Determining futility 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)

Version 1

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Abstract: 250 words

Manuscript: 3250 words (excluding abstract, references and tables)

Number of tables: **4** Number of figures: **2** Number of supplementary files: **2**

Keywords: Acute on chronic liver failure; antimicrobial therapy; bloodstream infection; cirrhosis; septic shock; spontaneous bacterial peritonitis

List of Abbreviations

ACLF	acute-on-chronic liver failure
APACHEII	acute physiology and chronic health evaluation II score
AUROC	area under receiver operating characteristic
BSI	bloodstream infection
CATSS	Cooperative Antimicrobial Therapy of Septic Shock
CI	Confidence interval
CIF	Cumulative incidence function hazard
CTP	Child Turcotte Pugh
HE	hepatic encephalopathy
HR	heart rate
ICU	intensive care unit
INR	Internationalized ratio
MELD	model for end stage liver disease score
MV	mechanical ventilation
OR	odds ratio
RRT	renal replacement therapy
SBP	Spontaneous bacterial peritonitis
SD	Standard deviation
SOFA	Sequential organ failure assessment

Statement of Interest

Conflict of interest: All authors have no personal or funding conflicts of interest.

Financial support: The EASL-CLIF Consortium has an unrestricted grant from Grifols.

Format: This paper followed the STROBE guideline for reporting retrospective studies (BMJ 2007): See Supplementary File #1.

ABSTRACT

BACKGROUND: Acute-on-chronic liver failure (ACLF) is a syndrome characterized by high short-term mortality. Critical care physicians are often faced with difficult decisions regarding ongoing life support or palliation. This study aimed to evaluate the previously described CLIF-C ACLF score in a high-risk population of ACLF patients admitted to intensive care units (ICU) from different global regions (Europe and North America) and compare discrimination ability with previously published scores.

METHODS:

Sample of analysis was composed of data from 867 cirrhotic patients with ACLF from ICUs in Canada (University of Alberta, University of British Columbia) and Europe (Paris, Barcelona) and from patients enrolled from ICU in the original CANONIC study who on ICU admission met criteria for ACLF. Cumulative Incidence Functions (CIF) of survival were estimated by ACLF grade at admission and at day 3. A concordance index (C-index) was used to compare the survival discrimination abilities of CLIF-C ACLF, MELD, APACHEII, and Child-Pugh (CTP) scores.

RESULTS:

In this pooled sample (n=867; mean age 56 years, 30% female), the most common etiology was alcohol (53%) and the most common reason for ICU admission was infection (32%). Of 867 ICU ACLF patients, on admission 169(19%) had ACLF-1, 302(35%) ACLF-2 and 396 (46%) had ACLF-3 with corresponding 90-mortality rates of 33%, 40% and 74% respectively ($p< 0.001$).

In a subgroup of the sample (419/867) where data on day 3 were also available, 90-day mortality rates were as follows: NO ACLF on Day 3= 12%, ACLF-1 22%, ACLF-2 47%, ACLF-3 80%; (p<0.001). Plots of CIF for survival based on ACLF grade on admission and day 3 are shown in Figures 1 and 2. Differences among strata (ACLF grades) were statistically significant (Gray's test p < 0.001 for both).

In evaluating admission prognostic scores in pooled ICU patients, CLIF-C ACLF demonstrated superior discrimination between survivors and non survivors at 90 days compared with APACHE II (n=532, C-index 0.67 (0.64-0.70) vs. 0.62 (0.58-0.65), p=0.0027) and Child Pugh (n=666; C-index 0.68(0.66-0.71) vs. 0.64 (0.61-0.67), p=0.0035) but not MELD (n=845; C-index (0.68 (0.66-0.70) vs. 0.67 (0.64-0.69), p=0.3) or CLIF-OF (n=848; 0.68 (0.66-0.71) vs. 0.71 (0.68-0.73) p=0.051). A CLIF-C ACLF score > 70 was associated with mortality rates of 86% at 28 days and 90% at 90 days. Comparing CLIF-C ACLF vs. MELD at 48-72 hours post-ICU (n=188), there were no statistically significant differences in model discrimination at day-90 (0.74(0.69-0.79) vs. 0.73(0.68-0.79), p=0.83).

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. In high risk ICU patients (CLIF-C ACLF > 70), decisions regarding transition to palliation should be explored between patient families and the ICU providers.

