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Acute decompensation and acute-on-chronic liver failure

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Abstract

Acute decompensation is defined as the development of ascites, bleeding due to portal hypertension, jaundice, or hepatic encephalopathy in the presence of known or unknown chronic liver disease. Acute-on-chronic liver disease is defined as a clinical entity reflecting acute worsening in liver function along with extrahepatic organ failure with significantly higher 28-day mortality. In the common pathogenesis, severe systemic inflammation and portal hypertension and varying degrees of reaction to these conditions play a major role. Triggering factors act as accelerators in the development of acute decompensation and acute-on-chronic liver failure. The extrahepatic organ failure in acute-on-chronic liver failure is mainly due to tissue hypoxia due to decreased perfusion and cellular edema. The number of organ failure in acute-on-chronic liver failure is considered to be the most important prognostic indicator. Liver transplantation remains the most appropriate treatment option for selected patients, even though supportive therapies based on the severity of the disease and the clinical findings that have developed are at the forefront.

Keywords

Acute decompensation, acute-on-chronic liver failure, liver transplantation, mortality, organ failure

Introduction

A guide means someone who shows the way. So, in which diseases, in which situations, and which guidelines should we use as a guide and how should we decide? Currently, this situation is confusing for acute decompensation (AD) and acute-on-chronic liver failure (ACLF). Here is only one truth, which is perceived differently by different consensus groups. Therefore, many different guidelines have been developed. Regardless of which guideline is accepted as the definition, the transition from compensated to decompensated cirrhosis should be considered as a prognostic turning point. The main difference between AD and ACLF is the degree of systemic inflammatory response involved in the pathogenesis. In the presence of cirrhosis or chronic liver disease, there is an increase in proinflammatory cytokines such as TNF-α, and IL-6 mediated by damage-inducing factors, leading to severe systemic inflammation (SI) and oxidative stress. Triggering factors play a role in the development of both clinical presentations. Differences in

clinical definitions in different geographical regions and the fact that the clinical condition is accepted as AD in one center while the same patient is accepted as ACLF in another center cause difficulties in terminology and the sharp distinction between AD versus ACLF. In this article, the definitions, pathophysiologies, and treatment approaches for AD and ACLF were tried to be analyzed especially through 3 main guidelines.

Definition

Acute decompensation

Classically, it is defined as the development of ascites, jaundice, oesophageal variceal bleeding, or hepatic encephalopathy (HE) in a patient with cirrhosis due to many factors such as bleeding, infection, alcohol use, drugs, constipation, and dehydration. Although there are uncertainties about the duration, it is generally accepted to develop within 2 weeks. Currently, the European Association for the Study of the Liver (EASL) guidelines have introduced new nomenclature to classify AD [1]. According to this:

- Non-AD: Progressive liver-related complication not requiring hospitalization
- AD: Liver-related complication requiring hospitalization
  - Stable decompensated cirrhosis (SDC): Discharged and did not require re-hospitalization at 3-month follow-up
  - Unstable decompensated cirrhosis (UDC): Developed liver-related complications, but did not meet the definition of ACLF, needing re-hospitalization at a 3-month follow-up
  - Pre-ACLF: Decompensation with ACLF at a 3-month follow-up is defined

Non-AD: includes slow ascites formation, mild/moderate HE, or progressive jaundice. These patients can usually be treated in outpatients, regardless of the number of decompensating factors, as their clinical condition is favorable. SDC is characterized by complications of cirrhosis, low SI, and the possibility that this can be compensated by timely and appropriate treatment. Organ failure (OF) is rarely observed during this period. Although it can be easily controlled with appropriate treatment, 1-year mortality is accepted as 10%. UDC is associated with significant portal hypertension, indicating a significantly increased incidence of bacterial infections during this period. OFs are usually not associated but are still more common than SDCs. Although it can be easily controlled with appropriate treatment, 1-year mortality is accepted as 36%. Pre-ACLF represents the AD period when ACLF is developing. It is associated with severe SI and has a high probability of developing OF. It is the subtype of AD with the worst prognosis and its 1-year mortality is considered to be 67% [2]. In the PREDICT study of 1,071 patients with decompensated cirrhosis, and systemic inflammatory markers, it is noteworthy that the cumulative mortality rate in the pre-ACLF group had the highest mortality rate after ACLF-3 [3].

ACLF

It is a clinical condition that develops through a triggering factor in patients with known chronic liver disease. The most prominent pathophysiological mechanism that distinguishes this syndrome from AD is the presence of more severe SI. Different consensuses have different definitions involving different patient groups. The Asian Pacific Association for the Study of the Liver (APASL) and the World Gastroenterology Organisation (WGO) considered patients with previously diagnosed or undiagnosed chronic liver disease, the EASL considered only acutely decompensated patients, and the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) considered cirrhotic patients with infection and requiring hospitalization. Socioeconomic and geographical differences have led to the need to investigate different definitions and underlying aetiological considerations in Asia, Europe, and North America. The differences between definitions are summarised in Table 1.

APASL-ACLF definition

In patients with diagnosed or undiagnosed chronic liver disease, liver failure complicated by ascites and/or HE occurring within 4 weeks with total bilirubin ≥ 5 mg/dL, international normalized ratio (INR) ≥ 1.5 or

Table 1. Interguideline differences in ACLF definition

Characteristics	APASL	EASL-CLIF	NACSELD
Definition	Acute jaundice and coagulopathy, followed by ascites ± HE within 4 weeks	Specified criteria using CLIF-OF score for OF, 28-day mortality rate > 15%	≥ 2 extrahepatic OF (circulation, kidney, cerebral, respiratory)
Organ failure	AARC score	CLIF-C OF score	MELD score
Liver	T. Bil ≥ 5 mg/dL + INR ≥ 1.5	T. Bil ≥ 12 mg/dL	-
Kidney	AKI Network criteria	Cr ≥ 2 or RRT	RRT
Cerebral	HE 3–4	HE 3–4	HE 3–4
Coagulopathy	-	INR ≥ 2.5	-
Circulatory	-	Need to use of vasopressor (terlipressin and/or catecholamines)	Shock (MAP < 60 mmHg or > 40 mmHg systolic BP reduction from baseline)
Respiratory	-	PaO_2/FiO_2 ≤ 200 or sPO_2/FiO_2 ≤ 214 or need for mechanical ventilation (≤ 300 for ALI or ≤ 200 for ARDS)	Need for mechanical ventilation
Inclusion criteria	Undiagnosed or diagnosed chronic liver disease, including cirrhosis	Cirrhosis ± prior decompensation	Inpatient cirrhosis (± prior decompensation) with infection at or during admission
Exclusion criteria	Prior decompansation	HCC with beyond Milan criteria	Outpatients with infection
	Bacterial infection	Receiving immunosuppressive treatment	Cirrhosis without infection
	GI bleeding	HIV	HIV
	HCC	Severe chronic extrahepatic disease	Prior organ transplantation
			Disseminated malignancies
Time frame	4 weeks	4–12 weeks	Not defined
Major organ failure	Hepatic	Hepatic + extrahepatic	Extrahepatic
Time of diagnosis	Early	Moderate	Too late

