Dynamic prognostication in critically ill cirrhotic patients with multiorgan failure in intensive care units in Europe and North America: a multicenter analysis.

(Short Title: CLIF-C ACLF in the Critically Ill)

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List of Abbreviations

ACLF	Acute-on-chronic liver failure
APACHEII	Acute physiology and chronic health evaluation II score
CI	Confidence interval
CIF	Cumulative incidence function
CLIF-C ACLF	CLIF consortium acute on chronic liver failure score
CLIF-C OF	CLIF consortium organ failure score
CLIF-SOFA	CLIF consortium sequential organ failure assessment
CTP	Child Turcotte Pugh
HE	Hepatic encephalopathy
HR	Heart rate
ICU	Intensive care unit
INR	Internationalized ratio
IQR	Interquartile range
MELD	Model for end stage liver disease score
MV	Mechanical ventilation
PH-CR	Proportional-hazards model for competing risks
RRT	Renal replacement therapy
SBP	Spontaneous bacterial peritonitis
SD	Standard deviation
SOFA	Sequential organ failure assessment

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CJK: Conceived the idea for the study, performed data analysis, drafted the manuscript.
EGL: Performed statistical analyses, significantly revised final manuscript
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ABSTRACT

Objective: To evaluate the CLIF-C ACLF score in acute on chronic liver failure (ACLF) patients admitted to intensive care units (ICU) from different global regions and compare discrimination ability with previously published scores.

Design: Retrospective pooled analysis.

Setting: Academic ICUs in Canada (Edmonton, Vancouver) and Europe (Paris, Barcelona, CANONIC study).

Patients: Sample of analysis of 867 cirrhotic patients with ACLF admitted to ICU. Cumulative Incidence Functions (CIF) of death were estimated by ACLF grade at admission and at day 3. Survival discrimination abilities of CLIF-C ACLF, MELD, APACHEII, and Child-Pugh (CTP) scores were compared.

Interventions: ICU admission for organ support.

Measurements and main results: On admission 169 (19%) subjects had ACLF-1, 302 (35%) ACLF-2 and 396 (46%) had ACLF-3 with 90-mortality rates of 33%, 40% and 74% respectively ($p< 0.001$). On admission, CLIF-C ACLF demonstrated superior discrimination at 90 days compared with APACHE II (n=532, C-index 0.67 vs. 0.62, p=0.0027) and Child Pugh (n=666; 0.68 vs. 0.64, p=0.0035) but not MELD (n=845; 0.68 vs. 0.67, p=0.3). A CLIF-C ACLF score > 70 at admission or on day 3 was associated with 90-day mortality rates of approximately 90%. 90-day mortality in Grade 3 ACLF patients on admission who demonstrated improvement by Day 3 was 40% (vs. 79% in patients who did not).

Conclusions: The CLIF-C ACLF demonstrated better discrimination at day 28 and day 90 compared to APACHEII and CTP. Patients who demonstrated clinical improvement post-ICU admission (e.g. ACLF-3 to 1 or 2) at day 3 had better

outcomes than those who did not. In high risk ICU patients (CLIF-C ACLF > 70), decisions regarding transition to palliation should be explored between patient families and the ICU providers after a short trial of therapy.

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a syndrome characterized by acute decompensation of cirrhosis, organ dysfunction and high short-term mortality that has been recently defined in the CANONIC study(1). In this study of 1343 patients, 30% of hospitalized decompensated cirrhotics had ACLF at study inclusion or developed it afterwards with an associated 90-day mortality of 51% (1). Derived and validated from this study, the CLIF-C ACLF score is a clinically relevant scoring system that can be used sequentially to stratify the risk of mortality in ACLF patients(2). It takes into account the CLIF-C OF (a simplified version of the original Sequential Organ Failure Assessment (SOFA) having 3 points by organ system) along with age and white cell count (http://www.efclif.com/scientific-activity/score-calculators/clif-c-aclf)(2). However only a small proportion of patients (198/1343) in the CANONIC study were managed in the intensive care unit (ICU) setting (1).

