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Mortality from spontaneous bacterial peritonitis among hospitalized patients in the United States

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Abstract

Background and Aim—Spontaneous bacterial peritonitis (SBP) is a serious complication of cirrhosis and is associated with significant morbidity and mortality. In this study, we examined the clinical characteristics and risk factors associated with mortality in hospitalized patients presenting with SBP.

Methods—The Nationwide Inpatient Sample (NIS) was queried for all hospitalizations involving SBP from 2006 to 2014 using the International Classification of Disease-9-CM Code. Logistic regression was performed to evaluate the association between SBP mortality and factors such as

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age, gender, race/ethnicity, and concomitant medical conditions at presentation (e.g., variceal hemorrhage, hepatic encephalopathy, acute renal failure, coagulopathy, and other infections including pneumonia). The lengths of stay (LOS) and total charges were also examined.

Results—From 2006 to 2014, there were 88,167 SBP hospitalizations with 29,963 deaths (17.6% in-hospital mortality). The mean age of patients who died in the hospital was older (58.2 years vs. 55.8, $p<0.01$) than those who survived the admission. Acute alcoholic hepatitis was noted among a higher proportion of patients who died (7.0% vs. 5.9%, $p<0.01$), who were also likely to have more medical comorbidities. In multivariable analysis, older age, female gender, hepatic encephalopathy, coagulopathy, variceal hemorrhage, sepsis, pneumonia, and acute kidney injury were associated with increased in-hospital mortality. This group also had longer LOS (11.6 days vs. 9.1, $p<0.01$) and higher total charges (\$138,273 vs. \$73,533, $p<0.01$).

Conclusion—SBP is associated with significant in-hospital mortality, especially in patients with concurrent risk factors. SBP remains a significant burden to the healthcare system.

Keywords

spontaneous bacterial peritonitis; in-hospital; mortality; risk factors; cirrhosis

Introduction

Spontaneous bacterial peritonitis (SBP) is an infection of the ascitic fluid without an identifiable, surgically treatable intra-abdominal source. SBP most commonly occurs as a complication of ascites from advanced cirrhosis (1). The diagnosis is made in the presence of an elevated absolute polymorphonuclear leukocyte count ≥ 250 cells/mm³ in the ascitic fluid (2). The prevalence of SBP in hospitalized patients with cirrhosis and ascites is estimated at 11-14% (3-5). Various cohort studies have examined in-hospital mortality associated with SBP through the last few decades. From 1984 to 1989, the Liver Unit at the University of Barcelona Hospital Clinic reported a 38% in-hospital mortality in 185 consecutive cirrhotic patients with SBP (6). In a study using the Maryland Health Services Cost Review database of all patients admitted to Maryland hospitals with SBP as a diagnosis from 1988 to 1998, the rate of in-hospital mortality was 32.6% (7). Whereas, from 1998 to 2007, in-hospital mortality associated with SBP using the National Inpatient Sample (NIS) appears to have lowered to 20.2% (8). In this study, we examine SBP-related in-hospital mortality using the NIS during the subsequent period from 2006 to 2014.

As a serious complication in cirrhosis, SBP can trigger a cascade of events in other organ systems; specifically, renal impairment in cirrhotic patients has been associated with worse prognosis (9). In a landmark study in 1999, Sort et al. showed the incidence of renal dysfunction in patients with SBP decreased from 33% to 10% with intravenous albumin infusion given together with antibiotic therapy versus antibiotic therapy alone, and the mortality decreased from 29% to 10% (10). Besides renal impairment, other risk factors have been identified including age, intensive care unit (ICU) stay, blood urea nitrogen level, and site of peritonitis acquisition (community or hospital) (6,7). Furthermore, early identification of SBP patients who are at risk for poor outcomes may provide the best opportunity for improving survival (11).

In the present study, we provide a more recent estimation of SBP-related in-hospital mortality in a United States cohort, and investigate the clinical characteristics and risk factors associated with the mortality.

