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REVIEW ARTICLE

Liver transplantation in patients with acute-on-chronic liver failure

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Abstract
Acute-on-chronic liver failure (ACLF) is a dynamic syndrome associated with a very high short-term mortality. Hence, the ongoing assessment of treatment response, an expedited liver transplant evaluation and listing, and the determination of futility of treatment are critical for optimal outcomes. In this review, we appraise our current understanding of the timing and futility of liver transplantation, and the short- and long-term outcomes including the quality of life after deceased or live donor liver transplantation in those with ACLF.

Keywords Acute-on-chronic liver failure (ACLF) · Deceased donor liver transplant (DDLT) · Live donor liver transplant (LDLT) · Model for end-stage liver disease (MELD) · And Child–Pugh–Turcotte (CPT)

Abbreviations

NACSELD	North American Consortium for Study of End-stage Liver Disease
EASL-CLIF	European Association for the Study of the Liver-Chronic Liver Failure
CLIF-C	Chronic Liver Failure-Consortium

Introduction

Acute-on-chronic liver failure (ACLF) is a recently recognized clinical syndrome in patients with chronic liver disease. It is characterized by intense systemic inflammation, acute decompensation, one or more organ failure(s) (OF), and a very high short-term mortality. To date, more than 13 different definitions of ACLF have been proposed; however, due to the lack of objective clinical or biochemical parameters, there is no consensus on a standard definition. Three most widely accepted definitions are the ones proposed by the European Association for the Study of the Liver-chronic liver failure (EASL-CLIF) Consortium, the North American Consortium for Study of End-stage Liver Disease (NACSELD) and by the Asia Pacific Association for Study of Liver (APASL), ACLF Research Consortium (AARC) [1–4]. An increase in the number of organ failures, irrespective of the definition of ACLF, is associated with worsening short-term mortality. In the CANONIC study, the average 28-day transplant-free mortality in patients with decompensated cirrhosis without ACLF was only 4.7% but were 22%, 32%, and 77% in those with ACLF grade 1, grade 2, and grade 3, respectively [1]. Similarly, in the North American study, the 30-day mortality in hospitalized patients with decompensated cirrhosis triggered by infection was 8% without OF, 27% with 1 OF, 49% with 2 OFs, 64% with 3 OFs and 77% with 4 OFs [2].

Liver transplant (LT) is the only therapeutic option in ACLF that improves patient survival, but the window for LT is very short in the presence of ACLF with multiple OFs. Patients' selection criteria, optimal LT timing, and prioritization on the LT list are areas without a consensus. In this review, we will discuss the current controversies in LT for ACLF and make an evidence-based proposal for LT (Fig. 1).

Prognostic indicators in ACLF

The dynamic nature of ACLF makes firm prognostication a real challenge. Traditional scoring models for decompensated cirrhosis such as the model for end-stage liver disease (MELD), MELD-sodium (MELD-Na), and Child–Pugh–Turcotte (CPT) scores are sub-optimal for

