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Current and future perspectives on acute-on-chronic liver failure: Challenges of transplantation, machine perfusion, and beyond

Bianca Della Guardia, Amanda P C S Boteon, Celso E L Matielo, Guilherme Felga, Yuri L Boteon

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Abstract

Acute-on-chronic liver failure (ACLF) is a syndrome that occurs in patients with chronic liver disease and is characterized by acute decompensation, organ failure and high short-term mortality. Partially due to the lack of universal diagnostic criteria, the actual ACLF prevalence remains unclear; nevertheless, it is expected to be a highly prevalent condition worldwide. Earlier transplantation is an effective protective measure for selected ACLF patients. Besides liver transplantation, diagnosing and treating precipitant events and providing supportive treatment for organ failures are currently the cornerstone of ACLF therapy. Although new clinical specific therapies have been researched, more studies are necessary to assess safety and efficacy. Therefore, future ACLF management strategies must consider measures to improve access to liver transplantation because the time window for this life-saving therapy is frequently narrow. Thus, an urgent and global discussion about allocation and prioritization for transplantation in critically ill ACLF patients is needed because there is evidence suggesting that the current model may not portray their waitlist mortality. In addition, while donor organ quality is meant to be a prognostic factor in the ACLF setting, recent evidence suggests that machine perfusion of the liver may be a safe tool to improve the donor organ pool and expedite liver transplantation in this scenario.

Key Words: Acute-on-chronic liver failure; Liver cirrhosis; Liver transplantation; Machine perfusion; Hypothermic oxygenated machine perfusion

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Core Tip: Acute-on-chronic liver failure (ACLF) is characterized by high short-term mortality. Although new clinical specific therapies have been researched, more studies are necessary to assess safety and efficacy. Conversely, earlier transplantation is effective for selected patients. Therefore, future ACLF management strategies must consider measures to improve access to liver transplantation. Discussions about donor organ allocation and recipient prioritization are necessary because there is evidence suggesting the current model may not portray the waitlist mortality of these patients. In this scenario, machine perfusion of the liver may prove to be a safe tool to improve the donor organ pool.

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INTRODUCTION

Despite the heterogeneity in the diagnosis criteria, consensually, acute-on-chronic liver failure (ACLF) is a condition that occurs in patients with chronic liver disease developing multi-organ failure in the presence of one or more hepatic or extrahepatic precipitant events. In addition, it is associated with high 28-d mortality[1-4]. Several international consortiums proposed different definitions of ACLF, reflecting their own types of underlying liver disease and precipitant events. The Asian Pacific Association for the Study of the Liver (APASL), the European Association for the Study of the Liver (EASL), formed by the Chronic Liver Failure (CLIF) Consortium and the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) are the most widely accepted[1,5,6].

Because of the lack of universal diagnostic criteria and study design limitations, the actual ACLF prevalence remains unclear. However, it is expected to be a highly prevalent condition worldwide. For example, in the CANONIC study (EASL-CLIF Acute-on-Chronic Liver Failure in Cirrhosis study), a prospective evaluation of 1343 patients admitted for acutely decompensated cirrhosis, 22.6% met the EASL-ACLF criteria for ACLF, and 8.3% developed the condition during hospitalization. In another study using APASL criteria, 12% of complicated cirrhotic patients were diagnosed with ACLF[1,7]. Recently, a large meta-analysis of global epidemiological data found about 35% of ACLF in patients admitted due to acutely decompensated cirrhosis using EASL-ACLF criteria, with a higher prevalence in South Asia, reaching 65%[8]. Notably, the overall mortality in ACLF is about 32% and increases in parallel with the number of organ failure (OF). The 28-d mortality rate for ACLF - grades 1 to 3 - ranges from 20% to 80%, 49% to 77%, and 13% to 86% for EASL-CLIF Consortium, NACSELD, and APASL-ACLF, respectively[4,9].

In recent years, several studies have investigated the pathophysiology, prognosis, and treatment options for ACLF. Although the benefit of timing liver transplantation (LT) in ACLF is undeniable, issues still exist with assessing the mortality risk of patients on the waiting list to avoid futile LT. In addition, another urgent and global discussion is about allocation and prioritization for LT in critically ill ACLF patients, as the time window for transplantation is frequently narrow[2,10,11].

This review provides an overview of ACLF management, focusing on the current challenges of LT in this scenario and future perspectives, including machine perfusion of the liver.

DIAGNOSTIC CRITERIA FOR ACLF

The natural history of cirrhosis is characterized by a long asymptomatic phase called compensated cirrhosis. The increase of portal pressure above the hepatic venous pressure gradient of 10 mmHg plays a central role in the transition to decompensated cirrhosis. Acute decompensation (AD) is defined by the new development of ascites, hepatic encephalopathy, hepatorenal syndrome, variceal bleeding, or infection[1,9].

