DEFINITIONS OF ACUTE-ON-CHRONIC LIVER FAILURE: THE PAST, THE PRESENT, AND THE FUTURE

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ABSTRACT

Acute-on-chronic liver failure (ACLF) is an entity used to define patients with liver cirrhosis presenting with acute decompensation. For over 20 years, ACLF has taken multiple definitions and/or classifications. Unfortunately, to date, there has not been a universally accepted definition/classification of this entity. In this short review, we discuss the definition evolution of ACLF, the strengths and weaknesses of the existing definitions and classifications, and finally the potential role of the 'omic' approaches for the diagnosis of this complex syndrome.

Keywords: Acute-on-chronic liver disease, definition, classification, cirrhosis, chronic liver disease, metabolomics.

INTRODUCTION

Chronic liver diseases (CLD) are defined by the following triad: 1) prolonged course of a hepatic disease >6 months; 2) inflammatory and/or degenerative morphological findings; and 3) uncertain prognosis.[1] CLD consist of several aetiologies and different states of functional and/or morphological liver deterioration. Nevertheless, regardless of the aetiology, CLD could lead to both histological modifications of the liver and chronic liver insufficiency. CLD caused by steatohepatitis (alcohol or obesity) or chronic viral hepatitis leads to morphological changes in the liver. These changes could be attributed to four processes: 1) cell damage and degeneration; 2) cell death and necrosis; 3) liver regeneration; and 4) fibrogenesis. Cirrhosis is the consequence and final stage of various CLD.[2] Associated to this phenomenon, in cirrhotic patients, increased intrahepatic vascular resistances leads to portal hypertension and its complications, namely gastrointestinal (GI) bleeding from varices and/or ascites. Moreover, major functions of the liver are also impaired such as immunological function with increased infection sensibility and several perturbations in anabolism and catabolism liver function. Unfortunately, there are no correlations between morphological changes and the severity of functional impairment. Nevertheless, put together, all these perturbations, often asymptomatic when cirrhosis is 'compensated', become symptomatic when the cirrhosis is 'decompensated'.

Natural history of the disease could be progressive, with a slow decrease of liver function but without the potential for full recovery leading to end-stage of cirrhosis. End-stage of cirrhosis is characterised by chronic decompensation of the liver. At which point, the only definitive treatment is liver transplantation (LTx). Patients with CLD may have acute decompensation (AD) that is usually precipitated by an event that represents a direct or indirect hepatic insult. For example, indirect insult could be infection or extra-hepatic surgery. Direct insult could be new viral hepatitis infection (like virus Delta or E), viral hepatitis reactivation, or hepatotoxic drug misuse. In case of AD, partial or full recovery to the original liver function level is assumed after treatment. In those patients, short-term mortality increases dramatically when extra-

hepatic organ failures are present. Three clinical scenarios are possible regarding the natural history of the CLD: CLD without cirrhosis and AD, CLD with cirrhosis and AD, and CLD with cirrhosis and end-stage liver disease. These three categories of patients are different in terms of mechanism and prognosis (Figure 1).

Acute-on-chronic liver failure (ACLF) is a complex syndrome with an acute deterioration of liver function superimposed on CLD. Both the exact definition and underlying pathogenesis of ACLF remain unclear. Instead of using the term 'acute decompensation', ACLF is used to define and classify all acute events of liver decompensation in patients with CLD or cirrhosis regardless of the presence of other organ failure. In >20 years, this syndrome has taken several different definitions, leading different outcomes according to mortality.

From all the available definitions, three common points are emphasised: 1) Presence of CLD; 2) Rapid deterioration but theoretically reversible liver function; and 3) high short-term mortality. ACLF is associated with a short and medium-term mortality of 50-90%.[3,4] A new definition and classification will allow to better stratify patients with ACLF. Nevertheless, proposed definitions by Asian and Americano-European Study of the Liver societies are not clear with the definition of the CLD. On the other hand, new classifications proposed by the European and North American studies focus only on cirrhotic patients and define the patient principally with extra-hepatic failure which could be confusing too. None of those definitions or classifications takes into account the probability of liver function recovery. Unfortunately, despite recent efforts to well define this syndrome, there is no universally accepted definition.

