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Original Contribution

Patients with cirrhosis in the ED: early predictors of infection and mortality☆,☆☆

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ABSTRACT

Background: Patients with cirrhosis have high risk of bacterial infections and cirrhosis decompensation, resulting in admission to emergency department (ED). However, there are no criteria developed in the ED to identify patients with cirrhosis with bacterial infection and with high mortality risk.
Study objective: The objective of the study is to identify variables from ED arrival associated with bacterial infections and inhospital mortality.
Methods: This is a retrospective single-center study using a tertiary hospital's database to identify consecutive ED patients with decompensated cirrhosis. Clinical variables and laboratory results were obtained by chart review. Logistic regression models were built to determine variables independently associated with bacterial infection and mortality. Scores using these variables were designed.
Results: One hundred forty-nine patients were enrolled, most of them males (77.9%) with alcoholic cirrhosis (53%) and advanced liver disease (Child-Pugh C, 47.2%). Bacterial infections were diagnosed in 72 patients (48.3%), and 36 (24.2%) died during hospital stay. Variables independently associated with bacterial infection were lymphocytes less than or equal to 900/mm^3 (odds ratio [OR], 3.85 [95% confidence interval {CI}, 1.47-10]; $P = .006$) and C-reactive protein greater than 59.4 mg/L (OR, 5.05 [95% CI, 1.93-13.2]; $P = .001$). Variables independently associated with mortality were creatinine greater than 1.5 mg/dL (OR, 4.35 [95% CI, 1.87-10.1]; $P = .001$) and international normalized ratio greater than 1.65 (OR, 3.71 [95% CI, 1.6-8.61]; $P = .002$). Scores designed to predict bacterial infection and mortality (Mortality in Cirrhosis Emergency Department Score) had an area under the receiver operating characteristic curve of 0.82 and 0.801, respectively. The Mortality in Cirrhosis Emergency Department Score performed better than Model for End-Stage Liver Disease score.
Conclusions: In this cohort of ED patients with decompensated cirrhosis, lymphopenia and elevated C-reactive protein were related to bacterial infections, and elevated creatinine and international normalized ratio were related to mortality. Scores built with these variables should be prospectively validated.

1. Introduction

1.1. Background

Bacterial infections are diagnosed in 30% to 50% of all hospital admissions for cirrhotic decompensation and are directly responsible for up to 50% of deaths in cirrhosis [1,2]. These patients are twice as likely to die of sepsis than individuals without cirrhosis [3]. Furthermore, bacterial infections carry significant morbidity, precipitating cirrhosis decompensation (hepatic encephalopathy, ascites, variceal bleeding, and/or jaundice) and acute kidney injury (AKI) development [4]. In fact, renal failure occurs in 33% of patients with cirrhosis who have spontaneous bacterial peritonitis (SBP) and in 27% of those with sepsis unrelated to SBP, with a mortality rate of 41% to 66% [5,6]. These severe complications frequently result in admission to the emergency department (ED) [2,7].

Patients with cirrhosis require frequent visits to the ED. In a large population study performed in England, 47.3% of patients had a first diagnosis of cirrhosis during an emergency admission. The remaining 52.7% were diagnosed in an outpatient setting, but 37.8% of them had a subsequent emergency hospital admission over a 5-year period [8].

Early recognition and treatment of severe complications are generally related to better clinical outcomes. In patients with SBP, the most common bacterial infection in cirrhosis, treatment with suitable antibiotics and large volume albumin infusion in the first 6 hours from diagnosis have reduced mortality rates from 80% to 20% in the last 3 decades, in addition to reducing renal failure development in almost 70% [5,9].

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However, the benefit of such treatment may be restricted to high-risk patients (serum creatinine >1 mg/dL and/or serum bilirubin >4 mg/dL), who should be recognized as early as possible [10-12].

1.2. Importance

Despite the great importance of identifying high-risk patients among cirrhotic decompensated individuals, there are no current criteria developed or validated in the emergency setting, although this is the place where most patients with decompensated cirrhosis will be evaluated and would benefit from early detection and treatment of bacterial infections and other severe complications.

1.3. Goals of this investigation

In this article, we evaluated patients with decompensated cirrhosis who visited the ED and were admitted to the hospital. Our aim was to evaluate the early predictors, on the arrival to the ED, of the presence of bacterial infection and inhospital mortality.

2. Materials and methods

2.1. Study design and setting

This was a retrospective single-center study performed in the ED of a Brazilian university hospital. The Hospital das Clínicas, which belongs to the University of São Paulo's Medical School (HCFMUSP), is a tertiary university hospital with more than 180 000 annual ED visits, of which 14 000 result in hospital admission. In this hospital, the hepatology service includes a 24-hour endoscopy unit, interventionist radiology, a hepatology intensive care unit, and a liver transplantation service. The study was approved by the ethical review board of HCFMUSP (CAPPesq).