In the PREDICT study (PREDICTing ACLF), a prospective and observational analysis of 1071 patients hospitalized with AD, 218 (20%) developed ACLF in 90 d (3-mo mortality rate of 53.7%), called pre-ACLF. Two hundred and thirty-three patients (22%) required frequent hospitalization unrelated to ACLF, called unstable decompensated cirrhosis (3-mo mortality rate of 21.0%), and 620 (58%) reached a state called stable decompensated cirrhosis (1-year mortality rate of 9.5%). These three clinical courses revealed by the PREDICT Study group originated from data of the CANONIC study, which created the EASL-CLIF definition of ACLF - probably the most widely accepted definition used to date[1,12]. Therefore, cirrhotic patients with pre-ACLF should be promptly identified due to the high risk of death in the short term.

THE EASL-CLIF CONSORTIUM DEFINITION OF ACLF

The EASL-CLIF definition considers ACLF in cirrhotic patients with or without prior episodes of decompensation and one or more OF. The CANONIC study enrolled 1343 patients from 29 centers in 12 European countries. Chronic hepatitis C virus and alcohol were the most frequent underlying causes of chronic liver diseases. The OF definitions were adapted from the Sequential Organ Failure Assessment (SOFA) score and called the CLIF-SOFA score. The CLIF-SOFA score includes subscores ranging from 0 to 4 for each of the six components (liver, kidney, brain, coagulation, circulation, and lungs). Aggregated scores range from 0 to 24 and provide information on overall severity[13].

OF was defined by liver failure (level of serum bilirubin) or extrahepatic failure. The latter includes kidney failure (defined by serum creatinine), cerebral (by grade of encephalopathy according to West-Haven classification), coagulation (by the international normalized ratio [INR]), circulatory (by blood pressure or need of vasopressors), and respiratory failure (by partial pressure of oxygen [PaO₂]/fraction of inspired oxygen [FiO₂] or oxygen saturation [SpO₂]/FiO₂) (Table 1). The most prevalent OF was kidney (43.6%), followed by coagulation (27.7%) and cerebral (24.1%). At presentation, the prevalence of ACLF grades 1, 2, and 3 were 49%, 35%, and 16%, respectively. The mortality in 28 d without LT was 32.8% in the seminal study.

THE APASL ACLF RESEARCH CONSORTIUM DEFINITION

This definition was based on an expert opinion on ACLF from the APASL, published in 2009 with updates in 2014 and 2019, using data from 1402 and 3300 patients, respectively[5,14,15]. This definition considers patients with compensated cirrhosis (diagnosed or not) and non-cirrhotic liver disease patients with a first episode of acute liver deterioration due to an insult directed to the liver. This reflects most of the patient population seen in Asia. In Asia, there is mainly hepatitis B virus reactivation or superinfection with hepatitis viruses A, D, or E. Patients with extrahepatic precipitants and those with kidney, circulatory or respiratory failures are excluded, meaning the liver dysfunction is the basis of the APASL definition. Extrahepatic OF may subsequently develop but are not needed for diagnostic criteria. The acute hepatic insult can be manifested by jaundice (serum bilirubin \geq 5 mg/dL), coagulopathy (INR \geq 1.5) and complications within 4 wk such as ascites, encephalopathy, or both. With these criteria, there is an estimated 25% to 37% 30 d-mortality[16].

THE NACSELD DEFINITION OF ACLF

ACLF was defined as the development of two or more OF (maximum of four) in patients with AD cirrhosis with or without prior episodes of decompensation. They used a prospective multicenter Canadian and American cohort of 507 patients with non-elective hospitalization in 18 centers. The OF criteria were: Kidney if dialysis is required; brain if encephalopathy grades 3 or 4 as West Haven classification occurs; respiratory if mechanical ventilation is needed; circulatory if vasopressor support is required or a reduction in systolic blood pressure by 40 mmHg from baseline despite adequate fluid resuscitation. The most prevalent OF was cerebral (36%), followed by circulatory (16%), kidney (13%) and respiratory (9%)[6]. Lately, these criteria were validated in a cohort of 2675 patients with or without infections, and mortality was higher in patients with infections, whatever the number of OF[17].

