

Renal Dysfunction Induced by Bacterial Infection other than Spontaneous Bacterial Peritonitis in Patients with Cirrhosis: Incidence and Risk Factor

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Background/Aims: Deterioration of renal function in cirrhotic patients with spontaneous bacterial peritonitis (SBP) is a predictor for in-hospital mortality; however, the clinical significance of renal dysfunction during bacterial infection other than SBP is unknown. The aim of this study was to investigate the prevalence and clinical significance of renal dysfunction due to bacterial infections other than SBP in patients with liver cirrhosis. **Methods:** Retrospective data from inpatients with bacterial infections other than SBP were analyzed. **Results:** Eighty patients were recruited for the analysis. The types of infections included that of urinary tract (37.5%), pneumonia (23.8%), biliary tract (20%), cellulitis (12.5%), and bacteremia of unknown origin (6.3%). Renal dysfunction developed in 29 patients (36.3%), of which 11 patients had irreversible renal dysfunction. The initial MELD score, neutrophil count, albumin, and blood pressure were significant risk factors in the univariate analysis, whereas only the MELD score was an independent risk factor for the development of renal dysfunction ($p < 0.001$) after multivariate analysis. **Conclusions:** The prevalence of renal dysfunction during bacterial infection other than SBP in patients with liver cirrhosis was 36.3%, and its development was related to the severity of the liver disease. Occurrence of irreversible renal dysfunction seemed to affect the prognosis of these patients. (*Gut and Liver* 2009;3:292-297)

Key Words: Liver cirrhosis, Bacterial infection, Renal dysfunction

INTRODUCTION

Bacterial infection is a complication that occurs at a higher incidence in patients with liver cirrhosis.¹⁻⁴ In particular, cases in which renal dysfunction occurs during the course of bacterial infection have a poor prognosis, and renal dysfunction is a key indicator predicting death in patients with bacterial infection.¹ Bacterial infections commonly observed in patients with liver cirrhosis are, in descending order of frequency, urinary tract infection, pneumonia, and spontaneous bacterial peritonitis (SBP).⁵⁻⁸

Most of the studies concerned about the clinical significance of renal dysfunction in patients with SBP.⁹⁻¹¹ In patients with bacterial infection other than SBP, despite its higher prevalence, the clinical significance of renal dysfunction which might have the same pathophysiology as SBP, has not been thoroughly examined.

The objectives of this study were to examine the incidence of renal dysfunction in the presence of bacterial infections other than SBP and to evaluate the incidence, risk factors, and prognosis for irreversible renal dysfunction.

MATERIALS AND METHODS

1. Patients

The current study included patients with liver cirrhosis resulted from bacterial infections other than SBP and who were hospitalized at our medical institution between 1 January 2005 and 30 May 2008. Diagnosis of liver cir-

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rhosis was made based on clinical, radiological, or histopathological findings. Diagnostic criteria for each bacterial infection were as follows. Pneumonia was diagnosed when chest X-ray abnormalities were accompanied by fever, coughing, and leukocytosis. Urinary tract infection was diagnosed when fever and recurrent urinary tract symptoms that were positive for bacteriuria by urine culture existed. Biliary tract infection was suggested when fever, abdominal pain, leukocytosis, coexisted with findings suggestive of biliary tract infection on ultrasonography or abdominal CT scans. Gastrointestinal infection was defined as having vomiting, diarrhea, fever, abdominal pain, leukocytosis, and positive findings on a stool culture test. Cellulitis was defined as a skin infection, fever, and leukocytosis. Bacteremia of unknown origin was defined as positive findings on a blood culture in the absence of other infectious causes.^{4,8} For cases who had ascites, ascitic fluid culture and analysis were done to exclude SBP and culture-negative neutrocytic ascites.

Renal dysfunction following bacterial infection was defined as >50% increase in serum creatinine level over the base line value with abnormal peak serum creatinine level (>1.5 mg/dL) after the bacterial infection was diagnosed.¹² Reversible renal dysfunction was defined as return to that of the normal value in 2 weeks of treatment period after renal dysfunction occurred. For cases in which the serum creatinine levels did not return to that of the normal value in 2 weeks of treatment period or were persistently elevated, an irreversible renal dysfunction was diagnosed.

2. Methods

The clinical characteristics and serum biochemistry findings, including age, gender, blood pressure, liver cirrhosis etiology, type of bacterial infection, Child-Pugh score, WBC count, prothrombin time, Model for End-Stage Liver Disease (MELD) score, and serum sodium, BUN, creatinine, bilirubin, and albumin concentrations during the course of bacterial infection, were retrospectively analyzed in all patients to determine risk factors for renal dysfunction.

