestinal bleed, hepatic encephalopathy and sepsis in previous 4 weeks; and significant pulmonary disease were excluded from the study. Patients on probiotics or acid-suppressive therapy were also excluded. Antibiotics, if any, were stopped 7 days prior to the study and lactulose was stopped 2 days before the study. Patients on immunosuppressives or narcotics were also excluded.

Cirrhosis was diagnosed by clinical, biochemical, histological or imaging studies. Each patient underwent detailed clinical evaluation and investigations to determine the aetiology and severity of liver disease. The laboratory investigations included serum bilirubin, serum creatinine, serum albumin and prothrombin time. Portal hypertension was assessed by endoscopic evidence of varices and hepatic venous pressure gradient (HVPG) measurement in a subgroup of patients. Cirrhosis was said to be compensated if there was no clinical ascites, clinical jaundice or history of variceal bleed.

Glucose–hydrogen breath test

Glucose–hydrogen breath test was performed using a breath gas analyzer (Micro H2; Micro Medical Limited, Kent, UK). The subjects were asked to avoid slowly absorbed carbohydrates (bread, potato, corn) and fibre the previous evening to avoid delayed excretion of hydrogen in the breath.[12] Basal breath specimens were obtained after the overnight fast. Cigarette smoking and physical exercise were not permitted for 2 h before and during the test, to prevent hyperventilation and consequent changes in breath hydrogen content.[13] The subjects then brushed their teeth, rinsed their mouths with an antiseptic wash followed by tap water,

to eliminate an early hydrogen peak due to action of oral bacteria on test sugars.[14] An average of four values was taken as the basal breath hydrogen level. Subjects then ingested 100 g glucose dissolved in 200 mL water. Thereafter, breath hydrogen was estimated every 15 min for 3 h. An increase in hydrogen excretion, in parts per million (ppm), following glucose administration, was calculated by subtracting the fasting value from the highest value of hydrogen excretion obtained. A rise of breath hydrogen by ≥12 ppm above basal level following glucose administration was taken as evidence of SIBO.[15] Average value of basal breath hydrogen >20 ppm despite adequate preparation for breath test on at least 2 days was considered as high basal breath hydrogen and this was also considered as positive test.[16] Nonhydrogen producer status was confirmed by lactulose–hydrogen breath test.[17]

HVPG measurement

Hepatic venous pressure gradient was measured after the breath analysis test, in a subgroup of patients who consented for the procedure. HVPG measurement was performed after overnight fast, and under antibiotic cover. Under local anaesthesia, a 7F central venous catheter (Arrow Medical, Athens, TX, USA) was placed in the right femoral vein or internal jugular vein under fluoroscopic guidance, using the Seldinger technique. HVPG was measured by the standard technique[18] in which a balloon catheter was introduced into the right hepatic vein under fluoroscopic guidance. The zero reference point was set at the mid-axillary point. The free hepatic venous pressure (FHVP) was obtained by keeping the catheter free into the lumen of the hepatic vein. The balloon of the catheter was then inflated to wedge the lumen of hepatic vein. Presence of wedging was confirmed by absence of reflux into the inferior vena cava, after the injection of 2 mL intravenous contrast, and appearance of a sinusoidogram. The pressure tracing at this juncture showed absence of wave forms and the pressure was labelled as wedged hepatic venous pressure (WHVP). HVPG was determined by subtracting free from WHVPs (HVPG = WHVP − FHVP). All measurements were performed in triplicate. If the difference between the two readings was more than 1 mmHg, all the readings were discarded and fresh set of measurements were taken. The normal value of the HVPG in our hemodynamic laboratory is between 1 and 4 mmHg.

Calculations and statistical analyses

Prevalence of SIBO in cirrhotics was compared with healthy controls. Additionally, prevalence of SIBO was correlated with severity and aetiology of liver disease. The results were expressed as mean with standard deviation (s.d.) or median with range. Comparisons between groups were performed by using Student's *t* test, Mann–Whitney *U*-test or Pearson's chi-square test with Yates' continuity correction. A value of $P < 0.05$ was taken as significant. All statistical analyses were performed using the SPSS 15.0 statistical package (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Eighty-nine patients of cirrhosis were enrolled in the study; 27 were excluded due to following reasons: gastro-intestinal bleed in previous 4 weeks ($n = 14$), hepatic encephalopathy ($n = 5$), bacterial infections with sepsis ($n = 4$), hepato-pulmonary syndrome ($n = 2$), chronic obstructive pulmonary disease ($n = 1$) and significant pleural effusion ($n = 1$). Remaining, 62 patients were included in the study. Six patients were on antibiotics for secondary prophylaxis of SBP, which was stopped 7 days prior to the study.

