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Liver (J Bajaj, Section Editor)

ACLF and Liver Transplantation

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Abstract

Purpose of review The prevalence, mechanisms, and outcomes of acute-on-chronic liver failure (ACLF) pretransplant that affect post-transplant results are herein summarized.
Recent findings ACLF, defined by organ failures, continues to increase in incidence and now affects almost a quarter of patients before liver transplant. MELD-lactate has emerged as a useful tool to predict inpatient mortality in ACLF patients. ACLF is characterized by bioenergetic failure and increased immunologic response. Specific stool microbiome and serum metabolomic signatures on admission can help predict who is at greatest risk for ACLF pretransplant. Known pretransplant risk factors in patients with ACLF for post-transplant death, such as ongoing respiratory failure, are discussed.
Summary Highly selected patients with 1-2 organ failures pretransplant seem to have equivalent post-transplant outcomes to those transplanted without organ failures. However, patients with three or more organ failures, especially those with ongoing respiratory failure at transplant, have an increased risk for death post-transplant.

Introduction

Liver transplantation has continued to evolve in the last decade in several ways that has impacted outcomes. After the introduction of direct acting antiviral therapy for HCV, indications for liver transplant have changed with a continued increase in alcohol and non-alcoholic steatohepatitis-related liver diseases as a larger proportion of the transplant indications (www.unos.org). More donors after cardiac death are being used (18.6% increase from 2019 to 2020); alterations to the allocation system have improved equity and access to liver allografts across the USA, although allografts often travel farther before implantation; and more patients have experienced acute-on-chronic liver failure (ACLF) pretransplant (www.unos.org) [1]. The increase in ACLF prevalence pretransplant results in

a need for the transplant hepatologist and surgeon to better understand the course, prognostic importance, mechanism of injury, and immunologic consequences both pre-liver and post-liver transplant of pretransplant ACLF.

ACLF definitions and prevalence

It is well accepted that ACLF is defined by the development of organ failures [2]. However, there are still 3 competing diagnostic criteria for ACLF in use worldwide [3–6]. Although APASL (Asian Pacific Association for the Study of the Liver) was the first group to propose criteria [6], EASL-CLIF (European Association for the Study of the Liver – Chronic LIver Failure) remains the most widely used criteria in publications [4], and NACSELD (North American Consortium for the Study of End-stage Liver Disease) created the most user-friendly definition [3, 5]. Regardless of the definition used, it is clear that the incidence of ACLF is increasing [1]. In a study looking at approximately 2 million admissions for cirrhosis in the national inpatient sample, defining ACLF by ICD codes as ≥ 2 organ failures, despite an increase in incidence of ACLF over time, mortality from ACLF decreased [7]. As a result, more patients are being transplanted with and after ACLF, and now ACLF has occurred in approximately 21% of patients who undergo liver transplantation [8].

Rare publications have compared the utility of the different published criteria. In the VA dataset of approximately 80,000 outpatients with compensated cirrhosis, there was marked discordance between those that developed APASL-ACLF vs. EASL-CLIF-ACLF with only 14% of patients with ACLF meeting both criteria [9]. In a recent publication comparing EASL-CLIF to NACSELD, 29.3% of non-electively admitted cirrhotic patients met criteria for EASL-CLIF ACLF vs. 7.4% met criteria for NACSELD ACLF [10]. As a result, EASL-CLIF is more sensitive and identifies a larger group with ALCF, while NACSELD is more specific and better identifies patients at the highest risk for death [10]. A second comparison of EASL-CLIF ACLF to NACSELD ACLF also found EASL-CLIF ACLF to be more sensitive, but NACELD ACLF to be more specific for negative outcomes, specifically the need for ICU care and in-hospital mortality [11]. In a survey of transplant professionals, approximately half felt NACSELD ACLF and half felt EASL-CLIF ACLF was the most useful definition, while few preferred the APASL-ACLF definition [12]. Currently, no studies have compared the utility of different criteria to predict post-liver transplant mortality, and this is an important area of interest for future research.

