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Liver Transplantation for Acute-on-Chronic Liver Failure: Science or Fiction?

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Acute clinical deterioration of a patient with chronic liver disease remains a decisive time point both in terms of medical management and prognosis. This condition, also known as acute decompensation (AD), is an important event determining a crossroad in the trajectory of patients. A significant number of patients with AD may develop hepatic or extrahepatic organ failure, or both, which defines the syndrome acute-on-chronic liver failure (ACLF), and ACLF is associated with a high morbidity and short-term mortality. ACLF may occur at any phase during chronic liver disease and is pathogenetically defined by systemic inflammation and immune metabolic dysfunction. When organ failures develop in the presence of cirrhosis, especially extrahepatic organ failures, liver transplantation (LT) may be the only curative treatment. This review outlines the evidence supporting LT in ACLF patients, highlighting the role of timing, bridging to LT, and possible indicators of futility. Importantly, prospective studies on ACLF and transplantation are urgently needed.

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The development of ascites, jaundice, variceal hemorrhage, hepatic encephalopathy (HE), acute bacterial infection, or any combination of these defines acute decompensation (AD) and initiates a new chapter in the natural history of patients with cirrhosis. There are 2 forms of AD: AD and acute-on-chronic liver failure (ACLF). ACLF differs from AD by rapidly evolving multiorgan dysfunction, significant systemic inflammation (SI), and high short-term mortality.[1,2] There are several definitions of ACLF in different societies, and this may render the direct comparison of studies difficult. Nevertheless, there is consensus that ACLF is a distinct syndrome characterized by organ failures with a high morbidity and mortality.

ACLF may occur at any phase during chronic liver disease, from compensated cirrhosis to refractory decompensation. Acutely decompensated cirrhosis has been found to be associated with high circulating levels of proinflammatory molecules, which may be increasing well before ACLF develops.[3] In ACLF, this increase in inflammatory cytokines is more striking and correlates with the number of organ failures.[4] In the last several years, evidence has emerged that ACLF may be treated with LT because the post-LT survival rate may be similar to that of patients without

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; ARDS, acute respiratory distress syndrome; CANONIC, Chronic Liver Failure Acute-on-Chronic Liver Failure in Cirrhosis; CLIF-C OF, Chronic Liver Failure Consortium Organ Failure; CLIF-SOFA, Chronic Liver Failure–Sequential Organ Failure Assessment; ECLS, extracorporeal liver support; FiO_2, fraction of inspired oxygen; GCSF, granulocyte colony-stimulating factor; GMCSF, granulocyte-macrophage colony-stimulating factor; HDU, high dependency unit; HE, hepatic encephalopathy; HIV, human immunodeficiency virus; HNA2, human nonmercaptalbumin-2; HRS, hepatorenal syndrome; ICU, intensive care unit; IFN, interferon; IL, interleukin; IL1RA, interleukin 1 receptor antagonist protein; IP10, 10 kDa interferon gamma-induced protein (C-X-C-motif chemokine 10); LT, liver transplantation; MCP1, monocyte chemotactic protein 1; MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease–sodium; MIP1β, macrophage inflammatory protein 1 beta; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PaO_2, partial pressure of arterial oxygen; RRT, renal replacement therapy; SALT, Sustained Alcohol Use Post-LT; SI, systemic inflammation; TIPS, transjugular intrahepatic portosystemic shunt; TNF-α, tumor necrosis factor α; UNOS, United Network for Organ Sharing; WBC, white blood cell.

ACLF.[5,6] Yet, the selection of ACLF patients suitable for LT, timing of LT in the setting of ACLF, and the role of expeditious LT remain unexplored. This review outlines the current evidence concerning these topics and suggests the design of a specific strategy for allocation of LT to patients with ACLF, taking into account contraindications.

