

The Effect of the First Spontaneous Bacterial Peritonitis Event on the Mortality of Cirrhotic Patients with Ascites: A Nationwide Population-Based Study in Taiwan

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Background/Aims: Spontaneous bacterial peritonitis (SBP) contributes to poorer short-term mortality in cirrhotic patients with ascites. However, it is unknown how long the effect of the first SBP event persists in these patients. **Methods:** The National Health Insurance Database, derived from the Taiwan National Health Insurance Program, was used to identify and enroll 7,892 cirrhotic patients with ascites who were hospitalized between January 1 and December 31, 2007. All patients were free from episodes of SBP from 1996 to 2006. **Results:** The study included 1,176 patients with SBP. The overall 30-day, 90-day, 1-year, and 3-year mortality rates in this group were 21.8%, 38.9%, 57.5%, and 73.4%, respectively. The overall 30-day, 90-day, 1-year, and 3-year mortality rates in the non-SBP group were 15.7%, 32.5%, 53.3%, and 72.5%, respectively. After adjusting for gender, age, and other medical comorbidities, the adjusted hazard ratios of SBP for 30-day, 30- to 90-day, 90-day to 1-year, and 1- to 3-year mortality were 1.49 (95% confidence interval [CI], 1.30 to 1.71), 1.19 (95% CI, 1.02 to 1.38), 1.04 (95% CI, 0.90 to 1.20), and 0.90 (95% CI, 0.77 to 1.05), respectively, compared with the non-SBP group. **Conclusions:** The effect of SBP on the mortality of cirrhotic patients with ascites disappeared in those surviving more than 90 days after the first SBP event. (*Gut Liver* 2016;10:803-807)

Key Words: Cirrhosis; Spontaneous bacterial peritonitis; Ascites; Mortality

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) has been highlighted on the mortality of cirrhotic patients in many studies. However,

there still exist limited population-based data for evaluating the real impact of the first SBP event. It is well known that SBP-related mortality is high in cirrhotic patients.¹⁻⁴ However, unlike patients with other bacterial infections, the cirrhotic patients with SBP are always in decompensated status and always present with refractory ascites. It is difficult to know whether the mortality in these instances is due primarily to infection itself or to the decompensated status of liver. The real effect of the first SBP event on short- and long-term mortality for cirrhotic patients with ascites needs to be thoroughly evaluated.

Most cirrhotic patients enrolled in previous studies have been selected without regard for presence or absence of ascites. It would be more reliable to only enroll cirrhotic patients with ascites to compare the effect of the first SBP event on the long-term mortality of cirrhotic patients. In order to enroll more cirrhotic patients with ascites, we used Taiwan's nationwide population-based dataset to determine the effect of the first SBP event on the short- and long-term mortality of cirrhotic patients, by comparing ascites-positive patients with and without SBP.

MATERIALS AND METHODS

1. Database

The Taiwanese National Health Insurance (NHI) program was initiated in 1995, and the National Health Insurance Bureau (NHIB) currently covers more than 99% of the population in Taiwan. All medical records from all contracted medical institutions are required by the NHIB for medical payment. The National Health Insurance Research Database (NHIRD), which is maintained by NHIB and the National Health Research Institute (NHRI), was the source for the secondary, de-identified data in

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Received on December 26, 2013. Revised on March 6, 2014. Accepted on March 10, 2014.

pISSN 1976-2283 eISSN 2005-1212 <http://dx.doi.org/10.5009/gnl13468>

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this study, including all diagnostic coding information of the hospitalized patients in Taiwan. Investigators using the NHIRD are required to undergo evaluation by the NHRI, and this study was approved by the NHRI (application and agreement number: 101516). The privacy of patients and the health care providers in this study was protected. The details of the database of NHIRD have been described previously.⁵⁻⁷

