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Original Research Article

Study of Frequency and Factors Associated with Small Intestinal Bacterial Overgrowth in Patients with Cirrhosis of the Liver – A Prospective Observational Cohort Study

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Abstract:

Introduction: The bacterial environment of the gastrointestinal tract has long been investigated for its role in health maintenance and relationship to various disease states. In healthy hosts, microorganisms are present throughout the gastrointestinal tract and are essential for gut barrier function, digestive support, and immune homeostasis. Small intestinal bacterial overgrowth (SIBO) is pathology of gut microbiota dysregulation.

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

Materials & Methods: This is a prospective observational cohort study. This Study was conducted from January 2021 to October 2021 at Department of Gastroenterology, NH Rabindranath Tagore International Institute of Cardiac Sciences.

Result: In our study, our patients with cirrhosis had mean age of 43.59 ± 5.04 years and frequency of SIBO in them was 46%. SIBO was more prevalent in patients with decompensated cirrhosis than in patients with compensated cirrhosis. Majority of our patients with cirrhosis belonged to CTP class B followed by class A and C. Frequency of SIBO increased progressively with increase in CTP class. The most common etiology of cirrhosis was alcohol followed by NAFLD, Hepatitis B and Hepatitis C.

Conclusion: We found that, we found the frequency of SIBO was 46% in the patients with cirrhosis of liver. SIBO was statistically significantly associated with decompensated cirrhosis, high CTP score, ascites, low serum albumin and high serum total bilirubin.

Keywords: Bacterial overgrowth, small intestinal bacterial overgrowth, NAFLD and steatosis.

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Introduction

The gastrointestinal tract's bacterial ecosystem has long been studied for its connection to different disease states and function in maintaining health. Microorganisms are found throughout the gastrointestinal tract of healthy hosts and are critical for immunological homeostasis, digestive support, and gut barrier function. The disorder known as small intestinal bacterial overgrowth (SIBO) is caused by imbalance of the gut microbiota.[1]

SIBO is defined as the presence of excess bacteria in the small intestine, either quantitatively (>10^5 colony forming units/milliliter (cfu/mL)) or qualitatively (excess bacteria of colonic origin), along with extra-intestinal or intestinal symptoms that are believed to be caused by this excess.Patients who have cirrhosis from a variety of causes have been found to have a high frequency of SIBO. Bacterial translocation is the primary pathogenic mechanism of spontaneous bacterial peritonitis (SBP), a potentially lethal consequence of liver cirrhosis with death rates ranging from 10 to 42%. The prevalence is 33% in cirrhosis patients who are hospitalized and 3.5% in asymptomatic outpatients.[2]

One of the factors linked to the emergence of spontaneous bacterial peritonitis is SIBO.A few studies have also found that patients with cirrhosis

and SBP have a higher incidence of SIBO. While some research revealed SIBO was linked to portal hypertension and ascites, others suggested it might be connected to the degree of liver impairment. [3] Studies that have demonstrated that portal hypertension may result in abnormalities of small bowel motility, which may lead to SIBO, further support this.

The culture of jejunal aspirates has long been the gold standard for diagnosing SIBO; colonic-type bacteria and a concentration of $>10^5$ cfu/mL of jejunal aspirate are believed to be indicators of SIBO. Breath tests that measure hydrogen and methane in the breath are the most commonly used SIBO tests.

It is crucial to comprehend the connection between SIBO and cirrhosis because of the significance of bacterial translocation and the microbiota as essential variables linked to liver disease.The current investigation aims to address our hypothesis that the degree of liver illness and hepatic decompensation may play a pathogenic effect in changing the bacterial composition of the small intestine in individuals with cirrhosis.

By identifying patients at high risk for SIBO and focusing therapy on bacterial overgrowth in this high-risk group, biochemical tests for liver function and clinical signs of liver dysfunction can be used as supplemental tools in the prevention of some of the serious complications of cirrhosis.

Materials and Methods

Type of Study: This is a prospective observational cohort study.

Place of Study: Department of Gastroenterology, NH Rabindranath Tagore International Institute of Cardiac Sciences.

Study Duration: January 2021 to October 2021.

Sample Size: 100 patients.

Inclusion Criteria

- Patients of hepatic cirrhosis, attending the out-patient or in-patient departments of Gastroenterology and Hepatology, of our hospital.
- Age of patients should be at least 18 years.
- Patients need to give written informed consent.