Surviving ACLF to transplant

Surviving ACLF to receive a liver transplant can be challenging, and several important factors can increase the risk for death pretransplant in listed patients with ACLF (Table 1). ACLF is more common in patients who are delisted or die awaiting liver transplant than in patients who are successfully transplanted [13, 14]. It has been documented that ACLF-3 by EASL-CLIF criteria has a higher waitlist mortality than status 1; approximately 30% of patients with ACLF-3 die in 15 days [15]. Of note, even after adjusting for MELD-Na, patients with ACLF-

Table 1. Risk factors for death pretransplant in patients with ACLF. ACLF, acute-on-chronic liver failure; TIPS, transjugular intrahepatic portosystemic shunt

1) Older age
2) Increasing number of organ failures
3) Circulatory failure
4) Respiratory failure
5) High serum lactate
6) Poor Karnofsky performance status
7) Variceal bleed without a preemptive TIPS
8) Specific types of infections:
   a. Multidrug-resistant infections
   b. Nosocomial infections
   c. Fungal infections

3 have a higher risk for death in 14 days than patients without ACLF-3. Most patients with ACLF have high MELD-Na scores, although with recovery (which portents a better prognosis) the MELD-Na score often falls. Pretransplant risk for death is affected by not just ACLF, but also the precise number and type of organ failures present. In another analysis of listed patients, the number of organ failures was critical to determining outcome, and those with circulatory failure had the highest rate of delisting or death pretransplant followed closely by those with respiratory failure [14]. Fortunately, SHARE35 has improved access to liver transplantation for patients with ACLF in the USA. [16]

As yet we do not know the impact of ACLF on frailty progression pretransplant; however, one might assume that it will increase sarcopenia and further impair performance status. In a study of non-electively admitted cirrhotic patients, the risk for death post-discharge was significantly negatively impacted by not just MELD, but also age and Karnofsky performance status [17]. In another evaluation, patients who underwent liver transplantation after experiencing at least one organ failure pretransplant had an incremental decrease in Karnofsky performance status at 1-year post-transplant as their number of organ failures pretransplant increased [18].

As a result of the increased risk for death in listed patients with ACLF, it is critical to relist patients as soon as possible in order to optimize their chance to receive an allograft. A consensus conference recommended not listing patients until >72 h of antibiotics for SBP [19]. However, 86% of patients with SBP have a sterile abdomen within 6 h of antibiotic administration [20]. Therefore, in the absence of sepsis, one may consider this at 48 h to maximize MELD points in a patient who is improving (Fig. 1).

Infection is the most common precipitant of ACLF in North America and Europe [3]. When infection occurs in a listed patient, it is essential to administer antibiotics in the emergency room as every hour delay impairs survival [21]. When choosing antibiotics, take into consideration the following factors: (1) the etiology of the infection; (2) the severity of the infection; (3) your local resistance patterns; (3) how and when the infection was acquired (i.e., community acquired, heath care associated, or nosocomial) [22]. Multidrug-resistant infections are increasing in prevalence and more commonly lead to

