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Liver transplantation for acute-on-chronic liver failure

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1 Abstract

2

3 Acute-on-chronic liver failure (ACLF) occurs in the context of advanced liver disease and is associated with
4 hepatic and extrahepatic organ failure, eventually leading to major short-term mortality risk. Thus far,
5 effective therapeutic options have been lacking. In many cases, liver transplantation (LT) is the only life-saving
6 treatment that achieves acceptable outcomes in carefully selected recipients. LT for ACLF is now a subject of
7 major interest, considering the prevalence and prognosis of the syndrome and absence of therapeutic
8 alternatives. This review addresses key aspects of use of LT in the setting of ACLF, providing an in-depth review
9 of existing evidence with discussion of candidate selection, the optimal window for transplantation, the
10 arguments regarding potential prioritised allocation of liver grafts for this indication, and the global
11 management of ACLF to 'bridge' patients to LT.

12

13 Search strategy and selection criteria

14

15 References for this review were identified through searches of PubMed with the search terms "cirrhosis AND
16 intensive care", "acute on chronic liver failure", "acute on chronic liver failure and liver transplantation", and
17 "liver transplantation" from January 1st, 2000 until May 31st, 2023. Articles were also identified through
18 searches of the authors' own files. Only papers published in English were reviewed. The final reference list was
19 generated on the basis of originality and relevance to the scope of this review.

20

1 1. Introduction

2 Acute-on-chronic liver failure (ACLF) is a life-threatening syndrome in patients with advanced chronic liver
3 disease (CLD) associated with intense systemic inflammation causing hepatic and extrahepatic organ failure
4 with high short-term mortality (up to 80%). It mostly affects individuals below 60 years of age and often
5 requires management in a critical care setting for multi-organ support. Despite its prevalence and grave
6 prognosis, it lacks effective therapeutic options, with liver transplantation (LT) being the only life-saving
7 treatment for many cases. In contrast to longstanding dogma of poor post-LT survival, case series in recent
8 years have reported a 1-year patient survival rate post-LT exceeding 80%. Based on these results, ACLF is
9 emerging as a novel indication for LT. This review will discuss this treatment option whose effective delivery
10 will require a paradigm shift in clinician practice, resource allocation and liver graft allocation policy.
11 We will provide an in-depth review of existing evidence with discussion of candidate selection, the optimal
12 but narrow time window for transplantation, the arguments regarding potential prioritised allocation of liver
13 grafts for this indication, and the field of supportive therapies to 'bridge' patients to LT.

14

1 2. Definitions of ACLF

2 A consensus definition of ACLF was issued by the World Gastroenterology Organization (WGO) in 2014. It
3 defined a syndrome characterised by acute hepatic decompensation with liver failure (jaundice and
4 coagulopathy) and one or more extrahepatic organ failures, with increased mortality up to 3 months from its
5 onset (1). Nevertheless, scientific societies continue to disagree on central aspects of the definition (Table 1).
6 Thus, the stage of underlying liver disease, prior episodes of decompensation, and the requirement for specific
7 magnitudes of liver failure to define the syndrome differ between commonly utilised definitions of ACLF. The
8 definition of the Asian Pacific Association for the Study of the Liver (APASL) incorporates liver failure (bilirubin
9 $\geq 85 \mu\text{mol/l}$ and international normalised ratio (INR) ≥ 1.5 or PT $< 40\%$) complicated within 4 weeks by ascites
10 and/or hepatic encephalopathy in a patient, whether cirrhotic or not, who has never experienced prior
11 decompensation (2). This definition positions ACLF early in the natural history and does not include patients
12 with the most advanced liver diseases. In contrast, the definition by the European Association for the Study of
13 the Liver (EASL) considers ACLF as the combination of acute decompensation (AD) of cirrhosis and organ
14 failures arbitrarily defined by thresholds merged in the CLIF-C OF score (Appendix, page 1). Although EASL-
15 ACLF can identify most cirrhotic patients with a poor short-term prognosis, it has been suggested that the
16 elevated bilirubin threshold used to define liver failure in the EASL classification ($204 \mu\text{mol/l}$) may fail to
17 identify certain individuals with a poor prognosis, who are better identified by APASL-ACLF (3).

18 The North American Consortium for the Study of End-Stage Liver Disease's (NACSELD) definition aimed to
19 capture patients with cirrhosis and active infection with the worst short-term prognosis. This focused on the
20 presence of extrahepatic organ failures (brain, kidney, circulatory and respiratory) and did not establish
21 specific thresholds for liver dysfunction markers (e.g. bilirubin or INR) to define the syndrome (4). NACSELD-
22 ACLF has been further validated as simple reliable bedside tool to predict 30-day survival in patients without
23 active infection in a large multinational prospective cohort (5). Additionally, the Chinese group on the study
24 of severe hepatitis B (COSSH) has recently introduced its own classification resembling the EASL-ACLF but
25 distinct in its inclusion of patients at any stage of CLD (6).

1 To better characterise the stage of initial disease pre- ACLF, the WGO proposed distinguishing type A ACLF as
2 occurring in a patient with non-cirrhotic CLD, type B in the context of compensated cirrhosis, and type C in the
3 context of decompensated cirrhosis (1). Despite these differences, there remain important points of
4 agreement. Western and Eastern scientific societies agree that ACLF is different from AD with distinct
5 prevalence and prognosis. While it is estimated that 20% to 30% of cirrhotic patients hospitalized for AD have
6 ACLF upon admission, approximately 10% develop ACLF during hospitalization (7). These patients have a worse
7 short-term prognosis than patients with decompensated cirrhosis without ACLF, with estimated mortality
8 rates of 35% and 50% at 1 and 3 months, compared to 5% and 10%, respectively (7).

9 In all ACLF definitions, the number of organ failures is closely related to mortality risk. Thus, the severity grades
10 correspond to an increasing number of organ failures and progressively greater risk of death. As an example,
11 APASL-ACLF and EASL-ACLF, grades 1, 2, and 3 exhibit mortality rates of 13% and 22%, 45% and 32%, and 86%
12 and 77% at 28 days, respectively (2,8). EASL-ACLF grades 2 and 3 are often grouped under the term "severe
13 ACLF." ACLF is a dynamic syndrome, and during the first days of treatment, severity can undergo rapid changes,
14 sometimes within hours. More than 80% have reached their final grade of ACLF by 7 days (9). Hence,
15 reassessing the ACLF grade between day 3 and day 7 allows for an accurate identification of patients for whom
16 the chances of survival without transplantation are minimal (9–11) (Figure 1a,b,c,d). For example, in patients
17 with EASL-ACLF grade 3 after 3 to 7 days, the risk of death is as high as 70-100% at 28 days (Figure 1d).

18

19 2. Pathophysiology

20 Understanding the mechanisms driving the pathophysiology of ACLF help develop and target therapeutic
21 interventions. Systemic inflammation and immunoparesis are crucial components. Systemic inflammation is
22 primarily linked to hepatic cell death (necrosis, apoptosis, necroptosis) and inflammatory processes, as well as
23 intestinal dysbiosis associated with portal hypertension, which leads to increased bacterial translocation from
24 the gut (7). This triggers a pro -then compensatory systemic anti-inflammatory response, resulting in immune
25 suppression and elevated risk of infectious events (12–14). Immune system activation is energetically
26 expensive, and, in tandem with mitochondrial dysfunction and hypo-perfusion, results in extra-hepatic organ

1 failure (15,16). The severity of systemic inflammation and immune dysfunction progressively worsens across
2 the stages of compensated cirrhosis, decompensated cirrhosis, and ACLF making ACLF-3 the ultimate
3 manifestation. These mechanisms are described further in Figure 2.

