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CLINICAL STUDIES

# Outcome predictors of cirrhotic patients with spontaneous bacterial empyema

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**Keywords**
cirrhosis – MELD score – MELD–Na score – spontaneous bacterial empyema

**Abbreviations**
HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, model for end-stage liver disease; SBE, spontaneous bacterial empyema; SBP, spontaneous bacterial peritonitis.

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## Abstract

*Background:* Spontaneous bacterial empyema (SBE) is a complication of cirrhotic patients in which a pre-existing pleural effusion becomes infected. This retrospective study was designed to investigate the bacteriology and outcome predictors of SBE in cirrhotic patients. *Methods:* Medical records of cirrhotic patients treated in a tertiary care university hospital from December 2004 to December 2008 were retrospectively reviewed. *Results:* Of 3390 cirrhotic patients seen during the study period, 81 cases of SBE were diagnosed. The incidence of SBE was 2.4% (81/3390) in cirrhotic patients and 16% (81/508) in patients with cirrhosis with hydrothorax. There were 46 monomicrobial infections found in 46 SBE patients. Aerobic Gram-negative organisms were the predominant pathogens ($n = 29$, 63%), and *Escherichia coli* ($n = 9$, 20%) was the most frequently isolated sole pathogen. The mortality rate of SBE was 38% (31/81). Univariate analysis showed that Child–Pugh score, model for end-stage liver disease (MELD)–Na score, concomitant bacteraemia, concomitant spontaneous bacterial peritonitis, initial intensive care unit (ICU) admission and initial antibiotic treatment failure were predictors of poor outcomes. Multivariate regression analysis demonstrated that the independent factors related to a poor outcome were initial ICU admission [odds ratio (OR): 4.318; 95% confidence interval 1CI) 1.09–17.03; $P = 0.037$], MELD–Na score (OR: 1.267; 95% CI 1.08–1.49; $P = 0.004$) and initial antibiotic treatment failure (OR: 13.10; 95% CI 2.60–66.03). *Conclusion:* Spontaneous bacterial empyema in cirrhotic patients is a high mortality complication. The independent factors related to poor outcome are high MELD–Na score, initial ICU admission and initial antibiotic treatment failure. High MELD–Na score may be a useful mortality predictor of SBE in cirrhotic patients.

Bacterial infections are responsible for significant morbidity and mortality in patients with cirrhosis. Such patients are predisposed to infection because of impaired immune function, increased passage of bacteria from the gut and bacterial overgrowth (1). Cirrhosis patients have an increased risk of pulmonary infections (2). Among pulmonary infections, spontaneous bacterial empyema (SBE) is a complication of cirrhotic patients in which a pre-existing pleural effusion becomes infected. SBE may be confused with pleural empyema, because in most cases there is no evidence of pus or abscess in the thoracic cavity and the pathogenesis, clinical course and treatment strategy is different from pleural empyema, which is usually secondary to pneumonia.

To date, there is little known about the exact clinical characteristics, bacteriology and outcome of SBE in patients with cirrhosis. To identify potential risk factors in order to predict the outcomes of cirrhosis patients with SBE, we retrospectively reviewed the clinical features, causative pathogens and outcomes of SBE patients treated from December 2004 to December 2008 at China Medical University Hospital (CMUH), Taichung, Taiwan. In this retrospective study, we proposed to determine whether clinical and laboratory findings and causative micro-organisms may predict the outcomes of cirrhosis patients with SBE.

## Patients and methods

### Patients

This study retrospectively collected and carefully reviewed the medical records of patients with cirrhosis treated from December 2004 to December 2008 at CMUH, a 2062-bed tertiary care medical centre located

in central Taiwan. The hospital's internal review board approved this study, and waived the requirement for informed consent. The diagnosis of cirrhosis was based on liver biopsy or typical clinical findings (i.e. splenomegaly, ascites and/or oesophageal varices), imaging studies [i.e. abdominal sonography and/or computerized tomography (CT)] and laboratory findings.

All patients underwent chest radiography, abdominal sonography or CT after admission to detect the existence of pleural effusion and/or ascites. Thoracentesis was performed on patients with pleural effusions when it was detected for the first time, or when an infection was suspected during admission. If ascites was present, paracentesis was also performed. Pleural fluid and ascites analysis included red blood cell count, polymorphonuclear (PMN) leucocyte count, glucose, protein and lactic dehydrogenase (LDH) levels, cytology and bacterial and mycobacterial culture. Bacterial culture was performed using a conventional method (on chocolate agar, blood agar, MacConkay agar and thioglycolate broth), with 10 ml of fluid collected in an empty sterile container and immediately sent to the laboratory.

