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OBSERVATIONAL STUDY

Clinical Features and Outcomes of Spontaneous Bacterial Peritonitis Caused by *Streptococcus pneumoniae*
A Matched Case-Control Study

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Abstract: *Streptococcus pneumoniae* is a well-known cause of spontaneous bacterial peritonitis (SBP) in cirrhotic patients. However, little information is available regarding clinical characteristics and outcomes of SBP caused by *S. pneumoniae*. It has been suggested that spontaneous pneumococcal peritonitis (SPP) often spreads hematogenously from concomitant pneumococcal pneumonia, and is associated with a higher rate of mortality.

During the period between January 1997 and December 2013, 50 SPP cases were identified. These cases were then age/sex-matched with 100 patients with SBP due to causes other than *S. pneumoniae* (controls).

SPP accounted for 4.3% (50/1172) of all culture-proven SBPs. The baseline Child-Pugh class, etiology of cirrhosis, and model for end-stage liver disease scores were comparable for the 2 groups. SPP patients were more likely than control patients to have a community-acquired infection (90.0% vs. 76.0%; $P = 0.04$), concurrent bacteremia (84.0% vs. 59.0%; $P = 0.002$), and to present with variceal bleeding (10.0% vs. 1.0%; $P = 0.02$). None of the study patients had pneumococcal pneumonia. The most common initial empirical therapy for both groups was third-generation cephalosporins (96.0% vs. 91.0%; $P = 0.34$) which was active against a significantly higher proportion of the cases than of the controls (97.8% vs. 78.7%; $P = 0.003$). Thirty-day mortality was significantly lower in the case group than in the control group (10.0% vs. 24.0%; $P = 0.04$).

SPP was not associated with pneumococcal pneumonia and showed lower mortality than SBP caused by other organisms. However, the present study was constrained by the natural limitations characteristic of a small, retrospective study. Therefore, large-scale, well-controlled studies are required to demonstrate the influence of SPP on mortality, which was marginal in the present study.

Abbreviations: AOR = adjusted odds ratio, CI = confidence interval, CLSI = Clinical and Laboratory Standards Institute, ICU = intensive care unit, IPD = invasive pneumococcal diseases, IQR = interquartile range, MELD = model for end-stage liver disease, MIC = minimum inhibitory concentrations, PCV-7 = 7-valent pneumococcal conjugated vaccine, PMN = polymorphonuclear cell, SBP = spontaneous bacterial peritonitis, SPP = spontaneous pneumococcal peritonitis, WBC = white blood cell.

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is a common and serious complication seen in cirrhotic patients with ascites.[1,2] Enteric bacteria are the most common causative organisms,[3,4] and are thought to cause SBP via bacterial translocation (i.e., the passage of viable bacteria from the gastrointestinal lumen to extra-intestinal sites such as the mesenteric lymph nodes, liver, spleen, blood, or peritoneal cavity).[5-7] Nonenteric bacteria are the cause of SBP in about 20% of all culture-proven cases.[3,4] Most nonenteric bacteria are thought to enter the peritoneal cavity from the bloodstream permitted by impaired liver function and altered portal circulation which result in a defect in the filtration control.[1,6,8-10]

Streptococcus pneumoniae is a well-recognized gram-positive organism that can cause SBP, accounting for 3.0% to 5.8% of all culture-proven cases.[3,11,12] *S. pneumoniae* is not considered a component of the gastrointestinal flora. It has been postulated to cause SBP in association with a respiratory tract infection such as pneumonia and subsequent bacteremia.[12,13] More than a decade ago, a Spanish group reported that cirrhotic patients with spontaneous pneumococcal peritonitis (SPP) had more frequent pneumonia (35.6% vs. 2.2%, $P < 0.001$) and higher early mortality rate (26.7% vs. 8.9%, $P = 0.05$) than those with SBP caused by *E. coli*.[12] Recent small cases series, however, reported that no SPP patients had pneumonia.[14,15] Previous studies also suggested that endoscopic procedures or variceal bleeding allow *S. pneumoniae* to reach the bloodstream from oropharyngeal colonization, particularly in cirrhotic patients with preexisting gastric lesions.[10,12,15]

Although *S. pneumoniae* has long been regarded as an important pathogen that causes SBP in cirrhotic patients, few studies have examined SPP. Therefore, the aim of the present study was to determine the clinical characteristics and treatment outcomes for patients with SPP and to compare them with those of patients with SBP caused by other organisms.