AARC: APASL-ACLF research consortium; ACLF: acute-on-chronic liver failure; AKI: acute kidney injury; ALI: acute lung injury; APASL: Asian Pacific Association for the Study of the Liver; ARDS: adult respiratory distress syndrome; Cr: creatinine; EASL-CLIF: European Association for the Study of the Liver-Chronic Liver Failure; FiO_2: fraction of inspired oxygen; GI: gastrointestinal; HCC: hepatocelluler carcinoma; HE: hepatic encephalopathy (West-Haven criteria); HIV: human immunodeficiency virus; INR: international normalized ratio; MAP: mean arterial pressure; MELD: Model of the End Liver Disease; NACSELD: North American Consortium for the Study of End-Stage Liver Disease; OF: organ failure; PaO_2: partial pressure of arterial oxygen; RRT: renal replacement therapy; BP: blood pressure; sPO_2: pulse oximetric saturation; T.Bil: total bilirubin

prothrombin (PT) activity < 40% is defined as liver failure. In later consortia, 28-day mortality was emphasized, and bacterial infection and vascular liver diseases such as portal vein thrombosis were added as precipitating factors [4]. APASL specifies single-OF as liver failure in the definition. However, if we consider coagulopathy as a separate OF as stated in the EASL guidelines, we can also consider that there are 2 OFs. In addition, patients with cirrhosis presenting with complications such as gastrointestinal (GI) bleeding, ascites, sepsis, HE, or hepatorenal syndrome (HRS) are considered AD in the APASL definition. However, it is noteworthy that in a study conducted in the East, on which APASL is based, involving 1,040 HBV-ACLF patients diagnosed according to APASL criteria, 15.9% of the patients had at least one prior episode of decompensation [5]. According to the CANONIC study, 23% of patients with ACLF have a known history of decompensation. In addition, 11.3% of these patients developed ACLF within 28 days and half of the patients who developed ACLF died within 3 months [6]. The APASL-ACLF research consortium (AARC) data, based on liver biopsy studies that cirrhosis is not necessarily present when ACLF develops, has determined that the majority of patients with ACLF do not have a diagnosis of cirrhosis. Nevertheless, 28-day mortality was found to be over 33% in this patient group [4]. The diagnostic criteria for ACLF according to the APASL definition define a clinical phenotype of early-stage liver disease characterized by primary liver failure without a specific hepatotropic injury and extrahepatic involvement [7]. According to APASL, ACLF definitions including sepsis are considered as "acute decompensation accompanied by hepatic and extrahepatic organ failures" and have higher short-term mortality [8]. It has been stated that this patient

group is exempt from the diagnosis of APASL-ACLF, as it is thought that situations such as early deterioration in previously decompensated patients or recurrence of ACLF after improvement will cause confusion. According to APASL, organ dysfunction rather than OF is required to diagnose ACLF. Thus, organ-specific approaches can be prioritized [4].

EASL-ACLF definition

It is defined as a specific syndrome characterized by OF and high short-term mortality in patients with cirrhosis.

Grade 1 is defined as renal failure alone (grade 1a) or liver, coagulation, circulatory or respiratory failure with serum creatinine (Cr) level of 1.5–1.9 mg/dL or HE grade 1–2 (grade 1b), and 28-day mortality is 22%.

Grade 2 is defined as the coexistence of 2 OFs, and 28-day mortality is 32%.

Grade 3 is defined as the presence of ≥ 3 OFs together, and 28-day mortality is 77% [6].

In the EASL-ACLF definition, hospitalization for planned procedure or treatment, non-Milan hepatocelluler carcinoma (HCC), presence of severe chronic extrahepatic disease, human immunodeficiency virus (HIV) infection, and ongoing immunosuppressive treatment were excluded. It is argued that both patients with prior decompensation and patients without decompensation should be included in the definition of ACLF [1]. The presence of liver failure (bilirubin ≥ 12 mg/dL) is not a prerequisite for ACLF according to the EASL definition. Conversely, even patients with isolated renal failure are considered to have ACLF [9].

In the CANONIC study, in which 1,343 cirrhotic patients hospitalized for AD were evaluated, 27.8% of patients without ACLF and only 23.2% of patients with ACLF had no previous decompensation and it was concluded that previous decompensation did not affect the occurrence of ACLF [6]. However, it has been established that patients without prior decompensation are likely to have more severe degrees of ACLF. In addition, the 28-day mortality rate was 42.2% in patients without previous decompensation and 29.6% in patients with previous decompensation. Therefore, excluding patients with a previous history of decompensation from the definition will prevent the use of prognostic models that allow early recognition of possible poor outcomes, which may delay appropriate treatment [1].

NACSELD-ACLF definition

A clinical condition in patients with chronic liver disease with or without cirrhosis, associated with multiorgan failure and high mortality within 3 months if not treated appropriately [10]. It can potentially be reversible. It is considered a state of acute hepatic failure characterized by 2 or more extrahepatic OFs due to infection in a patient with cirrhosis. Patients with cirrhosis without infection, patients with infection not requiring hospitalization, and patients with organ transplantation, disseminated malignancy, and HIV infection were excluded from the definition. According to NACSELD-ACLF, the development of extrahepatic OF after SI is considered essential for the diagnosis of ACLF.

Overall, NACSELD was developed from understanding the epidemiology and natural history of infected patients with cirrhosis in North America to identifying “bedside” critically ill patients with cirrhosis. The definition of renal impairment differs from other consortia in that it does not include serum Cr levels [9]. Although infection status remains an important determinant of mortality, the NACSELD-ACLF is a simple, reliable diagnostic tool to predict 30-day survival in both infected and non-infected patients hospitalized with a diagnosis of cirrhosis. It may be useful to facilitate earlier liver transplantation (LT) assessment, but possibly more importantly, it may be useful in terms of the earlier judgment of the futility of care and subsequent palliative care [11].

WGO-ACLF definition

To unify these different guidelines on a middle ground, AD leading to jaundice or an increase in INR, 1 or more OFs, and increased 28- and 90-day mortality without any exclusion criteria were defined.

In AASLD 2023 guideline, ACLF is defined as the presence of at least 1 extrahepatic (cerebral, circulatory, respiratory, or renal) OF in chronic liver disease patients with or without cirrhosis, with the presence of liver failure with acute onset and rapid deterioration in clinical status, defined by increase in bilirubin and INR [12]. Patients with severe OF and requiring ICU management were included in the definition.

APASL describes patients in the early stage of the disease. NASCELD defines patients in very advanced stages of the disease. For ACLF diagnosed using the EASL criteria, the NACSELD classification overestimates the 28-day and 90-day mortality of AD patients, while the APASL criteria underestimate it [1, 12, 13]. In the study of Leao et al. [14], when ACLF criteria following these 3 guideline definitions were applied to 48 patients, 14 patients fulfilled APASL criteria, 41 patients fulfilled EASL criteria, and 6 patients fulfilled NACSELD criteria, and mortality rates at follow-up were found 78%, 82%, and 100%, respectively.