### Data collection

The following data were collected for each patient: age, gender, underlying disease, initial haemogram, biochemistry results, pleural effusion culture results, treatment strategies, surgical interventions and outcomes.

### Definitions

Both the Child–Pugh and the model for end-stage liver disease (MELD) scores were based on clinical and laboratory parameters collected at the time of diagnosis of SBE. Child–Pugh score was determined on the basis of the presence and the severity of ascites and hepatic encephalopathy, prolongation of prothrombin time and levels of total serum bilirubin and albumin (3). MELD score was calculated with the following equation: $11.2 \times \log_e$ (INR) $+ 9.57 \times \log_e$ (serum creatinine, in milligrams per decilitre) $+ 3.78 \times \log_e$ (bilirubin, in milligrams per decilitre) $+ 6.43$, with a lower limit of 1 for all variables, and with creatinine capped at 4. Creatinine was set at 4 if the patient was receiving renal replacement therapy (4). The MELD score ranges from 6 to 40, with higher values indicating more severe disease. The MELD–Na score was based on the MELD and Na: MELD $+ 1.59 \times (135 - \text{Na})$, with maximum and minimum Na values of 135 and 120 mmol/l respectively (5).

The diagnosis of SBE was based on previously reported criteria (6): (i) positive pleural fluid culture and a PMN cell count $> 250$ cells/mm$^3$ or, if negative culture, pleural fluid PMN count $> 500$ cells/mm$^3$; (ii) no evidence of pneumonia on chest radiograph or CT; and (iii) evidence of pleural effusion before the infectious episode or pleural fluid transudate characteristics during infection.

Diagnosis of spontaneous bacterial peritonitis (SBP) was established by a PMN count in ascitic fluid of $\geq 250$ cells/mm$^3$ and clinical or laboratory data not suggestive of secondary peritonitis (7). Cases of mononuclear or polymicrobial bacterascites were excluded. The episode was considered to be community acquired when it was present at admission or when it developed within the first 48 h after admission, and hospital acquired if it presented more than 48 h after admission.

Bacteriological diagnosis based on the microbiological examination of the pleural fluid and other samples was also made. Bacteraemia was defined as the isolation of bacterial pathogens from two or more blood culture samples. Bacteria found in pleural effusion specimens were classified as aerobic Gram-positive, aerobic Gram-negative, anaerobic or polymicrobial. Polymicrobial infection was defined as the isolation of more than one strain of a pathogen on pleural effusion culture.

Antimicrobial treatment was defined as inadequate if the antibiotics did not cover the infectious pathogens, or if because of resistance the pathogens were not susceptible *in vitro* to the antibiotics. SBE resolution was considered when all signs of infection had resolved and the PMN count in the pleural fluid had decreased to $< 250$ cells/ml. Treatment failure was defined as a persistent PMN count in the pleural fluid $> 250$ cells/ml after 72 h treatment, or persistent clinical signs of infection after 72 h treatment. Patients who died before follow-up thoracentesis for the assessment of treatment efficacy were also classified as having treatment failures. In-hospital mortality was defined as death from any cause during hospitalization.

All SBE patients received antibiotic treatment, and some received pigtail drainage based on the attending physician's decision. Percutaneous pigtail catheters (SKATER; PBN Medicals, Stenlose, Denmark) sized 12–16 F were placed using a modified Seldinger technique and connected with a one-way valve to a drainage bag.

### Statistical analysis

The data were compiled and analysed using commercial statistical software (SPSS for Windows, version 12.0; SPSS Inc., Chicago, IL, USA). All continuous variables were reported as the mean $\pm$ standard deviation and compared using the two-tailed Student's *t*-test. Categorical variables were reported as numbers and percentages. Differences in categorical variables were examined using the Fisher's exact test. All tests of significance were two sided and a $P$ value $\leq 0.05$ was considered statistically significant.

Univariate analysis was used to identify factors predicting in-hospital mortality. Tested variables included age, sex, renal function, cause of cirrhosis, concomitant SBP, cirrhosis-related clinical and laboratory data obtained at the time of the diagnosis of infection (including Child–Pugh, MELD and MELD–Na scores), other standard laboratory data and source of SBE infection (community vs. nosocomial). Variables that had statistical significance ($P < 0.05$) by univariate analyses were

subjected to multivariate analysis using a step-wise binary logistic regression procedure to identify independent predictors of survival. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to determine significance by multivariate analysis. To assess the ability of serum Na and Child–Pugh, MELD and MELD–Na models in predicting the risk of in-hospital mortality, the analysis was performed by measurement of the *c*-statistic equivalent to the area under the receiver-operating characteristic curve (AUC). The comparisons of the AUCs and the examinations of statistical significance were performed with the method of Hanley and McNeil (8).