4 Despite numerous immunological therapeutic approaches being proposed no specific treatment is currently
5 recommended (17–20). Although immune-modulation holds theoretical promise, it requires careful
6 adjustment due to adverse effects, such as those seen with granulocyte-colony stimulating factor (G-CSF)
7 where worsening of inflammation responsible for aggravation of organ failure was reported (21). Such
8 deleterious effects have been corrected with the use of Toll-like receptor 4 (TLR4) antagonists inhibiting
9 excessive inflammation and promoting liver regeneration in animal models (18). Whilst awaiting validated
10 therapies, the current management of ACLF relies on specialised organ support, treatment of the precipitating
11 event, and, in cases of persistent severe ACLF, consideration of LT.

12

13 3. Outcome of LT for ACLF

14 The majority of studies assessing the role of LT in the context of ACLF have primarily employed the EASL-ACLF
15 definition, with the APASL-ACLF definition being less commonly utilised. This manuscript will focus on the
16 existing data from both EASL-ACLF and APASL-ACLF perspectives.

17 The results are summarized in Table 2. Most are from 2017 onwards but prior to that period, several studies
18 examined the outcomes of LT in patients with multiple organ failure (MOF) that would be consistent with the
19 western definitions of ACLF (22–25). The largest study, published in 2013, reported favourable results in
20 carefully selected patients, with a 3-month patient survival rate reaching as high as 84% in the context of MOF
21 (22). The severity of MOF did not predict outcome post-LT in this population. In the past decade, numerous
22 reports have indicated positive results in patients with ACLF following LT with one-year patient survival rate
23 frequently exceeding 80% (26–35). Despite limited data, the longer-term reported outcomes in this indication
24 also seem acceptable, with 5-year survival rates of approximately 70% (28,35–38). This percentage aligns with
25 the recently-revised threshold of a 5-year survival of $\geq 70\%$ to define utility of LT, a core principle for allocation
26 in the context of scarce medical resources, in patients who undergo transplantation primarily for

1 hepatocellular carcinoma (39). Even more favourable results may follow living-donor LT (LDLT) for patients
2 with severe ACLF (40–44). Donor evaluation can be condensed to 1-2 days, and in contrast to deceased-donor
3 LT (DDLT) cases, recipient condition rather than deceased donor graft availability may determine the timing of
4 the procedure and can significantly improve outcome of LT (40–42,44).

5 A consistent observation in long-term studies is that, as with patients with acute liver failure undergoing
6 transplantation in MOF (45), most deaths occur within one year following LT (28,35–38), mostly related to
7 infectious and adverse cardiovascular events (36,38).

8

9 4. Factors associated with outcomes following LT

10 Table 2 presents the published outcomes of LT in the context of ACLF. Though retrospective, these studies
11 make possible the identification of factors associated with the risk of short-term mortality after ACLF-LT. Three
12 main groups of factors influence outcomes following ACLF-LT: those related to the patient at admission, to the
13 stay in ICU, and to the donor.

14 Of non-modifiable recipient-related variables, age is consistently associated with a lower survival after
15 ACLF-LT. The risk of adverse outcomes increases steadily beyond the age of 50, with a threshold of 60 years
16 recognized to identify those at significantly higher risk of mortality (22,27,28,32,46,47). In patients older than
17 60 years, the mortality risk has been reported to increase by 70% to 100% (32,48). While waiting for data on
18 the outcomes of patients of 65 or older, it seems reasonable to only consider LT in very exceptional cases. The
19 presence of diabetes has also been reported to be associated with mortality, with an increased risk of 18% to
20 56% for death after transplantation (36,47,48). Besides diabetes, the presence of cardiac risk factors, such as
21 a history of arrhythmias, severe valvular disease and significant coronary artery disease are independently
22 associated with mortality after ACLF-LT (24). Other specific comorbidities may also be important adverse
23 factors. The Charlson-Comorbidity Index (CCI) is a well validated predictive tool assessed in a wide variety of
24 chronic diseases, includes diabetes, cardiac and other comorbidities and is adjusted by age. After exclusion of
25 the points attributed to the presence of end-stage liver disease, age-adjusted CCI ≥ 6 has been associated with
26 poor prognosis after LT (24).

1 While the etiology of cirrhosis does not appear to significantly impact the outcomes, performance status and frailty
2 /malnutrition manifest by sarcopenia, sarcopenic visceral obesity or extremes of body mass index have been
3 independently associated with mortality following ACLF-LT (36,47,49,50). Although sarcopenic recipients with ACLF
4 showed worse outcomes compared to non-sarcopenic individuals, they still achieved satisfactory one-year survival.
5 This underscores the significance of considering other factors, which can help reduce the mortality risk associated
6 with sarcopenia (49). An international panel of experts has identified severe frailty, defined by a clinical frailty scale
7 (CFS) ≥ 7 , as a definitive contra-indication to LT in these patients when it is determined before admission to the ICU.
8 According to CFS, severe frailty indicates patients are completely dependent for personal care (51). The presence
9 of portal thrombosis, and infection with multi-drug resistant organisms before ACLF-LT are also associated with
10 elevated risk of complications and death following transplantation (32,46).
11 Again, assessment of suitability for ACLF-LT tends to avoid the use of specific thresholds to define candidacy, rather
12 seeking to assess their cumulative burden. However, an age of 65 or older, an age-adjusted CCI of ≥ 6 , or a pre-ICU
13 CFS ≥ 7 are associated with a highly unfavorable prognosis and these factors alone could be regarded as
14 contraindications to ACLF-LT (24,38,51).

15 Besides the number of organ failure, three consistent factors relating to ICU stay have been identified
16 as influencing the outcomes of ACLF-LT. First, respiratory failure (defined by a PiO_2/FiO_2 ratio ≤ 200 mmHg) or
17 endotracheal intubation and mechanical ventilation, regardless of the indication, is a major predictive factor
18 for post-LT death (26–29,32). Conversely successful weaning from mechanical ventilation is a strong argument
19 for proceeding with LT. Similarly, the requirement for pre-LT renal replacement therapy (RRT) or the use of
20 vasopressors (singly or in combination) prior to transplantation is associated with poorer post-LT patient
21 survival, though the association with RRT is less consistent than after elective LT (28,32,47,52). Second is the
22 evolution of organ failures; the dynamics of the organ failure severity before ACLF-LT may have an important
23 impact on post-LT patient survival. Stabilisation or improvement of the severity of MOF in the days before LT
24 as reflected by organ failure scores and low arterial lactate level on the day of surgery (≤ 4 mmol/l), is
25 associated with improved survival after transplantation (26,27,32,48,53). The combination of these first
26 factors and type and course of organ failure, allows for the delineation of a period referred to as the
27 "transplantation window" (54). Its boundaries are currently ill-defined and subjective but outline periods when

1 transplantation will be associated with unacceptably poor outcomes (Figure 3). These boundaries, which are
2 individualised in balance with the risks associated with non-modifiable factors, should be continually assessed
3 by the multi-disciplinary transplant team. The third factor is time to access transplantation. Most studies
4 reporting favorable outcomes after LT observed that the median time between admission to intensive care or
5 listing on the waiting list is between 7 to 15 days (26,28,29,32,33,48). A longer pre-transplant stay in intensive
6 care, in addition to the increased risk of death while on the waiting list, increases the risk of infection with
7 multi-drug resistant organisms and deterioration of the patient's general condition, and is associated with an
8 increased risk of post-LT mortality (52). Active sepsis is considered an absolute contra-indication to LT in
9 patients with severe ACLF given the expected introduction of immunosuppressive agents (26,51). Moreover,
10 experts recommend that individuals with leukopenia $< 500/\text{mm}^3$ and a history of infection caused by pandrug-
11 resistant Enterobacteriaceae should consider delaying or declining the procedure (51).