2.2. Selection of participants

From January 1, 2009, to June 30, 2011, consecutive patients seen in the ED of HCFMUSP with decompensated cirrhosis were identified in the hospital database. Medical records of patients with ED diagnosis of cirrhosis (*International Statistical Classification of Diseases, 10th Revision* [*ICD-10*], code K74) or correlated conditions (viral hepatitis [*ICD-10* code B18], alcoholic liver disease [*ICD-10* code K70], autoimmune hepatitis [*ICD-10* code K75.4], hemocromatosis [*ICD-10* code E83.1], Wilson disease [*ICD-10* code E83.0], other liver diseases [*ICD-10* code K76], ascites [*ICD-10* code R18], esophageal varices [*ICD-10* code I85], and peritonitis [*ICD-10* code K65]) were screened for inclusion by 2 independent researchers. For patients with more than 1 hospital admission during the study period, only data from the first admission were considered.

Inclusion criteria were (*a*) patients aged 18 years or older; (*b*) cirrhosis diagnosis by liver biopsy or a combination of clinical, laboratory, radiological, and endoscopic data; and (*c*) admission to the ED related to cirrhosis decompensation (hepatic encephalopathy, ascites, variceal bleeding, and/or jaundice).

Exclusion criteria were (*a*) patients with terminal illness (metastatic neoplasia or severe cardiopulmonary or neurologic disease); (*b*) hospital discharge in less than 24 hours after admission; and (*c*) patients with previous solid organ transplantation.

The medical record review was performed by 3 fifth year medical students and 2 members of the medical staff (1 emergency physician and 1 hepatologist). Medical students were trained on the first 20 charts and could then contact the staff at any time to clarify doubts.

Data from ED admission were inserted into standardized electronic spreadsheets (software Excel, Microsoft Office 2007), which included age, sex, cirrhosis etiology, cirrhosis complications (ascites, encephalopathy, variceal bleeding, hepatorenal syndrome, and spontaneous bacterial peritonitis), comorbidities, clinical variables (heart rate, blood pressure, temperature, and Glasgow Coma Scale), laboratory results (C-reactive protein [CRP], leukocytes, neutrophils, lymphocytes, neutrophil/lymphocyte relationship, creatinine, urea, sodium, international normalized ratio [INR], bilirubin, and albumin), culture results, Child-Pugh classification, Model for End-Stage Liver Disease (MELD) score, MELD-Na score, site of infection, and infection classification according to International Sepsis Definitions Conference (ISDC) 2001 (absent, possible, probable, or definite and sepsis, severe sepsis, or septic shock) [13]. Standardized electronic spreadsheets also included all creatinine values measured during the first 48 hours from hospital admission, length of hospital stay, and cause of death in nonsurvivors.

The presence of AKI was defined according to Acute Kidney Injury Network criteria [14]. For AKI determination, we considered serum creatinine measures during the first 48 hours from hospital admission. *Acute kidney injury* was defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL or a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline). In this study, data on urine output were not available [15].

All collected data were assessed by another investigator (AQF) for the identification of disagreements and obvious problems.

2.3. Interventions

Emergency physicians managed patients with cirrhosis at their discretion. At HCFMUSP, most physicians follow American Association for Study of Liver Disease or European Association for Study of the Liver guidelines for cirrhosis complications management. Physicians were not aware of this study.

2.4. Outcome measures

Patients' infection status was defined according to the ISDC 2001 [13]. Patients classified with definite, probable, or possible infection were considered to be patients with bacterial infection.

The severity of their infection was then classified in sepsis, severe sepsis, or septic shock, according to standard definitions [13].

Mortality was determined during hospital stay. Patients who were discharged from hospital were considered survivors. There was no follow-up after hospital discharge.

2.5. Statistical analysis

Statistical analysis was performed with the software R 3.0.1 (The R Foundation for Statistical Computing, 2013). Discrete variables were reported as percentages. Continuous variables were presented as medians with interquartile ranges.

Using area under the receiver operating characteristic (ROC) curve (AUROC) and maximum Youden Index, the continuous variables' effectiveness and best cutoff values to identify patients with bacterial infection and to identify survivors were determined. Continuous variables were categorized according to these cutoff values.

Simple binary logistic regression models were built, and variables with $P \leq .1$ were inserted in multiple binary logistic regression models to determine variables independently associated with bacterial infection and to determine variables independently associated with mortality according to the Akaike Information Criterion.

Scores using variables associated with bacterial infection and mortality were built from the resized regression coefficients giving a range of scores from 0 to 100 points. Receiver operating characteristic curve analysis was performed to evaluate the scores' discrimination effectiveness using AUROC and maximum Youden Index. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were calculated at maximum Youden Index cutoffs.