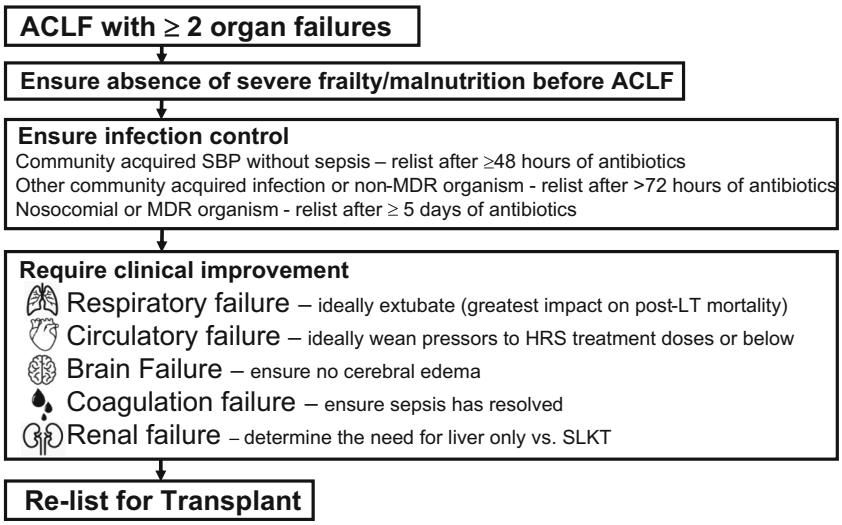

Fig. 1. A recommended pathway from ACLF to relisting for liver transplantation. ACLF, acute-on-chronic liver failure; HRS, hepatorenal syndrome; LT, liver transplant; MDR, multidrug resistant; SBP, spontaneous bacterial peritonitis; SLKT, simultaneous liver-kidney transplant.

ACLF than infections with pan-sensitive organisms [23–25]. In addition, transplant-free survival is least likely in patients who developed fungal and nosocomial infection pretransplant [13, 26–29]. Patients with multidrug-resistant and nosocomial infections likely require longer adequate antibiotic coverage, in addition to sepsis resolution (when present), prior to relisting.

In addition to infection, variceal hemorrhage can precipitate ACLF. In a large prospective multicenter observational study, 17.8% of patients admitted with variceal bleeding met criteria for EASL-CLIF ACLF [30]. Those with ACLF had a 2-fold increased rate of rebleeding and a greater than 4-fold increased risk for death, both of which were mitigated by preemptive transjugular intrahepatic portosystemic shunt (TIPS) placement [30]. In listed patients who are not TIPS candidates, a removable esophageal stent should be placed instead of a Blakemore tube in refractory or recurrent variceal hemorrhage not amenable to endoscopic therapy [31].

ACLF mechanisms that may impact liver transplant

In a metabolomic analysis of patients with ACLF analyzed by hieratical unsupervised cluster analysis, ACLF was found to result in bioenergetic failure and marked systemic inflammation [32].

Many patients with ACLF remain without nutrition, which may further exacerbate bioenergetic failure and accelerate muscle catabolism. Therefore, during pretransplant ACLF and early post-transplant after ACLF, patients need enteral nutrition early, even if trickle tube feeds via a nasojejunal Dobhoff tube is all they can tolerate. Enteral nutrition may help diminish the bioenergetic failure from ACLF and attenuate muscle loss from catabolism that can worsen sarcopenia.

ACLF is also characterized by an exaggerated immunologic response [32]. The immunologic consequences of being transplanted in the throws of ACLF are currently unknown. However, most patients are transplanted days to weeks after ACLF resolution and are likely in the midst of the compensatory anti-inflammatory response syndrome [33]. In a UNOS analysis of post-transplant causes of death in patients transplanted with ACLF, there was a trend toward an increased risk for infection-related mortality when patients were transplanted within 4-6 weeks of organ failure [34]. More interestingly, even after 1-year post-transplant, ACLF patients had a higher rate of infection-related death, and those transplanted with 4-6 organ failures had the highest risk for 5-year mortality [34]. Other factors that increased the post-transplant risk for death in this group with the highest number of organ failures were age >60, presence of diabetes, liver allograft donor risk index (DRI) ≥1.7, and year of transplant. Future translational research should determine if ACLF patients have more prolonged immunologic exhaustion and may need either less intense or different immunosuppression post-liver transplant to decrease their short-term and long-term infection risk. The immunologic consequences of ACLF perioperatively are likely impacted by the time between ACLF and transplant. The optimal immunosuppression medications and intensity after ACLF have never been studied and will require further evaluation in the near future.