METHODS

Study Design and Patients Selection

This case-control study was performed at Asan Medical Center, a 2700-bed tertiary care institution in Seoul, Republic of Korea. The records of all cirrhotic patients over 17 years-of-age who were admitted between January 1997 and December 2013 with a diagnosis of SBP were examined retrospectively. Every patient with culture-proven SBP due to *S. pneumoniae* was included in the analysis. Two nonpneumococcal SBP patients were successfully matched for each case patient, by the age-group, sex, and the date of the episode of SBP (date closest to when the case presented). Only 1 episode per patient was included in the analysis. Cases of secondary peritonitis and peritoneal dialysis-associated peritonitis were excluded.

Definitions

Patients were regarded as having SBP if they had fever or abdominal pain concomitant with the neutrocytic ascites (polymorphonuclear cell [PMN] count in the ascites > 250 cells/mm³). The study population (those with culture-proven SBP) comprised the following groups: a group with classic SBP (defined as monobacteriascites); and a group with probable SBP (defined as monobacteremic neutrocytic ascites without any other primary focus).[16–18] SBP was defined as "community-acquired" if a culture performed within the first 48 hours after admission was positive. SBP was defined as "hospital-acquired" when the first positive culture was obtained >48 hours after admission and the patient did not have a clinical syndrome compatible with infection at the time of admission.[19] Initial antimicrobial therapy (administered within 24 hours of acquisition of culture samples) was considered appropriate if it included at least 1 antibiotic that was active against the isolated pathogen in vitro. Thirty-day and in-hospital mortalities refer to the number of days from diagnosis of SBP, and the in-hospital mortality included the 30-day mortality.

Data Collection

We retrospectively reviewed the medical records of all enrolled patients and collected the following information: age, gender, cause of cirrhosis, comorbid diseases, Child-Pugh class, model for end-stage liver disease (MELD) score,[20] underlying issues such as antiulcer medication, hepatic artery chemoembolization, recent history of variceal bleeding or endoscopic intervention, and recent surgery. A previous history of SBP, prior antimicrobial therapy, initial clinical manifestations, concomitant infections and complications, laboratory findings, the antimicrobial susceptibility of isolates, seasonality, and outcomes were also reviewed. This study was approved by the institutional review board of Asan Medical Center, Seoul, Korea, which waived the requirement for informed patient consent due to its retrospective design. This study also performed in accordance with the ethical standards laid down in the Declaration of Helsinki and its later amendments.

Microbiology

Ascitic fluid was cultured using conventional culture method or the BACTEC system (Becton Dickinson, Franklin Lakes, NJ). Blood samples were cultured using the BACTEC system. Isolates were identified using manual identification. Oxacillin disks (1 μg) were used to examine the penicillin resistance of *S. pneumoniae* isolates, and the minimum inhibitory concentrations (MIC) of penicillin and ceftriaxone were determined using disk diffusion test or E-test (AB Biodisk, Solna, Sweden). Antimicrobial susceptibility testing of isolates other than *S. pneumoniae* was performed using the MicroScan (Dade Behring, Deerfield, IL) system. The present study used the MIC breakpoints and quality-control protocols established by the Clinical and Laboratory Standards Institute (CLSI). The susceptibility of *S. pneumoniae* to penicillin was determined by establishing the breakpoints for penicillin in nonmeningeal *S. pneumoniae* infection according to the revised 2008 CLSI guidelines (susceptible, ≤2 μg/mL; intermediate, 4 μg/mL; resistant, ≥8 μg/mL). The resistance of Enterobacteriaceae to third-generation cephalosporins was also defined according to the 2008 CLSI breakpoints (susceptible, ≤8 μg/mL; intermediate, 16–32 μg/mL; and resistant, ≥64 μg/mL), because the revised MIC breakpoints of these antibiotics in 2010 were feasible in our hospital since 2014.