The baseline characteristics of included patients are given in Table 1. The mean age of patients was 42 (±15) years, and 50 (81%) were males. The most common aetiologies of cirrhosis were hepatitis B (34%), alcohol (26%) and cryptogenic (21%). None of the patients with alcoholic liver disease was actively consuming alcohol. For comparison, 15 age- and gender-matched healthy controls were included.

Results of breath analysis

Nine of 62 patients (14%) and 2 of 15 (13%) healthy controls were nonhydrogen producers ($P = 0.906$) (Table 2). SIBO could be assessed in remaining 53 patients and 13 controls.

Twenty-six of 53 (49%) patients were positive for SIBO compared to only one of 13 (8%) controls ($P = 0.010$). Positivity by high baseline breath hydrogen (≥20 ppm) criteria was in 16 (62%) positive patients and none (0%) of the controls while positivity by rise (≥12 ppm) over baseline criteria was in 10

Table 1. Baseline characteristics of included patients

Parameter	Cases (n = 62)	Healthy controls (n = 15)	P-value
Mean (±s.d.) age, years	42 (±14)	36 (±12)	0.131
Male:female, n	50:12	11:4	0.531
Aetiology of cirrhosis, n (%)			
Hepatitis B	21 (34)		
Alcohol	16 (26)		
Cryptogenic	13 (21)		
Hepatitis C	10 (16)		
Other	2 (3)		
History of variceal bleed, n (%)	25 (40)		
History of SBP, n (%)	6 (10)		
History of chronic diarrhoea, n (%)	2 (3)		
Ascites, n (%)			
Absent	38 (61)		
Present	24 (39)		
Median (range) serum bilirubin, mg/dL	1.4 (0.3–9.4)		
Prothrombin time prolongation in s, n (%)			
0–3	22 (35.5)		
4–6	18 (29)		
>6	22 (35.5)		
Mean (±s.d.) serum albumin, g/dL	3.2 (±0.7)		
Mean (±s.d.) serum creatinine, mg/dL	0.9 (±0.5)		
Varices, n (%)			
Small (<5 mm)	32 (52)		
Large (≥5 mm)	30 (48)		
Mean (±s.d.) HVPG*, mmHg	16.5 (±5.1)		
CTP class, n (%)			
A	18 (29)		
B	28 (45)		
C	16 (26)		
Median (range) CTP score, n/15	8 (5–13)		
Status of cirrhosis, n (%)			
Compensated	18 (29)		
Decompensated	44 (71)		

* HVPG was measured in 30 patients.
s.d., standard deviation, SBP, spontaneous bacterial peritonitis; HVPG, hepatic venous pressure gradient; CTP, Child–Turcotte–Pugh.

Table 2. Results of glucose hydrogen breath analysis

Status	Cases (n = 62), n (%)	Healthy controls (n = 15), n (%)	P-value
Nonhydrogen producers	9 (14)	2 (13)	0.906
Negative breath hydrogen test	27 (44)	12 (80)	0.010
Positive breath hydrogen test	26 (42)	1 (7)	0.010
High baseline criteria	16 (62)	0 (0)	
Rise criteria	10 (38)	1 (100)	

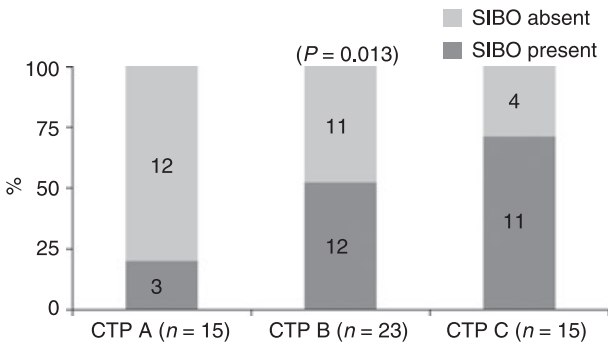

Figure 1. Frequency of small-intestinal bacterial overgrowth (SIBO) in Child–Turcotte–Pugh (CTP) class A, B and C.

