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REVIEW

Extracorporeal liver support and liver transplantation for acute-on-chronic liver failure

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Abstract

Acute-on-chronic liver failure (ACLF) is defined by acute decompensation, organ failure and a high risk of short-term mortality. This condition is characterized by an overwhelming systemic inflammatory response. Despite treating the precipitating event, intensive monitoring and organ support, clinical deterioration can occur with very poor outcomes. During the last decades, several extracorporeal liver support systems have been developed to try to reduce ongoing liver injury and provide an improved environment for the liver to regenerate or as a bridging therapy until liver transplantation. Several clinical trials have been performed to evaluate the clinical efficacy of extracorporeal liver support systems, but no clear impact on survival has been proven. DIALIVE is a novel extracorporeal liver support device that has been built to specifically address the pathophysiological derangements responsible for the development of ACLF by replacing dysfunctional albumin and removing pathogen and damage-associated molecular patterns (PAMPs and DAMPs). In phase II clinical trial, DIALIVE appears to be safe, and it seems to be associated with a faster time to the resolution of ACLF compared with standard medical treatment. Even in patients with severe ACLF, liver transplantation saves lives and there is clear evidence of transplant benefit. Careful selection of patients is required to attain good results from liver transplantation, but many questions remain unanswered. In this review, we describe the current perspectives on the use of extracorporeal liver support and liver transplantation for ACLF patients.

KEYWORDS
acute-on-chronic liver failure, liver support systems, liver transplantation

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; ALF, acute liver failure; DAMPs, damage-associated molecular patterns; DRI, donor risk index; EF-CLIF, European Foundation for the Study of Chronic Liver Failure; ELS, extracorporeal liver support; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; HVPE, high-volume plasma exchange; LT, liver transplantation; MARS, molecular adsorbent recirculating system; PAMPs, pathogen-associated molecular patterns; Prometheus, fractionated plasma separation and adsorption system; SMT, standard medical therapy; SPAD, single-pass albumin dialysis.

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1 | INTRODUCTION

Liver cirrhosis is a major non-communicable chronic disease, which is estimated to be responsible for at least 170000 European deaths and over 1 million deaths globally each year[1] equating to approximately 2% of all deaths worldwide. Most of these patients die in a condition referred to as acute-on-chronic liver failure (ACLF).[2] Compensated liver cirrhosis remains largely asymptomatic, but patients may develop acute decompensation (AD) due to precipitating events such as bacterial infections, alcohol binge, variceal bleeding, drug-induced liver injury or superimposed infection with hepatitis viruses, among others. These patients present with liver-related decompensation manifested by hepatic encephalopathy, ascites, portal hypertensive bleeding or bacterial infection that can be associated with ACLF or progress to its occurrence.

ACLF was re-defined in 2013 by the European Foundation for the Study of Chronic Liver Failure (EF-CLIF) consortium describing a subgroup of patients with AD who develop organ failures and have a poor short-term prognosis.[3] The grade of ACLF is defined by the number of organ failures (Table 1). The 28-day and 90-day mortality rates are 22% and 41% for ACLF grade 1 (ACLF-1), 32% and 52% for ACLF-2 and 77% and 79% for ACLF-3 respectively.[4] The CLIF-Consortium ACLF score (CLIF-C ACLFs) incorporates organ failures, patients' age and white blood cell count and is the most accurate predictor of patients' outcomes if they are diagnosed with ACLF. In patients with ACLF and CLIF-C ACLFs >70, the mortality is over 90%.[5] ACLF, therefore, represents a major global health burden and is highly relevant for patients with cirrhosis. Co-existence of an overwhelming systemic inflammatory response with high levels of circulating pro-inflammatory cytokines and activated immune cell subsets together with immune paralysis predisposing to infectious complications are potential pathogenic mechanisms of ACLF.[6] Since targeted treatments for ACLF are currently not available, management of ACLF per se mainly consists of treatment of the precipitating event, intensive monitoring and organ support. Clinical deterioration or lack of recovery despite maximal supportive management is common (>50%), associated with very poor outcomes and leads physicians to consider potential salvage liver transplantation (LT).[5] This article describes the current evidence for the use of extracorporeal liver support (ELS) systems and LT.

Key points

- Acute-on-chronic liver failure is characterized by multiorgan failures, high rates of short-term mortality and an overwhelming systemic inflammatory response.
- Treatment of ACLF is an unmet clinical need.
- Clinical trials and meta-analyses of several extracorporeal liver support devices have been performed but no clear impact on survival has been proven.
- DIALIVE is a novel extracorporeal liver assist device, which shows promise in early clinical trials.
- Liver transplantation saves the lives of carefully selected patients with severe ACLF.

2 | ROLE OF LIVER SUPPORT SYSTEMS

2.1 | Design of liver support devices

The overall goal of ELS systems is to try to modify the disease state by reducing ongoing liver injury and providing an improved environment for the liver to regenerate or as a bridging therapy until LT. In general, ELS techniques take blood from the patient, which then passes through an external filter that removes circulating toxins and/or provides functional substances to the patient. ELS devices are classified into two types based on the primary function: those that purely detoxify blood (artificial) and those that incorporate hepatocytes to provide biological activity (bio-artificial). In this section, we described the design of the main ELS systems that have been tested in relatively large clinical trials and elaborated on the design and early clinical data of a novel liver assist device, DIALIVE.

