

Novel Approaches and Therapeutics in Acute on Chronic Liver Failure

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Acute-on-Chronic Liver Failure (ACLF) in cirrhosis has recently been characterized by the CANONIC study as a highly prevalent syndrome consisting in acute decompensation (AD), organ/system failure(s) and high 28-day mortality (32%).¹ Until the publication of the CANONIC study, conventional scoring systems developed to define the prognosis of patients with cirrhosis such as the Child Pugh and Model for End-Stage Liver Disease (MELD) scores or their variations were the only tools available to prognosticate in this patient cohort. They were limited in their prognostic accuracy in ACLF due to a failure to incorporate two central prognostic determinants; (a) extra-hepatic organ failures and (b) measures of systemic inflammation, which fundamentally underlie the pathophysiological basis of the syndrome.

The CANONIC study¹ was a large scale multi-centre prospective clinical study evaluating over 1300 patients hospitalized with a complication of cirrhosis was conducted to describe the clinical phenotypes of patients with acute on chronic liver failure (ACLF). A further specific aim of the study was to assess the currently available prognostic scoring systems and develop a new score if required. Indeed, the aims of the study were met and led to the description of the ACLF phenotype and the development and validation of novel scoring systems for the prognosis of patients with ACLF and acute decompensation (AD).^{2,3} The resultant CLIF Consortium ACLF score (CLIF-C ACLFs) has since been independently validated with proven superior prognostic accuracy for ACLF compared to conventional measures such as MELD, and Child-Pugh scores. The temporal clinical course of these patients was identified as an important prognostic indicator and dynamic assessment of the patient's clinical course using these scoring systems has also been validated as an important prognostic tool.⁴

This chapter will consider the phenotype of ACLF and acute decompensation (AD) and how the nature of this influences outcome. Secondly, a description of the scoring systems developed from the CANONIC study data, how they compare with other scoring systems and a proposed algorithm of how they may be applied in clinical practice, in particular liver transplantation. Finally,

we will discuss the PIRO concept, which may be a useful model to consider the development of new approaches to therapy of ACLF.

The main results of the CANONIC study

The data from the CANONIC study showed that the presence of ACLF as diagnosed using an organ failure scoring system, distinguished patients with a 28-day mortality of greater than 15% (referred to as ACLF group) and described several grades of ACLF. A modified sequential organ failure assessment (SOFA) score, evaluating liver, kidney, brain, coagulation, circulation and respiratory function was used (Tables 1, 2). ACLF grades (1-3) were found to be highly predictive of mortality with strikingly different outcomes (Figure 1). In addition to ACLF score at presentation, the temporal course of ACLF (particularly over the first 7 days) was found to be strongly predictive of outcome. Heterogeneity was observed in the ACLF clinical course in which improvement was observed in 50% of patients, a steady or undulating course in 30% with deterioration in 20% of cases. The frequency of the clinical course was dependent upon the initial ACLF grade. Patients who resolved to no ACLF were found to have outcomes similar to those with acute decompensation. Conversely, patients with ACLF-3 had a very high mortality. Once ACLF was established, the prognosis relied on factors independent of the precipitating events such as the presence of systemic inflammation at the outset.¹⁻⁴

Scoring Systems to Assess ACLF

A window of opportunity exists in ACLF to reverse organ failure and improve outcome but accurate prognostic tools are required to inform the clinical decision-making process. This allows for better stratification of patients to determine suitability for intensive care, fast-track listing for liver transplantation, or determination of futility of further supportive care. Modified scoring systems validated in large prospective clinical studies such as the CANONIC study have facilitated more accurate prognostication in patients with ACLF. The recently described CLIF scoring systems CLIF-C OF score, the CLIF-C ACLF score and the CLIF-C AD score discriminate between ACLF

and acute decompensation and prognosticate allowing a step-wise algorithm for a rational management of patients with decompensated cirrhosis.

CLIF-OF score and CLIF-ACLF score

The CLIF-OF score (Table 1,2) may be used on admission to determine the presence or absence of ACLF. The scores are freely available on the CLIF Consortium website and also as an app that is downloadable on any mobile platform (ACLF Calculator, Cyberliver, UK). Response to treatment of ACLF patients may be monitored by daily calculation of the CLIF-C ACLF score, incorporating the CLIF-OF score, age and white cell count. Ultimately, resolution of ACLF is the most important determinant of short and medium term mortality and the CLIF-C scores provide an objective measure of this.