12 Finally, donor variables may impact post-transplant outcomes; in the United States, the Donor Risk Index (DRI)
13 is a composite measure of graft quality and has been associated with patient and graft survival in other
14 transplant indications. In the context of LT for severe ACLF, a high DRI threshold (≥ 1.7) has been associated
15 with a higher risk of short- and long-term mortality and it has been suggested that ACLF recipients should
16 receive a good quality graft with DRI below a threshold of 1.5 (29,36,55). However, these findings have not
17 been replicated (22,32,38,56). In practice, the combination of a limited number of offers and need to perform
18 the LT rapidly may constrain the utilisation of the most optimal organs for these patients. The benefit of earlier
19 transplantation with a sub-optimal organ may outweigh the risk of waiting for an optimal graft (52).

20 Few scoring systems allow for the assessment of mortality risk post LT and only two have been
21 dedicated to patients with ACLF. The UCLA-futility risk score (UCLA-FRS), which assesses the Charlson
22 comorbidity index adjusted for age, the presence of septic shock before transplantation, and cardiac risk
23 factors has been developed to identify patients with MELD score >40 exhibiting the highest risk of death
24 following LT (24). The transplantation for ACLF grade 3 model (TAM), developed specifically for this population,
25 includes age (threshold 53 years), respiratory failure ($\text{PiO}_2/\text{FiO}_2$ ratio ≤ 200), lactate levels (threshold 4
26 mmol/l), and circulating leukocyte count (27). This score appears to be more effective when calculated on the

1 day of transplantation and was associated with improved post-LT outcome when used to identify the LT
2 window (34). However, when recently evaluated in a retrospective multicenter French series, it did not help
3 identifying patients at risk of death at one year post-LT suggesting scope for improvement (57). Recently the
4 Sundaram ACLF LT model (SALT-M) derived from a large North American cohort was published. It combines
5 non-modifiable risk factors related to the patient (age > 50 years, diabetes, BMI) with modifiable ones related
6 to the ICU stay (the number and use of vasopressors, and presence of respiratory failure) (47). Whilst
7 potentially useful, these scores require validation in independent external cohorts before clinical application
8 (57). Ultimately, it is unlikely that a single score can serve as the final arbiter in these complex therapeutic
9 decisions which will continue to rely upon clinical judgement (49,57). Based on these factors, a proposed
10 algorithm for the management of potential candidates for ACLF-LT is illustrated in Figure 4.

11

12 5. Ongoing controversies and unsolved questions

13 Inequity of access to LT

14 Most national organ allocation systems rely on the Model for End-Stage Liver Disease (MELD) or MELD-Na
15 scores. However, these do not assess extrahepatic organ failures that are associated with the risk of death.
16 Consequently, as compared to patients without ACLF, for the same MELD(-Na) score patients with ACLF have
17 an increased risk of death while on the waiting list of approximately 50%, are therefore disadvantaged by the
18 organ allocation system (58), being even more pronounced in patients with severe ACLF. By example, patients
19 with ACLF-3 and a MELD-Na score between 20 and 29 have an observed death risk of 64% at 3 months,
20 whereas it is predicted to be only 20% based on the MELD-Na score alone. Similarly, for the same patients
21 with a MELD-Na score between 30 and 39, the observed risk is 70% at 3 months compared to 53% predicted
22 based on the MELD-Na score alone (58). Patients with ACLF-3 may have a higher risk of death while on the
23 waiting list than those listed with ALF (59).

24 Debate continues on the need to prioritise patients with ACLF on the transplant waitlist. The integration of
25 organ failures into organ allocation scores shows promise (60,61). From this perspective, recognising that their
26 organ allocation policy did not adequately prioritise patients with severe ACLF awaiting transplantation, the

1 United Kingdom has implemented a dedicated ACLF-based tier within their national allocation program since
2 March 2021. Concurrently, the Spanish Society of Liver Transplantation has proposed granting regional priority
3 to grade 3 ACLF patients eligible for LT (60). Additionally, access to liver transplantation for ACLF patients is
4 dependent on the local practices of the transplant centre. In a multicentre European study, the percentage of
5 patients with ACLF-3 admitted to the intensive care unit and subsequently listed for LT varied from 0% to 80%
6 illustrating the differences in local practices (33).

7

8 Impact on resource utilisation

9 Given the limited number of studies investigating long-term survival after LT for ACLF, further confirmatory
10 studies are needed to validate the absence of any impact on graft utility. This is important considering recent
11 conflicting results from some centers reporting 5-year survival rates of approximately 60% (62). While LT is a
12 life-saving treatment, its financial cost in ACLF is significantly higher than patients transplanted without ACLF
13 (63). This is due to longer post-transplant stays in the ICU and hospital, a greater likelihood of transfer to a
14 rehabilitation center, and an elevated risk of hospital readmission following LT (62,63). Finally, prioritisation
15 of these recipients carries the risk of reduced access to LT for those with other conditions showing more
16 reliably better short and long-term outcomes after LT impacting organ utility (60). As some countries shift to
17 prioritizing longer-term outcomes as important metrics, 5-year patient and graft survival, resource utilisation,
18 long-term quality of life are worthy of study for evaluating liver transplant activity in the field of ACLF.
19 Balancing individual vs. collective benefit is a pivotal factor that could influence the decision to place an ACLF
20 patient on the LT waiting list. Such decision should be taken wisely with the consideration of all the factors
21 that might negatively affect post-LT outcome (Appendix, page 2). While, encouraging living donor liver
22 transplantation (LDLT), given the favourable outcomes reported (Table 2) could alleviate the burden of ACLF
23 prioritisation, it is not anticipated that employing lower-quality donors (e.g. older age, significant steatosis)
24 would be a satisfactory alternative, as it has been suggested to independently worsen post-LT outcome
25 (28,29,52).

26

1 Pre-Transplantation Candidate Assessment

2 Two clinical scenarios can occur in patients undergoing LT in the context of ACLF. The more straightforward,
3 (~ one-third of patients), involves patients experiencing an ACLF episode while already on the transplant
4 waiting list. In this setting, elective pre-transplant assessments have been conducted following usual standards
5 with regard to comorbidity, addiction, oncologic, and cardiorespiratory issues. However, for many potential
6 candidates, consideration of LT first arises only after admission to ICU. In this scenario, the pre-transplant
7 evaluation needs to be rapidly performed during the ICU stay and active critical illness. Currently, very limited
8 data is available guide the specific elements of this evaluation or of its impact on post-transplant survival, and
9 the assessment tools that may be employed in this setting are much more limited (64).