Outcomes of ACLF

ACLF is present in 10%-20% of the patients admitted for acutely decompensated cirrhosis and develops in an additional 10% of patients during hospitalization.[7] In a European study, the majority of patients with ACLF presented with alcohol-induced cirrhosis, though a precipitating event was identified only in 60% of patients.[1] The overall 28-day transplant-free mortality ranges between 30% and 40%, underlying the need for urgent and aggressive medical treatment.[1,8] The Chronic Liver Failure Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study developed the Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score and Chronic Liver Failure Consortium Organ Failure (CLIF-C OF) score.[1,9] One of the primary findings from this study was that 3 main risk factors from the patient's CLIF-SOFA score at enrollment are associated with a high 28-day mortality rate:

1. The presence of 2 organ failures or more.
2. The presence of 1 organ failure when the organ that failed was the kidney.
3. The coexistence of a single nonkidney organ failure with kidney dysfunction (ie, serum creatinine level ranging from 1.5 to 1.9 mg/dL) and/or mild-to-moderate HE.[1]

Therefore, it is not only the number of organ failures that determines short-term mortality but also dysfunction of 2 organs, specifically the kidney and brain (Table 1). After its development, ACLF will take a course that may vary, wherein a certain proportion of the patients improve and others may worsen. Data have shown, though, that the presence and grade of ACLF at 3-7 days from admission determines the short-term prognosis (Table 1).[1,8,10]

The usual scores used to assess mortality risk in patients with cirrhosis, such as the Model for End-Stage Liver Disease–sodium (MELD-Na) and Child-Pugh scores, are strongly related to the development of ACLF and also predict survival in patients with ACLF.[1,11,12] However, these prognostic models still miss important determinants of mortality among ACLF patients, such as HE in the Model for End-Stage Liver Disease (MELD) score and age and creatinine in the Child-Pugh score. Additionally, neither of these models incorporates circulatory or respiratory failure nor do they include any biomarkers of SI, which seem to correlate with outcomes in ACLF patients. Therefore, a new score was designed specifically to assess the risk of mortality specifically in patients who have developed ACLF, known as the CLIF-C ACLF score.[5] The CLIF-C ACLF score includes baseline factors, such

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Jonel Trebicka performed the literature review. Jonel Trebicka, Richard Moreau, Rajiv Jalan, and Vicente Arroyo participated in the interpretation of literature. Jonel Trebicka, Richard Moreau, and Vicente Arroyo drafted the manuscript. All authors provided critical revision of the manuscript regarding important intellectual content.

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TABLE 1. AD and ACLF Grades, Their Clinical Characteristics, Prevalence, and Associated Mortality According to the Time of Assessment

		At Diagnosis of ACLF*		3-7 Days After Diagnosis of ACLF†	
Condition	Clinical Characteristics	Prevalence	28-Day Mortality	Prevalence	28-Day Mortality
AD	No organ failure or single nonkidney organ failure, creatinine <1.5 mg/dL, and no HE	78.2	4.7	57.3	5.5
ACLF 1	Single renal failure or single nonkidney organ failure, and creatinine 1.5-1.9 mg/dL or HE grade 1-2, or both	10.9	22.1	24.3	17.1
ACLF 2	2 organ failures	7.5	32.0	20.5	33.9
ACLF 3a	3 organ failures	1.9	68.0	25.0	33.9
ACLF 3b	4 organ failures or more	1.4	88.9	36.8	96.0

NOTE: Data are given as percentages. Adapted from Moreau et al.[1] (2013), Gustot et al.[8] (2015), and Jalan et al.[9] (2014).
*See Moreau et al.[1] (2013) and Jalan et al.[9] (2014).
†See Gustot et al.[8] (2015).

as age and white blood cell (WBC) count, that are not included in other scoring systems but that are associated with short-term and longterm mortality in the setting of ACLF.[5] Taken together with the presence of CLIF-C OF score, age, and log-transformed WBC count were found to be the best predictors of mortality and, therefore, were included to compute CLIF-C ACLF score.

The CLIF-C ACLF score seems to have greater accuracy in predicting outcomes in patients with ACLF compared with other scores, suggesting that it should be involved in decision making during the management of patients with ACLF. An analysis of the CANONIC study addressing the course of ACLF showed that a CLIF-C ACLF score >64 may also be useful for identifying patients in whom full supportive medical care is futile and goals of care should be discussed if LT is not an option.[8] Recently, a large data set validated a different and simpler score as a predictor of inpatient mortality, namely, the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) ACLF score.[13] Although this score could predict better survival than other commonly used scores, it does not include variables such as bilirubin, age, or markers of inflammation, and the definition of organ failure relies on the physician response, such as mechanical ventilation, use of vasopressors, or renal replacement therapy (RRT) for the diagnosis of organ failures.[13] Among those features, RRT, in particular, is very well documented because it is relevant for the MELD score, which is the main prioritizing tool. RRT may be avoided in ACLF by using vasoconstrictors,[14] for which terlipressin seems more effective than noradrenaline.[15] The need for RRT is associated with substantially high mortality independent of LT.[16] Only a small proportion of patients requiring RRT shows renal recovery after intensive care unit (ICU) discharge. A recent small study suggested that intermittent hemodialysis might be more beneficial than continuous RRT.[17] However, a recent consensus article stated that there was insufficient evidence to issue a recommendation for the ACLF population regarding use of intermittent hemodialysis or continuous RRT.[18]

