Acute-on-chronic liver failure: **A distinct clinical syndrome that has re-classified cirrhosis.**

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Introduction

Conventionally, the severity of cirrhosis is classified into compensated, decompensated and late decompensation, which defines prognosis. Acute-on-chronic liver failure (ACLF) adds substantially to this classification by identifying a subgroup of cirrhotic patients who may progress rapidly following acute decompensation (AD) to develop organ failure(s) (OFs), and high short-term mortality.

Definition of ACLF

More than 13 distinct definitions of ACLF, largely based on personal experience or consensus agreements, have been proposed [1] but the only one that was specifically developed to define the diagnostic criteria for ACLF was by the European Association for the Study of the Liver – Chronic Liver Failure (EASL–CLIF) Consortium. In 2009, they started a prospective, multicenter European observational study that included 1343 patients hospitalized for AD of cirrhosis (the CANONIC study) [2]. This study aimed to define ACLF in cirrhosis, to propose diagnostic criteria, to assess the prevalence and clinical course of the syndrome and to develop new prognostic scores. The current review is largely based on this investigation. According to EASL-CLIF Consortium definition, ACLF is a specific syndrome characterized by AD of cirrhosis, OF(s) and high short-term mortality. AD means development of ascites, hepatic encephalopathy (HE), gastrointestinal hemorrhage and/or bacterial infections; ACLF may develop in patients with or without a prior history of AD. OFs (liver, kidney, brain, coagulation, respiration, circulation) are defined by the original CLIF-SOFA score (the Sequential Organ Failure Assessment Scale adapted for liver patients) or its simplified version CLIF-C OF score [3] (Table 1). High short-term mortality means a 28-day mortality rate ≥15%.

Diagnostic criteria and ACLF grades

Mortality rate of the patients in the CANONIC study was clearly related to the presence and number of OFs. Also, renal dysfunction (as defined by a serum creatinine of 1.5–1.9 mg/dL) and/or cerebral dysfunction (grade 1–2 HE), when associated with single OF, were found to predict

prognosis. Based on the presence of OF, renal and/or cerebral dysfunction, and short-term mortality rate, the following groups of patients were proposed to have ACLF or no ACLF:

a. No ACLF – No OF or a single non-renal OF without renal dysfunction and cerebral dysfunction.

b. ACLF grade 1 – Single renal failure, single non-renal OF that is associated with renal dysfunction and/or cerebral dysfunction.

c. ACLF grade 2 – Two OFs of any combination.

d. ACLF grade 3 – Three or more OFs of any combination.

Among the different organ failures in ACLF, the most frequently affected organs were the kidneys (56% of patients), followed by the liver (44%), coagulation (28%), the brain (24%), circulation (17%) and the lungs (9%). Kidney failure is the most prevalent organ failure in ACLF grade 1. For ACLF grade 2, liver failure is the most prevalent OF followed by kidney, brain and coagulation failure. For ACLF grade 3, the prevalence of all OFs is high.

Epidemiology, health burden and mortality

ACLF is a major worldwide medical problem, with prevalence rates in at risk populations in the region of 20–35%. The worldwide reported mortality according to the EASL-CLIF Consortium definition ranges between 30% and 50% and correlates closely with the number of OFs. In Europe, most of the prevalence and natural history data comes from the CANONIC study [2]. Approximately 23% of patients admitted to the hospital for an AD of the disease had ACLF at admission. Furthermore, 11% of the patients without ACLF at enrollment developed the syndrome during hospitalization, which gives a total prevalence of ACLF in patients admitted to the hospital with AD of 31%. Among ACLF patients, 51% had ACLF grade 1, 35% ACLF grade 2, and 13% ACLF grade 3. The average 28-day and 90-day mortality rate without liver transplantation (LT) was 1.9% and 10% in patients with AD without ACLF and 33% and 51% in patients with ACLF (Table 2). The healthcare burden of ACLF and cirrhosis is associated with extremely high costs, exceeding the yearly costs of inpatient management of more common medical conditions.