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a syndrome characterized by acute decompensation of cirrhosis, organ dysfunction and high short-term mortality[1] and has been recently defined in the CANONIC study. In this study of 1349 patients, 30% of hospitalized decompensated cirrhotics had ACLF at study inclusion or developed it afterwards with an associated 90-day mortality of 51%[2]. However only a small proportion of patients (198/1349) in the CANONIC study were managed in the intensive care unit (ICU) setting[2].

ACLF patients admitted to the ICU are a high risk subset. In the United States, of approximately 200,000 patients with cirrhosis admitted to hospital each year, about 26000 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 discussion of goals of care and appropriate use of palliative care are underutilized in ACLF patients[5].

The diagnostic criteria of ACLF in the original CANONIC study were based on the Chronic Liver Failure-SOFA score which was modified from the original SOFA score derived for the general ICU population by Vincent and colleagues[6]. Subsequently the CLIF-C ACLF score was derived from the original CANONIC study and was shown to outperform traditional liver specific scores such as MELD, MELD-Na and Child-Turcotte Pugh[1]. 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 intensive care units 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 sample of 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. Approval was obtained from the Institutional Review Boards of all participating institutions. This study was written according to the STROBE guideline for reporting retrospective studies[7].

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) post-liver transplantation.

Operational Definitions

Diagnostic criteria of ACLF grades have been previously described elsewhere[2]. 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 kidney dysfunction (serum creatinine ranging from 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-C ACLF score was recently defined based on the CLIF organ failure scores with the inclusion of age and white blood count[1].

The ***Acute Physiology and Chronic Health Evaluation (APACHE) II Score*** is an illness severity classification system based upon initial values of 12 routine physiologic measurements, age, and previous health status to provide a general measure of severity of disease. An increasing score (range 0 to 71) correlates with increasing risk of hospital death [8]. The *MELD* (Modified End-stage Liver Disease) score is currently used for organ allocation in Europe and North America .[9, 10] The **Child-Turcotte Pugh** score is described elsewhere[11].

Variables and Outcomes

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

Statistical Analysis

Categorical variables are described by means of counts and percentages. Continuous variables are reported as the mean (standard deviations) or median (interquartile range) following testing for normality. In univariate statistical comparisons among ACLF grades, the χ^2 test was used for categorical variables and analyses of variance or Kruskal-Wallis test for continuous variables depending on their nature. The proportional-hazards model for competing risks (PH-CR) proposed by Fine and Gray[12] 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 based on the consideration that transplantation at a given time clearly modifies the probability of death of a specific patient at each subsequent time-point. Cumulative Incidence Functions (CIF) of survival were estimated by ACLF grade at admission and at day 3. Harrell's concordance index (C-index) was used to estimate the discrimination abilities of scores[13, 14]. As a PH-CR model was used, C-index values and the corresponding 95% confidence intervals (CIs) were estimated treating the transplanted patients as censored at the end of the follow-up, assuming that none of them could die before[12]. Statistical comparisons of C-indexes were performed assuming normal distribution. 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 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 primary etiology of cirrhosis was alcohol (53%). 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. Biochemical derangement increased significantly with ACLF grade as demonstrated in Table 1 (white blood count, creatinine, INR and lactate).

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 ~ 23%, ACLF-2 30%, ACLF-3 64%) and 90-day (ACLF 1 ~ 33%, ACLF-2 40%, ACLF-3 74%) mortality ($P<0.001$ for both). Increasing number of CLIF organ failures on ICU admission was 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 survival to 90 days accounting for death and LT stratified by ACLF grade on admission are shown in Figure 1. 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 Table 3 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. 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 (MELD, CTP, APACHEII) on admission in patients available for both scores (e.g. CLIF-C ACLF

and MELD) are shown in **Table 4**. 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). However on admission, the CLIF-C OF score performed significantly better than the CLIF-C ACLF (n=848) at day-28 (0.72 (0.70-0.75) vs. 0.69 (0.67-0.72), p=0.045) but not (only a trend) at day-90 (0.71 (0.68-0.73) vs. 0.68 (0.66-0.71) p=0.051).