Organ failures

First of all, it is important to know that the definition of OF is defined differently in guidelines established according to geographical location. According to APASL, OF includes liver, kidney, cerebral, and coagulation systems, while EASL includes circulatory and respiratory system failure in addition to these criteria. However, NACSELD recognizes renal, cerebral, circulatory, and respiratory system failure as OF [11]. If we go into more detail, the definition of the same criteria in these guidelines is also different. For example, APASL defines liver failure as a bilirubin level above 5 mg/dL and INR above 1.5, while EASL defines liver failure as a bilirubin level above 12 mg/dL. Therefore, unless a global consensus is established, the issue of classifications or the nomenclature of the disease will continue to be controversial for a long time.

The number of OFs is the biggest determinant of mortality in hospitalized cirrhotic patients. Although it is generally stated that the diagnosis of ACLF requires ≥ 2 OFs, since it has been observed that patients with renal failure have a disproportionately poor prognosis, single renal failure or cerebral dysfunction with any non-renal OF is also included in the definition of ACLF in western guidelines [2]. Gut dysbiosis causes an increase in intestinal wall permeability. There are opinions that it may contribute to the development of OFs that may lead to shock due to the development of endotoxaemia through bacterial translocation [1, 4, 15]. APASL predominantly considers liver failure as major OF, NACSELD is based on extrahepatic OF, and EASL considers combined failures [10].

Liver failure

The optimal laboratory cut-off values to distinguish between liver failure and AD are still unclear. In definitions, APASL is based on total bilirubin and PT/INR; EASL is based on total bilirubin; NACSELD does not include liver failure in the ACLF definition.

Renal failure

It is the most common extrahepatic OF seen in ACLF. Its prevalence is higher in patients with infection. It is important to differentiate from functional causes secondary to structural or hemodynamic changes. According to the International Ascites Club criteria [16], the diagnosis of acute kidney injury (AKI) in patients with cirrhosis is defined as an absolute increase of ≥ 0.3 mg/dL in serum Cr level within 48 hours or ≥ 50% absolute increase of Cr level from baseline within 7 days regardless of the last Cr level within the last 3 months.

AKI has 3 stages:

Stage 1; increase in Cr ≥ 0.3 mg/dL or increase in Cr ≥ 1.5 to 2-fold from baseline;

Stage 2; increase in Cr ≥ 2 to 3-fold from baseline;

Stage 3; increase in Cr ≥ 3-fold from baseline or Cr ≥ 4 mg/dL with an acute increase of 0.3 mg/dL or initiation of renal replacement therapy (RRT).

To diagnose HRS-AKI, the presence of cirrhosis with ascites; presence of one of the AKI criteria, no response despite discontinuation of diuretics and plasma volume expansion with albumin (1 g/kg/day) for 48 hours; absence of shock; absence of a recent history of nephrotoxic drug use; absence of proteinuria (> 500 mg/day), microhematuria (50 red blood cells/high-power field) and/or abnormal renal ultrasonography signs indicating structural renal damage. Chronic kidney injury is defined as a permanent decrease in glomerular filtration rate to < 60 mL/min for > 3 months. It should be differentiated from AKI [16]. In the definitions, APASL is based on serum Cr; EASL is based on Cr level or the need for RRT; NACSELD is based on RRT only. In addition to the serum Cr level, biomarkers such as urinary neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and IL-18 may be helpful for the development of renal failure, exclusion of the diagnosis of ATN, and the need for early RRT or artificial liver support [4, 8]. Since it is known that morbidity and mortality are worse in the presence of AKI, serum Cr levels were kept lower in the APASL criteria. It was claimed that many patients with ACLF would be missed if other criteria were applied [4].

Cerebral failure

Neuroinflammation and impaired brain energy metabolism lead to cerebral edema. In all 3 main ACLF definitions, the presence of HE grades 3 and 4 according to West Haven criteria is accepted as an indicator of cerebral insufficiency. A Glasgow Coma Scale < 8 is an indicator of severe damage [12]. There are studies indicating that detection of ammonia levels above 140 mg/dL in patients with HE grades 3–4 at any time point within the first week after presentation is a poor prognostic marker for 28- and 90-day survival [4, 8].

Cardiovascular failure

In patients with decompensated cirrhosis, systemic vascular resistance decreases. In this case, a hyperdynamic circulation develops, manifested by low blood pressure and increased cardiac output. These physiological changes become even more pronounced in patients with ACLF secondary to increased acute inflammation. This pathophysiology is exacerbated by increased acute inflammation in patients with ACLF [17, 18]. In definitions, APASL is based on lactate, whereas EASL and NACSELD consider the need for mean arterial pressure (MAP) and vasopressors.

Respiratory failure

The etiology of acute lung injury (ALI) may be due to hydrostatic or non-hydrostatic pulmonary edema or underlying pulmonary disorders associated with portal hypertension. In particular, there is an increased risk of developing ALI in ACLF. It can occur in a wide range of cases, progressing to acute respiratory distress syndrome (ARDS) [19]. In definitions, EASL is based on PaO_2 or sPO_2/FiO_2, NACSELD is based on the need for mechanical ventilation, and APASL does not include respiratory failure in the definition of ACLF.

Coagulopathy

EASL defines coagulopathy as a separate OF and the definition is based on the INR value. APASL also includes INR in its definition as an indicator of liver failure. Changes in primary and secondary hemostasis in ACLF result in a rebalancing of coagulation, leading to bleeding or thrombotic episodes. Furthermore, OFs in the ACLF can further disrupt the cirrhotic hemostatic imbalance. INR and platelet values provide information about the coagulation system in liver diseases. However, there are recommendations that the INR value should not be used to measure the risk of bleeding in patients with cirrhosis since it does not cause an increased risk of bleeding in cirrhotic patients [4, 12]. Traditional measures of coagulation including PT, activated partial thromboplastin time (aPTT), INR, fibrinogen levels, and bleeding time do not reflect the risk of bleeding risk that may develop in patients with ACLF status. In AD and ACLF, viscoelastic tests (TEG-thromboelastography and ROTEM-rotational thromboelastometry) are recommended more prominently because they can measure platelet function, hyperfibrinolysis, and early clot dissolution in real time [20].

Scores

AD and especially ACLF is a dynamic clinical condition. Therefore, close follow-up is required. Therefore, the scores used to predict prognosis should be reproducible at certain intervals. The EASL-AD score for patients with AD, is calculated using age, white blood cells (WBC), Cr, INR, and sodium levels and shows 1-, 3-, 6- and 12-month expected mortality rates. EASL-AD score, Model of the End Liver Disease (MELD) score, or MELD-Na score can be used to define the risk of developing ACLF to provide mortality in patients without ACLF [1]. In a study related to the prediction of nosocomial ACLF development in patients hospitalized for AD, it was found that the MELD score, leukocyte count, and hemoglobin levels at the time of admission were independent and reliable predictive values [7]. In the presence of ACLF, each guideline claims that its score is superior to other scores.

