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Renal Dysfunction Is the Most Important Independent Predictor of Mortality in Cirrhotic Patients With Spontaneous Bacterial Peritonitis

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Abstract

BACKGROUND & AIMS—Spontaneous bacterial peritonitis (SBP) is the most common infection among patients with cirrhosis. To improve stratification of patient care, we performed a systematic review to identify the most robust predictors of mortality in cirrhotic patients with SBP.

METHODS—We reviewed prognostic studies (English language only) of adult patients with SBP, defined as a polymorphonuclear ascitic fluid cell count of 250 cells/mm³ or more, with or without positive results from culture of ascitic fluid. We reviewed only studies that performed survival and multivariate analyses and reported in-hospital or mortalities within 30 days.

RESULTS—Of 2008 available references, 18 were included in the study (median, 115 patients per trial). The median age of patients was 56 years (68% male). The most common predictors of death were renal dysfunction, lack of SBP resolution, immunosuppressive factors, and hospital-acquired SBP. Sensitivity analysis using the 12 best-quality studies identified renal dysfunction and levels of blood urea nitrogen and creatinine as the most important variables. The mortality rate among patients with renal dysfunction was 67%, compared with only 11% of patients who maintained normal renal function.

CONCLUSIONS—Renal dysfunction is the main prognostic factor for cirrhotic patients with SBP, followed by the MELD score. Further studies are needed to determine whether these factors identified retain prognostic value in high-risk patients who receive albumin. Risk stratification might be used to select additional treatments, such as early vasoconstrictor therapy, for the highest-risk group.

Keywords

Hospital-Acquired Infections; Liver Disease; Prognosis; BUN

Bacterial infections represent a major cause of morbidity and mortality in hospitalized patients with cirrhosis. Spontaneous bacterial peritonitis (SBP) is the most common,

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Conflicts of interest

The authors disclose no conflicts.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at doi:10.1016/j.cgh.2010.11.038.

accounting for at least 24% of these infections.^{1,2} Overall, mortality from an episode of SBP is around 20% to 30%, with the lowest mortality rates reported in patients with community-acquired SBP in the absence of encephalopathy or renal failure, in whom the mortality is nil,³ and in patients who receive adjuvant intravenous albumin in whom the mortality is 10%, with a particular benefit in patients with abnormal renal function or jaundice at diagnosis.⁴ Determining prognosis is an essential part of the baseline assessment of any disease, not only because it provides the physician with information to convey to the patient, but also because it is important in risk stratification, decision making, and individualized medical therapy for different at-risk populations. For prognostic parameters that are modifiable, early therapeutic strategies could be investigated. Over the past 2 decades, several studies have attempted to identify prognostic indicators of in-hospital mortality in patients with SBP with variable results. The aim of this systematic review was to identify those that are the most robust and that will allow for a better patient stratification.

Methods

On January 21, 2010, a MEDLINE search was performed using the following search terms: survival (ALL) OR mortality (ALL) OR predictor (ALL) OR prognosis (ALL) OR prognostic (ALL) AND spontaneous bacterial peritonitis OR SBP (ALL). Additional studies were identified by a manual search of the reference lists of the retrieved articles. The inclusion criteria for the studies were as follows: (1) English language, (2) adult patients, (3) SBP defined as a polymorphonuclear ascitic fluid cell count of 250 cells/mm³ or greater with or without a positive ascitic fluid culture, (4) survival analysis reported, (5) multivariate analysis of prognostic indicators of mortality, and (6) reporting of in-hospital mortality or mortality within 30 days. Trials were excluded if they were randomized trials comparing 2 different therapies with varying outcomes in the 2 groups, studies in which the prognostic indicators and in-hospital mortality were not provided for the entire cohort of patients with SBP, or abstracts only.