Evolution of ACLF grade in ICU: Admission vs. 48-72 hours post-admission

In the overall cohort, 419 patients had physiological data available to calculate ACLF grade on admission and day 3 (48 hours post-ICU admission). 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 (Supplementary file 2). Numbers of organ failures and CLIF_C ACLF score for Day 3 are shown in supplementary file 3.

Cumulative Incidence Functions (CIF) of survival to 90 days accounting for competing risks stratified by ACLF grade on **Day 3** are shown in **Figure 2**. Increasing ACLF grade (Day 3) was significantly associated with increased 90-day mortality (Gray's test $p<0.001$).

Cross tabulated comparisons of ACLF grade on admission vs. Day 3 are shown in Table 5 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 both).

Data on ACLF grade evolution is shown in Supplementary File 2. 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 4.

In 188 patients, there were sufficient data 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).

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 long term outcomes 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[15-17], mortality remains high, particularly in those patients with septic shock and multiorgan failure[18]. Sepsis/bacteremia, which is not formally captured in prognostic scores has been demonstrated to significantly impact outcome. O'Brien and colleagues in 2012 reported in more than 16000 cirrhotic patients admitted into UK ICUs, those patients who presented with septic shock and at least one organ failure had a mortality rate > 90%[19]. 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 the most at risk patients (ACLF Grade 3), bacterial infection was found to be a precipitating event in their

deterioration. While not assessed in this analysis, 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[20].

This study builds on previous literature that demonstrated that current prognostic scoring systems, including the CLIF-C ACLF score are approximately 75% accurate[21]. Although CLIF-C ACLF takes into account extra-hepatic organ failures, there are some confounders. For example, ACLF patients are often started on vasopressors (terlipressin, vasopressin, norepinephrine) 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[22].

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. Traditionally, addressing goals of care in non-cancer populations, particularly in cirrhotic patients has been done poorly. Poonja and colleagues demonstrated that 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. While incorporation of palliative care in cirrhosis is increasing, its use in the intensive care unit and advanced care planning may decrease unnecessary and futile use of life support while potentially improving patient and family satisfaction with a focus on symptom control and quality of life[23].

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[21]. Potential rationale includes earlier detection of evolution of ACLF syndrome in cirrhotic patients where an intervention may prevent progression to the most severe forms of ACLF (e.g. CLIF_C ACLF > 70).

Inflammation and oxidative stress are believed to be key pathophysiological processes in the development of ACLF[24]. 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[25]. 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)[26]. Recently, Ariza and colleagues demonstrated that urinary neutrophil gelatinase-associated lipocalin (NGAL) in a series of 716 patients with cirrhosis that urine NGAL was markedly increased in patients with ACLF and correlated with mortality and also warrants potential further investigation in concert with current prognostic scores[27].

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 ICU's (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[28].

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 long-term 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.

Guarantor of the article for manuscript submission: Dr. Karvellas accepts full responsibility for this study. He has access to the data and accepts for responsibilities association with its publication.

Figure Legends

Figure 1: Cumulative incidence functions of survival stratified by ACLF grade on admission (inclusion). Gray's test p < 0.0001

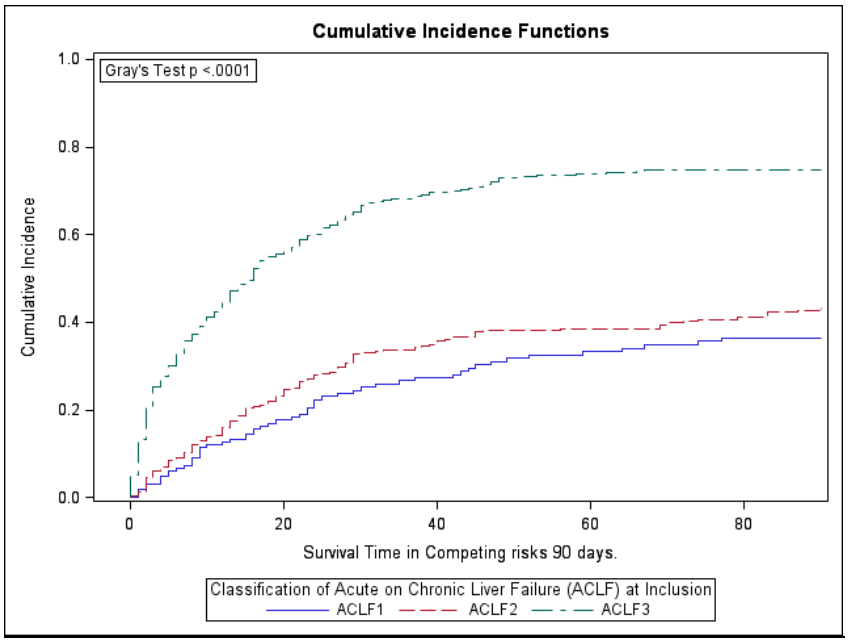

Figure 2: Cumulative incidence functions of survival stratified by ACLF grade on Day 3. Gray's test $p < 0.0001$