ACLF patients admitted to the ICU are a high-risk subset. In the United States, about 26,000 cirrhotics require ICU care for organ support with an overall cost of $3 billion dollars to the health care system (3, 4). Given these significant costs, discriminating between ACLF patients with good and poor prognosis in the ICU is of importance to the healthcare provider as it may influence decisions regarding either escalating care or palliation. Currently discussions regarding goals of care and appropriate use of palliative care are underutilized in ACLF patients (5, 6).

The diagnostic criteria of ACLF in the original CANONIC study were based on the Chronic Liver Failure-SOFA (CLIF-SOFA) score which was modified from

the original SOFA score derived for the general ICU population by Vincent and colleagues(7). Subsequently the CLIF-C ACLF score was shown to outperform traditional liver specific scores such as MELD, MELD-Na and Child-Turcotte Pugh (2). Given the relative small number of ACLF patients in ICU in the original CANONIC study, the importance of evaluating the CLIF-C ACLF score in a high-risk ACLF population admitted to ICUs in Europe and North America is warranted.

In this analysis of 867 ACLF patients admitted to ICU's in Europe and North America, we examined the CLIF-C ACLF score and ACLF grade on admission and at Day 3 after ICU admission and evaluated its ability to discriminate between survivors and non-survivors at 28 and 90 days. We also compared the performance of CLIF-C ACLF to other ICU specific (APACHEII) and liver-specific (MELD, Child-Pugh) scores.

MATERIALS AND METHODS

This pooled analysis was composed of 867 consecutively admitted ACLF patients to ICUs in Canada (University of Alberta in Edmonton, University of British Columbia in Vancouver), Europe (Hôpital Paul Brousse in Paris, Hospital Clinic in Barcelona) and patients enrolled from ICU in the original CANONIC study who on ICU admission met criteria for ACLF. Patients were enrolled in discrete, continuous periods between 2001-2015. Approvals were obtained from Institutional Review Boards of all participating institutions and all participating centers abide by the Declaration of Helsinki. This study was written in accordance with the STROBE guideline for reporting observational studies(8).

Study Design: Patients and Setting.

Data were extracted for all (n=867) adult cirrhotic (biopsy-proven cirrhosis, documented variceal hemorrhage or portal hypertension, hepatic ascites, or encephalopathy) patients meeting criteria for ACLF on admission to ICU. *Inclusion criteria* were: 1) prior diagnosis of cirrhosis; 2) age ≥18 years; and 3) admission to an ICU with ACLF (see below). *Exclusion criteria* were: 1) primary diagnosis of acute (fulminant) liver failure; and 2) liver transplantation prior to ICU admission.

Operational Definitions

Diagnostic criteria of ACLF grades have been previously described elsewhere (1). ACLF grade 1 (ACLF-1) at diagnosis was defined by presence of kidney failure (serum creatinine ≥2 mg/dL) or other single organ/system failure (liver: serum bilirubin ≥12 mg/dL; brain: grade III-IV hepatic encephalopathy [HE] based on West Haven criteria; coagulation: international normalized ratio [INR] ≥2.5 or platelet

count ≤20 ×10^9/L; circulation: treatment with vasoconstrictors to maintain arterial pressure or inotropes to improve cardiac output; lungs: PaO_2/FiO_2 ≤200 or SpO_2/FiO_2 ≤214) if associated with renal dysfunction (serum creatinine ~ 1.5 to 1.9 mg/dL) and/or mild-to-moderate (grade I-II) HE. ACLF grade 2 (ACLF-2) and ACLF grade 3 (ACLF-3) were defined by the presence of 2 or ≥3 organ failures, respectively. The CLIF Consortium Organ Failure (CLIF-C OF) score is a simplified version of the CLIF-SOFA score based on 6 organ failures with a maximum total score of 18 and is described elsewhere(9). The CLIF-C ACLF score is based on the CLIF-C OF score with the inclusion of age and white blood count (2). The ***Acute Physiology and Chronic Health Evaluation (APACHE) II Score*** is described elsewhere (10). The *MELD* (Modified End-stage Liver Disease) score is currently used for organ allocation in Europe and North America(11, 12). The **Child-Turcotte Pugh** score is described elsewhere(13).