PRECIPITANTS FACTORS FOR ACLF AND PROGNOSIS

This section will discuss the most frequent precipitants for ACLF, its pathophysiology, and prognosis; nevertheless, a more thorough review of these subjects is outside the scope of this manuscript. Regardless of the ACLF definition employed, the precipitant factors can be recognized in only about 50% of patients with ACLF[9]. In 2021, the EASL-CLIF Consortium published a second paper derived from the PREDICT study reporting the precipitant factors which could influence the clinical course and the prognosis of ACLF patients. The most prevalent, more than 96% of cases, were bacterial infections (documented) and severe alcoholic hepatitis, whereas gastrointestinal bleeding with shock and toxic encephalopathy were rare. Although not so common, other precipitant factors like drug-induced liver injury, surgery, viral hepatitis, and ischemia can also be considered[18]. Mezzano *et al*[8] in a recent review and meta-analysis using ACLF-EASL-CLIF criteria in patients from Europe, East/South Asia and North/South America, showed that bacterial infections (35%), followed by gastrointestinal bleeding (22%) and acute alcohol consumption (19%) were the most frequent triggers to ACLF, with kidney dysfunction being the most common organ failure (49%). Although it is crucial to identify precipitant factors for ACLF, a recent study reported that they could not be detected in up to one-third of patients [12,19].

Table 1 European Association for the Study of the Liver Chronic Liver Failure Consortium acute-on-chronic liver failure grades

ACLF grades	Number of organ failures
1	Single organ kidney failure Single liver, coagulation, circulatory or lung failure with creatine levels ranging from 1.5 mg/dL to 1.9 mg/dL or encephalopathy grade 1 or 2, or both Single brain failure with creatinine ranging from 1.5 mg/dL to 1.9 mg/dL
2	2 organ failures
3	3 or more organ failures

ACLF: Acute-on-chronic liver failure.

Data from the CANONIC cohort showed that ACLF is a dynamic syndrome and may evolve to resolution, improvement or worsening in a short period[1]. ACLF grade 1 could be reversible in most patients (54.0%), while 21.0% remain stable in grade 1, and 24.5% progress to a higher grade. The clinical course after 3-7 d from diagnosis of ACLF may be a better predictor of outcome than its initial severity. Indeed, patients with grade 3 ACLF 3-7 d after diagnosis showed the worst prognosis[20,21]. This was called the opportunity window, wherein LT could reach the best results.

In severely ill patients, the prognosis differed according to the number of OF. For example, three OF had lower 28-d transplant-free mortality than those with four OF, 53.0% *vs* > 90.0%, respectively[20,21]. Indeed, the number of OF - according to the EASL-CLIF definition - along with age and white cell count compose the EASL-CLIF ACLF score. This predictive tool developed by the CANONIC study group proved superior to older models (Acute Physiology and Chronic Health Evaluation [APACHE] II, Child-Turcotte-Pugh, Model for End-stage Liver Disease [MELD]) to predict ACLF patients' mortality [22]. Accordingly, a recent study demonstrated that patients with an EASL-CLIF ACLF score of greater than 70 had 90% mortality at 90 d, regardless of care setting[23]. Another study reported a 28-d mortality rate of 100% for patients with a score greater than 70 at 48 h post-intensive care unit (ICU) admission[24].

Nevertheless, importantly, a 90-d and a 1-year post-LT survival rate of 90% and 81%, respectively, were reported for ACLF patients with 5 to 6 OF[25]. Conversely, without LT, survival rates dropped dramatically[25]. Therefore, although application and reassessment of the EASL-CLIF ACLF score may prevent prolongation of futile therapy, especially after a short trial of ICU stay, withdrawal of care must only be considered if the patient is not a LT candidate.

Recent evidence suggests systemic inflammation is the key to AD and ACLF disease progression[3,10,26]. Briefly, in patients with sepsis as the precipitant event, the inflammatory response is triggered by the recognition of pathogen-associated molecular patterns by pattern recognition receptors. The inflammatory response is then exacerbated, resulting in organ damage, cell death and release of damage-associated molecular patterns, which could aggravate and accelerate OF development in the ACLF setting. In addition, cirrhotic patients have portal hypertension, secondary intestinal congestion, and splanchnic endothelial dysfunction. These features can enhance gut permeability and facilitate bacterial translocation, driving local and systemic inflammation. Traditionally, inflammatory response causes organ dysfunction and stimulation of nitric oxide production, worsening pre-existing circulatory collapse and activation of immune cells. Another mechanism involved is mitochondrial metabolic impairment, resulting in metabolic disorder and cellular dysfunction with a preferential allocation of circulant nutrients to innate immune cells due to high metabolic demands. Secondly, this process decreased mitochondrial energy production and enhanced organ dysfunction. So, inflammation and immunoparesis are thus key features of ACLF[3,26].

CURRENT MANAGEMENT OF ACLF

Besides LT, diagnosing and treating precipitant events and providing supportive treatment for OF are currently the cornerstone of ACLF therapy.