Statistical Analysis

Statistical analyses were performed using the χ^2 test or Fisher exact test (categorical variables) or Student t test or Mann–Whitney U test (continuous variables). Survival curves were estimated using the Kaplan–Meier method and the log-rank test used to determine significant differences between groups for the time-to-event. To identify prognostic factors for mortality, and clinical factors more closely associated with SPP than with SBP caused by other organisms, univariate and multivariate analyses were conducted using logistic regression models. Factors with $P \leq 0.05$ in the univariate analyses as well as risk factors identified in previous studies were considered for entry of the multivariate logistic regression models, which were limited to 5 factors because of the number of events.[11,21,22] Correlations among the variables (multicollinearity) were also considered. Therefore, factors such as the place of acquisition and concomitant bacteremia significantly differed between the case and control groups. Moreover, ICU care during admission and serum creatinine levels were significantly associated with the presentation of septic shock. Thus, we chose one of these correlated variables and included it in adjusted analysis. The final models were assessed using backward elimination. Variables with a P value <0.05 were considered to be statistically significant. All analyses were performed using SPSS software (version 21.0; IBM Co, Armonk, NY).

RESULTS

Study Population

During the study period, a total of 3405 SBP cases were identified in 2625 cirrhotic patients. A total of 1172 cases of SBP (in 1009 patients) satisfied the criteria for culture-proven SBP. Of these, 693 (59.1%) were classic SBP and 479 (40.9%) were probable SBP. The most common organism isolated from SBP patients was *Escherichia coli,* (536 isolates [45.7%]), followed by *Klebsiella* species (194 isolates [16.6%]), streptococci other than *S. pneumoniae* (118 isolates [10.1%]) and *Aeromonas* species (62 isolates [5.3%]). Fifty patients had pneumococcal SBP, accounting for 4.3% of culture-proven SBP cases. These 50 patients were successfully age- and sex-matched with 100 control subjects. *E. coli* was the most common pathogen (n = 43) isolated from control subjects, followed by *Klebsiella* species (n = 15), streptococci other than *S. pneumoniae* (n = 12), and *Aeromonas hydrophila/Enterobacter* species (n = 6).

Demographic Characteristics and Underlying Conditions

The demographic characteristics and underlying conditions of the study population are presented in Table 1. The

TABLE 1. Demographic Characteristics and Underlying Conditions of Patients With Spontaneous Pneumococcal Peritonitis and Patients With SBP Caused by Other Organisms

	No. (%) of Patients		
Variable	**Due to *S. pneumoniae* (n = 50)**	**Due to Other Organisms (n = 100)**	***P***
Age, median years (IQR)	53 (44–61)	53 (44–61)	1.00
Male	33 (66.0)	66 (66.0)	0.99
SBP subtype			0.02
Classic SBP[*]	23 (46.0)	66 (66.0)	
Probable SBP[*]	27 (54.0)	34 (34.0)	
Place of SBP acquisition			0.04
Community	45 (90.0)	76 (76.0)	
Hospital	5 (10.0)	24 (24.0)	
Causes of liver cirrhosis			0.94
Hepatitis B virus (HBV)	32 (64.0)[†]	67 (67.0)[†]	
Hepatitis C virus (HCV)	5 (10.0)	10 (10.0)	
Alcoholism	10 (20.0)	16 (16.0)	
Others	3 (6.0)	7 (7.0)	
Concomitant hepatocellular carcinoma	16 (32.0)	31 (31.0)	0.90
Comorbid diseases			
Diabetes mellitus	10 (20.0)	25 (25.0)	0.50
Solid cancer (other than HCC)	5 (10.0)	4 (4.0)	0.16
CRF without hemodialysis	1 (2.0)	4 (4.0)	0.67
End-stage renal disease	0	2 (2.0)	0.55
Child-Pugh class			0.08
A	1 (2.0)	2 (2.0)	
B	13 (26.0)	14 (14.0)	
C	36 (72.0)	84 (84.0)	
MELD score, median (IQR)	21 (15–24)	22 (19–28)	0.39
Underlying condition			
Anti-ulcer medication (at admission)	26 (52.0)	49 (49.0)	0.73
Transarterial chemoembolization (<3 mo)	7 (14.0)	17 (17.0)	0.64
Recent variceal bleeding or endoscopic intervention[‡] (≤ 1 mo)	4 (8.0)	3 (3.0)	0.22
Recent surgery (<1 mo)	2 (4.0)	2 (2.0)	0.60
Previous history of pneumonia	0	9 (9.0)[ǁ]	0.03
Previous history of SBP (<1 y)	6 (12.0)	23 (23.0)	0.13
Prior antimicrobial therapy[§] (<30 d)	8 (16.0)	37 (37.0)	0.009