2.1.1 | Artificial

The best-studied artificial modalities are based on either albumin dialysis [the molecular adsorbent recirculating system (MARS), fractionated plasma separation and adsorption system (Prometheus) and the single-pass albumin dialysis (SPAD)] or high-volume plasma exchange (HVPE) (Figure 1).

2.1.2 | Albumin dialysis systems

MARS was invented by Mitzner and Stange and used for the first time in 1993. It is still the most studied ELS system worldwide.[8] It has been designed to circulate the patient's whole blood across an albumin-impermeable 50-60 kDa cut-off membrane that is then dialysed against a counter-current flow of exogenous 20% human albumin solution in a secondary circuit. Given the difference in the concentration gradient of the albumin-bound toxins and the water-soluble substances between the two compartments, the toxins move from the patient's plasma to the exogenous albumin. This albumin is then recycled and detoxified by sequential passage through charcoal and an anion exchanger column. Setting up the system takes from 1 to 2 h, depending on the expertise of the team. Therapy takes place in sessions, and typically, each session of MARS treatment takes around 6–8 h using a blood flow rate of 150–250 mL/min.[9,10] During therapy, there can be episodes of hypotension that can be managed by reducing the blood flow speed or providing volume expansion. The most frequent technical complication is clotting of the extracorporeal circuit, which leads to discontinuation of the therapy session. Anticoagulation increases the likelihood of completing

TABLE 1 Criteria for the diagnosis of ACLF.

Organ/system	Subscore = 1	Subscore = 2	Subscore = 3
Liver	Bilirubin <6 mg/dL	Bilirubin ≥6 mg/dL and < 12 mg/dL	Bilirubin ≥12 mg/dL
Kidney	Creatinine <1.5 mg/dL Creatinine 1.5–1.9 mg/dL	Creatinine ≥2 mg/dL and <3.5 mg/dL	Creatinine ≥3.5 mg/dL or renal replacement
Brain (West-Haven grade for HE)	Grade 0	Grades 1–2	Grades 3–4
Coagulation	INR <2.0	INR 2.0–2.4	INR ≥2.5
Circulatory	MAP ≥70 mmHg	MAP <70 mmHg	Vasopressor requirement
Respiratory	$PaO_2/FIO_2 > 300$ $SpO_2/FIO_2 > 357$	PaO_2/FIO_2 201–300 SpO_2/FIO_2 215–357	$PaO_2/FIO_2 \leq 200$

Abbreviations: ACLF, acute-on-chronic liver failure; Fio2, fraction of inspired oxygen; INR, international normalized ratio; MAP, mean arterial pressure; Pao_2, partial pressure of arterial oxygen; Spo_2, oxygen saturation as measured by pulse oximetry.

Source: Adapted from Ref. [7].

treatment and is generally recommended unless severe anticoagulation disorders are associated.[11] In addition, the risk of bleeding was not higher in patients treated with MARS versus standard medical therapy (SMT) in the large clinical trials.[12,13] Unfractionated heparin and regional citrate are the most widely used strategies. The slower speed of blood flow can also increase the risk of clotting of the circuit. Therefore, balancing the severity of liver failure, risk of hypotension and severity of coagulopathy are important considerations when setting up the treatment for the session.

Prometheus was developed by Falkenhagen in 1999 and comprises fractionated plasma separation, adsorption and haemodialysis.[14] In Prometheus, the patient's blood passes through a larger albumin-permeable 250–300 kDa cut-off membrane into a secondary circuit where purification of albumin-bound toxins takes place by direct absorption on special adsorbers. Afterwards, conventional high-flux dialysis is performed inside the primary circuit to remove the water soluble substances. In contrast to MARS, it has the advantage that the system relies on endogenous albumin and there is no need for external albumin. Similar to MARS, clotting of the extracorporeal circuit was the main reason for premature termination of the sessions followed by hypotension and bleeding in the main Prometheus clinical trials.[15]

SPAD is one of the simplest approaches to remove albumin-bound toxins and water soluble substances. Like MARS, SPAD dialyzes whole blood against an albumin-rich solution in a single pass through the dialyzer; nonetheless, albumin is not recycled but discarded. Compared with the previous modalities, it has the advantage that can be performed using conventional renal replacement therapy devices, and therefore, the setting is simpler.[16]

2.1.3 | Plasma exchange

HVPE has been widely used in other medical conditions and it has started to prove clinical efficacy in patients with acute liver failure (ALF) and ACLF.[17,18] Its mechanism is based on plasma separation from whole blood for the removal of plasma cytokines and drivers of systemic inflammation with the subsequent replacement of fluid most commonly with fresh frozen plasma.[19]

2.1.4 | Bio-artificial

In bio-artificial devices, plasma is separated and run through hollow-fibre dialysis that contains either human hepatoblastoma cell lines (HepG2/C3A) (extracorporeal liver-assist device, ELAD) or porcine hepatocytes (HepatAssist). These systems have less detoxifying capacity than artificial systems but have the advantage of reproducing functions of the liver such as albumin synthesis.[20] Nonetheless, these systems are complex, and the need for the preservation of viable hepatocytes and metabolic activities renders them challenging.[21]

2.2 | Clinical efficacy results from clinical trials of these devices

The clinical efficacy of ELS systems has been tested in several randomized trials. The most studied clinical syndromes for the use of these devices are ALF and ACLF, but some of the ELS systems have also been tested in other types of liver failure including liver failure after LT and after major hepatectomy, in refractory pruritus and drug overdose. The following section will review the most relevant clinical trials performed on ACLF patients (Table 2).