Exclusion Criteria

- Patients with gastro-intestinal bleed, hepatic encephalopathy (more than grade 2) and sepsis in previous 4 weeks.
- Patients with significant pulmonary disease.
- Patients on probiotics or acid suppressive therapy.
- Patients who took antibiotics within 7 days prior to the study.
- Patients who took lactulose within 48 hours prior to the study.
- Patients on immunosuppressive drugs or narcotics.

Study Variables

- Age
- Gender
- Severity of liver disease
- Presence of ascites
- Serum albumin levels
- Serum total bilirubin levels

Statistical Analysis

Data Were Entered Into Excel and Analyzed Using SPSS And GraphPad Prism. Numerical Variables Were Summarized Using Means And Standard Deviations, While Categorical Variables Were Described With Counts And Percentages. Two-Sample T-Tests Were Used To Compare Independent Groups, While Paired T-Tests Accounted For Correlations In Paired Data. Chi-Square Tests (Including Fisher's Exact Test For Small Sample Sizes) Were Used For Categorical Data Comparisons. P-Values ≤ 0.05 Were Considered Statistically Significant.

Result

Table 1: Association between Etiology of Cirrhosis: SIBO group

Etiology of Cirrhosis	Patients with SIBO	Patients without SIBO	P Value
Alcohol (n=31)	14 (45.16%)	17 (54.83%)	0.226
Hepatitis B (n=25)	14 (56%)	11 (44%)	
Hepatitis C (n=14)	3 (21.42%)	11 (78.57%)	
NAFLD (n=29)	14 (48.27%)	15 (51.72%)	
Others (n=1)	1 (100%)	0	

Table 2: Association between Cirrhosis due to Hepatitis B: SIBO group

Etiology of Cirrhosis	Patients with SIBO	Patients without SIBO	P Value
Cirrhosis due to Hepatitis B (n=25)	14 (56%)	11 (44%)	0.258
Cirrhosis Due to Causes Other than Hepatitis B (n=75)	32 (42.66%)	43 (57.33%)	