Given the high mortality associated with ACLF, LT remains a critical option in the treatment of these patients. Recently, data available from public registries in the United States elucidated information regarding wait-list and post-LT mortality, including among patients with multiple organ failures. As we address organ allocation policy in the ACLF population, we must consider wait-list mortality to be an outcome equally as important as posttransplant survival. In this regard, the CLIF-C ACLF and NASCELD ACLF scores may be useful to allocate LT in patients with ACLF because they may have a greater ability to predict mortality.[19] When clinicians list patients for transplant, the true intention to treat should encompass these 2 endpoints. Moreover, in the real world, the information given to patients by clinicians at the time of listing generally relates to the outcomes before and after transplant.

LT in ACLF

Although many patients with ACLF undergo transplantation, neither the presence of ACLF nor ACLF-specific

scores are used to allocate LT to patients on the waiting list. The prognosis of ACLF, however, is distinct from that of decompensated cirrhosis, which may explain why the traditional scores, such as MELD and MELD-Na, which lack parameters assessing extrahepatic nonrenal organ failure and SI, do not fully reflect mortality in ACLF. The CLIF-C ACLF score and CLIF-SOFA may predict with up to 75% accuracy the prognosis in ACLF better than the MELD score,[9] although they are similar to MELD in retrospective studies.[20] Though many publications have outlined the high mortality associated with ACLF without LT,[1,21,22] patients transplanted with ACLF have a higher rate of complications and a lower survival than patients transplanted without ACLF.[5,6,23] Therefore, the question arises as to which patients with ACLF should be transplanted.

There is likely to be consensus across all societies that patients with ACLF grade 1 and 2 should be listed for LT. Even among patients who have recovered from an episode of ACLF, there is still an increased likelihood of developing a higher grade of ACLF in the future[24] and an inherent mortality at 6 months between 40% and 50%.[8] Therefore, evaluating and listing these patients for LT may build a "safety net" in the event of future deterioration and development of multiple organ failures.

The presence of ACLF grade 3 should not be considered an absolute contraindication for LT. A large retrospective analysis of the United Network for Organ Sharing (UNOS) database with more than 50,000 patients very clearly shows that LT improves outcomes in these patients.[5] Similar results were obtained in different European countries evaluating retrospective and prospective cohorts.[8,22,25] Indeed, transplanted ACLF patients from the CANONIC study showed 80% survival in the first year,[8] underlining the important role of offering LT to those patients. According to this study, patients with up to 3 organ failures, or CLIF-C ACLF score <64, as well as those who showed an improvement of ACLF grade in the short term should be considered for LT because they have poor nontransplant survival and relatively high posttransplant survival, with a low post-LT complication rate.[8] Multicenter studies with more granular data described a good prognosis after LT, even among patients with ACLF, but these results were obtained in the absence of active gastrointestinal bleeding, hemodynamic instability, uncontrolled sepsis, and respiratory failure or mechanical ventilation, but without acute respiratory distress syndrome (ARDS).[6,22]

There are several conditions associated with cirrhosis, which are known to increase mortality and are not reflected by MELD-Na score, such as sarcopenia, frailty, or recurrent HE. These conditions may be improved by LT due to the replacement of the diseased liver. In the case of ACLF, systemic inflammatory response, as reflected by WBC count in the CLIF-C ACLF score, crucially influences the outcome in ACLF patients, but it is also not incorporated into the MELD-Na score.[9] In a study of patients who underwent transjugular intrahepatic portosystemic shunt (TIPS) procedure, it was demonstrated, based on serum samples of the portal and hepatic veins, that the liver was a source of these systemic inflammatory markers.[26] A separate study found that other markers of cell death, such as caspase-cleaved keratin 18 and keratin 18, are typically derived from injured hepatocytes and correlate with ACLF development and mortality.[27] These findings, therefore, indicate that one of the benefits of LT in patients with ACLF may be removal of the primary source of SI.

