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Chapter

Acute Decompensated Liver: When to Transplant?

Dipesh Kumar Yadav, Rajesh Kumar Yadav and Tingbo Liang

Abstract

Currently, liver transplant (LT) is only the effective treatment for an acute decompensated liver. Yet, a result of LT in the background of acute decompensated liver largely depends upon the cause of decompensation. Acute-on-chronic liver failure (ACLF) should not be confused with acute liver failure (ALF), where a patient with ACLF presents with a distinct clinical feature than ALF and often requires LT as the only definitive treatment option. However, ACLF patients are generally not listed for the emergency LT due to advanced age, ongoing sepsis, multiple organ failures and active alcoholism. Then again, about 40% of the patients with ALF recover spontaneously with medical care and hence do not need LT. In between these all perplexities and contentions, it's critical to comprehend the clinical course of liver failure. In addition, physicians should also understand when it is necessary to enlist a patient for LT and which patient are likely to get benefit from LT. Thus, utilizing a “golden window” time for LT before the development of multi-organ failure. In this chapter, we focus on the current situation of LT for ALF and ACLF and further discuss the current decision making strategies used to indicate LT in this difficult clinical scenario.

Keywords: liver transplant, acute liver failure, acute-on-chronic liver failure, decompensated liver

1. Introduction

 Decompensated liver or liver failure refers to the incompetence of the liver to accomplish its routine physiological functions. Generally, three forms of the liver failure have been outlined in the literature, i.e. acute liver failure (ALF), chronic liver failure (CLF) and more recently acute-on-chronic liver failure (ACLF) [1, 2].

 ALF is described as an acute insult of the liver with encephalopathy and progressing worsening of the synthetic function of the liver (International normalized ratio (INR) ≥ 1.5) in a patient without cirrhosis or prior liver disease within 26 weeks of the onset of jaundice [3]. Whereas, CLF is broadly referred to the liver failure in end-stage liver diseases in the presence of cirrhosis. Cirrhosis is a dynamic chronic liver disease characterized by the histological progression of regenerative nodules encased by the fibrous tissues in response to chronic liver injury, that results to portal hypertension and liver failure [4]. Traditionally, the development of cirrhosis has been divided into two stages: 1. Compensated cirrhosis and 2. Decompensated cirrhosis [5]. Particularly,
compensated cirrhosis endures between the onset of cirrhosis to the first considerable complication, that usually takes more than 10 years. However, most of the patients are usually asymptomatic or with minor complications. Further, the progression of compensated cirrhosis to decompensated cirrhosis occurs when there is development of ascites, variceal hemorrhage and/or hepatic encephalopathy and it is associated with a short-term survival. Nevertheless, the concept of the cirrhosis as an irreversible disease has been changed to the reversible disease, where the decompensated cirrhosis still can be reversed to the compensated cirrhosis or even to the pre-cirrhotic stage if the underlying disease is treatable [6]. Hence, it is apparent that the patients seldom dies as a result of an end-stage irreversible demolition of the liver. Relatively, in many patients, the reason for the death is an acute crumbling in their clinical condition advanced by a causative event, recently termed as ACLF [2]. ACLF is a syndrome characterized by an acute decompensation of the cirrhosis associated with the organ/system(s) failures and has a high 28 day mortality rate of 30–40% [7]. ACLF should not be confused with ALF, where a patient with ACLF present with a distinct clinical feature than ALF, and routinely require a different management approach. Liver transplant (LT) remains to be the only definitive treatment option for the patients with ACLF. However, the ACLF patients are generally not listed for an emergency LT due to an advanced age, ongoing sepsis, multiple organ failure, and active alcoholism. On the other hand, about 40% of the patients with ALF recover spontaneously with the medical care and hence do not need LT [8]. Therefore, it is extremely important to understand the clinical presentation and timing of the liver failure, so that the transplant surgeons can perceive when it is necessary to proceed with LT and which patients are likely to get benefit from LT.

In this chapter, we focus on the current scenario of LT for ALF and ACLF and further discuss the current decision making strategies used to indicate LT in this challenging clinical scenario.

2. Acute liver failure

ALF remains a rare condition that develops most commonly in the patients without pre-existing liver disease [9]. However, ALF is the matter of a concern for an apparent reason that it is typically associated with a high death rate. Often, the possible causes and precise mechanism of ALF are unspecified and uncertain [10]. Following the major hepatectomy, the patients with or without underlying liver disease, may typically develop a clinical syndrome similar to that of ALF. The clinical presentation is similar to that of the “small for size syndrome” following LT. These disorders are not considered inside the sphere of ALF, but rather are highlighted in some databases of ALF, for example, the European Liver Transplant Registry (ELTR). Moreover, the major liver injury has also been incorporated in ALF databases; however, it is not a cause of ALF except if there is loss of blood supply. Similarly, acute liver injury (ALI) should also be further differentiated from ALF, where the patients develop coagulopathy without vary in their level of consciousness.