Required clinical and study quality data were predefined and collected for each study. Good-quality studies were defined arbitrarily as those that fulfilled the following 3 quality criteria: (1) listing relevant baseline data (age, sex, an indication of the severity of liver dysfunction [Child–Pugh score, model for end-stage liver disease (MELD) score, or their components]); (2) defining SBP as a polymorphonuclear ascitic fluid cell count of 250 cells/mm³ or greater independent of ascitic fluid culture results; and (3) reporting the number of deaths. In-hospital or mortality within 30 days data were recorded. The number of factors entered into each univariate analysis, those carried forward to the multivariate analysis, and those that were significant in the multivariate analysis were recorded.

Results

The trial flow is shown in Figure 1. Of 2008 references identified through a MEDLINE search, 1930 were excluded based on the abstract and the title because they did not meet inclusion and exclusion criteria. Of the remaining 78 full-text articles, 60 were excluded because they did not meet inclusion and exclusion criteria, leaving 18 studies for inclusion in this review.^{3,5–21}

Description of Prognostic Studies

Of the 18 studies, 14 (78%) were explanatory, that is, their aim was to evaluate a specific prognostic variable according to a biologically plausible hypothesis (Table 1). The remaining 4 studies (22%) were predictive, assessing the prognostic value of multiple variables. Two studies were randomized controlled trials,^{3,9} both of which had equivalent

outcomes in the treatment and control arms. A majority of the studies (15 of 18) were retrospective and 78% (14 of 18) stated relevant baseline data. The accepted definition of SBP was applied in 11 of 18 (61%) of the studies, whereas the rest required culture positivity in addition to an increased neutrophil count,^{11,14,15,18–20} or based the diagnosis of SBP on hospital diagnostic codes.¹⁰ Three studies evaluated only *Escherichia coli*-positive SBP.^{11,18,19} All studies reported the number of deaths but only 50% (9 of 18) stated the causes of death and only 3 studies did not overfit variables.^{10,15,20} Ten studies fulfilled our predefined quality criteria.^{3,5–9,12,13,17,21}

Description of Patients Included in Prognostic Studies

Overall, 2381 patients were included in the 18 studies with a median of 115 patients per trial. The patient characteristics are reported in Table 2. Median age was 56 years and 68% of patients were male. In the studies that reported etiology, hepatitis B and alcohol were the major etiologic factors. One study included only patients with hepatitis B.²¹ Of the trials with reported information, baseline Child–Pugh was class C in 77%. Sixty-eight percent of the patients had community-acquired SBP.

Survival in Prognostic Studies

All studies evaluated mortality within 30 days or in-hospital mortality. When all studies were considered, the median short-term mortality rate was 29% with an interquartile range (IQR) of 21% to 38%. In the 7 studies providing information about mortality associated with renal dysfunction,^{6,7,11,14,16,18,20} median in-hospital mortality was 67% (IQR, 54%–77%) as compared with only 11% (IQR, 9%–26%) in those patients who maintained a normal renal function (Table 2).

Prognostic Variables

A total of 108 different variables were evaluated in these studies. Table 3 shows the grouping of these variables according to their purported clinical and pathophysiological role in SBP.

As shown in Table 4, the variable that was found to be the most common independent predictor of death in patients with SBP was renal dysfunction because it was introduced in multivariable analysis in 9 studies and was among the first 5 significant predictors in all of them (100%). In addition to renal dysfunction, another robust variable was the MELD score. Both variables were found to be independently predictive of death in all of the studies that incorporated them in the multivariable analysis, the most robust being renal dysfunction because it was analyzed in 9 studies compared with only 3 studies using MELD. Other significant variables were lack of SBP resolution, presence of immunosuppressive factors, and hospital-acquired SBP. In the 10 studies that met all of our quality criteria, the top 2 prognostic indicators were renal dysfunction (4 of 4 studies) and blood urea nitrogen (BUN) and creatinine levels (5 of 9 studies).