HCC = hepatocellular carcinoma, IQR = interquartile ratio, MELD = model for end-stage liver disease, SBP = spontaneous bacterial peritonitis.
[*]Patients were regarded as having SBP if they had a clinical manifestation (fever or abdominal pain) with the neutrocytic ascites (polymorphonuclear cell [PMN] count in ascites >250 cells/mm^3) and at least 1 of the following: a positive ascites culture (classic SBP); culture-negative ascites and positive blood culture results without any other primary focus (probable SBP).
[†]One patient in each group had both HBV infection and alcoholic cirrhosis.
[‡]Endoscopic interventions such as endoscopic variceal ligation or sclerotherapy.
[§]For more than 48 hours.
[ǁ]There was no case of pneumococcal pneumonia.

median age of each group was 53 years (interquartile range [IQR], 44–61 years) and the male-to-female ratio in each group was 2:1. Community-acquired infection was more common in SPP patients than in controls (90.0% vs. 76.0%, respectively; $P = 0.04$). There were no statistically significant differences between the case and control groups with respect to liver cirrhosis, concomitant hepatocellular carcinoma, comorbid diseases, Child-Pugh class, or MELD scores. The history of endoscopic interventions to treat or prevent variceal bleeding, or recent variceal bleeding prior to SBP was comparable between groups (8.0% vs. 3.0% in the case and control groups, respectively; $P = 0.22$). The control patients were more likely than the SPP patients to have a history of pneumonia (9.0% vs.

0%, respectively, $P = 0.03$). None of enrolled patients had a history of pneumococcal disease including pneumococcal pneumonia, and more control patients than cases received antimicrobial therapy prior to SBP (16.0% vs. 37.0%, respectively; $P = 0.009$). None of the patients was infected with HIV.

Clinical Manifestations, Laboratory Findings, and Annual and Monthly Distribution

Table 2 compares the clinical manifestations and laboratory findings for the case and control groups. Abdominal pain and fever were the most common manifestations in both groups. Case patients were more likely to present with variceal bleeding

TABLE 2. Clinical Manifestations and Laboratory Findings of Patients With Spontaneous Pneumococcal Peritonitis and Patients With SBP Caused by Other Organisms

Variable	No. (%) of Patients		
	Due to *S. pneumoniae* (n = 50)	Due to Other Organisms (n = 100)	*P*
Initial clinical manifestation			
Abdominal pain	35 (70.0)	71 (71.0)	1.00
Fever (≥38°C)	32 (64.0)	55 (55.0)	0.29
Hepatic encephalopathy	11 (22.0)	15 (15.0)	0.29
Septic shock	7 (14.0)	16 (16.0)	0.75
Diarrhea[*]	5 (10.0)	5 (5.0)	0.30
Variceal bleeding	5 (10.0)	1 (1.0)	0.02
Concomitant pneumonia	0	3 (3.0)	0.55
Concomitant bacteremia	42 (84.0)	59 (59.0)	0.002
Laboratory findings			
Serum WBC, median cells/μL (IQR)	9150 (6600–12,475)	6650 (4200–9200)	<0.001
Platelet, median cells/μL (IQR)	59,000 (45,000–85,250)	49,500 (33,250–77,750)	0.06
C-reactive protein, median mg/dL (IQR)	2.9 (0.0–7.3)	0.6 (0.0–3.5)	0.06
Serum Creatinine, median mg/dL (IQR)	1.0 (0.8–1.2)	1.1 (0.8–1.6)	0.16
Ascites neutrophil, median cells/μL (IQR)	4100 (1201–7897)	2732 (1164–8015)	0.64