Worldwide, viral hepatitis infection accounts for most cases of ALF. Where, hepatitis A and E are frequent causes in developing nations, while hepatitis B is a prevalent cause in some Asian and South American countries [11–13]. However, drug-induced ALF, particularly paracetamol induced ALF represents roughly half of the cases in the developed nations [14]. Moreover, ALF may likewise be diagnosed in the patients who earlier undiagnosed with Wilson’s disease, vertically transmitted hepatitis B infection and autoimmune hepatitis, in whom concealed cirrhosis might
be present, given the illness has been perceived for less than 26 weeks [15]. Then
again, the patients with an acute alcoholic hepatitis, regardless of whether perceived
for less than 26 weeks are considered to have ACLF since most have a protracted
history of an excessive alcohol intake. ALF is commonly subdivided into hyperacute
(<7 days), acute (>8 and <28 days), and subacute (>29 days and <26 weeks) contingent
upon the time slipped by between the appearance of jaundice and progression
of encephalopathy [16]. Nevertheless, the legitimate cut-off value of INR to define
different subtype of ALF has not been documented yet.

The outcome of ALF is tough to predict. A few patients with ALF have fulminant
progression, causing death without LT within a few days; others have fulminant
progression of 2–4 weeks, and some patients even have an extended progression of
1–3 months. As stated earlier, the full recovery of damaged liver is conceivable. Thus,
around 40% of the patients with ALF may recover completely without the need of LT
[8]. Nonetheless, LT is shown to be a highly effective treatment for ALF where a mor-
tality rate has been dropped down to 30% from 80% [17]. Despite that, a few issues
still need to be taken into consideration while listing the patient with ALF for an
emergency LT. 1. The hazard of LT for the patients who may recover spontaneously.
2. The hazard of not providing LT for the patients who really need it. 3. The survival
benefit of the critically ill patients after LT.

2.1 Prognostic models and criteria for the selection of the patients with ALF for LT

Survival of the patients without LT varies upon the cause and subtypes of ALF
[16]. In other words, the lessened the time spell between the commencement of
jaundice and encephalopathy the better the prognosis. However, subacute liver
failure where hepatic encephalopathy often develops just weeks after the beginning
of jaundice has an especially low transplant-free survival and has a lower chance of
spontaneous recovery in comparison to that of the hyperacute ALF [18]. In a study
series of 300 consecutive ALF patients revealed that, ALF due to paracetamol and
hepatitis A had an over 60% transplant-free survival rate, which was higher than
that of ALF due to an idiosyncratic drug reaction, autoimmune hepatitis, hepatitis
B virus, Wilson’s disease, Budd-Chiari syndrome, and ALF due to an unknown
cause [19]. Not too surprisingly, it has been found that the patients with lower
grades of encephalopathy (Table 1) are more likely to have spontaneous recovery
[20]. Additionally, it has also been revealed that the patients aged less than 10 or
more than 40 years may have a lower probability of spontaneous recovery com-
pared to those amidst these ages [19]. Furthermore, several other variables, for
example gender, prothrombin time, renal function, Alpha-fetoprotein, arterial
pH, factor V, serum lactate level, INR, liver biopsy, arterial ammonia level, and cell
death marker level (CK 18/M65/M30) have been utilized to foresee the likelihood
of recovery [21–24].

The choice to continue with LT relies on the likelihood of unconstrained hepatic
recovery. Nonetheless, the objective is to enhance the organ allocation system and
accurate identification of the patients who are probably to get benefited from LT from
those who are apparently going to recover spontaneously. Thus, avoiding the need of
lifelong immunosuppressant in those patients who are supposedly to recover without
LT. Additionally, reliable prognostic criteria are needed to make decisions on the
proper timing of LT. Assuming that LT is performed too early, it might be performed
when it is not needed, and if LT is delayed, there might be a higher risk of a poor
outcome due to worsening condition of the patient.
Conditions such as hypoxic hepatitis, liver ischemia following liver trauma or liver surgery, haemophagocytic lymphohistiocytosis (HLH) precipitated by viral or fungal infections or hematological malignancy, and pregnancy related ALF are not an indication for emergency LT [18]. ALF may recover completely once the underlying causes are treated. However, in a condition like an autoimmune hepatitis patients should be listed for an emergency LT if the ALF fails to improve within 7 days [18]. Thus, the clinical skill of a doctor is important to make the proper decisions whether LT or other medical treatment is required in the above conditions.

