ACUTE-ON-CHRONIC LIVER FAILURE: DEFINITION, DIAGNOSIS AND CLINICAL CHARACTERISTICS.

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ABSTRACT

Acute-on-chronic liver failure (ACLF) is a recently recognized syndrome in cirrhosis characterized by acute decompensation (AD), organ failure(s) and high short-term mortality. Organ failure(s) is defined by the CLIF-SOFA score or by its simplified version CLIF-OF score. They include 6 types of organ failure (liver, renal, coagulation, cerebral, respiratory and circulatory) failure. One third of patients hospitalized with AD present with ACLF at admission or develop ACLF during hospitalization. ACLF frequently occurs in closed relationship to a precipitating event. According to the number of organ failures, ACLF is graded into three stages (ACLF-1: single renal failure or single non-renal organ failure if associated to renal dysfunction and/or cerebral dysfunction, ACLF-2: 2 organ failures and ACLF-3: 3-6 organ failures) with increasing 28-day mortality rate (from 23% to 74%). ACLF may develop at any phase during the clinical course of the disease. Patients without prior AD develop a severe form of ACLF.

Key words: Decompensated cirrhosis, organ failure, acute on chronic liver failure

CIRRHOSIS AS A MULTIORGAN DISEASE

The clinical course of cirrhosis is traditionally divided into two phases[1]: Compensated cirrhosis defines the time period between the onset of cirrhosis and the first major complication. During this period (10-15 years) patients have no or minor symptoms, but histological liver lesions and portal pressure steadily progresses if the etiological factor of cirrhosis persists. The term decompensated cirrhosis is used following the development of ascites, variceal hemorrhage and/or hepatic encephalopathy. Decompensated cirrhosis is associated with a short survival (3-5 years).

In addition to liver failure, cirrhotic patients with decompensated cirrhosis present several extra-hepatic organ function abnormalities that complicate the clinical course of the disease. Renal dysfunction is the most frequent. It is characterized by renal sodium retention, which plays a major role in the pathogenesis of ascites, an impaired renal ability to excrete water, which is the cause of dilutional hyponatremia (an excessive total body sodium diluted by a greater proportion of retained water) and hepato-renal syndrome[2]. Two types of HRS have been identified[3]. Type 2 HRS is characterized by moderate and steady impairment in renal perfusion and GFR and increase in serum creatinine. It is the main cause of refractory ascites. In contrast, type 1-HRS consists in a rapidly progressive impairment in renal perfusion and GFR and severe renal failure. Type 1 HRS is associated with a high probability of death within days or 1-2 weeks.

Renal dysfunction and HRS occurs in the setting of a profound impairment of circulatory function due to selective splanchnic arterial vasodilation[2]. In compensated cirrhosis and initial phases of decompensated cirrhosis the reduced systemic vascular resistance is compensated by an increase in cardiac output (hyperdynamic circulation). However, as the disease advances there is a progressive decrease in cardiac chronotropic function and left ventricular inotropic function (cirrhotic cardiomiopathy) and cardiac output[4]. The net effect of both processes, operating simultaneously, is a reduction in effective arterial blood volume and marked activation of the renin-angiotensin system, sympathetic nervous system and antidiuretic hormone to maintain arterial pressure within limits compatible with life. Despite the activation of these vasoconstrictor systems, arterial hypotension is a common finding in these patients.

Patients with decompensated cirrhosis, particularly those with severe complications such as sepsis, are prone to develop relative adrenal insufficiency, a syndrome in which the adrenal secretion of cortisol is insufficient to cover the peripheral demands[5]. The mechanism is complex and may be related to a defect at

the three levels of cortisol secretion, the hypothalamus, the hypophysis and the adrenal glands. Cortisol is essential for the vascular response to endogenous vasoconstrictors (angiotensin 2 and norepinephrine). Not surprisingly relative adrenal insufficiency is associated to severe impairment in circulatory function and hepatorenal syndrome.

Vasodilation is also an important feature in the pulmonary circulation. It develops by the release of local vasodilators to allocate the increase in cardiac output. When pulmonary vasodilation is severe, there is impairment in the ventilation/perfusion ratio and patients develop hypoxia and dyspnea (hepatopulmonary syndrome)[6].

Brain dysfunction is by frequency the second extra-hepatic organ dysfunction in cirrhosis. It ranges from minimal hepatic encephalopathy to hepatic coma. The circulating levels of ammonia and other endogenous substances that inhibit cerebral function are increased in cirrhosis, and play a major role in the pathogenesis of brain dysfunction[7]. Impairment in cerebral perfusion and local inflammation, which potentiates the toxic effect of ammonia, may play a contributory role.