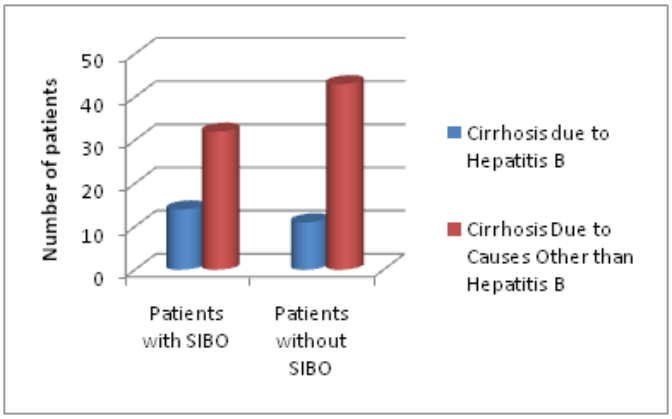

Figure 1: Association between Cirrhosis due to Hepatitis B:SIBO group

Our patients (n=100) ranged in age from 36 to 62 years old, with a median age of 43 and a mean age of 43.59 ± 5.04 years. There were 14% females and 86% males in the population. SIBO did not exhibit a statistically significant correlation with the patients' age or gender. SIBO was present in 46% of the patients with hepatic cirrhosis in our research. Of the 100 cirrhosis patients, 46 had SIBO and 54 did not. Prior to positive GHBT-rise criterion (27%) and positive GHBT-high baseline criteria (19%), the majority of patients (54%) had negative GHBT. We did not have any patients who did not create hydrogen. Of our patients, 38% had compensated cirrhosis while the majority (62%) had decompensated cirrhosis. Compared to patients with compensated cirrhosis, SIBO was more common in those with decompensated cirrhosis. SIBO was found in 18.42% of patients with compensated cirrhosis and 62.90% of individuals with decompensated cirrhosis. The presence of SIBO and decompensated cirrhosis were statistically significantly correlated. Of our cirrhosis patients, the majority (44%) were in CTP class B, followed by CTP classes A (28%) and C (28%).The patients' CTP scores ranged from 5.00 to 13.00, with a mean of 8.28±2.16 and a median of 8.00. SIBO was found to be 17.85% common in individuals with CTP class A cirrhosis, 50% in those with class B cirrhosis, and 67.85% in those with class C cirrhosis. Compared to patients in classes B or A, patients with CTP class C had a statistically significant greater frequency of SIBO. The frequency of SIBO gradually rose as the CTP class increased. SIBO was present in 37.50% of patients with CTP classes A and B combined, and 67.85% of patients with class C. The CTP score distribution in SIBO patients was found to be normal. The CTP score for patients with SIBO ranged from 5 to 13, with a median of 9.00 and a mean of 9.04±1.86. With a median score of 7.00 and a range of 5–13, the mean CTP score for patients without SIBO was 7.63±2.20. There was a statistically significant difference in the mean CTP score between patients with SIBO and those without. Hepatitis B (25%) and Hepatitis C (14%), followed by NAFLD (29%), was the most frequent cause of cirrhosis in our patients (31%).One case of autoimmune hepatitis (Others: 1%) was reported. The etiology of cirrhosis and SIBO did not statistically significantly correlate. SIBO was less common in patients with cirrhosis from hepatitis C (21.42%) than in those with cirrhosis from other causes (50%); however, the difference was not statistically significant. Only 10% of the patients in our study had a history of chronic diarrhea, compared to 90% of the patients who did not. Eleven percent of patients had a history of spontaneous bacterial peritonitis, while eighty-nine percent did not.39% of patients had a history of varicealhemorrhage, whereas 61% did not. Of the patients, 53% had no ascites, 42% had mild to moderate ascites, and 5% had severe ascites. SIBO did not statistically significantly correlate with a history of varicealhemorrhage, spontaneous bacterial peritonitis, or persistent diarrhea. Compared to patients without ascites (30.18%), SIBO was more common in individuals with ascites (63.82%). The presence of SIBO and ascites were statistically significantly correlated. SIBO was present in 60 percent of patients with severe ascites, 64.28% of individuals with mild to moderate ascites, and 30.18% of patients without ascites. SIBO and ascites severity were statistically significantly correlated. Our patients' blood albumin levels ranged from 1.50 to 3.80 gm/dl, with a median of 3.20 gm/dl and a mean of 3.00±0.51 gm/dl. The patients' mean serum total bilirubin was 1.75±0.88 mg/dl, with a range of 0.30 to 3.80 mg/dl and a median of 1.60 mg/dl. The patients' blood creatinine ranged from 0.40 to 1.30 gm/dl, with a median of 0.90 gm/dl and a mean of 0.87±0.18 gm/dl. We discovered that the frequency of SIBO was higher in patients with low serum albumin, or less than 3.2 gm/dl (median of serum albumin = 3.2 gm/dl), than in those with high albumin >= 3.2 gm/dl (30.18%).SIBO was more common in patients with low serum albumin, defined as those with a mean of less than 3 gm/dl

(i.e., <3 gm/dl), than in those with high albumin >=3 gm/dl (37.5%). Low serum albumin was statistically substantially linked to SIBO. The frequency of SIBO was higher in patients with serum total bilirubin >1.3 mg/dL (Biological Reference Interval of serum total bilirubin 0.2–1.3 mg/dL) than in individuals with serum total bilirubin <=1.3 mg/dL (26.66%) who participated in our study. The frequency of SIBO was higher in individuals with serum total bilirubin >1.6 mg/dl (median of serum bilirubin = 1.6 mg/dl) than in those with serum total bilirubin <1.6 mg/dl (25%).SIBO was more common (69.38%) in individuals with serum total bilirubin ≥1.7 mg/dl (mean of serum total bilirubin = 1.7 mg/dl) than in those with serum total bilirubin <1.7 mg/dl. The presence of SIBO and elevated serum total bilirubin are statistically significantly correlated. Serum creatinine levels in all of our patients were normal (<=1.3 mg/dl). Serum creatinine and SIBO do not statistically significantly correlate. Prothrombin time prolongation of 4–6 seconds was present in the majority of patients (52%) in our study, followed by 0–3 seconds (38%) and >6 seconds (10%). SIBO was present in 34.21%, 51.92%, and 60% of patients with prothrombin time prolongation of less than 4 seconds, 4–6 seconds, and >6 seconds, respectively. Prothrombin time prolongation and SIBO existence were not statistically significantly correlate.

