Current Hepatology Reports (2020) 19:168–173
https://doi.org/10.1007/s11901-020-00519-9

MANAGEMENT OF THE CIRRHOTIC PATIENT (A CARDENAS AND P TANDON, SECTION EDITORS)

Early Transplantation in Acute on Chronic Liver Failure: Who and When

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Published online: 18 June 2020

Abstract

Purpose of Review Acute on chronic liver failure (ACLF) is a unique syndrome that afflicts patients with chronic liver disease and results in high short-term mortality, > 50% at 28 days in patients with severe ACLF (grade 3, ACLF-3). Given this prognosis, there is an urgent need to understand risk factors for this condition, as well as selection criteria for patients who may benefit from liver transplantation (LT).

Recent Findings Several studies have identified risk factors for developing ACLF, including higher model for end-stage liver disease score, anemia, and morbid obesity, as well ACLF mortality, such as infection, increasing organ failures, and higher white blood cell count. Prognostic tools are now available as online calculators. Regarding LT in ACLF, data suggest that even patients with ACLF-3 may do well after LT, with 1-year survival > 80% in several studies. Improvement in organ failures prior to LT, higher donor quality, and lack of mechanical ventilation further improve outcomes. Importantly, ACLF-3 patients may have higher short-term wait list mortality than patients listed status-1a, suggesting that increased LT prioritization may be warranted.

Summary ACLF is a high-mortality condition that frequently responds well to LT. Ongoing efforts to understand the natural history of ACLF and predictors of improved post-LT survival will facilitate LT criteria for this condition, which may ultimately include increased LT prioritization for selected patients.

Keywords End-stage liver disease · Portal hypertension · MELD score · UNOS database

Introduction

Acute on chronic liver failure (ACLF) is a condition characterized by an acute insult in a patient with chronic liver disease that results in high short-term mortality. ACLF may be precipitated by a variety of primary hepatic or extrahepatic causes, including infection, gastrointestinal bleeding, alcoholism, relapsed chronic viral hepatitis, surgery, and medications. Regardless of the precipitant, however, ACLF is uniformly characterized by short- and medium-term mortality rates of

This article is part of the Topical Collection on *Management of the Cirrhotic Patient*

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ACLF ranging from 50 to 90%, highlighting the severity of the condition.

A key concept in understanding ACLF is to recognize features that distinguish it from other conditions (Fig. 1). ACLF is distinct from acute liver failure (ALF), which describes an acute hepatic insult resulting in abrupt liver decompensation in a patient with previously normal underlying liver function. ACLF is also distinct from decompensated cirrhosis, which marks the natural history of ongoing, chronic liver injury. Rather, ACLF occurs in patients with established chronic liver disease who experience a superimposed acute insult, triggering a collapse in liver function with systemic inflammation and uniquely high short-term mortality that may even exceed patients with acute liver failure [1••]. These considerations have established ACLF as a unique clinical syndrome.

Definitions of ACLF

Given the recent recognition of ACLF, there has been considerable effort to better understand and encapsulate the syndrome. There are numerous definitions of ACLF, but the most prominent comes from the following major societies and research groups: the European Association for the Study of the Liver (EASL), the Asian Pacific Association for the Study of the Liver (APASL), and the North American Consortium for the Study of End-Stage Liver Disease (NACSELD). Each definition is unified by the identification of patients with chronic liver disease who have a short-term mortality exceeding 50%, though they vary considerably in terms of criteria to establish a diagnosis of ACLF.

