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Corresponding Author:	Mihai Popescu Institutul Clinic Fundeni ROMANIA
First Author:	Dana Tomescu, MD, PhD
Order of Authors:	Dana Tomescu, MD, PhD
	Mihai Popescu
	Gianni Biancofiore, MD
Abstract:	Acute-on-chronic liver failure represents a newly defined entity in patients with liver disease leading to multiple organs failures and increased mortality. To date, no universally accepted definition exists, and different academic societies developed guidelines on the early diagnosis and classification of Acute-on-chronic liver failure. Recently published trials focused on factors associated with a poor outcome and on the development of severity scores aimed to identify patients who may benefit for advanced monitoring and treatment. No specific therapies are demonstrated to improve survival and liver transplantation remains the only treatment associated with improved outcome.

LIVER TRANSPLANTATION FOR ACUTE-ON-CHRONIC LIVER FAILURE

Dana Tomescu[1,2] MD, PhD, Mihai Popescu MD, PhD[1,2], Gianni Biancofiore[3] MD

1. "Carol Davila" University of Medicine and Pharmacy, Department of Anesthesiology and Critical Care, Bucharest, Romania

2. Fundeni Clinical Institute, Department of Anesthesiology and Critical Care III, Bucharest, Romania

3. University School of Medicine, Department of Anesthesia and Critical Care, Pisa, Italy

Corresponding author:

Mihai Popescu

Address: 258 Fundeni street, 2nd district, Bucharest, Romania, Zip code 022328

Email: mihai.popescu@umfcd.ro

Tel: +(40) 21 2750700

Fax: +(40) 21 3183595

Abstract

Acute-on-chronic liver failure represents a newly defined entity in patients with liver disease leading to multiple organs failures and increased mortality. To date, no universally accepted definition exists, and different academic societies developed guidelines on the early diagnosis and classification of Acute-on-chronic liver failure. Recently published trials focused on factors associated with a poor outcome and on the development of severity scores aimed to identify patients who may benefit for advanced monitoring and treatment. No specific therapies are demonstrated to improve survival and liver transplantation remains the only treatment associated with improved outcome.

Our review focuses on current evidence for early diagnosis and prognostication of disease in patients with Acute-on-chronic liver failure, as well of criteria for intensive care unit admission, indication and futility markers of liver transplantation, as well as bridging therapy and optimal timing of surgery.

Keywords: liver failure, acute-on-chronic liver failure, liver transplantation, bridging therapies

A. Definition, epidemiology and early diagnosis of Acute on chronic liver failure

Acute on chronic liver failure (AoCLF) represents a recently defined syndrome in patients with liver disease that is associated with increased mortality and morbidity [1]. The definition and clinical understanding of AoCLF is still developing and challenging our current perspective on hospitalized patients with liver disease. Thus, current research in the field of liver disease has been aimed in helping the early diagnosis and medical treatment of AoCLF without reaching definitive results in terms of improving outcome. Although liver transplantation (LT) may represent a suitable treatment for the disease, choosing both the right patient and the appropriate timing is still under debate.

The worldwide burden of liver disease has been demonstrated by many epidemiological studies pointing out the greater number of patients that are admitted both in hospitals and intensive care units (ICUs) with AoCLF [2]. A ten-year inquiry [3] of the United States National database demonstrated a two-fold increase in the number of patients hospitalized due to liver cirrhosis with a two-fold increase in associated costs. Unfortunately, this is not paralleled by an increase in organ donation [4]. Hence, in present times, more and more patients need emergency LT but, due to the low availability of liver grafts, alternative measures, like living related LT or bridging therapies until a suitable graft is available, need to be taken into consideration.

The definition of AoCLF is still under debate with different international societies giving their own recommendations [1,5,6] on the definition criteria (Table 1). Of these, the EASL-CLIF definition was developed in Europe based on the CANONIC study [1]. This multicenter international study was conducted in 29 liver units across 8 European countries. Definition criteria were based on organ failures that were assessed using a modified SOFA sore – the CLIF-SOFA score. When considering this definition, patients had a 28 days mortality of 34% and a subsequent

classification based on number of organ failure and predicted mortality was proposed (Table 1). Since then, the CLIF-SOFA score and derived scores had been considered a key tool in the diagnosis and severity classification of AoCLF (Table 2).