In APASL, the presence of OF is determined according to the AARC criteria, and the grade of ACLF is calculated according to the score (Table 2). The AARC score is reproductible model that can be applied at the bedside to predict disease severity. It has been shown to be superior to the MELD/MELD Na, Chronic Liver Failure-sepsis-related organ failure assessment (CLIF-SOFA), and SOFA scores for patients with ACLF. The need for LT can be predicted by the change of the AARC score in the first week. An AARC score below 10 calculated at presentation or at the end of the first week is a good prognostic indicator. Patients with an AARC score > 10 should be listed for LT.

Table 2. The scores of organ failure (OF) [1, 25]

Characteristics	APASL-AARC	Simplified EASL-SOFA
Liver	1: < 15	1: < 6
Total bilirubin (mg/dL)	2: 15–25	2: 6–12
	3: > 25	3: > 12
Kidney	1: < 0.7	1: < 2
Creatinine (mg/dL)	2: 0.7–1.5	2: 2–3.5
	3: > 1.5	3: > 3.5 or RRT
Cerebral	1: 0	1: 0
Degree of HE (West-Haven)	2: 1–2	2: 1–2
	3: 3–4	3: 3–4
Coagulation	1: < 1.8	1: < 2
INR	2: 1.8–2.5	2: 2–2.5
	3: > 2.5	3: > 2.5
Circulation	1: < 1.5	1: ≥ 70
APASL: lactate (mmol/L)	2: 1.5–2.5	2: < 70
CLIF-SOFA: MAP (mmHg)	3: > 2.5	3: need for vasopressors
Respiration	-	1: > 300; > 357
PaO_2/FiO_2 or sPO_2/FiO_2		2: 200–300; 214–357
		3: ≤ 200; ≤ 214
Score	Grade 1: 5–7	Age and WBC count are added and the CLIF-ACLF score is calculated:
	Grade 2: 8–10	10 × [0.33 × CLIF-C OFs + 0.04 × age + 0.63 × Ln(WBC) − 2]
	Grade 3: 11–15	

ACLF: acute-on-chronic liver failure; APASL: Asian Pacific Association for the Study of the Liver; AARC: APASL-ACLF research consortium; CLIF-SOFA: Chronic Liver Failure-sepsis-related organ failure assessment; EASL: European Association for the Study of the Liver; HE: hepatic encephalopathy; INR: international normalized ratio; MAP: mean arterial pressure; PaO_2: partial pressure of arterial oxygen; FiO_2: fraction of inspired oxygen; sPO_2: pulse oximetric saturation; RRT: renal replacement theraphy; WBC: white blood cell

There are opinions that the Tongji prognostic predictor model (TPPM) is superior to the MELD and CLIF-C OF models in HBV-ACLF patients. Lactate should be used to define the severity of ACLF syndrome [4].

According to the EASL-ACLF score, the expected mortality rate is determined by the presence of OF. The EASL-SOFA score includes both hepatic and extrahepatic OF along with age and WBC value and repeated measurements can be made (Table 3) [1, 6, 21]. EASL-ACLF score performs better than Child Turcotte Pugh (CTP) score, MELD, and MELD-Na scores in predicting 28-day mortality [22]. The performance of the EASL-ACLF score in predicting 28-day mortality was found to be even better at different time points than at the time of diagnosis [9].

Table 3. Triggering factors in AD and ACLF

Triggering factors	AD	ACLF
Unknown	57%	10–50%
Known	Infections (58%)	Infections (48%)
	HBV reactivation	HBV reactivation
	HAV infection	HAV infection
	HEV infection	HEV infection
	Alcohol-related hepatitis	Alcohol-related hepatitis
	DILI	DILI
	Neurotoxic drugs	Neurotoxic drugs
	GI bleeding	GI bleeding*
	Surgery	Native American ancestry
	Trauma	
	TIPS	
	TACE	
	RFA	
	Portal vein thrombosis	

* Gastrointestinal (GI) bleeding is not accepting a trigger factor for ACLF in APASL unless it fulfills the APASL-ACLF criteria and causes jaundice and coagulopathy. AD: acute decompensation; ACLF: acute-on-chronic liver failure; DILI: drug-induced liver injury; RFA: radiofrequency ablation; TACE: transarterial chemoembolization; TIPS: transjugular intrahepatic portosystemic shunt

The NACSELD-ACLF score includes advanced extrahepatic OF in addition to age, MELD score, WBC value, and albumin level measured on admission [11]. CTP score > 12 and MELD score > 28 are independent predictors of mortality in patients with ACLF, and there are opinions indicating that early LT is required if there is still no clinical improvement despite 7-day treatment [8]. It has been demonstrated that the NACSELD criteria perform better than the EASL-ACLF score in predicting 7-day mortality. Therefore, it seems that the EASL-ACLF score can be used to prioritize patients for LT and the NACSELD-ACLF score can be used to exclude patients from LT [10].

After the relationship between serum lactate level and OF and mortality was found, APASL and MELD-lactate scores were superior in predicting in-hospital mortality. In addition, it has been reported that the addition of lactate to the EASL-ACLF score showed a more successful performance than other scores in predicting 28-day, 90-day, and 1-year mortality [12]. In the study of Leao et al. [14], the highest diagnostic accuracy in noninvasive scoring was found to be the LBi (Lactate/Bilirubin) ratio, and it was concluded that EASL-SOFA and EASL-ACLF scores were more successful in predicting short-term mortality and MELD and CTP scores were more successful in predicting long-term mortality.

The Acute Physiology and Chronic Health Evaluation (APACHE) model can be successful in predicting mortality risk in the ICU. No significant superiority was found between the MELD, MELD-Lactate, EASL-ACLF, and EASL-ACLF-Lactate scores. Therefore, a new prognostic model was developed to predict mortality in ACLF patients admitted to the ICU. In this new model, age, alveolar-arterial gradient, blood urea nitrogen, total bilirubin, INR, and grade of HE were evaluated and it was found to be superior to these scores in predicting mortality at different time points [23].

Clinical presentation

Decompensation is characterized by ascites, variceal bleeding, encephalopathy, and jaundice. Ascites is the first decompensating event in more than 70% of patients with cirrhosis; half of these patients present with ascites alone and the rest with other complications. Most of the complications seen in cirrhosis [ascites, HE, oesophageal variceal hemorrhage, HRS, spontaneous bacterial peritonitis (SBP), portal hypertensive gastropathy, hepatopulmonary syndrome, cirrhotic cardiomyopathy] are associated with portal hypertension. In the decompensated phase, patients become more susceptible to bacterial infections, especially as a result of cirrhosis-related immune dysfunction. Therefore, bacterial infections may cause ACLF and mortality in patients with AD. In decompensated cirrhosis, they should be considered LT candidates especially if complications develop. Treatments other than LT are accepted as standard medical treatments for complications.