Precipitating illness

In most cases, the development of ACLF is associated with a precipitating factor. The most common precipitating events are bacterial infections, active alcoholism, and reactivation of HBV, particularly in patients with underlying hepatitis B virus infection in the East. However, in up to 40% of patients, no precipitating factor can be identified. The potential role of drug-induced liver injury as a precipitating event in ACLF has been insufficiently explored in both the East and the West. Data from the CANONIC study [2] showed that mortality was independent of the type of precipitating factor and that it was mainly related to other factors such as the type and number of OFs, the intensity of inflammatory response, and the early clinical course of the syndrome. Nearly 40% of patients with ACLF had a bacterial infection as a precipitating event. Nosocomial infections may be associated with a higher risk of ACLF compared with that of community-acquired infections. Bacterial infections tend to cause ACLF more frequently in patients without a previous history of decompensation compared with patients with previous decompensation. Severity of infection also increases the risk of ACLF. A recent study evaluated the prevalence and characteristics of bacterial and fungal infections causing and complicating ACLF, predictors of new bacterial infections and impact of bacterial infections on survival [4]. The main findings were that patients with ACLF are (1) at high risk of developing new bacterial infections (2) severe infections (spontaneous bacterial peritonitis, pneumonia, severe sepsis/shock, nosocomial infections and infections caused by multi-resistant organisms) are more prevalent in patients with ACLF (3) bacterial infections, either at diagnosis or during follow-up, are key prognostic determinants (4) bacterial infections are independent predictors of 90-day mortality in patients with ACLF-1 and ACLF-2 and (5) inappropriate empirical antibiotic strategies increase 90-day mortality.

Mechanisms of ACLF

The specific pathophysiologic features of ACLF are systemic and hepatic inflammation [2,5]. It is not clear if systemic inflammation, manifested by elevated white cell count and C-reactive protein, represents an alteration of host response to injury or whether it is due to an inability to resolve inflammation. Another feature is the increases in the circulating cytokines; the changes in the

pattern of cytokines are not consistent and depend upon the severity of ACLF, the underlying cause of the liver disease and the precipitating event. These changes in circulating markers of inflammation are associated with changes in the functional characteristics of the circulating inflammatory cells. Clària and colleagues [5] demonstrated that: (1) patients with ACLF have significantly higher levels of inflammatory cytokines, human non-mercaptalbumin-2 (HNA-2), and plasma renin concentrations than those without ACLF (2) different cytokine profiles were identified according to the type of ACLF precipitating event (3) and there was a good correlation between the course of systemic inflammation and the clinical course of ACLF. It has also become clear that molecules released following cell death (damage associated molecular patterns) have immunogenic properties and can result in systemic inflammation. Recently, it has been shown that the predominant mechanism of cell death in ACLF is non-apoptotic [6], which may provide an explanation for the severity of systemic inflammation observed.

Clinical course

ACLF is an extraordinarily dynamic syndrome that has potential for reversibility [7]. Overall, ACLF resolves or improves in 49.5% of patients, followed by a steady or fluctuating course with unchanged final ACLF grade in 30.4%, and worsened in 20.1%. Frequency of ACLF resolution was high in patients with initial ACLF-1 and low in those with initial ACLF-3. In contrast, the proportion of patients with final ACLF-3 was low in patients with initial ACLF-1 and very high in those with ACLF-3.

Overall, the 28-day transplant-free mortality rate was low in patients with ACLF resolution (5.8%), moderate in those with final ACLF-1 (18.2%), high in those with final ACLF-2 (41.7%), and very high in those with final ACLF-3 (91.8%), independently of whether they presented ACLF-1, -2, or -3 at diagnosis. The final ACLF grade was already defined at days 3-7 in 81% patients. ACLF-grade at days 3-7 after diagnosis predicted significantly better 28- and 90-day mortality rates than ACLF grade at diagnosis. The probability of 28-day transplant-free survival was high for patients with no ACLF at days 3-7 and ACLF-1 at days 3-7 (89.6% and 78.7%, respectively) and low to very low for

patients with ACLF-2 and -3 at 3-7 days (42.9% and 12.8%, respectively). These differences were maintained at 90 and 180 days.