2. Study sample

This retrospective study enrolled the patients discharged with International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnoses of cirrhosis (ICD-9-CM code 571.5 or 571.2) and ascites (ICD-9-CM code 789.5, or ICD-9 v3 Procedure Codes 54.91) between January 1, 2007 and December 31, 2007. In the cases of multiple hospitalizations, only the first episode was included. As in previous studies, the patients with SBP were defined as those with diagnosis codes for both cirrhosis and peritonitis (ICD-9-CM codes 567.2, 567.8, or 567.9).⁷⁻⁹ We also checked the other diagnostic codes of the enrolled patients. Patients with additional diagnostic codes for secondary peritonitis, like appendicitis, biliary tract or hollow organ perforation, peritoneal dialysis catheter-related peritonitis, ischemic bowel disease, and those having an additional procedure code for abdominal surgery were not included. Patients with a past history of liver transplantation or receiving liver transplantation in 3-year follow-up period were not included in our study. Patients with a past history of SBP were excluded. However, because the NHI program in Taiwan was initiated in 1995, allowing us to trace medical services only from 1996 to 2007, patients who had an episode of SBP before 1996 could not be identified.

Because many factors will affect the mortality in cirrhotic patients with ascites, the comorbid medical disorders included alcoholic-related disorders (ICD-9-CM codes 291, 303, 305.00 to 305.03, and 571.0 to 571.3), hepatocellular carcinoma (HCC) (ICD-9-CM code 155.0), renal function impairment (RFI) (ICD-9-CM code 584, 585, 586, 572.4, or the procedure codes relate to hemodialysis), peptic ulcer disease (PUD) (ICD-9-CM code 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, and 533.6), esophageal variceal bleeding (EVB) (ICD-9-CM code 456.0, 456.20), and hepatic encephalopathy (HE) (ICD-9-CM code 572.2).

3. Statistical analysis

The SPSS statistical package SPSS System for Windows version 13.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Student t-test was used to compare continuous variables, and the chi-square test or Fisher exact test was used to compare categorical variables. The proportional hazards Cox regression model was used to identify risk factors for mortality. Hazard ratios (HRs) with the 95% confidence intervals (CI) for mortalities over 30 days, 30 to 90 days, 90 days to 1 year, and 1 to 3 years were calculated for comparisons between the SBP

and non-SBP groups. Values of $p < 0.05$ were considered statistically significant.

RESULTS

A total of 7,892 cirrhotic patients with ascites (average age, 59.2 ± 14.2 years) were included in the study, among whom 5,510 (69.8%) were male and 1,176 (14.9%) were diagnosed with SBP. The demographic characteristics for cirrhotic patients with and without SBP are shown in Table 1. There were more patients with HCC and EVB in non-SBP group. However, more patients with RFI and HE were found in SBP group. The overall 30-day, 90-day, 1-year, and 3-year mortalities in SBP group were 21.8%, 38.9%, 57.5%, and 73.4%, respectively. The overall 30-day, 90-day, 1-year, and 3-year mortalities in non-SBP group were 15.7%, 32.5%, 53.3%, and 72.5%, respectively.

Because there is a large difference between both groups, we used logit transformation of propensity scores (logit_PS) which were obtained from logistic regression of SBP on age, gender, EVB, and PUD. In a Cox proportional hazards regression model adjusted by logit_PS, HCC, HE, alcoholism, and RFI, the adjusted HRs of the first SBP event on the 30-day mortality was 1.49 (95% CI, 1.30 to 1.71; $p < 0.001$) (Table 2). In order to evaluate the late effect of the first SBP event on the mortality, we calculated the 90-day mortality of the patients surviving more than 30 days, the 1-year mortality of the patients surviving more than 90 days, and 3-year mortality of the patients surviving more than 1 year. The adjusted HRs of SBP for 30- to 90-day decreased to 1.18 (95% CI, 1.01 to 1.37; $p = 0.033$) (Table 2). However, the adjusted HRs of 90-day to 1-year and 1- to 3-year mortalities were only 1.04 (95% CI, 0.90 to 1.20; $p = 0.630$) and 0.92 (95% CI, 0.79 to 1.07; $p = 0.280$) without statistical significance (Table 3). We found that the effect of SBP on the mortality of cirrhotic patients with ascites disappeared 90 days after the first SBP

