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Hepatic Encephalopathy in Cirrhotic Patients With Bacterial Infections: Frequency, Clinical Characteristics, and Prognostic Relevance

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Background: **/Objectives: Bacterial infections (BIs) are well-recognized precipitants of hepatic encephalopathy (HE). Nevertheless, there is a paucity of data in patients with HE associated with BI. Our aim was to describe clinical characteristics, recurrence, and prognosis of HE in patients with BI.** ***Methods:*** **A prospective study with inclusion of hospitalized cirrhotic patients with BI, followed until discharge, death, or liver transplantation.** ***Results:*** **172 patients (age 57 ± 13, model of end-stage liver disease [MELD]-sodium 22 ± 8) were included. Infections were more commonly due to spontaneous bacterial peritonitis and cellulitis (22% and 23%), non-nosocomial (70%), and associated with systemic inflammatory response syndrome and septic shock in 40% and 9%, respectively. HE was diagnosed in 66 patients (grade ≥2 in 58%). In multivariate analysis, MELD-sodium, albumin, and prior HE were associated with HE at diagnosis of BI. Recurrence of HE was diagnosed in 30 patients (median 13 [interquartile range 5–22] days), more commonly manifested as overt HE (90% vs. 60% at first episode, $P = 0.012$) and more frequently in patients with hyponatremia (54% vs. 27% for patients without, $P < 0.001$). In-hospital mortality was 34% and was more common for patients with HE (51% vs. 22%, $P < 0.001$), irrespective of grade, and for those with recurrence (63% vs. 42%, $P < 0.001$). In multivariate analysis, HE at diagnosis of infection and MELD-sodium were predictors of mortality.** ***Conclusions:*** **HE is frequent in cirrhotic patients with BI and is associated with severity of liver disease, but not with infection. These patients are at increased risk of short-term HE recurrence, especially those with hyponatremia. The presence and recurrence of HE, independent of severity, are associated with in-hospital mortality. (J Clin Exp Hepatol xxxx;xxx:xxx)**

Hepatic encephalopathy (HE) is a frequent complication of cirrhosis related to toxic effects of ammonia in astrocytes.[1] The development of HE is associated with a high burden for health systems and caregivers, frequent recurrence, and high morbidity and mortality.[2–5] Even though it may occur spontaneously, an acute episode of HE is frequently precipitated by one or more conditions, such as dehydration, diuretic overdosage, constipation, and/or bacterial infection (BI).[6] Prompt recognition and removal of precipitating factors has long been recognized as of paramount importance to effectively treat HE.[7] In contrast, there is very little data on the relationship between specific precipitating events and prognosis in patients with HE.

Patients with cirrhosis are at an increased risk of BI due to multiple alterations in gut microbiota and the innate and adaptative immune system.[8] The development of BI in cirrhosis leads to a huge production of proinflammatory cytokines and profound activation of endogenous vasoactive systems, which in turn exert their deleterious effects through hypoperfusion and direct organ injury.[9,10] Concerning HE specifically, infections may further worsen astrocyte dysfunction already caused by hyperammonemia through the direct effect of inflammatory mediators, as well by changes in cerebral micro vascularization and endothelial metabolism.[11]

BIs have been associated with the development of diverse complications of cirrhosis, of which the best studied thus far is acute kidney injury (AKI).[12,13] Recognition of

Keywords: cirrhosis, hepatic encephalopathy, bacterial infections, hyponatremia

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Abbreviations: ACLF: acute-on-chronic liver failure; AKI: acute kidney injury; AUROC: Area under the ROC curve; BCLC: Barcelona clinic for liver cancer; BI: bacterial infections; CA: community-acquired; CI: confidence interval; CLIF-C OF: CLIF Consortium Organ Failure; GOLD: Global Initiative For Chronic Obstructive Lung Disease; HE: hepatic encephalopathy; HCAI: healthcare-associated infection; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HR: hazard ratio; INR: international normalized ratio; IQR: interquartile range; MELD: model of end-stage liver disease; NaCl: sodium chloride; NASH: non-alcoholic steatohepatitis; NYHA: New York Heart Association; OR: odds-ratio; PMN: polymorphonuclear; ROC: receiver operating characteristic; SAD: sepsis-associated *delirium*; SBP: spontaneous bacterial peritonitis; SIRS: systemic inflammatory response syndrome; SSTI: skin and soft-tissue infection; UTI: urinary tract infection; WBC: white blood cell

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poor prognosis associated with this complication was of fundamental importance, as it led to further studies proving that prophylactic administration of albumin for patients with spontaneous bacterial peritonitis (SBP) reduces the frequency of AKI and mortality.[14]

In contrast to the large amount of data concerning AKI in patients with BI, there is a paucity of data with respect to HE in these patients. The objectives of the current study were to assess the frequency and clinical characteristics of HE in cirrhotic patients with BI, evaluate the frequency and predictive factors of HE recurrence and determine prognosis of patients with BI-associated HE in comparison to patients with infections without HE.