Prognostic score

To allow on-going stratification of patients for intensive care, fast-track listing for LT, early hospital discharge or determination of futility of further intensive care, the CANONIC investigators developed and validated two prognostic scores for patients with ACLF, referred to as the CLIF-C ACLF score [3], and for patients with AD who did not fulfil criteria for the diagnosis of ACLF, which is called the CLIF-C AD score [8]. These two scores were designed because a single score was insufficient to satisfactorily delineate the prognosis associated with AD and ACLF. The CLIF-C ACLF and AD scores provided a significantly better estimate of the risk of death compared with the Model for End Stage Liver Disease (MELD) score, the MELD-Sodium score and the Child-Pugh score. Organ allocation for LT using the MELD score seriously disadvantages the patient with ACLF. The performance of the CLIF-C ACLF score improved over the period of follow-up, suggesting that it should be updated daily [3].

Management, futility of intensive care support and role of liver transplantation

Currently, the accepted strategy for management of ACLF consists of early recognition and treatment of the precipitating event, and supportive care with intensive monitoring and support of failing organs. There is currently no evidence to justify alternative strategies for the management of OFs in patients with cirrhosis compared to other critically ill patients [9,10]. In case of contraindication of LT, the presence of ≥4 OFs or a CLIF-C ACLF score >70 at days 3-7 after diagnosis could indicate the futility of care [7].

LT represents the only definitive therapeutic option for patients with ACLF. There seems to be a clear agreement in the literature regarding outcomes of urgent LT in patients with ACLF, with acceptable to excellent 1- and 5-year post-LT survival reported in some studies. Some patients, particularly those with respiratory failure, do less well. As severe ACLF patients have a high mortality rate on the waiting list, salvage LT is feasible and associated with a clear survival benefit

in selected patients with ACLF grade 3 [11-14] (Table 3). It is possible that many patients with ACLF are not listed for LT on the assumption that they are too ill to survive LT. There could also be a significant delay in listing for logistical reasons or because of indecisiveness about the utility or futility of LT in such a situation. Additionally, there also may be center specific differences in listing for LT in the presence of multiple OF. These factors introduce a dimension of selection bias in the studies published to date. Because a large proportion of patients with ACLF die on the waiting list, a better rule for organ allocation is needed for this group. The specific scores for ACLF are more accurate for prediction of short-term outcomes than the MELD score. The implementation of these scores could decrease the mortality on the waiting list, but they need further evaluation and validation. The limits defining when a patient should be considered too sick for transplantation and LT should be considered futile are currently largely unknown.

Conclusions

The accumulated data in over 1000 papers following its initial description [15] has confirmed that ACLF is clinically, prognostically and pathophysiologically distinct from mere AD. Better clinical characterization and understanding of the pathophysiology of the syndrome has re-classified cirrhosis and proposes a new framework to develop new therapies for this syndrome, which has an unacceptably high risk of death.

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Table 1. The CLIF-organ failure (CLIF-OF) score system [3]

Organ/system	Subscore = 1	Subscore = 2	Subscore = 3
Liver	Bilirubin <6 mg/dL	Bilirubin ≥6 mg/dL and <12 mg/dL	Bilirubin ≥12 mg/dL
Kidney	Creatinine <2 mg/dL	Creatinine ≥2 mg/dL and <3.5 mg/dL	Creatinine ≥3.5 mg/dL or renal replacement
Brain (West-Haven grade for HE)	Grade 0	Grade 1-2	Grade 3-4*
Coagulation	INR <2	INR ≥2.0 and <2.5	INR ≥2.5
Circulatory	MAP ≥70 mmHg	MAP <70 mmHg	Use of vasopressors
Respiratory PaO_2/FiO_2 or SpO_2/FiO_2	>300 or >357	>200 and ≤300 or >214 and ≤357	≤200[#] or ≤214[#]