In addition to the digestion and absorption of nutrients, one of the major functions of the intestines is to allocate trillions of bacteria without significant adverse effects. A complex process that includes the intestinal production of antibacterial molecules, the barrier effect of the intestinal mucosa and an effective local immune system prevents the translocation of bacteria and bacterial products from the intestinal lumen to the systemic circulation[8]. This function is severely impaired in cirrhosis[9]. Translocation of viable bacteria from the intestinal lumen to the systemic circulation is the mechanisms of endogenous bacterial infections (spontaneous bacteremia and peritonitis). On the other hand there is also translocation of bacterial products (lypopolysaccharide, bacterial DNA and other pathogen associated molecular patterns) without viable bacteria that causes chronic systemic inflammation. A recent hypothesis proposes that translocation of bacteria and bacterial product is in the origin of multi-organ dysfunction in cirrhosis[10]. Inflammation would initially be allocated in splanchnic area, leading to arterial vasodilation and contributing to the development of portal hypertension and circulatory dysfunction. As intestinal dysfunction progresses inflammation became systemic and affects the peripheral organs. Inflammation impairs organ function by two different mechanism. The first is by causing arterial vasodilation. However, the second and perhaps the most important is organ inflammation. Inflammation decreases organ function by impairing organ microcirculation, mitochondrial function and cell function and by increasing cell death.

THE CONCEPT OF ACLF

The concept of Acute-on-Chronic Liver Failure (ACLF) was introduced for the first time by Jalan and Williams in 2002[11] to define an acute syndrome that develops in patients with compensated cirrhosis in close chronological relationship to a precipitating event and characterized by multi-organ failure and high short-term mortality. Following this paper Williams several other proposals for the diagnostic criteria of ACLF have been suggested.

R. Jalan and R. Williams proposal (2002)[11]

Acute deterioration in liver function over a period of 2-4 weeks in a patient with well compensated cirrhosis, usually associated to a precipitating event (hepatotoxic: superimposed hepatitis viral infection, drug-induced liver injury, hepatotoxins or excessive alcohol consumption; extra-hepatic: variceal bleeding or sepsis), leading to severe deterioration in clinical status with jaundice and hepatic encephalopathy and/or HRS.

Asian Pacific Association for the Study of the Liver (APASL) proposal (2004-2009)[12,13]

ACLF is an acute direct hepatic insult (hepatotropic viral infections, active alcohol consumption or drug-induced liver injury) that causes liver failure [jaundice (serum bilirubin ≥ 5 mg/dl) and coagulopathy (INR≥1.5 or prothrombine activity < 40%)] complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis. Both compensated cirrhosis and non-cirrhotic chronic liver disease (NAFLD-related chronic hepatic injury or chronic hepatitis with significant fibrosis or significant fibrosis due to other reasons) qualify as chronic liver disease. Bacterial infections are not considered hepatic insults. Patients with cirrhosis and known prior decompensation (jaundice, encephalopathy or ascites) developing acute deterioration in clinical status related or unrelated to precipitating events are considered as acute decompensation but not ACLF.

North-American Consortium for the Study of End Stage Liver Disease (NACSELD) proposal (only for infected patients) (2014)[14]

Patients with decompensated cirrhosis and bacterial infections developing 2 organ failures: grade III-IV hepatic encephalopathy, septic shock or need for mechanical ventilation or renal replacement therapy qualify as organ failure.

American Association for the Study of Liver Diseases (AASLD)/European Association for the Study of the(EASL) proposal (2014)[15]

ACLF is an acute deterioration of a pre-existing chronic liver disease (compensated or decompensated cirrhosis) usually related to a precipitating event (including bacterial infections) and associated with increased mortality at 3 months due to multi-organ failure.

European Association for the Study of the Liver- Chronic Liver Failure Consortium (EASL-CLIF Consortium) proposal (2013-2015)[16,17].