METHODS

Study Group

Patients with cirrhosis and BIs hospitalized at the Gastroenterology and Hepatology Unit of Bonsucesso General Hospital between October 2011 and July 2014 were consecutively included in a prospective observational study aimed at evaluating the clinical characteristics and prognosis of patients admitted for treatment of complications of cirrhosis. Patients were included if they had (1) a diagnosis of cirrhosis; (2) a diagnosis of BI at admission or during hospitalization, and (3) were aged ≥18 years. Exclusion criteria were the following: (1) advanced hepatocellular carcinoma (Barcelona clinic for liver cancer stage C or D); (2) HIV infection; (3) previous solid organ transplantation, (4) extrahepatic malignancy, (5) advanced cardiac (New York Heart Association class ≥2) or respiratory (Global Initiative For Chronic Obstructive Lung Disease score ≥2) failure.

Study Design

At diagnosis of infection, demographic and clinical data, liver, kidney, and circulatory function, as well as parameters of systemic inflammation were recorded. The development of complications of cirrhosis throughout hospitalization was registered. Patients were followed until discharge, liver transplantation, or death. The main study objective was to determine the frequency of HE in patients with cirrhosis and BI. Secondary objectives were to determine the recurrence rate and in-hospital survival in patients with HE at diagnosis of infection. The study was approved by the local ethics committee (registration number 01112912.5.0000.5253) and written informed consent was given by patients or a legal surrogate before inclusion.

Management of Patients

All patients with decompensations of cirrhosis and BIs were examined using the following criteria: (i) medical history and physical examination with an emphasis on the symptoms and signs of specific infectious site; (ii) measurement of blood pressure, body temperature, heart, and respiratory rate; (iii) laboratory tests including complete blood count, C-reactive protein, liver and kidney function parameters, and urine sediment; (iv) diagnostic paracentesis in patients with ascites with sample analysis for polymorphonuclear cell count, protein and albumin concentration and culture; (v) chest X-ray; (vi) culture of blood, urine, and other biological fluids (e.g. sputum, pleural fluid) when clinically indicated. Patients with proved or suspected community-acquired (CA) or healthcare-associated infections (HCAI) were started on treatment as follows: (1) *spontaneous bacterial peritonitis*: ceftriaxone; (2) *pneumonia*: ceftriaxone plus azithromycin; (3) *urinary tract infection*: ciprofloxacin; (4) *skin and soft-tissue infection*: amoxicillin-clavulanic acid; (5) *undetermined source*: ceftriaxone. Nosocomial infections were initially treated with piperacillin-tazobactam ± teicoplanin. Other types of infection were diagnosed and treated according to usual definitions. Diagnosis and treatment of complications of cirrhosis were carried out in accordance with current guidelines at the time of the study. Specifically, patients with HE had diuretics withdrawn and received saline infusions (NaCl 0.9% 1000–1500 ml/day) in case of dehydration. Lactulose (10–20 ml tid) was started orally or via nasogastric tube in order to obtain 2-3 bowel movements per day, associated or not with non-absorbable antibiotics (metronidazole or neomycin). Patients also received enemas in case of fecal retention. Central nervous suppressants/stimulants (like benzodiazepines) were not allowed. Albumin was only administered to patients with SBP or after large volume paracentesis.

Definitions of BIs and Complications of Cirrhosis

Diagnostic criteria of BIs were as follows: (i) SBP: polymorphonuclear cell count in ascitic fluid >250/mm^3; (ii) pneumonia: presence of pulmonary infiltrate or consolidation on chest X-ray together with 2 or more of the following: fever, productive cough, dyspnea, pleuritic pain, signs of pulmonary consolidation on physical examination; (iii) urinary tract infection: abnormal urine sediment (>10 leukocytes/field, positive leucocyte esterase) together or not with positive culture, associated with 2 or more of the following: dysuria, urinary urgency, frequency, suprapubic tenderness; (iv) skin and soft-tissue infection: presence of signs of inflammation like swelling, erythema, heat, and tenderness in the skin; (v) undetermined source: presence of fever (≥37.8 °C) and leukocytosis (white blood cell count >12.0 × 10^9/L or a 50% increase from baseline with final value >8.0 × 10^9/L) without any identifiable source.

Systemic Inflammatory Response Syndrome: diagnosis of systemic inflammatory response syndrome (SIRS) was established if any 2 of the following criteria were fulfilled

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Table 1 Baseline Characteristics of the 172 Patients.