Several prognostic models (Table 2) have been developed to predict the outcome and prognosis in the patients with ALF. The most broadly used criteria is the King’s College Criteria for choosing the patients for LT [10, 15, 20, 25, 26]. Moreover, the Model for End-Stage Liver Disease (MELD) score, which is utilized to anticipate mortality in the patients with chronic liver disease, has additionally been tested to the patients with ALF [26]. Some other scores that may likewise anticipate mortality in the patients with ALF incorporates the Sequential Organ Failure Assessment (SOFA score) [27, 28], the Clichy criteria [26, 29, 30], Acute Physiology and Chronic Health Evaluation II (APACHE II) score [31], Acute Liver Failure Early Dynamic model (ALFED) [32], and the Acute Liver Failure Study

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mental status</th>
<th>Asterixis</th>
<th>Neurological findings</th>
<th>EEG findings</th>
<th>Spontaneous recovery from ALF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal; potentially mild decrease in intellectual ability and coordination</td>
<td>Absent</td>
<td>Normal; if impaired psychomotor testing, consider minimal hepatic encephalopathy (MHE)</td>
<td>Normal</td>
<td>65–70%</td>
</tr>
<tr>
<td>1</td>
<td>Mild lack of awareness; hypersonnia, insomnia, or inversion of sleep pattern. Euphoria, depression, or irritability; mild confusion</td>
<td>May be present</td>
<td>Impaired addition or subtraction</td>
<td>Usually normal</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Lethargic; moderate confusion</td>
<td>Present</td>
<td>Disoriented; inappropriate behavior; slurred speech</td>
<td>Abnormal</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Somnolent but arousable; gross disorientation; bizarre behavior</td>
<td>Present</td>
<td>Muscular rigidity and clonus; hyperreflexia</td>
<td>Abnormal</td>
<td>40–50%</td>
</tr>
<tr>
<td>4</td>
<td>Coma</td>
<td>Absent</td>
<td>Abnormal</td>
<td>&lt;20%</td>
<td></td>
</tr>
</tbody>
</table>

ALF, acute liver failure.

West-haven criteria for hepatic encephalopathy (HE).

Table 1.
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<table>
<thead>
<tr>
<th>Criteria</th>
<th>Prognostic factors affecting outcome of patients</th>
<th>Sensitivity and Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clichy-Villejuif</td>
<td>• Coma and confusion (encephalopathy grade 3 or 4) and factor V &lt; 20% of its normal value in patients under 30 years  or  • Coma and confusion (encephalopathy grade 3 or 4) and factor V &lt; 30% of its normal value in patients over 30 years</td>
<td>75% and 56% for Paracetamol induced ALF; 69% and 50% for non-Paracetamol induced ALF</td>
</tr>
<tr>
<td>King's College Hospital (KCH) criteria</td>
<td>Non-Paracetamol: • INR &gt;6.7;  or  • Any three of the following:  • Drug toxicity, regardless of whether it was the cause of ALF  • Age &lt; 10 or &gt; 40 years  • Jaundice to coma interval &gt; 7 days  • Bilirubin &gt;300 μmol/L  • INR &gt;3.5  Paracetamol: • Arterial pH &lt;7.3, or lactate &gt; 3 μmol/L after adequate volume resuscitation  or  • Encephalopathy grade 3 or 4 + creatinine &gt;300 μmol/L + INR &gt;6.5</td>
<td>58% and 74%</td>
</tr>
<tr>
<td>MELD score</td>
<td>• 10 × (0.957 LnCreatinine [mg/L] + 0.378 LnTotal Bilirubin [mg/dL] + 1.12 LnINR + 0.643)  MELD, Model for End-Stage Liver Disease.</td>
<td>79% and 71% for non-Paracetamol induced ALF</td>
</tr>
<tr>
<td>CK18/M65 MELD score</td>
<td>• 10 × (0.957 LnCreatinine [mg/L] + 0.378 LnM65 [U/μl] + 1.12 LnINR + 0.643)</td>
<td>81.3% and 82.3%</td>
</tr>
<tr>
<td>ALF Early dynamic model (ALFED)</td>
<td>• ALFED score ≥ 4 on day 3</td>
<td>87.3% and 89.5%</td>
</tr>
<tr>
<td>Acute Liver Failure Study Group (ALFSG) index</td>
<td>• Admission coma grade  • INR  • Bilirubin  • Phosphorus  • log10 value of the apoptosis marker cleaved cytokeratin-18 (M30)</td>
<td>85.6% and 64.7%</td>
</tr>
</tbody>
</table>

Table 2.
Commonly used criteria as prognosis indicators in acute liver failure (ALF).