WBC = white blood cells.
[*]Diarrhea is defined as >3 loose stools per day.

than control patients (10.0% vs. 1.0%, respectively; *P* = 0.02) and to have concurrent bacteremia (84.0% vs. 59.0%, respectively; *P* = 0.002). Diarrheal episodes were comparable in the 2 groups (10% vs. 5%, *P* = 0.30). None of the case patients had concomitant pneumonia. There were no significant differences in the laboratory findings, including the neutrophil count in the ascites, between the groups. The only exception was the white blood cell (WBC) count: the median WBC counts were 9150 and 6650 cells/μL in the case and control groups, respectively (IQR 6600–12,475 vs. 4200–9200; *P* <0.001). Figure 1A and B shows the annual- and monthly distribution of SPP during the study period, respectively. SPP cases numbered 1 to 6 per year. The lowest incidence was in July to August and the peak incidence was in December.

Initial Antimicrobial Therapy and Susceptibility to Third-Generation Cephalosporins

Table 3 shows the susceptibility of bacteria to third-generation cephalosporins (cefotaxime or ceftriaxone) and

the initial type of antimicrobial therapy. Microbial isolates susceptible to third-generation cephalosporins were more common in the case group than in the control group (97.8% vs. 78.7%, respectively; *P* = 0.003). Antimicrobial susceptibility rates to penicillin, erythromycin, levofloxacin, and vancomycin in case group were 91.4%, 51.1%, 100%, and 100%, respectively. Third-generation cephalosporins were the most common initial therapy in both the case and control groups (96.0% vs. 91.0%, respectively; *P* = 0.34). The proportion of patients in the case group that received appropriate initial antimicrobial therapy was significantly higher than that in the control group (97.8% vs. 85.1%, respectively; *P* = 0.02).

Factors Associated With Spontaneous Pneumococcal Peritonitis

Community acquisition of SBP, variceal bleeding as initial manifestation, concomitant bacteremia, blood WBC counts, and susceptibility to third-generation cephalosporin were seemed to associate with SPP in the univariate analysis. Multivariate
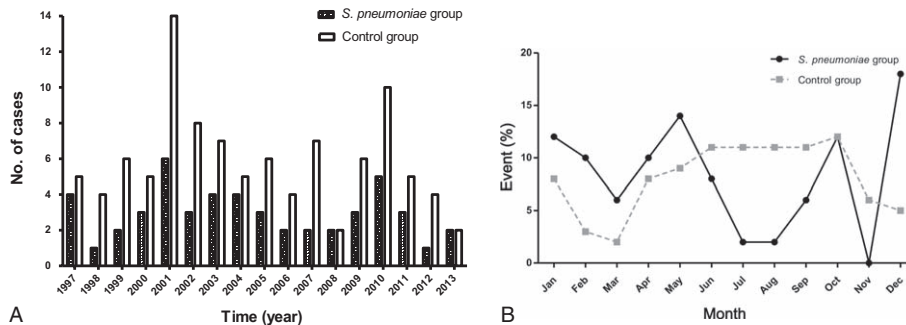

FIGURE 1. A, Annual distribution of spontaneous bacterial peritonitis caused by *S. pneumoniae* (patterns) versus that caused by other organisms (open) during the study period, between 1997 and 2013. B, Monthly distribution of spontaneous bacterial peritonitis caused by *S. pneumoniae* (circles) versus that caused by other organisms (squares).