Variables and Outcomes

Our primary exposure of interest was ***severity of organ dysfunction,*** as defined by the CLIF-C ACLF score and ACLF grade assessment on ICU admission and at day 3 (48-72 hours post-ICU admission). Other scores evaluated in this analysis at similar time points included CLIF-C OF, MELD, Child Turcotte Pugh and APACHEII (admission only). Co-primary outcomes were mortality at 28 and 90 days from ICU admission.

Statistical Analysis

For univariate statistical comparisons among ACLF grades, the χ^2 test was used for categorical variables and analyses of variance and Kruskal-Wallis test for

continuous variables following testing for normality. The proportional-hazards model for competing risks (PH-CR) proposed by Fine and Gray (14) was used to assess scores (CLIF-C ACLF, MELD, APACHEII, and CTP) as predictors of mortality. This model was chosen to account for liver transplantation as a 'competing' event with mortality as transplant at any given time modifies the probability of death of a specific patient. Cumulative Incidence Functions (CIF) of death were estimated by ACLF grade at admission and at day 3. Harrell's concordance index (C-index) was used to assess the discrimination ability of different scores (15, 16). Since a PH-CR model was used, C-index values and their corresponding 95% confidence intervals (CI's) were estimated treating the transplanted patients as censored at the end of the follow-up (14, 17). For the calculation of C-index CI's, standard errors were estimated by the jack-knife method, based on the assumption of normality following Fieller's theorem (18). Accordingly, c-index comparisons were performed assuming normal distributions. Significance level was set at $p<0.05$. Statistical analysis was performed using SAS v9.4.

RESULTS

Baseline characteristics of 867 ACLF patients in ICU

In total, 867 cirrhotic patients with ACLF (mean age (SD) 56 (11) years, 70% male) were included in this analysis (see **Table 1**). Data stratified by individual site is reported in **Supplementary File 1**. On ICU admission, mean APACHEII (SD) score was 22 (9), MELD 27 (9) and Child Turcotte Pugh 11(2). The mean CLIF-C

ACLF score on admission was 56 (10). The most common indication for ICU admission was infection/sepsis (32%). Of 867 ACLF patients on admission, 169(19%) had ACLF Grade 1, 302 (35%) had ACLF Grade 2 and 396 (46%) ACLF Grade 3.

Mortality based on ACLF Grade and CLIF Organ Failures on Admission

Mortality rates (28 and 90 day) were stratified based on ACLF grade, number of organ failures and CLIF-C ACLF score in **Table 2**. Increasing ACLF grade on admission was significantly associated with higher 28-day (ACLF 1 ~ 22%, ACLF-2 30%, ACLF-3 64%) and 90-day (ACLF 1 ~ 33%, ACLF-2 40%, ACLF-3 74%) mortality ($p< 0.0001$ for both). Increasing number of CLIF organ failures on ICU admission were associated with increased mortality at day 28 (1 organ failure ~ 23%, 5 or more ~ 87%) and day 90 (1 organ failure ~ 33%, 5 or more ~ 91%). CIF of death to 90 days accounting for death and LT stratified by ACLF grade on admission are shown in **Figure 1a**. Increasing ACLF grade (admission) was significantly associated with increased 90-day mortality (Gray's test $p<0.001$).

Mortality based on admission CLIF-C ACLF score

Mortality at 28 and 90 days post-ICU admission stratified by CLIF-C ACLF score on admission (n=867) are shown in **Table 2**. A CLIF-C ACLF score of < 40 on admission was associated with 14% mortality at day 28 and 20% at day 90. In

contrast, an admission CLIF-C ACLF score of > 70 was associated with 86% mortality at day 28 and 90% at day 90.