Methods

Data source

The NIS is the largest database of hospital discharges in the United States, estimating a 20% stratified sample of non-federal, acute care hospitals participating in the Healthcare Cost and Utilization Project, excluding rehabilitation and long-term care facilities (12). Patient demographics, diagnoses, procedures, lengths of stay (LOS), expected payment source, and hospital characteristics (e.g. size, region, teaching status) are included in each discharge record. Using a previously validated algorithm, the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 567.23 was applied in the NIS from 2006-2014 to identify inpatient admissions for SBP (13). We selected this range of years to reduce potential misclassification bias associated with major changes in diagnostic coding for SBP in 2005 (i.e., introduction of the ICD-9-CM code 567.23 in October 2005) and 2015 (i.e., the transition to ICD-10-CM system in October 2015) (12,14). Box 1 lists all ICD-9-CM codes used in the present analysis. We chose the validated Deyo modification of the Charlson Index to represent medical comorbidities (15,16).

Outcome variables and statistical analysis

Data analysis was performed in accordance with the stratified and weighted sampling design of the NIS. The main outcomes in this analysis were in-hospital mortality, length of stay, and total charges. To compare patient characteristics by mortality outcome, we performed χ^2 tests for categorical variables and t tests for continuous variables. Multivariable logistic regression was performed to estimate the relative odds of in-hospital mortality given various exposures, after adjusting for age, gender, race/ethnicity, Charlson-Deyo Index score, and hospital size. Controlled covariates were chosen a priori for their potential to confound.

SAS release 9.3 (SAS Institute, Cary, NC) and Stata/MP version 15.1 (Stata Corp, College Station, Texas) were used for analyses. P-values less than 0.05 were considered statistically significant.

Ethical considerations

The study protocol was reviewed and approved by the Johns Hopkins Institutional Review Board (number NA_00086245). The NIS protects patient confidentiality by providing de-identified publicly available data.

Results

There were 170,430 admissions with SBP from 2006 to 2014, including 29,963 deaths (17.6% in-hospital mortality). While yearly admissions with SBP steadily rose from 2006 to 2014, the mortality rate generally decreased after 2008, with a peak at 18.9% in 2008 and nadir at 16.6% in 2011 (Figure 1). The mean age of hospitalized patients was 56.2 years, and

36.2% were females. The SBP diagnosis was frequently associated with increased medical comorbidities: over 70% of admitted patients had a Charlson-Deyo Index score of 3 or higher.

Patient characteristics were analyzed for comparisons between the group that died and those who survived (Table 1). The mean age of patients who died in the hospital was older (58.2 years vs. 55.8, $p<0.01$) than those who survived the admission. In contrast to the group that died, the group that survived consisted of fewer White patients (62.5% vs. 64.5%) and more Hispanic patients (18.8% vs. 15.6%) (overall $p<0.01$). There was no difference in payer sources between the two groups ($p=0.10$). The majority of patients, both those who survived (65.8%) and those who died (68.4%), were admitted to large size hospitals ($p<0.01$).

Baseline liver diseases were analyzed according to mortality outcome (Table 2). A significantly higher proportion of patients with SBP who died had a diagnosis of acute alcoholic hepatitis (7.0% vs. 5.9%, $p<0.01$). Conversely, smaller proportions of patients with SBP who died had hepatitis C (26.0% vs. 31.7%, $p<0.01$), NAFLD (2.2% vs. 3.3%, $p<0.01$), or alpha-1 antitrypsin deficiency (0.2% vs. 0.4%, $p<0.01$).

A significantly higher proportion of patients who died (85.6% vs. 77.1%, $p<0.01$) had a score of 3 or more on the Charlson-Deyo Index (Table 3). In addition, the proportions of comorbidities were overall higher in those who died compared to those who survived, including hepatic encephalopathy (34.5% vs. 21.5%, $p<0.01$), coagulopathy (28.3% vs. 17.5%, $p<0.01$), variceal hemorrhage (1.2% vs. 0.6%, $p<0.01$), sepsis (68.4% vs. 22.6%, $p<0.01$), pneumonia (19.5% vs. 7.5%, $p<0.01$), urinary tract infection (UTI) (15.5% vs. 12.1%, $p<0.01$), acute kidney injury (72.4% vs. 35.3, $p<0.01$), and human immunodeficiency virus (HIV) (1.8% vs. 1.2%, $p<0.01$). The exception was diabetes mellitus, which was identified in a smaller proportion of patients who died (16.4% vs. 24.5%, $p<0.01$).