10 Cardiovascular events are a leading cause of mortality following LT, necessitating minimum of 12-lead ECG and
11 transthoracic echocardiogram (TTE) during workup. In patients of 40 or older or those with risk factors of
12 coronary artery disease stress-TTE is commonly recommended. For patient with abnormalities on ECG, TTE or
13 stress-TTE we consider invasive coronary angiography (ICA). However, in this situation, coronary stent
14 placement would be a contraindication to LT for the next three months and the finding of coronary artery
15 disease may simply preclude LT (65). Additionally, performing ICA in hemodynamically compromised patient
16 is challenging and the value of more practicable coronary CT angiography and calcium scoring requires
17 evaluation. Infectious events must also be screened and prevented considering their impact on outcome after
18 LT in this population. We recommend conducting standard infectious work-up at admission and listing
19 including screening of fungal colonization and infection, and thoracic CT. Throughout the pre-LT ICU stay, we
20 suggest repeating screening for active infection as this will impact the immediate peri-operative period and
21 may necessitate delaying LT. Furthermore, to assess for global patient condition and as an alternative to the
22 assessment of sarcopenia using CT-scans, ultrasound (US)-based sarcopenia assessment is a promising tool in
23 this setting due to its applicability to bedridden patients (66). The CFS is easily applicable to this population
24 unlike other scores such as liver frailty index. In patients in ICU, the most promising approaches to detect
25 malnutrition and frailty include measuring mid-arm muscle circumference (MAMC) and handgrip strength.

1 These measures can provide valuable information upon admission and can be easily, as US-based sarcopenia
2 assessment, repeated during the course of ACLF and while on the waiting list.

3 The assessment of substance dependence and addiction issues is often limited by hepatic encephalopathy
4 and/or mechanical ventilation and time pressures and may be insufficient to identify individuals at risk of
5 relapse after transplantation. Very limited data exist to support such evaluations in this setting. These key
6 questions should be explored in prospective multicenter studies to standardise practices and optimise
7 transplantation outcomes.

8

9 Studies based on data from registries.

10 Most published data (>90% of patients in Table 2) are derived from retrospective data from the United
11 Network for Organ Sharing (UNOS) database. However, this database does not precisely assign organ failures
12 by the EASL classification. By example the use of invasive ventilation is also recorded, but its indications are
13 not, and it cannot be assumed that its utilisation reflects respiratory failure, as it may be to protect the airway
14 for high grade encephalopathy. There may be low concordance (approximately 60%) between ACLF grades
15 evaluated by registry data and those assessed by reviewing patient records (67,68). The presence of AD of
16 CLD, as included in the definition of ACLF, is not clearly documented: on patient record review, approximately
17 30% of patients classified as having severe ACLF according to UNOS did not have ACLF due to the absence of
18 AD. Therefore, some registry data should be interpreted with caution.

19

20 6. Optimising bridge to transplantation: general management and place of extracorporeal liver support (ECLS)

21 Ensuring physiologic and metabolic stability through multi-organ support is key to ensuring that an ACLF
22 recipient is in optimal condition for LT (69).

23 Circulatory failure should be managed similarly to patients without cirrhosis with norepinephrine as the first
24 line agent and a mean arterial pressure target of 60-65 mmHg. Positive fluid overload after few days in ICU
25 has been associated with increased mortality and should therefore be avoided where possible (70). Kidney
26 failure whether due to hepatorenal syndrome (HRS)- or non-HRS acute kidney injury (AKI) represent the most

1 common failure in ACLF patients. Continuous renal replacement therapy (CRRT) is preferably used in the ICU
2 in HRS-AKI or in non-HRS AKI. CRRT can also be beneficial in treating severe refractory ammonia in severe
3 hepatic encephalopathy (HE) (69,70). Patients with CGS ≤ 8 require airways protection to prevent hypoxia and
4 hypercapnia. Using benzodiazepines for sedation should be avoided. In the absence of specific mechanical
5 ventilation (MV) settings tailored to ACLF patients, a standard lung protective ventilator strategy should be
6 used. For patients awaiting LT or receiving steroids, antifungal prophylaxis should be initiated after infectious
7 screening to mitigate the risk of invasive fungal infection. Individuals with ACLF and suspicion of bacterial
8 infection should undergo a rapid and exhaustive infection workup and should receive, as early as possible,
9 broad-spectrum empirical antibiotic therapy according to local epidemiology. De-escalation of empirical
10 antibiotics should be applied when possible based on microbiological results and multi-drug resistant organism
11 colonisation (69,71). Liver failure necessitates a tight monitoring of blood glucose levels and nutritional
12 support (ideally enteral) with an energy intake targeted to range between 20-30 kcal/kg/day and protein
13 intake of no less than 1.2-1.5/kg/day (69,70). In addition, there is interest in ECLS as a 'bridge' to LT (71–73).
14 ECLS aim to either replace certain hepatic function, and/or contribute to the control of systemic inflammation
15 by removing inflammatory mediators to assist in achieving metabolic and hemodynamic stability. ECLS can be
16 categorized as artificial (A-ECLS) and bio-artificial (B-ECLS). Most evidence comes from A-ECLS, which use
17 albumin to bind and remove hepatotoxins through membrane-based filtration. These devices were evaluated
18 over a decade ago and did not focus on improving access to LT or optimising outcomes following LT, but rather
19 on improving survival in ACLF cases. Though changes in some physiologic parameters and laboratory variables
20 are reported, in randomised controlled trials these did not translate into survival benefit, nevertheless even a
21 short-term prolongation of survival could bridge to LT (74,75). A novel, ACLF-specific, liver dialysis device
22 (DIALIVE) combining albumin removal and replacement with endotoxin removal demonstrated promising
23 early results. Most patients in this study had a non-severe course of ACLF and the impact of this device on
24 patients awaiting LT has yet to be determined (76). Therapeutic plasma exchange (TPE) has been shown to
25 improve transplant-free survival in acute liver failure (ALF), attenuating innate immune dysfunction with
26 improvement of multi-organ failure (77,78). Scientific evidence supporting TPE efficacy on short-term

1 mortality in the ACLF setting remains low (79) . Early continuous renal replacement therapy (CRRT) is now
2 recommended in patients with ALF and acute kidney injury before the development of traditional indications
3 such as hyperkalemia, uremia, and oliguria due to its association with improved survival (71). However, in
4 ACLF, its place as a therapeutic option to bridge to LT remains to be determined. Up to this point, the goal of
5 achieving complete liver function replacement with B-ECLS has not been realised and there is conflicting data
6 concerning its impact on transplant-free survival in the field of ACLF (80,81). In a large multicentre
7 international study, the extracorporeal liver assist device (ELAD), a human hepatic cell-based including
8 multiple cartridges of hepatoblastoma-derived C3A cells, has failed to improve prognosis in severe alcohol
9 related hepatitis (81).

10 Palliative care (PC) should be integrated in the management of patients with ACLF (82), especially those
11 ineligible for LT. Additionally, for wait listed patients with low likelihood of LT due to a high number or organ
12 failures and/or a deteriorating clinical course. Persistence of 4 organ failures or more and/or a CLIF-C ACLF
13 score exceeding 64, especially if ≥ 70 , after day 3-7 from admission in ICU is associated with almost no chance
14 of survival in the absence of LT (9,11). In such cases PC is integral to management (Figure 4). but are
15 underutilised in end-stage liver disease and ACLF. Recent data emphasize that cardiopulmonary resuscitation
16 (CPR) is associated with exceedingly low chances of survival in patients with advanced CLD, and most such
17 patients would not wish for invasive or intrusive interventions of LT is not an option (82). Advance planning of
18 goals of care is key – where practical. Future research should focus on integrating PC into the care of patients
19 with ACLF regardless of LT eligibility.