TABLE 3. Susceptibility to Third-Generation Cephalosporins and Outcomes of Patients With Spontaneous Pneumococcal Peritonitis and Patients With SBP Caused by Other Organisms

	No. (%) of Patients		
Variable	Due to *S. pneumoniae* (n = 50)	Due to Other Organisms (n = 100)	*P*
Susceptibility to third-generation cephalosporin[*,†]			0.003
Susceptible	45/46 (97.8)	74/94 (78.7)	
Intermediate or resistant	1/46 (2.2)	20/94 (21.3)[‡]	
Appropriate initial antimicrobial therapy	45/46 (97.8)	80/94 (85.1)	0.02
ICU care during admission	5 (10.0)	14 (14.0)	0.49
Hospital stay, mean days ± SD	19 ± 13.9	27 ± 44.1	0.20
Hospital stay[§] mean days ± SD	15 ± 8.9	20 ± 19.1	0.06
Mortality[‖]			
30-day mortality	5 (10.0)	24 (24.0)	0.04
In-hospital mortality	8 (16.0)	32 (32.0)	0.04

ICU = intensive care unit, SD = standard deviation.

[*]Indicates treatment with either cefotaxime or ceftriaxone. Susceptibility of microbial isolates to third-generation cephalosporins was defined according to breakpoints listed in the revised (2008) CLSI guidelines (Enterobacteriaceae: susceptible, $\leq 8\,\mu g/mL$; intermediate, 16–$32\,\mu g/mL$; and resistant, $\geq 64\,\mu g/mL$; *S. pneumoniae*: susceptible, $\leq 1\,\mu g/mL$; intermediate, $2\,\mu g/mL$; and resistant, $\geq 4\,\mu g/mL$).

[†]Susceptibility test results of some isolated organisms were unavailable.

[‡]Includes extended spectrum β-lactamase-producing *E. coli* (n = 7), *P. aeruginosa* (n = 4), *E. faecium* (n = 4), MRSA (n = 2), *K. pneumoniae* (n = 1), *E. cloacae* (n = 1), and *B. cereus* (n = 1).

[§]In-hospital deaths were excluded.

[‖]The 2 mortality variables refer to days after diagnosis of SBP.

analysis for SPP showed that concomitant bacteremia and blood WBC counts were significantly associated with pneumococcal peritonitis (adjusted odds ratio [AOR] 3.49; 95% confidence interval [CI] 1.26–9.63; $P = 0.02$, and AOR 1.16, 95% CI 1.05–1.27; $P = 0.002$, respectively) (Table 4).

Outcomes and Prognostic Factors for 30-Day Mortality

Table 3 compares clinical outcomes of both groups. The mean duration of hospital stay tended to be longer in the control group ($P = 0.06$). Also, the 30-day mortality (10.0% vs. 24.0%; $P = 0.04$), and in-hospital mortality (16.0% vs. 32.0%; $P = 0.04$) rates were significantly lower in the case group than in the control group. Figure 2 shows the 60-day Kaplan–Meier survival curves in the 2 groups. Multivariate analysis revealed that SPP was significantly associated with a favorable outcome (AOR 0.28; 95% CI 0.08–0.98; $P = 0.046$), whereas concomitant hepatocellular carcinoma (AOR 3.27; 95% CI 1.22–8.81; $P = 0.02$) and SBP presenting with septic shock (AOR 6.61; 95% CI 2.18–20.02; $P = 0.001$) were significant risk factors for

30-day mortality. Inappropriate initial antimicrobial therapy was not a significant predictor of mortality (Table 5). Factors associated with in-hospital mortality are also shown in Table 5.

A comparison between survivors and nonsurvivors was also performed (Supplementary Table 1, http://links.lww.com/MD/A998). Age, nonpneumococcal SBP, hospital acquisition, concomitant HCC, presentation with septic shock, higher serum creatinine, and intensive care unit (ICU) care during admission differed significantly between the 2 groups. Bacteremia, a well-known risk factor for mortality in SBP, was less frequent among the nonsurvivors than the survivors.