The methodology used for the above mentioned proposals were similar and consisted in two steps. The first was the elaboration of a definition and diagnostic criteria of ACLF based on personal opinions or consensus agreement among experts. Subsequently, the proposal was tested in retrospective studies in patient cohorts. Not surprisingly, this methodology determined major discrepancies among proposals. Due to this lack of agreement between proposals and the subjectivity in the methodology used for the elaboration of these definitions, investigators from the EASL-CLIF Consortium decided apply a more pragmatic approach to define ACLF. They designed a prospective multicenter observational investigation in 1343 patients hospitalized in 29 European Hospitals for the treatment of an acute decompensation of cirrhosis aimed to define ACLF in cirrhosis and to propose diagnostic criteria (CANONIC Study)[17]. At the time of patient enrolment, important clinical data from 3 months prior to enrolment were retrospectively obtained. Thereafter, patients were prospectively studied at enrolment and during a 28-day follow-up period by a pre-specified detailed protocol. Finally, data on liver transplantation, patient survival and causes of death were obtained during one year.

Pre-defined assumptions

Three assumptions had to be taken for the study design and data analysis. They were based on the experience of the investigators and on prior proposals.

1. ACLF may develop in patients with or without prior history of acute decompensation. ACLF development, however, always occurs in the setting of acute decompensation (ascites, encephalopathy, gastrointestinal hemorrhage and/or bacterial infections).

2. Extrahepatic failure(s) is a major differential feature of the syndrome.

3. ACLF is associated with high short-term mortality (arbitrarily defined as a 28-day mortality rate greater than 15% after diagnosis).

Therefore, acute decompensation, organ failure(s) and high short-term mortality rate were the predefined characteristics of the syndrome. All other features (definition, prevalence, diagnostic criteria of organ failure, diagnostic criteria of ACLF, precipitating events, clinical course, ACLF grades, prognosis, and potential mechanism) were obtained after a detailed analysis of the CANONIC database.

Diagnostic criteria of organ failure

The Chronic Liver Failure SOFA score (CLIF-SOFAs) was the original scale used to define organ failures in the CANONIC Study (Table 1). It derived from Sequential Organ Failure Assessment score (SOFAs), a scale widely used for the diagnosis of organ failures and to predict short-term mortality in intensive care[18], adapted to liver patients. Adaptation was made based on prior studies and on the clinical experience of the CANONIC investigators. Cut-off values were established after assessing the risk increase of 28-day mortality rate in each category compared to that of the previous one using the CANONIC database. A simplified version of the CLIF-SOFAs, the CLIF Consortium Organ Failure score (CLIF-C OFs)[19], with identical criteria to diagnose organ failure and similar prognostic accuracy, has been incorporated into new prognostic scores for ACLF (Table 2). The CLIF-SOFAs and the CLIF-OFs score showed similar prognostic values as MELDs in the overall patients included in the CANONIC study.

Liver failure, was defined by a serum bilirubin level ≥ 12 mg/dl. As indicated this threshold was based on short-term mortality criteria. Renal failure was defined by a serum creatinine level ≥ 2 mg/dl or the use of renal replacement therapy. The reason to use this serum creatinine threshold of serum creatinine levels in cirrhosis is that relatively low increases of serum creatinine levels in decompensated cirrhosis indicates marked reduction in GFR, and that there is a large body of evidence indicating that serum creatinine levels over this cut-off are associated with poor prognosis. Cerebral failure was defined by grade 3 or 4 hepatic encephalopathy according to the West Haven classification. Coagulation failure was defined be an INR> 2.5 and/or a platelet count $\leq 10^9$ (platelet count was not included to define coagulation failure in the CLIF-OFs). INR was included because it is widely used in cirrhosis and has been validated as an important prognostic marker. Circulatory failure was defined by the use of vasoconstrictors (norepinephrine, epinephrine, dopamine, dobutamine or terlipressin) to increase arterial pressure. Respiratory failure was defined by a ratio of partial pressure of arterial oxygen to FiO_2 of ≤ 200 or by a SpO_2 to FiO2 ratio ≤ 214. The possibility of using SpO_2 to FiO_2 ratio was offered because arterial catheterization is not a standard procedure in patients with cirrhosis admitted to regular wards.

Table 3 shows the prevalence and number of organ failures in the patients included in the CANONIC study. Organ failure was present in 33% of the patients. Most patients had single organ failure. Liver failure was the most frequent organ failure observed followed by renal, coagulation, cerebral, circulatory and respiratory failure.