## Results

### Patient characteristics, underlying diseases and clinical features

Throughout the 48-month study period, 3390 patients with cirrhosis were admitted to CMUH. Among these patients, 1729 (51%) had ascites, 508 (15%) had a detectable pleural effusion and 387 (11%) had both. Seventy-eight patients had only a minimal pleural effusion that was detectable, but impractical or technically not feasible to sample via thoracentesis, and 28 patients refused to undergo thoracentesis because they thought the procedure was not necessary or the hydrothorax was not troublesome. In 12 patients, thoracentesis was not performed because of severe coagulopathy. In total, the pleural fluid of 390 patients was obtained by thoracentesis. Of the 390 patients who underwent a thoracentesis, 81 (16% of the hepatic hydrothorax and 2.4% of the cirrhotic patients) met the criteria of SBE. Data of these 81 patients are presented in Table 1.

The aetiologies of the cirrhosis in the SBE patients were chronic hepatitis B virus infection in 34 cases, chronic hepatitis C virus infection in 28, alcoholism in 13 and other or unknown aetiologies in six. Forty patients were Child–Pugh class C, 39 were Child–Pugh class B and two patients were Child–Pugh class A. Most patients ($n = 52$, 77%) had chronic underlying disease or associated medical conditions, and the most common concomitant conditions were hepatocellular carcinoma ($n = 25$, 31%), chronic kidney disease ($n = 18$, 22%) and diabetes mellitus ($n = 15$, 19%). Forty-four patients (54%) had concurrent SBP when SBE was diagnosed. The in-hospital SBE-related mortality rate was 38% (31/81). Age, gender, body height, body weight, underlying conditions and length of hospital stay did not differ between the survivor and the non-survivor groups (Table 1). However, the survivors had lower Child–Pugh, MELD and MELD–Na scores and a lower rate of intensive care unit (ICU) admission than the non-survivors.

Comparisons of the serum laboratory values and the pleural effusion parameters of the survivors and the non-survivors are shown in Table 2. There was no difference in laboratory findings between the survivors and non-survivors, except for serum sodium level; serum sodium was significantly lower in the non-survivors. Moreover, the rate of concomitant bacteraemia was significantly higher in non-survivors.

**Table 1.** Demographical comparison of 81 patients based on mortality secondary to spontaneous bacterial empyema

| | | Patient group | | |
|---|---|---|---|---|
| Patient characteristics | All patients ($n = 81$) | Survivors ($n = 50$) | Non-survivors ($n = 31$) | *P* value* |
| Age, mean years ± SE | 60.0 ± 12.8 | 58.7 ± 12.4 | 62.0 ± 13.5 | NS |
| Male | 55 (67.9) | 35 (70.0) | 20 (64.5) | NS |
| Aetiology of cirrhosis | | | | |
| HBV/HCV/alcohol† | 34/28/13 | 22/14/10 | 12/14/3 | |
| Child–Pugh score‡ | 9.7 ± 2.1 | 9.0 ± 1.8 | 10.7 ± 2.0 | < 0.001 |
| With encephalopathy† | 39 (48.1) | 19 (38.0) | 20 (64.5) | 0.02 |
| With ascites† | 67 (82.7) | 29 (58.0) | 22 (71.0) | NS |
| Total bilirubin, mg/dl‡ | 4.7 ± 6.6 | 3.2 ± 3.1 | 7.2 ± 9.4 | 0.006 |
| Serum albumin, g/dl‡ | 2.0 ± 0.5 | 2.1 ± 0.5 | 1.9 ± 0.5 | NS |
| Prothrombin time, INR‡ | 1.7 ± 0.5 | 1.6 ± 0.5 | 1.9 ± 0.6 | < 0.001 |
| Child–Pugh class A† | 2 (2.5) | 1 (2.0) | 1 (3.2) | NS |
| Child–Pugh class B† | 39 (48.1) | 32 (64.0) | 7 (22.6) | 0.001 |
| Child–Pugh class C† | 40 (49.4) | 17 (34.0) | 23 (74.2) | 0.001 |
| MELD score‡ | 20.5 ± 8.0 | 18.6 ± 6.6 | 27.1 ± 9.3 | < 0.001 |
| MELD–Na score‡ | 23.1 ± 7.7 | 19.9 ± 6.3 | 28.1 ± 7.1 | < 0.001 |
| Concomitant with SBP† | 44 (54.3) | 21 (42.0) | 20 (64.5) | 0.04 |
| Community acquired | 55 (67.9) | 37 (74.0) | 18 (58.1) | NS |
| Hospital acquired | 36 (32.1) | 23 (26.0) | 13 (41.9) | NS |
| ICU admission† | 26 (32.1) | 9 (18.0) | 17 (54.8) | 0.001 |
| Length of hospital stay‡ | 20.8 ± 13.0 | 19.1 ± 13.4 | 22.3 ± 12.5 | NS |

**P* values are compared between groups of survivors and non-survivors SBE patients.

†Data are presented as number and percentage of total.