DISCUSSION

Here, we examined the clinical characteristics and treatment outcomes of SPP in cirrhotic patients. Community acquisition, variceal bleeding, and concomitant bacteremia were significantly more common in the SPP group than in the control group. Also, more SPP patients received appropriate initial antimicrobial therapy. SPP was neither more frequently associated with pneumonia, nor did it have a higher mortality rate,

TABLE 4. Multivariate Analysis of Factors Associated With Spontaneous Pneumococcal Peritonitis (SPP)

| Variable	Univariate Analysis Unadjusted Odds Ratio (95% Confidence Interval)	*P*	Multivariate Analysis Adjusted Odds Ratio (95% Confidence Interval)	*P*
Community acquisition	2.84 (1.01–7.97)	0.047	1.68 (0.47–5.99)	0.43
Presentation with variceal bleeding	11.0 (1.25–96.90)	0.031	8.76 (0.94–81.59)	0.06
Concomitant bacteremia	3.65 (1.55–8.58)	0.003	3.49 (1.26–9.63)	0.02
Blood WBC (1000 cells/μL)	1.10 (1.02–1.18)	0.008	1.16 (1.05–1.27)	0.002
Appropriateness of initial antibiotics	7.88 (1.00–61.87)	0.05	9.02 (0.90–90.26)	0.06

WBC = white blood cells.
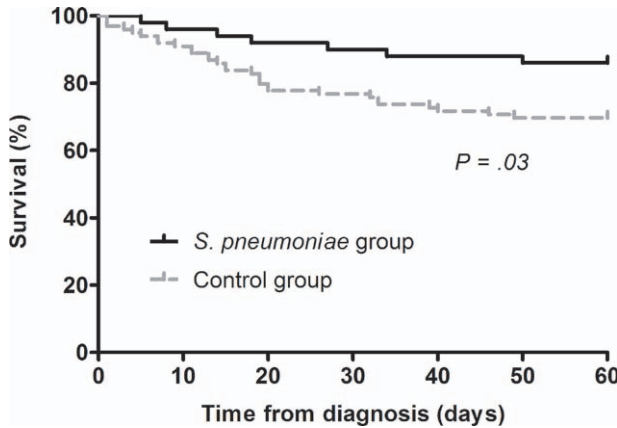
FIGURE 2. Sixty-day Kaplan–Meier survival curves for the group of patients with spontaneous bacterial peritonitis caused by *S. pneumoniae* (solid-line) and the control group (dotted-line).

than SBP caused by other organisms. To the best of our knowledge, this is the largest study of SPP performed to date and straddles the periods before and after the introduction of the pneumococcal conjugate vaccine.

S. pneumoniae is not commonly found in the gastrointestinal tract because it is susceptible to the bactericidal effects of bile salts and gastric acid.[10,23] A Spanish group previously reported that the most common cause of SPP was hematogenous spread from the respiratory tract, and that early mortality was higher for SPP than for *E. coli*-mediated SBP.[12] By contrast, none of the SPP patients examined herein had concomitant pneumonia, and the mortality of SPP patients was significantly lower than that of control patients. These contrasting results might be due to differences in geographical area and patient populations. The time gap between the 2 studies may also have affected the results. The Spanish study was performed between 1979 and 1998, whereas the present study encompassed the period between 1997 and 2013. In addition, epidemiological changes in pneumococcal serotypes might have influenced the results of the present study. Previous reports suggest that some serotypes, such as 1, 3, and 5, are more commonly associated with pneumococcal peritonitis than with other invasive

pneumococcal diseases.[14,24–26] None of these serotypes was included in the 7-valent pneumococcal conjugated vaccine (PCV-7), which was first introduced in 2000. Widespread usage of PCV-7 has led to a significant decrease in invasive pneumococcal diseases by the pneumococcal serotypes covered by PCV-7. The incidence and proportion of non-PCV7 serotypes, however, have increased significantly.[27–29] This may also have led to the absence of pneumococcal pneumonia-related SPP cases in the present study. Since pneumococcal serotypes were not determined in either the Spanish study or the current study, it is difficult to validate this hypothesis. Further investigations are required.

We found that significantly more case patients than control patients initially presented with variceal bleeding. This finding is consistent with those of previous reports showing that pneumococci colonizing the oropharynx might spread to the bloodstream via upper gastrointestinal bleeding or endoscopic procedures.[12,30,31] However, this route would account for only 10% of the SPP cases reported herein; the majority of SPP cases had no documented source of pneumococcal infection, as in other SBP cases the organisms are believed to arise from intestinal tract. Although *S. pneumoniae* is destroyed by bile salts and gastric acid, intra-abdominal pneumococcal infections (including cholangitis, enteritis, and liver abscess) have been reported in the literature.[10,32–34] A decade ago, Dugi et al[10] suggested that if ingested *S. pneumoniae* escaped the effects of gastric acid and bile salts, it could colonize the intestine, thereby posing a risk due to potential bacterial translocation. Dysfunctional phagocytosis of encapsulated pathogens in cirrhotic patients[23,35] might also lead to a failure to clear pneumococci effectively.

