Shizuma J Clin Trials 2014, 4:3
DOI: 10.4172/2167-0870.1000166

Journal of Clinical Trials
ISSN: 2167-0870

Research Article Open Access

Retrospective Investigation of Bacterascites and Spontaneous Bacterial Peritonitis in Liver Cirrhosis Patients Undergoing Paracentesis

Toru Shizuma*

Department of Physiology, School of Medicine, Tokai University, 143, Shimokasuya, Isehara, Kanagawa, 259-1193, Japan

Abstract

Objective: There have been few studies of bacterascites among liver cirrhosis (LC) patients, although spontaneous bacterial peritonitis (SBP) has been well studied. Moreover, there have been no comparative studies of bacterascites and sterile ascites among LC patients. Therefore, we compared the characteristics of bacterascites, SBP, and sterile ascites among LC patients.

Methods: Characteristics of bacterascites, SBP, and sterile ascites were retrospectively compared among 476 LC patients with ascites (547 paracentesis procedures, which included laboratory examinations and bacterial cultures of ascitic fluid) in Japan.

Result: The frequencies of bacterascites and SBP were 2.6% (14/545) and 6.1% (33/545), respectively. Serum albumin and total protein levels in the ascitic fluid were significantly lower in the bacterascites group than in the sterile ascites group (498/545). However, no significant differences were observed in the Child–Pugh scores, incidence of type I hepatorenal syndrome (HRS), or short-term mortality rates between the bacterascites and sterile ascites groups. However, these parameters were significantly higher in the SBP group than in the sterile ascites group.

Conclusion: No significant differences in short-term prognosis were observed among the groups because there appears to be no significant difference in the severity of liver dysfunction associated with underlying LC and the incidence of type I HRS between patients with bacterascites and sterile ascites. However, SBP was associated with a significantly poorer prognosis than sterile ascites.

Keywords: Ascites; Bacterascites; Spontaneous bacterial peritonitis; Sterile ascites; Hepatorenal syndrome; Liver cirrhosis

Introduction

Liver Cirrhosis (LC) patients are predisposed to bacterial infection [1], and the mortality rate among LC patients with complications arising from bacterial infection is markedly high [2]. Consequently, Spontaneous Bacterial Peritonitis (SBP) and bacterascites is relatively frequent in decompensated LC. The incidence of SBP and bacterascites in LC inpatients with ascites is reportedly 7%–30% [3,4] and 3% – 4% [5,6], respectively.

The clinical features, risk factors, and prognosis of SBP, which is considered life-threatening, have been well documented [2,7,8]. On the other hand, most previous reports on bacterascites were published in the 1980s [9,10] and early 1990s [11,12] with very few reports published in recent years. In addition, to the best of our knowledge, there have been few comparative studies of bacterascites and SBP [11,12] and no comparative study of bacterascites and sterile ascites has been reported to date.

We conducted a retrospective comparative study of bacterascites, SBP, and sterile ascites by examining laboratory findings and bacterial cultures of ascitic fluid in Japanese LC patients undergoing paracentesis.

Methods

Subjects

We retrospectively reviewed the medical records of 476 LC patients who underwent a total of 1717 paracentesis procedures using standard sterile techniques, of which 547 procedures also involved laboratory examinations and bacterial cultures of ascitic fluid. Of the 476 patients, 469 were hospitalized and 7 were treated as outpatients from 1983 through 2012 at 4 hospitals located in the Kanto district of Japan. The frequency of refractory ascites, regardless of the administration of therapeutic agents, such as diuretics, was 12.4% (59/476), resulting in ascites control in 87.6% (417/476) of cases. Patients with LC and infectious pleural effusion, secondary peritonitis (e.g., digestive tract rupture), peritonitis carcinomatosa, hemorrhagic ascites (e.g., hepatocellular carcinoma rupture), or ascites due to renal or heart failure were excluded from analysis. We also excluded those who were treated with antimicrobial agents within the preceding month.