TREATMENT OF PRECIPITANT EVENTS

Infections: antimicrobial therapy should commence as quickly as possible based on the suspected site involved, existing culture results and local antimicrobial sensitivity patterns. Empirical broad-spectrum antimicrobials should be promptly initiated and deescalated once the results are available. Empirical

antifungals should be considered in patients without clinical improvements within 48-72 h. In addition, antifungal therapy may also be used in ACLF patients with multiple risk factors, such as corticosteroid use, prolonged antimicrobial therapy, long-term central venous access devices, parenteral nutrition, renal replacement therapy, sarcopenia and malnutrition[4,17,21]. Recent studies also recommended avoiding proton pump inhibitors unless there is a clear indication (like stress-ulcer prophylaxis) because they increase the risk of infection, mainly due to *Clostridioides*. Nonselective beta-blockers, when tolerated, and rifaximin may be beneficial by reducing bacterial translocation and intestinal dysbiosis.

Alcoholic hepatitis: although corticosteroids are indicated in patients with alcoholic hepatitis, especially when Maddrey's discriminant function score is higher than 32, the response negatively correlates with the number of OF in ACLF. The risk of new infections is one of the most critical factors in the decision-making process for steroid therapy[4,21]. The response to steroids should be assessed with the Lille score on day 7.

Acute viral hepatitis or reactivation: potent nucleotide or nucleoside analogues should be started in the event of hepatitis B infection or reactivation.

Surgical procedures: surgery of any type in patients with cirrhosis is associated with a significant risk of OF and ACLF. Consequently, it must be carefully considered. For example, open abdominal non-liver surgery, high preoperative cardiovascular risk, or hepatic venous pressure gradient greater than 16 mmHg were frequently associated with ACLF. Recently, a new score, the VOCAL PENN score, demonstrates an excellent ability to predict 30-d mortality when surgery is needed in patients with ACLF[18,27].

SUPPORTIVE THERAPY

ACLF patients frequently require admission to an ICU for advanced OF support and assistance from a multidisciplinary team.

Hemodynamic: Early goal-directed therapy using intravenous fluid resuscitation, preferably with crystalloids, must target mean arterial pressure > 65 mmHg. If vasopressors are required, norepinephrine is the first option, and a low dose of vasopressin can be necessary. Next, terlipressin or epinephrine can be added, though they are no longer the second option. Finally, intravenous hydrocortisone can be indicated in refractory septic shock, whereas no long-term survival benefit exists [28].

Acute kidney injury (AKI): It is essential to eliminate or avoid nephrotoxic drugs. The assessment of AKI severity using the modified Kidney Disease Improving Global Outcomes (KDIGO) criteria established the use of albumin in patients with stages 2-3 and albumin plus terlipressin or norepinephrine in type-1 hepatorenal syndrome. In non-responders, it should be necessary to start renal replacement therapy, mainly in patients with LT perspectives[29,30].

Lungs and respiratory failure: The airway should be protected in West-Haven grade 3 or 4 hepatic encephalopathy patients with elective intubation. Patients should be sedated with short-acting agents such as propofol. Benzodiazepines should be avoided. Hypoxemia ($\text{PaO}_2 < 80$ mmHg) should be prevented, and paracentesis is clinically indicated in case of tense ascites[28].

Gastrointestinal: Consider the use of stress-ulcer prophylactic drugs. As soon as possible, initiate oral or enteral feedings[18].

Coagulation: Consider prophylaxis for deep-vein thrombosis in the absence of severe coagulopathy. However, avoid correction of INR alterations with fresh frozen plasma. Instead, assessing the risk of bleeding and thrombosis in ACLF patients should be done with viscoelastic testing (rotational thromboelastography or rotational thromboelastometry), which must also guide correction when needed or before invasive procedures[31,32].

NEW PERSPECTIVES FOR ACLF MANAGEMENT

The use of albumin has been well recommended to prevent AKI and renal failure in spontaneous bacterial peritonitis, besides preventing post-paracentesis circulatory dysfunction[18,26,33,34]. Recent data have highlighted the non-oncotic properties of albumin as homeostatic effects, antioxidants, immunomodulation, endothelial stabilization, and toxic binding metabolites, including bile acids. Three studies recently evaluated the routine outpatient administration of intravenous albumin. One of them, the ANSWER trial, which included outpatients in an early stage of liver disease, showed improvement in mortality and reduction in cirrhosis-related complications, mainly when the albumin level was maintained above 4 g/dL[35]. However, further studies are necessary to indicate albumin infusion use routinely[18,28].

Various artificial and bioartificial extracorporeal liver support systems have been attempted to treat ACLF. However, artificial liver support such as molecular adsorbent recirculating system and fractionated plasma separation and adsorption system (Prometheus) have failed to show any survival benefit in this setting. Some bioartificial liver supports with a source of cells, traditionally human or

porcine hepatocytes, are under investigation, but the clinical benefit is still unclear[18,21].

While the use of plasma exchange has been shown to improve survival in acute liver failure, the actual effect in the ACLF scenario is unknown. Some studies in Asia using selected patients with ACLF showed improvement in 30 and 90-d survival in non-transplanted patients. Still, randomized trials are needed on the duration and amount of plasma exchange required[36].