Age (years)	57 ± 13
Male gender	100 (58%)
Etiology of cirrhosis	
Hepatitis C	53 (31%)
Alcohol	43 (25%)
HCV + Alcohol	20 (12%)
Cryptogenic/NASH	24 (14%)
Other	32 (19%)
Previous decompensations of cirrhosis	
Ascites	115 (67%)
Hepatic encephalopathy	47 (27%)
Esophageal variceal bleeding	42 (24%)
Any previous decompensation	38 (22%)
Complications of cirrhosis at admission	
Ascites	126 (73%)
Hepatic encephalopathy	66 (38%)
Grade at diagnosis (1/2/3/4)	28 (42%)/22 (33%)/13 (20%)/3 (5%)
Gastrointestinal bleeding	9 (5%)
Hyponatremia	35 (20%)
Characteristics of Infectious episode	
Type of bacterial infection	
Spontaneous bacterial peritonitis	37 (22%)
Pneumonia	27 (16%)
Urinary tract infection	25 (15%)
Skin and soft tissue	40 (23%)
Undetermined	24 (14%)
Other	19 (10%)
Origin of infection	
Community-acquired	56 (33%)
Health care associated	63 (37%)
Nosocomial	53 (30%)
SIRS	69 (40%)
Septic shock	16 (9%)
Clinical and laboratorial data	
Mean Arterial Pressure (mmHg)	86 ± 15
Heart rate (bpm)	79 ± 14
Bilirubin (mg/dL)	4.5 ± 6.2
Albumin (g/L)	24 ± 6
International normalized ratio	1.7 ± 1.3
Creatinine (mg/dL)	1.6 ± 1.3
Sodium (mEq/L)	134 ± 6
Hemoglobin (g/dL)	10.7 ± 3.0
Platelet count (x 10^9/L)	148 ± 118
Leucocyte count (x 10^9/L)	8.4 ± 5.8
C-reactive protein (mg/dL)	5.4 ± 4.4
Child-Pugh score A/B/C-(%)	10/65/76 (7%/43%/50%)
MELD score	19 ± 8
MELD-Sodium score	22 ± 8
ACLF (grade I/II/III)	47 (29%) 29/13/5 (62%/28%/10%)

NASH, non-alcoholic steatohepatitis; HCV, hepatitis C virus; SIRS, systemic inflammatory response syndrome; MELD, model of end-stage liver disease; ACLF, acute-on-chronic liver failure.

in the first 48 h of infection: (i) body temperature >38 °C or <36 °C; (ii) heart rate >90 beats/minute; (iii) respiratory rate >20 breaths/minute; (iv) white blood cell count >12.0 or <4.0 × 10^9/L.

Septic shock: presence of SIRS and mean arterial pressure lower than 65 mmHg after adequate fluid expansion or need of vasopressor drugs.

Origin of infection: Infection was considered nosocomial if it developed more than 48 h after hospital admission. Infections diagnosed within 48 h of hospitalization in patients with recent contact with a healthcare system (attendance in emergency department, day-hospital for paracentesis or other scheduled procedure, hemodialysis clinic, or chemotherapy infusion unit in the last 30 days; hospitalization for >24 h or surgery in last 6 months) were classified as HCAI. Infections developing within 48 h after hospitalization in patients without recent contact with a healthcare system were classified as CA.

Cirrhosis was defined according to clinical, laboratory, histological, ultrasonographic, and endoscopic criteria.

Hepatic encephalopathy was defined and graded from 1 to 4 according to West Haven criteria. Patients with grade ≥2 were considered as overt and those with grade ≥3 as high-grade HE. Recurrence was defined as the reappearance of signs and/or symptoms of HE irrespective of original grade >48 h after resolution of the first bout of HE.

Hyponatremia was defined by a serum sodium concentration lower than 130 mEq/L.

Acute-on-chronic liver failure (ACLF) was defined and graded according to CLIF consortium organ failure score.

Statistical Analysis

Categorical variables were reported as frequencies and percentages and compared using the chi-square or McNemar test. Continuous variables were reported as means and standard deviations and compared using Student's t test or as median and interquartile range (IQR). Factors significantly associated with HE at diagnosis of BI and in-hospital mortality were selected for multivariate analysis. Binary logistic regression models using a stepwise backward elimination were used in order to identify independent predictors of the above-mentioned outcomes. For the recurrence of HE, factors associated with 28-day recurrence were selected in multivariate analysis using Cox-regression models

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(backward stepwise selection method). HE was selected for multivariate analysis models instead of variables in which HE is a component (like ACLF and Child-Pugh) to avoid collinearity whenever indicated. The same was done for the model for end-stage liver (MELD)-sodium score and its individual components. Survival curves were constructed using the Kaplan–Meier method and comparisons were performed using the log-rank test. The prognostic capability of variables independently associated with study outcomes were evaluated using receiver operating characteristic curves and the optimal threshold for prediction was identified using the point nearest to the upper left corner of the receiver operating characteristic curve. For the purposes of studying survival outcomes, transplanted patients were analyzed together with those who died during hospital stay. In all analyses, a significance threshold of $P < 0.05$ was considered. Statistical analyses were performed using the IBM SPSS 21 program for Windows.

