Liver transplantation for Acute-on-Chronic Liver Failure: Science or fiction?

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Abbreviations:
ACLF: acute-on-chronic liver failure; AD: acute decompensation; BT: bacterial translocation; CHE: cholinesterase; G-CSF: granulocyte-colony stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; HE: hepatic encephalopathy; HNA2: human non-mercaptalbumin-2; HRS: hepatorenal syndrome; IL: interleukin; INR: international normalized ratio; IP-10 (CXCL10): 10kDa interferon gamma-induced protein (C-X-C-motif chemokine 10); MELD: model for end-stage liver disease; NASH: non-alcoholic steatohepatitis; PBC: primary biliary cirrhosis; SI: systemic inflammation; RRT: renal replacement therapy; TNFα: tumor necrosis factor alpha.

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Abstract

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

Word count (max. 250): 170
Introduction

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

ACLF may occur at any phase during chronic liver disease, from compensated cirrhosis to refractory decompensation. Acutely decompensated cirrhosis has been found to be associated with high circulating levels of proinflammatory molecules, which may be increasing well before ACLF develops (3). In ACLF, this increase in inflammatory cytokines is more striking and correlates with the number of organ failures (4). In the last several years, evidence has emerged that ACLF may be treated with LT, since the post-LT survival may be similar to patients without ACLF. (5, 6) Yet, the selection of ACLF patients suitable for LT, timing of LT in the setting ACLF, and the role of expeditious LT remains unexplored. This review outlines the current evidence concerning these topics and suggests the design of a specific strategy for allocation of LT to patients with ACLF, taking into account contraindications.
Outcomes of acute on chronic liver failure

ACLF is present in 10-20% of the patients admitted for acutely decompensated cirrhosis, and develops in an additional 10% of patients during hospitalization (7). In a European study, the majority of patients with ACLF presented with alcohol-induced cirrhosis, though a precipitating event was identified only in 60% of patients (1). The overall 28-day transplant-free mortality ranges between 30% and 40%, underlying the need for urgent and aggressive medical treatment (1, 8). The CANONIC study developed the chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score and CLIF Consortium Organ Failure (CLIF-C OF) score (1, 9). One of the primary findings from this study was that three main risk factors from the patient's CLIF-SOFA score at enrollment are associated with high 28-day mortality rate: (1) the presence of 2 organ failures or more, (2) the presence of one organ failure when the organ that failed was the kidney, and (3) the coexistence of a single “non-kidney” organ failure with kidney dysfunction (ie, serum creatinine level ranging from 1.5 to 1.9 mg/dL) and/or mild to moderate hepatic encephalopathy (HE) (1). Therefore, it is not only the number of organ failures that determine short-term mortality, but also dysfunction of two organs, specifically the kidney and brain (Table 1). After its development, the course of ACLF may vary where a certain proportion of the patients improve, whereas in others the course may worsen. Data have shown, though, that the presence and grade of ACLF at 3-7 days from admission determines the short-term prognosis (Table 1) (1, 8, 10).

The usual scores used to assess mortality-risk in patients with cirrhosis, such as the MELD-Na, and Child-Pugh scores are strongly related to the development of ACLF and also predict survival in patients with ACLF (1, 11, 12). However, these prognostic models still miss important determinants of mortality among ACLF patients, such as HE in the MELD score and age and creatinine in Child-Pugh score. Additionally, neither of these models incorporates circulatory or respiratory failure, nor any biomarkers of systemic inflammation, which seem to correlate with outcomes in ACLF patients. Therefore, a new score was designed specifically to assess risk of mortality specifically in patients who have developed ACLF, known as the CLIF-C ACLF score. (5) The CLIF-C ACLF score includes baseline factors, not included in other scoring systems, but which are associated with short- and long-term mortality in the setting of ACLF, including age and white blood cell (WBC) count. (5) Taken together with the presence of CLIF-C OF-score, age and log-
transformed white blood cell count were found to be the best predictors of mortality and therefore were included to compute CLIF-C ACLF score.