Renal dysfunction was defined somewhat variably in the studies, but most defined it as a creatinine level greater than 1.5 mg/dL. Four studies defined it as a BUN level greater than 30 mg/dL or a creatinine level greater than 1.5 mg/dL in those without pre-existing renal disease and an increase of greater than 50% in those with pre-existing renal disease.^{6–8,16} Three studies defined it as a BUN level greater than 25 mg/dL and/or a creatinine level of greater than 1.35 mg/dL,¹³ a serum creatinine level increasing 3.0 mg/dL more than the baseline value¹⁴ or a serum creatinine level greater than 1.5 mg/dL.¹¹ Renal dysfunction was measured at baseline in 4 studies,^{7,13,16,20} during the SBP episode in 3 studies,^{6,8,14} and at an unclear time point in 2 studies.^{11,18} Two studies did not define the variable.^{18,20}

Lack of SBP resolution was either not defined,¹¹ was defined as persistently positive cultures despite antibiotic use for 48 to 72 hours,¹⁵ or a persistence of an ascitic fluid neutrophil count of greater than 250 cells/mm³ after 6 days of antibiotic therapy.¹⁸

Immunosuppressive factors included diabetes mellitus,^{5,6,14} human immunodeficiency virus,¹³ a combination of immunosuppressive drugs, human immunodeficiency virus infection or cancer,¹¹ or these variables plus diabetes mellitus.¹⁸ In both of the studies by Cereto et al,^{11,18} the immunosuppressive factors were statistically significant for mortality as a group, but not individually.

Nosocomial (or hospital-acquired) infection was distinguished from community-acquired SBP in 8 studies.^{5,6,8,13,14,19,20,22} Nosocomial SBP was either acquired after 48 hours¹⁹ or after 72 hours^{13,14,20} of being admitted to the hospital or was defined by a normal ascitic fluid polymorphonuclear leukocyte count on entry into the hospital that subsequently became positive while in the hospital.^{3,5,6,8}

The use of albumin was not tested as a prognostic indicator in the evaluated studies, likely because a majority of them did not use albumin therapy. Albumin use was clearly mentioned in only 4 of 18 studies.^{17–19,21} Of these, the proportion of patients using albumin was described in 3 studies, at 28%,¹⁹ 78%,¹⁷ and 90% of patients.¹⁸ Of the studies^{3,5–14,16} that recruited the majority of their patients before the beneficial effect of albumin was reported,⁴ the mortality rate was 26% (IQR, 20%–33%).

Discussion

In this series of patients, the majority of whom did not receive albumin therapy, renal dysfunction was by far the most robust predictor of SBP-related mortality. This supports stratifying patients with SBP into a group at a high risk of death, defined by the presence of renal dysfunction at the time of diagnosis of SBP. In these patients, the administration of albumin prevents further deterioration in renal function and improves survival.⁴ On the other hand, patients with SBP without evidence of renal dysfunction at diagnosis do not benefit from albumin administration^{4,16,23} and are considered a low-risk SBP group in whom the timely administration of antibiotics alone is adequate. Because the studies in our series did not routinely administer albumin to high-risk SBP patients, prognostic factors in this patient population remain to be determined. We can infer, however, that renal dysfunction also plays an important prognostic role in this setting because the antibiotic plus albumin arm of the Sort study⁴ reported no in-hospital deaths in patients with a BUN of less than 30 mg/dL. In contrast to the universal prognostic value of renal dysfunction, the variables BUN and creatinine were evaluated in the majority of studies only at baseline and were robust at predicting in-hospital mortality only in high-quality studies.

The MELD score also shows promise as a means for risk-stratifying patients with SBP because it was found to be a predictor of death in all 3 studies in which it was investigated. Although one could assume that its predictive value was owing to serum creatinine being part of the MELD score, in 2 of the 3 studies MELD was predictive of death independent of BUN level, creatinine level, or renal dysfunction. The MELD score is known to have an independent prognostic value in patients with non-SBP-related infection.²⁴ The predictive value of MELD will be important to validate in a group of high-risk patients who are consistently given albumin. If MELD retains its predictive value in this setting, a MELD threshold could be identified as a target for initiating more intensive therapeutic options.

