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ORIGINAL ARTICLE

Survival benefit associated with early detection of spontaneous bacterial peritonitis in veteran inpatients with cirrhotic ascites

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Introduction

Spontaneous bacterial peritonitis (SBP) is a significant source of morbidity and mortality in hospitalized patients with cirrhosis and ascites.¹ While studies have shown a low SBP prevalence (3.5%) for asymptomatic cirrhotics in the outpatient setting, this number rises to 11–29% for those admitted to the hospital for any reason.² In acknowledgement of the subtle, often-insidious course that characterizes early stages of SBP, current practice guidelines recommend diagnostic paracentesis in all patients with ascites admitted for management of complications of cirrhosis.^{3–5}

Nonetheless, the potential to improve clinical outcomes through early paracentesis has not been fully explored. A recent retrospective study of a large national database concluded that patients with paracentesis performed on the day of admission or

Abstract

Background: Spontaneous bacterial peritonitis (SBP) is common in hospitalized cirrhotic patients with ascites and carries high mortality. This study aimed to determine whether early diagnostic paracentesis (EDP) <12 h of hospitalization conveys an intermediate-term (6-month) survival benefit in cirrhotic patients diagnosed with SBP.

Methods: Consecutive US veterans with cirrhosis diagnosed with SBP over 13 years at a single VA medical center were reviewed retrospectively. Kaplan-Meier analyses assessed the effects of EDP on survival.

Results: A total of 79 cirrhotic patients were diagnosed with SBP (61.8 ± 8.8 years, *n* = 77 male, *n* = 52 [66.8%] Caucasian, *n* = 23 [29.1%] African-American). Underlying liver diseases included hepatitis c viral infection (HCV) (17.5%), alcohol (28.6%), alcohol and HCV (30.1%), and cryptogenic/metabolic (15.9%). Median baseline model for end-stage liver disease (MELD) was 12 (range 6–34), and median MELD at presentation was 18. Seven subjects had a history of hepatocellular carcinoma (11.1%), and 26 (41.3%) presented with sepsis. Thirty-three (52.4%) subjects died within 6 months after the SBP admission. Of the subjects, 41 (65.1%) underwent EDP, of which 23 (56.0%) survived at least 6 months, compared to only 7 of the 22 patients (31.8%) undergoing paracentesis >12 h from presentation (*P* = 0.057). The maximal benefit of EDP on survival was observed beyond days 14 and 30; at these time points, no statistical difference in mortality was discernable (*P* = 0.55 and 0.71). In a multivariate model including age, MELD at admission, hepatocellular cancer, and sepsis criteria, EDP (*p* 0.034) positively impacted patient survival at 6 months.

Conclusions: EDP is associated with improved 6-month mortality in cirrhotic patients with ascites. In this veteran cohort, EDP was as important as MELD as a predictor of intermediate-term survival.

the following day were observed to have a lower mortality rate (5.5 vs 7.4%, odds ratio [OR] 1.11, 95% confidence interval [CI] = 0.96–1.28) compared to those who underwent paracentesis later in the course of their stay.⁶ Another retrospective study from two tertiary care centers demonstrated higher rates of in-house mortality (adjusted OR 2.7, 95% CI = 1.3–4.8) among patients receiving delayed paracentesis, defined as later than 12 h from presentation.⁷ This, along with model for end-stage liver disease (MELD) scores, has been shown to be a significant predictor of mortality in hospitalized patients.^{8,9}

Like many medical centers, our facility does not have a protocol in place to perform paracentesis in patients admitted with cirrhosis and ascites. This retrospective analysis was thus performed to determine whether the timing of paracentesis is

associated with increased morbidity and mortality in patients admitted with cirrhosis-related complications.

Methods

Study subjects. A retrospective cohort study of consecutive US veterans, ages 20–80 years, with cirrhosis and a diagnosis of SBP during hospitalization over a 13-year period (1 July 2005 to 1 July 2018) was performed at this single VA Medical Center. Inclusion criteria were: (i) diagnosis of cirrhosis by ICD-9 and ICD-10 codes or index history and physical exam (H&P) note, with ascites noted on index H&P exam; (ii) SBP based on peritoneal fluid analysis (ascitic fluid absolute neutrophil count [ANC] of ≥ 250 cells per mm^3)^{3,10}; and (iii) admission for cirrhosis-related complications (bleed, encephalopathy, worsening ascites, liver mass, or portal vein thrombosis)¹¹ or nonspecific symptoms, including fever, tachycardia, leukocytosis, and hypotension. Exclusion criteria included: (i) admission for a noncirrhosis-related etiology (e.g. scheduled admission for elective surgical procedures); (ii) documentation of a bedside ultrasound without appreciable ascites to attempt for drainage; and (iii) emergent surgery or patient demise precluding attempt at paracentesis within the first day of presentation.