In 2018, Karvellas et al. [7] conducted an observational multicenter study that included the original CANONIC patients and consecutive patients admitted in 4 ICUs in Canada and Europe. Their comparison of CLIC-C ACLF score with APACHE II score (a dedicated score for critical ICU patients) or more specific liver scores (Model for End-Stage Liver Disease or Child-Turcotte-Pugh score) showed superior discriminative power for 90 days mortality and hence can provide a better tool for ICU admission and organ support. Their results were confirmed [8,9] by different studies that showed that CLIF-C ACLF score is a better predictor of mortality over a wide range of etiologies and triggering factors.

B. ICU admission and bridging to liver transplantation

Regardless of the definition, AoCLF is associated with short term mortality ranging from 25% to 70% [10,11]. Due to the high early mortality seen in these patients, early admission to a transplant center and dedicated ICU or high-dependency gastroenterology ward is advisable. Recently, Hernaez et al. [12] demonstrated on a large cohort of more than 72.000 patients that those who were admitted in a dedicated LT center had a 20% lower chance of dying at 28 days. Whether this may be attributed to aggressive treatment and LT, or not, is still under debate. However, it is undoubtable that early recognition is a key factor influencing patient outcome.

Current research could not provide definitive criteria for admission of cirrhotic patients in the ICU. As we previously mentioned, scoring systems can help identify those patients who have a high risk of early mortality. Nevertheless, most ICUs have adapted individualized protocol for admission. At present, patients are admitted due to life-threatening organ dysfunction and need for

advanced organ support. Of these, infection, variceal bleeding, hepatic encephalopathy, renal, respiratory or cardiovascular failure represent the most common reasons for ICU admission [13].

In a recently published study, Cardoso et al. [14] identified lactate levels and number of organ failures as early predictors of mortality. Based on these factors they proposed and validated a prognostication score that can stratify the risk of mortality and optimize organ support. In another study, Drolz et al. [15] showed that lactate levels at admission was significantly associated with the number of organ failures and 28 days mortality. Moreover, a low lactate clearance was also associated with an unfavorable outcome.

When compared [16] to the general ICU patients, those with AoCLF had similar ICU length of stay, organ failure, development of new infection and incidence of septic shock. Hence, at least the same criteria used for non-cirrhotic ICU admission should be used in patients with AoCLF. The issue at hand is whether a subset of patients who don't fulfil these criteria but could benefit from intensive care management prior to LT can be identified but adequate evidence is lacking.

Aside from organ support, like vasopressors, mechanical ventilation and renal replacement therapy, extracorporeal liver support therapies (ELST) represent the main indication for ICU admission as a bridging therapy to LT. Current studies have demonstrated the benefits of ELST on biochemical parameters [17,18] and hepatic encephalopathy [19]. The two major randomized control trials looking at the effects of ELST on survival in patients with AoCLF, the RELIEF [20] and the HELIOS [21] study, have failed to demonstrate a significant effect on patient survival. So, at this time, based on current research we cannot recommend ELST as routine use to bridge patients to LT.

Newer technologies have been recently researched to either bridge patients to LT or to assure organ remission of AoCLF and associated organ dysfunction. Inflammation is considered a hallmark of acute decompensation of liver failure [22,23]. AoCLF patients with a high neutrophil-to-lymphocyte ratio, as a marker of systemic inflammation, have increased mortality compared to non-AoCLF patients [24]. Thus, balancing the immune response may represent a more pathophysiological approach to the medical treatment of AoCLF. Plasma exchange may offer a feasible theory in bridging patients to liver transplantation [25,26], although its exact impact on survival needs further assessment. Hemoadsorbtion represents a new therapy for the management of inflammation and biochemical parameters in patients with liver failure. Although no randomized control trial has been published to date, data from case series [27] offers promising results.

C. Indications and outcome variable associated with liver transplantation

One of the main concerns in these patients after ICU admission is the decision for liver transplantation balanced by futility in those patients who are considered “to sick to transplant”. Although no recommendations are clearly stated, some factors are associated with a worse outcome in patients with AoCLF after ICU admission. Based on the EASL-CLIF criteria for the definition of AoCLF, Sundaram et al. [28] identified those who had a high mortality after LT for AoCLF. AoCLF grade 3, regardless of the MELD score, mechanical ventilation and early transplantation after inclusion on the waiting list were the associated with a decreased 1-year survival. In another study, Huebener et al. [29] showed a decreased 90 days survival in patients with AoCLF compared to those without AoCLF (72.4% vs 96.1%). They noted that clinical improvement of at least one organ dysfunction prior to LT was associated with improved outcome.