One potential therapy for ACLF is the administration of granulocyte colony-stimulating factor (G-CSF). Several trials, mainly in patients with hepatitis B from Asia and India, have studied the efficacy of G-CSF and showed an increased leukocyte and neutrophil count, reduced severity of the disease and a protective effect on the development of sepsis, hepatorenal syndrome and hepatic encephalopathy[3]. However, trials in Western cohorts did not demonstrate survival benefits, CLIF OF scores modification or recurrence of infections. Therefore, to date, G-CSF cannot be recommended as part of routine treatment for ACLF[3,18,33,37].

Another promising therapy is mesenchymal stem cell transplantation, which can be a bridge to stabilization in patients with ACLF until LT. However, if the concept is interesting in theory, the studies were made with a few patients, and consequently, many questions remain open[38].

In addition to treatment for hypercholesterolemia, statins may have a role in ACLF therapy because of their potential hepatoprotective and anti-inflammatory properties. Currently, two clinical trials are underway to address the benefits and safety of statin (simvastatin and atorvastatin) in cirrhotic patients [26,39,40].

The gut microbiota plays an important role in complications associated with cirrhosis, with specific intestinal microbiomes being associated with adverse outcomes. The changes in the gut microbiome parallel the disease stages reaching their peak in ACLF. ACLF patients were shown to present an increase of *Enterococcus* and *Peptostreptococcus* sp and a reduction of some autochthonous bacteria[41]. Individual microbiome signatures could possibly identify ACLF patients and their prognosis, leading to more personalized treatment, a topic under investigation in the MICROB-PREDICT study (<https://microb-predict.eu/>). Manipulation of the gut microbiome using fecal microbiota transplantation may positively impact the course of cirrhosis, as shown in patients with severe alcoholic hepatitis. In addition, one novel-engineered carbon bead (Carbalive™) designed to absorb toxins from the gut and prevent translocation is under investigation[26]. Whereas promising, more studies are necessary to assess the clinical significance of gut microbiome manipulation in managing ACLF.

PRIORITISATION CRITERIA FOR LIVER TRANSPLANTATION

Although the MELD has enhanced equity in organ allocation in LT, there is evidence suggesting it may not portray the waitlist mortality of ACLF patients. This is in accordance with distinct pathological mechanisms in decompensated cirrhosis and ACLF[42].

Sundaram *et al*[43], in a large retrospective study, reported that irrespective of the MELD-Na score, ACLF-3 patients had a worse prognosis (ACLF grades refer to the EASL-CLIF classification hereafter unless contrarily stated). They found that 43.8% of patients with ACLF-3 and MELD-Na < 25 died or were removed from the waitlist at 28 d, having the worst prognosis among ACLF groups. This is probably associated with the more frequent occurrence of extrahepatic failures, which, although not fully captured by the MELD score, result in a high mortality rate. In addition, the authors report that LT within 30 d of listing was the only significant independent protective factor for 1-year patient survival after transplantation. More importantly, in this study, yet ACLF-3 patients had a greater mortality risk, they presented a similar probability of being transplanted than non-ACLF-3 patients with similar MELD scores[44].

In the CANONIC study, Jalan *et al*[22] developed an organ function scoring system (CLIF Consortium Organ Failure score, CLIF-C OFs) to diagnose ACLF and the prognostic EASL-CLIF ACLF score. The latter score discussed previously revealed significantly higher mortality 28-d predictive accuracy than the MELD and MELD-Na[22].

Allocation systems must privilege ACLF patients once so far earlier transplantation is the cornerstone of their successful management. The question remains whether ACLF-3 patients must be prioritized or whether a new scoring system that depicts better OF must be implemented for these cases[44-46].

DONOR CHARACTERISTICS AND OUTCOMES AFTER TRANSPLANTATION

Donor organ selection in the ACLF scenario can be a real conundrum for transplant teams to solve. This is because there is evidence that donor characteristics may be associated with a poor outcome after transplantation[25,47,48], which adds complexity to the decision of whether to accept or not a donor organ offer. This aspect is troubling, considering that strict donor organ selection may even postpone further transplantation to this threatened population, especially in regions with frequent high MELD recipients.

A recent retrospective analysis from the United Network for Organ Sharing (UNOS) involving 50552 transplanted ACLF patients reported the donor risk index (DRI) above 1.7 as an independent risk factor for mortality within 1 year after LT (hazard ratio [HR] 1.22; 95% confidence interval [CI] 1.09-1.35)[47]. On the other hand, independently of the MELD score, they described LT within 30 d of the ACLF diagnosis as a predictor of improved 1-year survival after transplantation[47]. Other authors also reported similar results[48,49]. These findings together pressurize even more transplant teams, which face the dilemma of whether to proceed with a high-risk donor or wait for an ideal donor which might not come on time.