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

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

Although many patients with ACLF undergo transplantation, neither the presence of ACLF nor ACLF-specific scores are used to allocate LT to patients on the waitlist. The prognosis of ACLF, however, is distinct from that of decompensated cirrhosis, which may explain why the traditional scores such as MELD and MELD-Na, which lack parameters assessing extrahepatic non-renal organ failure and systemic inflammation, do not fully reflect mortality in ACLF. The CLIF-C ACLF-Score and CLIF-SOFA may predict with up to 75% accuracy prognosis in ACLF better than MELD score (9), although similar to MELD in retrospective studies (20). Though many publications have outlined the high mortality associated with ACLF without LT (1, 21, 22), patients transplanted with ACLF have a higher rate of complications and a lower survival than patients transplanted without ACLF (5, 6, 23). Therefore, the question arises as to which patients with ACLF should be transplanted.

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

The presence of ACLF grade 3 should not be considered an absolute contraindication for LT. A large retrospective analysis of the UNOS database with more than 50,000 patients shows very clearly that LT improves outcomes in these patients (5). Similar results were obtained in different European countries evaluating retrospective and prospective cohorts (8, 22, 25).

Indeed, transplanted ACLF patients from the CANONIC study showed 80% survival in the first year (8) underlining the important role of offering LT to those patients. According to this study, patients with up to three organ failures, or CLIF-C ACLF score < 64, as well as those who show an improvement of ACLF grade in the short term should be considered for LT considering as they have poor non-transplant survival and relatively high post-transplant survival, with low post LT complication rate. (8) Multicenter studies with more granular data describe good prognosis after LT, even among patients with ACLF, but these results were obtained in the absence of active
gastrointestinal bleeding, hemodynamic instability, uncontrolled sepsis, and respiratory failure or mechanical ventilation, but without ARDS (6, 22).

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

Most studies investigating post-transplant outcomes of patients with ACLF have been performed in the context of deceased donor liver transplantation. Although living donor transplantation is used for ACLF in East Asia, including Korea, Japan, Taiwan, Hong Kong and India (28), there are few data about the outcome of transplantation performed in this context. Among 321 Asian patients with high-MELD who received living donor transplantation, the 5-year survival did not significantly differ between those with ACLF and those without (72.1% versus 81.8%) (29). However, in this study, the 5-year graft survival was significantly lower among patients of the ACLF-group than among those of the non-ACLF-group (70.5% versus 81.0%) (29). Together these findings indicate that studies should be performed on large series of patients who receiving living donor transplants for ACLF.

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

Due to the lack of availability of donor organs, LT is often considered to be contraindicated when the survival or quality of life after transplantation is lower than without transplantation. There is a general consensus that survival should be greater than 50% at 5 years, with an acceptable quality of life (30, 31). In the setting of ACLF, an additional consideration in the decision to proceed with LT exists, which is the precipitating event leading to ACLF may be also contraindications at the same time (32).

Active alcoholism was one of the main precipitants of ACLF in the CANONIC study. This is a controversial topic, since in many countries demonstration of abstinence for at least six months is the prerequisite for admission into the waitlist (33). It has been shown that well-selected patients with severe alcoholic hepatitis have a good outcome after liver transplantation, with survival ranging between 77-97%, and a return to harmful drinking of around 10-12.5% (33). There are several studies which provide evidence that certain patients who meet specific social and psychological requirements may benefit from an early LT in severe alcoholic hepatitis, with low likelihood of relapse (34-37). A recent study identified a score associated with sustained use of alcohol post-LT (38). The Sustained Alcohol Use Post-LT (SALT) score was composed by four variables assessing the drinking pattern of the patients at initial hospitalization (10 drinks per day: +4 points), prior rehabilitation attempts (multiple: +4 points) or alcohol-related legal issues (+2 points), and prior illicit substance abuse (+1 point), a SALT score of <5 had a 95% negative predictive value for sustained alcohol use post-LT (38).