A hospital-acquired infection was an independent predictor of death in only 3 of the 8 studies in which it was evaluated. In the study by Cheong et al,²⁰ the increase in mortality was attributed to a higher rate of multidrug resistance (resistance to third-generation

cephalosporins). These results are in keeping with recent data showing higher rates of drug resistance in patients with nosocomial SBP and increased rates of septic shock and death in patients with multidrug resistance.^{25,26} That the lack of SBP resolution is a variable that is predictive of mortality is not surprising and this as well may tie into resistance to standard therapies. As suggested by recent guidelines, patients with hospital-acquired infections may require broader-spectrum empiric antibiotic coverage.²⁷

In conclusion, of the prognostic indicators identified by this review, prevention of renal dysfunction and the broadening of the empiric antibiotic spectrum in patients with nosocomial infections are potentially modifiable. It is clear that factors that further compromise the effective circulating volume (nephrotoxins, vasodilators, large-volume paracenteses) should be avoided in all patients with SBP, and that intravenous albumin should be given to those patients at high risk of renal dysfunction. It remains to be seen whether the prognostic indicators identified in this series are the same as for a group of patients in whom those at high risk of renal dysfunction are routinely given albumin therapy. Moreover, in the setting of routine albumin therapy, the relative prognostic impact of nosocomial infections, multidrug-resistant organisms, and immunosuppressive factors on the development of renal dysfunction and mortality deserves further study. The MELD score may prove to be a more practical alternative for the identification of patients who develop progressive renal dysfunction and mortality despite the use of albumin. Once identified, these high-risk patients may benefit from alternate therapies such as the initiation of early vasoconstrictor therapy.

Abbreviations used in this paper

BUN	blood urea nitrogen
IQR	interquartile range
MELD	model for end-stage liver disease
SBP	spontaneous bacterial peritonitis

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Figure 1.
Flow of trials through the review.

Table 1

Study Characteristics

Study characteristics	N (%)
Aim	
Explanatory	14 (78)
Predictive	4 (22)
Design	
Prospective	3 (17)
Retrospective	15 (83)
Patients were included consecutively	9 (50)
Inclusion and exclusion criteria defined	12 (67)
Number of excluded patients specified	10 (56)
Diagnosis of SBP defined correctly ^{a,b}	11 (61)
Relevant baseline data shown ^{a,c}	14 (78)
Number of deaths reported ^a	18 (100)
Causes of death reported	9 (50)
Ratio of number of deaths/number of variables >10 (ie, no overfitting)	3 (17)

NOTE. Eighteen studies were included.

^a Good study defined by the presence of these quality variables.

^b SBP defined as a polymorphonuclear cell count in the ascitic fluid of 250 cells/mm³ or more in the absence of clinical, radiologic, or laboratory data suggesting secondary peritonitis.

^c At a minimum, studies should have reported age, sex, and an indication of the severity of liver dysfunction (Child–Pugh score, MELD score, or their components).

Table 2

Patient Characteristics

Variable	No. of studies with available information	Median (IQR)
Sample size (patients included/study)	18	115 (73–188)
Age, <i>y</i>	17	56 (54–59)
% Male	15	68 (64–74)
Etiology of cirrhosis		
Hepatitis C, %	12	15 (7–42)
Alcohol, %	14	45 (23–57)
Hepatitis B, %	8	63 (10–76)
Other, %	10	10 (5–13)
Child–Pugh class		
B (%)	6	23 (17–27)
C (%)	6	77 (73–83)
Child–Pugh score	7	10.7 (10.5–10.9)
MELD score	4	23 (19–27)
Community-acquired SBP, %	10	68 (54–72)
Associated bacteremia, %	6	31 (15–48)
Previous SBP, %	8	19 (4–25)
Norfloxacin prophylaxis, %	4	25 (15–31)
Concurrent hepatocellular carcinoma, %	7	18 (15–28)
Renal dysfunction, %	9	38 (26–48)
Median or mean follow-up period, <i>d</i>	7	21 (16–22)
Mortality, %	18	29 (21–38)
Causes of death	6	
SBP or recurrence of SBP, %	6	33 (23–44)
Variceal bleeding, %	6	13 (6–16)
Renal dysfunction, %	3	10 (4–30)
Multiorgan failure, %	3	52 (17–60)
Liver failure, %	5	28 (8–59)
Hepatocellular carcinoma, %	2	4 (0–8)
Other, %	4	6 (1–14)
N variables assessed, total	17	16 (11–37)
N deaths	18	26 (21–53)
N variables entered on multivariate analysis	17	7 (5–11)
N variables independently predictive of death	18	3 (2–4)