‡Data are presented as mean SD.

HBV, hepatitis B virus; HCV, hepatitis C virus; NS, not significant; SBE, spontaneous bacterial empyema; SBP, spontaneous bacterial peritonitis.

**Table 2.** Comparison of laboratory data based on mortality secondary to spontaneous bacterial empyema

| Patient characteristics | All patients ($n = 81$) | Patient group | | *P* value |
|---|---|---|---|---|
| | | Survivors ($n = 50$) | Non-survivors ($n = 31$) | |
| Initial serum laboratory value | | | | |
| Leucocyte count, $\times 10^3$ cells/mm$^3$ | $10.6 \pm 7.1$ | $9.5 \pm 4.9$ | $12.3 \pm 9.5$ | NS |
| Haemoglobin, g/dl | $10.3 \pm 1.8$ | $10.4 \pm 2.0$ | $10.2 \pm 1.7$ | NS |
| Platelet count, $\times 10^3$ cells/mm$^3$ | $107 \pm 85$ | $97 \pm 77$ | $125 \pm 96$ | NS |
| GOT, IU/l | $96 \pm 132$ | $95 \pm 158$ | $98 \pm 82$ | NS |
| GPT, IU/l | $57 \pm 118$ | $63 \pm 149$ | $46 \pm 35$ | NS |
| BUN, mg/dl | $37 \pm 27$ | $32 \pm 28$ | $44 \pm 24$ | NS |
| Creatinine, mg/dl | $1.8 \pm 1.4$ | $1.7 \pm 1.5$ | $2.1 \pm 1.2$ | NS |
| Sodium, mol/l | $134 \pm 7$ | $137 \pm 4$ | $130 \pm 9$ | $< 0.001$ |
| Potassium, mmol/l | $4.0 \pm 0.6$ | $4.0 \pm 0.7$ | $3.9 \pm 0.6$ | NS |
| C-reactive protein, mg/dl | $6.2 \pm 5.8$ | $5.7 \pm 6.2$ | $6.9 \pm 5.0$ | NS |
| Positive blood cultures | 22 (27.2) | 8 (16.0) | 14 (45.2) | 0.004 |
| Side of SBE | | | | |
| Right, *n* (%) | 60 (74.1) | 37 (74.6) | 23 (74.2) | NS |
| Left, *n* (%) | 21 (25.9) | 13 (26.0) | 8 (25.8) | NS |
| Initial SBE laboratory value | | | | |
| Nucleated cells, $\times 10^3$ µl | $5.3 \pm 17.1$ | $3.3 \pm 5.1$ | $8.6 \pm 26.7$ | NS |
| Neutrophils, % | $76 \pm 17$ | $76 \pm 17$ | $76 \pm 17$ | NS |
| LDH, IU/l | $108 \pm 40$ | $105 \pm 40$ | $112 \pm 41$ | NS |
| Glucose, mg/dl | $130 \pm 45$ | $134 \pm 67$ | $123 \pm 62$ | NS |
| Total protein, g/dl | $1.5 \pm 0.7$ | $1.5 \pm 0.8$ | $1.6 \pm 0.8$ | NS |
| Positive of pleural effusion culture | 46 (56.8) | 28 (56.0) | 18 (58.1) | NS |

Data presented as number (%) or mean ± SD.

LDH, lactic dehydrogenase; NS, not significant; SBE, spontaneous bacterial empyema.

The pleural effusion parameters of the 309 sterile hepatic hydrothorax were nucleated cells, $455.5 \pm 552.4$ µl; neutrophils, $22.4 \pm 22.8\%$; LDH, $90.1 \pm 50.4$ IU/l; glucose, $150.4 \pm 54.8$ mg/dl and total protein, $2.1 \pm 1.0$ g/dl. Compared with the pleural effusion parameters of sterile hepatic hydrothorax, patients with SBE had significantly higher nucleated cells ($P < 0.001$), neutrophils ($P < 0.001$) and LDH ($P = 0.011$) and significant lower glucose ($P = 0.0023$) and total protein ($P < 0.001$).