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

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

Respiratory failure already plays an important role in the prognosis of decompensated cirrhosis, and in the CANONIC study similar activation of systemic inflammation in acute decompensated cirrhosis and ACLF patients was observed in the presence of respiratory failure (Figure 1). Although the management of respiratory failure may be similar in acute decompensation and ACLF (48), it may be a contraindication according to the majority of the experts, for transplantation in ACLF (51). Still recent data suggest that a degree of respiratory failure (PaO\textsubscript{2}/FiO\textsubscript{2} ≥150), especially when not due to pneumonia or acute respiratory distress syndrome, may be acceptable for LT with adequate outcome (22).

Among patients with acute decompensation, the transplant waitlist can be used as a “safety net” in the event that patients may be offered an organ due to an increase of their MELD-Na score. But the bigger question is the timing of liver transplantation in ACLF patients, who may die before reaching that point and/or the window of liver transplantation closes rapidly. Recognizing the relatively short window available to patients with more advanced grades of ACLF, the first pilot allocation system is being introduced in the UK for these patients. The new system will allocate organs to patients with ACLF as a priority, immediately after allocation to patients with acute liver failure and those with hepatoblastoma. It is expected that about one organ will be available in the UK each day for these high-risk patients. The patients that are eligible for this programme are cirrhotic patients that have unplanned admissions to ICU/HGU

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and have an ACLF grade consistently predicting a 28-day survival of less than 50%, i.e. those with ACLF Grade 3. Where patients with alcohol-related liver disease are being considered, the standard guidelines for acceptance of such cases will apply and it is not considered that alcohol itself was the precipitant of the ACLF. This pilot programme will be tested in about 30 patients and the a one-year survival of greater than 60% will be defined as a successful outcome. The programme is due to start in the third quarter of 2020.
Timing of liver transplantation

One of the primary challenges in transplantation of patients with ACLF, particularly ACLF-3, is the timing of transplantation. The published literature addressing this issue has consisted primarily of studies utilizing the EASL-CLIF definition of ACLF. Though all grades of ACLF are associated with greater mortality than decompensated cirrhosis, patients with ACLF-3 have a particularly high short-term mortality without transplantation and therefore would appear to gain the most from early LT (1). Therefore, one would expect that performing LT as early as possible would yield the greatest overall survival benefit. However, the potential advantages of rapid transplantation may also include improved post-transplant survival. In an analysis of the UNOS registry, greater 1-year survival probability was demonstrated when transplantation occurs in less than 30 days on the waiting list among patients with ACLF-3, compared to greater than 30 days (82.2% vs 78.7%) (5). Further analysis of this database revealed even greater post-LT survival when transplantation occurred within 14 days, and furthermore, the survival benefit increases with greater number of organ failures. Although patients with ACLF-2 did not see significant improvement when transplanted within 14 days of listing (89.5 vs 87.6%, p=0.053), greater post-LT survival was demonstrated among patients transplanted with three organ failures (85.6 vs 82.6%, p=0.012), four organ failures (80.9 vs 75.8%, p=0.007), and five organ failures (79.3 vs 67.2%, p<0.001) (52).