Diagnostic criteria of ACLF and ACLF grades

Patients without organ failure showed very low 28-day transplant-free mortality rate (4.6%). In the remaining patients mortality increased according to the number of organ failures (table 4). Patients with one organ failure showed a mortality rate 3 folds higher than patients without organ failure but it was lower than the predefined-mortality rate of 15% required for the diagnosis of ACLF. Therefore, a refinement in the prognostic assessment of patients with single organ failure looking for additional risk factors had to be performed. The type of organ failure was clearly a risk factor in these patients. It was higher than 15% in patients with kidney failure (18.6%), but lower than 15% (10%-13.9%) in those with single “non-kidney” organ failure. We, therefore, further compared additional factors included in the CLIF-SOFAs between patients with single organ failure who did and did not survive for 28 days. Significant differences were found only in serum creatinine levels and in the prevalence of grade 1 or 2 hepatic encephalopathy (West Haven classification). The presence of a serum creatinine between 1.5 and 1.9 and of moderate hepatic encephalopathy were defined as renal and cerebral dysfunction, respectively (as indicated the terms renal and cerebral failures are applied to patients with serum creatinine ≥ 2 mg/dl or with grade 3-4 hepatic encephalopathy). Table 4 shows the 28-day mortality rate after grouping the patients according to these prognostic markers. It was low in patients without ACLF or with single non-renal organ failure without renal and/or cerebral dysfunction. In patients with single renal failure or with single non-renal organ failure if associated to renal dysfunction or hepatic encephalopathy was well above the predefined cut-of level of 15%. The 28-day transplant free mortality rate after enrolment in patients with 2 and 3 organ failures were 32% and 78.6%, respectively. In summary, 3 different risk factors obtained by the CLIF-SOFAs at enrolment were used to identify the subgroups of patients with decompensated cirrhosis with ACLF: 1. The presence of 2 organ failures or more; 2. The presence of one organ failure when the organ that fails was the kidney; and 3. The coexistence of a single “non-kidney” organ failure with kidney dysfunction and/or cerebral dysfunction.

Based on these criteria, patients with decompensated cirrhosis were stratified into 4 groups.

*ACLF grade 1***.** ACLF grade 1 is diagnosed with one of the following: 1/ Single kidney failure; 2/Single liver, coagulation, circulatory or lungs failure associated with serum creatinine between 1.5 and 2 mg/dL and/or hepatic encephalopathy grades 1 or 2; 3/ single cerebral failure with serum creatinine between 1.5 and 2 mg/dL.

ACLF grade 2. ACLF grade 2 is diagnosed when there are two organ failures, whatever the combination is.

*ACLF grade 3***.** ACLF grade 3 is diagnosed when there are three or more organ failures.

No ACLF. With these diagnostic criteria, patients with cirrhosis without ACLF are those patients who either do not have any organ failure, have single organ failure but not involving the kidneys with serum creatinine < 1.5 mg/dl and no hepatic encephalopathy, or single cerebral failure with serum creatinine < 1.5 mg/dL.

According to data from the CANONIC study, approximately one fourth (23%) of patients admitted to hospital for an acute decompensation of the disease had ACLF at admission. Furthermore, 11% of the patients without ACLF at enrolment developed the syndrome during hospitalization which gives a total prevalence of ACLF in patients admitted to hospital with decompensated cirrhosis of 31%. Among ACLF patients, 51% had ALCF grade 1, 35% ACLF grade 2, and 13% ACLF grade 3. Besides providing the diagnosis of the syndrome, these diagnostic criteria also provide data for rapid prognostic information. In patients without ACLF mortality is low, 1.9% and 10% for 28-day and 90-day mortality, respectively. By contrast, mortality is

higher in patients with ACLF (33% and 51%, respectively) and parallels ACLF grades: 23% and 41%, 31% and 55%, and 74% and 78%, in grades 1, 2, and 3, respectively.

The usefulness of these classification criteria as well as that of CLIF-SOFA and CLIF-OF scores in assessing prognosis has been validated in independent series of patients[20-23]. Nonetheless, these criteria may require future refining.