### Bacteriological characteristics and relationship with clinical characteristics

Overall, 46 organisms including 45 aerobic bacteria and one anaerobic bacteria were isolated from 46 SBE patients (Table 3). The most common bacteria were aerobic Gram-negative organisms ($n = 29$, 36%), the most common of which were *Escherichia coli* ($n = 11$, 14%), *Klebsiella pneumoniae* ($n = 10$, 12%) and *Pseudomonas aeruginosa* ($n = 4$, 5%). The second most common organisms were aerobic Gram-positive organisms ($n = 13$, 16%), of which *Enterococcus* spp. ($n = 6$, 7%) was the major Gram-positive SBE-causing organism.

The 81 SBE patients were further categorized into community-acquired (57 patients) and hospital-acquired (24 patients). Twenty-nine organisms were isolated from community-acquired SBE patients and 17 organisms from hospital-acquired patients. Aerobic Gram-negative pathogens were the main organisms responsible for both community-acquired and hospital-acquired SBE. The most common causative pathogen responsible for community-acquired SBE was *E. coli* ($n = 8$, 14%), and the most common causative pathogen

**Table 3.** Bacteriology of spontaneous bacterial empyema patients

| Patient characteristics | All patients ($n = 81$) | | Patient group | | | |
|---|---|---|---|---|---|---|
| | | | Survivors ($N = 50$) | | Non-survivors ($N = 31$) | |
| | CA | HA | CA | HA | CA | HA |
| Aerobic Gram-positive cocci | 8 | 5 | 5 | 2 | 3 | 3 |
| *Staphylococcus aureus* (ORSA) | 0 | 1 | 0 | 0 | 0 | 1 |
| *S. aureus* (OSSA) | 3 | 0 | 3 | 0 | 0 | 0 |
| *Streptococcus* group D | 1 | 1 | 0 | 0 | 1 | 1 |
| *Streptococcus mitis* | 1 | 0 | 1 | 0 | 0 | 0 |
| *Enterococcus* spp. | 3 | 3 | 1 | 2 | 2 | 1 |
| Aerobic Gram-negative bacilli | 19 | 10 | 14 | 5 | 5 | 5 |
| *Klebsiella pneumoniae* (ESBL) | 1 | 3 | 1 | 2 | 0 | 1 |
| *K. pneumoniae* (non-ESBL) | 5 | 1 | 3 | 0 | 2 | 1 |
| *Escherichia coli* (ESBL) | 2 | 0 | 1 | 0 | 1 | 0 |
| *E. coli* (non-ESBL) | 6 | 3 | 5 | 1 | 1 | 2 |
| *Pseudomonas aeruginosa* | 3 | 1 | 2 | 1 | 1 | 0 |
| *Proteus mirabilis* | 0 | 1 | 0 | 1 | 0 | 0 |
| *Acinetobacter baumannii* | 1 | 0 | 1 | 0 | 0 | 0 |
| *Aeromonas hydrophila* | 1 | 1 | 1 | 0 | 0 | 1 |
| Gram-positive bacilli | 2 | 1 | 2 | 0 | 0 | 1 |
| Anaerobes | 0 | 1 | 0 | 0 | 0 | 1 |
| *Peptostreptococcus micros* | 0 | 1 | 0 | 0 | 0 | 1 |
| Unidentified | 28 | 7 | 19 | 3 | 9 | 4 |

CA, community acquired; HA, hospital acquired.

in hospital-acquired SBE was *K. pneumoniae* ($n = 4$, 17%).

The culture results were positive in 54% (34 of 63) of patients in the survivor group, and in 67% (12 of 18) of patients in the non-survivor group. Thirty-four organisms were recovered in the survivor group, including 33 aerobic and one anaerobic bacterium. In the non-survivor group, 12 organisms were recovered, and all were aerobic bacteria. In both survivor and non-survivor culture-positive SBE groups, the main causative pathogen was aerobic Gram-negative organisms [62% (21/34) in the survivor group and 67% (8/12) in the non-survivor group]. Aerobic Gram-positive organisms were the second most common organisms in both groups [26% (9/34) in the survivor group and 33% (4/12) in the non-survivor group]. *Escherichia coli* ($n = 8$) in the survivor group and *K. pneumoniae* ($n = 3$) in the non-survivor group were the major causative organisms among aerobic Gram-negative organisms, and *Enterococcus* spp. ($n = 4$ in the survivor group; $n = 2$ in the non-survivor group) was the major causative organism among the aerobic Gram-positive organisms.