Despite the presence of concomitant bacteremia, a known poor prognostic factor for SBP,[36] the mortality rate for patients with SPP was significantly lower than that for the control group; these findings do not agree with those of the Spanish report. We speculate that absence of concomitant pneumococcal pneumonia, fewer cases of hospital-acquired infection, fewer cases of Child-Pugh class C cirrhosis in the SPP group than in the control group, and higher rate of initial appropriate empirical therapy in the case group may have contributed to this finding.

The current study has some limitations. First, the study was retrospective in design and was performed at a single Korean tertiary care center and had a relatively limited sample size;

TABLE 5. Factors Prognostic for 30-Days Mortality and In-Hospital Mortality

	Univariate Analysis		Multivariate Analysis	
	Unadjusted Odds Ratio (95% Confidence Interval)	**P**	**Adjusted Odds Ratio (95% Confidence Interval)**	**P**
Category for 30-day mortality				
Spontaneous pneumococcal peritonitis	0.35 (0.13–0.99)	0.047	0.28 (0.08–0.98)	0.046
Age	2.50 (0.95–6.59)	0.03	1.01 (0.97–1.06)	0.73
Concomitant hepatocellular carcinoma	3.57 (1.55–8.26)	0.003	3.27 (1.22–8.81)	0.02
Presentation with septic shock	7.06 (2.69–18.52)	<0.001	6.61 (2.18–20.02)	0.001
Inappropriate initial antimicrobial therapy	2.34 (0.73–7.53)	0.15	1.76 (0.49–6.32)	0.39
Category for in-hospital mortality				
Spontaneous pneumococcal peritonitis.	0.41 (0.17–0.96)	0.04	0.36 (0.13–1.04)	0.06
Age	1.05 (1.02–1.09)	0.006	1.02 (0.98–1.07)	0.34
Concomitant hepatocellular carcinoma	3.07 (1.44–6.55)	0.004	3.10 (1.22–7.86)	0.02
Presentation with septic shock	9.81 (3.63–26.48)	<0.001	9.31 (3.05–28.41)	<0.001
Inappropriate initial antimicrobial therapy	2.02 (0.67–6.13)	0.21	1.48 (0.42–5.21)	0.54

therefore, our findings may be biased and may not be generalizable. The number of study patients and events is limited, and the *P* values are too marginal to reach a robust conclusion. In addition, as the present study is retrospective matched case-control study, the interpretation should be made with caution. Second, as the 2 groups are not completely comparable in their baseline characteristics, the result may have been influenced by a selection bias, including the Child-Pugh class, and MELD scores. Moreover, to some extent, these moderate imbalances (i.e., slightly more advanced liver diseases in the non-SPP group) could have influenced the higher mortality rate in the control group than in the SPP group, regardless of the microbiological factors. Thus, we performed additional multivariate analysis, including the Child-Pugh class as a covariate, using backward elimination. In this multivariate analysis, the Child-Pugh class was not a significant risk factor for 30-day mortality and non-SPP, whereas SPP, concomitant HCC, and the initial presentation with septic shock were still remained as significant prognostic factors for 30-day mortality (data not shown). Third, we did not know the pneumococcal vaccination status of many of the patients. Therefore, vaccination status could not be included as a variable for analysis.

In conclusion, none of the SPP cases was associated with pneumonia. Also, SPP was more commonly associated with variceal bleeding and a lower mortality than SBP caused by other organisms. However, the present study was associated with the natural limitations characteristic of a small-scale, retrospective study. Therefore, large-scale, well-controlled studies are required to demonstrate the influence of SPP on mortality, which was only marginal in the present study.

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