In multivariable logistic regression analysis (Table 4), the risk factors for in-hospital mortality in those diagnosed with SBP included age (odds ratio [OR] 1.01, 95% confidence interval [CI] 1.01-1.02), female gender (OR 1.08, 95% CI 1.01-1.16), hepatic encephalopathy (OR 1.34, 95% CI 1.24-1.45), coagulopathy (OR 1.33, 95% CI 1.22-1.44), variceal hemorrhage (OR 1.90, 95% CI 1.38-2.63), sepsis (OR 5.53, 95% CI 5.14-5.94), pneumonia (OR 1.73, 95% CI 1.57-1.91), and acute renal injury (OR 3.07, 95% CI 2.85-3.30). Diabetes mellitus again was a notable exception (OR 0.60, 95% CI 0.55-0.66). Statistically significant associations during univariable analysis between in-hospital mortality in SBP and race/ethnicity and HIV infection disappeared after the adjustment of potential confounders.

Inpatient mortality is associated with higher healthcare resource utilization. Those who died had significantly longer LOS (11.6 days vs. 9.1, $p<0.01$) and accrued significantly higher total hospital charges (\$138,273 vs. \$73,533, $p<0.01$).

Discussion

In our study, the overall in-hospital mortality was 17.6% for patients with SBP in the United States from 2006 to 2014. This rate is lower than reported by several previous cohort studies in the United States and abroad examining in-hospital mortality of patients with SBP from 1984 to 1989 (38%), 1988 to 1998 (32.6%), and 1998 to 2007 (20.2%) (6–8). The decreasing mortality over the past decades may be attributable to earlier identification of disease and better care. In fact, an improved awareness of SBP and its recommended diagnostic guidelines may help explain the rising annual admissions with SBP in the present study cohort even with the generally declining trend of in-hospital mortality since 2008 (Figure 1).

Better management of ascites stems from a few pivotal studies. Two doses of intravenous albumin given two days apart, along with antibiotics, reduced absolute 3-month mortality by 19% and led to decreased renal impairment (10). Patients with prior SBP should receive long-term prophylaxis with antibiotics to prevent recurrence, as the rate of recurrence is 70% in the first year (17,18). Low protein ascites predisposes to the development of SBP (19), and primary prophylaxis with antibiotics has been shown to prevent SBP and improve short term survival (20–22). Cirrhotic patients admitted with gastrointestinal bleeding also benefit from short-term antibiotic prophylaxis that is cost-effective (23,24).

SBP has been implicated as an infectious trigger of events that impairs the function of several other organ systems (25,26). Renal failure may be a major factor that predicts mortality. Our multivariable analysis shows a significant association between AKI and in-hospital mortality. In fact, 70.3% of all patients who died with SBP had AKI as a diagnosis compared with only 33.2% of patients who survived. Similarly, another study found the mortality of patients with renal failure and SBP was 50% compared to 6% without renal failure (9). Hepatorenal syndrome, sepsis, and renal failure have been used in several predictive models for mortality in SBP (27–29).

Furthermore, our study showed infectious events such as pneumonia and sepsis are significant risk factors for mortality in SBP. Particularly, sepsis was noted in 65.4% of those who died and showed significant association with in-hospital mortality. The infectious agent in SBP is commonly a single bacterial organism that is thought to translocate across the intestinal mucosa into the lymphatic and hematologic systems before inoculating the peritoneal fluid (30). Recently, a change in the epidemiology of SBP has been characterized by an increase of multi-drug resistant (MDR) bacteria (31,32). The risk factors for SBP from MDR organisms include nosocomial acquisition, hospital acquisition, and long term SBP prophylaxis with fluoroquinolones (33). Unsurprisingly, ascitic fluid culture positivity for MDR bacteria has been shown to be an independent risk factor of 30-day mortality in a recent study (34).