The APASL ACLF definition involves an acute insult with jaundice (serum bilirubin ≥ 5 mg/dL) and coagulopathy (international normalized ratio [INR] ≥ 1.5) accompanied by hepatic encephalopathy and/or ascites that develops within 4 weeks [2]. This is defined for patients with compensated cirrhosis or chronic liver disease but not for patients with prior decompensation (ascites, hepatic encephalopathy, or bleeding esophageal varices). The EASL Chronic Liver Failure (EASL-CLIF) ACLF definition is determined by an acute decompensation (gastrointestinal bleeding, hepatic encephalopathy, ascites, or bacterial infection) followed by the development of various organ failures [3•]. These include kidney, liver, coagulation, respiratory, circulatory, and brain failures. Based on the number and type of organ failures present, patients may be scored from grade 1 (least severe, ACLF-1) to grade 3 (most severe, ACLF-3). Finally, the NACSELD definition incorporates simplified assessments of only four of the six organ failures in an effort to create a tool that may be used at the bedside. NACSELD ACLF requires at least two of following organ failures: brain (grade 3–4 hepatic encephalopathy), renal (need for dialysis), respiratory (mechanical ventilation), or circulatory (shock) [4]. Of the three ACLF definitions detailed above, the EASL-CLIF definition is the most widely used in the transplantation literature. As such, we focus on this definition of ACLF for the remainder of this review.

Risk Factors for ACLF

In an Italian study of 466 outpatients with cirrhosis, variables independently associated with ACLF included low baseline mean arterial pressure, higher model for end-stage liver disease (MELD) score, the presence of ascites, and anemia [5]. In the North American setting, a large analysis of two US public registries identified class III obesity (body mass index ≥ 40 kg/m^2) as an independent risk factor for developing ACLF [6]. The authors noted that these patients also had an increased prevalence of renal failure, which could be the basis of

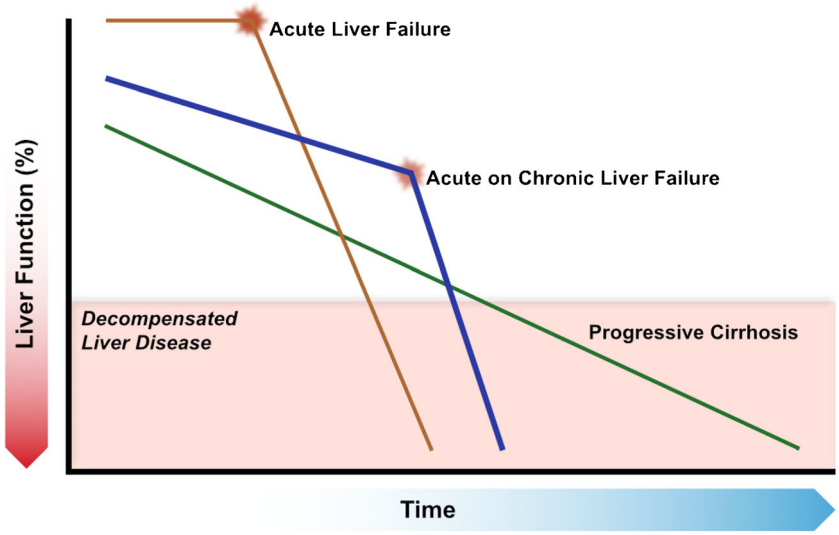

Fig. 1 Trajectories of declining liver function in acute on chronic liver failure as compared to acute liver failure and progressive cirrhosis

ACLF predisposition. Additional risk factors were identified in a nationwide analysis of veterans with cirrhosis who were followed over an 8-year period for the development of ACLF [7], including alcohol use disorder, hypoalbuminemia, thrombocytopenia, and diabetes mellitus, which may have served as a surrogate for obesity. Finally, it has recently been demonstrated, using national registry data, that lower grade ACLF is a significant risk factor for future higher-grade ACLF, particularly in the setting of liver or circulatory failure [8].

Mortality Risk after Development of ACLF

As noted previously, ACLF is associated with high short-term mortality. The CANONIC study [3•], which established the EASL-CLIF definition of ACLF, identified a 15% mortality rate at 28 days after enrollment as the threshold selected for identifying subgroups of patients with high mortality in the process of defining ACLF. Because all participants had decompensated cirrhosis at enrollment, the presence of organ failure(s) was the key component to differentiate acute decompensation from ACLF. Furthermore, the grade of ACLF as determined by the number of organ failures present significantly influences ACLF-related mortality. Findings from the CANONIC study demonstrated mortality within 28 days from presentation to be 22.1% among those with ACLF-1, 32.0% for ACLF-2, and 76.7% for ACLF 3 [3•]. Additionally, patients with 4–6 organ failures by day 7 after presentation had a 28-day mortality approaching 100%.