20

21 7. Conclusion and perspective

22 Current approaches to candidate selection and supportive care for patients with ACLF undergoing urgent LT
23 consistently achieve a one-year survival rate of approximately 80%, albeit with markedly increased resource
24 use. After one year, these recipients do not seem to have an increased risk of death or graft loss compared to
25 patients without ACLF. However, key issues remain to be clarified. Of central importance is establishing a
26 definitive understanding of patient and treatment factors associated with waitlist and post-transplant

1 mortality. This will optimise selection of recipients and inform waitlist prioritisation. Any changes in allocating
2 the limited pool of grafts must both ensure equitable access, while respecting utility. These issues are the
3 subject of current study in the ongoing prospective multicentre observational CHANCE study (Liver
4 Transplantation in Patients With Cirrhosis and Severe Acute-on-Chronic Liver Failure: iNdications and
5 outComEs) which is recruiting from more than 90 centers and 27 countries.

6

7

1 **Legends to Figures:**

2 **-Figure 1:** Course of acute on chronic liver failure (ACLF) grades during hospitalisation and impact on 90-day
3 survival: Sankey-plot of the course of ACLF grades according to EASL classification from D1 to D3-7 with respect
4 to 90-day outcome (survival vs. mortality) (a) of 807 patients with ACLF all grades, (b) of 284 patients with
5 ACLF grade 1 on D1, (c) of the 295 patients with ACLF grade 2 on D1, (d) with ACLF grade 3 on D1 from studies
6 by Gustot et al.(9) and Karvellas et al.(10). D1, day 1 or initial grade; D3-7, days 3-7 after diagnosis; 90D, 90
7 days after diagnosis.

8 **-Figure 2:** Pathophysiology of Acute-on-chronic Liver Failure (ACLF). Systemic inflammation, liver injury,
9 alterations in the gut microbiome and mitochondrial dysfunction all play a role in the pathophysiology of ACLF.
10 Systemic inflammation is triggered by PAMPs and DAMPs, which can arise from a combination of bacterial
11 infections, intestinal translocation of bacterial components, and an acute liver injury. High levels of PAMPs
12 enter the circulation from the gut because of increased gut permeability, bacterial translocation and dysbiosis.
13 Liver injury results in cell death through pro-inflammatory cell death pathways, resulting in DAMP release.
14 Hepatocyte regenerative capabilities are also reduced. DAMPs and PAMPs are recognised by various PRRs,
15 activating intracellular signalling pathways that result in pro-inflammatory cytokine secretion. Alongside this
16 there is an excessive anti-inflammatory response, with functional defects of circulating immune cells and an
17 increase in anti-inflammatory mediators. Systemic inflammation is associated with increased usage of glucose
18 through glycolysis and the pentose phosphate pathway, leading to reduced mitochondrial ATP production
19 through oxidative phosphorylation. Diminished oxidative phosphorylation results in the production of reactive
20 oxygen species, which induce oxidative stress and cell death. Decreased mitochondrial beta-oxidation of fatty
21 acids contributes further to the reduced ATP production. Organ failures therefore result from a combination
22 of immune-mediated tissue damage, tissue hypoperfusion and mitochondrial dysfunction. ATP, adenosine
23 triphosphate; DAMP, damage-associated molecular pattern; IL, interleukin; OXPHOS, oxidative
24 phosphorylation; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; TCA,
25 tricarboxylic acid cycle; TNF, tumour necrosis factor.

1 **-Figure 3:** Illustration of the "transplantation window" during critical care hospitalisation in the context of
2 severe acute-on-chronic liver failure (ACLF). The first "transplantation window" is likely to be more favourable
3 (greener) than the second in a patient with fewer complications related to hospitalization (deconditioning,
4 colonization by multidrug-resistant organisms, etc.).

5 **-Figure 4:** Proposal of an algorithm for the management of a cirrhotic patient with severe acute-on-chronic
6 liver failure (ACLF) and potential eligibility for liver transplantation, taking into account the assessment of post-
7 transplant complication risk factors (*limited evidence in the literature) and the transplantation window.
8 Green: combination of favorable factors; gray: area of uncertainty combining favorable and unfavorable
9 factors; orange: combinations of unfavorable factors. A collaborative decision by the transplant team should
10 always be made at the time of offer and before transfer to the operating room. AF, atrial fibrillation; CI, contra-
11 indication, GI, gastrointestinal; LT, liver transplantation; MDROs, multi-drug resistant organisms; MV,
12 mechanical ventilation; PVT, portal vein thrombosis

13

14 **Tables:**

15 **-Table 1:** Main discrepancies regarding the definition of acute-on-chronic liver failure according to the four
16 scientific societies

17 **-Table 2:** Outcomes of studies evaluating liver transplantation for Acute-on-chronic Liver Failure (ACLF)
18 according to EASL and APASL definitions

19 **-Supplementary Table 1, Appendix page 1:** Chronic liver failure consortium organ failure score (CLIF-C OF)

20 **-Supplementary Table 2, Appendix page 2:** Factors negatively impacting outcome after liver transplantation
21 in the context of acute-on-chronic liver failure (ACLF)