Comparison of Admission Model Performance at Day 28 and Day 90

Comparisons of discrimination abilities of CLIF-C ACLF, MELD, CTP and APACHEII on admission are shown in ***Supplementary File 2*** for patients with available data for each score. In 848 patients with complete information available to calculate CLIF-C ACLF at admission, CLIF-C ACLF discriminated between survivors and non-survivors with a C-index 0.70 (0.67-0.72) at day 28 and 0.68 (0.66-0.71) at day 90. The CLIF-C OF score (n=852) discriminated between survivors and non-survivors with a C-index 0.72 (0.70-0.75) at day 28 and 0.71 (0.68-0.73) at day 90. MELD (complete data n=864) demonstrated a C-index of 0.68 (0.65-0.71) at day 28 and 0.67 (0.64-0.69) at day 90. CTP (n=674 complete data) demonstrated a C-index of 0.65 (0.61-0.68) at day 28 and 0.64 (0.61-0.67) at day 90. Finally, in 543 patients with complete data, APACHEII demonstrated a C-index of 0.63 (0.59-0.66) at day 28 and 0.62 (0.58-0.66) at day 90.

Direct comparisons between CLIF-C ACLF and other (CLIF-C OF, MELD, CTP, APACHEII) on admission in patients available for both scores (e.g. CLIF-C ACLF and MELD) are shown in **Table 3**. In comparing CLIF-C ACLF and MELD (n=845) on admission, there were no statistically significant differences in model discrimination at day-28 (0.69 (0.67-0.72) vs. 0.68 (0.65-0.70), p=0.25) and day-90 (0.68(0.66-0.70) vs. 0.67(0.64-0.69), p=0.32). However, admission CLIF-C ACLF discriminated survivors from non-survivors significantly better than CTP

(n=666) at day-28 (0.70 (0.67-0.73) vs. 0.65 (0.61-0.68), p=0.002) and day-90 (0.68 (0.66-0.70) vs. 0.64 (0.61-0.67) p=0.004). CLIF-C ACLF on admission also performed significantly better than APACHEII (n=532) at day-28 (0.68 (0.65-0.72) vs. 0.62 (0.59-0.66), p=0.003) and day-90 (0.67 (0.64-0.70) vs. 0.62 (0.58-0.65) p=0.003).

Evolution of ACLF grade in ICU: Admission vs. Day 3

In the overall cohort, 419 patients had physiological data available to calculate ACLF grade on admission and day 3 (48-72 hours post-ICU admission; see **Supplementary file 3)**. In this subset of patients (n=419) on admission, 82 (20%) had ACLF Grade 1, 159 (38%) Grade 2 and 178 (42%) Grade 3. On Day 3, 82 (20%) had no ACLF, 76 (18%) had ACLF Grade 1, 110 (26%) Grade 2 and 151 (36%) Grade 3. CIF of death to 90 days stratified by ACLF grade on **Day 3** are shown in **Figure 1b**. Increasing ACLF grade (Day 3) was significantly associated with increased 90-day mortality (Gray's test p<0.001).

A tabulated flow diagram of comparisons of ACLF grade on admission vs. Day 3 are shown graphically in **Figure 2** ***(numerically in Supplementary File 4)*** with associated 28 and 90 day mortalities. Corresponding 28 and 90 day mortality were significantly different per ACLF grade on admission and Day 3 (p< 0.001 for all).

Data on ACLF grade evolution is shown in ***Supplementary File 5***. By day 3 after ICU support, 167 patients had at least a 1 grade improvement, 200 had no change in ACLF grade and 52 patients deteriorated by at least 1 grade despite ICU support. Patients that presented with ACLF Grade 3 on admission who

demonstrated some improvement by Day 3 had a 90-day mortality of 40% (27/67) while those were still ACLF Grade 3 at Day 3 (no change) had a corresponding 90-day mortality of 79% (88/111).