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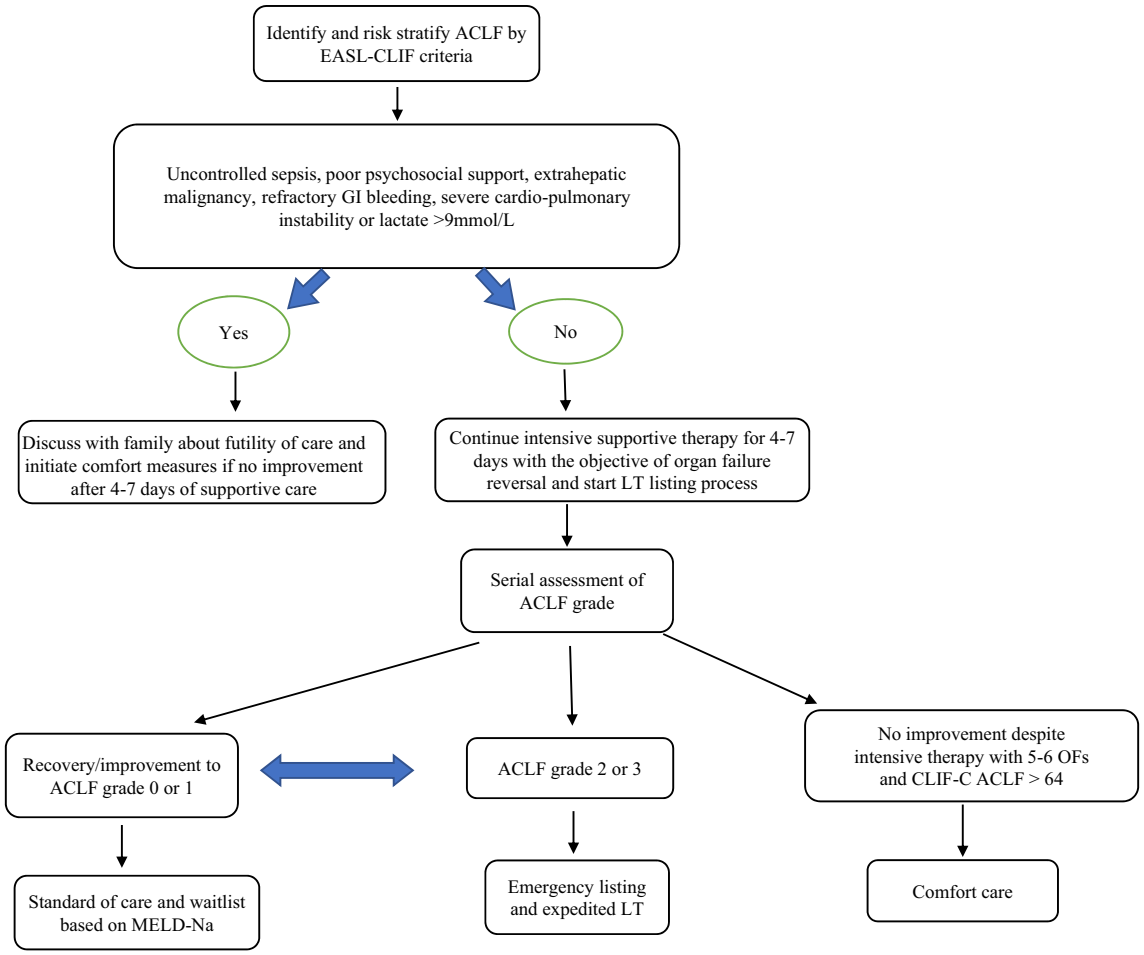

Fig. 1 An algorithm for liver transplantation in ACLF. *ACLF* Acute-on-chronic liver failure, *MELD* Model for end-stage liver disease, *CLIF-C* chronic liver failure-consortium

accurately predicting prognosis in ACLF. MELD-Na score, currently used for organ allocation in the USA, may not identify a substantial number of patients with a very high short-term mortality [5].

There is no consensus on the optimal criteria for the diagnosis and prognostication of ACLF. The important differences between European or North American and APASL definition are the precipitating causes of ACLF and the prerequisite for underlying cirrhosis [1–3]. APASL criteria do not require the presence of cirrhosis unlike EASL-CLIF and NACSELD [4]. The precipitating events could be either hepatic or non-hepatic for EASL-CLIF and NACSELD whereas for APASL criteria, ACLF results from an acute direct hepatic insult leading to liver failure (serum bilirubin > 5 mg/dl and international normalized ratio of ≥ 1.5 or prothrombin activity of < 40%) followed by clinical onset of ascites and/or encephalopathy within 4 weeks. [4] EASL-CLIF and NACSELD define ACLF by the number of OFs precipitated by either hepatic or non-hepatic insults; EASL-CLIF utilizes 6 OFs and NACSELD 4 OFs [1, 3]. There is a considerable overlap between the three major definitions, but the differences (presence of cirrhosis and type of precipitating insult) make it difficult to compare the predictive accuracy and the associated mortality of ACLF diagnosed by different criteria. This is corroborated by a large study based on Veterans Affairs (VA) database that followed ~ 80,000 patients with cirrhosis over 3.3 years; the study found that 4296 patients developed EASL-ACLF, while only 574 developed APASL-ACLF [6].