2.2.1 | Artificial

Focusing on the treatment with extracorporeal albumin dialysis, 13 patients with type 1 hepatorenal syndrome (HRS) were studied in

the first trial evaluating the clinical impact of MARS on 30-day survival. Mortality rates were 100% in the control group on day 7 and 62.5% and 75% in the MARS group on day 7 and day 30 respectively ($p<0.01$). This improved survival was associated with a significant decrease in bilirubin and creatinine levels ($p<0.01$), an increase in serum sodium level and prothrombin activity ($p<0.01$).[22] With these promising results, a second controlled study of MARS versus SMT was conducted 2 years later investigating 24 patients with bilirubin >20 mg/dL with the primary aim of evaluating a 3-day stable reduction of serum bilirubin below 15 mg/dL. The study achieved its primary endpoint and showed survival benefit at 30 days in the MARS group (11 of 12 in the treatment arm and 6 of 11 in the controls; log-rank $p<0.05$) as well as improvement of hepatic encephalopathy (HE) and renal function.[23]

Subsequent randomized controlled trials were designed to determine the effect of MARS on the pathophysiological basis of ACLF. A study that included 18 alcohol-related ACLF patients, showed HE improvement in patients in the treatment arm compared to SMT, but no differences were observed in the primary endpoint of plasma cytokines or ammonia levels. No benefit on survival was observed in this study either.[24] Similarly, two studies including 8 patients with ACLF treatments with either MARS or Prometheus in a randomized cross-over design showed that cytokines were cleared from plasma by both MARS and Prometheus but neither system was able to change serum cytokine levels in the first study; and although MARS and Prometheus removed total bile acids to a similar extent (reduction ratio, 45% and 46%, respectively), clearance of individual bile acids was different, leading to a slight change of the bile acid profile toward hydrophobic bile acids during Prometheus treatment in the second study.[25,26] These results suggested that despite albumin being purified from bounded toxins, other systemic inflammatory mediators such as cytokines or ammonia were not cleared at the same level with these extracorporeal albumin devices.

The effect of ELS albumin systems on haemodynamic parameters was evaluated in two studies. A randomized controlled trial of either MARS or Prometheus versus SMT in 18 patients with alcohol-related ACLF showed that MARS but not Prometheus significantly attenuated the hyperdynamic circulation of ACLF patients reflected by an improvement in the mean arterial pressure, the systemic vascular resistance index and the decrease in plasma renin activity, aldosterone, norepinephrine, vasopressin and nitrate/nitrite levels. Similar results were seen in the second study performed on 24 patients with decompensated cirrhosis randomized to either MARS, Prometheus or SMT. Systemic haemodynamics did not differ between groups apart from an increase in arterial pressure in the MARS group ($p=0.008$). Overall survival was not evaluated in any of the studies.[27,28]

The next randomized trial studied 70 patients with severe HE with the aim of evaluating the impact of MARS on the improvement of HE. It showed a significant improvement in patients undergoing therapy compared with SMT (34% vs. 18.9%; $p=0.044$), but it failed to provide survival benefits.[13] The largest randomized controlled trial, the RELIEF study, was specifically designed to evaluate 28-day survival and included 187 patients with bilirubin >20 mg/dL and/or HE >grade 2 and/or HRS. Despite the improvement of bilirubin, creatinine, HE and HRS were more frequently seen in patients undergoing MARS, no beneficial effect in either 28- or 90-day survival was observed (60.7% vs. 58.9%; $p=0.79$).[12]

To define the group of patients that would benefit from MARS treatment, a systematic review and meta-analysis including individual patient data from three of the previously mentioned randomized trials was recently performed. It evaluated the effect of disease severity and the intensity of the treatment on mortality. MARS therapy did not show survival benefit compared with SMT in the general analysis; nonetheless, survival was significantly improved in the subgroup of patients receiving high-intense therapy (>4 MARS sessions) both in the entire cohort (10-day survival: 98.6% versus 82.8%, $p=0.001$; 30-day survival: 73.9% vs. 64.3%, $p=0.032$) and within the ACLF patients (10-day survival: 97.8% vs. 78.6%, $p=0.001$; 30-day survival: 73.3% vs. 58.5%, $p=0.041$). Remarkably, high-intense therapy increased survival independently of ACLF grade, which suggests that appropriate treatment schedules should be determined in future clinical trials.[29] However, the device is used sparingly in some units and the authors are not aware whether further evaluation of this device is planned or underway.

Considering the impact of Prometheus on survival in ACLF, the most important study was the HELIOS study, a large randomized, controlled multicentre trial including 145 patients. No survival benefit was observed at either 28 (66% in the treatment arm versus 63% in the SMT group; $p=0.70$) or 90 days (47% vs. 38%, respectively; $p=0.35$). However, patients with HRS type I or MELD score >30 showed a significant survival benefit under therapy in a predefined subgroup analysis. Therefore, there is no robust evidence-based data to recommend the use of Prometheus in clinical practice outside clinical trials.[15] The authors understand that further development of this device has been stopped.

High-quality evidence evaluating the clinical efficacy of SPAD on ACLF is lacking. HVPE has demonstrated promising results in patients with ALF, with improved survival in a multicentre randomized control trial of 182 patients, especially in those no candidates for LT.[18] In ACLF patients, several cohort studies have shown improved survival compared with SMT.[19] There is only one open-label, randomized, controlled study of 234 patients with HBV-associated ACLF not eligible for LT, which showed higher 90-day survival in the treatment group compared with SMT (60% vs. 47%, respectively; $p<0.05$).[30] Although the fact that this trial was performed only in Hepatitis B patients limits the general applicability, current evidence suggests that HVPE could be an option in patients not eligible for LT. Nonetheless, more robust data in other settings are needed and a large clinical trial, the APACHE (NCT03702920) is underway.