CLINICAL CHARACTERISTICS

The CANONIC study provided relevant clinical information regarding the characteristics of the syndrome in Europe (table 5)[16]. Patients with ACLF were younger and more frequently alcoholics than patients without ACLF. Clinically detectable ascites was present in approximately 80% of patients with ACLF. However if clinically detectable ascites and surrogates of ascites (diuretic treatment prior or after admission and paracentesis or SBP prior to admission) are considered together, the vast majority of patients (98%) had evidences of ascites. Among the laboratory data, the most relevant were a significantly increased blood white cell count (WCC) and C reactive protein in comparison to patients with decompensated cirrhosis but without ACLF suggesting that ACLF develops in the setting of systemic inflammation. Bacterial infection and active alcoholism, which are important mechanisms of systemic inflammation, were the most frequent precipitating events. However, no identifiable precipitating event was recognized in approximately 40% of patients. Among bacterial infections, spontaneous bacterial peritonitis (SBP), sepsis and pneumonia were more frequently associated to ACLF than other infections. The presence and type of precipitating events was not related with mortality, indicating that once ACLF develops, prognosis depends more on the number of organ failures than on the trigger. Kidney failure was the most prevalent organ failure in ACLF-1. For ACLF-2 liver failure is the most prevalent followed by kidney, cerebral and coagulation failure. For ACLF grade 3, the prevalence of all organ failures is high (table 6). Previous history of episodes of acute decompensation was absent in 23% of patients with ACLF, indicating that development of ACLF as the initial manifestation of decompensated cirrhosis is a relatively common feature. These patients without prior history of decompensation were younger, more frequently alcoholics, had more severe systemic inflammation and grade of ACLF and higher short-term mortality than patients with ACLF and prior history of acute decompensation.

Li et al have recently reported the characteristics of ACLF in 890 consecutive patients with HBV associated cirrhosis and AD using the diagnostic criteria derived from the CANONIC Study[24]. Their results indicate that ACLF associated to HBV infection in China is similar to ACLF associated to alcoholism or chronic hepatitis C in Europe although with some peculiarities. The prevalence of ACLF in the Chinese study was higher (40%) than in the CANONIC series, with ACLF-2 being the most frequent ACLF grade followed by ACLF 1 and 3. Liver and coagulation failures were the commonest organ failures. The most frequent precipitating event was bacterial infections followed by reactivation of hepatitis B and active alcoholism. In half of patients no precipitating event were identified. As in the CANONIC study, patients with ACLF showed systemic inflammation independently on the type of precipitating event. Mortality rates (28-day and 90-day) in patients with no ACLF, ACLF and ACLF grades 1, 2 and 3 were similar to those in CANONIC series. Fifty-per-cent of patients had no prior AD episodes. Mortality was unrelated to the presence or type of precipitating events or prior history of AD.

ABBREVIATIONS

ACLF	acute-on-chronic liver failure
AD	acute decompensation
CANONIC	EASL-CLIF Acute on Chronic Liver Failure Study
CLIF	chronic Liver Failure;
CLIF-C OFs	CLIF-consortium organ failure score
CLIF-SOFAs	CLIF-sequential organ failure assessment score
CRP	C-reactive protein;
E	epinephrine
EASL	European association for the study of the liver
FIO_2	fraction of inspired oxygen
HBV	hepatitis B virus;
HE	hepatic encephalopathy
INR	international normalized ratio
MELDs,	model of end-stage liver disease score
NE	norepinephrine
PAMPs	pathogen-associated molecular patters
PaO_2	partial pressure of arterial oxygen
SOFA	sequential organ failure assessment;
SpO_2	pulse oximetric saturation

Acknowledgments

The CLIF Consortium is supported by an unrestricted grant from Grifols.

REFERENCES

1. Ginès P, et al. Compensated cirrhosis: natural history and prognostic factors. Hepatology 1987;7:122-128. 111.

2. Schrier RW, Arroyo V, Bernardi M, et al. Peripheral Arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988 ;8:1151–1157

3. Arroyo V, Ginès P, Gerbes AL, et al. Definition and diagnóstic criteria of refraxctory ascites and hepatorenal síndrome in cirrhosis. Hepatology 1996; 23: 164-176

4. Ruiz-del-Arbol L, Monescillo A, Arocena C, et al. Circulatory function and hepatorenal syndrome in cirrhosis. Hepatology 2005;42:439–447.

5. Fede, G et al. Adrenocortical dysfunction in liver disease: a systematic review. Hepatology, 2012; 55 1282-1291.

6. Grace JA, Angus PW. Hepatopulmonary syndrome: Update on recent advances in pathophysiology, investigation, and treatment. J Gastroenterol Hepatol 2013; 2: 213–219

7. Vilstrup H, et al. Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol 2014; 60: 715-735.
8. Qiu N, et al. Alterations of gut microbioma in liver cirrhosis. Nature 2014; 513: 59-64
9. Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. J Hepatol. 2014;60:197-209.
10. Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol. 2015 Jul 17. pii: S0168-8278(15)00466-3. doi: 10.1016/j.jhep.2015.07.004

11. Jalan R, Williams R. Acute-on-chronic liver failure: Pathophysiological basis of therapeutic options. Blood Purif 2002; 20:252-261.