### Treatment and resolution of infection

Twenty-eight (35%) SBE patients received pigtail catheter drainage according to the managing physician's decision. A greater number of patients who received drainage had positive effusion cultures than those who did not receive drainage (86 vs. 42%, respectively, $P < 0.001$). There were no statistically significant differences in the effusion laboratory data and length of stay between these two groups, and mortality rate in patients treated with pigtail drainage was not significantly higher than in those who did not receive drainage (50 vs. 32%, respectively, $P = 0.15$). Complications of pigtail placement included subcutaneous haematoma ($n = 3$), wound infection ($n = 2$) and haemothorax ($n = 1$). Complications after pigtail placement included renal dysfunction ($n = 9$), electrolyte imbalance ($n = 11$), persistent drainage of the pleural effusion after removal of the catheter ($n = 2$) and delayed wound healing ($n = 1$).

Cefotaxime was the most frequently used antibiotic as a first-line treatment (35 cases, 43.2%), followed by cefazolin (14 cases, 17.3%), ampicillin/sulbactam (12 cases, 14.8%) and flomoxef (eight cases, 9.9%). First-line antibiotics were used for $9 \pm 5$ days, and follow-up thoracentesis was performed $7 \pm 5$ days after commencement of treatment. Of all patients, 58 patients (71.6%) experienced resolution of the SBE after treatment, and still 13 patients died after SBE resolution. In 23 patients (28.4%), first-line antibiotic treatment failed; 10 cases treated with cefazolin, five cases treated with cefotaxime and four cases treated with ampicillin/sulbactam. Of the 23 first-line treatment failures, 11 patients died before commencement of second-line antibiotics. Second-line antibiotic treatment was successful only in 5 of 12 cases (41.7%). In total, 17 patients died after first-line antibiotic treatment failure.

### Mortality and outcome predictors of spontaneous bacterial empyema patients

Complications that developed during hospitalization included acute renal failure (17 patients, 21%), gastrointestinal bleeding (nine patients, 11%), septic shock (22 patients, 14%) and hepatic encephalopathy (eight patients, 10%). Thirty-one patients (38.3%) died during hospitalization. The causes of in-hospital mortality were hepatorenal syndrome (eight patients, 25.8%), gastrointestinal bleeding (four patients, 12.9%), hepatic encephalopathy (one patient, 3.2%) and SBE-related septic shock (18 patients, 58.1%). The results of univariate and multivariate analysis to evaluate factors associated with mortality in SBE patients are shown in Table 4. In univariate analysis, a positive correlation was observed between mortality and Child–Pugh score (OR: 1.59), MELD–Na score (OR: 1.21), initial ICU admission (OR: 5.53), concomitant bacteraemia (OR: 4.32), concomitant SBP (OR: 2.51) and initial antibiotic treatment failure (OR: 7.46). Moreover, initial ICU admission (OR: 4.318; 95% CI 1.09–17.03; $P = 0.037$), MELD–Na score (OR: 1.267; 95% CI 1.08–1.49; $P = 0.004$) and initial antibiotic treatment failure (OR: 13.10; 95% CI 2.60–66.03; $P = 0.002$) remained as independent factors predictive of mortality in multivariate analysis.

Using the *c*-statistic and in-hospital mortality as the endpoint, the estimated AUCs for the four prognostic models (Child–Pugh, MELD, MELD–Na score and serum Na) in predicting mortality are shown in Figure 1.

**Table 4.** Univariate and multivariate analysis of factors associated with mortality in spontaneous bacterial empyema patients

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Variables | Odds ratio for death | 95% confidence interval | *P* value | Odds ratio for death | 95% confidence interval | *P* value |
| Child–Pugh score | 1.587 | 1.222–2.061 | 0.001 | 0.937 | 0.599–1.464 | NS |
| MELD–Na score | 1.208 | 1.100–1.326 | < 0.001 | 1.266 | 1.076–1.489 | 0.004 |
| Concomitant bacteraemia | 4.324 | 1.535–12.176 | 0.006 | 1.399 | 0.244–8.038 | NS |
| Concomitant with SBP | 2.511 | 0.995–6.336 | 0.05 | 0.521 | 0.105–2.591 | NS |
| ICU admission | 5.532 | 2.014–15.194 | 0.001 | 4.318 | 1.094–17.037 | 0.037 |
| First-line treatment failure | 7.459 | 2.566–21.681 | < 0.001 | 13.104 | 2.600–66.035 | 0.002 |

ICU, intensive care unit; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis.