ACLF is a clinical presentation with high mortality in the presence of chronic liver disease, due to a triggering factor and independent of the stage of the disease, manifested by acute hepatic decompensation or extrahepatic OF. The most important difference between AD and ACLF in clinical presentation is the absence of cerebral edema in AD. HE is observed in approximately 40% of patients [4]. In the APASL guideline, it is accepted that signs of liver failure develop before other OFs. According to EASL, renal failure developing as a result of SI is accepted as primary OF. In ACLF, the first 7-day period after the onset of symptoms is called the "Golden Window". This period is accepted as the period until the onset of SI and the development of immune paralysis. Studies are showing that the course of the disease can be reversed if correct and effective interventions are performed in this period [24, 25].

SBP, urinary and respiratory tract infections, and soft tissue infections are most commonly involved in patients with cirrhosis. It is also difficult to diagnose infection in patients with cirrhosis. Because these patients often do not have fever and WBC values are low secondary to hypersplenism. Infection should be suspected in cases such as worsening of mental status, hyponatremia, AKI, the relative increase in WBC count, changes in hemodynamics, or higher ACLF grade. Biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), lactate, and bacterial DNA are frequently elevated in patients with cirrhosis, both with and without infection, and progressive elevation of these markers are much lower than in patients without liver disease [12].

There is still a need for an "early diagnosis biomarker" that can be. Useful in predicting ACLF status. IL-6 predicts outcomes (90-day and 1-year mortality) of patients with cirrhosis better than CRP and WBC [26]. Soluble triggering receptors expressed on myeloid cells-1 (sTREM-1) and presepsin (inflammatory biomarker that stimulates monocyte phagocytosis) showed higher diagnostic efficacy compared to traditional markers in diagnostic sepsis in ACLF. Moreover, the combination of presepsin and CLIF-SOFA scores revealed the highest diagnostic accuracy in diagnosing sepsis in ACLF patients [26]. If invasive fungal infection is present in patients with ACLF, galactomannan or betaglucan can be used to support the diagnosis [4].

Triggering factors

It may vary depending on the underlying disease and geographical changes. The triggering factor cannot be detected in 57% of AD and approximately 10–50% of ACLF [2, 27]. 58% of the precipitating factors that can be identified in AD are caused by infections [2]. The most common triggering factor that can be detected in ACLF is infections, with a prevalence of 48% (Table 3) [28]. Cirrhosis-related immunopathy causes susceptibility to infections and OF. In addition, some invasive procedures may cause an increase in the risk of infection. Bacterial infections, especially multidrug-resistant infections, increase the risk of ACLF development and mortality and constitute at least 40% of culture-positive infections [12, 29, 30]. Fungal infections occur nosocomial in 2–16% of patients with ACLF. Antibiotic use causes intestinal fungal dysbiosis, thus increasing the risk of fungal infection [31]. Intestinal dysbiosis, loss of intestinal integrity, bacterial translocation, and portosystemic shunt in AD make patients with cirrhosis more prone to bacterial infection [2]. Preventing the development of systemic inflammatory response syndrome (SIRS) or

preventing the progression from SIRS to sepsis due to immune modulation during the "Golden Window" period may reduce the incidence of OF and improve survival. It shows that infection and sepsis develop after liver failure in patients who do not have SIRS or who develop SIRS or sepsis within 1–2 weeks and that persistent inflammation causes immunoparalysis, providing an opportunity for infection and sepsis to occur [4]. Sepsis can cause multiorgan failure in any patient, regardless of its source [5]. Approximately half of AD patients with proven infection develop ACLF. The 28-day mortality in AD patients with proven infection is 5–8%, but in the case of ACLF, it is 27–37%. Therefore, antimicrobial treatment should be started as early as possible [2, 32].

As the number of OFs increases in infected ACLF patients, the mortality rate also increases [32]. In addition, patients with infection are more likely to develop cerebral, cardiovascular, and respiratory failure than those who are not infected [33]. It is controversial whether sepsis alone causes or is a consequence of liver failure. SI markers such as leukocytes, CRP, and IL-6 increase in both AD and ACLF, making them an inadequate discriminator between AD- and ACLF-triggered by infection [2].

Chronic B reactivation, hepatitis A or E virus infection, alcohol-related hepatitis, and drug-induced liver injury (DILI) may also be among other triggering causes. Wang et al.'s study [34] consisting of 1,736 patients with HBV-related cirrhosis and AD, the probability of developing ACLF within 28 days was found to be 9.6%, and 3-month and 1-year LT-free mortality was found to be 61.6% and 70.9%. It was emphasized that these values were similar to patients with ACLF status at presentation. In addition, the same study states that the development of ACLF often occurs within 2 weeks and the risk of progression from AD to ACLF gradually decreases. HBV-ACLF has been noted to exhibit specific phenotype and prognosis different from patients with ACLF of other etiologies and is the sole precipitator associated with the progression of AD to ACLF [34]. Pre-ACLF also appears to be important in patients with HBV-associated cirrhosis. Worsening SI occurred before the development of OF in HBV-related pre-ACLF patients. In HBV-ACLF, the process progresses very rapidly and short-term mortality is observed at a high rate [35].

Approximately one-third of AD cases are triggered by severe alcoholic hepatitis. Corticosteroids used in the treatment of severe alcoholic hepatitis have been shown to improve survival in the short term, but do not improve prognosis in the medium or long term [2]. Neurotoxic drugs such as opioids and benzodiazepines also accelerate AD. However, such an effect of hepatotoxic or nephrotoxic drugs has not been demonstrated [2].

In case of GI bleeding, the risk of developing shock and therefore developing severe AD and ACLF increases. Infections, GI bleeding, electrolyte disturbances, AKI, alkalosis, dehydration, constipation, under or excessive use of lactulose, and use of central nervous system depressant tranquilizers are among some known trigger factors for HE [12]. In a large cohort of Latin American patients with acute decompensated cirrhosis, increased Native American ancestry was noted as a factor independently associated with ACLF [36].

From APASL's perspective, both hepatotropic and non-hepatotropic effects should first appear in the patient with liver failure. In the case of GI bleeding, which is among the triggering factors in Western guidelines, it is stated that it should not be considered a triggering factor unless there are patients who meet the APASL-ACLF criteria and cause jaundice and coagulopathy. In addition, although it has been emphasized that portal vein thrombosis can also lead to hepatic dysfunction by causing liver ischemia, it has not been accepted as a triggering factor due to lack of evidence. Although it is accepted that surgery, trauma, transjugular intrahepatic portosystemic shunt (TIPS) placement, transarterial chemoembolization, or radiofrequency ablation may also have the potential risk for hepatic decompensation, it has been stated that this situation may vary depending on the underlying hepatic reserve and these situations are not considered as a triggering factor [4].

Any type of surgical intervention in patients with cirrhosis is associated with significant risks of developing OF and ACLF compared with patients without cirrhosis. The presence of hepatic AD and infection plays an important role in the development of postoperative ACLF. The development of postop ACLF significantly reduces survival. Therefore, patients with cirrhosis who require surgery should be

selected carefully [10]. Nonsurgical interventions may also precipitate ACLF, but the exact incidence is unknown. Therefore, the benefit-risk ratio should be taken into account when deciding on a non-surgical intervention recommended for cirrhotic patients [10].