Group (ALFSG) index [33]. Sadly, none of these prognostic models have been found to be accurate. However, urgent LT is indicated in ALF where prognostic models suggest a high likelihood of death.
3. Acute-on-chronic liver failure

In the past ACLF has generally been used in critical care units to contemplate the patients who are on an artificial liver support a bridge to LT. As the name implies, the main concept in ACLF is an acute decompensation of the liver in a patient with chronic liver diseases and is associated with a high short-term mortality within 28 days [7]. Moreover, it is further characterized by hepatic and/or extrahepatic organ failure(s) [7, 34]. The pathophysiology of ACLF is yet largely not clear. Intense systemic inflammation and oxidative stress are considered to play a major role in the progression of the syndrome [35]. It has also been found that some patients with ACLF may recover with medical care to the state before onset of ACLF; and hence, such patients may not need emergency LT [36]. According to the CANONIC database, ACLF resolved or improved in 49.5% of the patients with medical treatment [37]. However, the prognosis is critical in the patients with no signs of improvement, and it is recommended that all the patients should be listed for LT before the development of multi-organ failure [36, 37]. Thus, these patients have a “golden window” period for LT before the development of extrahepatic organ failure(s) [38].

Numerous definitions of ACLF have been proposed [39, 40]; however, none of the definitions has acquired a global acceptance. The two most generally acknowledged ones are from an Asian Pacific Association for the Study of the Liver (APASL) [1] and the European Association for the Study of the Liver (EASL) Chronic Liver Failure (EASL-CLIF) consortium [2].

According to APASL consensus definition, ACLF can be defined as “an acute hepatic injury with an evidence of jaundice (a serum bilirubin of $\geq 5$ mg/dl or $\geq 85 \mu$mol/l) and coagulopathy (an INR of $\geq 1.5$ or prothrombin activity of $<40\%$) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease, i.e. with or without cirrhosis and is associated with a high short-term mortality within 28 days.” [1] Criteria based on APASL definition, 90-day mortality is reported to be 13.1%. However, the APASL definition of ACLF had been developed on a speculative rather than the experimental basis.

The EASL-CLIF Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study establish diagnosis of ACLF in the presence of organ failure as defined by the CLIF-Sequential Organ Failure Assessment (SOFA) score (Table 3) [41]. EASL-CLIF defines ACLF as “an acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event [41] (Table 4) and associated with an increased mortality at 3 months due to multisystem organ failure” [2]. Currently, the time for the mortality has been defined by reducing to 4 weeks [42]. Overall, 28-day and 90-day mortality, according to EASL-CLIF criteria were reported to be 33% and 51%, respectively [2]. The EASL-CLIF definition is relevant to the patients with cirrhosis only (preferentially compensated or decompensated to represent chronic liver disease), in contrast, the APASL definition incorporates the patients with both cirrhotic and non-cirrhotic liver disease (yet not decompensated cirrhosis as interpreting “chronic”). Moreover, the EASL-CLIF definition also incorporates extrahepatic organ failures which are excluded by the APASL definition. Likewise, the precipitating events in the APASL definition are mainly hepatic in origin, though the EASL-AASLD definition incorporates sepsis [43]. The inconstancy in the standard definition and lack of an established management protocol for the ACLF patients further creates controversy among the physicians and surgeons.

As per EASL definition, the patients of ACLF are divided into four grades based on the numbers of organ failure (Table 5). Organ failures are a critical piece of prognosis.
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When to Transplant?

In the patients with ACLF and with a higher number of organ failures (higher ACLF grades) the prognosis is poor [2]. It was found that the course of ACLF varies fast i.e. improves or deteriorates. Gustot et al. in his study demonstrated that the grade of ACLF can change unreasonably fast within 48 h in 40% of the patients, fast in between 3 and 7 days in approximately 14.7% of the patients and slowly in 8–28 days in 14.7% of the patients. Additionally, they also found that the ACLF grade at day 3–7 was better to anticipate the prognosis than the ACLF grade at the time of admission. Moreover, the ultimate ACLF grade remained the same in 81% of the patients after day 3–7 [37]. The characterization and subgroup division of ACLF on the basis of numbers of organ failure have led to an enhanced prognostic evaluation and provides a premise for determining selection criteria for LT and evaluation of those patients which may recover spontaneously with medical treatment only.

Table 3.
Organ failures and CLIF-C ACLF subscores.

<table>
<thead>
<tr>
<th>Organ/system</th>
<th>Subscore 1</th>
<th>Subscore 2</th>
<th>Subscore 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver (bilirubin, mg/dl)</td>
<td>&lt;6</td>
<td>≥6 to &lt;12</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Kidney (creatinine, mg/dl)</td>
<td>&lt;2</td>
<td>&gt;2 to &lt;3.5</td>
<td>≥3.5 or renal replacement therapy</td>
</tr>
<tr>
<td>Brain (West-Haven grade for hepatic encephalopathy (HE))</td>
<td>Grade 0</td>
<td>Grade 1 or 2</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Coagulation (INR)</td>
<td>&lt;2.0</td>
<td>≥2.0</td>
<td>INR ≥ 2.5</td>
</tr>
<tr>
<td></td>
<td>and &lt; 2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulation (mean arterial pressure)</td>
<td>≥70 mm/Hg</td>
<td>&lt;70 mm/Hg</td>
<td>Use of vasopressors</td>
</tr>
<tr>
<td>Respiratory (PaO2/FiO2)</td>
<td>&gt;300</td>
<td>≤300</td>
<td>≤200</td>
</tr>
<tr>
<td>Or</td>
<td>or</td>
<td>and &gt; 200</td>
<td>or</td>
</tr>
<tr>
<td>SpO2/FiO2</td>
<td>&gt; 357</td>
<td>or</td>
<td>≥214</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>and ≤ 357</td>
<td></td>
</tr>
</tbody>
</table>