The importance of a diagnostic paracentesis cannot be overstated. A recent study found septic shock from SBP leads to mortality of greater than 80%, and each hour of delay in appropriate antimicrobial therapy is associated with a 1.86 times increased hospital mortality (35). Kim et al. concluded that hospitalized patients with SBP who received a diagnostic

paracentesis >12 hours after admission had a 2.7-fold increased risk of mortality adjusting for Model for End-Stage Liver Disease (MELD) score and renal dysfunction (11). Due to duty hours and residency structures, there has been a shift in referrals from primary teams to radiology or hospital procedure teams for many bedside procedures. A study examining academic medical centers found an average of 3.2-hour delay in procedure completion for those done in radiology instead of at the bedside (36). We believe the ability to perform a bedside diagnostic paracentesis is an important skill in internal medicine that improves patient care.

Notably, our study found a higher proportion of patients with SBP who survived to be diagnosed with diabetes mellitus. Diabetes was also significantly associated with lower in-hospital mortality on multivariable regression analysis. The mechanism for this association is unknown, but we offer two hypotheses. First, gut dysbiosis is increasingly recognized in certain chronic conditions including diabetes, chronic liver disease, and complications of cirrhosis including SBP (37–39); however, the expected patterns of microbiota alteration and their clinical implications remain poorly characterized. It is perhaps possible – though admittedly a conjecture at this point – that gut microbiota changes specific to diabetes can somehow attenuate the severity of SBP episodes. A second possible explanation for the finding is related to ICD-9-CM diagnosis coding practices. Medical providers generally are encouraged to code all applicable clinical conditions, but due to time constraints may often provide only the most active, pressing diagnoses (40). As shown in our analysis, patients with SBP who died are more likely to suffer other concomitant acute conditions, such as sepsis or AKI. Preexisting chronic conditions like diabetes may be less likely to be captured by administrative coding in this sicker cohort, leading to an artifactual “protective” inference. Further studies using microbiota sequencing or more granular clinical data will help to better assess this correlation.

Our results concur with those of Thuluvath et al. from 2001 in that older age was associated with in-hospital death while race was not a significant risk factor in SBP mortality (7). However, in contrast to Thuluvath et al., we also found an increased length of stay for patients with SBP who died compared to those who survived, perhaps due to the level of intensive care that can be provided in more recent years. The costs of care in both studies were markedly increased for those who died compared to those who survived. This suggests aggressive management in SBP and increased use of resources in those who were sicker.

Several large population-based studies on this topic have been published from other countries. One study from Spain reported 16.9% in-hospital mortality associated with SBP via data from the Catalan Health Service registry using ICD-9-CM codes from 2003 to 2010 (41). The Spanish study was similar to ours in included time period, analytical methodology, and reported mortality. Another study from Taiwan, using the National Health Insurance Database, examined the nationwide mortality of cirrhotic patients with SBP in 2004 (42). The authors found a 30-day mortality of 24.2%. Variations in mortality from SBP in different parts of the world may be in part due to local practices and guidelines.

There are limitations to our study, namely those inherent to the use of administrative data. First, the accuracy of ICD-9-CM codes can be susceptible to variations in coding practices.

The code for SBP used in this study was validated with a positive predictive value of 90% in a Veterans Administration-based cohort (13). Given the NIS does not provide personally identifiable information or individual medical records, further confirmation of the ICD-9-CM code in this database is not possible. Second, the NIS does not contain information on MELD or Child-Pugh scores, nor does it capture laboratory results either individually or in aggregate format to allow the calculation of these classic prognostic scores of cirrhosis for our analysis. On the other hand, the NIS provides a robust sample size. It circumvents inherent biases of single-centered studies by encompassing hospitals across the country, thereby including patients of varying ethnicities, insurers, and socioeconomic background.

In summary, SBP is associated with a considerable – albeit gradually improving – in-hospital mortality rate, for which infections and renal injury are the most significant risk factors. It remains a burden on the healthcare system, particularly with increased resource utilization among succumbed patients.