It is ideally argued that the benefit of transplantation to this population surpasses the potential negative impact of a suboptimal graft when comparing this risk with a 1-year survival probability without transplantation. This is especially true for ACLF-3 patients, whose reported 1-year survival probability with and without transplantation is 83.9% and 7.9%, respectively[50,51]. Nevertheless, the scarce literature available also reports extra caution during donor organ selection for ACLF-3 patients in real life. For example, in the UNOS database retrospective study, ACLF-3 patients received organs from younger donors (mean age 38.7 years) with the cause of death predominantly related to head trauma (38.0%) and a small percentage of organs from high-risk donors with DRI ≥ 1.7 (22.9%)[47].

Kitajima *et al*[52] using the Organ Procurement and Transplantation Network and the UNOS registry, recently analyzed 17300 transplanted ACLF patients between 2002 and 2019. They grouped the patients by eras, Era 1 (2002-2007, $n = 4,032$), Era 2 (2008-2013, $n = 6,130$), and Era 3 (2014-2019, $n = 7,138$). Donor characteristics were classified according to the DRI (DRI < 1.2 , 1.2-1.6, 1.6-2.0, and > 2.0). They have shown a significant improvement in overall patient survival and transplant outcomes throughout eras. However, although donors with DRI > 2.0 were associated with a lower risk of patient death in Eras 2 and 3 than Era 1 in ACLF-1 and 2, this was not confirmed for ACLF-3[52]. Therefore, the authors advise the need for particular caution for high-risk donors (DRI > 2.0) for ACLF-3 patients.

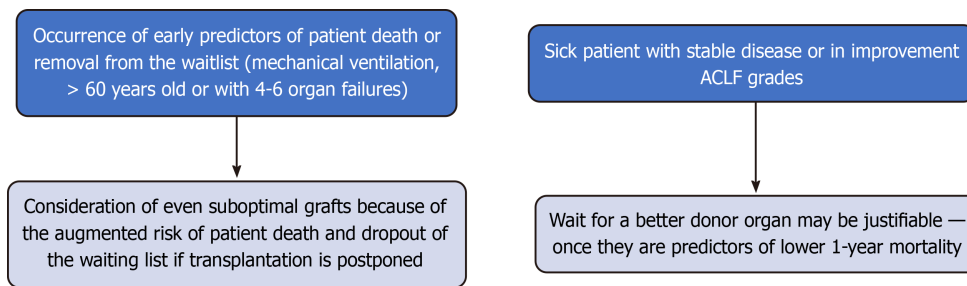
Comparatively, ACLF grades 1 and 2 are associated with lower mortality than ACLF grade 3. The reported 28-d and 90-d mortality rates for ACLF grades 1 and 2 are 25.8% and 28.6%, and 41.1% and 65.4%, respectively[1]. Therefore, more judicious donor organ selection could be applied, mainly when disease progression is evaluated concomitantly. Whereas data regarding the impact of donor organ selection on postoperative outcomes are scarcer for this population, the results of the study mentioned above support a wider acceptance of suboptimal grafts in ACLF-1 and 2 patients[52]. Nevertheless, the quality of evidence (retrospective study) must be considered before drawing definitive conclusions.

In the setting of donor organ shortage, another question to consider is the allocation of an ideal organ to a very sick recipient who may not survive the procedure. Again, the coexistence of additional risk factors and the real-time change in OF may guide the decision to accept a non-ideal donor organ offer rather than wait (Figure 1). Accordingly, there is evidence suggesting that in ACLF-3 patients, a better survival rate can be achieved if the transplant occurs after organ failure recovery[48].

Indeed, the timing for LT in ACLF patients is critical. In a recent study involving specifically ACLF-3 patients, authors investigated the optimal timing for transplantation and the impact of extended criteria donor (ECD) organs (defined exclusively by the DRI ≥ 1.7)[49]. They analyzed three variables to define the groups of patients (age ≤ 60 or > 60 years, 3 OF or more, and hepatic or extrahepatic ACLF-3). Through two-way sensitivity analyses, they found that overall survival is optimized by earlier transplantation, especially among candidates > 60 -years-old or with 4-6 OF[49]. These findings are in accordance with the proposal mentioned above and reinforce the need to consider early transplantation, even with suitable suboptimal grafts, to this population of ACLF patients.

To date, just the DRI was evaluated as a donor parameter within ACLF studies. The DRI is a quantitative score developed to predict the risk of graft failure[53]. It identified seven donor characteristics associated with graft failure, donor age, donation after circulatory death (DCD), split/partial grafts, race, height, and cause of brain death[53]. Yet, the DRI has known limitations which must be considered in this analysis. First, the DRI does not account for steatosis, a known risk factor for postoperative graft dysfunction. Second, cold ischemia time cannot be anticipated in all cases, especially in challenging logistical scenarios, such as in countries with long territorial extensions and complex surgical cases. Consequently, a more thorough evaluation of the impact of donor features within ACLF studies is needed.