Table 1. Demographic Characteristics of Cirrhotic Patients with Ascites, with and without SBP

	SBP group (n=1,176)	Non-SBP group (n=6,716)	p-value
Male sex	825 (70.2)	4,685 (69.8)	0.786
Age, yr	58.5 ± 13.5	59.3 ± 14.4	0.053
HCC	282 (24.0)	1,890 (28.1)	0.003
Hepatic encephalopathy	199 (16.9)	972 (14.5)	0.029
EVB	115 (9.8)	807 (12.0)	0.028
Alcoholic-related	308 (26.2)	1,614 (24.0)	0.112
RFI	122 (10.4)	533 (7.9)	0.005
PUD	45 (3.8)	327 (4.9)	0.120

Data are presented as number (%) or mean \pm SD.

SBP, spontaneous bacterial peritonitis; HCC, hepatocellular carcinoma; EVB, esophageal variceal bleeding; RFI, renal function impairment; PUD, peptic ulcer disease.

Table 2. Adjusted HR of the Prognostic Factors for 30-Day and 30- to 90-Day Mortality of Cirrhotic Patients with Ascites Adjusting for the Logit Transformation of Propensity Scores

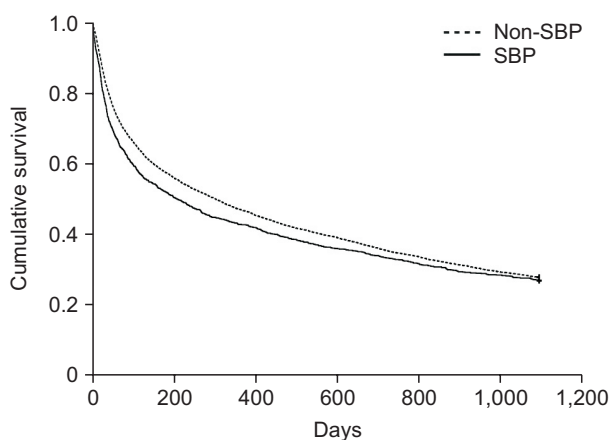
Variable	30-Day mortality			30- to 90-Day mortality		
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p-value	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p-value
SBP	1.47 (1.29–1.69)	1.49 (1.30–1.71)	<0.001	1.14 (0.98–1.33)	1.18 (1.01–1.37)	0.033
HCC	2.50 (2.24–2.79)	2.58 (2.30–2.88)	<0.001	3.02 (2.71–3.37)	2.94 (2.63–3.29)	<0.001
RFI	2.62 (2.27–3.03)	2.76 (2.39–3.20)	<0.001	1.82 (1.53–2.18)	2.03 (1.70–2.43)	<0.001
Alcoholism	0.58 (0.50–0.68)	0.77 (0.66–0.90)	0.001	0.47 (0.40–0.55)	0.62 (0.53–0.73)	<0.001
HE	1.63 (1.43–1.86)	1.72 (1.50–1.96)	<0.001	1.35 (1.17–1.56)	1.56 (1.34–1.80)	<0.001
logit_PS	0.25 (0.16–0.38)	0.28 (0.18–0.45)	<0.001	0.37 (0.25–0.54)	0.48 (0.31–0.74)	0.001

HR, hazard ratios; CI, confidence interval; SBP, spontaneous bacterial peritonitis; HCC, hepatocellular carcinoma; RFI, renal function impairment; HE, hepatic encephalopathy; logit_PS, logit transformation of propensity scores, which were obtained from logistic regression of SBP by age, gender, esophageal variceal bleeding, and peptic ulcer disease.