Medical records were reviewed to determine baseline characteristics, including age, gender, race/ethnicity, body mass index (BMI), etiology of chronic liver disease (including alcohol, viral Hepatitis B/C, or other metabolic, genetic, autoimmune causes), use of SBP prophylaxis before hospitalization, and other complications of cirrhosis at presentation (hepatocellular carcinoma [HCC], renal dysfunction, etc.). Clinical diagnosis of “sepsis” as listed in the medical record or Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score of ≥ 2 were documented.¹² MELD scores at the time of admission were calculated. Time from admission to paracentesis was recorded, as was administration of albumin and antibiotics. Early diagnostic paracentesis (EDP) was defined as the performance of the paracentesis within 12 h of presentation; those undergoing paracentesis >12 h postadmission were categorized in the late diagnostic paracentesis (LDP) group. Data on patient mortality were collected up to 6 months beyond the index hospital admission.

Statistical analysis. Grouped values are reported as mean \pm standard deviation unless otherwise indicated. Between-group comparisons were performed using Student’s *t*-tests, and chi-square analyses were performed for binomial data. Nonparametric testing using independent sample median tests were performed to assess between-group differences in central tendency for variables with non-Gaussian distribution.

Six-month survival following SBP admission was implemented, and Kaplan-Meier analyses assessed the effects of EDP (≤ 12 h from presentation) on survival, with generation of survival plots. Logistic regression models were used to control for potentially relevant clinical and demographic factors. Patient factors identified as significant in univariate analysis were implemented in a final multivariate Cox proportional hazards model. In each case, $P < 0.05$ was required for statistical significance.

Results

Demographics and baseline clinical characteristics. A total of 79 cirrhotic patients (61.8 ± 8.8 years, $n = 77$ male, $n = 52$ [66.8%] Caucasian, $n = 23$ [29.1%] African-American) had documentation of SBP following admission to the Saint Louis Veterans Administration Medical Center (STLVAMC) during the study period. Of these patients, 16 were excluded from further analysis due to the performance of a diagnostic paracentesis prior to presentation. Of the remaining 63 cirrhotic patients, 32 (65.1%) underwent an early diagnostic paracentesis. The demographic features and baseline clinical characteristics of these patients are reported in Table 1. Those who underwent EDP were younger ($P = 0.039$) and trended toward having lower rates of chronic kidney disease ($P = 0.055$). There were no significant differences in baseline MELD, the etiology underlying chronic liver disease, malignancy diagnoses, or medication regimens between the EDP and LDP groups.

Presenting clinical characteristics. The median time to paracentesis was 5 h in the EDP group, compared to 42 h in the LDP cohort (Table 2). There were no significant differences in presenting MELD in the EDP and LDP subgroups (17.2 vs 18.6, $P = 0.47$), although a higher percentage of the LDP group (45.5

Table 1 Baseline patient demographics and clinical characteristics

	Early diagnostic paracentesis ($n = 41$)	Late diagnostic paracentesis ($n = 22$)	<i>P</i> value
Age, years (mean \pm SD)	60.3 \pm 7.0	65.9 \pm 11.1	0.039
Male, n (%)	39 (95.1)	22 (100)	0.29
Race, n (%)			
Caucasian	26 (63.4)	16 (72.7)	
African-American	12 (29.3)	6 (27.3)	0.40
Other	3 (7.3)	0 (0)	
Body mass index, kg/m^2 (mean \pm SD)	29.6 \pm 6.9	28.6 \pm 7.7	0.63
Cirrhosis etiology, n (%)			
Hepatitis C	8 (19.5)	3 (13.6)	
Alcohol	13 (31.7)	5 (22.7)	
Hepatitis C and alcohol	13 (31.7)	6 (27.3)	0.34
Cryptogenic	4 (9.8)	6 (27.3)	
Non-alcoholic steatohepatitis	3 (7.3)	1 (4.5)	
Hepatitis B	0 (0)	1 (4.5)	
Medical comorbidities, n (%)			
Any malignancy	8 (19.5)	4 (18.2)	0.89
Hepatocellular carcinoma	4 (9.8)	3 (13.6)	0.69
Chronic kidney disease	3 (7.3)	6 (27.3)	0.055
Baseline serum creatinine, mg/dL (mean \pm SD)	0.93 \pm 0.43	1.22 \pm 0.64	0.07
Baseline MELD score (mean \pm SD)	17.2 \pm 6.6	18.5 \pm 7.0	0.48
Medication regimen, n (%)			
Diuretics	30 (73.2)	13 (59.1)	0.25
Prophylactic antibiotics	6 (14.6)	1 (4.5)	0.41
Proton pump inhibitor	18 (43.9)	6 (27.3)	0.20