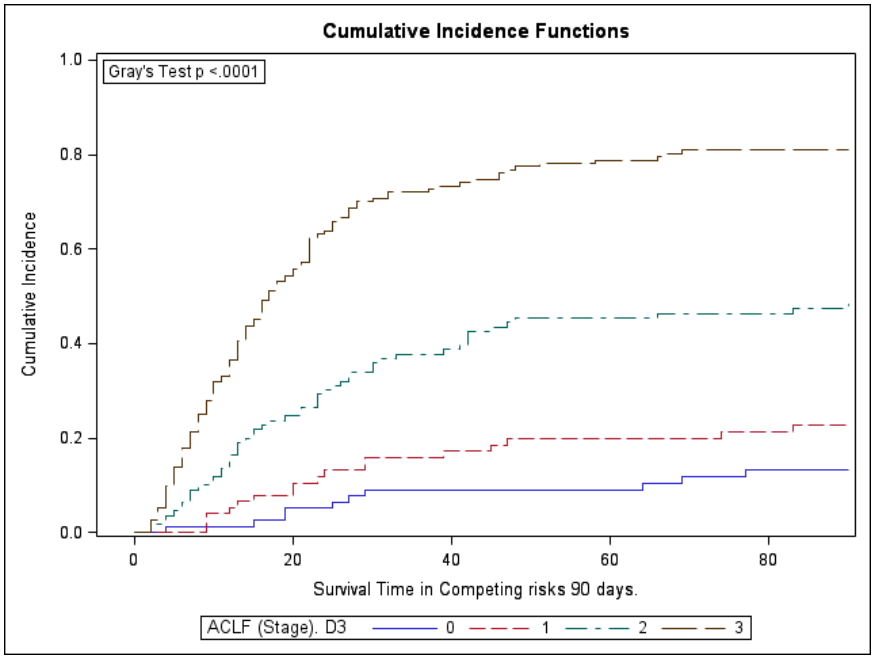

Table 1. Baseline characteristics of 867 patients with acute on chronic liver failure admitted to Intensive Care units.