The type of organ dysfunction is also an important factor that must be taken into account. In their study, Levesque et al. [30] assessed the risk factors associated with increased mortality on a cohort of patients with AoCLF who underwent LT. As expected, coagulation, liver failure and renal injury were the most frequent organ dysfunctions recorded. However, these patients may have a good outcome after LT due to rapid postoperative reversal of these organ failures. Even in patients with severe preoperative hepatic encephalopathy, full neurologic recovery is demonstrated within the first 48 hours after LT [31]. Also, patients who have acute kidney injury and require renal replacement therapy prior to LT have the same survival as patients who do not and consequent renal failure at 6 months postoperatively is similar to non-AoCLF transplant recipients [32]. On the other hand, Levesque et al. have also reported a significant number of patients who had circulatory failure requiring vasopressor support (17%) or respiratory failure requiring mechanical ventilation (21%) of who 55% due to pulmonary infection. Such patients, more often in AoCLF-3, have a higher mortality. Moon et al. [33] compared patients with and without AoCLF who underwent LT and found that patients who were admitted to the ICU prior to liver transplantation and those requiring vasopressor support had decreased graft survival (HR 0.76 and HR 1.95, respectively).

It is clear that the grade of AoCLF and the severity and type of organ dysfunction represent the main factors associated with a negative outcome in the early postoperative period of liver transplantation. Of those, respiratory and cardiovascular dysfunction represent the most serious complications and can be considered as relative contraindications [34]. Patients who have hepatic encephalopathy or acute renal failure seem to have the same outcome as compared to general LT recipients. Nevertheless, objective data that can be applied to all patients are lacking and hence a

personalized decision has to be made on a case by case basis whether liver transplantation is indicated.

D. The role of precipitating event

Precipitating factors have an important role in referral of patients with liver failure to LT as they themselves may represent (relative) contraindications for transplantation. The main pathophysiological triggers are represented by [1,35]: acute alcoholism, reactivation of or superimposed viral hepatitis, drug induced liver failure, bacterial infection, gastro-intestinal bleeding and surgery. Nevertheless, in up to 43% of patients, the precipitating factors may remain unknown [1].

Approximately one third of patients are admitted to the ICU due to an infection as a precipitating factor for AoCLF and another one third will develop an infection after their admission [36]. Of these patients, fifty percent are in septic shock or have a life-threatening organ dysfunction. The main sites of infection are spontaneous bacterial peritonitis, urinary tract infection, pneumonia and blood stream infection. Unfortunately, half of the infections are nosocomial in nature and multi-drug resistant bacteria like E. coli and Klebsiella spp. are the most frequent responsible microorganism [37]. Mortality associated with infection-triggered AoCLF is higher than AoCLF due to other factors [38] and the higher the number of organ dysfunctions, the higher the mortality [39,40]. If infection is suspected antibiotic therapy should be quickly started as every hour delay leads to an increase in mortality [41].

The diagnosis of infection is not straightforward. Classical paraclinical markers of sepsis, like leucocyte count, C-reactive Protein and IL-16 are increased in patients with AoCLF regardless of underling infection [42,43]. Unfortunately, at present, no paraclinical test has a significant discriminative value between systemic sterile inflammation and infection. Bacterial cultures,

although offer the definitive diagnosis, may take up to 72 hours for a definite result to be confirm. In cirrhotic patients, the new definition of sepsis based on the qSOFA and the Sepsis-3 criteria is better predictor of infection severity than the classical systemic Inflammatory Response Syndrome criteria and qSOFA is better correlated with patient mortality [44].

Co-existing bacterial or fungal infection has a tremendous implication for both patient management and decision making for LT. The NACSELD study [45] showed that patients who are infected have a higher chance to be delisted or to die on the waiting list for LT. Also, the primary cause of delisting or death was attributed to either respiratory or circulatory failure. It is cleat that most centers are reluctant to transplant patients with severe infections or sepsis [46] but an individualized approach should be sought out. In fact, recent research has pointed out that although patients who are infected prior to LT have a higher rate of postoperative infections and longer ICU length of stay, the incidence of postoperative complications and mortality do not differ significantly [47,48].

E. Timing of liver transplantation

The perfect time of LT in patients with AoCLF is a subject of great debate. The downfalls of inappropriate timing are represented by the fact that AoCLF patients may undergo unnecessary emergency LT when they are clinical course is improving and hence are exposed to increased risks of postoperative complications and increased mortality. On the other hand, the patients' clinical course may rapidly deteriorate and they may leave the therapeutic window for transplantation due to irreversible organ failure. At the same time, patients who undergo liver transplantation while in the ICU for AoCLF show increased mortality independent of their MELD score [49].