Table 3**List of the 108 Variables Evaluated**

Patient demographics (3 variables)
<i>Age</i> (4/18) ^{5,6,10,17}
Race (0/1)
Sex (0/13)
Cause of liver disease (7 variables)
Active alcoholism (0/2)
Etiology of cirrhosis (0/2)
Alcohol-related liver disease (0/4)
Viral hepatitis-related liver disease (0/1)
Hepatitis B virus-related liver disease (0/1)
Hepatitis C virus-related liver disease (0/1)
Other etiology of liver disease (0/1)
Symptoms and signs at presentation (5 variables)
<i>Abdominal pain</i> (1/5) ¹²
Ileus (0/4)
Ascites volume (0/2)
Vomiting (0/1)
Diarrhea (0/2)
Systemic inflammatory response syndrome, sepsis, and septic shock (24 variables)
<i>Renal dysfunction</i> (9/9) ^{6-8,11,13,14,16,18,20}
<i>Baseline creatinine level</i> (1/10) ¹²
<i>Creatinine level 48 hours after diagnosis of SBP</i> (1/1) ⁹
<i>Baseline BUN level</i> (3/6) ^{3,5,6}
<i>Shock</i> (2/6) ^{14,20}
<i>Acute physiology and Chronic Health Evaluation score</i> (1/1) ¹⁵
<i>Intensive care unit stay</i> (1/1) ¹⁰
<i>Bacteremia</i> (1/7) ¹⁵
<i>Serum white blood cell count 48 hours after diagnosis of SBP</i> (1/1) ⁹
Fever (0/4)
Serum polymorphonuclear cell count at 48 hours (0/1)
Systolic blood pressure (0/2)
Diastolic blood pressure (0/1)
Heart rate (0/1)
Mean arterial pressure before diagnosis of SBP (0/1)
Mean arterial pressure (0/1)
Creatinine level before diagnosis of SBP (0/1)
BUN level before diagnosis of SBP (0/1)
BUN level during admission for SBP (0/2)
Baseline white blood cell count (0/6)
Baseline PMN (0/6)

PMN 48 hours after diagnosis of SBP (0/1)

Percentage reduction rate of PMN (0/1)

Other cultures positive (0/1)

Hepatic insufficiency (15 variables)

Hepatic encephalopathy at presentation or during SBP episode (2/11)^{3,13}

Gastrointestinal hemorrhage at presentation or 1 week before SBP (1/6)¹⁴

MELD score (3/3)^{15,17,19}

Child-Pugh score (2/10)^{5,11}

Baseline albumin level (1/6)⁸

Baseline bilirubin level (1/12)⁶

Bilirubin level before diagnosis of SBP (0/1)

Albumin level before diagnosis of SBP (0/1)

Prothrombin time before diagnosis of SBP (0/1)

Baseline prothrombin time (0/7)

Previous history of hepatic encephalopathy (0/5)

Previous history of variceal hemorrhage (0/4)

Previous history of ascites (0/3)

Time since diagnosis of cirrhosis (0/3)

Time since first decompensation (0/1)

Ascitic fluid analysis (10 variables)

Culture-positive ascites (2/6)^{6,21}

Ascites white cell count (0/4)