Underlying cirrhosis is a prerequisite for the diagnosis of ACLF by both EASL-CLIF and NACSELD criteria, and therefore comparable. The chronic liver failure-consortium (CLIF-C) ACLF score, proposed by the investigators of the CANONIC study, appears to be better than other currently available models to predict prognosis in those with ACLF [3]. It was recently shown that CLIF-C ACLF score was better in identifying and predicting prognosis than NACSELD-ACLF [7]. In that study, the area under the ROC (AUROC) to predict 30-day all-cause mortality and 30-day transplant-free mortality using CLIF-C ACLF score was 0.76 and 0.80,

respectively while it was only 0.59 and 0.63, respectively, with NACSELD-ACLF criteria [7]. EASL-CLIF identified 10,198 patients who met ACLF criteria, however, according to NACSELD definition only 15% of these patients had ACLF (> 2 OFs). More importantly, out of 2,562 patients with ACLF-3 per EASL-CLIF, only 49% had ACLF, according to NACSELD. These observations may suggest that the North American definition perhaps leads to an under-diagnosis of ACLF.

A novel score based on the interaction between MELD and ACLF grade was recently developed to predict 90-day waitlist mortality [8]. This model included variables such as age, gender, race, calendar year of listing, liver disease etiology, ACLF grade, MELD score at listing, obesity, and Karnofsky's performance status. This model stratified ACLF patients into four quartiles; Q1 (score < 10.42), Q2 (10.42–12.81), Q3 (12.82–15.50), and Q4 (> 15.50). The waitlist mortality increased with each quartile; 13% with Q1, 18% with Q2, 23% with Q3, and 36% with Q4. This model, however, included too many variables, and it will be challenging to translate this model for organ allocation purposes and a simple model that incorporates some aspects of ACLF and MELD-Na would be preferable.

Clinical course of ACLF

The CANONIC study demonstrated that the clinical course of ACLF is variable, with a potential for a few to recover, especially during the early stages [9]. In their study, 55% of ACLF-1, 35% of ACLF-2, and 16% of ACLF-3 improved with supportive care; CLIF-C ACLF score and the presence of liver failure (bilirubin > 12 mg/dL) at the time of diagnosis were independent predictors of the disease course. Based on the final ACLF grades, irrespective of the initial ACLF grade, the 28-day transplant-free mortality was 18.2% in ACLF-1, 41.7% in ACLF-2, and 91.8% in ACLF-3. Moreover, the clinical course of ACLF was best predicted by the ACLF grade on days 3 to 7 suggesting that aggressive supportive treatment options should be pursued at least for the first 7 days after ACLF diagnosis before a decision is made on treatment withdrawal in those who are not eligible for an expedited LT.

Timing of liver transplant

Currently, there are no organ allocation policies to prioritize patients with ACLF for a liver transplant. A recent UNOS database analysis showed that the 14-day waitlist mortality in ACLF-3 is higher than those listed as status-1A (reserved for adults with acute liver failure), suggesting a need for evidence-based organ allocation policy changes [10]. ACLF being a dynamic syndrome, serial assessment of the disease severity using the CLIF-C ACLF scores during the first week of hospitalization may be helpful to expedite patients for LT listing and transplantation. An early LT after the listing is associated with a marginal (~ 3%) improvement in 1-year survival, especially in those with three or more OFs based on the UNOS data.