In a follow up of the CANONIC study [50], the natural history of AoCLF was towards resolution or improvement in 49% of patients, 30% of patients had a steady or fluctuating course

and 21% showed worsening of organ dysfunction. One-year survival in patients who underwent LT was 75%. It is important to note that 28-day survival in patients who were not severely ill was high (82-94%) compared to that of patients with AoCLF grade 2 or 3 (8-58%). Also, the AoCLF grade at 3-7 days accurately predicted 28-days and 90-days mortality. These data suggest that patients who show no clinical improvement at 3-7 days after AoCLF is diagnosed should be considered for emergency LT.

A paper published by the APASL ACLF Research Consortium [51] considered the same 7 days threshold for reassessment and possible indication for LT. In their cohort of 1021 patient, those who did not have a new onset of hepatic encephalopathy or acute kidney dysfunction within the first 4 days and showed a decline in bilirubin, creatinine and INR values by day 7 had increased survival. On the other hand, patients who had a bilirubin>22 mg/dL, grade III or IV hepatic encephalopathy and INR>2.5 with either creatinine>1 mg/dL or lactate>1.5 mmol/L at baseline or persistence of these values at day 4-7 had a 100% 28-days mortality.

In a study conducted by Artru et al. [52], the median time to LT after management of AoCLF associated organ dysfunction was 9 days. Patients who underwent LT had a higher 1-year survival compared to controls (84% vs. 8%) and this was independent of AoCLF grade at the time of transplantation. Their proposal of a ”transplantation window” is feasible and an individualized, center-specific, decision algorithm should be adopted in order to optimize the timing for LT.

F. Choosing the right liver graft

Both deceased donor and living donor LT are feasible options in patients with AoCLF and current data suggest no difference in outcome in regard to the type of liver graft used [53]. Liver donor’s mortality and reported complications after donation has limited the use of this technique in Western countries in recent years [54]. Nevertheless, due to organ shortage such decision should

be evaluated on a case-by-case basis. The excellent outcome of patients who underwent living donor LT reported by different studies [33,34,55] may represent a turning point and reconsideration of living donation in the case of AoCLF patients.

Unfortunately, the scarcity of donor organs is not the only problem. As the general population gets older and sicker, so does the donor pool [56]. Sundaram et al. [28] demonstrated that AoCLF patients who receive liver graft from marginal donors (as defined by a donor risk index above 1.7) have increased postoperative mortality. We do not consider that there are sufficient data to support one type of organ graft over another, but rather that availability of grafts, center experience and timing of LT should be taken into consideration.

G. Futility of liver transplantation

Futility of LT in patients with AoCLF is a controversial problem that has recently gained more attention as there are no universally accepted criteria. In a study performed by Petrowsky et al. [57], MELD score, pretransplant septic shock, cardiac risk and co-morbidities represented independent predictors of transplant futility. In a single-center study, Michard et al. [58] identified pretransplant lactate levels and the presence of Acute Respiratory Distress Syndrome as being independently associated with increased mortality and proposed them as markers of futility. Also, we could observe from follow-up data from the CANONIC study [50] that patients with respiratory failure (defined as a PaO2/FiO2<200) did not undergo LT, suggesting that most European centers agree on Acute Respiratory Distress Syndrome being a contraindication for transplantation. Severe malnutrition has been considered a valuable predictor for mortality in patients with liver cirrhosis [59] and should also be considered as a marker for futility in patients with AoCLF.

On the other hand, recent evidence may shade a new light on what was once believed to be a marker of futility. Thuluvath et al. [60], showed that the risk of postoperative mortality in liver

transplant recipients increased with increasing number of OFs but short term and 1-year survival were similar (only 9% difference) in patients with no organ dysfunction and those with 5-6 organ dysfunctions. As previously stated, the severity of AoCLF alone should not represent the basis for canceling LT. Unfortunately, due to the lack of more objective criteria to support the idea of ”to sick to transplant”, each decision is made on a case-by-case approach and it is based on personal experience and the lack of absolute contraindications.

In summary, the number of cirrhotic patients with AoCLF is increasing worldwide. Due to the rapid progression of disease and high mortality, such patients are best managed in an intensive care environment. Transplantation in such patients is becoming more frequent with good outcome but both timing and contraindications for LT are still under debate, with most centers agreeing on cardiovascular and/or respiratory failure as being associated with a worse outcome. Until international consent, center criteria should be considered taking into account personal experience, local protocols and severity of associated organ dysfunction.

Practice points:

- The increased mortality of acute-on-chronic liver failure is associated with the number and severity of organ failures.
- Patients with severe organ dysfunction or cardiovascular or respiratory failure are best treated in an intensive care unit.
- Advanced monitoring and appropriate organ support should be initiated early. Recent evidence does not support the use of extracorporeal liver support therapies as it is not associated with increased survival.