Pathophysiology

In cirrhosis, extracellular matrix accumulation, sinusoidal remodeling, and intrahepatic vascular shunts develop with proliferative hepatic stellate cell activation. Hepatic endothelial functions are impaired along with parenchymal damage, apoptosis, and impaired angiogenesis. As a result of endothelial dysfunction, the release of vasodilator mediators such as nitric oxide (NO) decreases, and the production of vasoconstrictor mediators, especially the renin-angiotensin-aldosterone system (RAAS), increases. With the effect of these factors, portal pressure increases as a result of increased intrahepatic resistance. Along with the increase in blood flow to the portal venous system, splanchnic vasodilation also accompanies the increase in portal pressure. GI bleeding may occur due to spontaneous rupture of varicose veins, ascites due to hydrostatic pressure, or SBP due to a leaky intestinal barrier.

Two hypotheses are thought to play a role in the development of AD. In the peripheral arterial vasodilation hypothesis, it is vasodilation that develops with the irregular production of endogenous vasodilator substances in splanchnic arterioles. This irregular splanchnic vasodilation causes relative hypovolemia. The increase in cardiac output through activation of neurohumoral systems such as the RAAS, sympathetic nervous system, and arginine-vasopressin induces a hyperdynamic circulatory state to maintain perfusion of peripheral organs. However, as the disease progresses, these mechanisms can lead to microvascular dysfunction and further effective volume reduction over time. This situation causes peripheral hypoperfusion and contributes to multiorgan failure [7]. The other hypothesis is the SI hypothesis. On the one hand, increased permeability of the intestinal mucosa caused by portal hypertension allows the translocation of bacterial products identified as pathogen-associated molecular patterns (PAMPs). Furthermore, damaged or dying hepatocytes due to chronic liver injury release circulating damage-associated molecular proteins (DAMPs) that bind and activate specific pattern recognition receptors (PRR). Recognition of DAMPs and PAMPs results in the release of multifactorial pro-inflammatory mediators. They can activate inducible NO synthesis from splanchnic arteriolar walls, thereby increasing splanchnic vasodilation, which can worsen hypovolemia, and may also trigger RAAS overactivation. Neurohumoral mediators specifically affect renal circulation, causing renal hypoperfusion and AKI. Additionally, DAMP may maintain and exacerbate SI; thus, SI may provide the link between cell damage and OF. Finally, SI in peripheral organs leads to mitochondrial dysfunction and accumulation of free fatty acids and reactive oxygen species [2, 7, 37, 38].

Cirrhosis-associated immune dysfunction is a dynamic feature [37]. ACLF represents the situation in which all these pathophysiological mechanisms reach very high levels as an SI explosion. Although the pathophysiology of ACLF has not yet been fully elucidated, it can be explained by the PIRO system, as in sepsis:

P: predisposition (underlying cause);

I: insult (triggering factor);

R: response to injury;

O: organ failure.

Although some shreds of evidence suggest a role for inflammation, it is not exactly clear whether inflammation is specific to ACLF [10]. Recently, a randomized controlled study conducted in patients with severe alcoholic hepatitis proved that anti-IL-1 treatment was ineffective, indicating that causes other than the inflammation pathway play a more active role in the pathophysiology of alcoholic hepatitis patients [39].

It is accepted that severe and prolonged SIRS plays a role in the pathophysiology of extrahepatic OF in ACLF. It is known that a clinical condition characterized by immune paralysis develops in ACLF, as in severe sepsis [8]. Early diagnosis and initiation of treatment, especially in the first 7-day "Golden Window" period, provides the opportunity for the syndrome to return [8].

Patients with AD and ACLF often have neutrophilia and lymphopenia, and monocyte function is significantly reduced. Despite impaired phagocytic and bacterial killing capacity, activated neutrophils can tight adhesion to endothelial cells. And, it can be the first step in the migration of neutrophils into tissues. Moreover, neutrophils of patients with ACLF cause hepatocyte death [37, 40]. Platelets have important pro- and anti-inflammatory functions, and platelet count is an important determinant of prognosis in patients with liver cirrhosis. SI and bacterial translocation can induce endothelial cell damage, leading to platelet activation and thromboinflammation. It can also increase SI and promote ACLF [38].

Both circulatory dysfunction and systemic and renal inflammation are the major mechanisms to develop AKI and ACLF [38]. The pathophysiology of HE has not been adequately investigated, making it particularly difficult to prevent and differentiate occult HE. Following the stimulation of astrocytes with inflammatory mediators, there is a significant increase in sphingosine-1-phosphate (S1P) receptors and sphingolipid-metabolizing enzymes [38]. Pulmonary dysfunction develops in 4–41% of patients with liver cirrhosis. The underlying mechanism for the progress of ACLF is probably multifactorial, but still unclear [38]. In the PREDICT study, ACLF itself was shown to greatly increase the infection rate [3]. Frequent exposure to antibiotics in clinics leads to the spread of resistant pathogens and overgrowth of the gut microbiota. This progressive imbalance results in further translocation of bacteria and fungi into the bloodstream [38].

Treatment management

Since AD and ACLF are a dynamic process, the treatment approach should be individualized. Although there are many differences in definition, treatment management is similar in both clinical situations. Although the main and most effective treatment method is LT, the patient who needs LT, its timing, close follow-up of patients to prevent bridging treatments or unnecessary LT in the period until transplantation, and correct and effective treatment of complications that have developed are important. ACLF treatment should be decided by a multidisciplinary team. The goals of treatment are reversal of the triggering cause, treatment of sepsis, and supportive treatments for OF, and LT in selected patients [10]. Treatment strategies are summarized in Table 4.

Table 4. Treatment strategies in both acute decompensation (AD) and acute-on-chronic liver failure (ACLF)

Characteristics	Treatment
Underlying cause and acute triggering factors	Cause-specific treatment
Infection	Antibacterial, antiviral, antifungal
Coagulopathy	LMWH, DOACs, warfarin, platelet replacement, cryoprecipitate, FFP, 4-FPCC
Renal Failure	Fluid resuscitation, withdraw diuretics, albumin, vasoconstrictors, RRT
Hepatic encephalopathy	Lactulose/polyethylene glycol, *L*-ornithine *L*-aspartate/ornithine phenylacetate, rifaximin*, albumin*
Cardiovascular failure	Fluid resuscitation, albumin, vasopressors (norepinephrine, vasopressin), hydrocortisone
Respiratory failure	Pulmonary vasodilators (inhaled NO, epoprostenol), NIV, high-flow oxygen, MV
Sarcopenia	Nutrition
Liver failure	Liver transplantation
Bridge treatments	Plasma exchange, single-pass albumin dialysis, MARS, Prometheus
Next generation treatments	G-CSF, MSC transplantation, TLR-4 inhibition, TAK-242, recombinant alkaline phosphatase, gDNA, emricasan, mitofusin-2, oxysterol sulfates, statin, NAC