It also appears that those who improve from ACLF-3 at listing to ACLF 0–2 at the time of LT may have a better probability of 1-year survival than those who remained at ACLF-3 at listing and at the time of LT (88% vs. 82%) [11]. Recovery from circulatory, respiratory, or cerebral failure was associated with an improved post-transplant survival. In those who were transplanted within 7 days after listing, there was a better (88% vs. 83%) survival in those with ACLF-3 who recovered to ACLF 0–2 than those who remained at ACLF-3 at both listing and the time of LT. These observations may indicate that in a few patients with ACLF-3, LT is futile, or perhaps an improvement in OF's could improve their chances of survival. However, since there is only a small window for LT for these patients, the decision to list patients with ACLF-3 should be made expeditiously.

Another study using the UNOS database showed that LT within 30 days of listing in those with ACLF-3 was an independent predictor of 1-year survival (HR 0.89; 95% CI 0.81–0.98), but the use of marginal donor livers (DRI > 1.7) was associated with increased mortality (HR 1.22; 95% CI 1.09–1.35) [5]. After listing, in the absence of any apparent contraindications, it may be prudent to proceed with a marginal donor rather than waiting for an ideal organ.

Futility of liver transplant in ACLF

Currently, there are no well-validated models to predict the futility of supportive care in ACLF-3. The CANONIC study suggested that the withdrawal of supportive care should perhaps be a consideration for patients with 4 or more OF, or a CLIC-C ACLF score > 64 (at day 3–7) if they have other contraindications for LT [9]. In that study, 90-day transplant-free mortality in patients with 4 or more OF or those with CLIF-C ACLF score > 64, was 100%.

In general, contraindications for LT in those with decompensated cirrhosis also apply to those with ACLF. These include uncontrolled sepsis (uncontrolled positive blood cultures > 48 h despite antibiotics, invasive fungal infections), active alcoholism/poor psychosocial support, extrahepatic malignancy, refractory gastrointestinal bleeding, or severe cardio-pulmonary instability. The studies that utilized UNOS data have shown that respiratory failure/mechanical ventilation is an independent predictor of post-transplant mortality in ACLF-3 [5, 12]. The large retrospective studies using databases do not have the granularity to differentiate

various reasons for mechanical ventilation. It is reasonable to assume that the outcomes for those who are on mechanical ventilation for ARDS/pneumonia will be different from those that are intubated for airway protection in the presence of severe hepatic encephalopathy.

A multidisciplinary panel of experts recommended delaying LT in the presence of severe frailty (clinical frailty score > 7), ongoing sepsis as demonstrated by persistent fever > 39 °C or leukopenia < 500/mm [3], pneumonia/SBP treated for less than 72 h, respiratory failure ($PaO_2/FiO_2 < 150$), circulatory failure (norepinephrine dose > 1.0 µg/kg/min) or metabolic failure (arterial lactate > 9 mmol/L) [13]. These contraindications are applicable to all LT candidates and not very specific for ACLF. Another prognostic model that has been developed to predict the futility of LT in ACLF-3 is the Transplantation for ACLF-3 Model (TAM) score. This model is based on 4 objective variables: recipient age ≥ 53 years, arterial lactate level ≥ 4 mmol/L, mechanical ventilation with $PaO_2/FiO_2 \leq 200$ mmHg, and leukocyte count ≤ 10 G/L. The study found that ACLF-3 patients with more than 2 risk factors had a dismal 1-year survival probability of 8.3% and should not be transplanted [14]. This model needs to be corroborated in prospective studies before it can be utilized in clinical practice.

Outcomes of liver transplantation

There are many single-center studies that have examined the outcomes of ACLF after deceased donor and living donor LT (Tables 1, 2). The 1-year survival rates following LT in ACLF-1 and ACLF-2 are similar (~ 90%) to that of patients without ACLF. Therefore, those with ACLF-1 and ACLF-2 should be evaluated for LT in a similar manner as those with decompensated cirrhosis.