Of these 476 subjects, 322 (67.6%) were males and 154 (32.4%) females, and their mean age was 63.2 ± 6.8 (range, 38–85) years. The hepatitis B surface antigen positivity rate was 10.9% (52/476), and the hepatitis C virus (HCV) antibody positivity rate was 70.4% (326/463), although HCV antibody analysis was not performed for 13 cases between 1983 and 1987. The characteristics of the 476 subjects are summarized Table 1.

Diagnosis of SBP and bacterascites

SBP was diagnosed regardless of the presence of bacteria in the ascitic fluid of cases where the polymorphonuclear (PMN) cell count in the ascitic fluid was ≥250/mm^3 [7]. Bacterascites was diagnosed when the PMN cell count in the ascitic fluid was <250/mm^3, although bacteria were isolated [7]. Sterile ascites was diagnosed in cases without

***Corresponding author:** Toru Shizuma, Department of Physiology, School of Medicine, Tokai University, 143, Shimokasuya, Isehara, Kanagawa, 259-1193, Japan, Tel: +81-0463-93-1121; Fax: 81-0463-93-6684; E-mail: shizuma@is.icc.u-tokai.ac.jp

Received February 06, 2014; **Accepted** March 13, 2014; **Published** March 17, 2014

Citation: Shizuma T (2014) Retrospective Investigation of Bacterascites and Spontaneous Bacterial Peritonitis in Liver Cirrhosis Patients Undergoing Paracentesis. J Clin Trials 4: 166. doi:10.4172/2167-0870.1000166

Patients(inpatients/outpatients)	476(469/7)
Age(years)	63.2±6.8 (range:38～85)
Gender (male/female)	322/154
Paracenteses	547
Child-Pugh class	
A	0 (0%)
B	98 (20.6%)
C	369 (77.5%)
Uncertain	9 (1.9 %)
Positive rate of HBs antigen	10.9% (52/476)
Positive rate of HCV antibody	70.4% (326/463)
Occurrence of hepatocellular carcinoma	22.5% (102/454)

Table 1: Characteristics of patients.

isolation of bacteria in ascitic fluid if the PMN cell count was <250/mm^3 in the ascitic fluid. We excluded LC cases in which the normal skin flora, such as Micrococcus species (sp.) or Propionibacterium sp., were isolated from the ascitic fluid because of the possibility of contamination.

Diagnosis of hepatorenal syndrome

Cases with serum creatinine levels of ≥1.5 mg/dL and no evident disease associated with renal failure were diagnosed with Hepatorenal Syndrome (HRS) according to the criteria of the International Ascites Club [13]. These cases were then classified into two types: type I (in which the creatinine level increased two-fold or reached 2.5 mg/dL within 2 weeks and rapid progression of renal failure), and type II (in which the creatinine level was ≥ 1.5 mg/dL, but no rapid deterioration of renal function was detected). We compared the incidence of type I HRS among subjects with bacterascites, SBP, and sterile ascites because LC patients complicated with type I HRS are considered to have a poor prognosis [14-16].

Frequency of symptomatic cases

Based on the criteria of Evans et al. [3], we defined symptomatic cases as LC patients with ascites who had a fever of >37.5°C, gastrointestinal bleeding within 3 months, abdominal pain or tenderness, other than that which could be explained by ascites, or worsening renal function with any increase in the serum creatinine level to >2.5 mg/dL over the previous 2 weeks. We compared the frequency of symptomatic cases in the bacterascites and SBP groups.

Analyses of serological tests and ascitic fluid

We compared the serological laboratory findings (prothrombin time [%], and levels of albumin, total bilirubin, and creatinine) and Child–Pugh scores of subjects with bacterascites, SBP, and sterile ascites. Laboratory analysis of the ascitic fluid included differential cell counts and bacterial cultures.

After bedside inoculation of a volume of 10 mL of ascites on growth medium, bacterial cultures were processed using the Bactec system (Nippon Becton Dickinson Co., Tokyo, Japan); the BACTEC™ NR660 system until 1996 and the BACTEC™ 9240 system since 1997. We also compared the total protein concentration and pH values of the ascitic fluid samples among subjects with bacterascites, SBP, and sterile ascites.