22

23

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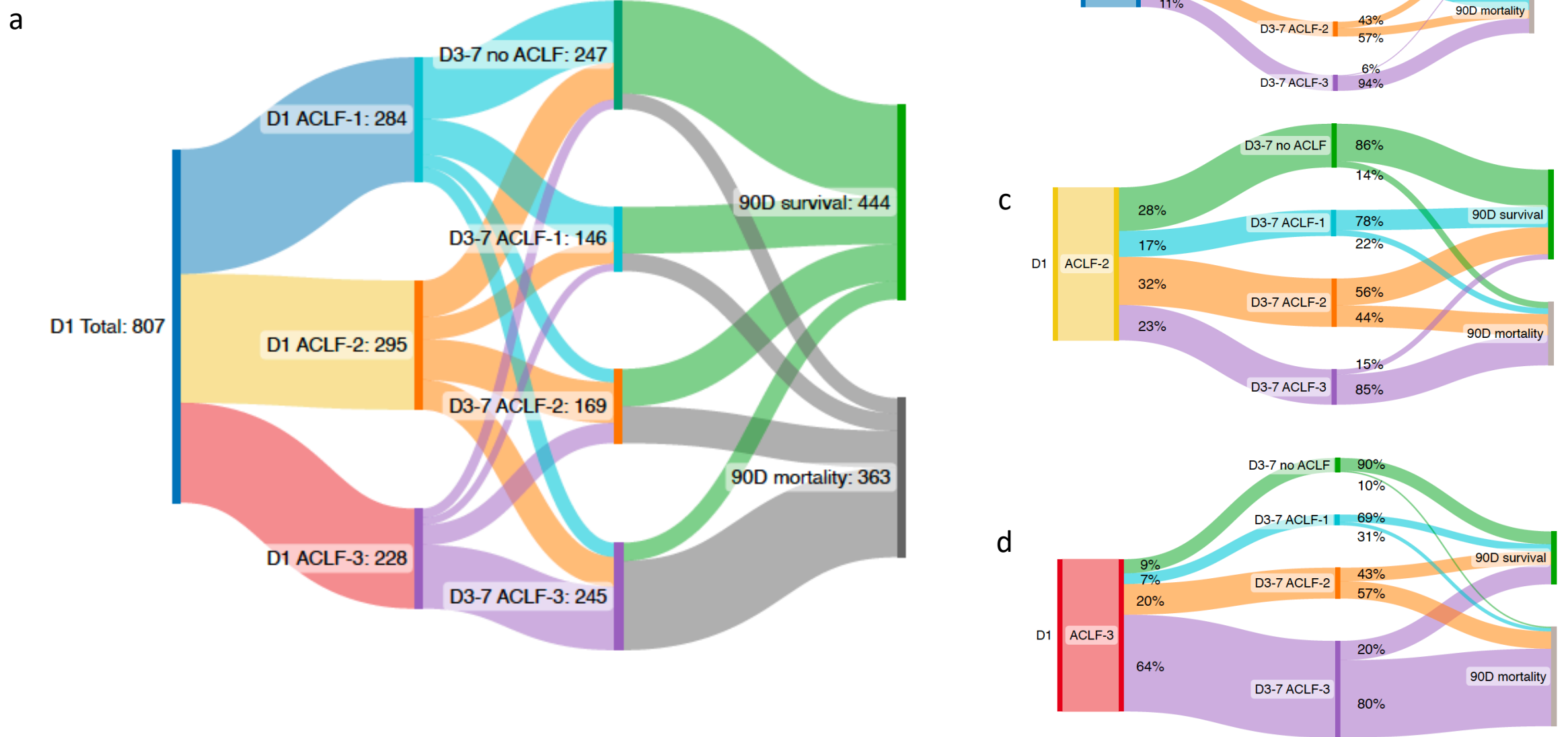
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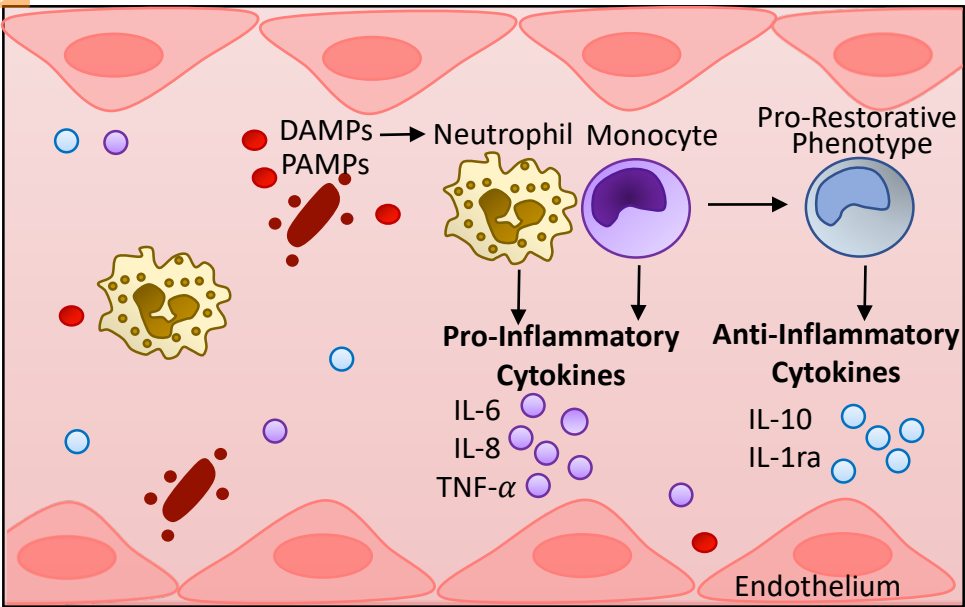
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- 33

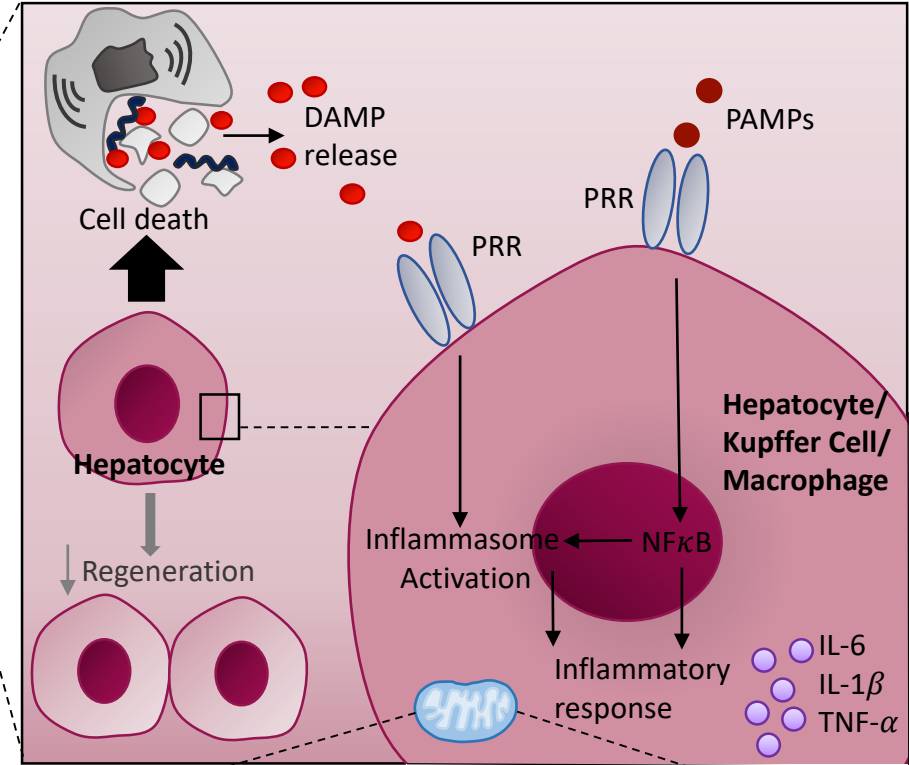
Figure 1. Course of organ failures during hospitalisation and impact on 90-day survival