(38%) positive patients and one (100%) controls (P = 0.219) (Table 2).

Association of SIBO with severity of liver disease, portal hypertension and aetiology

Small-intestinal bacterial overgrowth was more prevalent in patients with decompensated cirrhosis than in patients with compensated cirrhosis. Among patients with compensated cirrhosis, SIBO was present in three of 15 (20%), while in patients with decompensated cirrhosis, SIBO was present in 23/38 (61%) (P = 0.019). Prevalence of SIBO increased progressively with increase in Child–Turcotte–Pugh (CTP) class. The prevalence of SIBO in patients with CTP class A was 20% (3/15), with CTP class B was 52% (12/23) and with CTP class C was 73% (11/15) (P = 0.013) (Figure 1). The mean CTP score in patients with SIBO was 9.2 ± 1.9, while it was 7.4 ± 2.1 in patients without SIBO (P = 0.001) (Figure 2).

Patients with serum bilirubin ≥1.4 mg/dL had higher frequency of SIBO [19/30 (63%)] than patients with

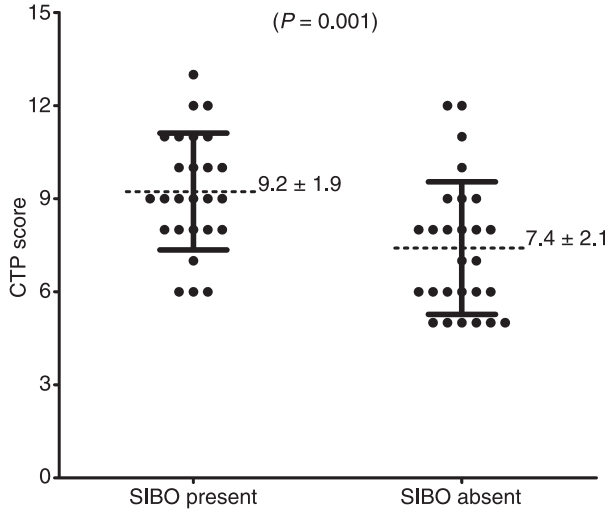

Figure 2. Mean (±s.d.) and individual values of Child–Turcotte–Pugh (CTP) score in patients with and without small-intestinal bacterial overgrowth (SIBO).

serum bilirubin <1.4 mg/dL [7/23 (30%); $P = 0.036$]. Similarly, patients with low serum albumin (<3.2 g/dL) had higher frequency of SIBO than patients with high albumin ($P = 0.020$). However, no association could be found between derangement of prothrombin time and presence of SIBO ($P = 0.338$). SIBO was present more frequently in patients with ascites than in patients without ascites [16/22 (72%) vs. 10/31 (32%); $P = 0.009$]. We had very few patients who had history of SBP ($n = 6$), hence no association could be found with these patients and presence of SIBO.

Among patients with large oesophageal varices (≥5 mm) 15/28 (54%) had SIBO while among patients with small oesophageal varices, 11/25 (44%) had SIBO ($P = 0.674$). Among patients who had history of variceal bleed in past, 12/20 (60%) had SIBO, while among patients who were nonbleeders, 14/33 (42%) had SIBO ($P = 0.338$). In a subgroup analysis of patients whose HVPG values were available ($n = 30$), no significant association could be found with HVPG and SIBO ($P = 0.165$).

Patients with cirrhosis due to hepatitis C had lower prevalence of SIBO [1/8 (13%)] compared with cirrhosis due to other aetiology [25/45 (56%)]; however, it did not reach statistical significance ($P = 0.063$). There was no correlation of presence of SIBO with other aetiologies of liver disease (Table 3).