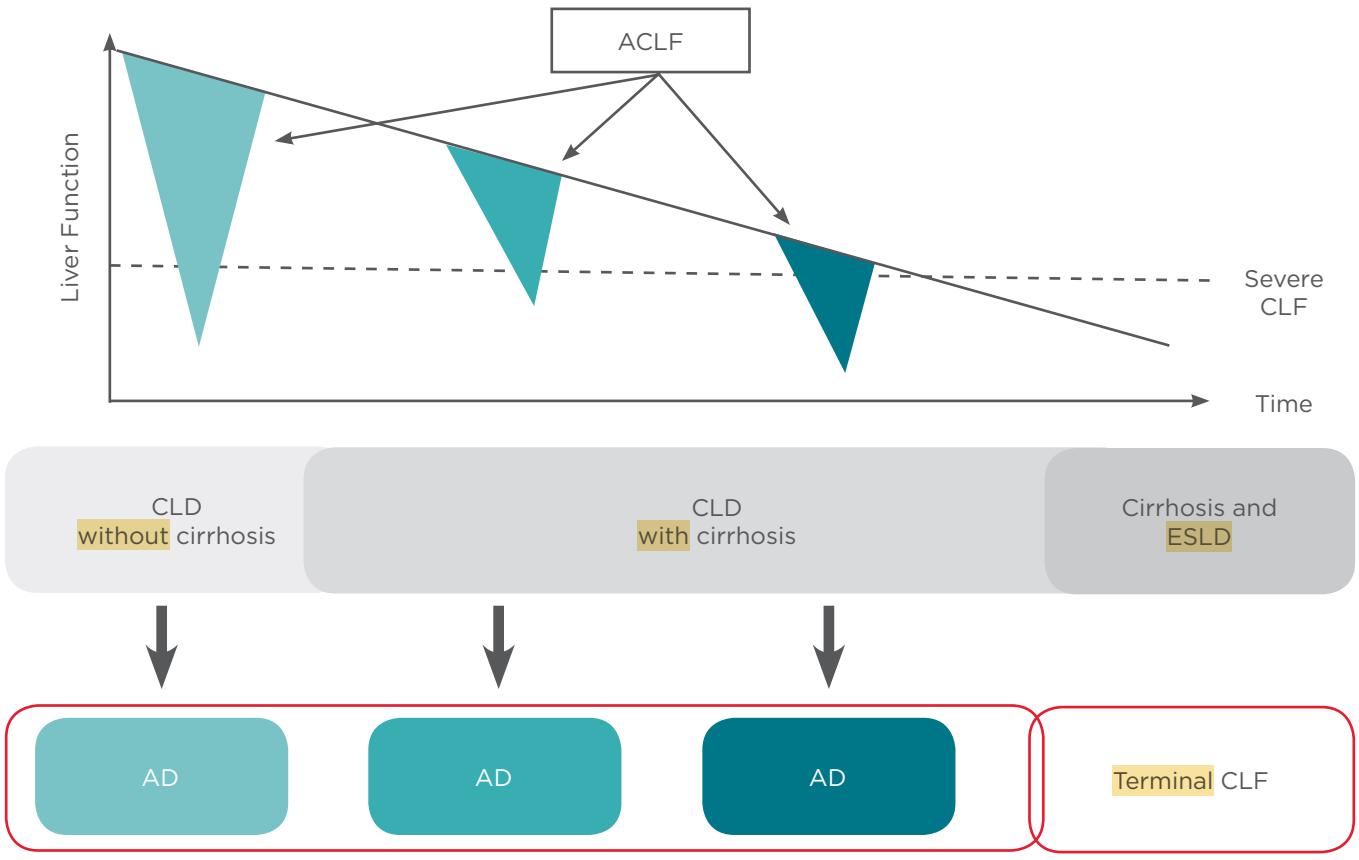

Figure 1: Schematic representation of natural history of chronic liver disease (CLD), acute decompensation (AD), and end-stage liver disease (ESLD).