Most studies investigating posttransplant outcomes of patients with ACLF have been performed in the context of deceased donor liver transplantation (LT). Although living donor LT is used for ACLF in East Asia, including Korea, Japan, Taiwan, Hong Kong, and India,[28] there are few data about the outcomes of transplantation performed in this context. Among 321 Asian patients with high MELD scores who received living donor LT, the 5-year survival did not significantly differ between those with ACLF and those without (72% versus 81.82%).[29] However, in this study, the 5-year graft survival was significantly lower among patients of the ACLF group than among those of the non-ACLF group (71% versus 81%).[29] Together, these findings indicate that studies should be performed on a large series of patients receiving living donor transplants for ACLF.

Importantly, because all available studies of transplant in ACLF were retrospective, they are confounded by selection bias. Human subjective decisions are made to delist patients, and often the worst patients never receive a graft. Therefore, even though many studies to date show reasonable outcomes in ACLF patients on mechanical ventilation, these studies likely report data obtained in a selected population of patients.

Relative Contraindications for LT in ACLF

Because of the lack of availability of donor organs, LT is often considered to be contraindicated when the

survival or quality of life after transplantation is lower than without transplantation. There is a general consensus that survival should be >50% at 5 years, with an acceptable quality of life.[30,31] In the setting of ACLF, an additional consideration in the decision to proceed with LT exists, which is that the precipitating event leading to ACLF may also be a contraindication at the same time.[32]

Active alcoholism was one of the main precipitants of ACLF in the CANONIC study. This is a controversial topic because in many countries demonstration of abstinence for at least 6 months is the prerequisite for admission on the waiting list.[33] It has been shown that well-selected patients with severe alcoholic hepatitis have a good outcome after LT, with survival ranging between 77% and 97% and a return to harmful drinking of approximately 10%-13%.[33] There are several studies that provide evidence that certain patients who meet specific social and psychological requirements may benefit from an early LT in severe alcoholic hepatitis, with low likelihood of relapse.[34-37] A recent study identified a score associated with sustained use of alcohol after LT.[38] The Sustained Alcohol Use Post-LT (SALT) score was composed by 4 variables: the drinking pattern of the patients at initial hospitalization (10 drinks per day: +4 points), prior rehabilitation attempts (multiple attempts: +4 points), alcohol-related legal issues (+2 points), and prior illicit substance abuse (+1 point). A SALT score of <5 had a 95% negative predictive value for sustained alcohol use after LT.[38]

Bacterial infection, which is the most frequent precipitating event in the recently conducted PREDICT study (NCT03056612), is also a common feature of ACLF in both the NASCELD and EASL-CLIF definitions.[1,39] Interestingly, infections are not only precipitants, but also complications of ACLF.[40,41] Uncontrolled culture-positive infections and/or severe sepsis usually worsen with the use of immunosuppression after LT and should be considered as general contraindications.[42] However, successfully treated and controlled bacterial infections or specific infections not considered as contraindications (eg, cholangitis in primary sclerosing cholangitis) may not hinder survival after LT, even if associated with a longer hospital stay.[22,43-45] Similar to poorly controlled bacterial infections, uncontrolled human immunodeficiency virus (HIV) infection should be considered as a contraindication for LT.[46,47] Invasive fungal infections should also be a contraindication for LT, though these data are limited in the setting of ACLF. In ACLF, empiric antibiotic therapies should be considered in specific cases, which should be taken into account for the decision to transplant.[48]

Another frequent clinical feature in decompensated patients is gastrointestinal bleeding. In a recent study with more than 2000 patients, the presence of ACLF was a key determinant of rebleeding and mortality (unpublished), whereas the insertion of a pre-emptive TIPS[49] improved survival in those patients (unpublished). In patients with ACLF and variceal bleeding, early TIPS placement within 72 hours may break the vicious circle of bleeding, infection, and organ failure leading to deterioration and patient death.[50] Additional means, such as self-expanding esophageal stents (Danis stent), are also recommended to control bleeding[51] and may be of use to bridge to TIPS and transplantation.