Ascites polymorphonuclear cell count (0/10)

Ascites polymorphonuclear cell count, % (0/1)

Ascites protein (0/7)

Ascites tumor necrosis factor level (0/1)

Ascites interleukin-6 level (0/1)

B2 *E coli* isolate (0/2)

Pneumococcal etiology (0/1)

Virulence factor score (0/2)

Predisposition to SBP or SBP with drug-resistant organisms (8 variables)

Immunosuppressive factors (HIV, steroid use, cancer, diabetes) (3/6)^{11,13,18}

Hospital-acquired SBP (3/8)^{5,19,20}

Lack of SBP resolution (2/3)^{15,18}

Previous history of SBP (0/5)

Immunosuppressive therapy (0/1)

HIV stage (0/1)

CD4 count (0/1)

Antiretroviral therapy (0/1)

Antibiotic-associated factors (8 variables)

History of antibiotic use (0/7)

Receipt of inappropriate antibiotics (not active against the isolate) or no antibiotics (0/4)

Trimethoprim-sulfamethoxazole resistance (0/1)

Amoxicillin resistance (0/1)
 Amoxicillin-clavulanate resistance (0/1)
 Cefotaxime resistance (0/2)
 Ciprofloxacin resistance (0/3)
 Duration of antibiotic therapy (0/1)
 Other (28 variables)
Hepatocellular carcinoma (2/7)^{8,20}
Baseline aspartate aminotransferase level (2/6)^{5,12}
Baseline γ -glutamyltransferase (1/2)⁸
 Hepatocellular carcinoma single lesion (0/1)
 Okuda (0/1)
 α -fetoprotein level (0/1)
 Sodium level before diagnosis of SBP (0/1)
 Sodium level during SBP admission (0/1)
 Hemoglobin level (0/1)
 Platelet count (0/2)
 Baseline alanine aminotransferase level (0/3)
 Baseline potassium level (0/5)
 Baseline sodium level (0/9)
 Baseline triglyceride level (0/1)
 Cholesterol level (0/1)
 Urine sodium excretion (0/1)
 Plasma tumor necrosis factor level (0/1)
 Plasma interleukin-6 level (0/1)
 History of severe infection other than SBP (0/2)
 Cause of admission (0/1)
 Delay between admission and infection (0/1)
 Nutritional status (0/1)
 Service to which the patient was admitted (0/1)
 Baseline γ -globulin level (0/3)
 Private vs government hospital (0/1)
 Teaching vs community hospital (0/1)
 Disease complexity score (0/1)
 Albumin therapy (0/1)

NOTE. For each variable, the numbers in parentheses represent the number of studies in which the variable was among the top 5 significant variables over the number of studies in which it was tested. Significant variables are italicized, and their relevant study references are included.

HIV, human immunodeficiency virus; PMN, polymorphonuclear leukocyte.

Table 4

Variables That Were Most Commonly Found to Be Significant Predictors of Death in Spontaneous Bacterial Peritonitis in 18 Studies

Variable	No. of studies in which variable was among the first 5 significant variables	No. of studies evaluating the variable	% of studies in which variable was among first 5/total of studies
Renal dysfunction ^a	9	9	100
At baseline	4	4	
During SBP	3	3	
Timing unclear	2	2	
MELD score	3	3	100
Lack of SBP resolution	2	3	67
Immunosuppressive factors ^b	3	6	50
Hospital acquired	3	8	38

NOTE. Five variables were the most common.

HIV, human immunodeficiency virus.

^aDefinitions of renal dysfunction varied between trials (BUN >30 mg/dL or creatinine >1.5 mg/dL in those without pre-existing renal disease and an increase of >50% in those with pre-existing renal disease; BUN >25 mg/dL and/or creatinine of >1.35 mg/dL, serum creatinine increasing 3.0 mg/dL more than the baseline value; serum creatinine >1.5 mg/dL).

^bImmunosuppressive factors included HIV, steroid use, cancer, and diabetes.