This figure describes the concept of acute-on-chronic liver failure (ACLF) in CLD patients with or without cirrhosis, chronic liver failure (CLF), and ESLD. It also describes arbitrary evolution of CLD with cirrhosis, at the top of the figure, progressive decreases of the liver function leading to terminal liver failure and, on the bottom of the figure, three categories of patients: CLD without cirrhosis, CLD with cirrhosis, and cirrhosis and ESLD. ACLF (at the top) is characterised by acute liver impairment but with partial or total recovery of the liver function after treatment.

Table 1: Different definitions of acute-on-chronic liver failure (ACLF) found in the literature.

	Definition	Aetiology of CLD	Ref
1	Acute insult manifesting as jaundice (bilirubin ≥10 mg/dl) and coagulopathy (PTA <40%), complicated within 4 weeks with ascites and/or HE with previously diagnosed or undiagnosed chronic hepatitis B (with or without cirrhosis).	Hepatitis B virus	[18]
2	Acute deterioration of liver function in established and compensated CLD following a life-threatening complication (HE or ascites or bleeding or HRS) in patient with or without cirrhosis.	Hepatitis B virus	[19]
3	Defined as a rise in MELD score of >5 points within 4 weeks before transplantation.	Various	[20]
4	Acute decompensation of cirrhosis manifested by increased jaundice.	Various	[21]
5	ACLF was diagnosed in cirrhotic patients with acute hepatitis A or E presenting with clinical evidence of liver failure (significant ascites and/or HE).	Various	[22]
6	Defined as acute decompensation of CLD with severe liver dysfunction and high grade of HE (2 or more).	Hepatitis B virus	[23]
7	Cirrhotic patient with decompensation such as GIB, HE, admitted to ICU required organ support	Various	[24]

PTA: prothrombin activity; HE: hepatic encephalopathy; CLD: chronic liver disease; HRS: hepatorenal syndrome; MELD: model for end-stage liver disease; GIB: gastrointestinal bleeding; ICU: intensive care unit.

New approaches, more global and biological, of this polymorphic syndrome are needed. 'Omic' approaches, such as metabolomic, are probably interesting biological approaches to help clinicians to best define and classify the patients with this syndrome and predict liver function recovery. In this review, we discuss the evolution and accuracy of the different definitions of the ACLF and propose the need for 'biological' approaches of this syndrome.

ACLF Definitions: the Past

The term 'acute-on-chronic liver failure' appears for the first time in 1995.[5] It gains interest at the end of the last century probably as a consequence of the development of the different kinds of liver support. Initially, it describes a condition with superimposed insult on the liver in patients with CLD. On the other hand, it describes the notion that an organ (the liver in this case) with chronic impairment could have superimposed acute impairment but with possible return to the previous state. Then, patients with chronic liver failure (CLF) and acute liver failure (ALF) should be treated by liver support as a bridge to the recovery of their function or to the LTx. Unfortunately, despite the first meta-analysis, which showed decreased mortality in the ALCF group, no controlled trials have been able to support this hypothesis.[6,7] Subsequently, several definitions were proposed to define this syndrome. At the beginning, all of them focused on the loss of liver function with various clinical and biological signs (Table 1). Few definitions take into account organs other than the liver in the definition. High short-term mortality of this syndrome (between 50-90%) was common in all of them. The presence of a large panel of definitions is a problem for the interpretation of the studies regarding outcomes or therapeutic trials on patients with ACLF. Taking into account this point and the increase of interest for these patients, notably regarding the LTx, more consensual definitions were raised at the beginning of the new century. Typically two definitions, especially due to the difference of CLD aetiology, from the 'Western countries' and 'Eastern countries' (i.e. mainly Asian) were proposed.