2.2.2 | Bio-artificial

Only a few randomized studies have evaluated the impact of ELAD on survival in ACLF. In the setting of ALF, an old pilot-controlled trial of 24

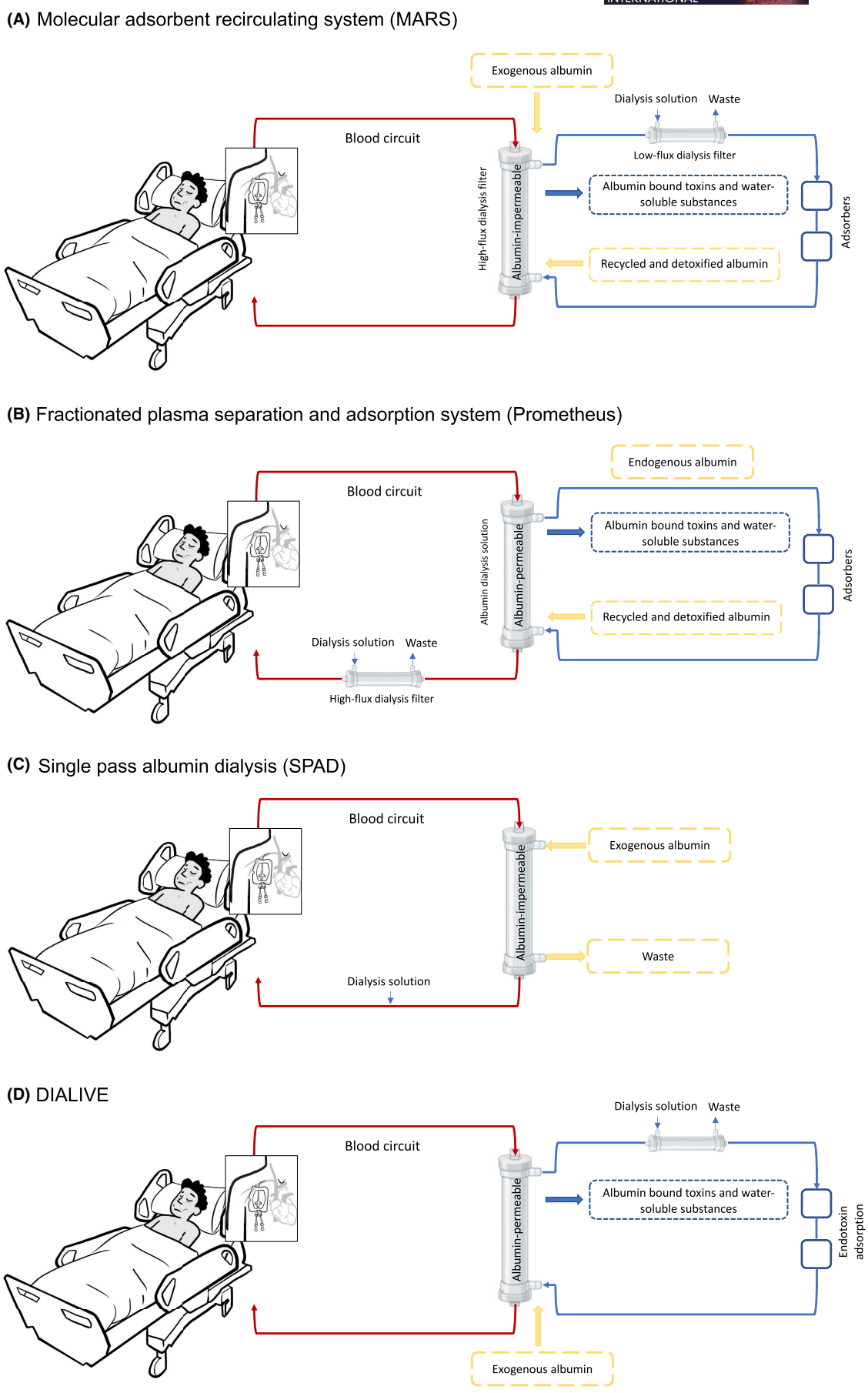

FIGURE 1 Design of the most studied albumin dialysis circuits considering its similarities and differences. Please see text for details.

TABLE 2 Selected randomized controlled studies on the efficacy of ELS systems for ACLF.