12. Sarin SK, et al. Acute-on-chronic liver failure: consensus recommendation of the Asian Pacific Association for the Study of the Liver (APASL). Hepatology Int 2009; 3:269-282.

13. Sarin SK, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASl) 2014. Hepatol. Int 2014; 8: 453-471.

14. Bajaj JS, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. Hepatology 2014;60:250-256.

15. Jalan R, et al. Acute-on chronic liver failure. J Hepatol. 2012;57:1336-1348.

16. Moreau R, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426-1437.

17. Arroyo V, Moreau R, Jalan R, Ginès P. Acute-on-chronic liver failure: A new syndrome that will re-classify cirrhosis. J Hepatol. 2015;62:S131-S143.
18. Vincent JL, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1966; 22:707-710.

19. Jalan R, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol 2014; 61: 1038-1047
20. McPhail MJ, et al. Increased survival for patients with cirrhosis and organ failure in liver intensive care and validation of the Chronic Liver Failure-Sequential Organ Failure Scoring System. Clin Gastroenterol Hepatol. 2015;13:1353-1360.
21: Dhiman RK, et al. Chronic Liver Failure-Sequential Organ Failure Assessment is better than the Asia-Pacific Association for the Study of Liver criteria for defining acute-on-chronic liver failure and predicting outcome. World J Gastroenterol. 2014;28:14934-41.

22: Silva PE, et al. Single-centre validation of the EASL-CLIF consortium definition of acute-on-chronic liver failure and CLIF-SOFA for prediction of mortality in cirrhosis. Liver Int. 2015;35:1516-1523.
23: Lee M, et al. CLIF-SOFA scoring system accurately predicts short-term mortality in acutely decompensated patients with alcoholic cirrhosis: a retrospective analysis. Liver Int. 2015;35:46-57

24 Li , Pavesi M, Zeng B, et al. “Eastern” type of acute on chronic liver failure (ACLF) is similar in pathophysiologic, diagnostic and prognostic criteria to the “Western” type: a comparison between Chinese hospitalized patients with hepatitis B with CANONIC data (abstract). Hepatology 2014; 60: 480A-481A.

Table 1. The Chronic Liver Failure (CLIF)-Sequential Organ Failure Assessment (SOFA) Score

Organ/system	0	1	2	3	4
Liver (Bilirubin, mg/dL)	<1.2	≥1.2 - ≤2.0	≥2.0 - <6.0	≥6.0 - <12.0	≥12
Kidney (Creatinine, mg/dL)	<1.2	≥1.2 - <2.0	≥2.0 - <3.5[b]	≥3.5 - <5.0 or use of renal-replacement therapy	≥5.0
Cerebral (HE grade)	No HE	I	II	III[c]	IV
Coagulation (INR)	<1.1	≥1.1 – <1.25	≥1.25 - <1.5	≥1.5 – <2.5	≥2.5 or Platelets≤20x10^9/L[d]
Circulation (MAP mm Hg)	≥70	<70	Dopamine ≤5 or Dobutamine or Terlipressin[e]	Dopamine >5 or E ≤ 0.1 or NE ≤ 0.1	Dopamine >15 or E > 0.1 or NE > 0.1
Lungs PaO/FiO2: or SpO2/FiO2	>400 >512	>300 - ≤400 >357 - ≤512	>200 - ≤300 >214 - ≤357	>100 - ≤200 >8 - ≤214[f]	≤100 ≤89

Like the SOFA score, the CLIF-SOFA score includes sub-scores ranging from 0 to 4 for each of six components (liver, kidneys, brain, coagulation, circulation, and lungs) with higher scores indicating more severe organ impairment. Aggregated scores range from 0 to 24 and provide information on overall severity. HE denotes hepatic encephalopathy, INR, International Normalized Ratio; MAP, mean arterial pressure; E, epinephrine; NE, norepinephrine, PaO_2, partial pressure of arterial oxygen; FIO_2, fraction of inspired oxygen; SpO_2, pulse oximetric saturation. The highlighted area in light blue shows the diagnostic criteria for organ failures. The shaded area describes criteria for diagnosis of organ failure.

Table 2. CLIF-Organ Failure score system. Risk increase with respect to low-risk category (Odds Ratio, OR, and 95% Confidence Interval, CI) for each organ system sub-score.