* The roles of these treatments are unclear. DOACs: direct-acting anticoagulants; FFP: fresh frozen plasma; 4-FPCC: four-factor prothrombin complex concentrate; G-CSF: granulocyte colony stimulating factor; LMWH: low molecule weighed heparin; MARS: the molecular adsorbent recirculation system; MSC: mesenchymal stem cell; MV: mechanical ventilation; NAC: *N*-acetylcysteine; NIV: non-invasive ventilation; NO: nitric oxide; RRT: renal replacement therapy; TLR-4: Toll-like receptor 4

Treatment of underlying cause and acute triggering factors

Approximately 1/3 of patients presenting with ACLF require paracentesis for severe ascites. The presence of ascites in ACLF differs from AD in many aspects. The development of paracentesis-induced circulatory dysfunction (PICD) in ACLF is associated with very high mortality. Albumin infusion helps reduce the risk of PICD and also reduces the risk of developing hyponatremia, HE, and AKI [4]. Antiviral treatment is recommended for viral causes; steroid, tacrolimus, and mycophenolate mofetil for autoimmune hepatitis; and discontinuation of the drug is recommended for DILI [8]. In case of variceal bleeding, supportive treatment, vasoconstrictor (somatostatin, octreotide, or terlipressin) treatment, antibiotic prophylaxis, and endoscopic treatment should preferably be applied within 12 hours after admission [22]. Both preventive and rescue TIPS should be considered in patients with ACLF and variceal bleeding who have no contraindications to TIPS. Variceal bleeding in patients with ACLF is associated with a very high likelihood of rebleeding. The presence of HE in patients with ACLF should not be considered an absolute contraindication for TIPS [1]. In alcoholic hepatitis, cessation of alcohol, regulation of nutrition, psychological support, steroids, granulocyte-colony stimulating factor (G-CSF), pentoxifylline, *N*-acetylcysteine (NAC), *S*-adenosyl methionine, and artificial liver support systems can be applied. In the presence of ACLF, the decision to use steroids is hesitant due to increased sensitivity to new infections. Careful evaluation of ongoing infection is extremely important in deciding on steroid therapy. Response to steroids should be evaluated with the Lille score on the 7th day, and if there is no response, treatment should be discontinued [8, 10, 22]. There is no specific agent for acute viral hepatitis other than hepatitis B. In HBV infection at admission, potent nucleotide or nucleoside analogs should be started as soon as possible, especially in the absence of early virological response (< 2-log reduction) and lack of clinical improvement [1, 22]. It is recommended that patients with chronic liver disease be vaccinated against hepatitis A and hepatitis B if they are not already immune [10].

In cirrhotic patients with a history of SBP, the use of prophylactic antibiotics is recommended to prevent recurrent SBP [10]. In the presence of ACLF in autoimmune hepatitis, the decision to start corticosteroid treatment should be made based on the benefit-risk ratio to avoid uncontrolled infections [1]. Corticosteroids are not recommended in patients with EASL-ACLF-3 or patients with uncontrolled bacterial infection. As the severity of ACLF increases, corticosteroid sensitivity gradually decreases and the risk of infection increases [1]. The most common prescription drugs that cause DILI are antimicrobials. Self-treatment with alternative medicine is common, especially in the East. Most patients have an uneventful recovery. In the setting of advanced liver disease, DILI carries a higher risk of poor outcomes. The onset of ACLF occurs approximately 1–3 months after taking the medication. Mortality in ACLF associated with DILI is more than 50%. The degree of ACLF is the only significant determinant of mortality. Limiting the use of pharmacological agents and patient education are key to preventing DILI-associated ACLF [10].

In patients with ACLF, the decision to use NSBBs should be individualized, with close monitoring of MAP and renal function [1]. Rifaximin can prevent complications of cirrhosis other than HE [10]. In patients with cirrhosis, avoid PPI use unless there is a clear indication such as symptomatic gastroesophageal reflux or erosive esophagitis, or the presence of an ulcer, as it increases the risk of infection [10].

Management of infection treatment

Community-acquired infections are infections that develop 48 hours after admission in patients who have not been exposed to any health care in the last 90 days. Healthcare-associated infections are infections that develop within 48 hours of admission in patients with healthcare exposure in the past 90 days. Nosocomial infections are infections that develop within 48 hours of hospitalization. SBP is the most common infection in ACLF patients [28]. Antibiotics should be selected considering whether the infection is community-acquired/healthcare-acquired/nosocomial, its severity, local resistance patterns, and etiology. Empirical antibiotic treatment should be started after cultures are obtained, while the patient is still in the emergency room because the risk of mortality increases with every hour of delay [41]. Therefore, a full investigation for infection is recommended in hospitalized patients with complications of cirrhosis, especially in patients with AD and ACLF [12]. When suspected or diagnosed with bacterial infection, broad-spectrum

antimicrobial agents should be initiated alone or in combination, and then the treatment should then be adjusted based on antibiotic susceptibility testing results. Empirical antibiotic treatment should be determined according to the environment, local bacterial resistance profiles, severity, and type of infection. Mortality decreased significantly in patients who responded to bacterial infection treatment [4]. In patients with septic shock or worsening ACLF, broad-spectrum empiric antibiotics covering all potential pathogens should be used [1]. Healthcare-associated infections are more likely to be multidrug resistant (MDR). It is critical to determine when and how the infection was acquired in empirical antibiotic selection [10]. Early taper (within a 24–72 hours period) of empirical antibiotics is recommended for ACLF patients receiving broad-spectrum antibiotics if there is no sign of severe infection. Mitigation should be based on rapid microbiological testing and colonization data for MDR organisms [1]. Empirical antifungal therapy may be indicated in ACLF patients who have additional risk factors for fungal infection and develop nosocomial septic shock [1]. If there is still no clinical improvement after 48 hours in patients with ACLF in ICU, MDR or fungal infection should be considered, and antimicrobial treatment should be changed to broader spectrum antibiotics and rearranged to the extent of the fungus [28]. Although non-neutrocytic bactericidal disease does not necessarily require treatment in outpatients, inpatient bactericidal disease increases the risk of AKI, ACLF, and increased mortality [42]. Apart from SBP, the role of albumin in the prevention or treatment of other infections in ACLF is not clear [4].

Management of coagulopathy

Pharmacological venous thromboembolism prophylaxis is recommended for all hospitalized cirrhosis patients unless they have a recent history of bleeding or significant thrombocytopenia. In patients with well-controlled decompensated cirrhosis, low molecular weight heparin (LMWH) may reduce the risk of the episode of new decompensation. On the other hand, there is currently insufficient data on anticoagulated patients in the absence of thrombosis [10]. Uncertainties exist regarding the use of platelet replacement, cryoprecipitate, fresh frozen plasma, or four-factor PT complex concentrate. It can be used in cases of active bleeding or high-risk interventional procedures. LMWH is preferred in cirrhotic patients because it has been shown that it does not cause an increase in the risk of bleeding in the presence or prophylaxis of venous thromboembolism [12]. Although direct-acting anticoagulants (DOACs) are superior to warfarin in compensated cirrhosis, are contraindicated in cirrhotic patients with CTP-C.