- If no improvement is seen within 3-7 days emergency liver transplantation should be considered.
- Before liver transplantation criteria for futility must be revised and centre specific criteria for organ transplantation applied.
- Both deceased donor liver transplantation and living-donor liver transplantation are feasible options in acute-on-chronic liver failure and choosing one type of liver graft depends mainly on cultural criteria and organ availability.

Research agenda

- Guidelines are needed for both rapid diagnosis of acute-on-chronic liver failure and intensive care unit admission.
- Research on assessment of patients for suitability for liver transplantation is required and further research is needed to identify futility markers and develop "to sick to transplant" criteria.
- Future bridging therapies should focus on the modulation of the inflammatory response associated with liver failure.

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Table 1

	EASL definition [1]	APASL definition [5]	WGO definition [6]
Basis of definition	Prospective observational study	International consent	International consent
Patients included in the definition	Patient with acute decompensation of liver cirrhosis	Acute liver function deterioration in patients with or without liver cirrhosis (including (non-alcoholic fatty liver disease, related chronic hepatic injury or chronic hepatitis with fibrosis, or fibrosis due to other reasons)	Patients with chronic liver disease with or without previously diagnosed cirrhosis
Patients excluded from the definition	• Hepatocellular carcinoma outside Milan criteria • Severe immunodeficiency (including HIV) • Severe extrahepatic disease	• Acute decompensation defined in cirrhotic patients and known prior decompensation who develop acute deterioration related or	• None

		unrelated to the precipitating events • Patients with infection	
Definition	• No AoCLF: - No organ failure - Single organ failure in patients with a serum creatinine < 1.5mg/d Land no hepatic encephalopathy - Cerebral failure in patients with a serum creatinine < 1.5 mg/dL • AoCLF grade 1: - Single kidney failure - Single liver, coagulation, circulatory or respiratory failure	Combined criteria of: • Liver failure defined as jaundice (serum bilirubin level of ≥5 mg/dL) and coagulopathy (INR ≥1.5 or prothrombin activity of <40%) • Clinical ascites or encephalopathy within 4 weeks of liver failure	Combined criteria of: • acute hepatic decompensation that leeds to liver failure (jaundice and prolongation of the INR) • one or more extrahepatic organ failures

	associated with a serum creatinine between 1.5– 1.9 mg/dL and/or grade 1 or 2 hepatic encephalopathy - Single brain failure with a serum creatinine between 1.5– 1.9 mg/dL • AoCLF grade 2: - Two organ failures • AoCLF grade 3: - Three or more organ failures		
Organ failure assessment	• Liver : bilirubin levels > 12 mg/dL • Kidney: creatinine levels > 2 mg/dL or renal replacement therapy	• Liver: bilirubin levels > 5 mg/dL or INR > 1.5 • Kidney: Acute Kidney Injury	• None

	• Brain: hepatic encephalopathy grade -3 or -4 • Coagulation: INR > 2.5 • Circulation: need for vasopressors • Respiration: PaO2/FiO2 ratio or need for mechanical ventilation	Network criteria • Brain: hepatic encephalopathy grade -3 or -4 • Coagulation: INR > 1.5 • Circulation: none • Respiration: none	
Categories	AoCLF grade 1, -2 and -3	None	Type A: chronic liver disease Type B: compensated cirrhosis Type C: decompensated cirrhosis

Table 1. Current definitions of Acute-on-chronic liver failure

Table 2

Organ/Score	0	1	2	3	4
Liver (bilirubin mg/dL)	<1.2	≥1.2 to <2.0	≥2.0 to <6.0	≥6.0 to <12.0	≥12
Kidney (creatinine mg/dL)	< 1.2	≥1.2 to <2.0	≥2.0 to <3.5	≥3.5 to <5.0	≥5.0
	Or need for renal replacement therapy				
Brain (hepatic encephalopathy grade)	No encephalopathy	1	2	3	4
Coagulation (INR)	<1.10	≥ 1.10 to <1.25	≥1.25 to <1.50	≥1.50 to <2.50	≥2.50 or platelet count< $20x10^9$ /L
Circulation (mean arterial pressure)	≥70 mmHg	< 70 mmHg	Dopamine < 5 or dobutamine or terlipresine	Dopamine > 5 or epinephrine≤0.1 or norepinephrine≤0.1	Dopamine > 15 or epinephrine>0.1 or norepinephrine> 0.1
Respiratory (PaO_2/FiO_2)	>400	>300 to ≤400	>200 to ≤300	>100 to ≤ 200	≤100

Table 2. CLIF SOFA score