Organ / System	Sub-score = 1	Sub-score = 2	Sub-Score = 3
Liver	Bilirubin < 6mg/dL	6 ≤ Bilirubin ≤ 12mg/dL	Bilirubin >12mg/dL
OR vs Sub-score 1 (95%CI)		OR: 2·6 (1·6 – 4·3)	OR: 7·1 (4·7 – 10·7)
Kidney	Creatinine <2mg/dL	2 ≤ Creatinine<3·5 mg/dL	Creatinine≥3·5 mg/dL or renal replacement
OR vs Sub-score 1 (95%CI)		OR: 3·8 (2·3 – 6·3)	OR: 15·5 (8·9 – 26·8)
Brain (West-Haven grade for HE)	Grade 0	Grade 1-2	Grade 3-4 *
OR vs Sub-score 1 (95%CI)		OR: 2·1 (1·4 – 3·2)	OR: 9·7 (5·9 – 16·1)
Coagulation	INR < 2·0	2·0 ≤ INR < 2·5	INR ≥ 2·5
OR vs Sub-score 1 (95%CI)		OR: 5·2 (3·4 – 7·9)	OR: 7·5 (4·6 – 12·3)
Circulatory	MAP ≥70 mm/Hg	MAP <70 mm/Hg	Use of vasopressors
OR vs Sub-score 1 (95%CI)		OR: 2·6 (1·6 – 4·3)	OR: 9·2 (5·2 – 16·4)
Respiratory			
PaO2/FiO2	>300	≤300 - > 200	≤200 (#)
or			
SpO2/FiO2	>357	>214- ≤357	≤214 (#)
OR vs Sub-score 1 (95%CI)		OR: 2·7 (1·7 – 4·2)	OR: 6·4 (3·1 – 13·2)

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. MAP: Mean arterial pressure

* Patients submitted to Mechanical Ventilation (MV) due to HE and not to a respiratory failure were considered as presenting a cerebral failure (cerebral sub-score=3).

Other patients enrolled in the study with MV were considered as presenting a respiratory failure (respiratory sub-score=3).

Table 3. Prevalence and number of organ failures

	Patients (n=1,343)	**Prevalence (%)**
Number of organ failures		
No organ failure	901	67.1
One organ failure	287	21.4
Two organ failures	108	8.0
3-6 Organ failures	47	3.5
Type of organ failure		
Liver failure	207	15.4
Renal failure	169	12.6
Coagulation failure	105	7.8
Cerebral failure	99	7.4
Circulatory failure	64	4.8
Respiratory failure	32	2.4

Table 4. Diagnosis and grades of ACLF (CANONIC study)

	TX-free patients (n=1,287)	**28-Day mortality rate**	**ACLF grades**
No organ failure	879 (68.3%)	39/879 (4.4%)	➔ No ACLF
Single non-renal failure, creatinine<1.5 mg/dLm, no HE	128 (9.9%)	8/128 (6.3%)	
Single renal failure	86 (6.7%)	16/86 (18.6%)	➔ ACLF-1
Single non-renal failure, Creatinine 1.5-1.9 mg/dLm and/or HE	54 (4.1%)	15/54 (27.7%)	
2 organ failures	97 (7.5%)	31/97 (32.0%)	➔ ACLF-2
3 organ failures	25 (1.9%)	17/25 (68.0%)	➔ ACLF-3
4-6 organ failures	18 (1.4%)	12/18 (88.9%)	