However, other studies have indicated that the benefits of transplanting a patient with ACLF as quickly as possible should be weighed against the benefits yielded by recovery of one or more organ failures prior to transplantation. A single-center proof-of-concept study revealed that patients transplanted after improvement of ACLF, defined as recovery of at least one organ system failure, yielded a superior 90-day post-transplant survival as compared to recipients transplanted with ACLF and similar to that of patients without ACLF prior to transplantation (53). In a larger registry study, 1-year post-transplant survival substantially increased in patients listed with ACLF-3 who improved to ACLF grades 0-2 (88.2%) versus those who remained at ACLF-3 at listing and LT (82.0%) particularly after recovery of circulatory failure, brain failure, or requirement of mechanical ventilation (54). This study also compared the effect of timing of transplantation versus improvement in organ failures on post-LT survival. The findings demonstrated that patients transplanted after 7 days on the waiting list but who improved from...
ACLF-3 to ACLF grades 0-2 at transplantation had greater post-LT survival than candidates who were transplanted within 7 days but remained at ACLF-3 from listing to transplantation (87.6 vs 82.7%, p<0.001) (54). It should be noted, however, that less than 25% of patients with ACLF-3 at listing improved to a lower grade of ACLF. Therefore, although it would be ideal to perform transplantation after organ failure recovery, this may not occur in the majority of candidates with ACLF-3.

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

Currently, for many patients with ACLF the only therapy is LT. Unfortunately, given the lack of available donor organs, patients may be at high risk of waitlist mortality before a suitable organ is available. Additionally, many centers may not offer transplantation to patients with multi-organ failure, due to the possibility of low post-transplant survival. Extracorporeal liver support (ECLS) may be an option to bridge to transplantation in these patients, either to sustain life until a donor organ is offered or to allow for recovery of organ system failures prior to transplantation. Ultimately, an effective ECLS system should perform three primary hepatic functions: to detoxify, to stimulate liver regeneration, and to prevent further injury to the liver (55). Several systems have been studied in clinical trials of patients with ACLF, including Molecular Adsorbent Recirculating System (MARS), Prometheus, and stem-cell treatment (55-60). However, to date artificial liver support has not been demonstrated to improve mortality in ACLF in prospective trials.
Conclusions

ACLF patients with specific criteria may benefit from expeditious transplantation, since ACLF has a greater waitlist mortality and similar post-LT mortality as Status 1A patients (60, 61). Indeed, the first question is whether the patient is suitable for liver transplantation in general (e.g. exclusion of malignancy, other severe conditions precluding transplantation) and therefore should be further considered. The role of active alcoholism in these patients should be addressed with great care and appropriate patients may benefit from special protocols using liver transplantation, similar as for severe alcoholic hepatitis. Close monitoring is important to identify the window of opportunity in ACLF patients and also to identify patients who are ineligible for liver transplantation. Finally, the decision of listing for liver transplantation maybe given in all ACLF patients, but expeditious transplantation should be considered especially in patients with ACLF grade II and III (Figure 2). As the data from retrospective studies of transplant in ACLF may be confounded by selection bias, prospective studies on ACLF and transplantation are urgently needed. Significant work has still to be done, but we must start somewhere.
References


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<table>
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<th>Condition</th>
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<th>At diagnosis of ACLF (1, 10)</th>
<th></th>
<th>3-7 days after diagnosis of ACLF (8)</th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Prevalence (%)</td>
<td>28-day mortality (%)</td>
<td>Prevalence (%)</td>
<td>28-day mortality</td>
</tr>
<tr>
<td>AD</td>
<td>No organ failure, or single non-kidney organ failure, creatinine &lt; 1.5 mg/dL, no HE</td>
<td>78.2</td>
<td>4.7</td>
<td>57.3</td>
<td>5.5</td>
</tr>
<tr>
<td>ACLF I</td>
<td>Single renal failure or single non-kidney organ failure, and creatinine 1.5–1.9 mg/dL or HE grade 1-2, or both</td>
<td>10.9</td>
<td>22.1</td>
<td>24.3</td>
<td>17.1</td>
</tr>
<tr>
<td>ACLF II</td>
<td>2 organ failures</td>
<td>7.5</td>
<td>32.0</td>
<td>20.5</td>
<td>33.9</td>
</tr>
<tr>
<td>ACLF IIIa</td>
<td>3 organ failures</td>
<td>1.9</td>
<td>68.0</td>
<td>25.0</td>
<td>33.9</td>
</tr>
<tr>
<td>ACLF IIIb</td>
<td>4 organ failures or more</td>
<td>1.4</td>
<td>88.9</td>
<td>36.8</td>
<td>96.0</td>
</tr>
</tbody>
</table>