There are many studies showing that patients transplanted with ACLF-3 have 1-year survival above 80%. The survival

Table 1 Survival outcomes following liver transplantation in ACLF

Author and study year	Location and study type	ACLF patients who underwent LT	ACLF Criteria	Survival rate[a]
Xing et al. [24] (2013)	China, single center	133	APASL	1 year: 76% 3 years: 73% 5 years: 72%
Finkenstedt et al. [25] (2013)	Austria, single center	33	APASL	2.5 years-85%
Duan et al. [26] (2014)	China, single center	78	APASL	1 year: 78% 3 years: 74% 5 years: 74%
Levesque et al. [27] (2017)	France, single center	140	EASL-CLIF	1 year ACLF-3: 43%
Artru et al. [28] (2017)	France, multi-center	73	EASL-CLIF	1 year ACLF-1: 82% ACLF-2: 86% ACLF-3: 84%
Huebner et al. [29] (2018)	Germany, single center	98	EASL-CLIF	90 days: 72%
Thuluvath et al. [12] (2018)	USA, UNOS registry	ACLF-3: 1637	EASL-CLIF	1 year ACLF-3 OF: 84% ACLF-4 OF: 81% ACLF-5–6 OF: 81%
Marciano et al. [30] (2019)	Argentina, single center	60	EASL-CLIF	1 year: 85%
Sundaram et al. [5] (2019)	USA, UNOS registry	ACLF-3: 6381	EASL-CLIF	1 year ACLF-3: 85.4%
O`Leary et al. [31] (2019)	USA, multi-center	57	NACSELD	6 months: 93%
Sundaram et al. [15] (2020)	USA, UNOS registry	ACLF-3: 7891	EASL-CLIF	5 years ACLF-3:68%
Agbim et al. [32] (2020)	USA, single center	101	EASL-CLIF	1 year ACLF-3: 74%
Belli et al. [16] (2021)	Europe, multi-center	234	EASL-CLIF	1 year ACLF-1: 89% ACLF-3: 79%

APASL Asian pacific association for the study of the liver disease, *EASL-CLIF* European Association for the Study of the Liver-chronic liver failure

[a]Overall survival in all ACLF grades unless otherwise specifically mentioned

Table 2 Live donor liver transplant (LDLT) outcomes

Author and study year	Total number of patients	ACLF criteria	MELD score (mean)	Follow-up in months	Survival rate[a]
Liu et al. [33] (2003)	32	Not mentioned	36	23	2 years: 88%
Moon et al. [35] (2017)	190	WCG	38	60	1 year: 80% 3 years: 74% 5 years: 72%
Bhatti et al. [38] (2018)	60	EASL-CLIF	29	12	1 year ACLF-1: 91% ACLF-2: 93%
Yadav et al. [37] (2019)	117	EASL-CLIF	31	12	1 year ACLF-1: 93% ACLF-2: 85% ACLF-3:76%
Lu et al. [36] (2020)	24	APASL	29	36	1 year: 92% 3 years: 92%
Wang et al. [34] (2021)	112	APASL	28	60	3 years: 96% 5 years: 93%

APASL Asian pacific association for the study of the liver disease, *EASL-CLIF* European Association for the Study of the Liver-chronic liver failure, *WCG* World Congress of Gastroenterology

[a]Overall survival in all ACLF grades unless otherwise specifically mentioned

rates are similar after deceased or living donor (Table 2) transplantation. A study that analyzed 2515 ACLF patients (using the UNOS database from 2002 to 2016) showed that LT performed within 30 days of listing was associated with a 1-year survival of 84% with 3 OF, 81% with 4 OF, and 80% with 5–6 OF [12]. The difference in the 1-year survival between those with no OF and 5–6 OF was only 9%. Moreover, the 30-day probability of transplant-free survival in those with 3 or more OF was only 2–8%. Another analysis of UNOS data found that 5-year survival rates in ACLF-3 following the transplant are 68% as compared to 75–70% in those in ACLF-1 and 2 [15]. Even in those with 4–6 OF, 5-year survival rates were 63%, and these observations make a compelling case for LT in those with ACLF-3. We have recently analyzed recent UNOS data of post-LT outcomes (1-year patient survival) of ACLF-3 patients and found that ACLF-3b patients had only marginally lower survival than ACLF-3a (unpublished, Alukal JJ et al. EASL abstract 2022). However, these results are based on those who were carefully selected for LT and cannot be generalized, and many other confounders may influence the outcomes. Moreover, the UNOS database has a few limitations, such as misclassification, a limited granularity of data for the causes of mechanical ventilation, infection status at the time of LT, and subjective selection bias.