MELD, model for end-stage liver disease; SD, standard deviation.

Table 2 Presenting patient clinical characteristics and outcomes

	Early diagnostic paracentesis (n = 41)	Late diagnostic paracentesis (n = 22)	P value
Time to paracentesis, hours, median (range)	5 (0–12)	42 (13–192)	<0.001
Admission laboratories			
Serum creatinine (Scr), mg/dL (mean ± SD)	1.37 ± 1.15	1.84 ± 1.27	0.15
Acute kidney injury, [†] n (%)	7 (17.1)	10 (45.5)	0.02
MELD score (mean ± SD)	17.2 ± 6.6	18.6 ± 7.0	0.47
Leukocyte count, cells/mL (mean ± SD)	11.0 ± 7.9	10.4 ± 5.6	0.75
Serum sodium, mEq/L (mean ± SD)	132.0 ± 6.1	133.8 ± 4.9	0.23
Sepsis, [‡] n (%)	18 (43.9)	8 (36.4)	0.69
Medications provided at admission, n (%)			
Albumin	32 (78.0)	14 (63.6)	0.22
Diuretics	30 (69.8)	13 (30.2)	0.25
Death, 6 months, n (%)	18 (43.9)	15 (68.2)	0.057
Median time to death, days (range)	46 (3–175)	11 (1–131)	0.079

[†]Acute kidney injury defined as an increase in serum creatinine of ≥ 0.5 over baseline.

[‡]Sepsis defined as a documented clinical diagnosis of “sepsis” or a Sequential (Sepsis-related) Organ Failure Assessment score of ≥ 2 .

MELD, model for end-stage liver disease; SD, standard deviation.

vs 17.1%, $P = 0.02$) presented with acute kidney injury. Furthermore, there were no significant differences in leukocyte count, clinical evidence of sepsis, or medication regimens administered (antibiotics, albumin, and diuretics) between the paracentesis subgroups.

Outcomes. Overall, 33 (52.4%) of the study patients died within 6 months of the index SBP admission. Fewer patients undergoing EDP died during follow up (18/41, 43.9%) compared to the LDP group (15/22, 68.2%; $P = 0.057$). The median time to death was also considerably lower in the EDP group (46 vs 11 days, $P = 0.079$). The survival plot of the EDP and LDP groups is displayed in Figure 1. The survival benefit of EDP was discernible shortly after admission, with 14-day mortality rates in patients who underwent LDP, more than twice as high as the EDP group (6/22, 27.3% vs 5/41, 12.2%, $P = 0.13$).

Predictors of patient survival. A multivariate Cox Proportional Hazard model examining 6-month mortality by timing of paracentesis was generated (Table 3). Controlling for age, race, and significant medical comorbidities (malignancy, sepsis evidence, and acute kidney injury) and use of prophylactic antibiotics, patients who underwent EDP had a nearly 60% reduction in 6-month mortality compared to their LDP counterparts (Exp (B) 0.42, 95% CI 0.188–0.938, $P = 0.034$).