Comparison of short- and long-term mortality rates

We compared the short-term (one-month) mortality rates among subjects with SBP, bacterascites, or sterile ascites. Moreover, we compared the 1-year mortality rates among the 3 groups, although some patients who dropped out during the follow-up period were excluded.

Statistical analysis

Differences in Child–Pugh scores and laboratory findings of the serological and ascitic fluid analyses were compared between subjects with bacterascites and those with sterile ascites, between subjects with bacterascites and those with SBP, and between subjects with SBP and those with sterile ascites by one-way analysis of variance followed by Tukey's multiple comparison post-hoc test. Contingency tables were used to compare the frequency of symptomatic cases in the SBP and bacterascites groups and to compare the incidence of type I HRS and the short-term mortality rate among bacterascites, SBP, and sterile ascites cases. A probability (p) value of <0.05 was considered significant.

Results

Frequency of SBP and bacterascites

We excluded 2 patients from whom Staphylococcus epidermidis was isolated from the ascitic fluid because of the possibility of contamination (PMN cell counts in the ascitic fluid from both cases were <250/mm^3).

Among the 545 paracentesis procedures, which involved laboratory examinations and bacterial cultures, frequencies of bacterascites and SBP were 2.6% (14/545) and 6.1% (33/545), respectively, although these frequencies were not precise in all paracentesis procedures. The frequency of sterile ascites was 91.4% (498/545).

Patient characteristics

The frequency of symptomatic cases in the SBP and bacterascites groups was 84.8% (28/33) and 50.0% (7/14), respectively. The frequency of symptomatic cases was significantly greater ($p < 0.05$) in the SBP group compared with that in the bacterascites group.

The characteristics of patients with SBP, bacterascites, and sterile ascites are summarized in Table 2. The frequency of antimicrobial agents for treatment for SBP and bacterascites are also summarized in Table 2.

	SBP	Bacterascites	Sterile ascites
Age (years)	62.9 ± 6.4	62.8 ± 6.1	63.3 ± 6.9
Gender (male/female)	20/13	9/5	293/136
Fever (>37.5ºC) *	45.5%(15/33)	7.1%(1/14)	
Abdominal pain or tenderness	36.4%(12/33)	14.3%(2/14)	
Administration of antimicrobial agents	100%(33/33)	85.7%(12/14)	
Penicillin	(3/33)	(3/14)	
Cephem	(24/33)	(7/14)	
Quinolone	(6/33)	(2/14)	
Positive rate of HBs antigen	9.1% (3/33)	7.1% (1/14)	11.2% (48/429)
Positive rate of HCV antibody	71.9% (23/32)	57.1% (8/14)	70.7% (295/417)
Incidence of type I hepatorenal syndrome **	30.3% (10/33)	21.4% (3/14)	16.5% (79/478)
Occurrence of hepatocellular carcinoma	9.4% (3/32)	14.3% (2/14)	23.8% (97/408)

SBP: spontaneous bacterial peritonitis
* Statistically significant (SBP versus bacterascites)
* * Statistically significant (SBP versus sterile ascites)

Table 2: Characteristics of spontaneous bacterial peritonitis, bacterascites, and sterile ascites.

Organisms isolated from the ascitic fluid

Of the 33 SBP cases, ascitic cultures were positive in 12, which included 4 cases of Escherichia coli, Klebsiella pneumoniae in 3, and 1 each of Streptococcus sp., S. aureus, Listeria sp., Pseudomonas sp., and Bacteroides sp. The isolation rate of gram-positive bacteria was 25.0% (3/12).

The organisms isolated from the ascitic cultures of the 14 bacterascites cases included 4 of E. coli, 3 each of Streptococcus sp. and S. aureus, 2 of K. pneumoniae, and 1 each of Pseudomonas sp. and Enterococcus sp. The isolation rate of gram-positive bacteria in this group was 50.0% (7/14).