Hence, on univariate analysis, SIBO was significantly associated with ascites, high serum bilirubin,

Table 3. Association of various parameters with presence of small intestinal bacterial overgrowth

Parameter	Patients with SIBO ($n = 26$), n (%)	Patients without SIBO ($n = 27$), n (%)	P-value
Age, years			
<42	12 (46)	9 (33)	0.501
≥42	14 (54)	18 (67)	
Gender			
Males	19 (73)	24 (89)	0.263
Females	7 (27)	3 (11)	
Aetiology of cirrhosis			
HBV			
HBV	10 (38)	8 (30)	0.698
NonHBV	16 (62)	19 (70)	
Alcohol			
Alcohol	7 (27)	6 (22)	0.938
Non-alcohol	19 (73)	21 (78)	
Cryptogenic			
Cryptogenic	7 (27)	5 (18)	0.687
Noncryptogenic	19 (73)	22 (82)	
HCV			
HCV	1 (4)	7 (26)	0.063
NonHCV	25 (96)	20 (74)	
History of variceal bleed			
Yes	12 (46)	8 (30)	0.338
No	14 (54)	19 (70)	
History of SBP			
Yes	3 (12)	3 (11)	1.000
No	23 (88)	24 (89)	
History of chronic diarrhoea			
Yes	2 (8)	0 (0)	0.454
No	24 (92)	27 (100)	
Ascites			
No	10 (38)	21 (78)	0.009
Yes	16 (62)	6 (22)	
Serum bilirubin, mg/dL			
<1.4	7 (27)	16 (59)	0.036
≥1.4	19 (73)	11 (41)	
Prothrombin time prolongation, s			
0–6	14 (54)	19 (70)	0.338
>6	12 (46)	8 (30)	
Serum albumin, g/dL			
<3.2	17 (65)	8 (30)	0.020
≥3.2	9 (35)	19 (70)	
Serum creatinine, mg/dL			
<0.9	15 (58)	13 (48)	0.674
≥0.9	11 (42)	14 (52)	
Varices			
Small (<5 mm)	11 (42)	14 (52)	0.674
Large (≥5 mm)	15 (58)	13 (48)	

Table 3. (Continued)

Parameter	Patients with SIBO (n = 26), n (%)	Patients without SIBO (n = 27), n (%)	P-value
HVPG (n = 30), mmHg			
<16.5	5 (38)	12 (71)	0.165
≥16.5	8	5 (29)	
CTP class			
A/B	15 (12)	23 (44)	0.055
C	11 (46)	4 (41)	
CTP score			
<8	4 (15)	14 (52)	0.012
≥8	22 (85)	13 (48)	
Status of cirrhosis			
Compensated	3 (12)	12 (44)	0.019
Decompensated	23 (88)	15 (56)	

Grouping of various parameters is based on their mean or median values.
HBV, hepatitis B virus; HCV, hepatitis C virus; SBP, spontaneous bacterial peritonitis; HVPG, hepatic venous pressure gradient; CTP, Child–Turcotte–Pugh.

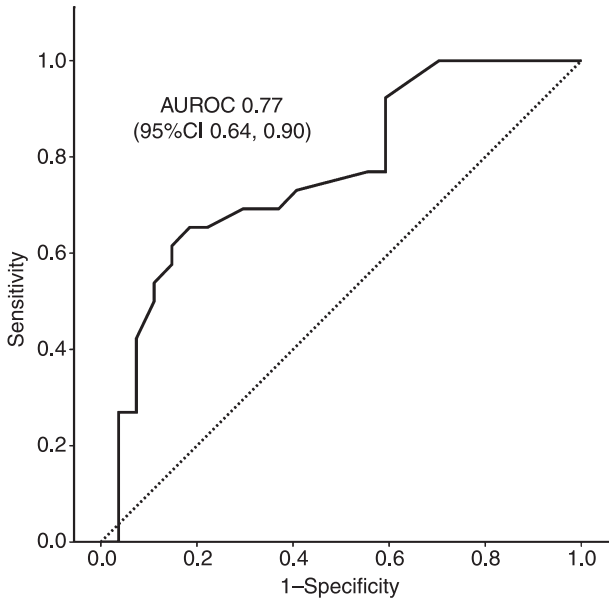

Figure 3. Receiver operating characteristic curve for serum bilirubin in predicting small-intestinal bacterial overgrowth. AUROC, area under receiver operating characteristic curve.