Study	LSS device	Indication	No. of patients	Technical details	Main endpoint	Survival outcomes	Other outcomes
Artificial							
Mitzner et al.[22]	MARS	Type 1 HRS in patients with bilirubin >15 mg/dL	13	Five sessions for 6–8 h with anticoagulation	Thirty-day survival	Increase survival on days 7 and 30	Improvement in bilirubin, creatinine, sodium and prothrombin activity
Heemann et al.[23]	MARS	Bilirubin >20 mg/dL	24	Ten sessions for 6 h with minimal anticoagulation	Three-day stable reduction of serum bilirubin <15 mg/dL	Survival improvement at 28 days	Improvement of HE, renal function and bilirubin
Sen et al.[24]	MARS	Alcohol-related ACLF	18	Four sessions for 8 h with anticoagulation	Cytokine profile, oxidative stress, nitric oxide and ammonia	No survival benefit	Improvement of HE
Laleman et al.[25]	MARS versus Prometheus	Alcohol-related ACLF	18	Three sessions in consecutive days for 6 h with anticoagulation	Potential changes in systemic haemodynamics	No survival benefit	Improvement in haemodynamics
Hassanein et al.[13]	MARS	HE (West Haven >2)	70	Three sessions for 6 h during 5 days or until 2-grade HE improvement	Difference in improvement proportion of HE	No survival benefit	Improvement of HE
Dethloff et al.[28]	MARS versus Prometheus	Decompensated liver disease	24	One session for 6 h with anticoagulation	Safety and hemodynamic changes	No survival benefit	Increase in arterial pressure in the MARS
Kribben et al.[15]	Prometheus	ACLF—Child–Pugh >10 and bilirubin >5 mg/dL	145	8–11 sessions for 4 h during 3 weeks with or without anticoagulation	Survival probabilities at days 28 and 90, irrespective of liver transplantation	No survival benefit globally, but in patients with HRS or MELD >30	Improvement in bilirubin
Bañares et al.[12]	MARS	Bilirubin >20 mg/dL, and/or HE >grade 2 and/or HRS	187	Up to 10 sessions for 6–8 h with anticoagulation	28-day survival	No improvement in 28- and 90-day survival	Improvement of bilirubin and creatinine, HE and HRS
Qin et al.[30]	HVPE	Hepatitis B virus-associated ACLF	234		90-day survival	Increase 90-day survival	
Bio-artificial							
Duan et al.[33]	ELAD	ACLF	49		Transplant-free survival	Improve transplant-free survival	Improvement in serum bilirubin

Abbreviations: ACLF, acute-on-chronic liver failure; ELAD, extracorporeal liver assist device; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; MARS, molecular adsorbent recirculating system; MELD, model for end-stage liver disease.

patients randomized to receive ELAD or SMT showed no significant differences in survival between the controls and the treatment arm (75% vs. 78%).[31] A Phase III prospective, controlled trial of 203 adult patients with severe alcoholic hepatitis randomized to receive ELAD versus SMT also failed its primary endpoint showing no difference in overall survival (51.0% vs. 49.5%; log-rank $p=0.90$).[32] In the setting of ACLF, a randomized controlled trial on 49 Chinese subjects with ACLF predominantly secondary to Hepatitis B virus infection showed better results. Treatment with ELAD was associated with a higher 28-day transplant-free survival compared with SMT ($p=0.022$). The duration of ELAD treatment was a significant predictor of transplant-free survival ($p=0.043$).[33] As noted by the authors, in China, SMT was different from Western countries, transplant frequency was lower and transplant allocation was determined primarily by acute need. Additionally, a further unpublished clinical trial of ELAD in a subgroup of highly selected patients with alcoholic hepatitis failed to show clinical benefit (NCT02612428). The lack of efficacy shown in these trials has led to the discontinuation of further development of this device.

In summary, despite the large number of trials and meta-analyses on the clinical efficacy of ELS systems, mainly with albumin dialysis systems, there is no clear consensus neither on the selection of the best treatment for each condition, the eligibility criteria of patients that may benefit from therapy nor the optimal treatment protocol.

2.2.3 | Possible reasons why these devices failed to show clinical benefit

Potential reasons for lacking the beneficial effect of the ELS systems on survival are diverse. First, none of the ELS devices has proven to impact some of the most important pathophysiological mechanisms of ACLF that determine the risk of infection and death such as albumin dysfunction, the severity of endotoxemia and PAMPs and DAMPs.[34,35] Second, the studies included a very heterogenious group of patients with varying degrees of severity of illness and many centres with different local standards of care. Third, there was no standard protocol for the administration of ELS therapies and as shown in the Bañares et al. meta-analysis, a high-intense therapy may have survival benefits regardless of the severity of ACLF.[29] Fourth, considering the high mortality rate in patients with ACLF grade 3,[4,5] clinical trials should have focused also on the role of ELS systems in patients who has a reasonable possibility to survive rather than those likely to be futile. A CLIF-C ACLFs >70 after 48 h of intensive care has a very high likelihood of mortality and these patients should be excluded from clinical trials unless they are also candidates for LT. In this latter situation, the bridge to transplantation may well be an endpoint.

2.2.4 | DIALIVE: Design and clinical effects

DIALIVE is a novel ELS device that has been built to specifically address the pathophysiological derangements responsible for the development of ACLF and avoid one of the reasons underlying the possible failure of previously used devices.[36] DIALIVE incorporates a renal dialysis machine and uses a dual filtration system connected in series. The first filter is comprised of a membrane that allows ultrafiltration of albumin and cytokines, and the second filter adsorbs PAMPs such as endotoxins and DAMPs such as genomic DNA. The removed albumin is replaced in similar quantities with bottled, 20% albumin. Major differences between DIALIVE system compared with MARS and Prometheus are that albumin removed is not recirculated in DIALIVE with wasted albumin replaced by bottled albumin, and the additional endotoxin filter in the DIALIVE system addresses endotoxemia by removing (adsorping) endotoxins.

