Research Article

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Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure

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Background & Aims: Acute-on-chronic liver failure (ACLF) is a frequent syndrome (30% prevalence), characterized by acute decompensation of cirrhosis, organ failure(s) and high short-term mortality. This study develops and validates a specific prognostic score for ACLF patients.

Methods: Data from 1349 patients included in the CANONIC study were used. First, a simplified organ function scoring system (CLIF Consortium Organ Failure score, CLIF-C OFs) was developed to diagnose ACLF using data from all patients. Subsequently, in 275 patients with ACLF, CLIF-C OFs and two other independent predictors of mortality (age and white blood cell count) were combined to develop a specific prognostic score for ACLF (CLIF Consortium ACLF score [CLIF-C ACLFs]). A concordance index (C-index) was used to compare the discrimination abilities of CLIF-C ACLF, MELD, MELD-sodium (MELD-Na), and Child-Pugh (CPs) scores. The CLIF-C ACLFs was validated in an external cohort and assessed for sequential use.

Results: The CLIF-C ACLFs showed a significantly higher predictive accuracy than MELDs, MELD-Nas, and CPs, reducing (19–28%) the corresponding prediction error rates at all main time points after ACLF diagnosis (28, 90, 180, and 365 days) in both the CANONIC and the external validation cohort. CLIF-C ACLFs computed at 48 h, 3–7 days, and 8–15 days after ACLF diagnosis predicted the 28-day mortality significantly better than at diagnosis.

Conclusions: The CLIF-C ACLFs at ACLF diagnosis is superior to the MELDs and MELD-Nas in predicting mortality. The CLIF-C ACLFs is a clinically relevant, validated scoring system that can be used sequentially to stratify the risk of mortality in ACLF patients.

Keywords: Acute-on-chronic liver failure; Cirrhosis; Multi-organ failure; Sepsis; Prognosis.

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Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; CANONIC study, EASL-CLIF Acute oN chrONIC liver failure study; CLIF, chronic liver failure; CLIF-C ACLFs, CLIF Consortium ACLF score; CLIF-C OFs, CLIF Consortium organ failure score; CLIF-SOFAs, CLIF-sequential organ failure assessment score; CPs, Child-Pugh score; E, epinephrine; EASL, European Association for the Study of the Liver; FiO_2, fraction of inspired oxygen; HE, hepatic encephalopathy; INR, international normalized ratio; MAP, mean arterial pressure; MELD, model of end-stage liver disease; MELD-Nas, MELD-sodium score; NE, norepinephrine; PaO_2, partial pressure of arterial oxygen; SOFA, sequential organ failure assessment; SpO_2, pulse oximetric saturation.

Introduction

Acute-on-chronic liver failure (ACLF) is a syndrome characterised by acute decompensation of cirrhosis, organ failure(s) and high short-term mortality [1], which was recently defined in the CANONIC study [2]. This was a large prospective observational investigation carried out in 29 European university hospitals. It included 1349 consecutive patients admitted with acute

decompensation of cirrhosis (ascites, bacterial infection, gastro-intestinal haemorrhage, and hepatic encephalopathy) and followed-up for one year. The CANONIC study was organised in the setting of the European Association for the Study of the Liver – Chronic Liver Failure Consortium (EASL CLIF-C).

The results of the CANONIC study showed that ACLF occurs most frequently in relatively young individuals, affects approximately 30% of hospitalised cirrhotic patients, may develop in patients without previous decompensation, is associated with a 28-day mortality rate of 33% (51% at 90 days) and is distinct from 'mere' decompensation of cirrhosis. ACLF is the most frequent indication for admission to the intensive care unit (ICU) [3]. In the US, about 200,000 patients with cirrhosis are hospitalised each year of which about 26,000 patients require ICU care [1,3,4]. An average ICU admission costs about $116,200 and costs for the health care system are $3 billion for cirrhotic patients requiring intensive care [3].

The diagnostic criteria for ACLF in the CANONIC study were based on the Chronic Liver Failure-SOFA score (CLIF-SOFAs), an adaptation for cirrhotic patients of the sepsis organ failure assessment score (SOFAs) widely used in the ICU [4]. The CLIF-SOFAs, however, is complex (based on 6 subscores, each with a 5-point range, assessing liver, kidney, brain, coagulation, respiration, and circulation), is based on consensus and expert opinion rather than data, and does not significantly improve the prediction accuracy of the model for end-stage liver disease (MELD) and MELD-sodium (MELD-Na) scores [5–6].

The current study was aimed to simplify the original CLIF-SOFAs and develop a new score for ACLF patients (CLIF Consortium ACLF score, CLIF-C ACLFs) with a higher prognostic accuracy than the CLIF-SOFA, MELD, MELD-Na, and the Child-Pugh (CP) scores [7] for patients with ACLF. The study therefore had four main objectives. First, to develop a simpler and validated organ failure score (CLIF Consortium Organ Function score, CLIF-C OFs) for the diagnosis and grading of ACLF. Second, to design a more accurate prognostic score for ACLF patients (CLIF-C ACLFs), using the CLIF-C OFs and other prognostic clinical and biochemical data. Third, to compare the prognostic accuracy of the CLIF-C ACLFs to that of MELDs, MELD-Nas, and CPs. Fourth, to validate the prognostic accuracy of the CLIF-C ACLFs in an external prospective cohort of consecutive patients hospitalized in a single ICU and assess the score for sequential use.