RESULTS

Clinical and laboratory characteristics at the time of diagnosis of infection of the 172 patients are shown in Table 1. The study group was mainly composed of male patients with cirrhosis due to alcohol and/or hepatitis C, with previous decompensations of cirrhosis. Skin and soft-tissue and SBP were the most common type of infections, and there was a fairly equal distribution between CA, HCAI, and nosocomial in terms of infection origin. Comparison between patients with bacterial infections acquired before or after hospitalization is provided in Supplementary Table S1. SIRS was a common finding, but not septic shock, being diagnosed in 40% and 9% of patients, respectively. Liver and circulatory function were severely compromised. MELD-sodium was lower than 14 in 17% and higher than 18 in 61%, and half of patients were classified as Child-Pugh C. Among patients classified as Child-Pugh C, 25% had been receiving treatment for HE before hospitalization and 61% had previous episodes of HE. Organ failure was also common, with a frequency of ACLF of almost 30%. HE was diagnosed in 66 (38%) patients and was classified as overt and high-grade in 38 and 16 of them, respectively.

Table 2 shows the clinical and laboratory data in patients with and without HE at diagnosis of infection. Patients with HE were older, more commonly male and with cirrhosis of alcoholic etiology. As expected, HE was more frequent in patients with previous episodes of HE. These patients also had worse liver and circulatory function, as evidenced by values of albumin, MELD, and sodium. Among patients with grade 1 HE, the majority (73%) were classified as Child-Pugh C and 21% were receiving treatment for HE. Of interest, there was no association between HE and ascites or type and severity of infection. A comparable frequency of SIRS and septic shock was observed in both groups.

Table 2 Comparison Between Patients with and without EH.

	Yes (n = 66)	No (n = 106)	*P*
Age	59 ± 10	55 ± 14	0.051
Male gender	68%	51%	0.035
Alcoholic etiology	44%	34%	0.019
Previous decompensations			
Ascites	75%	62%	0.056
Hepatic encephalopathy	49%	14%	<0.001
Esophageal variceal bleeding	19%	29%	0.31
Complications at admission			
Ascites	80%	70%	0.12
Gastrointestinal bleeding	6%	5%	0.73
Hyponatremia	30%	16%	0.04
Characteristics of Infectious episode			
Type of bacterial infection			0.48
Spontaneous bacterial peritonitis	21%	22%	
Pneumonia	21%	12%	
Urinary tract infection	14%	15%	
Skin and soft tissue	18%	27%	
Undetermined	15%	10%	
Other	11%	14%	
Origin of infection			0.06
Community-acquired	24%	38%	
Health care associated	47%	30%	
Nosocomial	29%	32%	
SIRS	57%	44%	0.15
Septic shock	8%	10%	0.56
Clinical and laboratorial data			
Mean Arterial Pressure (mmHg)	85 ± 14	87 ± 16	0.27
Heart rate (bpm)	75 ± 13	81 ± 14	0.008
Bilirubin (mg/dL)	5.7 ± 7.5	3.6 ± 5.1	0.03
Albumin (g/L)	23 ± 5	25 ± 6	0.04
International normalized ratio	1.9 ± 0.8	1.6 ± 0.4	0.007
Creatinine (mg/dL)	1.9 ± 1.5	1.4 ± 1.0	0.009
Sodium (mEq/L)	133 ± 7	135 ± 6	0.09
Hemoglobin (g/dL)	10.5 ± 2.1	10.9 ± 3.5	0.54
Platelet count ($\times 10^9$/L)	129 ± 113	160 ± 119	0.09
Leucocyte count ($\times 10^9$/L)	8.4 ± 5.7	8.4 ± 5.9	0.95
C-reactive protein (mg/dL)	4.7 ± 4.2	5.9 ± 4.6	0.19
Child-Pugh C	80%	31%	<0.001
MELD score	22 ± 8	16 ± 7	<0.001
MELD-sodium score	25 ± 8	20 ± 7	<0.001
ACLF	44%	19%	0.001

SIRS, systemic inflammatory response syndrome; MELD, model of end-stage liver disease; ACLF, acute-on-chronic liver failure.

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On multivariate analysis, MELD-sodium (odds-ratio [OR] 1.052 95% confidence interval [CI] 1.014–1.092, P = 0.007), serum albumin ([OR 0.922 [95% CI 0.889–0.958], P < 0.001), and previous episodes of HE (OR 4.184 [95% CI 1.908–9.174], P < 0.001) were associated with HE at diagnosis of BI. As information regarding previous episodes of HE is not always available or reliable, we constructed a second model without inclusion of this variable, and MELD-sodium (OR 1.063 [95% CI 1.026–1.101], P = 0.001) and serum albumin (OR 0.932 [95% CI 0.900–0.964], P < 0.001) remained as the variables independently associated with HE at diagnosis of BIs.