ACLF Definitions: the Present

Two definitions of the ACLF are mostly used. One is proposed by the Asian-Pacific Association of the Study of the Liver and the others by the American Association for the Study of the Liver (AASLD) and the European Association for the Study of the Liver (EASL).[8,9] The Asian definition focuses exclusively on liver failure. ACLF is defined asacute hepatic

insult manifesting as jaundice (with bilirubin ≥5 mg/dl), coagulopathy (with international normalised ratio ≥1.5 or prothrombin activity <40%), and complicated within 4 weeks by ascites and/or hepatic encephalopathy with previously diagnosed or undiagnosed CLD. Current definition of ACLF proposed by EASL-AASLD symposium includes the notion of high mortality and extra-hepatic organ failure. ACLF is then defined as an "acute deterioration of pre-existing CLD, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-organ failure." The precipitating event may be an extra-hepatic insult such as sepsis, or GI bleeding. It may also be a direct hepatic mechanism with viral infestation or reactivation, or drug induced liver injury.[3] Two points should be clarified; first, all patients with CLD are included in those definitions and not only patients with cirrhosis. CLD without cirrhosis does not have the same clinical presentation, treatment, or prognosis when compared to CLD with cirrhosis. Consensual definition of CLD is lacking. Future works are needed to establish new criteria (clinical, radiological, biological, and/or histological) to best define it. Moreover, those criteria of CLD will probably be also helpful to best recognise unknown underlying CLD and distinguish patients with ALF from a patient with ALF or CLF. Second, the notion of recovery is lacking in both of them. How so you differentiate between impairment of liver function that leads to end-stage disease or from the ones which will recover?

To address the first issue, Jalan et al.[10] attempted to classify patients with CLD. They proposed a new classification of ACLF in three categories (A, B, or C) according to underlying presence of cirrhosis and for the cirrhotic patient, history of pervious decompensation. Group A includes CLD patients without cirrhosis. Group B includes well-compensated cirrhosis, and group C includes patients with advanced cirrhosis with previous decompensation. Prospective evaluation of this new classification is necessary to determine its accuracy. Recently, two large studies have tried to better classify ACLF patients: one from EASL–Chronic Liver Failure Consortium (EASL-CLIF) Consortium in Europe, called the CLIF Acute On Chronic Liver Failure in Cirrhosis (CANONIC) study, and the other from the North-American Consortium for the Study of End-Stage Liver Disease study.[11,12] The first study included around 1,400 patients hospitalised with cirrhosis for an AD. This study classified ACLF based on mortality (Table 2).

Table 2: Definition of chronic liver failure consortium - acute-on-chronic liver failure (CLIF-ACLF) grades.

Grade	No ACLF	ACLF Grade 1	ACLF Grade 2	ACLF Grade 3
Definition	No organ failure or single organ failure (coagulation, circulation, or respiration) and creatininaemia <1.5 mg/dl and no hepatic encephalopathy.	Single kidney failure or single organ failure (coagulation, circulation, or respiration) and creatininaemia between 1.5 and 1.9 mg/dl or hepatic encephalopathy and creatininaemia between 1.5 and 1.9 mg/dl	Two organ failures	Three organ failures
1 and 3 months mortality	4.7% and 14%	22.1% and 40.7%	32% and 52.3%	76.7 and 79.1%

Coagulation failure is defined by the international normalised ratio >2.5 or platelet count <20 g/l; circulation failure is defined by use of any dose of terlipressin, dopamine, dobutamine, epinephrine, or norepinephrine. Lung failure is defined by PaO_2/FiO_2 ratio <200 or SpO_2/FiO_2 ratio <89. Kidney failure is defined by creatininaemia >2 mg/dl or need to renal replacement therapy. Hepatic encephalopathy Grade >2 defines neurological failure.