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Box 1**Diagnoses and associated International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes**

Diagnosis	Associated ICD-9-CM codes
SBP	567.23
Hepatitis B virus	070.2x, 070.3x
Hepatitis C virus	070.41, 070.44, 070.51, 070.54, 070.7x
Acute alcoholic hepatitis	571.1
Chronic ALD	571.2, 571.3
NAFLD	571.8
Autoimmune hepatitis	571.42
Hemochromatosis	275.0x
Wilson's disease	275.1
AAT deficiency	273.4
Hepatic encephalopathy	572.2
Coagulopathy	286.7, 286.9
Variceal bleeding	456.0
Sepsis	995.91, 995.92, 038.x
Pneumonia	480.x, 481, 482.x, 483.x, 484.x, 485, 486
Urinary tract infection	599.0
Acute kidney injury	584.x, 586, 593.9
HIV infection	042, V08, 795.3, 795.71
Diabetes mellitus	250.0, 250.1, 250.2, 250.3, 250.4, 250.5, 250.6, 250.7

SBP: Spontaneous bacterial peritonitis, ALD: Alcoholic liver disease, NAFLD: Non-alcoholic fatty liver disease, AAT: Alpha-1 antitrypsin, HIV: Human immunodeficiency virus

Figure 1. SBP admissions and mortality rate trend from 2006-2014

Table 1
Patient characteristics based on mortality outcome

	Survived (N = 140,467)	Died (N = 29,963)	p-value
Age (mean)	55.8	58.2	<0.01
Female gender (%)	36.1	36.4	0.66
Race/ethnicity (%)			<0.01
White	62.4	64.5	
Black	11.5	11.8	
Hispanic	18.8	15.6	
Other	7.3	8.1	
Insurance (%)			0.10
Medicare	37.1	38.2	
Medicaid	23.9	22.6	
Private/HMO	26.6	26.3	
Other	12.4	12.9	
Hospital size (%)			<0.01
Small	10.6	8.8	
Medium	23.6	22.8	
Large	65.8	68.4	

HMO: Health Maintenance Organization

Table 2
Baseline liver disease based on mortality outcome

	Survived (N = 140,467)	Died (N = 29,963)	p-value
Hepatitis B (%)	3.3	3.3	0.90
Hepatitis C (%)	31.7	26.0	<0.01
Acute alcoholic hepatitis (%)	5.9	7.0	<0.01
Chronic ALD (%)	38.9	38.7	0.73
NAFLD (%)	3.3	2.2	<0.01
Autoimmune hepatitis (%)	1.3	1.1	0.20
Hemochromatosis (%)	0.6	0.4	0.08
Wilson's disease (%)	0.0	0.0	0.46
AAT deficiency (%)	0.4	0.2	<0.01

ALD: Alcoholic liver disease, AAT: alpha-1 antitrypsin

Table 3
Patient co-morbidities based on mortality outcome

	Survived (N =140,467)	Died (N = 29,963)	p-value
Charlson-Deyo Index (%)			<0.01
0	3.5	3.0	
1 or 2	19.4	11.4	
3+	77.1	85.6	
Hepatic encephalopathy (%)	21.5	34.5	<0.01
Coagulopathy (%)	17.5	28.3	<0.01
Variceal hemorrhage (%)	0.6	1.2	<0.01
Sepsis (%)	22.6	68.4	<0.01
Pneumonia (%)	7.5	19.7	<0.01
Urinary tract infection (%)	12.1	15.5	<0.01
Acute kidney injury (%)	35.4	72.5	<0.01
HIV infection (%)	1.2	1.8	<0.01
Diabetes mellitus (%)	24.5	16.4	<0.01

HIV: Human immunodeficiency virus

Table 4
Multivariable adjusted odds ratio for in-hospital mortality*

	Odds Ratio (95% CI)	p-value
Age	1.01 (1.01-1.02)	<0.01
Female	1.08 (1.01-1.16)	0.03
Race/ethnicity		
Black	1.11 (0.99-1.23)	0.07
Hispanic	0.89 (0.80-0.99)	0.03
Others	1.11 (0.98-1.27)	0.11
Hepatic encephalopathy	1.34 (1.24-1.45)	<0.01
Coagulopathy	1.33 (1.22-1.44)	<0.01
Variceal hemorrhage	1.90 (1.38-2.63)	<0.01
Sepsis	5.53 (5.14-5.94)	<0.01
Pneumonia	1.73 (1.57-1.91)	<0.01
Urinary tract infection	0.90 (0.82-1.00)	0.04
Acute kidney injury	3.07 (2.85-3.30)	<0.01
HIV infection	1.12 (0.84-1.50)	0.43
Diabetes mellitus	0.60 (0.55-0.66)	<0.01

HIV: Human immunodeficiency virus

* Additionally adjusted for Charlson-Deyo score and hospital size