Note: Organ failures cutoff is highlighted in bold letters. Grade ACLF 1: patients with single kidney failure, patients with non-renal organ failure plus renal dysfunction (creatinine 1.5–1.9 mg/dl) and/or brain dysfunction (grade 1–2 HE). Grade ACLF 2: patients with 2 organ failures. Grade ACLF 3: patients with 3 or more organ failures.

Table 4.
Precipitating events for acute-on-chronic liver failure (ACLF).

<table>
<thead>
<tr>
<th>Hepatic factors</th>
<th>Extrahepatic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flare-up or exacerbation of Hepatitis B virus infection</td>
<td>Bacterial infection (Sepsis)</td>
</tr>
<tr>
<td>Active alcoholism</td>
<td>Gastrointestinal bleeding</td>
</tr>
<tr>
<td>Superimposed Hepatitis A virus or Hepatitis E virus infections</td>
<td>Surgery</td>
</tr>
<tr>
<td>Drug-induced liver injury (DILI)</td>
<td>Others non-identifiable factors</td>
</tr>
<tr>
<td>Flare-up of autoimmune hepatitis or Wilson’s disease</td>
<td></td>
</tr>
<tr>
<td>Transjugular intrahepatic portosystemic shunt (TIPS)</td>
<td></td>
</tr>
</tbody>
</table>

3.1 Prognostic models and criteria for the selection of the patients with ACLF for LT

It is critical to look at the course of ACLF, fail to improve organ(s) failure, despite maximal supportive treatment, especially by the day 3–7, is related to the
bad prognosis, leading to the futility of care or consideration of an option for LT [39]. However, LT should not be done in a patient who may recover with medical treatment, and on the other hand, early LT should be considered in a patient with worsening or no improvement with the medical treatment before the development of multi-organ failure, thus considering the golden window period for LT [44].

Several prognostic models have been proposed in the last few years to better foresee the outcomes and prognosis of the patients with ACLF which includes, CLIF-C OF, CLIF-SOFA, SOFA, MELD, MELD-Na, and CTP scores [45].

As reported by CANONIC, the original grade of ACLF, the clinical course of ACLF, and a CLIF-C ACLF score (CLIF-C ACLF score combined CLIF-OF score with age and WBC count, calculator at www.efclif.com) appeared to precisely project the outcomes [2, 46]. CLIF-C ACLF score of up to 30 are steady with spontaneous recovery and the patients ought to have sequential evaluation regularly to decide if they are recovering. Moreover, with a score between 30 and 65, the patient is not likely to survive without LT; thus, such patients should be listed for an emergency LT without any delay taking other co-morbidities into the consideration for better outcomes. However, CLIF-C ACLF score over 65 brings up an issue of the futility to transplant and the secession of ongoing treatments [41]. In a study by Jalan et al. the CLIF-C ACLF score performed better when it was compared with the MELD, MELD-Na, and CTP scores [46].

In a recent study by Fangyuan et al. the group developed an HINAT ACLF model based on the APASL definition for ACLF due to hepatitis B reactivation, which includes five independent risk factors: Hepatic encephalopathy, international normalized ratio, neutrophil-lymphocyte ratio, age, and total bilirubin. According to this model, with the cutoff value of 4.6 for the HINAT ACLF score, the sensitivity and the specificity were 82.0% and 74.5%, respectively. Further suggesting that the performance of the HINAT ACLF score was significantly better than that of CLIF-C OF, CLIF-SOFA, SOFA, MELD, MELD-Na, and CTP scores [47].