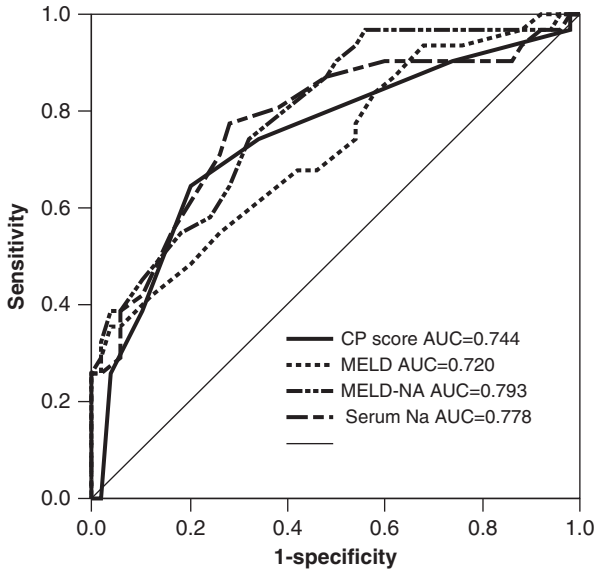


**Fig. 1.** Comparison of area under receiver-operating characteristic curves for MELD, MELD–Na, Child–Pugh scores and serum Na in predicting the spontaneous bacterial empyema hospital mortality.

The MELD–Na score had the highest AUC (0.793, 95% CI), followed by serum Na (0.778), Child–Pugh score (0.744) and the MELD score (0.720). MELD–Na score had a significantly higher AUC in comparison with the MELD score ($P = 0.002$). No significant difference was noted between the AUC of MELD–Na score, Child–Pugh score and serum Na.

## Discussion

Ours is the first report in the English language literature to focus on the outcome predictors of patients with cirrhosis and SBE. The mortality of SBE patients in our study was 38%. The independent factors related to a poor outcome were initial ICU admission, high MELD–Na score and initial antibiotic treatment failure. Furthermore, all infections in SBE patients were monomicrobial. Aerobic Gram-negative organisms were the predominant pathogens in SBE patients, and *E. coli* was the most frequently isolated sole pathogen.

There are two hypotheses regarding the development of SBE. One suggests that the infection is through spontaneous bacteraemia, as in SBP, and the other suggests that infection arises through the flow of infected ascites from the peritoneal to the pleural cavity via defects in the diaphragm, i.e. SBE is secondary to SBP (9, 10). Our results showed that 54% of SBE patients have concomitant SBP, which confirms that SBE has a close relationship with SBP.

Similar to other findings on SBE (11), high Child–Pugh score, decreased pleural fluid total protein and low levels of C3 component in pleural fluid are proved risk factors of SBE. In our study, the total protein of the pleural effusions in SBE patients was significantly lower than that in patients with sterile hydrothorax. Moreover, most patients ($n = 55$, 68%) who developed SBE had a total protein concentration of pleural fluid $< 1.5$ g/dl. Advanced liver disease and low pleural fluid protein level imply a low complement level, which impairs the osmotic activity of the pleural fluid and thus enhances bacterial translocation. In this situation, pleural fluid will become easily infected.

The Child–Pugh score is an important component of the prognostic assessment of patients with end-stage liver disease. However, this traditional scoring method has shortcomings mainly related to the limited number of disease categories, the inability to discriminate disease severity among the sickest patients and the subjectivity of the assessment of ascites and encephalopathy, which are also very much dependent on treatment. Moreover, the impact of impaired renal function on survival is well known in patients with a high Child–Pugh score (12); however, renal function is not included in the Child–Pugh score. These drawbacks limit the predictive accuracy of the Child–Pugh score. In our series, Child–Pugh score was not a significant predictive factor.

The MELD score has been evaluated for its predictive value in various liver disease-related research settings outside those of liver allocation. Indeed, it was originally developed to assess the short-term prognosis of patients with cirrhosis undergoing the transjugular intrahepatic portosystemic shunt procedure (13). In fact, it is a reliable measure of short-term mortality risk in patients with end-stage liver disease of diverse aetiologies, and is applicable over a wide spectrum of disease severity (12). The MELD has been demonstrated to have a better ability in short-term and intermediate-term outcome prediction in comparison with the Child–Pugh score (14, 15). Nonetheless, the MELD still has potential limitations (16, 17). Hepatic encephalopathy, oesophageal varices bleeding and SBP are common complications associated with cirrhosis, which had been considered one of the allocation policies of liver providing. However, there are no parameters correlated with these complications in the MELD. Portal hypertension is responsible for above-mentioned complications (18, 19). Hyponatraemia is a common event in cirrhosis, and it develops primarily as a result of free water retention (20), which is positively correlated with the severity of portal hypertension. Consequently, the serum sodium level may inversely reflect the severity of portal hypertension. Those with low MELD scores who have persistent ascites and low serum sodium are at a disadvantage. This group of patients has a higher mortality than predicted by the MELD score alone (21). Many studies have proposed that serum sodium can be used to exactly determine the prognosis and mortality of patients with cirrhosis. The incorporation of serum sodium level into the MELD may enhance prognostic accuracy (21, 22). In our series, we found MELD–Na score to be a strong independent predictor of in-hospital mortality in SBE patients, and it