HE: Hepatic encephalopathy

Table 5. Patients' Characteristics at Enrollment

Characteristic	No ACLF (N=1040)	ACLF All Grades (N= 303)	*P* value[a]	ACLF Grade 1 (N=148)	ACLF Grade 2 (N=108)	ACLF Grade 3 (N=47)	*P* value[b]
Age (yr)	58±12	56±11	0.02	58±12	54±11	52±12	<0.01
Ascites	656 (63.4)	236 (78.7)	<0.001	112 (76.2)	87 (82.1)	37 (78.7)	0.08
MAP (mm/Hg)[c]	85±12	79±13	<0.001	81±13	79±13	72±10	<0.001
Cause of cirrhosis							
Alcohol	483 (49.2)	170 (60.3)	<0.01	86 (61.9)	64(59.8)	26 (56.5)	<0.01
Hepatitis C	210 (21.4)	38 (13.0)	<0.01	15 (10.8)	17 (15.9)	6 (13.0)	0.01
Alcohol plus hepatitis C	95 (9.7)	27 (9.3)	0.83	14 (10.1)	9 (8.5)	4 (8.7)	0.97
Potential precipitating events of ACLF							
Bacterial infection	226 (21.8)	98 (32.6)	<0.001	44 (29.9)	33 (30.8)	21 (44.7)	<0.001
Gastrointestinal hemorrhage	180 (17.3)	40 (13.2)	0.09	15 (10.1)	14 (13.0)	11 (23.4)	0.06
Active alcoholism[d]	147 (14.9)	69 (24.5)	<0.001	22 (16.1)	28 (28.6)	19 (40.4)	<0.001
Other precipitating event[e]	34 (3.5)	25 (8.6)	<0.001	12 (8.5)	10 (9.6)	3 (6.7)	<0.01
No precipitating event[f]	584 (58.9)	126 (43.6)	<0.001	73 (51.4)	40 (40.0)	13 (27.3)	<0.001
>1 Precipitating event[g]	56 (5.7)	39 (13.5)	<0.001	17 (12.0)	14 (14.0)	8 (17.0)	<0.001
Organ failure							
Liver	75 (7.2)	132 (43.6)	<0.001	37 (25.2)	65 (60.2)	30 (63.8)	<0.001
Kidney	0 (0)	169 (55.8)	<0.001	87 (58.8)	49 (45.4)	33 (70.2)	<0.001
Cerebral	26 (2.5)	73 (24.1)	<0.001	5 (3.4)	35 (32.4)	33 (70.2)	<0.001
Coagulation	21 (2.0)	84 (27.7)	<0.001	11 (7.4)	42 (38.9)	31 (66.0)	<0.001
Circulation	13 (1.3)	51 (16.8)	<0.001	3 (2.0)	18 (16.7)	30 (63.8)	<0.001
Lungs	4 (0.4)	28 (9.2)	<0.001	5 (3.4)	7 (6.5)	16 (34.0)	<0.001
Kidney dysfunction	96 (9.2)	40 (13.2)	0.04	26 (17.6)	8 (7.4)	6 (12.8)	0.01
Cerebral dysfunction	254 (24.6)	108 (35.9)	<0.001	74 (50.3)	25 (23.1)	9 (19.6)	<0.001
Laboratory data							
Hematocrit (%)	31±6	29±6	<0.001	29±6	29±5	27±7	<0.001
Platelet count (x10^9/L)	110±76	100±69	0.02	107±73	98±67	77±56	0.01
Serum bilirubin (mg/dL)	4.8±6.8	12.8±17.7	<0.001	7.7±9.2	15..2±11.1	23.2±35.9	<0.001
INR[h]	1.5±0.4	2.1±0.9	<0.001	1.7±0.6	2.3±0.9	2.8±1.0	<0.001
Alanine aminotransferase (U/L)	55±123	67±118	0.14	44±53	65±121	169±217	<0.001
Aspartate aminotransferase (U/L)	93±148	143±268	<0.01	80±70	132±174	377±580	<0.001
Serum creatinine (mg/dL)	1.0±0.4	2.3±1.6	<0.001	2.4±1.4	2.1±1.8	2.6±1.7	<0.001
Serum sodium (mmol/L)	135±6	133±6	<0.001	133±7	133±6	134±7	<0.001
Time from previous decompensation							
No previous decompensation	279 (27.8)	66 (23.2)	0.12	21 (16.5)	27 (27.6)	18 (42.9)	<0.01
Less than 3 months	102 (10.8)	47 (17.6)		23 (18.1)	14 (14.3)	10 (23.8)	
From 3 to 12 months	165 (17.4)	43 (17.1)	0.02	21 (16.5)	19 (19.4)	3 (7.1)	<0.01
More than 12 months	402 (42.8)	111 (41.6)		62 (48.8)	38 (38.8)	11 (26.2)	

Data are are means±SD or number of patients (%).

[a]*P* value of comparisons between patients with and without ACLF

[b]*P* value of comparisons across ACLF Grades (No ACLF, ACLF grade 1, ACLF grade 2 and ACLF grade 3).

[c]Mean Arterial Pressure

[d]Active alcoholism was defined by more than 14 drinks per week in women and more than 21 drinks per week in men within 3 months prior to study enrolment.[20]

[e]Other precipitating event was defined by the presence of one of the following: transjugular intrahepatic porto-systemic shunting, major surgery, therapeutic paracentesis without use of intravenous albumin, hepatitis, or alcoholic hepatitis (liver biopsy required for diagnosis).

[f]No precipitating event denotes the absence of bacterial infection, active alcoholism, or other precipitating event.

[g] More than one precipitating event denotes the presence of at least two of these: bacterial infection, active alcoholism, or other precipitating event.

[h]International Normalised Ratio