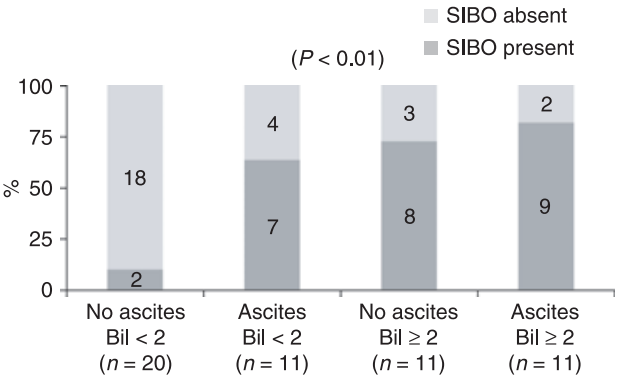

Figure 4. Frequency of small-intestinal bacterial overgrowth (SIBO) in patients with and without ascites and serum bilirubin (Bil) <2 or ≥2 mg/dL.

low serum albumin, high CTP score and decompensated cirrhosis (Table 3). When ascites, bilirubin and albumin were entered into multivariate analysis presence of SIBO was independently associated with presence of ascites (P = 0.011) and serum bilirubin level (P = 0.050) (Table 4).

Using serum bilirubin as test variable to predict presence of SIBO, an ROC curve was prepared (Figure 3). The area under ROC curve (AUROC) was 0.77 (95% CI 0.64–0.90). Based on the ROC curve the best cut-off of serum bilirubin obtained was ≥2 mg/dL which predicted SIBO with sensitivity of 65%, specificity of 81%, positive predictive value of 77%, negative predictive value of 71%, and accuracy of 74%. Patients having combination of ascites and serum bilirubin ≥2 mg/dL had 82% chance of having SIBO, while patients having neither of these had only 10% chance of having SIBO. Patients having one of these parameters had intermediate probability of SIBO (Figure 4).

DISCUSSION

The results of this novel study, using GHBT in cirrhotics, clearly show that SIBO is more prevalent in patients with cirrhosis than healthy subjects. Moreover, the prevalence of SIBO increases with severity of liver disease as determined by the CTP score. Presence of ascites and high serum bilirubin were independently associated with presence of SIBO.

SIBO can be diagnosed by several methods. We used GHBT to diagnose SIBO. We used the criteria of rise of breath hydrogen by ≥12 ppm above basal level following glucose administration or a high baseline breath

Table 4. Results of multivariate analysis of parameters associated with small-intestinal bacterial overgrowth

Parameter	*P*-value	Odds ratio	95% CI
Ascites present	0.011	5.02	1.44, 17.54
Serum bilirubin ≥1.4 mg/dL	0.050	3.45	1.00, 11.90

Ascites, serum bilirubin and serum albumin were entered into multivariate analysis.

hydrogen value of ≥20 ppm to diagnose SIBO. These are the most validated criteria of GHBT to diagnose SIBO.[15, 16, 19] Bauer *et al.*[20] had suggested that, in patients with cirrhosis, the GHBT correlates poorly with the diagnostic gold standard for SIBO. The gold standard is aspiration and culture of small bowel contents. This method is invasive, requiring intubation of the small bowel and a laboratory equipped with isolating anaerobes and is uncommon in general practice. Hence, GHBT remains the most commonly used non-invasive test to diagnose SIBO. The sensitivity and specificity of breath tests are variable; sensitivities as low as 62% and as high as 93% have been reported for GHBT.[15, 21]

We included 62 patients of cirrhosis of mixed aetiology in our study. We sought association of various severity parameters of liver disease with presence of SIBO. Patients included in our study were a carefully selected homogenous group of cirrhotics, without recent gastro-intestinal bleed, hepatic encephalopathy, sepsis, pulmonary disease, and not on treatment with probiotics, acid-suppressants, antibiotics, lactulose, immunosuppressives and narcotics. Unlike previous studies, our study excluded various extraneous influences, which could have affected the frequency of SIBO in cirrhotics.