In the CLIF classification (CLIF-ACLF Grades), cirrhotic patients were classified according to organ failure, mainly kidney and brain (i.e. hepatic encephalopathy) failure. The North American Study proposes classification of ACLF specific to cirrhotic patients with sepsis (infection-related acute-on-chronic liver failure [I-ACLF]). The goal of this classification is to help the clinician with bedside decision-making to accurately identify potential survivors for cost-effective healthcare resource utilisation. I-ACLF is defined as a cirrhotic patient with suspected or documented infection and at least one organ failure (hepatic encephalopathy Grade 2/3, renal replacement therapy, mechanical ventilation, shock). Approximately 500 patients were included in this multicentre prospective study. As expected, for both studies, mortality was well correlated with the number of organ failures. Major points of the new classifications are: 1) they included only patients with proven or strongly suspected liver cirrhosis; 2) they included all aetiologies of cirrhosis; 3) they included well-documented cirrhotic patients hospitalised for an acute event; 4) for one of them (European study), there is external validation of the accuracy of the classification.[13] The interesting point with these classifications is that they best stratify cirrhotic patients with ACLF according to the risk of death. The major implication is for its use in the inclusion criteria to have a more homogenous population for future randomised clinical trials. However, consensual definition of ACLF is still lacking. The ambiguity and variability in the definition/classification of ACLF does not allow the clinician to make rapid and proper diagnoses of ACLF, to distinguish between patients with ACLF that require transplantation and those that require only intensive medical treatment. Specific biomarkers that confirm the diagnosis, exclude other diseases, and best predict patients with poor outcome should be stated to best define ACLF.

ACLF Definition: the Future

Bioclinical classification as proposed by Moreau et al.[12] is probably a major improvement concerning the characterisation of the ACLF according to its prognosis. Nevertheless, the score used is complex and not readily adaptable to clinical care. The view of the ACLF syndrome as a systemic syndrome with extra-hepatic organ failures responsible of increased mortality is interesting, but it is also counterintuitive to define an 'acute hepatic failure' as 'extra-hepatic failure'. To better define ACLF syndrome, new biomarkers or biological fingerprints could probably be helpful. Nevertheless, it is now widely accepted that the search for a single biomarker that can be used in routine clinical practice to diagnosis patients with ACLF is probably unrealistic. Future definition and characterisation of this systemic syndrome could probably be completed and clarified using the 'omic' concept, and specifically, the metabolomic approach. Metabolomics, which is the study of metabolic changes in an integrated biological system using multiparametric analyses, may help identify biomarkers that characterise the metabolic profiles of a disease, and/or evaluate metabolic modifications after treatment has been initiated.[14] Metabolomics, using proton nuclear magnetic resonance (1H-NMR) spectroscopy, when applied to liver disease, has shown a close relationship between metabolic abnormalities and the severity of the disease in sera and tissues.[15,16] Recently, a serum metabolite fingerprint for ACLF, obtained with 1H-NMR, was identified.[17]

The hypothesis in this study was that cirrhotic patients with acute events have had a specific metabolic response as compared to cirrhotic patients with stable cirrhosis. Metabolomic profiles of the sera of 93 patients with compensated or decompensated cirrhosis (CLF group) but stable liver function, and 30 patients with cirrhosis and hospitalised for the management of an acute event who may be responsible of ACLF (i.e. ACLF group) were analysed. Both groups were well-separated using a multivariable statistic method and the specific metabolomics fingerprint of patients in intensive care unit was identified. Several metabolites were identified and reflected major changes in liver function, such as energy metabolism, urea metabolism, or amino acid metabolism, but also major extra-liver function changes, such as renal impairment, or were related to inflammation/necrosis. This primary results are interesting but should be confirmed by a large multicentric population including various aetiologies.

CONCLUSION

Despite major efforts, recent definitions and classifications proposed by leading organisations or studies are still confusing for the clinician notably to make difference between ACLF and CLD or ACLF in cirrhotic patient and cirrhosis decompensation. Future research should produce an accurate 'universal' definition of this complex syndrome, in-patients with CLD, and including

cirrhotic patients. In the same way, a study of the variations of different biomarkers or biological fingerprints could be interesting in order to best classify and define the prognostics of those patients. An interesting way to find it could be a biological approach using the 'omic' platforms.

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