Patients with high CLIF-C ACLF scores may be considered for liver transplantation. If ineligible for transplantation without a demonstrable treatment response in ACLF score by days 3-7, consideration should be made as to the appropriate ceilings of management.^{2,4}

CLIF-C Acute Decompensation score (CLIF-AD)

The CLIF-AD score may be used to stratify patients with acute decompensation but not ACLF into high, medium and low risk categories of mortality. The CLIF-C AD score includes age, white cell count, serum sodium, serum creatinine and INR. Variables in each score were combined to generate a score system ranging from 0 to 100. High-risk acute decompensation has been shown to have similar outcomes to ACLF-1 and patients with this diagnosis should be managed in a level 2/3 care environment. Patients in medium risk (score 46-59) have a 3-month mortality of 31% and warrant further management within level 1 care. Conversely, low risk patients (score ≤ 45) have a 3-month mortality of 1.8% and thus may be considered for early discharge. A proposed algorithm for the assessment of patients with ACLF and acute decompensation is highlighted in Figure 2.³

Other Scoring Systems

The CLIF-OFs and CLIF-SOFA scores have been shown to have superior prognostic accuracy compared to conventional measures such as MELD, MELD-Na and Child-Pugh score (Figure 3).⁵ Other scoring system that is relevant in the patients with infection was suggested by NACSELD and is a variant of the organ failure scoring system. Many aetiology specific scoring systems exist such as the Maddrey score, Lille score, Glasgow score that are specific for patients with acute alcoholic hepatitis. How the CLIF scores compare with these scores will have to be assessed in prospective studies in the future. Whilst capturing parameters relevant to hepatic failure, none of these commonly used scoring systems capture number of organ failures or incorporate markers of inflammation, key prognostic determinants in ACLF. In context of acute decompensation, the predictive value of the CLIF-C AD score improves prediction of 3 month and 12 month mortality by 10-20% compared to MELD, MELD-Na, and Child-Pugh scores.

Patient Selection for Liver Transplant in ACLF

At present, there is no priority given to patients being allocated organs for liver transplantation. 5-year survival outcomes following liver transplant for ACLF are good, ranging between 74 and 90 %. Eligibility may be precluded by number of organ failures, sepsis, co-morbidity, age or active alcoholism. The pre-transplant condition of patients with ACLF may play a key role in determining outcome and therefore careful patient selection is crucial.

Given the labile and rapidly progressive nature of the disease, a narrow window of opportunity exists when patients are sufficiently stable to consider this option. Current level of understanding does not allow clarity about which patients need urgent transplantation, regular transplantation, no transplantation or they are too sick to transplant (Figure 4). Medical response to supportive therapy has been conventionally measured by scoring systems such as MELD. The limitations inherent in these are highlighted by Duana et al who observed that MELD score did not predict outcomes of patients with hepatitis B ACLF following orthotopic liver transplantation.⁶ The data from the CANONIC study also very clearly demonstrates that the MELD score, which is what is currently used for organ allocation, under estimates the risk of death

of ACLF patients by 20-30% seriously disadvantaging ACLF patients.² Dynamic assessment of CLIF-C ACLF scores may facilitate this decision-making process although further validation studies are required to determine a more precise algorithm for optimal timing of transplantation. Furthermore, transplantation is usually only considered in patients assessed and listed for transplantation before an episode of ACLF.²

Data regarding liver transplantation outcomes for ACLF patients are limited and interpretation is complicated by variable definitions of ACLF, small patient cohorts, retrospective analysis and lack of availability of long term follow up data. 4.9% and 15% of patients from the CANONIC patient cohort with ACLF underwent transplantation within 28 and 90 days of admission respectively. Survival of patients with ACLF-2 or -3 without transplantation was less than 20% but 80% with transplantation, comparable to patients transplanted without ACLF.

Only one study (n=238) used intention-to-treat analysis and showed a 5-year post-transplant survival of greater than 80% for patients eligible for transplantation (<25% of patient cohort).⁷ The median transplant-free survival time was 48-days with deaths most commonly secondary to multi-organ failure. Successful transplant outcomes in carefully selected patients with corticosteroid-resistant acute alcoholic hepatitis further reinforce the importance of good patient selection using accurate prognostic criteria. Patients with ACLF appear to tolerate marginal grafts particularly well. Survival and post-transplant length of stay is known to be worse for patients hospitalized at the time of surgery than in those at home and markedly worse still for those in level 3 care. Increasing recipient age (>60 years) is consistently associated with increased mortality.

Inclusion of high-risk ACLF sub-groups as an indication for high urgency allocation is not currently practiced in most countries but should be the subject of further studies particularly given the good outcomes described. The US experience of this strategy is highly favourable with an improvement in waiting list mortality of 30% with no significant increase in post-transplant mortality.

Expedited transplantation assessment should also be considered for survivors of ACLF after discharge from the intensive care unit due to a substantial increase in medium-term mortality.