Approximately 14% patients and 13% controls were nonhydrogen producers in our study. This frequency of nonhydrogen producers is consistent with other studies.[22, 23]

We found that nearly half of patients with cirrhosis have SIBO compared to <10% healthy controls. Thus, SIBO forms an important component of varied manifestations of cirrhosis. The association between cirrhosis and SIBO was first reported in 1957.[24] Since then, several studies have confirmed the high prevalence of SIBO among patients with cirrhosis.[2, 25–27] Chesta *et al.*[25] demonstrated SIBO by jejunal cultures in 64% and by lactulose–H_2 breath test in 45% of cirrhotics. Bauer *et al.*[2] found SIBO by jejunal cultures to be present in 61% of cirrhotics. Gunnarsdottir *et al.*[26] found SIBO in 33% of cirrhosis with portal hypertension, but none in the cirrhosis without portal hypertension. In a study by Morencos *et al.*[27] on 89 patients with alcoholic cirrhosis and 40 healthy subjects, SIBO was documented in 30% of patients with alcoholic cirrhosis and in none of the healthy subjects.

In our study, SIBO was more prevalent in patients with Child's C than Child's A cirrhosis. SIBO was present in 61% of decompensated cirrhotics, three times more common than in compensated cirrhotics. Moreover, prevalence of SIBO increased progressively with increase in CTP class. Morencos *et al.*[27] and Yang *et al.*[28] found that CTP class had a significant influence on prevalence of SIBO. Madrid *et al.*[11] studied small bowel motility in cirrhosis patient. He noted that absence of cyclic activity was most frequently observed in Child–Pugh stage C patients compared to Child–Pugh stage A cirrhotics. A significant increase in clustered contractions in class C was recorded. The frequency and amplitude of contractions were also increased in CTP class C.

Among the components of CTP score, serum bilirubin, serum albumin and ascites correlated with SIBO while prothrombin time prolongation did not correlate. We could not correlate the presence of development of hepatic encephalopathy with SIBO as we had excluded these patients as per the study design. In Morencos *et al.*'s study[27] of alcoholic cirrhosis, the prevalence of SIBO was higher in cirrhotics with ascites than in those without ascites (37.1% vs. 5.3%); however, Yang *et al.*[28] did not find any relationship with the presence or absence of ascites.

We had very few patients who had history of SBP (n = 6); hence, no correlation could be found with these patients and presence of SIBO. In the study by Morencos *et al.*,[27] the prevalence of SBP was higher in patients who had SIBO (31%) than in patients who did not (9%). The authors concluded that SIBO may be a condition favouring infection of the ascitic fluid. However, Bauer *et al.*[2] did not find SIBO to be associated with SBP.

All patients in our study had portal hypertension as documented by presence of varices. However, the degree of portal hypertension as assessed by the size of oesophageal varices or HVPG did not correlate with SIBO. The frequency of SIBO was not different between patients who had large or small varices.

Similarly, there was no difference in the frequency of SIBO between patients with or without a past history of variceal bleed. We did not include any patient with recent (<4 weeks) history of gastro-intestinal bleed. In a subgroup analysis of patients whose HVPG values were available ($n = 30$), presence of SIBO was not associated with higher HVPG. No previous study has correlated degree of portal hypertension with SIBO.

In various studies, alcohol (with or without liver disease) seems to be an important cause of SIBO.[29, 30] Sadik *et al.*[7] found that small-bowel residence time was longer in male patients with alcoholic cirrhosis compared with male patients with other causes of portal hypertension, suggesting that aetiology of liver disease and gender may influence transit in patients with portal hypertension. In a study by Bode *et al.*[30] in patients with alcohol abuse, SIBO was almost three times (38%) that of controls not abusing alcohol (13.3%; $P < 0.001$). However, evaluation of alcoholics with cirrhosis in comparison with those without cirrhosis revealed no significant difference in the incidence of SIBO. Similarly in studies by Chesta *et al.*[25] and Yang *et al.*,[28] there was no difference in SIBO among various causes of cirrhosis. In our study too, there was no correlation of presence of SIBO with the aetiologies of liver disease (Table 3).