Characteristics of HE Episode According to Origin of Infection

Comparison of patients with HE in terms of diagnosis of HE before or after hospital admission (i.e. associated with CA/HCA and nosocomial infections) is presented in Supplementary Table S2. Groups were similar with respect to many clinical and laboratory data. However, patients with HE associated with nosocomial infections had a higher frequency of high-grade HE and septic shock, as well as in-hospital mortality.

HE Recurrence

Thirty patients developed a second episode of HE during hospitalization (45%). The majority of patients (sixteen, 53%) were classified as having grade 2, eleven patients were classified as high-grade, and the remaining three as grade 1 HE. Median time for recurrence was 13 (IQR 5–22) days. The 7-, 14-, and 28-day probability of recurrence was 14%, 28%, and 33%, respectively. In comparison to the first episode, recurrence was associated with more severe HE, as evidenced by a higher proportion of patients with overt HE (90% vs. 60% in the first episode of HE, P = 0.012). Even though the majority of these patients (twenty-six, 87%) developed a second infection throughout hospitalization, in only 7 of them recurrence of HE coincided with the diagnosis of BIs.

Table 3 shows factors associated with recurrence of HE. On multivariate analysis, only serum sodium (hazard ratio 0.93 [95% CI 0.98–0.88], P = 0.008) was associated with HE recurrence. The 7-, 14- and 28-day probability of recurrence in patients with hyponatremia at diagnosis of infection was 9%, 23%, and 54% (vs. 5%, 11%, and 27% for patients without hyponatremia, respectively; P < 0.001) (Figure 1).

HE *de novo*

Eighteen (17%) patients without HE at diagnosis of BI developed HE, a frequency significantly lower than that observed for recurrence of HE (P < 0.001 for comparisons). Median time for development was 26 (17–40) days after diagnosis of infection (P = 0.09 vs. recurrence). The proportion of patients with overt and high-grade HE was 72% and 28%, respectively (P = NS vs. recurrence). The 7-, 14-, and 28-day probability of HE *de novo* for patients without HE at diagnosis of infection was 1%, 3%, and 18%, respectively (P < 0.001 vs. recurrence). Twelve patients (67%) developed a second infection and in 4 of them HE coincided with this diagnosis.

Other Complications of Cirrhosis after BI

Nineteen and 9 patients developed ascites and a new episode of varicose gastrointestinal bleeding after diagnosis of BIs, respectively.

Table 3 Factors Associated with HE Recurrence.

	Hazard Ratio	95% CI	P
Age	1.025	0.986–1.067	0.21
Male gender	0.94	0.44–2.00	0.88
Alcoholic etiology	1.19	0.58–2.44	0.64
Previous HE	1.23	0.59–2.56	0.57
Complications at admission			
Ascites	1.80	0.54–6.00	0.34
Overt HE	4.03	1.22–13.3	0.02
High-grade HE	2.18	0.99–4.80	0.053
Gastrointestinal bleeding	0.52	0.07–3.82	0.52
Hyponatremia	2.05	0.98–4.27	0.055
Characteristics of Infectious episode			
Community-acquired infection	0.82	0.28–2.41	0.72
SIRS	1.45	0.69–3.01	0.32
Septic shock	1.08	0.25–4.61	0.91
Clinical and laboratorial data			
Mean Arterial Pressure (mmHg)	1.003	0.97–1.03	0.84
Heart rate (bpm)	0.99	0.96–1.02	0.52
Bilirubin (mg/dL)	1.024	0.98–1.018	0.29
Albumin (g/L)	0.96	0.89–1.03	0.25
International normalized ratio	0.94	0.51–1.76	0.86
Creatinine (mg/dL)	1.07	0.85–1.36	0.54
Sodium (mEq/L)	0.93	0.88–0.98	0.009
Hemoglobin (g/dL)	0.98	0.82–1.18	0.87
Platelet count ($\times 10^9$/L)	0.99	0.99–1.003	0.46
Leucocyte count ($\times 10^9$/L)	1.09	1.008–1.165	0.27
C-reactive protein (mg/dL)	1.09	0.97–1.22	0.14
Child-Pugh C	2.55	0.86–7.50	0.09
MELD score	1.03	0.98–1.08	0.18
MELD-sodium score	1.052	1.001–1.106	0.045
ACLF	1.88	0.90–3.93	0.09

HE, hepatic encephalopathy; SIRS, systemic inflammatory response syndrome; MELD, model of end-stage liver disease; ACLF, acute-on-chronic liver failure