significantly improved the AUC leading to prediction of prognosis as compared with MELD score alone.

As in previous literature (23), aerobic Gram-negative bacteria were the major pathogens isolated from the SBE patients in this study. This is because SBE has a close relationship with SBP. The capacity of Gram-negative bacteria to colonize ascitic fluid is known to be higher than that of Gram-positive cocci, and this certainly plays an important role in SBP. This may explain why aerobic Gram-negative bacteria remain the main organism responsible for SBE.

Previous studies have noted an important association between initial antimicrobial treatment failure of SBP and hospital mortality (24). In our study, initial first-line antibiotic treatment failure was also an outcome predictor of SBE patients. This is because initial antibiotic treatment failure was usually caused by the inappropriate use of a narrow-spectrum antibiotic. This treatment does not follow the accepted guidelines for treatment of SBP and SBE, and is associated with a rapid deterioration of clinical condition and subsequent death. In our study, 14 SBE patients were treated with cefazolin as the first-line antibiotic and resolution occurred only in four patients. Nine patients died after treatment failure. Currently, third-generation cephalosporins have become the antibiotics of choice in treating cirrhotic patients with SBP. We also suggest the use of third-generation cephalosporins as first-line treatment to reduce the mortality associated with SBE.

Tubal drainage is contraindicated in patients with hepatic hydrothorax and SBE because of the risk of life-threatening fluid depletion, protein loss and electrolyte imbalance (23, 25). However, chest tubes may be successfully removed in a majority of cirrhotic patients (26). In this study, 28 (35%) patients have received pigtail drainage based on the decision of their attending physician because of the bacteria isolated in the pleural effusion. Patients with cirrhosis may be at a greater risk of complications while a chest tube is in place including increased bleeding because of coagulopathy, infection because of poor wound healing, renal failure and electrolyte disturbances. Hence, we suggest that tube drainage is not necessary for SBE, even for culture-positive effusions. Treatment with broad-spectrum antibiotics alone can be successful without tube drainage.

Spontaneous bacterial empyema is a frequent but underdiagnosed complication of hepatic hydrothorax, and portends a poor prognosis. Its possible occurrence should be borne in mind in cases of hepatic hydrothorax that develop fever, encephalopathy or unexplained deterioration of renal function. Diagnostic thoracentesis is a useful and relatively safe procedure associated with low morbidity in patients with cirrhosis (27). A diagnostic thoracentesis with subsequent culture of pleural fluid should be performed in cirrhotic patients with hydrothorax when infection is suspected.

The present study had several limitations. First, all of the patients were from a single hospital. The prevalence of SBE may differ in other geographic regions. Second, the incidence of SBE in cirrhotic patients may have been underestimated because the pleural fluid from only 77% (390 of 508) of the patients was available for analysis. Third, this is a retrospective and non-randomized study, and there was potential of confounding and bias because of unknown factors during the analysis of the results. Fourth, the conventional method for bacterial culture of pleural fluid was used because of hospital policy. In this study, 56% of SBE patients had positive bacterial cultures. A previous study on SBP concluded that the inoculation of ascitic fluid into a tryptic soy broth blood culture bottle at the patient's bedside is more sensitive than the conventional culture method (19). This method should also be used for pleural fluid culture of cirrhotic patients with SBE to improve the culture yield rate, and to more accurately determine the bacteriology of SBE.

In conclusion, SBE in cirrhotic patients is a high mortality complication. The independent factors related to poor outcome were high MELD–Na score, initial ICU admission and initial antibiotic treatment failure. Aerobic Gram-negative organisms were the predominant pathogens in SBE patients, and *E. coli* was the most frequently isolated sole pathogen. Tube drainage is not necessary for SBE, even for culture-positive effusions. We hope this study will provide a better understanding of the prognostic factors in cirrhotic patients with SBE, and will help to optimize the therapeutic approach to this disease and decrease both its mortality and morbidity.

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