On multivariate analysis, presence of SIBO was independently associated with serum bilirubin level and presence of ascites. The best cut-off of serum bilirubin obtained was ≥2 mg/dL, which predicted SIBO with an accuracy of 74%. Moreover, patients having combination of ascites and serum bilirubin ≥2 mg/dL had 82% chance of having SIBO, while patients having neither of these had only 10% chance of having SIBO. These two simple clinical and laboratory parameters are excellent in predicting SIBO and can be used in clinical setting in situations where breath analysis or jejunal aspiration is not possible.

There are some limitations to our study. First, we did not use jejunal aspiration and culture to diagnose SIBO, which is considered the gold standard. This method is invasive requiring intubation of the small bowel and a laboratory equipped with isolating anaerobes. GHBT has remained the most commonly used non-invasive test to diagnose SIBO in most previous studies. Second, the present study is cross-sectional and patients with and without SIBO were not prospectively followed-up to document differences in outcome. Third, we did not have control group of patients with chronic hepatitis without cirrhosis, which could have sought an association between SIBO and a wider spectrum of severity of liver disease. Fourth, caution should be exercised in the interpretation of HVPG data. HVPG values are available only in 30 subjects and the study may not be powered to detect a difference in HVPG between SIBO positive and negative.

In conclusion, our study showed that SIBO was prevalent in about half of cirrhotics and its frequency increased with the increase in severity of liver disease. Presence of ascites and serum bilirubin ≥2 mg/dL are excellent parameters in predicting SIBO. Further prospective studies are needed to document difference in outcome between patients with and without SIBO and the influence of treating SIBO on survival.

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STUDY HIGHLIGHTS

What is current knowledge?

- Small-intestinal bacterial overgrowth (SIBO) is present in cirrhotics.
- It is thought to predispose to spontaneous bacterial peritonitis and hepatic encephalopathy.
- It also causes a proinflammatory state in these patients.
- Its correlation with severity of liver disease and portal hypertension is uncertain.

What is new here?

- Nearly half of patients of cirrhosis have SIBO.
- The frequency of SIBO increases with severity of liver disease.
- Small-intestinal bacterial overgrowth does not correlate with severity of portal hypertension.
- Combination of ascites and high serum bilirubin can reliably predict presence of SIBO in these patients.

REFERENCES

1 Almeida J, Galhenage S, Yu J, Kurtovic J, Riordan SM. Gut flora and bacterial translocation in chronic liver disease. *World J Gastroenterol* 2006; **12**: 1493–502.

2 Bauer TM, Steinbrückner B, Brinkmann FE, *et al.* Small intestinal bacterial overgrowth in patients with cirrhosis: prevalence and relation with spontaneous bacterial peritonitis. *Am J Gastroenterol* 2001; **96**: 2962–7.

3 Chang CS, Chen GH, Lien HC, Yeh HZ. Small intestine dysmotility and bacterial overgrowth in cirrhotic patients with spontaneous bacterial peritonitis. *Hepatology* 1998; **28**: 1187–90.

4 Floch MH, Katz J, Conn HO. Qualitative and quantitative relationships of the fecal flora in cirrhotic patients with portal systemic encephalopathy and following portacaval anastomosis. *Gastroenterology* 1970; **59**: 70–5.

5 Chesta J, Defilippi C, Defilippi C. Abnormalities in proximal small bowel motility in patients with cirrhosis. *Hepatology* 1993; **17**: 828–32.

6 Stewart JJ, Battarbee HD, Farrar GE, Betzing KW. Intestinal myoelectrical activity and transit time in chronic portal hypertension. *Am J Physiol* 1992; **263**: G474–9.

7 Sadik R, Abrahamsson H, Björnsson E, Gunnarsdottir A, Stotzer PO. Etiology of portal hypertension may influence gastrointestinal transit. *Scand J Gastroenterol* 2003; **38**: 1039–44.

8 Wiest R, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. *Hepatology* 2005; **41**: 422–33.

9 Riordan SM, Skinner N, Nagree A, *et al.* Peripheral blood mononuclear cell expression of toll-like receptors and relation to cytokine levels in cirrhosis. *Hepatology* 2003; **37**: 1154–64.

10 Liu Q, Duan ZP, Ha DK, Bengmark S, Kurtovic J, Riordan SM. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. *Hepatology* 2004; **39**: 1441–9.