Although most of our attention has focused on patients who developed ACLF, those at highest risk for ACLF have unique features potentially impactful on transplant. Admission microbiota differed between inpatients who later developed vs. did not develop ACLF [35]. Those at risk for poor outcomes had a lower cirrhosis dysbiosis ratio and a higher percentage of bacteria from the phylum Proteobacteria and a higher percentage of the Firmicutes members Enterococcaceae and Streptococcaceae. It will be worthwhile in the future to determine if these stool microbiota alterations impact post-transplant risk for infection and rejection. If they do alter important outcomes perioperatively, stool microbiome manipulations will need evaluation to determine if they improve outcomes. In a hospital admission serum metabolomic analysis, patients who later developed ACLF vs. those that did not had lower levels of indolpropionic acid, a stabilizer of the intestinal barrier [36]. These patients also had decreased amounts of the microbial metabolites phenylalanine and tyrosine, which promote local immunity. The relative dearth of these important metabolites may increase the rate of bacterial translocation perioperatively and therefore the risk of postoperative infections. The most impactful finding in this study was the strong link between the failure of the gut microbiota that resulted in the absence of these critical metabolites in serum that help prevent infections [36]. The perioperative risk for infection and mitigating strategies in patients transplanted either at the highest risk for or after ACLF will require further study.

ACLF's impact on post-transplant outcomes

Several factors pretransplant in patients with ACLF (especially with ≥ 3 organ failures) can increase the risk for death post-transplant (Table 2). Although ACLF with ≥ 3 organ failures has a negative impact on post-liver transplant outcomes, the type of organ failure(s) present also has an impact on outcomes [8, 15, 37, 38]. The most detrimental organ failure to post-liver transplant

Table 2. Risk factors for death post-liver transplant in patients with pretransplant ACLF. ACLF, acute-on-chronic liver failure; EASL-CLIF, European Association for the Study of the Liver – Chronic LIver Failure

1) Three or more organ failure pretransplant
2) Absence of improvement from ACLF to transplant
3) Donor risk index ≥ 1.7
4) Diabetes
5) Presence of frailty
6) Older recipient age (TAM model age ≥ 53*)
7) Respiratory failure (TAM model $Pa0_2/Fi0_2$ ratio ≤ 200*)
8) Pretransplant elevated serum lactate level (TAM model ≥ 4* mmol/L)
9) Pretransplant leucocyte count (TAM model ≥ 10* × 10^9/L)

*TAM (transplant for ACLF-3 model) defined transplant futility in patients with EASL-CLIF ACLF-3 as ≥ 2 of the 4 listed pretransplant factors

outcomes is respiratory failure [8, 38]. In contrast, renal failure does not seem to impact post-liver transplant outcomes as long as the patient either receives a simultaneous liver-kidney transplant or they recover renal function post-liver transplant. When the renal outcomes were compared between patients transplanted with and without NACSELD ACLF, those with ACLF had higher pretransplant serum creatinine values and a high rate of perioperative dialysis but similar survival and post-transplant 3-month serum creatine values [13]. In patients with ≥ 3 organ failures, the quality of the liver allograft (defined by DRI) may also play a role in post-liver transplant survival. In a UNOS study, patients with EASL-CLIF ACLF-3 had a lower survival if they received an organ with a DRI ≥ 1.7 [8]. Although patients with EASL-CLIF ACLF-3 transplanted within 30 days of listing had a lower risk for death, it is unclear if this factor is covariate with another more impactful data point, such as absence of frailty, not present in the UNOS data set. Therefore, this will require further granular investigation.

The greatest challenge in high MELD patients is when to relist them for transplant after an acute event such as ACLF. Improvement in MELD from hospital admission to discharge, reported as a negative delta MELD (discharge MELD—admission MELD), has been shown to portend a better survival post-liver transplant after ACLF [13]. In another study looking at factors that affected post-transplant survival, ACLF without improvement was the single largest factor affecting post-transplant survival (HR for death = 4.15), in addition to age [39]. As a result, it is critical to see clinical improvement for at least 48 h prior to relisting patients for transplant (see algorithm for transplant relisting after ACLF in Fig. 1).