3. Statistical analysis

The data are expressed as mean±standard error (SE) or number and percentage. Continuous variables were analyzed using independent *t*-test, and discontinuous variables were analyzed with Pearson's chi-square or Fisher's exact test. Multivariate analysis was performed using a multiple logistic regression for variables with significant *p*-values in univariate analysis. All statistical analyses were performed with SPSS (Windows release 10.0; SPSS

Inc., Chicago, IL, USA). A *p* value <0.05 was considered significant.

RESULTS

1. Patient characteristics and overall incidence of renal dysfunction

The current study was conducted with 80 patients who were hospitalized at our medical institution due to liver cirrhosis accompanied by a bacterial infection other than SBP. The mean age was 59.4±1.0 years; the male-to-female ratio was 7 : 3. Causative factors for liver cirrhosis included alcoholic liver disease in 30 patients, chronic hepatitis B in 28, chronic hepatitis C in 14, unknown causes in seven, and primary biliary cirrhosis in one. There were 30 cases of urinary tract infection, 19 cases of pneumonia, 16 cases of biliary tract infection, 10 cases of cellulites, and five cases of bacteremia of unknown origin (Table 1). Renal dysfunction developed in 29 (36%) of the patients with liver cirrhosis who concurrently had a bacterial infection.

2. Risk factors for developing renal dysfunction

The clinical characteristics of the 29 patients who had renal dysfunction occurred after diagnosis of bacterial infection and the 51 patients who did not had renal dysfunction were comparatively evaluated. The mean age was 59.8±9.9 years in patients with renal dysfunction and 59.1±9.5 years in patients without renal dysfunction.

Table 1. Baseline Characteristics of the 80 Patients with Bacterial Infection

Characteristic	Value
Age (yr)	59.4±1.0*
Gender	
Male	58 (72.5)
Female	22 (27.5)
Etiology	
HBV	28 (35)
HCV	14 (17.5)
Alcohol	30 (37.5)
Non-B, non-C	7 (8.8)
PBC	1 (1.3)
Infection	
UTI	30 (37.5)
Biliary tract infection	16 (20.0)
Pneumonia	19 (23.8)
Cellulitis	10 (12.5)
Primary bacteremia	5 (6.3)

HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; UTI, urinary tract infection.

*Mean years±SE. Other data are number (%) of patients.

Table 2. Comparison of Characteristics of Groups according to Development of Renal Dysfunction

Characteristic	Patients who developed renal dysfunction (n=29)	Patients who did not develop renal dysfunction (n=51)	p-value
Age (yr)	59.8±9.9*	59.1±9.5*	0.76
Gender			0.59
Male	20 (69)	38 (75)	
Female	9 (31)	13 (25)	
Blood pressure (mmHg)			
Systolic	99.5±16.6*	110.9±15.7*	0.003
Diastolic	64.5±10.1*	70.7±6.5*	0.004
Etiology			0.041
HBV	7 (24)	21 (41)	
HCV	6 (21)	8 (16)	
Alcohol	15 (52)	15 (29)	
Non-B, non-C	0	7 (14)	
PBC	1 (3)	0	
Infection type			0.161
UTI	15 (52)	15 (29)	
Biliary tract infection	2 (7)	14 (27)	
Pneumonia	7 (24)	12 (24)	
Cellulitis	3 (10)	7 (14)	
Primary bacteremia	2 (7)	3 (6)	
Child-Pugh score	9.1±1.6*	8.4±2.1*	0.083
Laboratory data			
WBC count (/μL)	11,915.0±7,568*	7,823.5±4,525*	0.011
Sodium (mEq/L)	133.0±6.7*	135.8±6.0*	0.056
Bilirubin (mg/dL)	6.9±7.9*	3.9±3.4*	0.067
Prothrombin time (%)	51.8±16.9*	58.8±20.4*	0.119
Albumin (g/dL)	2.6±0.4*	2.9±0.5*	0.015
MELD score	24.5±6.9*	15.8±5.7*	<0.0001
Creatinine (mg/dL)	0.82±0.2*	0.79±0.7*	0.096

HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; UTI, urinary tract infection; MELD, Model for End-Stage Liver Disease.

*Mean±SE. Other data are number (%) of patients.

There were no significant differences in gender, Child-Pugh score, or type of bacterial infection between the two groups. However, systolic and diastolic pressures were 99.5±16.6 mmHg and 64.5±10.1 mmHg, respectively, in 29 patients who had renal dysfunction developed and 110.9±15.7 mmHg and 70.7±6.5 mmHg, respectively, in 51 patients who did not have renal dysfunction ($p < 0.01$). Renal dysfunction was more prevalent in patients with alcoholic liver disease (Table 2).