Table 3. Adjusted HRs of the Prognostic Factors for 90-Day to 1-Year and 1- to 3-Year Mortality of Cirrhotic Patients with Ascites Adjusting for the Logit Transformation of Propensity Scores

Variable	90-Day to 1-year mortality			1- to 3-Year mortality		
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p-value	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p-value
SBP	1.01 (0.87–1.16)	1.04 (0.90–1.20)	0.630	0.90 (0.77–1.05)	0.92 (0.79–1.07)	0.280
HCC	2.56 (2.31–2.85)	2.55 (2.29–2.84)	<0.001	1.84 (1.61–2.10)	1.81 (1.58–2.07)	<0.001
RFI	1.51 (1.26–1.82)	1.64 (1.36–1.98)	<0.001	1.11 (0.88–1.39)	1.12 (0.89–1.42)	0.323
Alcoholism	0.66 (0.59–0.75)	0.80 (0.70–0.90)	<0.001	0.82 (0.73–0.92)	0.87 (0.77–0.98)	0.026
HE	1.39 (1.22–1.59)	1.54 (1.35–1.76)	<0.001	1.21 (1.04–1.41)	1.28 (1.10–1.49)	0.002
logit_PS	0.54 (0.40–0.73)	0.66 (0.48–0.92)	0.012	0.49 (0.36–0.67)	0.52 (0.38–0.72)	<0.001

HR, hazard ratios; CI, confidence interval; SBP, spontaneous bacterial peritonitis; HCC, hepatocellular carcinoma; RFI, renal function impairment; HE, hepatic encephalopathy; logit_PS, logit transformation of propensity scores, which were obtained from logistic regression of SBP by age, gender, esophageal variceal bleeding, and peptic ulcer disease.

**Fig. 1.** Cumulative survival plot for cirrhotic patients with ascites, with and without spontaneous bacterial peritonitis (SBP) (Kaplan-Meier method and log-rank test, $p=0.0135$).

event. Fig. 1 showed the cumulative survival plot for cirrhotic patients having ascites with and without SBP. After Kaplan Meier method and log-rank test, SBP group showed poorer survival than non-SBP group ($p=0.0135$).

Unadjusted and adjusted HRs of comorbid factors for 30-day,

30- to 90-day, 90-day to 1-year, 1- to 3-year mortalities of cirrhotic patients with ascites were listed in Tables 2 and 3. HCC and HE have a persistently effect on the mortalities of cirrhotic patients with ascites. RFI had a positive effect on the 30-day, 30- to 90-day, and 90-day to 1-year mortalities, but no effect on the patients surviving more than 1 year after SBP. Alcoholic-related cirrhosis had a persistently negative effect on the mortalities of cirrhotic patients with ascites.

DISCUSSION

In a prospective study, 5-year survival of cirrhotic patients with ascites was 56.5%.¹⁰ However, the present study showed 3-year survival of cirrhotic patients with ascites was lower than 30%. That is because the previous study only enrolled the patients which could be followed up prospectively for a minimum period of 6 months. They excluded the patients with HCC, refractory ascites, hepatic renal syndrome, and severe HE. The present study did not perform this selection and showed 90-day mortality of cirrhotic patients with ascites were more than 30%.

SBP is a major complication of cirrhosis and occurred in 10% to 25% of cirrhotic patients with ascites.^{11–13} High recurrence

rate of SBP was noted in cirrhotic patients with ascites,¹⁴ and some previous studies showed SBP is associated with high long-term mortality.^{15,16} Another study even showed the one-year survival rate after recovery from the first episode of SBP was 30% to 40%.¹⁷ The present study showed the first SBP event was indeed associated with 30-day and 30- to 90-day mortalities of cirrhotic patients with ascites. However, SBP did not affect those survived more than 90 days after the first SBP event. This phenomenon appeared that the effect of SBP for recurrence mainly focused on the first 90-day. This hinted that the intestinal mucosal damage predisposing bacterial translocation for SBP may need at least 90 days to recover. However, further study is needed to prove this ratiocination.