Liver transplant futility

Recent attention has been paid to defining pretransplant criteria that result in unacceptable post-transplant survival, defined as transplant futility. Most studies have found that patients with ≥ 3 organ failures have a higher risk for early postoperative demise [8, 13, 14, 34, 38–42]. A recent consensus conference agreed that transplant futility should be defined by 1-year post-transplant patient and graft survival; however,

precise percentages to define futility were not proposed [19]. They also agreed that organ failures were the best way to evaluate futility pretransplant and reached consensus that patients with any one of the following should not be offered transplant: (1) PaO2/FiO2 ratio <150 mmHg, (2) a norepinephrine dose >1 mcg/kg/min, or (3) a serum lactate >9 mmol/L. In addition to the above 3 contraindications to transplant, the group recommended patients with severe frailty (defined as a clinical frailty scale >7), persistent fever (>39 °C), leucopenia <0.5 G/L, appropriate antimicrobial therapy for <72 h for pneumonia or SBP, previous infection with pan-drug resistant Enterobacteriaceae, or a worsening clinical course should result in either postponing liver transplantation or delisting. However, all these criteria were created by expert opinion and will require formal study. In contrast, the transplant for ACLF-3 model (TAM) score was developed and validated to define transplant futility [37]. Patients who had >2 of the following 4 factors were deemed not to be candidates for liver transplant: (1) age ≥ 53; (2) serum lactate ≥ 4 mmol/L; (3) mechanical ventilation with a Pa02/FiO2 ratio ≤ 200; and/or (4) pretransplant leucocyte count ≥ 10 × 10^9/L. This was because those patients with >2 points had a 1-year post-liver transplant survival of just 8.3%.

Both expert opinion and data have confirmed the utility of serum lactate in predicting inpatient mortality in cirrhosis patients. To better quantify its utility, the serum lactate has been incorporated into the MELD score as the MELD-lactate [43]. This score was developed and validated in two separate cohorts as an excellent predictor of inpatient mortality. The serum lactate level differentially impacts patient's risk for death depending on the MELD score. There is a linear association but the rate of change increases more rapidly above a MELD of ∼15 to below a MLED of 15. The rate of change also increases with increasing serum lactate, but this rate of increase decreases at the inflection point of a serum lactate of ∼7.5 mmol/L. Utilizing the MELD-lactate to predict inpatient mortality improved the risk prediction in about a quarter of patients studied compared to the standard MELD. As a result, this useful tool is highly relevant in inpatients to determine their risk for death [13, 39]. In patients without improvement and those with poor performance status, palliative care consultation and/or hospice are needed sooner and more often, as it has been documented that hospice is underutilized in decompensated cirrhotic patients [44].

Conclusions

ACLF, regardless of the definition used, continues to increase in incidence and now affects 21% of patients before liver transplant [8]. Surviving from ACLF to liver transplantation is challenging, and patients with ACLF-3 by EASL-CLIF criteria have a worse prognosis pretransplant than patients listed status 1 [15]. Even after adjusting for MELD-Na score, the 14-day risk for death is higher in listed patients with vs. without ACLF [15]. Patients with ≥ 3 organ failures have a higher risk for death post-transplant especially if they are older, have respiratory

failure going into transplant, an elevated serum lactate level, or an elevated WBC count [37]. When control of infection and clinical improvement are seen, using an organ with a DRI <1.7 can help improve post-transplant outcomes [8, 13]. However, in ACLF patients with respiratory failure, especially those without clinical improvement, early palliative care intervention should be utilized to help avoid prolonged hospitalization and transplant futility.

The future

Despite substantial data documenting inferior outcome pretransplant in ACLF-3 listed patients, even compared to status 1 listed patients, it is unlikely that any definition of ACLF will be incorporated into liver allocation because transplant professionals are not yet endorsing ACLF incorporation into liver transplant allocation [12], and even if they do it remains a divisive topic that is slow to evolve. Instead, we should focus future efforts to (1) further explore ACLF pathophysiology to discover and trial treatment strategies and novel therapeutics to improve prognosis in patients with diagnosed ACLF. (2) Discover biomarkers present early in the course of ACLF before advanced organ failure is present. They will need to reproducibly predict outcome and allow early intervention to mitigate progression to advanced organ failure or ideally organ dysfunction. (3) Identify predictors of ACLF development both on hospital admission and in outpatients. This will allow true prevention trials to be undertaken.

Declarations

Conflict of Interest
Jacqueline G. O'Leary is in the speaker's bureau for Gilead and AbbVie and serves as a consultant for Astellas.

Human and Animal Rights and Informed Consent
This article does contain studies with human performed by the author but not animal studies performed by the author.

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