Up to this point, MELD, MELD-Na and CTP scores, have been used to evaluate the prognosis of cirrhotic patients, with ACLF. However, these scores have limited value for foreseeing the prognosis in the ACLF patients, as these scores do not

<table>
<thead>
<tr>
<th>ACLF grade</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ACLF</td>
<td>Patients who either:</td>
</tr>
<tr>
<td></td>
<td>• Do not have any organ failure</td>
</tr>
<tr>
<td></td>
<td>• Have a single organ failure that does not involve the kidneys with a serum creatinine level &lt; 1.5 mg/dl and no hepatic encephalopathy</td>
</tr>
<tr>
<td></td>
<td>• Have a single brain failure with a serum creatinine level &lt; 1.5 mg/dl</td>
</tr>
<tr>
<td>ACLF grade 1</td>
<td>Patients with one of the following:</td>
</tr>
<tr>
<td></td>
<td>• Single kidney failure</td>
</tr>
<tr>
<td></td>
<td>• Single liver, coagulation, circulatory or respiratory failure that is associated with a serum creatinine level 1.5–1.9 mg/dl and/or grade 1 or grade 2 hepatic encephalopathy</td>
</tr>
<tr>
<td></td>
<td>• Single brain failure with a serum creatinine level 1.5–1.9 mg/dl</td>
</tr>
<tr>
<td>ACLF grade 2</td>
<td>Two organ failures</td>
</tr>
<tr>
<td>ACLF grade 3</td>
<td>Three or more organ failures</td>
</tr>
</tbody>
</table>

Table 5.
Grades of acute-on-chronic liver failure (ACLF) based on the numbers of organ failure and types of organs.
incorporate all the extrahepatic organ failures, which holds a critical effect on the prognosis of the ACLF patients.

In addition to the above prognostic models and scoring systems, various biomarkers have been identified that are found to reflect liver injury and multi-organ failure. These biomarkers might be of value in early diagnosis and progression prediction of ACLF if they can be incorporated with the CLIF-C ACLF score. Hyponatremia has appeared to have an independent prescient impact on 90 days survival [48] and copeptin concentrations in blood plasma showing changes in vasopressin level have appeared to ameliorate the ability of the CLIF-C ACLF score [49]. Additionally, urinary neutrophil gelatinase-associated lipocalin (N-GAL), plasma S100A8/A9 and soluble CD163 have also been shown to be increased in ACLF and correspond with the prognosis [50–52]. Apart from the above prediction models, the liver biopsy has also been found to be helpful in predicting the outcome and poor prognosis of ACLF, and further need for an early LT in these patients [53].

4. Liver transplantation in an acute decompensated liver failure

LT remains to be potentially the best treatment option, with better outcomes for patients with an acute decompensated liver failure. However, as stated earlier in this chapter, it is important to understand the clinical presentation of liver failure, where about 40% of the ALF patients show response to medical treatment and recover spontaneously and may not need LT. On the other hand LT remains to be the only definitive treatment option for the patients with ACLF.

4.1 Liver transplantation in ALF

LT has successfully reduced the mortality rate and improved overall survival in the patients with ALF, yet nearly 30% of the patients have to accept death without LT [54]. Outcomes of LT for ALF vary largely between different geographical regions and underlying etiologies behind ALF, where one-year survival ranges between 74% and 84% [54]. Regardless of this reality, results are better contrasted with a 64% oneyear survival depicted in the patients in ICU before LT, and to 54% seen in the patients on mechanical ventilation at the time of listing for LT [14, 55]. Most deaths for the patients with ALF are reported within the first 3 months of LT, generally because of neurological complications, multi-organ failure, and sepsis [56–58]. Additionally, efforts to identify the risk factors have been made, according to a study, recipient age above 50 years, history of life support, body mass index (BMI) above 30 kg/m², and serum creatinine of more than 2.0 mg/dL were the factors associated with a poor outcome [57]. Additionally, this study revealed that 5-year survival was significantly lower i.e. 42% for those patients meeting all these four factors compared to those with none i.e. 81% [57].

LT for ALF is most of the time and always done in an emergency situation. Usually, it is conceivable to transplant the ALF patient within 72 h after including the patient to the LT waiting list. However, due to the emergency situation, the likelihood of getting the best liver graft is minimized. In such situations, most of the time marginal grafts from the cadaveric donor are used as an option. It has been demonstrated that the utilization of these high-risk grafts may deleteriously affect post-transplant results and patient survival [59]. Apart from cadaveric LT living donor liver transplant (LDLT) is also commonly used, and the outcome of LDLT in the patients with ALF is
found to be comparable to that of cadaveric LT [60]. Additionally, ABO-incompatible LT has also been tried out with a better survival outcome as compared with ABO-compatible LT. Indeed, ABO-incompatible LT has been found to be associated with a higher incidence of an antibody mediated rejection, Cytomegalovirus infection and biliary complications [61].