Variable	n	All Patients (n=867)	ACLF-1 (n=169)	ACLF-2 (n=302)	ACLF-3 (n=396)
Age*	867	(867) 56 +/- 11	(169) 58 +/- 10	(302) 55 +/- 11	(396) 56 +/- 10
Sex (Female)	867	264/867 (30.45 %)	52/169 (30.77 %)	93/302 (30.79 %)	119/396 (30.05 %)
Etiology of Cirrhosis	858				
Alcohol	451	451/858 (52.56 %)	91/167 (54.49 %)	154/299 (51.51 %)	206/392 (52.55 %)
HCV	166	166/858 (19.35 %)	37/167 (22.16 %)	66/299 (22.07 %)	63/392 (16.07 %)
Alc+HCV	108	108/858 (12.59 %)	14/167 (8.38 %)	36/299 (12.04 %)	58/392 (14.80 %)
Others	133	133/858 (15.50 %)	25/167 (14.97 %)	43/299 (14.38 %)	65/392 (16.58 %)
Primary ICU Admission Cause	848				
Infection/Sepsis	268	268/848 (31.60 %)	45/168 (26.79 %)	86/297 (28.96 %)	137/383 (35.77 %)
Bleeding	150	150/848 (17.69 %)	34/168 (20.24 %)	55/297 (18.52 %)	61/383 (15.93 %)
Hepatic Encephalopathy	132	132/848 (15.57 %)	25/168 (14.88 %)	51/297 (17.17 %)	56/383 (14.62 %)
Respiratory Failure	51	51/848 (6.01 %)	11/168 (6.55 %)	20/297 (6.73 %)	20/383 (5.22 %)
Acute Kidney Injury	122	122/848 (14.39 %)	25/168 (14.88 %)	39/297 (13.13 %)	58/383 (15.14 %)
Others	125	125/848 (14.74 %)	28/168 (16.67 %)	46/297 (15.49 %)	51/383 (13.32 %)
Precipitating Events					
Bacterial Infection	692	309/692 (44.65 %)	60/149 (40.27 %)	108/261 (41.38 %)	141/282 (50.00 %)
Active Alcoholism	553	262/553 (47.38 %)	56/136 (41.18 %)	92/199 (46.23 %)	114/218 (52.29 %)
No PE (Binf, ActAlcor Gblee as Adm Cause)	650	114/650 (17.54 %)	38/147 (25.85 %)	43/237 (18.14 %)	33/266 (12.41 %)
Ascites	769	584/769 (75.94 %)	118/160 (73.75 %)	179/243 (73.66 %)	287/366 (78.42 %)
Biochemistry					
WBC (x10^9cells/L)**	863	9.5 (6.1 - 14.3)	(168) 7.8 (4.9 - 11.9)	(301) 9.3 (5.9 - 13.7)	(394) 10.5 (6.7 - 15.7)
AST (U/L)**	852	69 (39 - 136.5)	(166) 53 (32 - 89)	(298) 64 (35 - 125)	(388) 85.5 (44.5 - 213)
ALT (U/L)**	841	50 (28 - 101)	(165) 42 (25 - 73)	(293) 48 (27 - 96)	(383) 55 (30 - 131)
Na (mEq/L)	521	135 +/-8	(88) 134 +/- 7	(150) 135 +/-7	(283) 136 +/- 8
Creatinine (mg/dL)**	867	1.8 (1.03 - 3)	(169) 1.64 (1 - 2.6)	(302) 1.3 (0.86 - 2.2)	(396) 2.21 (1.40 - 3.19)
INR**	775	2.0 (1.6 - 2.8)	(160) 1.7 (1.5 - 2.1)	(247) 2.0 (1.5 - 2.5)	(368) 2.4 (1.8 - 3.6)
Lactate (mg/dl)**	**259**	32.43 (17.1 - 68.0)	(27) 17.1 (11.7 - 29.7)	(64) 17.6 (11.3-34.2)	(168) 44.6 (25.2-93.1)
Scores at Admission					
MELD	864	27.03 +/- 8.64	(169) 22.51 +/- 6.15	(302) 24.17 +/- 8.23	(393) 31.17 +/- 7.99
CTP	674	10.85 +/- 2.07	(144) 9.84 +/- 1.86	(254) 10.53 +/- 2.03	(276) 11.66 +/- 1.89
APACHE II	543	22.1 +/- 9.1	(90) 17.3 +/- 6.5	(189) 19.9 +/- 10.4	(264) 25.3 +/- 7.5
CLIF-C ACLF	848	55.85 +/- 9.96	(163) 46.78 +/- 6.97	(297) 51.93 +/- 6.67	(388) 62.66 +/- 8.36

Table 2. Mortality Rates at 28 and 90 days in 867 ACLF patients based on admission characteristics