The excellent 1-year survival seen in ACLF patients following LT in registry studies was recently validated in a large multi-center study from Europe [16]. The study included 308 patients with ACLF of which 234 were transplanted (ACLF-1 = 58, ACLF-2 = 78, ACLF-3 = 98) and had a waitlist mortality of 24%. The overall 1-year survival following LT in ACLF-1 was 89% while it was 79% in those with ACLF-3, and more importantly, the survival in ACLF-3 with 4 or more OFs did not differ significantly from those with only 3 OFs. Unlike registry studies, respiratory failure at transplant did not have an impact on post-LT survival, whereas the presence of multi-drug-resistant infections (HR = 3.67), pre-LT arterial lactate > 4 mmol/L (HR = 3.14), and renal replacement therapy (RRT) at the time of transplant (HR = 2.74) were independent risk factors for mortality. Following LT, ACLF-3 patients also had a higher frequency of complications such as respiratory failure requiring prolonged intubation, renal replacement therapy (RRT), and new infections compared to ACLF grades 1 and 2.

In addition to other clinical variables, etiology of underlying liver disease also may have an impact on post-LT survival. To determine the independent effect of etiology on the outcome after LT in patients with ACLF requires a large sample size. To date, only reliable data come from large registry studies. In one study, hepatitis C and HCC were independent predictors of 1-year patient survival on multivariable analysis, but this study, based on UNOS data, included patients before (2002–2016) the direct acting anti-viral agents were available [12]. A recent analysis (2005–2021) of the UNOS data showed that the etiology, including hepatitis C, is not an independent predictor of 1-year patient survival (unpublished, Alukal JJ et al. EASL abstract 2022) in ACLF-3 patients.

The current evidence suggests that patients with ACLF should be considered for expedited LT if there are no obvious contraindications. However, there is a paucity of prospective data on selection criteria, but based on current

literature, it appears that contraindications of LT in those with acute liver failure may be applicable to ACLF.

Quality of life (QOL) and resource utilization

Data regarding health-related QOL in patients with ACLF are limited. A prospective study in ACLF patients discharged from the hospital without LT showed poor QOL compared to those with decompensated cirrhosis without ACLF as measured by the chronic liver disease questionnaire (CLDQ) [17]. QOL issues such as fatigue, emotional function, worry, activity, and systemic symptoms worsened with an increasing number of OFs. The study also found that caregivers of ACLF patients had a significant amount of psychosocial stress similar to that of caregivers of patients with decompensated cirrhosis.

A surveillance study in 27 patients who underwent LT for ACLF, using standardized and validated QOL questionnaires (EQ-5D-3L, PHQ4, and WHO-QOL-BREF), found a significantly impaired QOL than non-ACLF patients who underwent LT [18]. ACLF LT recipients reported more problems in the domains of self-care and ability to perform usual activities. The PHQ-4 survey revealed that more than 25% of ACLF transplant patients displayed signs consistent with anxiety and depression compared to only 12% of non-ACLF transplant recipients. Similarly, the WHO-QOL survey revealed that ACLF patients had higher impairments in terms of physical and psychological health (self-esteem, spirituality) but performed similarly to non-ACLF patients when it came to social relationships (social support and sexual activity) and environmental support (financial resources, transport, leisure, and recreation). The presence of ACLF at the time of LT, MELD scores, and the duration of ICU post-LT were associated with poor QOL. It is difficult to generalize the findings of this study to a heterogeneous and dynamic condition like ACLF.