Changes in prognostic scores between admission and day 3 (delta MELD, CLIF-C ACLF and CLIF-C OF) are shown in ***Supplementary File 6***. In 188 patients, where sufficient data were available to calculate both CLIF-C ACLF and MELD at Day 3, there were no statistically significant differences in model discrimination at day-28 (0.77 (0.71-0.82) vs. 0.76 (0.70-0.81), p=0.72) and day-90 (0.74(0.69-0.79) vs. 0.73 (0.68-0.79), p=0.83).

CIF of survival to 90 stratified by CLIF-C ACLF score on admission and at 48-72 hours post-admission are shown in ***Supplementary File 7***. Increasing CLIF-C ACLF score (both time points) were significantly associated with increased 90-day mortality (Gray's test $p<0.001$).

Discussion

Summary of Key results

In this analysis of 867 ACLF patients admitted to ICUs in Europe and North America, increasing ACLF grade on admission and at day 3 was associated with increased mortality at 90 days (Gray's test). Patients who demonstrated clinical improvement post-ICU admission (e.g. ACLF-3 to 1 or 2) at day 3 demonstrated better outcomes at 28 and 90 days than those who did not. A CLIF-C ACLF score of > 70 on ICU admission was associated with 90% mortality at day 90. CLIF-C ACLF discriminated well between survivors and non-survivors (C-index ~ 0.75) and significantly better on direct comparison with APACHEII and CTP at similar time points (and patients) but not MELD. CLIF-C ACLF and MELD performed better at Day 3 than on admission.

Comparisons with Previous Literature

While outcomes in ACLF patients admitted to ICU are improving in general (19-21), mortality remains high, particularly in those patients with septic shock and multiorgan failure (22). Sepsis from bacteremia, not formally captured in prognostic scores, has been demonstrated to significantly impact outcome (23). In our analysis, infection/sepsis was the primary reason for ICU admission in approximately one third (268/848) of ACLF patients. Furthermore, in 50% of patients at highest risk (ACLF Grade 3), bacterial infection was found to be a precipitating event in their deterioration. Late identification of infection and initiation of appropriate antimicrobial therapy has been shown elsewhere to be associated with adverse outcomes not necessarily accounted for in organ failures (24, 25).

This study builds on previous literature that demonstrates current prognostic scoring systems, including the CLIF-C ACLF score, are approximately 75% accurate(26). Although CLIF-C ACLF takes into account extra-hepatic organ failures, there are some confounders. For example, ACLF patients are often started on vasopressors for the management of AKI/HRS and it is unclear whether this truly represents cardiovascular failure or therapy for AKI. This has similarly presented challenges in other critically ill populations. For example, in the neurocritical care literature, patients will often be started on vasopressor therapy to increase mean arterial pressure as part of a neuroprotective strategy(27).

The CLIF-C ACLF does appear to identify ACLF patients with poor prognosis. In this analysis, patients with a CLIF-C ACLF score of greater than 70 were associated with a 90-day mortality of 90% whether identified on admission of by day 3. In cirrhotic/ACLF patients in this category who are ineligible for transplant and who do not respond to short term therapy (72 hours), consideration should be given to placing ceilings on critical care support and a re-evaluation of goals of care should be strongly considered. Poonja and colleagues demonstrated in a retrospective cohort of 102 cirrhotic patients declined for transplant, that goals of care were only documented in 29% of patients(5). Scores such as the CLIF-C ACLF score which is available on a mobile platform (ACLF calculator) may provide assistance in having appropriate discussions earlier in ACLF patients either prior to initiating life support or after deterioration despite organ support. Incorporation of palliative care in the intensive care unit may decrease unnecessary and futile use of life support while potentially improving patient and family satisfaction (28).

In the absence of ‘gold standard’ in current prognostic scores, there are opportunities for novel biomarkers in ACLF to improve existing models and potentially reflect information not currently captured in conventional clinical and biochemical data(26). Potential rationale includes earlier detection of the evolution of ACLF syndrome in cirrhotic patients where an intervention may prevent progression to its most severe forms (e.g. CLIF-C ACLF > 70).