A randomized, controlled trial of DIALIVE versus SMT has been recently performed in 30 patients with ACLF. Inclusion of patients with alcohol-related ACLF and with ACLF grades 1–3a allowed a degree of homogenization to avoid the second problem. DIALIVE system was shown to be safe with no differences in 28-day mortality or occurrence of serious adverse events between groups. A minimum of 3 DIALIVE sessions of 8–12 h each were needed for the patient to be evaluable for efficacy assessment under treatment. A significant reduction in the severity of endotoxemia and improvement in albumin function was observed in the DIALIVE group, which translated into a significant reduction in the CLIF-C organ failure and CLIF-C ACLF scores at day 10 and a faster time to the resolution of ACLF (Figure 2). Biomarkers of systemic inflammation, cell death, endothelial function and ligands for toll-like receptor 4 and inflammasome improved significantly in the DIALIVE group. These data including evidence of clinical and pathophysiological effects of DIALIVE provide a compelling rationale to proceed to registration clinical trials (clinical trial number: NCT03065699).[37]

3 | ROLE OF LIVER TRANSPLANTATION

3.1 | Current allocation systems and inadequacy of MELD

Although ACLF has been well established as a separate clinical entity with distinct pathophysiology, clinical course and prognosis, the current organ allocation systems do not consider ACLF status when listing these patients, yet they still rely upon the traditional disease severity scores such as MELD and MELD Na.[38] When considering LT for ACLF patients, many drawbacks of these traditional scores need to be considered in light of our current understanding of this life-threatening condition. The prognosis of ACLF patients can be extremely poor and is dependent on the severity of ACLF that is not captured by MELD-based scoring systems.[4] This is likely because the MELD score only evaluates three organs, namely the liver, kidneys and coagulation but it is clear that failures of the brain, respiratory or circulatory systems independently predict the risk of death.[39] This is reflected in the unsatisfactory performance of MELD, MELD Na and Child–Pugh scores compared with CLIF-C-ACLF score in predicting 28-day mortality.[7] Further validation of these observations comes from the discrepancy between the observed and expected 90-day mortality based on MELD

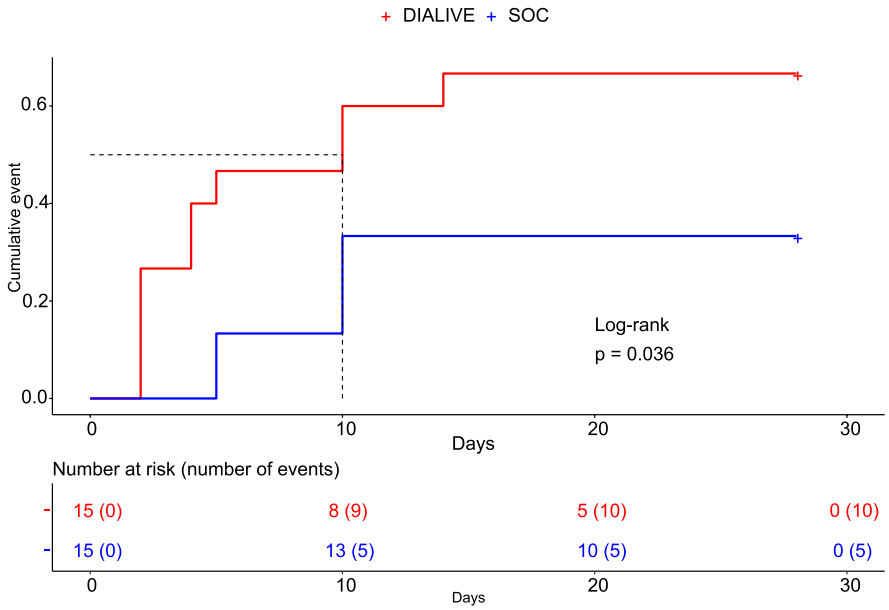

FIGURE 2 Time to resolution of acute-on-chronic liver failure in patients receiving DIALIVE versus standard medical therapy. *Source*: Adapted from Ref. [37].

Na calculations where the MELD Na score failed to capture the severity of the underlying disease severity in ACLF patients especially those with 1 or 2 extra-hepatic organ failures[40] (relevant studies are summarized in Table 3). Therefore, it is not surprising that the mortality of patients with ACLF grades 2 and 3 on the waiting list even if they have MELD scores of less than 25, is very high.[41] Similarly, the Canadian liver failure study group reported that survival on the waitlist beyond 30 days from the time of listing was 90% in the absence of organ failure or ACLF compared with only less than 10% in the presence of three or more organ failures.[42] Taken together, the data suggest that the current allocation systems underestimate the risk of death of patients with ACLF on the waiting list and it should be revised. In consideration of this, a pilot of the special tier for expedited organ allocation for ACLF grade 3 patients has been introduced in the UK.[43]

As per the current organ allocation policy in most liver transplant centres, patients with ALF have the highest priority for organ allocation following listing. This is justified on the basis of the significantly high short-term mortality rates in ALF patients if they do not undergo LT.[44] On exploring the waitlist mortality from the United Network for Organ Sharing (UNOS) registry between 2002 and 2014, it was found that patients with ACLF grade 3 have a greater risk of mortality or delisting within 14 days of listing compared to status 1A patients.[45] Keeping these findings in mind alongside the significant improvement of transplant-free survival in ALF populations from 32.9% to 61.0% since 1998,[46] one could argue that patients with severe ACLF should have the same priority for organ allocation as ALF patients.