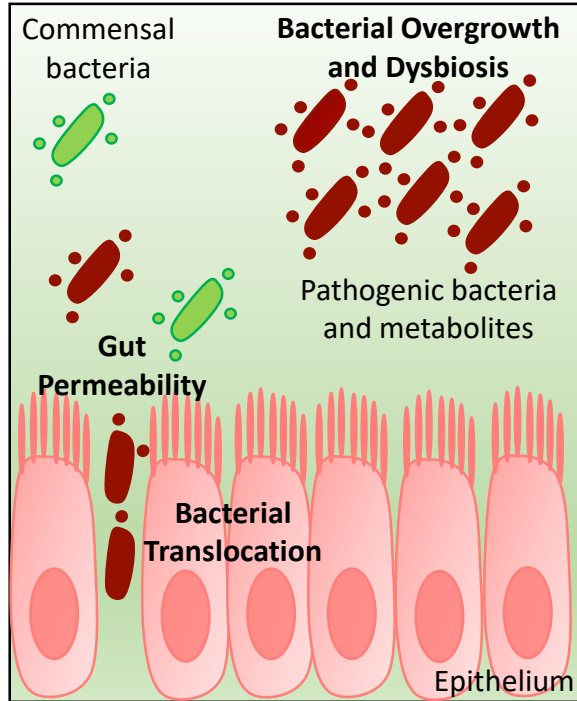
Systemic Inflammation



Liver Damage



Altered Gut Microbiome



Mitochondrial Dysfunction

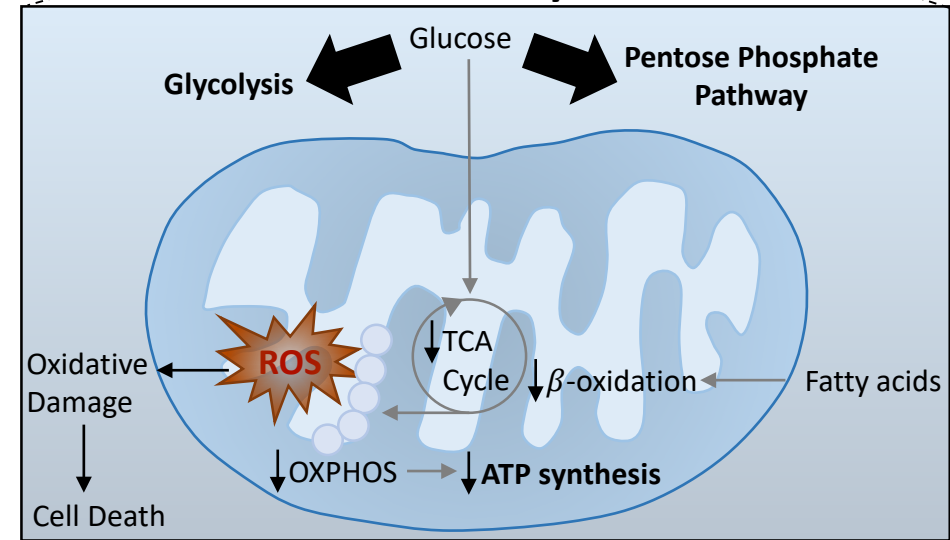


Figure 3. Illustration of the "transplantation window" during critical care hospitalisation in the context of severe acute-on-chronic liver failure (ACLF). The first "transplantation window" is likely to be more favourable (greener) than the second in a patient with fewer complications related to hospitalization (deconditioning, colonization by multidrug-resistant organisms, etc.).

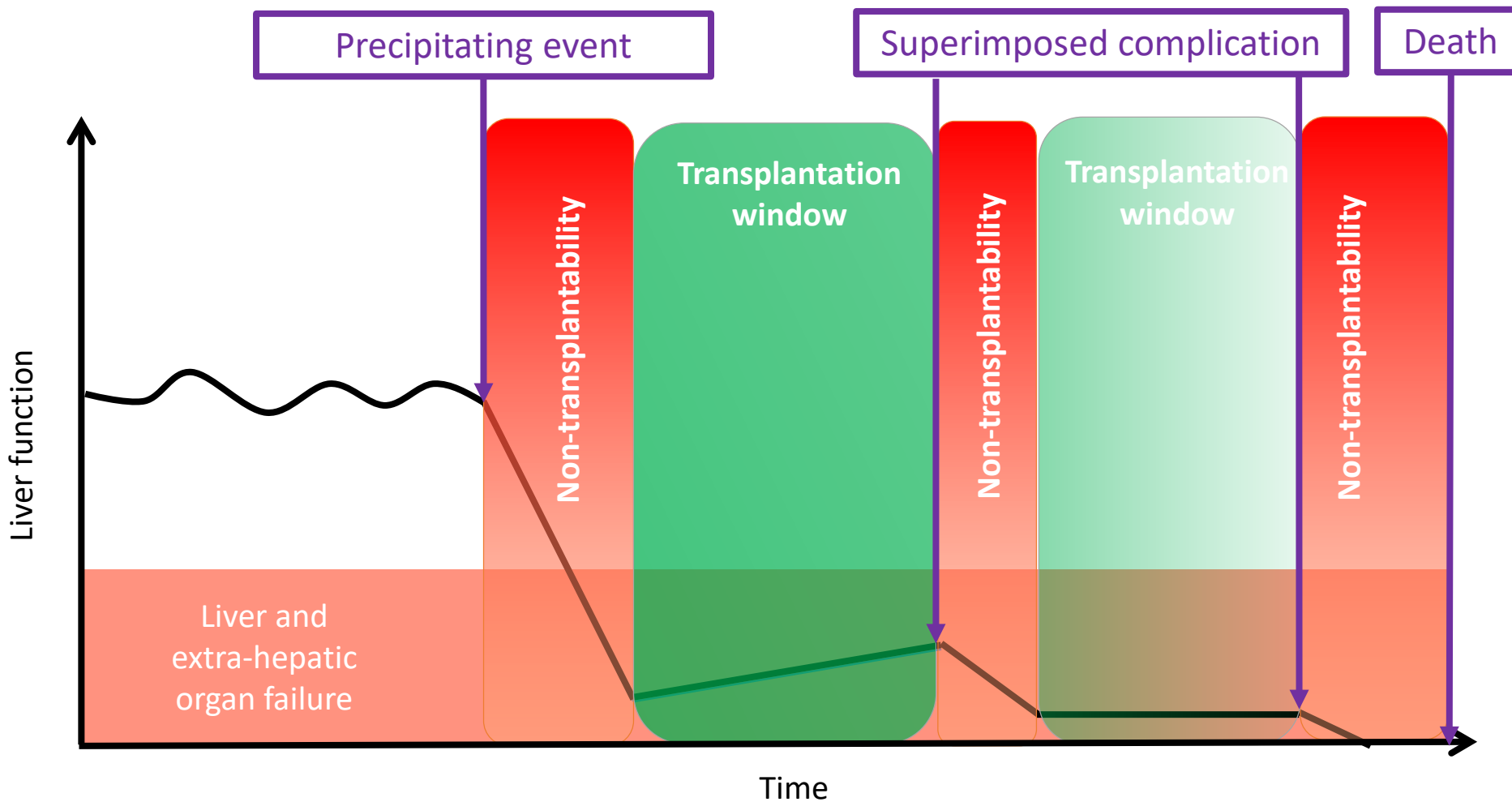




Figure 4: Proposal of an algorithm for the management of a cirrhotic patient with severe acute-on-chronic liver failure (ACLF) and potential eligibility for liver transplantation, taking into account the assessment of post-transplant complication risk factors (*limited evidence in the literature) and the transplantation window. Green: combination of favorable factors; gray: area of uncertainty combining favorable and unfavorable factors; orange: combinations of unfavorable factors. A collaborative decision by the transplant team should always be made at the time of offer and before transfer to the operating room. AF, atrial fibrillation; CI, contra-indication, GI, gastrointestinal; LT, liver transplantation; MDROs, multi-drug resistant organisms; MV, mechanical ventilation; Ofs, organ failures; PVT, portal vein thrombosis; TW, transplantation window



Patient with severe ACLF potentially eligible to LT

Exclusion of usual CI to LT
Addiction profile evaluation
Performance status evaluation

Factors associated with ↑ risk of death after AC
age, diabetes, BMI,
age adjusted CCI, sarcopenia- frailty, cardiac risk, M
PVT*

Potential factors considered as definitive CI to LT
taken individually:
age ≥ 65 years, age adjusted CCI ≥6, CFS≥7

Multidisciplinary meeting

*lower scientific evidence of association with outcomes

Placement on the waiting list

Definite CI to LT

Example:
Placement under MV, P/F ratio,
inotropes use and dosage, RRT

Define patient's specific boundaries of TW[#]