Future specific therapies for ACLF

At present, there is no specific therapy for ACLF. This is not surprising as it is only very recently that this syndrome has been defined. It is clear that the syndrome is complex and therefore, treatment strategies for ACLF are likely to be complex. In order to develop new therapies, two concepts may be useful. The first is the concept of an ACLF spiral, a hypothesis that defines the process of progression of liver injury started by systemic inflammation and perpetuated by effect of cell death, multiple organ failure and immune dysfunction. The second is the PIRO concept.⁸ This hypothesis suggests that a patient with ACLF is categorized into 4 domains; P: Predisposition, I: Injury (precipitating event), R: Response and O: type and number of organ failures. Using this concept, one can envisage therapeutic strategies targeted to modulated each of these variables to try and address the ACLF spiral.

The use of Tenofovir attempts to target the predisposing factor as well as the precipitating event in patients developing ACLF due to HBV reactivation and has been shown to be effective in a small study (targeting P).⁹ Granulocyte colony stimulating factor has been shown to reduce mortality in a subgroup of patients but the mechanisms how this is achieved is uncertain (possibly targeting R).¹⁰ Therapies aimed at targeting products of cell death and inflammation such as pan-caspase inhibitors have been studied in a small group of patients (final data not yet available) (targeting R).¹¹ More recently, on going treatment with beta-blockers were shown to reduce the mortality of patients developing ACLF, possibly by modulating inflammatory response (targeting R).¹² In patients with spontaneous bacterial peritonitis, administration of albumin in addition to antibiotics reduces mortality by improving inflammatory response and also improving circulatory function (targeting I).¹³ Targeting end organ dysfunction such as the kidneys using terlipressin and albumin has been shown to be effective (targeting O).¹⁴ In a trial of albumin dialysis in patients with hepatic encephalopathy, the

improvement in its severity was shown to improve patient survival irrespective of the kind of treatment used (targeting O).¹⁵ Extracorporeal liver support is a good example of a type of intervention that targets either the removal of mediators of cell death or attempts to reduce inflammation or provide liver support in the case of bioartificial devices (aims to target multiple factors; I, R and O). None of the available devices have been shown to be useful in reducing mortality of ACLF patients.¹⁶

Conclusions

ACLF is being increasingly recognized as an important cause of mortality of cirrhotic patients and the recent studies providing information about its diagnostic and prognostic criteria allows this syndrome to be better defined pathophysiologically. Once, the syndrome is better understood, novel, targeted therapies can be further developed.

Figure Legends

Figure 1. Mortality of patients with acute decompensation of cirrhosis and acute on chronic liver failure (Modified from Moreau et al. Gastroenterology 2013)

Figure 2. Proposed algorithm for diagnosis and risk stratification of ACLF and acute decompensation (Data from Jalan et al. J Hepatol 2014; J Hepatol 2015)

Figure 3. This figure shows the percentage improvement in the prediction error of the MELD, MELD Na and the Pugh Score in comparison with the CLIF-C ACLF score. (Data from Jalan et al. J Hepatology 2014)

Figure 4. A cartoon depicting potential outcomes of patients with ACLF and the possible timings of liver transplantation.

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Table 1 Diagnostic criteria of ACLF (Data reproduced from Jalan et al. J Hepatology 2014)

Diagnosis	Criteria
No ACLF	<ul style="list-style-type: none"> • Patients with no organ failure • Patients with single hepatic, coagulation, circulation or respiratory failure, serum creatinine <1.5 mg/dl and no HE • Patient with cerebral failure and serum creatinine <1.5 mg/dl
ACLF-1	<ul style="list-style-type: none"> • Patients with renal failure • Patients with other single organ failure with serum creatinine ≥ 1.5 and < 2 mg/dl and/or HE grade 1-2.
ACLF-2	<ul style="list-style-type: none"> • Patients with 2 organ failures
ACLF-3	<ul style="list-style-type: none"> • Patients with 3 or more organ failures

Table 2 The CLIF Organ Failure scoring system (Jalan et al., J Hepatol. 2015 62:831-40.)

Organ System	Score = 1	Score = 2	Score = 3
Liver (mg/dl)	Bilirubin < 6	6 ≤ Bilirubin ≤ 12	Bilirubin >12
Kidney (mg/dl)	Creatinine <2	Creatinine ≥2 <3.5	Creatinine ≥3.5 or renal replacement
Brain (West-Haven)	Grade 0	Grade 1-2	Grade 3-4
Coagulation	INR < 2.0	2.0 ≤ INR < 2.5	INR ≥ 2.5
Circulation	MAP ≥70 mm/Hg	MAP <70 mm/Hg	Vasopressors
Respiratory: PaO₂/FiO₂ or SpO₂/FiO₂	>300 >357	≤300 - > 200 >214- ≤357	≤200 ≤214

The colored areas represent organ failure.

INR: International Normalised Ratio; MAP: Mean arterial pressure; PaO₂: Partial pressure of oxygen; SpO₂: Oxygen saturation; FiO₂: Fractional inspired oxygen