Comparison of serological laboratory findings and Child–Pugh scores

The mean serum albumin (g/dL) levels among the subjects with SBP (2.39 ± 0.36) and bacterascites (2.36 ± 0.41) were significantly lower than those among the subjects with sterile ascites (2.69 ± 0.49). However, no significant differences were observed in serological laboratory findings (prothrombin time and levels of total bilirubin and creatinine) between bacterascites and sterile ascites cases or between SBP and sterile ascites cases. Moreover, no significant differences were observed in serological laboratory findings (prothrombin time and levels of albumin, total bilirubin, or creatinine) between the SBP and bacterascites cases (Table 3). The mean Child–Pugh score among the SBP cases (12.3 ± 1.32) was significantly higher than that among the sterile ascites cases (11.7 ± 1.62), but it was not significantly different between the bacterascites (12.1 ± 1.24) and sterile ascites cases or between the SBP and bacterascites cases (Table 3).

Comparison of ascitic fluid findings

The total protein concentration (g/dL) in the ascitic fluid of the bacterascites group (1.07 ± 0.41) was significantly ($p = 0.038$) lower than that of the sterile ascites group (1.54 ± 0.83). The total protein concentration in the ascitic fluid of the SBP group (1.26 ± 0.58) tended to be lower ($p = 0.057$) than that of the sterile ascites group. No significant differences were observed in the total protein levels in the ascitic fluid between the bacterascites and SBP groups (Table 4). Moreover, no significant difference was observed in the pH levels of the ascitic fluid among the bacterascites, SBP, and sterile ascites cases (Table 4). The proportion of subjects with an ascitic fluid pH of <7.3 was 48.5% (16/33) in the SBP group, 42.9% (6/14) in the bacterascites group, and 52.5% (234/446) in the sterile ascites group. No significant difference was observed in the proportion of subjects with an ascitic fluid pH of <7.3 among those with bacterascites, SBP, and sterile ascites.

Incidence and treatment of type I HRS

The incidence of type I HRS within 1 month was 30.3% (10/33) in the SBP group, 21.4% (3/14) in the bacterascites group, and 16.5% (79/478) in the sterile ascites group. The incidence of type I HRS was significantly ($p < 0.05$) higher in the SBP group than in the sterile ascites group. However, no significant differences were observed in the incidence of type I HRS between the SBP and bacterascites groups or between the bacterascites and sterile ascites groups.

Treatment of type I HRS in 10 SBP cases and 3 bacterascites cases was as follows: albumin infusion together with administration of antimicrobial agents and diuretics for 2 cases, albumin infusion with administration of diuretics for 6 cases, and administration of diuretics for 5 cases.

Short-term and long-term prognoses

All subjects with SBP and 12 (85.7%) of the 14 subjects with bacterascites were treated with antimicrobial agents (Table 2). Moreover, none of the 14 bacterascites cases developed peritonitis within 1 month.

The short-term (1-month) mortality rate was 33.3% (11/33) in the SBP group, 21.4% (3/14) in the bacterascites group, and 18.3% (89/487) in the sterile ascites group. The short-term mortality rate in the SBP group was significantly ($p < 0.05$) higher than that in the sterile ascites group. However, no significant differences were observed in short-term mortality rates between the SBP and bacterascites groups or between the bacterascites and sterile ascites groups. Although causes of death in patients with SBP or bacterascites are often complex, the main causes of death within 1 month were as follows: liver failure and HRS in 7 SBP cases and 3 bacterascites cases, hepatocellular carcinoma in 2 SBP cases, varix rupture in 1 SBP case, and bacterial infection in 1 SBP case.

The 1-year mortality rate was 44.8% (13/29) in the SBP group, 25.0% (3/12) in the bacterascites group, and 21.8% (104/476) in the sterile ascites group, although some patients dropped out during the follow-up periods.