Variable	N (%)	28-day Mortality	90-day Mortality
ACLF Grade	**N (%)**	**28-day Mortality**	**90-day Mortality**
Grade 1	169/867 (19.49 %)	38/169 (22.49 %)	55/169 (32.54 %)
Grade 2	302/867 (34.83 %)	90/302 (29.80 %)	121/302 (40.07 %)
Grade 3	396/867 (45.67 %)	253/396 (63.89 %)	292/396 (73.74 %)
p-value		<.0001	<.0001
Number of failures	**N (%)**	**28-day Mortality**	**90-day Mortality**
1	169/867 (19.49 %)	38/169 (22.49 %)	55/169 (32.54 %)
2	302/867 (34.83 %)	90/302 (29.80 %)	121/302 (40.07 %)
3	208/867 (23.99 %)	104/208 (50.00 %)	133/208 (63.94 %)
4	106/867 (12.23 %)	78/106 (73.58 %)	84/106 (79.25 %)
5	62/867 (7.15 %)	54/62 (87.10 %)	57/62 (91.94 %)
6	20/867 (2.31 %)	17/20 (85.00 %)	18/20 (90.00 %)
Type of Organ Failure	**N (%)**	**28-day Mortality**	**90-day Mortality**
Hepatic	253/867 (29.18 %)	147/253 (58.10 %)	170/253 (67.19 %)
Renal	422/867 (48.67 %)	232/422 (54.98 %)	265/422 (62.80 %)
Neurological	387/867 (44.64 %)	187/387 (48.32 %)	224/387 (57.88 %)
Coagulation	266/867 (30.68 %)	169/266 (63.53 %)	194/266 (72.93 %)
Cardiovascular	451/867 (52.02 %)	247/451 (54.77 %)	296/451 (65.63 %)
Respiratory	472/867 (54.44 %)	232/472 (49.15 %)	276/472 (58.47 %)
CLIF-C ACLF	**N (%)**	**28-day Mortality**	**90-day Mortality**
0 - 40	51	7/51 (13.73 %)	10/51 (19.61 %)
> 40 - 50	198	45/198 (22.73 %)	69/198 (34.85 %)
> 50 – 60	337	137/337 (40.65 %)	177/337 (52.52 %)
> 60 – 65	110	66/110 (60.00 %)	77/110 (70.00 %)
> 65 – 70	82	58/82 (70.73 %)	63/82 (76.83 %)
> 70 – 75	43	37/43 (86.05 %)	38/43 (88.37 %)
> 75	27	23/27 (85.19 %)	25/27 (92.59 %)
> 70	70	60/70 (85.71 %)	63/70 (90.00 %)

Table 3. Discrimination ability of MELD, CTP, APACHEII and CLIF-C ACLF for 28-day and 90-day Mortalities.

	28-day Mortality		90-day Mortality	
Score	**N (#Events)**	**c-index (95%CI)**	**N (#Events)**	**c-index (95%CI)**
MELD	864 (378)	0.679 (0.652, 0.706)	864 (465)	0.669 (0.644, 0.693)
CTP	674 (291)	0.646 (0.613, 0.679)	674 (352)	0.639 (0.609, 0.670)
APACHE II	543 (225)	0.625 (0.586, 0.664)	543 (276)	0.619 (0.584, 0.655)
CLIF-C OF	852 (376)	0.721 (0.697,0.746)	852 (462)	0.705 (0.683, 0.727)
CLIF-C ACLF	848 (373)	0.695 (0.669, 0.721)	848 (459)	0.681 (0.657, 0.705)

Table 4. Statistical comparison of discrimination abilities of CLIF-C ACLF versus MELD, Child Turcotte Pugh and APACHEII scores based on admission criteria**.**

	28-day Mortality			90-day Mortality		
Score	**N (#Events)**	**c-index (95%CI)**	**p-value***	**N (#Events)**	**c-index (95%CI)**	**p-value***
Patients with data for CLIF-C ACLF and MELD scores: N =845						
MELD	845 (370)	0.6772 (0.6498, 0.7046) SE = 0.0140	0,2531	845 (456)	0.6669 (0.6418, 0.6919) SE = 0.0128	0,3211
CLIF-C ACLF	845 (370)	0.6932 (0.6672, 0.7193) SE = 0.0133	REF	845 (456)	0.6796 (0.6555, 0.7037) SE = 0.0123	REF
Patients with data for CLIF-C ACLF and Child Turcotte Pugh scores: N = 666						
CHILD	666 (288)	0.6455 (0.6127, 0.6784) SE = 0.0168	0,0022	666 (348)	0.6388 (0.6083, 0.6692) SE = 0.0155	0,0035
CLIF-C ACLF	666 (288)	0.6970 (0.6673, 0.7268) SE = 0.0152	REF	666 (348)	0.6840 (0.6563, 0.7118) SE = 0.0142	REF
Patients with data for CLIF-C ACLF and APACHE II scores: N = 532						
APACHE II	532 (220)	0.6242 (0.5851, 0.6634) SE = 0.0200	0,0028	532 (271)	0.6182 (0.5825, 0.6539) SE =0.0182	0,0027
CLIF-C ACLF	532 (220)	0.6839 (0.6499, 0.7179) SE = 0.0173	REF	532 (271)	0.6728 (0.6415, 0.7041) SE = 0.0160	REF
Patients with data for CLIF-C ACLF and APACHE II scores: N = 532						
CLIF-C OF	848 (181)	0.7532 (0.7204, 0.7861) SE = 0.0168	0,0473	848 (373)	0.7213 (0.6968, 0.7458) SE = 0.0125	0,0455
CLIF-C ACLF	848 (181)	0.7171 (0.6813, 0.7528) SE = 0.0182	REF	848 (373)	0.6949 (0.6691, 0.7208) SE = 0.0132	REF