Determinants of Mortality in ACLF

Compared to hepatitis C, the presence of alcoholic liver disease or non-alcoholic fatty liver disease is associated with worse survival after the development of ACLF [6, 9]. Lower MELD-Na and lower Child-Turcotte-Pugh (CTP) scores also correlate well with improved survival, suggesting more functional reserve of the liver [10]. Of the different triggers of ACLF, infection is the one which has been consistently shown to be a poor prognostic factor [11]. For example, ACLF patients with infection had a mortality of 42.9% at 28 days, compared with 36.9% if ACLF was triggered by a gastrointestinal bleed. Furthermore, this distinction was more pronounced in ACLF-2 and ACLF-3. In addition to the number of organ failures, the type of organ failures present can also predict mortality. In particular, the presence of renal failure, the need for inotropes as a measurement for circulatory failure [5, 10], or liver failure [12] are critical components to predict short-term mortality in ACLF. Several clinically available biomarkers may also predict a high risk of death in the setting of ACLF, including increasing white blood cell (WBC) count [3•], high C-reactive protein [10], and increasing neutrophil-to-lymphocyte ratio [13].

Several mortality risk prognostic calculators have been used in ACLF, including liver-specific tools such as MELD-Na and CTP, as well as non-liver specific such as the Acute Physiology and Chronic Health Evaluation (APACHE II) and sequential organ failure assessment (SOFA). However, custom ACLF scores outperform global scores in ACLF [14]. For example, the CLIF Consortium Organ Failure score (CLIF-C OF), a liver-specific adaption of the SOFA score derived from the CANONIC study which includes organ failure, age, and WBC, showed better accuracy in predicting short-term mortality (C-statistic = 0.79) as compared with MELD-Na (C = 0.70) and CTP (C = 0.70) and is available online at http://www.efclif.com/scientific-activity/score-calculators/clif-c-aclf [15]. These data have also been recently validated in the Veterans Affairs population, with a more parsimonious variant of the CLIF-C ACLF model also published as an online calculator (available at: http://www.aclfcalc.com) [7].

Role of Transplantation

Though the prognosis of ACLF is poor, particularly in ACLF-3, liver transplantation (LT) can markedly improve survival, with 1-year post-transplant survival exceeding 80% [16, 17, 18••]. However, gaps remain regarding our understanding of optimizing survival among patients with ACLF. This next section reviews the current literature regarding organ allocation policy, outcomes after LT, and timing of transplantation for individuals who have developed ACLF, with a focus on ACLF-3.

Organ Allocation Policy among Candidates with ACLF

Current organ allocation policy gives highest priority to candidates with status-1A designation, while subsequent classification is based on the model for end-stage liver disease-sodium (MELD-Na) score. However, current policy may not fully account for non-transplant mortality in ACLF-3, partially because the MELD-Na score does not capture several of the extrahepatic organ failures that may be present in the setting of ACLF-3. Subsequently, patients with ACLF-3 and a MELD-Na score < 25 may have greater 90-day mortality than patients without ACLF and a MELD-Na score ≥ 35 [18••]. This discrepancy is likely related to a combination of mortality risk associated with the development of circulatory or respiratory failure, along with a perceived futility in full supportive care due to lower priority for transplantation. Additionally, a separate analysis indicated that patients with ACLF-3 have a greater risk of 14-day mortality relative to candidates listed status-1A, independent of MELD-Na score. Furthermore, over time, waitlist mortality rose significantly among ACLF-3 patients between 7 days (18.0%), 14 days (27.7%), and 21 days (32.7%, $p < 0.001$) but remained overall stable among

status-1A patients at 7 days, 14 days, and 21 days (17.9%, 19.3%, 19.8%, respectively, $p = 0.709$) [1••]. Given these findings, further investigation is warranted regarding whether patients with ACLF-3 would benefit from additional priority for transplantation beyond their MELD-Na score, to reduce waitlist mortality.