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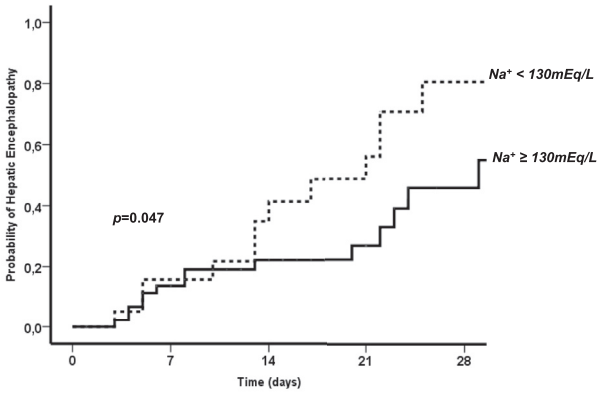

Figure 1 probability of recurrence of hepatic encephalopathy as determined by presence of hyponatremia.

Survival

Median hospital stay was 18 (IQR 12–33) days. One hundred and fourteen patients were discharged, 56 died, and 2 were transplanted. The most common cause of death was sepsis (41 patients, associated with ACLF in 22). The probability of survival at 7, 14, and 28 days was 91%, 82%, and 71%, respectively. Patients with HE at diagnosis had lower survival, as shown in Figure 2. Nevertheless, the severity of HE was not associated with prognosis. Survival for patients with grade 1, 2, and high-grade HE was 50%, 46%, and 50%, respectively (P = 0.94). On the other hand, recurrence of HE was associated with lower survival. Survival for patients with recurrence was 37%, which is lower than that observed for patients with HE at diagnosis and no recurrence (58%) and those without HE throughout hospitalization (77%), P < 0.001.

Table 4 shows the comparisons of baseline characteristics of patients according to hospital mortality. Mortality was associated with demographic variables, complications of cirrhosis, severity of infection, and liver and kidney function parameters.

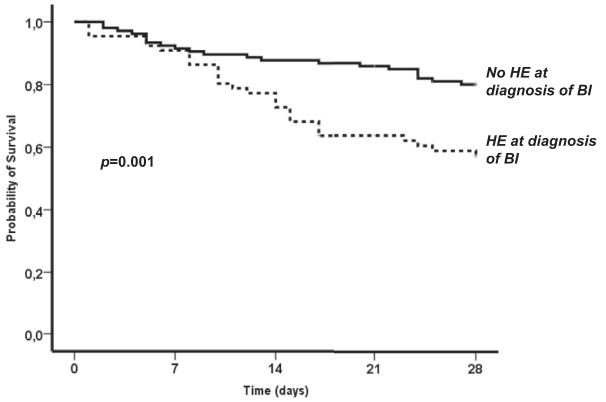

Figure 2 probability of survival in cirrhotic patients with bacterial infections according to presence of hepatic encephalopathy.

Table 4 Comparison Between Survivors and Non-survivors.

	Dead (n = 58)	Survival (n = 114)	*P*-value
Age	60 ± 10	55 ± 14	0.04
Male gender	69%	53%	0.04
Alcoholic etiology	52%	31%	0.007
Complications at admission			
Ascites	83%	69%	0.054
Hepatic Encephalopathy	59%	28%	<0.001
Gastrointestinal bleeding	3%	6%	0.72
Hyponatremia	34%	15%	0.005
Characteristics of Infectious episode			
Type of bacterial infection			0.72
Spontaneous bacterial peritonitis	16%	25%	
Pneumonia	29%	9%	
Urinary tract infection	7%	18%	
Skin and soft tissue	24%	23%	
Undetermined	14%	11%	
Other	10%	14%	
Community-acquired infection	21%	39%	0.02
SIRS	61%	43%	0.045
Septic shock	16%	6%	0.048
Clinical and laboratorial data			
Mean Arterial Pressure (mmHg)	84 ± 15	88 ± 15	0.10
Heart rate (bpm)	79 ± 15	79 ± 14	0.94
Bilirubin (mg/dL)	6.9 ± 8.2	3.2 ± 4.5	0.001
Albumin (g/L)	22 ± 5	25 ± 6	0.001
International normalized ratio	2.0 ± 0.8	1.5 ± 0.4	0.002
Creatinine (mg/dL)	2.3 ± 1.7	1.2 ± 0.7	<0.001
Sodium (mEq/L)	132 ± 7	135 ± 6	0.003
Hemoglobin (g/dL)	11.0 ± 4.0	10.6 ± 2.2	0.42
Platelet count ($\times 10^9$/L)	138 ± 89	153 ± 130	0.43
Leucocyte count ($\times 10^9$/L)	10.8 ± 6.0	7.2 ± 5.2	<0.001
C-reactive protein (mg/dL)	5.9 ± 3.9	5.2 ± 4.7	0.47
Child-Pugh C	77%	37%	<0.001
MELD score	24 ± 8	16 ± 6	<0.001
MELD-sodium score	27 ± 7	19 ± 6	<0.001
ACLF	54%	16%	<0.001

SIRS, systemic inflammatory response syndrome; MELD, model of end-stage liver disease; ACLF, acute-on-chronic liver failure.