Table 5a Crosstabs. Patients with available data in both Admission and Day 3

ACLF Grade Day 3	No ACLF (82)	Grade 1 (76)	Grade 2 (110)	Grade 3 (151)	
ACLF Grade Admission	**n/N (%)** 28-day Mortality 90-day Mortality	**n/N (%)** 28-day Mortality 90-day Mortality	**n/N (%)** 28-day Mortality 90-day Mortality	**n/N (%)** 28-day Mortality 90-day Mortality	
Grade 1 (82)	**32/82 (39.02%)** 0 2/32 (6.25 %)	**31/82 (37.80%)** 5/31 (16.13 %) 7/31 (22.58 %)	**12/82 (14.63%)** 5/12 (41.67 %) 7/12 (58.33 %)	**7/82 (8.54%)** 7/7 (100.00 %) 7/7 (100.00 %)	**82** 17/82 (20.73 %) 23/82 (28.05 %)
Grade 2 (159)	**37/159 (23.27%)** 6/37 (16.22 %) 7/37 (18.92 %)	**31/159 (19.50%)** 2/31 (6.45 %) 6/31 (19.35 %)	**58/159 (36.48%)** 16/58 (27.59 %) 23/58 (39.66 %)	**33/159 (20.75%)** 24/33 (72.73 %) 26/33 (78.79 %)	**159** 48/159 (30.19 %) 62/159 (38.99 %)
Grade 3 (178)	**13/178 (7.30%)** 0 1/13 (7.69 %)	**14/178 (7.87%)** 3/14 (21.43 %) 4/14 (28.57 %)	**40/178 (22.47%)** 16/40 (40.00 %) 22/40 (55.00 %)	**111/178 (62.36%)** 74/111 (66.67 %) 88/111 (79.28 %)	**178** 93/178 (52.25 %) 115/178 (64.61 %)
	82 6/82 (7.32 %)* 10/82 (12.20 %)**	**76** 10/76 (13.16 %)* 17/76 (22.37 %)**	**110** 37/110 (33.64 %)* 52/110 (47.27 %)**	**151** 105/151 (69.54 %)* 121/151 (80.13 %)**	**419**

- *p-value Chi-Square (Comparison 28-day Mort in ACLF_D3) = <.0001
- **p-value Chi-Square (Comparison 90-day Mort in ACLF_D3) = <.0001
- # p-value Chi-Square (Comparison 28-day Mort in ACLF) = <.0001
- # p-value Chi-Square (Comparison 90-day Mort in ACLF) = <.0001

Table 5b ACLF Grade Evolution

	ACLF Day 3		
	Improvement	**No change**	**Worsening**
ACLF at Admission	***ACLF Grades*** **n/N (%)** 28-day Mortality 90-day Mortality	***ACLF Grades*** **n/N (%)** 28-day Mortality 90-day Mortality	***ACLF Grades*** **n/N (%)** 28-day Mortality 90-day Mortality
ACLF 1 (82)	***No ACLF*** **32/82 (39.02%)** 0 2/32 (6.25 %)	***Grade 1*** **31/82 (37.80%)** 5/31 (16.13 %) 7/31 (22.58 %)	***Grade 2/3*** **19/82 (23.17%)** 12/19 (63.16%) 14/19 (73.68%)
ACLF 2 (159)	***No ACLF / ACLF 1*** **68/159 (42.77%)** 8/68 (11.76%) 13/68 (19.12%)	***ACLF 2*** **58/159 (36.48%)** 16/58 (27.59 %) 23/58 (39.66 %)	***ACLF 3*** **33/159 (20.75%)** 24/33 (72.73 %) 26/33 (78.79 %)
ACLF 3 (178)	***No ACLF / ACLF 1/2*** **67/178 (37.64%)** 19/67 (28.36%) 27/67 (40.30%)	***ACLF 3*** **111/178 (62.36%)** 74/111 (66.67 %) 88/111 (79.28 %)	--

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