Outcomes after Liver Transplantation

Outcomes for patients with ACLF at transplantation are variable due to the heterogeneity among studied populations. Initial data from the CANONIC study revealed a 75% 1-year post-LT survival among 25 patients transplanted with ACLF, of whom 38% had ACLF-3 and none of whom had respiratory failure [12]. In another single-center retrospective study of 140 transplanted patients with ACLF, of whom 30 had ACLF-3 at transplantation, the 90-day post-LT survival was 84.5% for those transplanted with ACLF-1, 77.2% for patients with ACLF-2, and 60% among recipients with ACLF-3. Multivariable analysis determined the presence of ACLF at LT to be the strongest risk factor for post-transplant mortality [19].

Recently, several multi-center and registry studies have demonstrated better outcomes. In a multi-center European study of over 250 patients transplanted with ACLF, and 73 patients transplanted with ACLF-3, 1-year survival was above 83% among all grades of ACLF [16]. It should be noted that individuals in this study who were transplanted with ACLF-3 were selected carefully, and those who had hemodynamic instability, acute respiratory distress syndrome, active gastrointestinal bleeding, or uncontrolled sepsis were denied LT [16]. Recently, two large studies from the UNOS registry have supported these findings, demonstrating a 1-year post-LT survival above 80%, even among recipients with 4–6 organ system failures at transplantation. Table 1 summarizes the current available studies regarding transplantation for ACLF, particularly ACLF-3.

Our knowledge regarding risk factors related to post-transplant mortality in the setting of ACLF is restricted primarily to registry studies, due to the relatively small sample of patients with ACLF-3 in single or multi-center studies. In two studies from the United Network for Organ Sharing (UNOS) registry, the requirement of mechanical ventilation at the time of LT was one of the strongest risk factors for 1-year post-transplant mortality among patients with ACLF-3 at the time of transplantation [17, 18••]. The presence of mechanical ventilation may yield a 10% decrease in survival rate (75.3% vs 85.4%), with only marginal improvement if using a higher quality donor organ (76.5%) or transplanting within 30 days of wait listing (76.5%) [18••]. Additionally, use of an optimal donor organ as determined by a donor risk index of < 1.7 also yields improved survival probability when compared to use of a sub-optimal organ [18••]. Recently, a separate study has revealed age to be a strong prognosticator for post-transplant survival among

Table 1 Summary of studies regarding transplantation for ACLF-3

Study (year)	Type of study	Total patients with ACLF-3	Waitlist outcomes	Post-LT outcomes	Significance	Limitations
Artru (2017)	Three single centers from January 1, 2008, to December 31, 2014	73 transplanted	N/A	1-year survival 83.6%	Found LT can improve survival of ACLF-3 (with similar rates as lower ACLF grades)	Lack of power for multivariate analysis Case-control study with control cases from one single center
Levesque (2017)	One single center from January 2008 to December 2013	30 transplanted	N/A	1-year survival 43.3%	Confirmed ACLF as independent predictor of 90-day mortality Proposed scoring system to identify potentially futile LT	Small sample Limited variables used to build statistical propensity score
Thuluvath (2018)	UNOS database from February 27, 2002, to September 30, 2016	2515 at listing 3556* transplanted	30-day mortality > 92%	1-year survival > 81.0%	Identified number of organ failures, age, and mechanical ventilation as independent predictors of post-LT survival	Short time to LT (up to 5 days after listing in > 3 organ failures) Unable to identify cause of decompensation
Sundaram (2019)	UNOS database from 2005 to 2016	5355 at listing 6381 transplanted	28-day mortality 43.8%	1-year survival 78.9%	Demonstrated waitlist mortality is highest among ACLF-3 patients regardless of MELD-Na Identified presence of mechanical ventilation as strongest predictor of post-LT mortality	Potential for misclassification of decompensating event in database Unclear indications for use of mechanical ventilation
Sundaram (2019)	UNOS database from 2002 to 2014	5099 at listing	21-day mortality 32.7%	N/A	Demonstrated 14-day waitlist mortality is greater in ACLF-3 patients compared to status-1a listed patients	Potential for misclassification of decompensating event in database Excludes patients listed status-1a with exception points

*Study separately analyzed number of organ failures by 3, 4, and 5–6 organ failures. Data shown in table reflect combination of 3 or more organ failures

patients with ACLF-3, as transplantation of patients with ACLF-3 above the age of 60 yields a 1-year survival of 74.9% [20••]. These findings are particularly relevant given the progressive aging of the transplant population [21].