Living-donor liver transplantation (LDLT) could expand the donor organ pool and expedite transplantation in ACLF patients. Whilst studies in countries where deceased donors are scarce for cultural reasons demonstrated good LDLT postoperative outcomes[54,55], concerns regarding the prognosis of the sickest patients leading to stringent patient selection criteria hinder the applicability of this option thus far. In a retrospective analysis of 60 patients with EASL-CLIF grade 1 and 2 ACLF, LDLT transplanted patients exhibited a 1-year survival rate of 92% *vs* 11% in those who did not undergo transplantation[55]. In another retrospective study involving 218 ACLF patients, employing strict selection criteria -no high vasopressors or respiratory failure- for LDLT transplantation, the 1-year postoperative patient survival was 92.9% for EASL-CLIF grade 1, 85.4% for grade 2, and 75.6% for grade 3[54]. Despite suggesting the benefit of LDLT in this setting, the justifiable caution patient selection may have biased the conclusions. In addition, right lobe LDLT is most often required, leading to a right hepatectomy in the donor, which increases their morbidity and mortality.



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Figure 1 Suggested flowchart on when to accept a non-ideal donor organ offer for transplantation in the acute-on-chronic liver failure setting. In this scenario, the coexistence of additional risk factors and the real-time change in organ failures are key components in deciding to proceed with transplantation. ACLF: Acute-on-chronic liver failure.

While nowadays, consensually amongst experts, ECD organs must be considered in ACLF patients due to the transplant benefit, further studies detailing the real impact of donor characteristics on posttransplant patient survival are awaited. This is particularly valid for ACLF-3 patients, in which the limited literature available urges caution before proceeding with a high-risk donor. Thus far, this general concept is more theoretical than practical and originates from the need to provide timely transplantation to these patients. Therefore, this is a warranted subject of deeper investigation for future studies.

WHAT ROLE DOES MACHINE PERFUSION OF THE LIVER MAY PLAY IN THE ACLF SETTING

Machine perfusion of the liver (MPL) is currently a hot topic in LT. It has gained growing attention from the transplant community with the expansion of the ECD population and, therefore, the need to prevent the frequent ischemia-reperfusion injury (IRI)-ECD postoperative-related complications. IRI is an intrinsic consequence of solid organ transplantation and the basis of major postoperative complications. Although ECD organs are highly vulnerable to IRI, surpassing the protective capacity of traditional static cold storage (SCS) preservation solutions and, consequently, associated with higher morbidity and mortality rates after transplantation, their increased utilization is needed to attend to the rising number of patients on the waiting list. Thus far, the two most studied modalities of MPL in LT are *ex situ* hypothermic and normothermic machine perfusion.

The hypothermic oxygenated machine perfusion (HOPE) of the liver was shown to enhance mitochondrial respiratory function[56]. The optimized mitochondrial respiratory chain and oxidative phosphorylation system increase cellular energy production -replenishing the exhausted stores of adenosine triphosphate-, avoid the reverse flow of electrons with the production of reactive oxygen species, and prevent the activation of the inflammatory cascade with subsequent tissue damage[56].

The normothermic machine perfusion of the liver (NMP) allows the recovery of the full metabolism of the organ at 37 °C. Consequently, it requires an oxygen carrier to attend to the cellular metabolic demand. NMP permits the assessment of parameters that traditionally indicate appropriate liver function such as bile production, vascular flow, lactate metabolism, glucose metabolism, and hepatocellular injury such as transaminases released into the perfusate[57]. In addition, NMP enables prolonged organ preservation and, potentially, *ex situ* organ treatments[57,58].

So far, most clinical trials on MPL in LT were intended to demonstrate the safety and feasibility of the technique and were centered in European countries. Arguably, the sickest patients with very high morbidity and mortality risk were not included in these studies and were not even on the waiting list in many of these countries. Therefore, regional divergence and particularities amongst geographical areas, such as mean MELD on the waiting list and territorial extensions, must also be considered.

Hurdles to timely access of ACLF patients to LT and their disadvantage in receiving a donor organ offer in the MELD allocation system were presented herein. In addition, concerns about accepting ECD organs to these sick patients were discussed beforehand. Consequently, none of the MP clinical trials has encompassed ACLF patients thus far. Nevertheless, hypothetically, MPL can be even more advantageous for this population.