There was no significant difference in serum sodium, serum bilirubin, serum creatinine, or prothrombin time during the course of bacterial infection between the two groups. However, in patients with renal dysfunction, the WBC count (11,915/ μ L) and MELD score (24.5) were significantly higher than those in patients without renal dysfunction ($p = 0.011$ and $p < 0.0001$, respectively). The albumin level also differed significantly between the groups ($p = 0.015$) (Table 2).

A multiple logistic regression analysis was performed

Table 3. Multiple Logistic Regression Analysis for the Variables Affecting Renal Dysfunction Development after Bacterial Infection

Variable	Odds ratio (95% CI)	p-value
Systolic BP < 100 mmHg	3.272 (0.80-13.33)	0.098
Diastolic BP < 60 mmHg	5.565 (0.31-98.98)	0.242
MELD score \geq 20	12.609 (3.01-52.77)	0.001
Albumin < 2.8 g/dL	1.147 (0.26-5.02)	0.856
WBC count > 10,000/ μ L	2.184 (0.59-8.08)	0.242
Alcoholism	4.042 (0.97-16.83)	0.055

CI, confidence interval; BP, blood pressure; MELD, Model for End-Stage Liver Disease; WBC, white blood cell.

on systolic and diastolic pressures, presence of alcoholic liver disease, WBC count, albumin level, and MELD score, which were all significant in the univariate analysis. The MELD score was significantly associated with the occurrence of renal dysfunction resulting from bacterial infection. The incidence of renal dysfunction in cases with

Table 4. Comparison of Characteristics of Groups according to Development of Irreversible Renal Dysfunction

Characteristic	Patients who developed irreversible renal dysfunction (n=11)	Patients who did not develop irreversible renal dysfunction (n=69)	p-value
Age (yr)	63.8±7.6*	58.7±9.8*	0.103
Gender			0.985
Male	8 (73)	50 (72)	
Female	3 (27)	19 (28)	
Blood pressure (mmHg)			
Systolic	99.1±17.0*	108.0±16.6*	0.128
Diastolic	67.2±10.1*	68.6±8.3*	0.677
Etiology			0.394
HBV	3 (27)	25 (36)	
HCV	4 (36)	10 (14)	
Alcohol	4 (36)	26 (38)	
Non-B, non-C	0	7 (10)	
PBC	0	1 (2)	
Infection type			0.210
UTI	5 (45)	25 (36)	
Biliary tract infection	0	16 (23)	
Pneumonia	3 (27)	16 (23)	
Cellulitis	1 (9)	9 (13)	
Primary bacteremia	2 (18)	3 (5)	
Child-Pugh score	9.0±1.4*	8.4±1.9*	0.285
Laboratory data			
WBC count (/μL)	11,985.0±8,122 *	8,879.71±5,670*	0.246
Sodium (mEq/L)	132.6±2.9*	135.5±6.4*	0.138
Bilirubin (mg/dL)	6.2±6.1*	4.3±4.3*	0.361
Prothrombin time (%)	49.3±14.5*	57.4±19.9*	0.126
Albumin (g/dL)	2.7±0.4*	2.8±0.5*	0.214
MELD score	27.2±7.9*	17.6±6.5*	0.003
Creatinine (mg/dL)	0.89±0.3*	0.76±0.6*	0.073

HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; UTI, urinary tract infection; MELD, Model for End-Stage Liver Disease.

*Mean±SE. Other data are number (%) of patients.

a MELD score >20 was 12.6 times the incidence in the other cases (OR, 12.609; 95% confidence interval, 3.01-52.77, p=0.001) (Table 3).

3. Incidence, risk factors, and prognosis of irreversible renal dysfunction

Irreversible renal dysfunction occurred in 11 patients, representing 14% of the total number of patients and 38% of those who had renal dysfunction. When cases with reversible and irreversible renal dysfunction were compared, there were no statistically significant differences in variables including MELD score. However, when patients with irreversible renal dysfunction were compared with those without irreversible renal dysfunction (reversible renal dysfunction and no renal dysfunction), the MELD score showed significant difference (p=0.003) (Table 4). This was in agreement with the results of the multivariate analysis in which only the MELD score was a significant risk factor for developing renal dysfunction

Table 5. Multiple Logistic Regression Analysis for the Variables Affecting Irreversible Renal Dysfunction after Bacterial Infection

Variable	Odds ratio (95% CI)	p-value
Systolic BP<100 mmHg	2.032 (0.44-9.48)	0.367
Diastolic BP<60 mmHg	0.295 (0.02-4.19)	0.476
MELD score≥20	12.057 (1.35-107.90)	0.026
Albumin<2.8 g/dL	1.127 (0.21-5.97)	0.888
WBC count>10,000/μL	3.514 (0.67-18.33)	0.136
Alcoholism	0.621 (0.12-3.23)	0.571

CI, confidence interval; BP, blood pressure; MELD, Model for End-Stage Liver Disease; WBC, white blood cell.