11 Madrid AM, Cumsille F, Defilippi C. Altered small bowel motility in patients with liver cirrhosis depends on severity of liver disease. *Dig Dis Sci* 1997; **42**: 738–42.

12 Anderson IH, Levine AS, Levitt MD. Incomplete absorption of the carbohydrate in all-purpose wheat flour. *N Engl J Med* 1981; **304**: 891–2.

13 Thompson DG, Binfield P, De Belder A, O'Brien J, Warren S, Wilson M. Extra intestinal influences on exhaled breath hydrogen measurements during the investigation of gastrointestinal disease. *Gut* 1985; **26**: 1349–52.

14 Thompson DG, O'Brien JD, Hardie JM. Influence of the oropharyngeal microflora on the measurement of exhaled breath hydrogen. *Gastroenterology* 1986; **91**: 853–60.

15 Kerlin P, Wong L. Breath hydrogen testing in bacterial overgrowth of the small intestine. *Gastroenterology* 1988; **95**: 982–8.

16 Hamilton LH. *Breath Tests and Gastroenterology*. Milwaukee, WI, USA: QuinTron Instrument, 1998: 48–53.

17 Robb TA, Goodwin DA, Davidson GP. Faecal hydrogen production in vitro as an indicator for in vivo hydrogen producing capability in the breath hydrogen test. *Acta Paediatr Scand* 1985; **74**: 942–4.

18 Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. *Hepatology* 2004; **39**: 280–2.

19 Simrén M, Stotzer PO. Use and abuse of hydrogen breath tests. *Gut* 2006; **55**: 297–303.

20 Bauer TM, Schwacha H, Steinbrückner B, *et al.* Diagnosis of small intestinal bacterial overgrowth in patients with cirrhosis of the liver: poor performance of the glucose breath hydrogen test. *J Hepatol* 2000; **33**: 382–6.

21 Corazza GR, Menozzi MG, Strocchi A, *et al.* The diagnosis of small bowel bacterial overgrowth. Reliability of jejunal culture and inadequacy of breath hydrogen testing. *Gastroenterology* 1990; **98**: 302–9.

22 Ghoshal UC, Ghoshal U, Das K, Misra A. Utility of hydrogen breath tests in diagnosis of small intestinal bacterial overgrowth in malabsorption syndrome and its relationship with oro-cecal transit time. *Indian J Gastroenterol* 2006; **25**: 6–10.

23 Majewski M, McCallum RW. Results of small intestinal bacterial overgrowth testing in irritable bowel syndrome patients: clinical profiles and effects of antibiotic trial. *Adv Med Sci* 2007; **52**: 139–42.

24 Martini GA, Phear EA, Ruebner B, Sherlock S. The bacterial content of the small intestine in normal and cirrhotic subjects: relation to methionine toxicity. *Clin Sci (Lond)* 1957; **16**: 35–51.

25 Chesta J, Silva M, Thompson L, del Canto E, Defilippi C. Bacterial overgrowth in small intestine in patients with liver cirrhosis. *Rev Med Chil* 1991; **119**: 626–32.

26 Gunnarsdottir SA, Sadik R, Shev S, *et al.* Small intestinal motility disturbances and bacterial overgrowth in patients with liver cirrhosis and portal hypertension. *Am J Gastroenterol* 2003; **98**: 1362–70.

27 Morencos FC, de las Heras Castaño G, Martín Ramos L, López Arias MJ, Ledesma F, Pons Romero F. Small bowel bacterial overgrowth in patients with alcoholic cirrhosis. *Dig Dis Sci* 1995; **40**: 1252–6.

28 Yang CY, Chang CS, Chen GH. Small-intestinal bacterial overgrowth in patients with liver cirrhosis, diagnosed with glucose H2 or CH4 breath tests. *Scand J Gastroenterol* 1998; **33**: 867–71.

29 Bode JC, Bode C, Heidelbach R, Dürr HK, Martini GA. Jejunal microflora in patients with chronic alcohol abuse. *Hepatogastroenterology* 1984; **31**: 30–4.

30 Bode C, Kolepke R, Schäfer K, Bode JC. Breath hydrogen excretion in patients with alcoholic liver disease–evidence of small intestinal bacterial overgrowth. *Z Gastroenterol* 1993; **31**: 3–7.