Early Transplantation for ACLF-3

Given the high mortality associated with ACLF-3, candidates who have developed this condition would likely benefit from early LT. However, the potential advantages of rapid transplantation may also include improved post-transplant survival. In an analysis of the UNOS registry, greater 1-year survival probability was demonstrated when transplantation occurs in less than 30 days on the waiting list compared to greater than 30 days (82.2% vs 78.7%) [18••]. Further analysis of this database revealed even greater post-LT survival when transplantation occurred within 14 days. Although patients with ACLF-2 did not see significant improvement when transplanted within 14 days of listing (89.5 vs 87.6%, $p = 0.053$), increased survival was demonstrated among patients transplanted with three organ failures (85.6 vs 82.6%, $p = 0.012$), four organ failures (80.9 vs 75.8%, $p = 0.007$), and five organ failures (79.3 vs 67.2%, $p < 0.001$) [22].

However, findings from other studies have indicated an alternative to early LT, which may enhance post-transplant survival: transplantation after clinical improvement. A single-center proof-of-concept study revealed that patients transplanted after improvement of ACLF, defined as recovery of at least one organ system failure, yielded a superior 90-day post-transplant survival as compared to recipients transplanted with ACLF and similar to that of patients without ACLF prior to transplantation [23]. In a larger registry study, 1-year post-transplant survival substantially increased in patients with ACLF-3 who improved to ACLF grades 0–2 (88.2%) versus those who remained at ACLF-3 at LT (82.0%) [20••]. In particular, improvement in circulatory failure, brain failure, and requirement of mechanical ventilation were associated with greater post-LT survival. This study also compared the effect of timing of transplantation versus improvement in organ failures on post-LT survival. The findings demonstrated that compared to transplantation of patients with ACLF-3 within 7 days of listing, improvement from ACLF-3 to ACLF 0–2 resulted in greater post-transplant survival (87.6 vs 82.7%, $p < 0.001$) even if performed after 7 days from listing [20••].

Future Directions and Studies

Several avenues of future research may be valuable to advance the field. First, attempts to model dynamic changes in organ failures during the course of ACLF may improve prognostication from an LT standpoint, and there may be meaningful interactions among different ACLF severity grades. Second, studies should evaluate the predictive value of other predictors of waitlist mortality and end-stage liver disease that are well-established in the non-ACLF literature, such as patient frailty. Finally, the identification and study of novel biomarkers may further improve risk stratification in ACLF. Ultimately, the goal of these studies would be to differentiate patients in whom LT would be futile from those in whom LT would be beneficial despite the presence of multiple organ failures.

Conclusion

In conclusion, ACLF is a syndrome associated with poor short-term, non-transplant survival, which correlates with increasing number of organ failures. As current organ allocation policy may not fully capture the mortality risk associated with ACLF, particularly ACLF-3, additional research is warranted to understand how to best prioritize these patients. Although LT can yield a 1-year survival above 80% and substantially improves overall patient survival, there remains a need for the development of risk stratification models to identify patients in whom transplantation would be futile. Factors which may be associated with futility of LT in patients with ACLF-3 include requirement for mechanical ventilation and age above 60 years. Transplantation within 30 days, and particularly within 14 days, may increase post-transplant survival in those who have developed ACLF-3. However, recovery of organ failures for patients with ACLF-3 prior to LT appears to yield the greatest benefit regarding post-transplant survival. Therefore, transplantation should be delayed in certain patients where organ failure can potentially improve.

Compliance with Ethical Standards

Conflict of Interest Dr. Sundaram serves on the speakers bureau for Abbvie, Gilead, Intercept, and Salix. Dr. Mahmud, Dr. Hernaez, and Dr. Wu have no disclosures to report.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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