Respiratory failure already plays an important role in the prognosis of decompensated cirrhosis, and in the CANONIC study, similar activation of SI in acute decompensated cirrhosis and ACLF patients was observed in the presence of respiratory failure (Fig. 1). Although the management of respiratory failure may be similar in AD and ACLF,[48] according to the majority of the experts, it may be a contraindication for transplantation in ACLF (Table 2).[52] Still, recent data suggest that a degree of respiratory failure (partial pressure of arterial oxygen [PaO_2]/fraction of inspired oxygen [FiO_2] $\geq$ 150), especially when not due to pneumonia or ARDS, may be acceptable for LT with adequate outcomes.[22]

Among patients with AD, the transplant waiting list can be used as a safety net in the event that patients may be offered an organ due to an increase of their MELD-Na score. However, the bigger question is the timing of LT in ACLF patients, who may die before reaching that point and/or for whom the window of liver transplantation closes rapidly. Recognizing the relatively short window available to patients with more advanced grades of ACLF, the first pilot allocation system is being introduced in the United Kingdom for these patients. The new system will allocate organs to patients with ACLF as a priority, immediately after allocation to patients with acute liver failure and those with hepatoblastoma. It is expected that approximately 1 organ will be available in the United Kingdom each day for these high-risk patients. The patients who are eligible for this program are patients with cirrhosis who have unplanned admissions to ICU/high dependency unit (HDU) and have an ACLF grade consistently predicting a

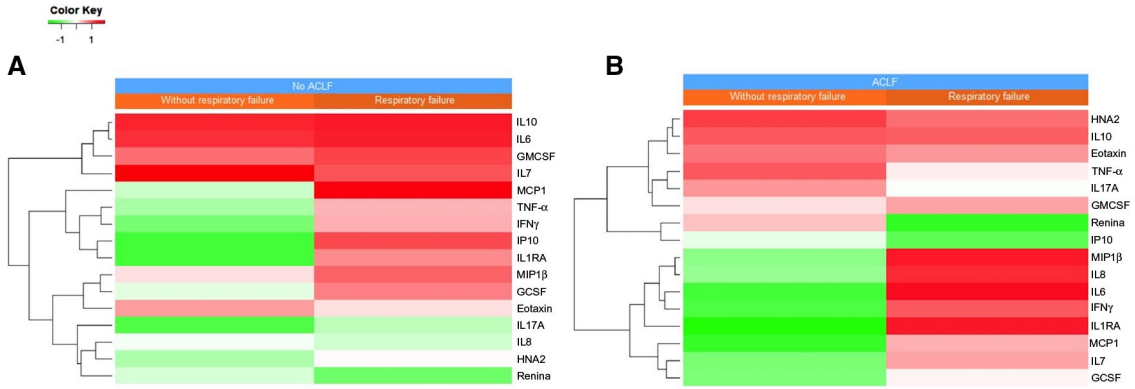

FIG. 1. Heat map showing the median levels of SI markers at enrollment of patients with (A) AD and (B) ACLF from the CANONIC study.[1,3] For the comparison, patients were divided into 2 groups according to the presence of respiratory failure. The magnitude of the levels is color-coded, and the clustering for each marker with the rest of the markers is shown to the left of the heat map.

TABLE 2. Acute Precipitants of ACLF and Types of Organ System Failure, Their Management, and Their Potential Influence on the Decision for LT

		Potential Influence on the Decision for LT	
Acute Precipitant or Organ System Failure	Management	Best Time for LT in ACLF	Relative Contraindication for LT in ACLF
Acute precipitants			
Active alcoholism or alcoholic hepatitis*	Assess psychosocial profile and personal behavior	3-7 days after diagnosis of ACLF	Severe uncontrolled psychiatric disorder
		SALT score <5	SALT score ≥5
Infections†	Use broad-spectrum antibiotic coverage and introduce empiric antifungals in patients not responding for 48 hours	≥48 hours of control of the infection	Uncontrolled culture-positive bacterial infection or controlled infection for less than 48 hours
	Use antibiotic prophylaxis in noninfected patients with ACLF		Uncontrolled HIV
Variceal hemorrhage‡	Use vasoconstrictors (terlipressin [not available in the United States], octreotide), endoscopic treatment, and prophylactic antibiotics	When bleeding is controlled and hemodynamics are stable	Refractory bleeding
	Prevent HE		Hemodynamic instability despite vasoconstrictors
	Use preemptive TIPS or Danis stent when indicated		
Organ system failures			
Respiratory failure§	Apply standards in critical care, including use of low tidal volumes, and positive-expiratory pressure for adequate oxygenation	When improvement of PaO_2/FiO_2 ≥150	PaO_2/FiO_2 <150
Renal failure‖	RRT	When improvement of ACLF grade at 3-7 days after diagnosis	CLIF-C ACLF score >64 persisting 3-7 days after diagnosis