(p=0.026) (Table 5).

Of the 80 patients with bacterial infection, seven patients, all of whom had irreversible renal dysfunction occurred, died during the hospitalization. There were no significant differences in clinical characteristics and blood test results between patients who died and those who did

not; only the MELD score was significantly different between the two groups ($p=0.004$).

DISCUSSION

Bacterial infection is one of the most common complications in patients with liver cirrhosis, and mortality has been higher.¹⁻⁴ Urinary tract infection, pneumonia, and SBP are bacterial infections commonly seen in patients with liver cirrhosis.⁵⁻⁸

Studies concerning bacterial infection in patients with liver cirrhosis have focused mainly on those with SBP. Renal dysfunction is concurrently present in approximately one-third of SBP cases and is one of the most powerful indicators predicting death during the hospitalization.⁹ In patients with liver cirrhosis accompanied by ascites, there is a concurrent presence of circulatory dysfunction characterized by arterial dilatation, hypotension, increased cardiac output, and decreased effective circulating volume. In patients with liver cirrhosis and concurrent SBP, cytokine (TNF-alpha and IL-6) and nitric oxide levels are elevated, resulting in the dilatation of blood vessels and decreased renal blood flow. The deterioration of compensatory mechanisms leads to renal dysfunction.^{9,13} It is well known that albumin infusion can prevent renal dysfunction and enhance survival in patients with liver cirrhosis and concurrent SBP.^{10,14} In all types of bacterial infection, the increased release of inflammatory cytokines and vasodilatory substances can lead to renal dysfunction and circulatory dysfunction.

According to a recent study, there was a concurrent presence of bacterial infection, including SBP, in 44.6% of hospitalized patients with liver cirrhosis and ascites. Of these, 33.6% had renal dysfunction.¹⁵ Other studies have reported renal dysfunction in 26% of patients who concurrently had a bacterial infection other than SBP.¹⁶ In our series, in which SBP was excluded, renal dysfunction occurred in 36% of all patients, which is close to the incidence of renal dysfunction previously reported in patients with liver cirrhosis and bacterial infection include SBP.

In our study, type of bacterial infection were similar to the recent studies,⁵⁻⁸ urinary tract infection was the most common, followed by pneumonia and biliary tract infection. In a recent study, renal dysfunction reportedly occurred more frequently in patients with biliary tract infection,¹⁵ however, we found no significant difference in the occurrence of renal dysfunction based on the type of infection.

The improvement in infection is well-known independent risk factors for developing renal dysfunction in pa-

tients with liver cirrhosis who concurrently have a bacterial infection.¹⁴ The MELD score is the best prognostic marker of patients with cirrhosis and sepsis.¹⁶ Other study which have examined renal dysfunction after SBP, reported that blood urea nitrogen, serum sodium concentration before peritonitis and band neutrophils count in blood at diagnosis were independent predictors for the development renal dysfunction.⁹ In the present study, the only risk factor identified for developing renal dysfunction was the MELD score, indicating that severe hepatic dysfunction is a risk factor for developing renal dysfunction in patients with liver cirrhosis and bacterial infection. Patients with liver cirrhosis in whom renal dysfunction occurred due to bacterial infections other than SBP had a poor prognosis; the hospitalization mortality rate is 42.8% (7.24% in cases without renal dysfunction),¹⁵ and the 3-month mortality is 66% (13% in cases without renal dysfunction).¹⁶ Particularly in cases with irreversible renal dysfunction, the 3-month mortality may reach 100%. In our series, the hospitalization mortality was 24% in patients who developed renal dysfunction, and all those who died during the hospitalization had developed irreversible renal dysfunction. The MELD score was a factor for predicting hospitalization death.

In summary, renal dysfunction occurred in 36% of patients with liver cirrhosis who developed a bacterial infection other than SBP. The MELD score was the only factor that independently predicted the occurrence of renal dysfunction. Patients with liver cirrhosis who concurrently had a bacterial infection and renal dysfunction had a poor prognosis. In particular, the prognosis was poor for those with irreversible renal dysfunction.

There were several limitations to the current study. This was retrospective in design and lacked data about the use of plasma expanders. Further studies are warranted to examine whether albumin treatment can prevent the occurrence of renal dysfunction and enhance survival in patients with bacterial infections other than SBP.

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