Studies suggest that MP may recondition ECD organs before transplantation, preventing further deterioration or even improving their quality. Although DCD LT has not been reported for ACLF patients, clinical trials described similar results for patients transplanted with DCD organs treated with HOPE and those transplanted with low-risk donors after brain death (DBD)[59]. Furthermore, in a randomized clinical trial, hypothermic machine perfusion reduced the occurrence of postreperfusion syndrome and early allograft dysfunction (EAD) after DCD LT. These factors contribute to the early

recovery of the sickest patients after the procedure[60]. Accordingly, concerning the applicability of the technique in ECD DBD LT, a multicenter randomized clinical trial recently reported that, compared to SCS, HOPE led to a significant reduction in 90-d complications with a shorter hospital stay and a trend toward a reduced rate of EAD[61].

Prolonged organ preservation and assessment of organ viability are two critical features related to NMP which may benefit ACLF transplantation. Whereas it could not find a difference in graft survival or patient survival compared to SCS, the first randomized clinical trial on NMP demonstrated that it could safely extend the organ preservation time[62]. The median total preservation time was close to 12 h for NMP-preserved livers. Driven mainly by the difference in peak aspartate transaminase, NMP also reduced the occurrence of EAD[62]. The VITTAL clinical trial (NCT02740608), from Birmingham, United Kingdom, transplanted twenty-two donor livers discarded by all United Kingdom centers of 31 meeting specific high-risk criteria based on the lactate clearance to levels ≤ 2.5 mmol/L within 4 h on NMP with 100% 90-d patient and graft survival[63]. Nevertheless, applying the Birmingham criteria, NMP could not prevent non-anastomotic biliary strictures in DCD livers, and 4 (18%) patients needed re-transplantation[63].

Our group recently reported for the first time the successful transplantation of an ACLF patient using an ECD DBD liver graft treated with HOPE[64]. The autoimmune hepatitis-related cirrhosis ACLF-2 patient (liver and coagulation failure) with a MELD-Na score of 42 was offered an ECD DBD organ with a DRI of 2.79 after 8 d from hospital admission (well above the previously identified threshold of 1.7). HOPE started after 06 h and 19 min of cold ischemia time and lasted 5 h and 19 min. The flavine mononucleotide was measured in the perfusate to assess the viability of the organ and revealed a low value after 30 min of perfusion (3097 A.U.) - permissive for transplantation in any recipient. During transplantation, the reperfusion was uneventful. Postoperatively, the graft recovered well, without EAD, according to the Olthoff criteria, and the patient developed AKI KDIGO stage 3 with complete recovery after 1 wk[64].

While the case suggests the feasibility and safety of employing MP within this setting, more conclusive evidence to prove the benefit of the technique is still needed. So far, because of the scarce existing literature, the evidence of the impact of ECD transplantation in ACLF grades 1 and 2 is still anecdotal. In addition, there are no reports on the application of MPL in ACLF-3 patients, those with greater risk and the subject of more concerns in the literature. Earlier transplantation was shown to improve overall survival in ACLF-3 patients > 60-years-old or with 4-6 OF[49]. This population and those with the coexistence of additional risk factors and worsening organ failures may be the target population for future MPL studies.

Yet the evidence is very limited currently, MPL may play a game-changing role in ACLF transplantation. First, it can expedite LT because it allows more liberal acceptance of ECD organs based on the properties of the technique. The proven capacity of MPL to recondition ECD livers reassures surgeons in their decision to accept an ECD organ. This effect is amplified with the application of biomarkers for organ viability assessment during perfusion. Second, rescuing discarded high-risk organs or prolonging the preservation of organs compromised by logistics *via* MPL may increase the donor organ pool, which may also help tackle the shortage of donor organs for transplantation. This is especially important in countries with frequent high MELD score patients and long cold ischemia time, which may need to adapt their organ preservations systems.

CONCLUSION

Although new clinical specific therapies have been researched for ACLF management, earlier transplantation -within the frequently narrow opportunity window- is a proven effective therapy for selected ACLF patients. Thus far, other options encompass diagnosing and treating precipitant events and supportive treatment for organ failures. Therefore, current and future perspectives on ACLF management must envisage improved access to LT. Accordingly, discussions about allocation and prioritization for transplantation in critically ill ACLF patients are awaited because there is evidence suggesting the current model may not portray their waitlist mortality. Furthermore, whereas donor organ quality is meant to be a prognostic factor in the ACLF setting, recent evidence suggests that MPL may be a safe tool to improve the donor organ pool and expedite access to this life-saving procedure.

FOOTNOTES

Author contributions: Boteon YL, Della Guardia B, and Boteon APCS designed this study; Boteon YL, Della Guardia B, Boteon APCS, Matielo CE, and Felga G performed the literature review and analysis; Boteon YL, Della Guardia B, and Boteon APCS drafted the manuscript; Boteon YL, Della Guardia B, Boteon APCS, Matielo CE, and Felga G reviewed the manuscript critically; All authors contributed to editing and approving the final manuscript version.

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