Discussion

At first, a total of 547 paracentesis procedures in this study may seem

	SBP	Bacterascites	Sterile ascites	p-value		
				SBP vs Bacterascites	SBP vs Sterile ascites	Bacterascites vs Sterile ascites
Albumin (g/dL)	2.39 ±0.36	2.36 ± 0.41	2.69 ± 0.49	0.804	<0.0001 ∗	0.014 ∗
PT (%)	47.2 ±13.1	46.3 ± 14.1	49.8 ±18.7	0.839	0.304	0.383
T-bil. (mg/dL)	5.4 ± 3.6	5.1 ± 4.2	4.9 ± 5.2	0.559	0.168	0.726
Creatinine (mg/dL)	1.24 ± 0.56	1.19 ± 0.41	1.21 ± 0.54	0.283	0.924	0.229
Child-Pugh score	12.3 ± 1.32	12.1 ± 1.24	11.7 ± 1.62	0.735	0.0056 ∗	0.144

Table 3: Comparison of serological laboratory findings and Child-Pugh score among subjects with spontaneous bacterial peritonitis, bacterascites, and sterile ascites.

	SBP	Bacterascites	Sterile ascites	p-value		
				SBP vs Bacterascites	SBP vs Sterile ascites	Bacterascites vs Sterile ascites
Concentration of total protein (g/dL)	1.26 ± 0.58	1.07 ± 0.41	1.54 ± 0.83	0.272	0.057	0.038*
pH	7.41 ± 0.33	7.46 ± 0.30	7.44 ± 0.38	0.644	0.665	0.845

SBP: Spontaneous bacterial peritonitis; vs: versus
∗ Statistically significant

Table 4: Comparison of laboratory findings relating to the ascitic fluid of subjects with spontaneous bacterial peritonitis, bacterascites, and sterile ascites.

to be low among a cohort of 476 patients because many patients with ascites usually undergo paracentesis more than twice. This discrepancy may be explained by the low opportunities for examinations of laboratory findings or bacterial cultures in the ascitic fluid even though multiple paracentesis procedures were performed. Therefore, 547 represents the number of times ascitic fluid was examined, and not the number of paracentesis procedures (the total number of paracentesis procedures was 1717).

Bacterascites is characterized by a PMN cell count of <250/mm^3 in ascitic fluid despite the isolation of bacteria. However, numerous factors associated with bacterascites remain unclear. First, it is controversial whether antibiotic treatment is necessary because bacteria may be cleared naturally in bacterascites cases [7], although SBP has been reported to be effectively treated with antimicrobial agents [17]. Moreover, the frequency of the development of bacterascites relative to SBP is unclear, although according to Pelletier et al. [12], 12 asymptomatic bacterascites cases not treated with antimicrobial agents did not progress to peritonitis. Previous reports comparing bacterascites and SBP have shown that the severity of liver dysfunction associated with underlying LC was equal to or slightly better in bacterascites cases and that the prognosis was equal to or more favorable for bacterascites cases [11,12]. On the other hand, to the best of our knowledge, there have been no comparative studies of bacterascites and sterile ascites.

In this study, although we retrospectively examined cases dating back 30 years, there were only 14 cases of bacterascites, thus limiting the power of the statistical analysis. However, a study with a larger number of cases may arrive at comparable conclusions between bacterascites and sterile ascites. On the other hand, the efficacy rate of bacterial isolation in ascitic fluid cultures seems to increase by generation (progression of culture system). Therefore, there may be differences in bacterial isolation rates because the duration in this study was from the 1980s to 2010s.

In this study, no significant differences in the severity of liver dysfunction associated with underlying LC (Child–Pugh score) or short-term prognosis were observed between the SBP and bacterascites groups or between the bacterascites and sterile ascites groups. Moreover, we found that the serum albumin and total protein levels in the ascitic fluid was significantly lower in the bacterascites cases than in cases with sterile ascites. However, no significant differences in relation to other laboratory findings and the incidence of type I HRS were observed between the bacterascites cases and sterile ascites cases.