On multivariate analysis, HE at diagnosis of infection was independently associated with mortality (OR 2.52 [95% CI 1.05–6.05], P = 0.04), together with MELD-sodium (OR 1.15 [95% CI 1.07–1.23], P < 0.001). The best cut-off point of MELD-sodium for prediction of mortality was 22, with a sensitivity and specificity of 79% and 71%, respectively, (area under the ROC curve: 0.81 [95% CI 0.74–0.88], P < 0.001).

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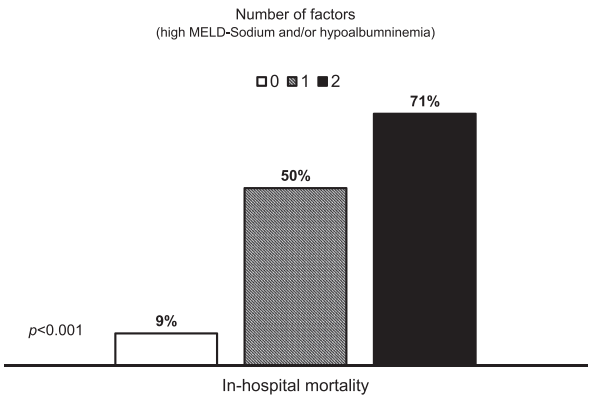

Figure 3 correlation between MELD-Sodium hypoalbuminemia and in-hospital mortality.

For both patients with high and low MELD-sodium score, the presence of HE was associated with worse prognosis. For high MELD-sodium, in-hospital mortality for patients with and without HE at diagnosis of infection was 70% and 47%, respectively ($P < 0.05$). For the group with low MELD-sodium, corresponding values were 25% and 9% ($P < 0.05$).

When analyzing only patients with HE, MELD-sodium (OR 1.082 [95% CI 1.004–1.165], $P = 0.038$) and serum albumin (OR 0.886 [95% CI 0.823–0.953], $P = 0.001$) were independent predictors of survival. The best cut-off points for the prediction of mortality were 22 for MELD-sodium and 25 g/L for serum albumin. In-hospital mortality for patients with HE and none, one or two of these characteristics is shown in Figure 3.

DISCUSSION

The present study has 3 main findings: (1) HE is common in patients with BIs, (2) recurrence of HE throughout hospitalization is common, and (3) HE impairs in-hospital survival of patients with BI.

Frequency of HE in patients with BIs has previously been reported, varying from 8% to 65%,[15,16] but data from most recent studies with the largest number of patients show a frequency around 36%–38%, with almost 30% of patients with high-grade HE.[17–19] These values are very similar to our own and reinforce the validity of our findings, despite the relatively low number of patients. It is also important to mention that this frequency is much higher than that reported for sepsis-associated *delirium* (SAD) in general populations.[20,21] Even though these conditions may share some common pathogenic mechanisms—such as cerebral hypoperfusion and altered metabolism—there are major differences between them, especially concerning neuronal injury and the role of cholinergic neurotransmission in SAD[22]. Corroborating this distinction, in our study group, severity of infection was not associated with HE, in contrast to what is described for patients with SAD.[23]

To the best of our knowledge, no studies thus far have evaluated factors associated with HE in cirrhotic patients with BIs. In our cohort, liver and kidney function parameters, like MELD-sodium and serum albumin, as well as an episode of HE prior to current hospitalization were associated with HE at diagnosis of BI. The central role of these variables as risk factors for HE in hospitalized patients has previously been demonstrated in patients hospitalized for decompensations of cirrhosis.[24] Patients with worse liver and kidney function have a decreased capacity to convert ammonia to urea and subsequently, to excrete urea. Increased intracellular concentration of ammonia produces astrocyte swelling which in turn leads to oxidative stress and formation of reactive oxygen species. This promotes further astrocyte edema in a self-reinforcing process that puts these individuals with previous HE at increased risk of new episodes of HE. Finally, apart from being a marker of liver function, albumin by itself has been demonstrated to have many anti-inflammatory and endothelial stabilizing properties that may have protective roles in HE,[25] as has been recently proposed.[26]