Define graft acceptance strategy

Involve palliative cares specialist
Especially if 4+ OFs or CLIF-C ACLF ≥ 64-70

[#]Consider help from SALT-M, UCLA-FRS and/or TAM score

Absence of uncontrolled sepsis

Organ offer AND patient within TW

**LT ≤ 7-15 days
AND
Organ failures stabilised/improved
(or low arterial lactate)**

**LT ≤ 7-15 days
AND
Worsening of organ failures
(or high arterial lactate)**

**LT > 7-15 days
AND
Organ failures stabilised/improved
(or low arterial lactate)**

**LT > 15 days
AND
Worsening of organ failures
(or high arterial lactate)**

Liver transplantation for acute-on-chronic liver failure

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Accepted manuscript

	EASL-CLIF	NACSELD	APASL-AARC	COSSH
Stage of liver disease	Cirrhosis	Cirrhosis	Chronic liver disease	HBV-related chronic liver disease
First episode of decompensation	Not necessarily	Not necessarily	Yes	Not necessarily
Precipitating event	Intra- or extrahepatic	Intra- or extrahepatic	Intrahepatic	Intra- or extrahepatic
Number of organ systems considered	6 systems	4 systems	2 systems	6 systems
Definition of liver failure	Bilirubin ≥ 12 mg/dl (INR=coagulation)	Not defined	Bilirubin ≥ 5 mg/dl or INR ≥ 1.5 or PA $< 40\%$	Bilirubin ≥ 12 mg/dl (INR=coagulation)
Liver failure required to define ACLF	No	No	Yes	No

Table 1. Main discrepancies regarding the definition of acute-on-chronic liver failure according to the four scientific societies. EASL-CLIF, European Association for the Study of the Liver - Chronic Liver Failure Consortium; NACSELD, North-American Consortium for the study of End-Stage Liver Disease; APASL-AARC, Asian Pacific Association for the Study of the Liver APASL-ACLF Research Consortium; COSSH, Chinese Group on the Study of Severe Hepatitis B.

Author and Publication Year	Study Period	Location	Study Type	LDLT or DDLT	n ACLF 1/2/3*	Criteria	MELD Score	1-Year Post-LT Survival ACLF 1/2/3*	Long-Term Post-LT Survival ACLF 1/2/3*
Deceased-donor liver transplantation									
Zhu et al. (2023)	2018-2020	China	Retrospective, Single centre	DDLT	75/64/73	EASL-CLIF	27 ± 8	93·3%/73·4%/60·3%	
Xia et al. (2022)	2015-2021	China	Retrospective, Single centre	DDLT	All grades: 162	EASL-CLIF	32 (27-38)	83%/83·2%/69·8%	3-year: 83%/80·3%/69·8%
Sundaram et al. (2022)	2018-2019	North America	Retrospective, Multi-centre	DDLT	61/74/77	EASL-CLIF	29	88·5%/87·8%/85·7%	
Cervantes-Alvarez et al. (2022)	2015-2019	Mexico	Retrospective, Single centre	DDLT	40/33/22	EASL-CLIF	25 ± 6	87·5%/97%/90·9%	6-year: 80%/93·9%/77·3%
Artzner et al. (2022)	2018-2019	Europe	Retrospective, Multi-centre	DDLT	ACLF-3: 98	EASL-CLIF	·	ACLF-3: 79%	
Goosmann et al. (2021)	2009-2014	Europe	Retrospective, Single centre	DDLT	All grades: 98	EASL-CLIF	32 (24-37)	-	5-year: 55·1%
Belli et al. (2021)	2018-2019	Europe	Retrospective, Multi-centre	DDLT	58/78/98	EASL-CLIF	34 (30-39)	1/3: 88·6%/78·9%	
Sundaram et al. (2020)	2004-2017	USA	Retrospective, UNOS registry	DDLT	ACLF-3: 2744	EASL-CLIF	41 (37-44)	ACLF-3: 82%	
Artzner et al. (2020)	2007-2017	Europe	Retrospective, Multi-centre	DDLT	ACLF-3: 152	EASL-CLIF	40 (37-40)	ACLF-3: 67·1%	
Agbim et al. (2020)	2006-2013	USA	Retrospective, Single centre	DDLT	50/32/19	EASL-CLIF	31 ± 7	86%/81%/74%	
Sundaram et al. (2020)	2004-2017	USA	Retrospective, UNOS registry	DDLT	8757/9039/7891	EASL-CLIF	33	89·5%/88·6%/80·6%	5-year: 75·2%/74·9%/67·7%
Sundaram et al. (2019)	2005-2016	USA	Retrospective, UNOS registry	DDLT	7375/7513/6381	EASL-CLIF	32 ± 6	89·1%/88·1%/81·8%	
Marciano et al. (2019)	2010-2016	Argentina	Retrospective, Single centre	DDLT	34/18/8	EASL-CLIF	27 (23-31)	82·3%/100%/62·5%	
Sundaram et al. (2019)	2002-2014	USA	Retrospective, UNOS registry	DDLT	ACLF-3: 2349	EASL-CLIF	40 (35-43)	ACLF-3: 79·8%	
Thuluvath et al. (2018)	2002-2016	USA	Retrospective, UNOS registry	DDLT	4330/3557/3556	EASL-CLIF	26 ± 11	88%/88%/83%	5-year: 74%/74%/70%
Huebener et al. (2018)	2009-2014	Germany	Retrospective, Single centre	DDLT	24/45/29	EASL-CLIF	35 (29-40)	3-month: 72·4%	2-year: 60·2%
Artru et al. (2017)	2008-2014	France	Retrospective, Multi-centre	DDLT	ACLF-3: 73	EASL-CLIF	40 (32-40)	ACLF-3: 83·6%	
Levesque et al. (2017)	2008-2013	France	Retrospective, Single centre	DDLT	68/42/30	EASL-CLIF	30 ± 8	76·5%/78·6%/43·3%	
Michard et al. (2017)	2007-2014	France	Retrospective, Single centre	DDLT	All grades: 55	EASL-CLIF	41 ± 9	60%	
Finkenstedt et al. (2013)	2002-2010	Austria	Retrospective, Single centre	DDLT	All grades: 33	APASL	27 (17-38)	87%	5-year: 82%
Xing et al. (2013)	2001-2009	China	Prospective, Single centre	DDLT	All grades: 133	APASL	25 (16-42)	75·9%	5-year: 72·1%
Living-donor liver transplantation									
Wang et al. (2021)	2002-2017	Taiwan	Retrospective, Single centre	LDLT	All grades: 112	APASL	28 ± 6	3-month: 97·3%	5-year: 92·9%
Lu et al. (2020)	2015-2019	Taiwan	Retrospective, Single centre	LDLT	All grades: 24	APASL	29 ± 10	92%	3-year: 92%
Yadav et al. (2019)	2014-2017	India	Retrospective, Single centre	LDLT	28/48/41	EASL-CLIF	31 ± 8	92·9%/85·4%/75·6%	
Bhatti et al. (2018)	2012-2016	Pakistan	Retrospective, Single centre	LDLT	43/15/2	EASL-CLIF	29 (20-42)	92%	
Lin et al. (2013)	2001-2009	Taiwan	Retrospective, Single centre	LDLT	All grades: 54	APASL	24	92·6%	

Table 2. Outcomes of studies evaluating liver transplantation for Acute-on-chronic Liver Failure (ACLF). APASL, Asian Pacific Association for the Study of the Liver; DDLT, deceased donor liver transplantation; EASL-CLIF, European Association for the Study of the Liver - Chronic Liver Failure Consortium; LDLT,

living donor liver transplantation; MELD, Model for End-Stage Liver Disease; UNOS, United Network for Organ Sharing. MELD, Model for End-Stage Liver Disease; UNOS, United Network for Organ Sharing. MELD scores are presented as mean \pm standard deviation or median (interquartile range), where available.
*Overall result across all grades of ACLF if individual grades not available

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