*Im et al.[33] (2019), Mathurin et al.[34] (2011), Im et al.[35] (2016), Weeks et al.[36] (2018), Lee et al.[37] (2018), and Lee et al.[38] (2019).
†Moreau et al.[1] (2013), Artru et al.[22] (2017), Bajaj et al.[39] (2014), Bajaj et al.[40] (2012), Fernández et al.[41] (2018), Martin et al.[42] (2014), Sun et al.[43] (2010), Lin et al.[44] (2013), Bertuzzo et al.[45] (2017), Baccarani et al.[46] (2011), Fox et al.[47] (2012), and Olson and Karvellas[48] (2017).
‡Hernández-Gea et al.[49] (2019) , Trebicka et al.[50] (2020), and de Franchis[51] (2015).
§Thuluvath et al.[6] (2018), Artru et al.[22] (2017), Olson and Karvellas[48] (2017), and Putignano and Gustot[52] (2017).
‖Moreau et al.[1] (2013), Arroyo et al.[7] (2016), Gustot et al.[8] (2015), and Jalan et al.[9] (2014).

28-day survival of <50%, ie, those with ACLF grade 3. Where patients with alcohol-related liver disease are being considered, the standard guidelines for the acceptance of such patient will apply if alcohol itself was not the precipitant of ACLF. This pilot program will be tested in approximately 30 patients, and a 1-year survival of >60% will be defined as a successful outcome. The program is due to start in the third quarter of 2020.

Timing of LT

One of the primary challenges in transplantation of patients with ACLF, particularly ACLF 3, is the timing of transplantation. The published literature addressing this issue has consisted primarily of studies using the EASL-CLIF definition of ACLF. Though all grades of ACLF are associated with greater mortality than decompensated cirrhosis, patients with ACLF 3 have a particularly high short-term mortality without transplantation and, therefore, would appear to gain the most from early LT.[1] So, one would expect that performing LT as early as possible would yield the greatest overall survival benefit. However, the potential advantages of rapid transplantation may also include improved posttransplant survival. In an analysis of the UNOS registry, greater 1-year survival probability was demonstrated when transplantation occurred in <30 days on the waiting list among patients with ACLF 3, compared with >30 days (82% versus 79%).[5] Further analysis of this database revealed even greater post-LT survival when transplantation occurred within 14 days, and furthermore, the survival benefit increased with a greater number of organ failures. Although patients with ACLF 2 did not see significant improvement when transplanted within 14 days of listing (90% versus 88%, $P = 0.053$), greater post-LT survival was demonstrated among patients transplanted with 3 organ failures (86% versus 83%, $P = 0.012$), 4 organ failures (81% versus 76%, $P = 0.007$), and 5 organ failures (79% versus 67%, $P < 0.001$).[52]

However, other studies have indicated that the benefits of transplanting a patient with ACLF as quickly as possible should be weighed against the benefits yielded by the recovery of 1 or more organ failures prior to transplantation. A single-center proof-of-concept study revealed that patients transplanted after improvement of ACLF, defined as recovery of at least 1 organ system failure, yielded a superior 90-day posttransplant survival as compared with recipients transplanted with ACLF and similar to that of patients without ACLF prior to transplantation.[54] In a larger registry study, 1-year posttransplant survival substantially increased in patients listed with ACLF 3 who improved to ACLF grades 0-2 (88%) versus those who remained at ACLF 3 at listing and LT (82%) particularly after recovery of circulatory failure, brain failure, or requirement of mechanical ventilation.[55] This study also compared the effect of timing of transplantation versus improvement in organ failures on post-LT survival. The findings demonstrated that patients transplanted after 7 days on the waiting list but who improved from ACLF 3 to ACLF grades 0-2 at transplantation had greater post-LT survival than candidates who underwent transplantation within 7 days but remained at ACLF 3 from listing to transplantation (88% versus 83%, $P < 0.001$).[55] It should be noted, however, that <25% of patients with ACLF 3 at listing improved to a lower grade of ACLF. Therefore, although it would be ideal to perform transplantation after organ failure recovery, this may not occur in the majority of candidates with ACLF 3.