In ALF, the liver has the potential to regenerate by replication and differentiation of dormant hepatocytes and cholangiocytes [62] and thus the patients may recover without the need of a LT. Based on this, the concept of auxiliary partial orthotopic liver graft (APOLT) has been developed, where part of the native liver of the patient is left after performing a partial heptectomy and a partial liver graft is transplanted in an orthotopic position [63]. In this way, the transplanted graft provides hepatic support to the patients while the native liver regenerates and recovers. Once the native liver returns to normal function, the dose of an immunosuppressant can be reduced slowly and finally withdrawn, further leading to the atrophy of the transplanted liver graft [64, 65]. However, the strategy of APOLT is challenging with the higher incidence of post-transplant complications [18, 66]. The native liver may not recover or regenerate significantly and may take a long time which depends upon multiple factors [66]. Therefore, use of APOLT should be limited to the patients with a high potential of liver regeneration, children, young adults, ALF due to hepatitis A virus and paracetamol poisoning [18, 66, 67]. Additionally, APOLT is not suitable for those patients with a high risk of brain death, high grade of hepatic encephalopathy, hemodynamically unstable patients who are on a higher dose of inotropes, or when ALF has advanced to a toxic liver syndrome [18, 66, 68].

4.2 Liver transplantation in ACLF

Taking LT for ACLF into consideration, most of the studies have indicated good results and equivalent survival rates in the patients transplanted for no ACLF [37, 69–73]; however, most of the earlier studies have not incorporated the patients with a high grade of ACLF i.e., with multi-organ failure. In the other studies, a poor outcome has been reported in the patients transplanted for the higher grades of ACLF [74–76], yet it still proves to be better than the survival rate of the patients without LT. In a similar context, a study by Gustot et al. demonstrated a survival rate of 80.9% at a half-year in the patients with ACLF grade 2 and 3, when contrasted with 10% in comparable grades of the ACLF patients who could not undergo LT [37]. Similarly, recent studies demonstrated a survival rate of >80% in the patients with ACLF grade 3 when contrasted with 7.9% in the controls, further suggesting a quick decision for LT to avoid high risk of mortality [74, 77].

It has been seen that the patients with ACLF showing development within 3–7 days are more likely to recover spontaneously [37, 38]. As reported by the CANONIC database, ACLF resolved or improved in 49.5% of patients with medical treatment. The resolution rates were 54.5%, 34.6% and 16% for ACLF grade 1, 2 and 3 respectively [37]. Additionally, the patients who fail to improve or with ongoing sepsis or multi-organ failure should immediately be considered for an early LT. However, precautions should be taken for the patients with respiratory failure and concomitant infection with multi-drug resistant organisms, due to risk of a higher rate of mortality and morbidity after LT [36, 77]. As of the dynamic nature of disease, the patients showing
signs of the improvement in an early stage course of the disease may worsen later; thus, these patients should be monitored closely and listed for an early LT whenever required. Studies should focus on developing an ideal prognostic score, considering an extrahepatic organ failure, is needed to prioritize organ allocation on the waiting list, subsequently, to diminish delisting and mortality on the waiting list.

In the era of an organ shortage, living donor liver transplantation (LDLT) is the alluring choice with comparable results to the deceased donor liver transplantation (DDLT) in the high volume centers. Most of the LDLT related studies are carried out in Asian countries. However, it is not so famous in Western countries due to a higher rate of complications associated with it compared to DDLT [78–80]. Apart from this, the possibility of death of the donors and donor related complications clarified why LDLT has dropped in Western nations in the course of recent years [81, 82]. In a study from Hong Kong by Duan et al. reported, LDLT for the ACLF patients had a comparable result to DDLT in ACLF patients. Moreover, this study, concluded that the liver graft did not affect the outcome, where the overall 5-year survival rate was 74% for the LDLT for the ACLF patients [73].

Nonetheless, the objective of LT is not just to guarantee the patient’s survival, yet additionally to offer an adequate quality of life. Sadly, the estimation of a quality of life in the general LT recipients, especially in the ACLF patients before LT, has not been thoroughly examined. For instance, stage 3 to 4 chronic kidney disease is developed in around 70% of the transplanted patients, with an increasing risk of end-staged renal disease needing a long-term hemodialysis or renal transplant within the initial 10 years after LT, that range somewhere between 3% and 9% [83, 84]. It has been found that, renal impairment is frequently encountered in the ACLF patients prior to LT, as is considered as an essential factor for the chronic kidney disease after LT [85]. Thus, the prevalence of end-staged renal disease after LT in the ACLF patients is as of now obscure and could enormously influence the post LT quality of life. Subsequently, a large database study is required on a long-term survival and quality of life after LT, not exclusively to affirm the prognosis of ACLF after LT, yet in addition to characterize rigorous selection benchmark that assist a good quality of life after LT.

