Journal of Critical Care 36 (2016) 234–239

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Prognostication of critically ill patients with acute-on-chronic liver failure using the Chronic Liver Failure–Sequential Organ Failure Assessment: A Canadian retrospective study☆,☆☆,★,★★

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ARTICLE INFO

Available online xxxx
Keywords:
Acute-on-chronic liver failure
SOFA
CLIF-SOFA
Cirrhosis
Prognostic scoring systems

ABSTRACT

Purpose: We evaluated the Chronic Liver Failure–Sequential Organ Failure Assessment (CLIF-SOFA) score to predict survival in a Canadian critically ill cohort with acute-on-chronic liver failure.
Methods: We retrospectively examined 274 acute-on-chronic liver failure patients admitted to a quaternary level intensive care unit (ICU) between April 1, 2000, and April 30, 2011. We evaluated severity of illness scores, including the Acute Physiology and Chronic Health Evaluation (APACHE) II, model for end-stage liver disease (MELD), Child-Turcotte-Pugh (CTP), SOFA, and CLIF-SOFA.
Results: On ICU admission, patients had the following median (interquartile range): APACHE II, 23 (19-28); MELD, 26 (19-35); CTP, 12 (10-13); SOFA, 15 (11-18); and CLIF-SOFA, 17 (13-21). In-hospital survival was 40%. There were no significant differences in survival for cirrhosis etiology, reason, or year of admission. The CLIF-SOFA score had the greatest area under receiver operating curve of 0.865 (95% confidence interval, 0.820-0.909) and outperformed the CTP, MELD, SOFA, and APACHE II scores. Sequential Organ Failure Assessment score performance improved on the third day of ICU admission (area under receiver operating curve, 0.935; 95% confidence interval, 0.895-0.975).
Conclusions: The CLIF-SOFA and SOFA scores during the first 3 days of ICU admission appear to be highly predictive of in-hospital mortality.

1. Introduction

Acute-on-chronic liver failure (ACLF) occurs in patients with previously compensated chronic liver disease and is distinct from chronic decompensation of cirrhosis [1-3]. Patients with ACLF present with worsening jaundice, coagulopathy, ascites, encephalopathy, and/or multisystem organ failure in the setting of an acute precipitant, such as sepsis, drug ingestion, viral reactivation, recent surgery, or gastrointestinal hemorrhage [4,5]. Patients with ACLF have high mortality, ranging from 29% to 77% [2,6-8].

Several risk factors are associated with higher mortality in critically ill cirrhotic patients. Patients with greater than 3 organ failures, higher fraction of inspired oxygen, higher serum lactate levels, higher serum bilirubin levels, older age, need for vasopressors, lower serum sodium levels, and renal failure have higher associated mortality on multivariate analyses [9-12]. Many liver-specific and general systems scores have

Abbreviations: ACLF, acute-on-chronic liver failure; APACHE, Acute Physiology and Chronic Health Evaluation; AUROC, area under receiver operating curve; CI, confidence interval; CLIF-SOFA, Chronic Liver Failure–Sequential Organ Failure Assessment; CTP, Child-Turcotte-Pugh; F_{IO_2}, fraction of inspired oxygen; GCS, Glasgow Coma Scale; ICU, intensive care unit; IQR, interquartile range; MELD, model for end-stage liver disease; RFH, Royal Free Hospital; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

☆ Author contributions: E.S. contributed to the study by planning design, collecting data, analyzing data, and drafting the manuscript. J.J.R. contributed to the study by planning design and reviewing the manuscript. R.S. assisted with collection of data and reviewing the manuscript. C.J.K. contributed to the study by planning design, collecting data, analyzing data, and drafting the manuscript. All authors reviewed the final manuscript and contributed to its content.

☆☆ Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

★ Disclosures: The authors declare that there are no conflicts of interest.

★★ Ethics approval: University of British Columbia/Vancouver Coastal Health Research Ethics Board.

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http://dx.doi.org/10.1016/j.jcrc.2016.08.003
0883-9441/

been used to predict mortality of critically ill cirrhotic patients [9,12-17]. The Sequential Organ Failure Assessment (SOFA) score has been validated to predict mortality better than other scoring systems, with potentially better prediction at 48 hours after admission [12,13].

In 2013, the European Association for the Study of the Liver–Chronic Liver Failure Consortium adapted the SOFA score into the Chronic Liver Failure–SOFA (CLIF-SOFA), and graded ACLF into 4 grades [7]. The CLIF-SOFA score evaluates organs over 6 domains similar to the SOFA score, but replaces the platelet count with the international normalized ratio (INR) as the hematologic parameter and replaces the Glasgow Coma Scale (GCS) score with hepatic encephalopathy grade as the neurologic parameter. It has been validated to predict mortality in several populations of patients with ACLF in Europe, Brazil, India, and Southeast Asia [6-8,16,18,19]. In critically ill patients, the CLIF-SOFA score has been compared with other scoring systems, with good discriminatory ability in cohorts from the United Kingdom and Taiwan [19-21].

The primary aim of our study was to evaluate the ability of the CLIF-SOFA score to predict mortality in North American critically ill patients with cirrhosis with ACLF. The secondary aim of our study was to identify risk factors or precipitants associated with higher mortality. We hypothesized that the CLIF-SOFA score will be better at discriminating mortality than other liver-specific or general scores in critically ill patients with ACLF.