3.2 | Review of data showing benefit of LT in patients with ACLF

Given the fact that the availability of organs is limited, one needs to weigh the benefit of liver transplantation against the utility of the organ, which is a scare resource and, judged by post-LT morbidity and mortality. This concept is further complicated by the absolute need for equity of access and justice for the patient with ACLF keeping in mind that patients on the regular transplant waiting list may be disadvantaged.[47] The data exploring benefits and utility are discussed below and summarized in Table 4.

Although many previous studies showed the potential of achieving potentially good results of LT in critically ill cirrhotic patients, the ACLF classification was applied retrospectively to a large number of patients from the UNOS database that provided important proof of concept for the potential role of LT in patients with ACLF. The data showed that the 1-year post-LT mortality of patients with ACLF grades 1 and 2 was not different to those with no ACLF and the survival of those with ACLF grade 3 was over 85%.[41] Further analyses of the same database showed that good survival rates were observed even in patients with 4–6 organ failures.[48] In order to confirm these observations from the large databases, a collaborative European study involving 308 consecutive ACLF patients from 20 liver transplant centres across eight European countries was performed, the ECLIS study.[49] The 1-year post-transplant survival across all ACLF grades was about 80%. Analysis of the 'CRISTAL' database of the French agency for transplantation from three transplant units revealed that 1-year post-LT survival of patients with ACLF grade 3 was not significantly different from their matched controls (no ACLF, ACLF-1 and ACLF-2). However, these good results came at a cost of longer hospital stays, higher rates of complications and more resource utilization.[50]

Extension of the studies using the UNOS database explored the potential 5-year post-LT survival of ACLF patients.[51] In patients with ACLF grade 3, the 5-year post-LT survival of 67.7% was observed, which was not significantly different to those undergoing LT without ACLF. In the same study, the sickest patients with 4–6 organ failures still had a transplant benefit with a 5-year survival of

TABLE 3 Studies evaluating CLIF-C-ACLF score performance against other disease severity scores.

Reference	Number of ACLF patients included (defined by EF-CLIF criteria)	Scores compared to CLIF-C-ACLF	Key findings
Jalan et al.[7]	Derivation group: 275 Validation group: 225	MELD MELD-Na CTP	CLIF-C-ACLF performed better than MELD, MELD-Na and the CTP in predicting mortality in both derivation and validation groups
Barosa et al.[58]	49	MELD MELD-Na CTP	The CLIF-C ACLF score was superior to MELD, MELD-Na and CTP in predicting mortality
Engelmann et al.[5]	202	MELD CTP CLIF-C-OF	CLIF-C-ACLF most accurately predicted 28-day mortality
Sonika et al.[59]	171	MELD MELD-Na CTP APACHE II Maddrey's DF ABIC	CLIF-C ACLF and APACHE II were significantly better than MELD, MELD-Na, DF and ABIC in predicting in-hospital, 90-day and 1-year mortality
Chen et al.[60]	249	MELD CTP CLIF-C-OF MPM0-III SAP III APACHE II APACHE III	CLIF-C ACLF and APACHE III scores were superior to other models in predicting overall mortality
Ramzan et al.[61]	75	MELD	CLIF-C ACLF score ≥70 at 48 h predicts mortality more accurately than MELD

Abbreviations: ACLF, acute-on-chronic liver failure; CTP, child Turcotte Paugh; EF CLIF, European Foundation for the study chronic liver failure; Maddrey's DF, Maddrey's discriminant function; MELD, model for end-stage liver disease; MPM0-III, mortality probability admission model; SAP III, simplified acute physiology Score III.

TABLE 4 Selected studies describing mortality following liver transplantation for ACLF Grade 3 using the EASL-CLIF criteria.

Reference	Total number of ACLF patients/ Grade 3 ACLF	1 year post-LT mortality for ACLF grade 3 patients (%)
Levesque et al.[62]	140/30	56.7
Artru et al.[50]	337/73	16.1
Bhatti et al.[63]	60/2	0 (3-month mortality)
Sundaram et al.[41]	21 269/6381	18.2
Marciano et al.[64]	60/8	17.5
Agbim[65]	101/19	17.5
Artzner et al.[56]	152/152	26
Belli et al.[49]	234/98	21.1
Xia et al.[66]	162/47	30.2 (3-year mortality)
Artzner et al.[67]	98/98	21

63%. Taken together, these data advocate strongly for the potential therapeutic benefits of LT in ACLF patients against the traditional concept of rendering them 'too sick to be transplanted'. However, this benefit of transplantation must be weighed against the risk and possible futile transplantation. It is also important to acknowledge that the excellent results of transplantation that have been described above do not take into account the deaths of the patients on the waiting list and the selection bias introduced by listing only patients with severe ACLF that have a high likelihood of survival with a transplant.

3.3 | Risks and potential futility of LT in patients with ACLF grade 3

3.3.1 | Timing of LT and use of marginal organs

The highly dynamic nature of ACLF syndrome is one of the major challenges that face clinicians when making decisions regarding LT, weighing the benefit of post-LT survival versus the high cost of futility. In this regard, two important notions should be kept in mind. First, the observed probability of evolution of the clinical course of ACLF towards improvement, plateau course and deterioration is 49%, 30% and 20% respectively. Second, the main determinant of the clinical course and prognosis is the evolution of ACLF status between the third and seventh day after ACLF diagnosis, rather than the initial ACLF grade at presentation.[52] Analysis of the UNOS database revealed that patients listed with ACLF grade 3 who were downstaged to ACLF grades 0–2 at the time of transplantation, had better 1-year post-LT survival compared to those who remained in ACLF grade 3 (88.2% vs. 82%, $p < 0.001$). Additionally, patients with ACLF grades 0–2, who deteriorated to ACLF grade 3 at the time of transplantation, had worse 1-year survival compared with those who were transitioned from ACLF grade 3 to lower ACLF grades (83.8%

vs. 88.2%, $p < 0.001$).[53] However, the overall likelihood of achieving this target of organ recovery was only in around 10% of patients.[54] Additionally, between the first and seventh day of listing ACLF grade 3 patients, each day of delay in transplantation reduced the overall survival probability by 4.4% and 5.2% for patients with 3 organ failures and 4–6 organ failures, respectively,[54] suggesting that earlier LT-focused management has better post-LT survival.