Ultimately, the optimal timing of LT in patients with severe ACLF has yet to be determined, and it is best addressed with data from multicenter prospective studies because of the lack of granularity and possible selection bias inherent to public registries. Several factors need to be considered concerning the timing of transplantation including patient mortality without transplantation, whether prognosis is fully captured by the MELD-Na score, and whether rapid transplantation leads to reduced post-LT survival compared with delayed transplantation after recovery of 1 or more organ failures.

Bridging to Expeditious LT

Currently, for many patients with ACLF, the only therapy is LT. Unfortunately, given the lack of available donor organs, patients may be at high risk of wait-list mortality before a suitable organ is available. Additionally, many centers may not offer transplantation to patients with multiorgan failure, due to the possibility of low posttransplant survival. Extracorporeal liver support (ECLS) may be an option to bridge to transplantation in these patients, either to sustain life until a donor organ is offered or to allow for recovery of organ system failures prior

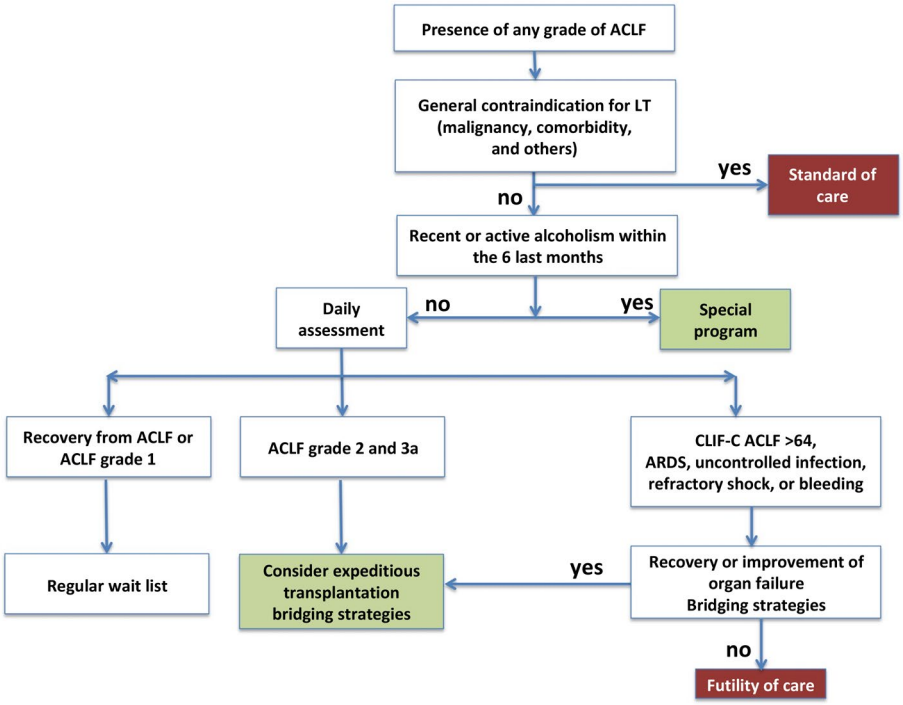

FIG. 2. The proposed algorithm to evaluate patients with ACLF for regular listing and expeditious LT.

to transplantation. Ultimately, an effective ECLS system should perform 3 primary hepatic functions: to detoxify, to stimulate liver regeneration, and to prevent further injury to the liver.[56] Several systems have been studied in clinical trials of patients with ACLF, including the Molecular Adsorbent Recirculating System, Prometheus, and stem cell treatment.[56-61] However, to date, artificial liver support has not been demonstrated to improve mortality in ACLF in prospective trials.

Conclusions

ACLF patients with specific criteria may benefit from expeditious transplantation because ACLF has a greater wait-list mortality and similar post-LT mortality as status 1A patients.[61,62] Indeed, the first question is whether the patient is suitable for LT in general (eg, exclusion of malignancy and other severe conditions precluding transplantation) and therefore should be further considered. The role of active alcoholism in these patients should be addressed with great care, and appropriate patients may benefit from special protocols using LT, which is similar for patients with severe alcoholic hepatitis. Close monitoring is important to identify the window of opportunity in ACLF patients and also to identify patients who are ineligible for LT. Finally, the decision of listing for LT may be given in all ACLF patients, but expeditious transplantation should be considered, especially in patients with ACLF grades 2 and 3 (Fig. 2). Because the data from retrospective studies of transplant in ACLF may be confounded by selection bias, prospective studies on ACLF and transplantation are urgently needed. Significant work is still to be done, but we must start somewhere.

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