2. Materials and methods

The reporting of this study followed the Strengthening of the Reporting of Observational Studies in Epidemiology statement [22]. The local health research and university research ethics boards approved the study and waived the requirement for individual informed consent.

2.1. Study design, setting, and participants

The study included patients admitted to a quaternary academic hospital intensive care unit (ICU) where liver transplantation is performed (Vancouver General Hospital, Vancouver, Canada) between April 1, 2000, and April 30, 2011. Patients were included if they met the following criteria: (*a*) adult patient (≥18 years of age); (b) history of cirrhosis, as determined by biopsy or information provided by a composite of laboratory tests, endoscopy, and radiologic imaging; (*c*) worsened ascites, jaundice, encephalopathy, or coagulopathy from baseline, and/or development of 2 or more organ failures; (*d*) suspected acute insult leading to decompensation; and (*e*) first admission to ICU. We did not include or exclude patients based on their eligibility for liver transplantation; however, patients were excluded if (*a*) they received a liver transplantation at any point during that hospitalization or (*b*) they were lost to follow-up.

2.2. Data collection

Patients were identified retrospectively using a local hospital ICU database. The ICU database was queried using the Intensive Care National Audit and Research Centre and Acute Physiology and Chronic Health Evaluation (APACHE) IV terms for cirrhosis, hepatic encephalopathy, ascites, variceal bleeding, and portal hypertension as the primary or secondary diagnoses for ICU admission. Cases were included if they met the above inclusion criteria after medical chart review.

Demographic, clinical, and laboratory data were collected including age, sex, weight, comorbidities, biopsy information, etiology of cirrhosis, complications of cirrhosis, acute precipitants of ACLF, reason for referral to ICU, laboratory data, and clinical parameters. We determined severity of illness scores when applicable for ICU admission and for day 3 of admission, using the Child-Turcotte-Pugh (CTP), APACHE II, APACHE IV, model for end-stage liver disease (MELD), SOFA, Royal Free Hospital (RFH), and CLIF-SOFA scores. The RFH score was a score developed by Cholongitas et al [9], and recently updated, to predict mortality in critically ill cirrhotic patients [14].

We applied the definitions of the CANONIC study retrospectively to define ACLF in our cohort of patients [7]. We used the CLIF-SOFA score to grade each patient into 4 grades as defined by the CANONIC study [7]. No ACLF includes (*a*) patients with no organ failure, (*b*) patients with a single organ failure who had a serum creatinine less than 1.5 mg/dL and no hepatic encephalopathy, and (*c*) patients with neurologic failure who had a serum creatinine level less than 1.5 mg/dL. Acute-on-chronic liver failure grade 1 includes (*a*) patients with single kidney failure; (*b*) patients with single failure of liver, coagulation, circulation, or respiration, with serum creatinine ranging from 1.5 to 1.9 mg/dL and/or mild-to-moderate hepatic encephalopathy; and (*c*) patients with single neurologic failure who had serum creatinine ranging from 1.5 and 1.9 mg/dL. The ACLF grade 2 refers to patients with 2 organ failures; ACLF grade 3 assigns patients with 3 or more organ failures [7].

2.3. Primary outcome

The primary outcome of this study was in-hospital mortality. Secondary outcomes included hospital length of stay, ICU length of stay, and ICU mortality.

2.4. Statistical analysis

Statistical analysis was performed using Stata version 14.1 (StataCorp LP, College Station. Tex). Only information on a patient's first admission to ICU was included in the analysis. Missing data were neither imputed nor replaced. The number of individuals with missing variable data was reported. Continuous variables were reported with the mean and SD or median and interquartile range (IQR), after testing for normality.

We used logistic regression to study the performance of different prognostic scores (CTP, MELD, SOFA, CLIF-SOFA, APACHE II, APACHE IV, RFH) on admission and at 48 hours where appropriate. Model performance was assessed using the *c* statistic (area under the receiver operator curve [AUROC]) and the Hosmer-Lemeshow goodness-of-fit test.

Univariate analysis was performed to identify predictors associated with the primary outcome. Measures of central tendency for continuous variables were compared using the Student *t* test or Wilcoxon rank sum test after normality testing. Categorical variables were reported as numbers and percentage, and were analyzed using the χ^2 or Fisher exact test. Multivariable logistic regression was used to study predictors of interest, controlling for severity of illness by CLIF-SOFA, age, sex, and comorbidities using the Charlson comorbidity index. All comparisons were reported with 95% confidence intervals (CIs) and 2-sided *P* values. A 2-sided *P* value less than .05 was considered statistically significant.

3. Results

3.1. Descriptive characteristics of all patients in the cohort

We identified 1046 potential cases in ICU database. Three hundred four cases met the inclusion criteria and had data collected. After excluding repeated visits to ICU, there were 274 unique admissions between April 1, 2000, and April 30, 2011. A summary of their descriptive characteristics, clinical parameters, and outcomes is presented in Tables 1 and 2.

Cirrhosis was biopsy proven in 20% of cases. The most common risk factors for cirrhosis were alcohol (50%), hepatitis C infection (40%), and hepatitis B infection (12%). Many patients had hypertension (20%), diabetes mellitus (19%), hepatocellular carcinoma (14%), and chronic obstructive pulmonary disease (12%). The most commonly identified precipitants of ACLF were sepsis (48%), recent variceal bleeding (30%), and recent surgical procedure(s) (23%). During their hospitalization,