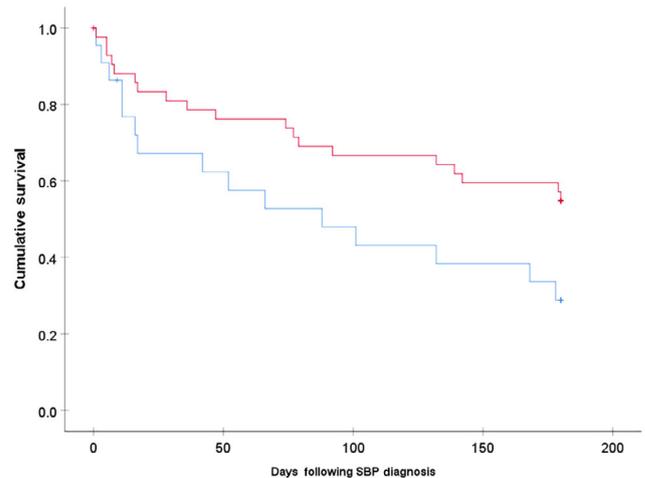


Figure 1 Survival plot of the early diagnostic paracentesis (EDP) and late diagnostic paracentesis (LDP) groups. SBP, spontaneous bacterial peritonitis. (—) LDP, (—) EDP, (+) LDP-censored, (+) EDP-censored.

Discussion

In this study of a single Veterans Affairs Hospital experience of consecutive cirrhotic patients hospitalized with an eventual diagnosis of SBP, we found a statistically significant survival benefit in those patients who underwent early diagnostic paracentesis. This improvement in mortality rate was borne out as far as 6 months beyond the time of presentation, and it held true after controlling for multiple clinical and demographic factors.

This study is consistent with previously performed studies showing the importance of the diagnostic paracentesis in any patient who is hospitalized with decompensated cirrhosis and a tangible amount of ascites. Our findings also are consistent with prior studies showing that earlier paracentesis trends toward a benefit in mortality. Orman and colleagues noted, in a large 2016 study of 17 500 cirrhotic patients, that delays in the performance of paracentesis (>1 day or 24 h) after admission resulted in a higher in-hospital mortality, although this observation did not remain significant in a multivariate analysis.¹³ Similarly, in a 2016 study by Gaetano *et al.*, there was a trend toward reduction in inpatient mortality among cirrhotic patients undergoing earlier paracentesis.⁶ Another study of nosocomial SBP observed that mortality impact was sustained through 90 days, even after the initial SBP episode had resolved.¹⁴ Our study additionally suggests that the mortality benefit of EDP may extend up to 6 months beyond the index SBP diagnosis.

Our study is bolstered by the robust nature of the VA Corporate Data Warehouse database, allowing for thorough and standardized collection of clinical and demographic data, as well as a full, time-sensitive account of diagnostic testing, administered therapies, and outcomes.¹⁵ From a demographic perspective, the racially diverse makeup of the examined VA center resulted in a strong African American representation in this study. Limitations of the study include its selection bias toward males, alcoholics, and those with hepatitis C—a quality inherent to all VA-based population studies on cirrhosis.¹⁶ Furthermore, this study was

Table 3 Cox proportional hazard model predicting patient mortality within 6 months of diagnosed spontaneous bacterial peritonitis

	Exp (B)	95% CI	P value
Age, years	1.080	1.02–1.142	0.006
Race	0.723	0.317–1.652	0.442
Early diagnostic paracentesis (<12 h)	<i>0.420</i>	<i>0.188–0.938</i>	<i>0.034</i>
Antibiotic prophylaxis	3.332	1.123–9.823	0.030
Malignancy, any	1.715	0.654–4.498	0.273
Sepsis	4.872	1.976–12.012	0.001
Acute kidney injury	1.704	0.659–4.408	0.272

CI, confidence interval.

Primary independent variables are shown in italics.

retrospective, allowing for potential confounding factors in the care of patients with SBP.

The decision to implement 12 h as the cutoff time to define early *versus* late paracentesis reflects the standard set by previous studies on this topic. At the same time, this time window highlights the challenges inherent to the current rubric of decompensated cirrhosis management in the inpatient setting. First, it necessitates a high index of suspicion in order for an early diagnosis of SBP may be made, particularly in patients who do not exhibit obvious vital sign instability to alert providers to the onset of sepsis. The timely diagnosis and management of SBP requires the recognition that a history of advanced liver disease with ascites alone is sufficient to mandate paracentesis. It is clear that clinical impression alone is inadequate to rule out a diagnosis of SBP.¹⁷ Secondly, as many of these patients are admitted through the emergency department and indeed may spend the majority of their initial 12 h following hospital presentation receiving triage care in this setting, the effectiveness of this EDP approach will require awareness and engagement of emergency department physicians. We believe this study provides a strong basis for prospective evaluation of protocolized early paracentesis strategies that could further establish the value of early (or immediate) paracentesis as a standard of care for the hospitalized cirrhotic patient with ascites.

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