Although good quality organs for LT are always desirable, particularly in patients with ACLF, one must consider using marginal organs because of the urgency and the relative lack of availability of good quality organs. However, the use of donor organs with a donor risk index (DRI) ≥1.7 for ACLF grade 3 patients was associated with reduced 1-year post-LT survival compared with using optimal organs (78.1% vs. 82.9% respectively).[41] Similar results were obtained in another study when the quality of donor organs was stratified against recipient age and a number of organ failures.[54] One-year post-LT survival in patients aged <60 years was 86.2% and 78.2% for those who received livers with low DRI and high DRI respectively. Although the overall 1-year survival for those aged >60 years was less than for younger patients, the effect of the quality of the donor's liver was still evident with one-year post-LT survival (77.1% in optimal liver recipients compared with 74.1% in marginal livers). The same impact was also noted when considering the number of organ failures (3 vs. 4–6 organ failures) as a confounding factor to the post-LT outcomes.[54]

The dilemma about the timing of LT in ACLF involves considerations about waiting for the improvement of ACLF and accepting a marginal organ. This dilemma was addressed through a Markov model applied to the UNOS database.[54] The results showed that following the listing of patients with ACLF-3, earlier LT is favoured over waiting for an optimal quality donor organ or for recovery of organ failures.

3.3.2 | Factors associated with potential futility

The benchmark for futility of LT in ACLF patients can be determined by two scenarios. The first is based on the probability of clinical improvement without the need for a transplant and the second is lack of benefit from transplantation owing to high disease severity, in other words, 'too sick to be transplanted'.[55] In this section, we will focus on the second scenario. For LT, in general, the aim is to try and achieve a 5-year survival of greater than 50%, which roughly translates to a 1-year post-LT survival of greater than 60%. The study from the UNOS database evaluating factors independently associated with a high risk of post-LT mortality concluded that respiratory failure, delayed LT and use of marginal organs were independently associated with a high risk of post-LT mortality.[41] The importance of respiratory failure was confirmed in the ECLIS study, which also identified elevated lactate levels, uncontrolled fungal infection and bacterial infection with multidrug-resistant organisms as independent factors associated with potential futility following liver transplantation.[49]

The first prognostic score that was developed to identify ACLF grade 3 patients at high risk of mortality and potential futility following LT was the 'Transplantation for ACLF-3 model (TAM) score' (https://www.chru-strasbourg.fr/transplantation-for-aclf-3-patients-model-tam-score/), which was derived from the analysis of 152 consecutive transplanted ACLF grade 3 patients. Recipient age ≥ 53 years, arterial lactate level ≥4 mmol/L, mechanical ventilation with $PaO_2/FiO_2 \leq 200$ mmHg, and leukocyte count $\leq 10^9$/L at the time of transplantation, were found to be predictive of worse 1-year post-transplant survival rates[56] and included in the score. This categorical score is relatively straightforward to use. A score of ≥2 identifies patients at high risk of mortality of 64–84% compared with 8.3% for patients with lower scores.[56] Since the numbers of patients in this study were small, further validation in independent cohorts is needed. More recently, the MODEL Consortium from the US has developed the Sundaram acute-on-chronic liver failure transplantation (SALT) score (https://vocal.shinyapps.io/MODEL/) to prognosticate on the post-LT mortality of patients with ACLF grades 2 and 3 using individual patient data from 521 patients collected from 15 centres. The model includes age > 50 years, use of one or two inotropes, presence of respiratory failure, diabetes mellitus and body mass index. The c-statistic was 0.72. The score was independently validated using data from 2 European centres. The c-statistic in the validation cohort was 0.80.[57] The same group also developed a model to determine the estimated length of stay in which age, respiratory failure, body mass index and presence of infection were independent variables. This score allows estimation of the length of hospital stay for patients undergoing LT for ACLF grades 2 and 3.

4 | CONCLUSIONS AND PERSPECTIVES

The development and validation of the diagnostic and prognostic criteria for ACLF have allowed the identification of cirrhotic patients with acute decompensation at high risk of short-term mortality. A better understanding of its pathophysiology is leading to several novel therapeutic approaches and the clinical trial data of DIALIVE, a novel ELS looks encouraging. Even in patients with ACLF grade 3, LT saves lives and has clearly shown evidence of transplant benefit, but many unanswered questions remain, which are being addressed in the global CHANCE study (NCT04613921).

CONFLICT OF INTEREST STATEMENT

Rajiv Jalan is the inventor of OPA, which has been patented by UCL and licensed to Mallinckrodt Pharma. He is also the founder of Yaqrit Discovery (the company that holds the intellectual property for DIALIVE), a spin-out company from University College London, Hepyx Limited and Cyberliver. He had research collaborations with Yaqrit Discovery. The rest of the authors do not declare any conflict of interest.

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