Adapted from Reference [3]
The shaded area describes criteria for diagnosing organ failures.
HE, hepatic encephalopathy; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; SpO_2, pulse oximetric saturation.
*Patients submitted to Mechanical Ventilation (MV) due to HE and not due to a respiratory failure were considered as presenting a cerebral failure (cerebral subscore = 3).
[#]Other patients enrolled in the study with MV were considered as presenting a respiratory failure (respiratory subscore = 3).

Organ/system	Subscore = 1	Subscore = 2	Subscore = 3
Liver	Bilirubin <6 mg/dL	Bilirubin ≥6 mg/dL and <12 mg/dL	Bilirubin ≥12 mg/dL
Kidney	Creatinine <2 mg/dL	Creatinine ≥2 mg/dL and <3.5 mg/dL	Creatinine ≥3.5 mg/dL or renal replacement
Brain (West-Haven grade for HE)	Grade 0	Grade 1-2	Grade 3-4*
Coagulation	INR <2	INR ≥2.0 and <2.5	INR ≥2.5

Table 2. ACLF grades and mortality without LT [2]

Category	28-day mortality without LT (%)	90-day mortality without LT (%)
No ACLF	1.9	10
ACLF (total)	33	51
ACLF grade 1	23	41
ACLF grade 2	31	55
ACLF grade 3	74	78

Adapted from Reference [2]

Category	28-day mortality without LT (%)	90-day mortality without LT (%)
No ACLF	1.9	10
ACLF (total)	33	51
ACLF grade 1	23	41
ACLF grade 2	31	55
ACLF grade 3	74	78

Adapted from Reference [2]

Table 3. ACLF and LT

Study	Experience	Criteria for ACLF diagnosis	Number of LT	Survival post-LT	Notes
Gustot et al. (2015) [7]	CANONIC	CLIF-C criteria	35 pts with initial ACLF: 25 pts with ACLF at LT, 10 pts with ACLF resolution at LT	1-year: 75.3% (ACLF-1, 80%; ACLF-2, 71.6%; ACLF-3, 77.8%) vs 90% for 10 pts with ACLF resolution before LT	LT within 28 days (median time between ACLF diagnosis and LT 11 days) 6-month probability of survival of d3-7 ACLF-2 or -3 pts undergoing LT compared to LT-free survival probability in d3-7 ACLF-2 or -3 pts: 80.9% vs 10%
Levesque et al. (2017) [11]	France, 1 centre	CLIF-C criteria	140 pts with ACLF at LT	1-year: 70% (ACLF-1 or -2, 77.2%; ACLF-3, 43.3%)	1-year survival post-LT in pts without ACLF: 91.4%
Artru et al. (2017) [12]	France, 3 centers	CLIF-C criteria	73 pts with ACLF-3	1-year: 83.6%	1-year survival of 119 non-LT controls: 7.9% 100% pts with ACLF-3 developed complications
Thuluvath et al. (2018) [13]	UNOS	CLIF-C criteria	3556 pts ≥3 OFs at LT; 677 pts 5-6 OFs at LT	1-year: 3 OFs, 84%; 4 OFs, 81%; 5-6 OFs, 81%	LT median time 4-5 days Only 2% of pts with 5-6 OFs remained on the list at 30 days
Sundaram et al. (2018) [14]	UNOS	CLIF-C criteria	6680 pts with ACLF-1; 6996 with ACLF-2; 6010 with ACLF-3	1-year: 81.1% in ACLF-3 vs 88.4-91.7% in the other groups	1-year survival without LT for ACLF-3: 23.5%

d3-7 ACLF: ACLF-grade at days 3-7 after diagnosis; ICU: Intensive Care Unit; LT: Liver transplantation; OFs: Organ Failures; Pts: Patients; UNOS: United Network for Organ Sharing