5. Bridging to liver transplantation using an artificial liver support

In the past few decades, artificial liver support devices were developed to the point of being utilized as a supportive therapy option until LT (bridge to transplantation) and/or hepatic regeneration (bridge to recovery). The most commonly used devices are the Molecular Adsorbent Recirculating System (MARS), the Fractionated Plasma Separation, the Single-Pass Albumin Dialysis System (SPAD), and the Adsorption system [86]. However, it is still not clear that artificial liver support systems can help to bridge the patients with an acute decompensated liver to LT by eliminating toxins and enhancing liver functions [87, 88]. A meta-analysis of 12 randomized controlled trials utilizing different bioartificial liver support devices did not find a significant difference in the mortality rate when compared to the standard medical therapy [89, 90]. Nonetheless, a meta-regression, recommended that their impact rely on the type of liver failure. A 33% decrease in mortality was seen in the patients with ACLF, while no significant advantage was identified in those with ALF [90]. In contrary to this, a recent meta-analysis concluded that MARS and SPAD aid recovery of ALF [88].
6. When and whom to transplant?

It is important to identify those patients who may die without LT and those who may have a chance of spontaneous recovery. Thereby, dodging the need for lifelong immunosuppressant in the patients who are supposedly to recover without LT, and acting early for those who need LT. The early use of the selection criteria for LT in case of ALF or ACLF is mandatory in all the patients at the time of admission. Taking consideration of the dynamic nature of disease, all patients should be monitored closely and should be re-assessed time to time with the available prognostic criteria for any improvement or deterioration in the patient’s status as discussed earlier in this chapter. Additionally, all patients presenting with an acute decompensated liver failure should be listed for an emergency or early LT to avoid any small margin of medical error, and thereby utilizing the “golden window” period for LT before the development of multi-organ failure (Figure 1).

LT is absolutely contraindicated in the patients with irreversible brain injury. Other conditions like vasoplegic shock with an increasing demand of vasopressor and uncontrolled ADRS are considered as a relative contraindication. Whereas, the bacteraemia is not considered as a contraindication providing that they can be treated with proper antibiotics. The concept of “Too Sick To Be Transplanted” is getting more popular in the recent years, considering the shortage of organs, the potential advantage of LT in the ALF or ACLF patients should likewise be adjusted against the requirement for proportioning of an insufficient resources [91, 92]. Similarly, the patients with alcohol-related liver disease (ARLD) should also be evaluated carefully for LT in light of constrained organ supply and the hazard that the ARLD liver recipient might return to risky drinking after LT [93]. Thus, the choice to proceed for

Figure 1.
The figure describes the an acute decompensated liver failure should be listed for an emergency or early LT in the first 1–2 weeks utilizing the "golden window" period for LT before the development of multi-organ failure.
LT should be discussed among all members of the multidisciplinary team taking both harm and benefit into the consideration.

Classically, disease severity scores like MELD have been used in several countries for an organ allocation. Nonetheless, the MELD score does not take an extrahepatic organ failure such as respiratory, brain, and circulatory failures into an account, thereby giving no preference for the patients with an acute decompensated liver failure. In a study, the patients undergoing LT with a MELD score > 30 had a 1-year overall survival rate of only 52.6% [94]. On the other hand, other studies have reported a poor outcome, particularly for those patients with a MELD score above 36 [95, 96]. Interestingly, Artru et al. showed a 1-year overall survival rate of 80% in the ACLF grade 3 patients with a median MELD score of 40 [74]. Thus, up to this point, there are no standard criteria and inadequate evidence to exclude too sick patients from a LT.

7. Conclusions

The choice to continue with LT for ALF relies on the likelihood of unconstrained hepatic recuperation and the underlying cause of ALF. Nonetheless, the objective is to enhance the organ allocation system and accurate identification of the patients who are probably to get benefited from LT from those who are apparently going to recover spontaneously. Thus, avoiding the need of lifelong immunosuppressant in those patients who are supposedly to recover without LT. Additionally, reliable prognostic criteria are needed to make decisions on the proper timing of LT. Assuming that LT is performed too early, it might be performed when it is not needed, and if LT is delayed, there might be a higher risk of poor outcome due to the worsening condition of the patient. In any case, the current evidence from the studies suggests that all the patients with ALF should be evaluated with an available criterion and should be listed for an emergency LT to avoid any small margin of medical error.

In spite of the assorted variety of early information on ACLF, two accord definitions by APASL and EASL have been developed recently, which exhibit two unique however coinciding circumstances. A few questions still have to be addressed in regards to which definition to utilize and whether there are contrasts inside a territory depending on the types of an underlying cause for ACLF found in each. Thus, albeit a few patients with an acute disintegration might not have ACLF initially at admission, considering ACLF as a dynamic syndrome that can improve or worsen during its course, clinicians should attempt to counteract patient vulnerability to new precipitating events and to identify the progression of ACLF immediately. ACLF patients are generally not listed for an emergency LT, regardless of the encouraging results. Thus, there is an urgent need for an ideal scoring system that can reveal the dynamic nature of ACLF and response to medical therapy.

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The authors declare no competing interests.

Data availability
All the data supporting the results are shown in the paper and are available from the corresponding author upon request.

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