The CANONIC study database was used as a derivation set for several reasons: first, it includes a large series of patients with acute decompensated cirrhosis and also with ACLF. Second, CANONIC patients were closely and prospectively followed-up for up to 1-year. Third, the population with ACLF included patients developing the syndrome either at study inclusion or during the hospitalization period. Finally, as patients were recruited from 29 centres in Europe, the CANONIC data are representative of the European patient population.

Patient and methods

Study populations

The study was performed in patients from three different populations. Both the derivation and the validation datasets came from studies approved by Ethical Review Boards of all study sites.

1. The CLIF-C OFs was developed using the baseline (i.e., enrolment) data of the whole CANONIC study population, which included 1349 patients (out of 2149 screened) admitted to 29-European hospitals within a period of 6 months for the treatment of decompensated cirrhosis. These patients were prospectively followed-up for one year [2]. In most patients (52%) the aetiology of cirrhosis was alcoholic, in 19.5% it was associated with chronic hepatitis C virus infection, and in 9.6% it was due to both alcohol and hepatitis C. In the remaining 18.9%, cirrhosis was due to other causes. 345 patients (26.8%) had no history of previous decompensation. Causes of hospitalization at study enrolment were ascites (66.8%), hepatic encephalopathy (34.3%), bacterial infections (24.2%), and/or gastro-intestinal haemorrhage (16.4%). 196 patients (14.6%) were admitted to the ICU. The MELDs at enrolment in the whole series was 18.8 (SD: 7.5), and CPs was 9.7 (SD: 2.1).
2. The CLIF-C ACLFs was developed using data from 275 CANONIC patients with ACLF at enrolment, or those who developed ACLF within 28-days post-enrolment. Diagnostic criteria for organ failures in the CANONIC study are described in Supplementary Table 1. The diagnosis of ACLF was based on the presence of at least renal failure or any other single organ failure if associated with renal dysfunction (serum creatinine 1.5–1.9 mg/dl) and/or grade I–II hepatic encephalopathy (ACLF-1). Patients with two organ failures were graded as ACLF-2 and those with three or more organ failures as ACLF-3. At study enrolment, 70.1% of these patients were admitted to the ICU.
3. The external validation of the CLIF-C ACLFs was carried out using data from 225 ACLF patients consecutively admitted to the ICU at the Paul Brousse hospital, Villejuif, France [8]. Despite differences in the proportion of patients admitted to the ICU, this series of patients was selected as the validation set for the following reasons: (1) it was a prospective cohort; (2) all patients had the data needed for ACLF diagnosis and score calculations; (3) patients were followed-up for 90-days. Table 1 shows the clinical characteristics of patients included in the derivation and validation sets.

Study outcomes

The main study outcomes included all-cause mortality at 28, 90, 180, and 365 days after enrolment. All CANONIC patients were closely followed-up during the first 28 days. Subsequently, data on vital signs, causes of death and liver transplantation were obtained 3, 6, and 12 months after enrolment. The same information was collected for all ACLF patients in the validation cohort, who were followed-up for 3 months only. In both derivation and validation sets, there were no losses due to follow-up. At 90 days, 38/275 (13.8%) ACLF patients underwent liver transplantation in the CANONIC dataset and 22/225 (9.8%) in the validation cohort. One year after study enrolment, 53/275 (20%) CANONIC patients with ACLF had been transplanted.

All the data required to compute CLIF-C ACLFs (as well as those used to compute MELDs, MELD-Nas, and CPs) were measured at the time of ACLF diagnosis (either at enrolment or within the 28-day post-enrolment follow-up). Patients' parameters were collected based on standard lab measurements performed at study enrolment and at day 2, 3–7, 8–14, 15–21, and 22–28 during the hospitalization. A central laboratory was not used for sample analyses. However, to assure the comparability of lab results, site labs were requested to use the same units and normal ranges; extensive remote monitoring and quality control were carried out during and after study termination.

Statistical methods

Variables used for the CLIF-C OFs and CLIF-C ACLFs were measured at enrolment and at ACLF diagnosis. The original CLIF-SOFAs included 6 subscores – one for each organ/system – each of them ranging from 0 to 4 (Supplementary Table 1). The 5 categories included in CLIF-SOFAs subscores and the corresponding cut-off values were derived from a consensus [2]. In the current study we assessed whether the cut-offs could be modified and/or if the number of the original categories of each subscore could be reduced maintaining the predictive ability of the aggregated score.

In univariate statistical comparisons, the χ^2 test was used for categorical variables, Student's t test and Mann-Whitney test for continuous variables. McNemar's test and paired t test were used to compare repeated measurements of categorical and continuous variables, respectively. Proportional hazards models considering liver transplantation as a competing risk (PH-CR) were used to identify additional independent factors of mortality not included in the CLIF-C OFs system. Transplanted patients were considered as censored and the survival function was adjusted for the risk of liver transplantation at each study time point [9,10].