Medical progress in the last two decades has improved the prognosis for cirrhotic patients with SBP. A recent meta-analysis showed the 30-day mortality for patients with SBP was as high as 44.4% for the period 1978 to 1999 and decrease to 31.5% for the years 2000 to 2009.¹⁸ The high mortality reflects both the presence of the infectious diseases and the underlying decompensated status. A recent study reported the long-term survival times of patients with SBP before liver transplantation are similar to those for patients without SBP.¹⁹ This result demonstrated that the effect of SBP on the mortality of cirrhotic patients disappeared when the underlying decompensated status was corrected. Our study demonstrated there were no significant differences between SBP group and non-SBP group for 90-day to 1-year mortality and 1- to 3-year mortality. The results suggest that the effect of SBP on the mortality of cirrhotic patients with ascites disappeared in those surviving more than 90 days after the first SBP event. We found recently that although SBP comprises about 50% of bacterial infections in cirrhotic patients with ascites, pneumonia carries the higher risk for mortality among common infectious diseases.¹³

In a previous study, alcoholic-related cirrhosis was more prone to have ascites but less to have HCC, compared to non-alcoholic-related cirrhosis.²⁰ Ascites was the leading initial hepatic decompensation pattern in 55% to 67% of cases with alcoholic-related cirrhosis.^{21,22} In addition, impaired survival was found in non-alcoholic-related cirrhosis once ascites occurred.²⁰ The present study also showed alcoholic-related cirrhosis had a better survival in cirrhotic patients with ascites. In our country, hepatitis B virus (HBV) infection and hepatitis C virus (HCV) infection contributed to nearly all non-alcoholic-related cirrhosis.^{23,24} This phenomenon hinted that HBV- or HCV-related cirrhosis had poorer prognosis than alcoholic-related cirrhosis once ascites occurred. However, the reason for this is still unknown.

The very large sample size in the present study provided the statistical power necessary detect different effects of the first SBP event on short- and long-term mortality in cirrhotic patients with ascites. Nonetheless, there are limitations to the study that warrant discussion. First, although the severity of

liver cirrhosis was commonly based on the Child-Pugh score or The Model for End-Stage Liver Disease (MELD) score, it was not possible to identify the laboratory data regarding albumin, bilirubin, creatinine, or prothrombin time by ICD-9 code in the database. However, the concept of stages of cirrhosis separated by easily defined clinical criteria was recently proposed.²⁵ The concept of four clinical stages of cirrhosis has been identified, and each stage has distinct clinical features and a different prognosis. Cirrhotic patients with ascites are in decompensated status and are at least in stage 3. In addition, complications of cirrhosis, such as EBV, HE, HCC, and RFI were also considered in this study. Hence, we believe the absence of these lab data does not represent a major flaw, because all the patients were at least at stage 3 according to the clinical stage system, and the other complications are well classified. Secondly, because the NHI program in Taiwan was initiated in 1995, the dataset only allowed us to follow medical services utilization from 1996 to 2006. Therefore, patients who had an episode of SBP before 1996 could not be excluded. However, the long-term mortality after an episode of SBP is high. In this study, the overall 3-year mortality after an episode of SBP was about 75%. Hence, we believe the effect of SBP cases before 1996 on the study population was very low. Thirdly, ascites aspiration was performed in cirrhotic patients diagnosed to have SBP. However, not all patients received paracentesis in non-SBP group. Some SBP patients without paracentesis may be mis-classified into non-SBP group. This is an uncorrectable limitation in the present retrospective study. In cirrhotic patients, clinical physicians only performed paracentesis for the patients suspected to have SBP or with refractory ascites. If we only included those receiving paracentesis, selection bias may occurred in the present study. Fourthly, we could not identify the patients with prophylactic antibiotics after the occurrence of SBP in the database. This is an uncorrectable limitation in the present study.

Despite these limitations, this study is the most complete recent nationwide population-based study investigating the effect of the first SBP event on the mortality of cirrhotic patients with ascites. Our results indicate that SBP has a predictable impact on short-term mortality in cirrhotic patients with ascites, but its effect disappeared in those surviving more than 90 days after the first SBP event.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, which is man-

aged by National Health Research Institutes (registered number: 101516). The interpretation and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health or National Health Research Institutes.

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