HE has been recognized as a complication with a high recurrence rate in ambulatory patients.[27,28] In sharp contrast, no studies thus far have evaluated recurrence rates in hospitalized patients, as well as predictive factors and prognostic relevance. Throughout hospitalization, almost half of patients with HE associated with BI had a second episode of HE, a frequency comparable with that observed in outpatients without prophylaxis after 12 months, and almost 3 times higher than that reported for *de novo* HE in our group. Recurrence was more severe, as evidenced by the higher proportion of patients with overt HE, and was associated with low serum sodium at diagnosis of infection. Hyponatremia has previously been associated with higher prevalence of HE and increased risk of HE development,[29,30] possibly due to low-grade astrocyte edema, which makes patients more susceptible to the neurotoxic effects of ammonia. No studies so far have associated low serum sodium levels with an increased recurrence rate, as is the case for Child-Pugh, MELD, and ammonia level.[28] This finding is of special interest, as hyponatremia is common in cirrhotic patients with BIs.[31] There are some possible explanations for these findings. Patients may not have entirely normalized serum sodium levels and remained hyponatremic and consequently, at risk for HE. Also, hyponatremia renders patients less responsive to treatment with lactulose, and consequently less likely to be protected from new episodes of HE. However, we can only speculate, as no information regarding serum sodium concentration or resolution of hyponatremia, as well as usage of lactulose, was collected in our study. Alternatively, hyponatremia may represent a stage of severe circulatory disfunction with concomitant cerebral vasoconstriction, a common finding in pathogenesis of HE. This may be less likely, however, as no other circulatory

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parameters were associated with HE recurrence, likely MAP or HR. Of particular interest, recurrence was not associated with higher frequency of BIs, as in only a small proportion of patients a second episode of HE coincided with a second BI.

HE was strongly associated with in-hospital mortality. HE has previously been demonstrated to be associated with lower survival in patients with AKI[32] but few studies thus far have evaluated the prognostic relevance of HE in patients with BI. Previous studies have demonstrated that among patients with HE, those with BI had a higher mortality rate.[33] Recently, one study demonstrated that multiple episodes (>3/year) of BI were associated with a higher probability of HE development, but nonetheless was not associated with mortality at 12 months.[34] As far as we know, our study is the first to clearly demonstrate this association of HE and mortality in patients with BI. Apart from denoting a stage of advanced decompensated cirrhosis, the presence of HE may have prognostic relevance presumably due to its tight relation with hyperammonemia. Beyond neurotoxicity, ammonia has several other deleterious effects in neutrophil and liver function, which may explain why it has been recently correlated with organ failure and prognosis in decompensated cirrhosis.[35] Assessment of HE, combined with MELD-sodium score (a well-known prognostic factor in patients with cirrhosis and infections) permits the identification of subgroups of patients with distinct prognoses, with an almost 7-fold higher mortality for those with high MELD-sodium and HE than those without these characteristics. This may help to decide which patients may benefit from more aggressive treatment for BI (possibly with broad spectrum antibiotics) together with measures to prevent or reverse organ failure, as those were the most common causes of in-hospital death, as well as immediate evaluation for liver transplantation. On the contrary, those with good short-term prognosis may benefit from early conversion to oral antibiotics and hospital discharge.

Some other points deserve comment. The grade of HE was not correlated with mortality, in contrast to some previous studies.[36] Nevertheless, this reinforces the importance of accurately diagnosing patients with grade 1 HE. These patients may be difficult to diagnose, as alterations in neuropsychological functions may be subtle, but show high short-term mortality even in comparison with those with minimal HE.[37] On the other hand, recurrence of HE was strongly associated with hospital survival. This highlights the significance of preventing further episodes of HE in the short-term with avoidance of diuretic overdosage, constipation and possibly, correction of serum sodium concentration. Our study has some limitations. It is a unicentric study with a modest number of patients. Antibiotic treatment for HCAI did not follow the current recommendations, due to the fact that no different treatment than that for CA infections was recommended for this population at the time of the study. Also, no specific information regarding antibiotic resistance or failure was available. Nevertheless, it seems unlikely that a lack of adherence to what is now recognized as the best antibiotic treatment for HCAI would have a substantial effect on HE frequency or prognostic capability, as factors associated with infection severity were associated neither with prevalence nor recurrence of HE. Additionally, the origin of infection was not a predictor of mortality.

In conclusion, HE is frequent in cirrhotic patients with BIs, affecting almost 40%. Severity of liver disease, not of infection, is associated with this complication. These patients are at increased risk of short-term recurrence, especially those with hyponatremia. Presence and recurrence of HE, independent of severity, are associated with in-hospital mortality.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Lívia Guimarães, Juliana Piedade, Joana Duarte, Caroline Baldin, Lívia Victor: Investigation; Writing - original draft. **Barbara Costa**, **Zulane Veiga, Camila Alcântara**: Investigation; Supervision; Data curation; **Flávia Fernandes:** Investigation, Supervision; Writing - review & editing **Gustavo Pereira**: Conceptualization; Methodology; Formal analysis; Resources; Project administration; Writing - review & Editing; Visualization.

CONFLICTS OF INTEREST

All authors have none to declare.

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APPENDIX A

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2023.01.004.

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