Bacterial translocation from the intestinal tract is considered to be a primary mechanisms in the development of SBP and enterobacteria reportedly account for a relatively large percentage of the causative bacteria [11,12]. Regarding bacterascites, the proportion of patients with ascitic fluid positive for gram-positive bacteria is reportedly greater than that in cases of SBP [6,12]. Our study showed similar findings, as the isolation rate of gram-positive bacteria in ascitic fluid was 50.0% in the bacterascites group and 25.0% in the SBP group. Moreover, in patients with SBP or bacterascites due to gram-positive bacteria, the PMN cell count in the ascitic fluid tended to be <250/mm^3 compared with SBP or bacterascites due to enterobacteria [18]. This may be another possible reason why gram-positive bacteria are commonly viewed as the causative agents of bacterascites.

PMN cell counts are essential for the diagnosis of SBP or bacterascites, but decreased protein concentrations in the ascitic fluid, elevated levels of lactic acid [11], and a decreased pH [19] have also been reported to be useful indicators for the diagnosis of SBP. A decrease in the protein concentration in ascitic fluid is considered a risk factor for the development of SBP [20,21], and the underlying mechanism is considered to be due to a decrease in complement and opsonic functions [17,22]. Our results showed that the protein concentration was significantly lower in the ascitic fluid of bacterascites cases and tended to be lower in the ascitic fluid of SBP cases compared with subjects with sterile ascites. Therefore, a decrease in the protein concentration in the ascitic fluid may be involved in the occurrence and growth of bacteria in the ascitic fluid of bacterascites cases. A pH of ascitic fluid <7.3 has also been reported to be a useful indicator for the diagnosis of SBP [19]. However, in our study, the proportion of patients with an ascitic fluid pH of <7.3 was not significantly different among the 3 groups (SBP, bacterascites, and sterile ascites), nor was there a significant difference in the mean pH, suggesting that the pH value of the ascitic fluid is not very useful for the differentiation of SBP, bacterascites, and sterile ascites.

Procalcitonin (PCT) is a relatively novel and helpful biomarker for the early diagnosis of bacterial infection. High PCT levels were estimated to be a sensitive and specific marker for the initial diagnosis of bacterial infection in patients with LC. Many previous reports have suggested that serum PCT level is a sensitive marker for diagnosis of SBP [23-26], although these findings remain controversial. Cekin et al. [26] reported that serum PCT levels in SBP (mean, 1.01 ng/mL) and bacterascites cases (mean, 1.9 ng/mL) were significantly higher than those in sterile ascites cases (mean, 0.3 ng/mL). However, the usefulness of PCT for the diagnosis of bacterascites in patients with LC remains unclear due to the relatively limited number of reports [26].

In SBP, renal dysfunction and the severity of the underlying hepatic disorder are considered important prognostic factors [14]. In particular, the development of type I HRS is potentially lethal and strongly implicated in vital prognoses [14-16]. Renal impairment in SBP is associated with reduced circulating volume [8] and the median survival of subjects with type I HRS is reportedly only 2–3 weeks [27], although treatment of SBP with albumin infusion together with administration of antimicrobial agents reportedly reduces the risk of HRS development and improves survival [28,29]. According to Sort et al. [28], the incidence of type I HRS among SBP cases is 30%, which is similar to our finding of 30.3%. We also found that the Child–Pugh score and the incidence of type I HRS were significantly higher among the SBP cases compared with those with sterile ascites. The fact that the severity of the underlying hepatic disorder and the incidence of type I HRS were significantly higher in the SBP group may be significant to the short-term prognosis of SBP.

Regarding bacterascites, the Child–Pugh score, the incidence of type I HRS, and the short-term prognosis were not significantly different from those among subjects with sterile ascites. Therefore, the significantly lower protein levels in ascitic fluid may be involved in the development of bacterascites. However, the absence of any significant difference between the bacterascites and sterile ascites groups in terms of the severity of the underlying LC and the incidence of type I HRS may have contributed to the lack of any significant difference in the short-term prognosis for those in the bacterascites and sterile ascites groups, although analysis of 14 bacterascites cases may have limited the relevance of assessment.

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