In a recent UNOS database analysis, improvement in Karnofsky performance status (KPS) scores were seen in all grades of ACLF, even in those with 5 to 6 OFs, when LT was performed within 30 days of listing [19]. The study found that at the time of transplant, a higher proportion of ACLF-3 patients (81–96%) had poor KPS scores (<40); however, following LT, excellent performance status (KPS score >80) was achieved in 60% of patients with 5 to 6 OFs, 64% with 4 OFs, 67% with 3 OFs and 70% with 2 OFs. Overall, 60–67% of ACLF-3 patients achieved a KPS score ≥ 80 at 3–12 months post-transplant.

The economic burden of hospitalized patients with ACLF is likely to be remarkably high as it involves not only the cost of prolonged hospitalization but also additional costs incurred following discharge to skilled nursing homes and short-term rehabilitation facilities. The expenses are also likely to be higher in those with higher ACLF grades and those who received LT, especially after a prolonged hospitalization. The analysis of the national inpatient sample (NIS) database showed that ACLF hospitalizations in the United States had increased between 2001 and 2011. As a result, the annual cost of ACLF hospitalization increased from $320 million in 2001 to $1.7 billion in 2011 [20]. The mean cost per ACLF hospitalization in 2011 was 3.5-fold higher than that for cirrhosis without ACLF.

A recent single-center study of ACLF patients compared the hospital costs in 86 (66 with ACLF-3) patients who were transplanted vs. 58 ACLF patients who were not transplanted for various reasons [21]. The transplanted patients had a lower number of OF (4 vs. 5, $p<0.001$) and lower incidence of ACLF grade 3 (76.7% vs. 94.8%, $p=0.014$) compared to non-transplanted patients. As to be expected, 1-year survival was 86% in transplanted and 12% in those who were not transplanted. The mean hospital charges were $227,886 for transplanted patients and $88,900 ($p<0.001$) for the non-transplanted patients. [21] Of those who were transplanted, 66 patients had ACLF-3, and they had longer median ventilation days (2 vs. 1, $p=0.001$), ICU (3 vs. 2, $p=0.001$), and hospital days (22.5 vs. 12, $p=0.04$) than 20 patients who were transplanted for ACLF grades 1 and 2 LT recipients with ACLF-3 incurred higher hospital charges ($244,444.8 vs. $ 173,240.5, $p<0.001$) than those with ACLF 1 and 2 but had similar 30-day and 1-year survival. Although this was a small single-center study, it shows that LT in ACLF-3 is likely to be associated with more resource utilization.

Future studies

The current MELD-Na-based organ allocation policy underestimates waitlist mortality of ACLF-3. Recognizing these limitations, in 2021, the Spanish Society of Liver transplantation and the National Health Service (NHS) Blood and Transplant Society created new organ allocation policies in Spain and the UK, respectively, to prioritize LT for patients with severe ACLF, thereby over-riding their MELD scores [22]. Currently, the UNOS allocation policy does not prioritize those with ACLF-3. Based on prediction models and the data from the UNOS indicate that patients with ACLF-3 have a very short transplant-free survival suggesting that the organ prioritization should be considered in these patients.

There are many other unanswered questions, the optimal timing of LT, futility criteria, pre-and-post-LT resource utilization, and the quality of life after LT. The European foundation for the study of chronic liver failure (EF-CLIF) is currently enrolling patients in a prospective global clinical trial (the CHANCE study) to answer some of these questions, and the study is expected to be completed by 2026 [23].

Conclusions

ACLF is a dynamic syndrome resulting in multiple OFs with a very high short-term mortality, and LT remains the only definitive therapeutic intervention. The management of ACLF is challenging and time-sensitive, and requires a multidisciplinary team involving ICU physicians, hepatologists, nephrologists, and transplant surgeons for the best outcomes. The available data, mostly retrospective, suggest that LT is feasible with excellent outcomes and good quality of life in carefully selected patients. There are many unanswered questions, but the field will evolve when more prospective data are available.

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Declarations

Conflict of interest Gandhi Lanke, Joseph J. Alukal, and Paul J. Thuluvath have not disclosed any competing interests.

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