*Adapted from references 1, 8, 10. AD denotes acute decompensation, ACLF acute-on-chronic liver failure, and HE hepatic encephalopathy.
<table>
<thead>
<tr>
<th>Acute precipitant or organ system failure</th>
<th>Management</th>
<th>Potential influence on the decision for LT in ACLF</th>
<th>Relative contraindication for LT in ACLF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active alcoholism or alcoholic hepatitis (33-38)</td>
<td>Assess psychosocial profile and personal behaviour</td>
<td>3-7 days after diagnosis of ACLF, SALT-score &lt;5</td>
<td>Severe uncontrolled psychiatric disorder, SALT-score ≥5</td>
</tr>
<tr>
<td>Infections (1, 22, 39-48)</td>
<td>Use broad-spectrum antibiotic coverage, and introduce empiric antifungals in patients not responding for 48 hours; use antibiotic prophylaxis in noninfected patients with ACLF</td>
<td>≥ 48 hours of control of the infection</td>
<td>Uncontrolled culture-positive bacterial infection, or controlled infection for less than 48 hours; uncontrolled HIV</td>
</tr>
<tr>
<td>Variceal hemorrhage (49, 50)</td>
<td>Use vasoconstrictors (terlipressin [not available in the US], octrotide), endoscopic treatment, and prophylactic antibiotics; prevent HE, use preemptive TIPS when indicated, use DANIS-stent when indicated</td>
<td>When bleeding is controlled and hemodynamics are stable</td>
<td>Refractory bleeding, hemodynamic instability despite vasoconstrictors</td>
</tr>
</tbody>
</table>

| Organ system failures | Respiratory failure | Apply standards in critical care, including use of low tidal volumes, | When improvement | PaO₂/FiO₂ <150 |
| Renal failure (1, 7, 8, 10) | and positive-expiratory pressure for adequate oxygenation of $\text{PaO}_2/\text{FiO}_2 \geq 150$ | Renal replacement therapy | When improvement of ACLF-grade at 3-7 days after diagnosis | CLIF-C ACLF-score > 64 persisting 3-7 days after diagnosis |
**Figure 1:** Heat-map showing the median levels of systemic inflammation markers at enrollment of patients with acute decompensation (A) and ACLF (B) from the CANONIC Study (1, 3). For the comparison, patients were divided into two groups according to the presence of respiratory failure. The magnitude of the levels is color-coded and the clustering for each marker with the rest of the markers is shown to the left of the heat-map. TNF, tumor necrosis factor; IL, interleukin; MCP-1, monocyte chemotactic protein 1; IP-10, 10 kDa interferon gamma-induced protein; MIP-1β, macrophage inflammatory protein 1-beta; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-1ra, interleukin-1 receptor antagonist protein; IFN, interferon; HNA2, human nonmercaptalbumin 2.

**Figure 2:** Proposed algorithm to evaluate patients with ACLF for regular listing and expeditious liver transplantation.
Figure 1

A

B

Color Key

-1 -1

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Figure 2

- Presence of any grade of ACLF
  - General contraindication for liver transplantation (malignancy, comorbidity, etc.)
    - Yes: Standard of care
    - No: Recent or active alcoholism within 6 last months
  - Daily assessment
    - No: Recovery from ACLF or ACLF grade 1
    - Yes: ACLF grade 2 and 3a
      - Consider expeditious transplantation, Bridging strategies
    - Special program
  - Recovery or improvement of organ failure
    - Bridging strategies
    - No: Futility of care
  - CLIF-C ACLF > 64, ARDS, uncontrolled infection, refractory shock or bleeding

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