Inflammation and oxidative stress are believed to be key pathophysiological processes in the development of ACLF(29). While white blood count is incorporated in the CLIF-C ACLF score, other markers of inflammation/oxidative stress involved in the activation of monocytes and neutrophils, such as HMGB1, has been demonstrated to be increased in non-survivors but needs to be validated in addition to currently used prognostic scores(30). Inflammatory markers of cell apopotosis (e.g. M30 antigen) which have been showed to be increased in non-survivors with ACLF, might help improve discrimination of existing prognostic scores such as CLIF-C ACLF (it has been demonstrated to improve MELD)(31). Recently, Ariza and colleagues demonstrated in a series of 716 patients with cirrhosis that urinary neutrophil gelatinase-associated lipocalin (NGAL) was markedly increased in patients with ACLF and correlated with mortality and also warrants potential further investigation in concert with current prognostic scores (32).

In evaluating future biomarkers in ACLF, it is important to take into account differences in etiologies (e.g. alcohol, viral hepatitis, fatty liver), geographic variation and complications which contributes to significant heterogeneity of

patient phenotypes. For example, in the acute lung injury/ARDS literature, the failure of pharmacologic therapies in ARDS highlighted the importance of recognizing heterogeneity and finding approaches to classify patients in categories or phenotypes (e.g. hyper vs. hypo inflammatory) that might be responsive to specific therapeutic approaches that may not be effective in all patients(33). In ACLF, where patients may be exhibit unregulated inflammation or conversely immunosuppression(34), stratifying patients into endotypes by biomarker concentrations or genomic profiling may enhance our ability to determine with greater certainty preemptively response to therapy.

Limitations

This study should be interpreted in the light of its strengths and limitations. The strengths include the inclusion of ACLF patients from both general ICUs (Edmonton, Vancouver) and Liver-specific ICUs (Barcelona, Paris) as well as other ICUs from sites who contributed to the CANONIC study. This analysis also included patients from multiple geographic sites (Europe and North America), lending the results of the study to wide generalizability. Regarding its limitations, this study is a retrospective pooled analysis and thus is observational in nature. Only association and not causation can be inferred. Observational studies such as this are subject to confounding and bias(35). Data regarding survival beyond 90 days, rates of re-hospitalizations, economic impact, and quality of life in survivors were not captured in this analysis. CLIF-C ACLF score at day one does not provide complete insight into who will or will not improve at day 3 and we did not have clinical data on patients to calculate clinical scores (e.g. CLIF-C ACLF) in patients

beyond Day 3. We only had complete data on 188 ACLF patients to compare model between CLIF-C ACLF and MELD on day 3.

CONCLUSIONS

In a high risk subpopulation of ACLF patients from different regions (Europe, North America) and ICU types (Specialty Liver and General ICUs), the CLIF-C ACLF demonstrated better discrimination at day 28 and day 90 compared to APACHEII and CTP. Patients who demonstrated clinical improvement post-ICU admission (e.g. ACLF-3 to 1 or 2) at day 3 demonstrated better outcomes than those who did not. In high risk ICU patients (CLIF-C ACLF > 70), decisions regarding transition to palliation should be explored between patient families and the ICU providers after a short trial of therapy.

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Figure Legends

Figure 1: 1a) Cumulative Incidence Functions of death stratified by ACLF grade on admission (Gray's test $p < 0.0001$, n=867) 1b) Cumulative incidence functions of death stratified by ACLF grade on Day 3 after admission (Gray's test $p < 0.0001$, n=419)

Figure 2: Dynamic changes in ACLF grade in patients with available data on both Admission and Day 3 and mortality.

- For each of the groups of patients defined by the ACLF grades at admission, comparisons of 28-day and 90-day mortality rates among final ACLF grades on Day 3 were statistically significantly different ($p<0.0001$). Similarly, for each of the groups of patients defined by the ACLF grades at Day 3, comparisons of 28-day and 90-day mortality rates among original ACLF grades at admission were also statistically significantly different ($p<0.0001$).