Discussion

Numerous studies have demonstrated the frequency of small intestine bacterial overgrowth (SIBO) in liver cirrhosis patients as well as its correlation with the severity and course of the illness. However, different research have used different diagnostic approaches, and stated prevalence rates of SIBO vary. Large prospective trials are required to determine the prevalence of SIBO in cirrhosis patients and how it relates to portal hypertension, liver dysfunction severity, and other variables. An abundant and/or aberrant type of bacteria in the small intestine is the hallmark of this diverse illness. [4] The culture of jejunal aspirates has long been the gold standard for diagnosing SIBO; the presence of colonic-type bacteria and more than 105 colony forming units per milliliter (cfu/mL) of jejunal aspirate are regarded diagnostic indicators of SIBO. However, a number of indirect tests have been developed to diagnose SIBO due to the challenges in directly measuring and quantifying small intestinal bacterial colonization. Breath tests that measure hydrogen and methane in the breath are the most commonly used SIBO tests. Understanding the connection between SIBO and CLD is crucial because of the significance of bacterial translocation and the microbiota as pertinent factors linked to liver disease. Our study's premise was that the degree of liver illness and hepatic decompensation may play a pathogenic effect in changing the bacterial composition of the small intestine in individuals with cirrhosis. By identifying patients at high risk for SIBO and focusing therapy on bacterial overgrowth in this high-risk group, biochemical tests for liver function and clinical signs of liver dysfunction can be used as supplemental tools in the prevention of some of the serious complications of cirrhosis. We investigated the prevalence of SIBO in patients with cirrhosis of different severity and in participants with cirrhosis as determined by the glucose hydrogen breath test (GHBT) in order to evaluate this hypothesis.

We investigated the relationship between SIBO and a number of clinical and laboratory characteristics in cirrhosis patients. In our study, 46% of the patients with liver cirrhosis had SIBO (as measured by GHBT) [5]. Cirrhosis-related SIBO prevalence in one study was 40.8%, whereas control-related SIBO prevalence was 10.7%.Although the frequency of SIBO was higher in individuals with grade 1-2 hepatic encephalopathy (56.81%) than in those without (37.50%), the difference was not statistically significant. Eight out of nine patients (88.9%) with a history of one or more episodes of hepatic encephalopathy were SIBO-positive in a research by Jun et al.; this was greater than the number of patients without a history of hepatic encephalopathy [6].

Age, gender, cirrhosis etiology, history of chronic diarrhea, history of spontaneous bacterial peritonitis, history of variceal hemorrhage, serum creatinine, prothrombin time prolongation, size of oesophageal varices, and hepatic encephalopathy were not statistically significantly associated with SIBO.To create guidelines for researchers and physicians, a consensus-building gathering of experts was called. Ten of the 17 clinician-scientists who received pre-meeting survey questions covering five domains—indications, preparation, performance, interpretation of results, and knowledge gaps—attended a live meeting. A consensus was obtained by applying an evidence-based approach. The lactulose, glucose, fructose, and lactose breath tests have consensus dosages of 10, 75, 25, and 25 g, respectively. The least invasive methods for diagnosing SIBO are still the glucose and lactose breath tests. The breath test was helpful in diagnosing methane-associated constipation, carbohydrate maldigestion, and bloating/gas, but it was not helpful in evaluating oro-cecal transit. During the glucose or lactulose breath test for SIBO, a rise in hydrogen of ≥20 p.p.m. by 90 minutes was deemed positive. Methane-positive was defined as having methane levels ≥10 p.p.m. To prevent false positives, SIBO should be ruled out before a breath test for carbohydrate malabsorption. During BT, an

increase in hydrogen of ≥20 p.p.m. from baseline was seen as a good sign for maldigestion [7].This approach is not commonly used in everyday life. Therefore, the most widely utilized non-invasive test for diagnosing SIBO is still GHBT. There were certain restrictions on our investigation. The gold standard for diagnosing SIBO, jejunal aspiration and culture, was not used by us. Patients with and without SIBO were not followed up to record differences in outcome because our investigation was cross-sectional. In order to look for a correlation between SIBO and a broader range of liver disease severity, we lacked a control group of patients with chronic hepatitis/NAFLD who did not have cirrhosis."

Conclusion

We discovered that 46% of individuals with hepatic cirrhosis had SIBO. Ascites, low serum albumin, high serum total bilirubin, decompensated cirrhosis, and a high CTP score were all statistically substantially linked to SIBO. We demonstrated that patients with CTP class C had a statistically significant greater prevalence of SIBO than patients with CTP class B or A. As the CTP class grew, the frequency of SIBO gradually increased as well. Age, gender, cirrhosis etiology, history of chronic diarrhea, history of spontaneous bacterial peritonitis, history of varicealhemorrhage, serum creatinine, prothrombin time prolongation, size of oesophageal varices, and hepatic encephalopathy were not statistically significantly associated with SIBO.

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