Management of renal failure

First of all, structural or functional causes that may cause AKI should be identified, the presence of precipitating factors should be investigated and treated, diuretic use should be discontinued, and intravenous fluid loading should be tried. While 5% albumin is recommended to be used in cases where rapid volume resuscitation is required [10], the recommended fluid loading therapy in AKI management is 25% albumin 1 g/kg/day intravenously (i.v.), with a maximum dose of 100 g/day for 48 hours due to its oncotic, anti-inflammatory and immunomodulatory properties. During this process, patients must be closely monitored for volume overload or pulmonary edema [12]. Daily albumin infusion is not recommended in hospitalized patients with cirrhosis and infections other than SBP to maintain serum albumin 3 g/dL to improve mortality and prevent renal dysfunction or infection [10]. The optimal duration of albumin administration is unclear. Because bacterial infection is a common precipitating factor for AKI, all patients should be monitored for evidence of infection and early empirical antibiotic therapy should be initiated. Avoiding possible nephrotoxic drugs in this process is of prognostic importance.

In patients who do not respond despite volume overload and discontinuation of diuretics, or who have AKI Stage 2–3, if there is no contraindication, it is recommended to use vasoconstrictors (terlipressin, norepinephrine, midodrine, octreotide) in addition to albumin to improve MAP and renal perfusion. Terlipressin (0.5–2.0 mg i.v. every 6 hours or 2 g/day continuous i.v. infusion) is recommended and it is stated that it can be administered with dose adjustments for up to 14 days in total [12]. However, it should be kept in mind that terlipressin may worsen ischemic conditions such as angina, digital ischemia, or arrhythmia, and treatment should be closely monitored and should not be administered to patients with ischemia. Norepinephrine increases hemodynamics and renal perfusion pressure, so it can be preferred in

patients with shock. Midodrine is used orally at 7.5–15 mg 3 times a day, usually in combination with Octreotide, but the effectiveness of this combination is not as high as terlipressin. There are currently no recommendations for the use of vasoconstrictors for Stage 1 AKI. The likelihood that the kidneys will respond to vasoconstriction varies multifactorially. The response depends on the severity of AKI, MELD score, and AARC grade and is inversely proportional to the number of OFs [4, 22]. Some opinions provide vasoconstrictor treatment for up to 14 days and that the treatment can be stopped earlier if there is no response to the treatment (< 25% decrease in Cr on the 4th day) [10].

RRT should be individualized and recommended for HRS-AKI patients who fail pharmacotherapy and are listed or considered for LT. Especially in ACLF patients, the threshold for starting RRT should be lower than other indications [4]. RRT can be considered as bridging therapy in patients who are candidates for LT. Continuous RRT may be preferred instead of intermittent RRT in hemodynamically unstable patients [43]. LT is the definitive treatment for patients with HRS-AKI. Simultaneous liver-kidney transplantation should be considered in patients who received RRT treatment for more than 6 weeks before LT, are over 60 years of age, have a long-term history of AKI, have underlying hereditary kidney disease, or meet the criteria for chronic kidney damage [10]. Because the strongest predictor of failure to recover renal function after LT is the duration of pretransplant RRT, LT referral should not be delayed. Pretransplant RRT of 14 days is the cut-off time to predict whether renal function will recover after LT [10]. Patients with cirrhosis and baseline serum Cr level require close follow-up as it is associated with worse renal outcomes and 30-day survival [10].

Management of HE

In the presence of HE, monitoring should be applied to prevent aspiration, differential diagnoses should be made, triggering factor(s) should be determined and their treatment should be carried out appropriately, and empirical treatment should be started [44, 45]. It should not be forgotten that conditions such as alcohol intoxication, opioid withdrawal, intracranial hemorrhage, psychiatric disorders, diabetic ketoacidosis, nonketotic hyperosmolar coma, nonepileptic seizures, or electrolyte disorders may also cause mental status changes. Intracranial imaging with CT or MRI may be useful in those experiencing a first episode of cerebral changes, those with a history of epileptic seizures or any new focal neurological symptoms, or those with inadequate response to treatment of precipitating factors and/or HE treatment. Routine ammonia measurement is not recommended for diagnosis. However, in patients with coma or confusion, low ammonia levels should indicate etiologies other than HE [44]. Although intubation is controversial in patients, intubation may be considered in cases such as failure to protect the airway, massive upper GI bleeding, or progression of respiratory distress. Also, elective intubation is recommended in patients with HE grades 3–4. Short-acting agents such as propofol or dexmedetomidine should be preferred for sedation and pain control [12, 46]. Opioids should be avoided. Prevention of delirium that may occur due to withdrawal in opioid-dependent patients should not be overlooked.

In the empirical treatment of HE, lactulose should be started immediately, taking care not to trigger the development of excessive diarrhea. In patients who are not expected to tolerate oral intake, treatment can be administered with the help of a nasogastric tube. Additionally, lactulose enema can be applied. Polyethylene glycol can also be used as an alternative. Ammonia scavengers such as *L*-ornithine *L*-aspartate and ornithine phenylacetate can also be applied. However, the role of rifaximin and intravenous albumin administration is still unclear [4, 12]. There are opinions that albumin dialysis can be used in patients with HE grades 3–4 that is resistant to lactulose treatment [22]. There are some opinions that patients with cirrhosis and ACLF who are unresponsive to optimal HE treatment or who continue to need mechanical ventilation due to respiratory failure should not be included in the LT list due to high mortality [10].

Management of cardiovascular failure

Physical examination evaluation is essential in the diagnosis and follow-up of cardiovascular failure. In addition, bedside transthoracic echocardiography helps to apply the treatment correctly by providing information about the patient's fluid load/deficit and cardiac status. In case of hypovolemia and shock,

intravenous fluid resuscitation is required. Balanced crystalloids (ringer lactate) are primarily recommended for fluid resuscitation. Additionally, albumin replacement contributes to the reduction of mortality, especially in patients with sepsis [12]. Albumin treatment reduces SI and circulatory disorders in patients with decompensated cirrhosis [47]. However, although albumin is indicated in cases such as large volume paracentesis, PICD, SBP, or HRS, its role in other decompensated cirrhosis or ACLF clinics remains unclear [7]. Patients with shock may require concurrent vasopressors to maintain end-organ perfusion while fluid resuscitation continues. Although the optimal MAP value for cirrhosis patients is unclear, there are generally opinions that 60–65 mmHg should be targeted [12]. Norepinephrine (0.01–0.5 μg/kg/min) is recommended as the first-line vasopressor agent to maintain adequate organ perfusion pressure in patients with septic shock [10, 48, 49]. Vasopressin is recommended as a second-line agent to be added to norepinephrine for septic shock [48]. However, these studies were conducted in patients without cirrhosis, and studies are insufficient for patients with cirrhosis or ACLF. Adrenal insufficiency is an overlooked condition and "relative adrenal insufficiency" is common in cirrhotic patients, and is associated with high mortality rates [50]. Specific studies on the effectiveness of steroids in shock in patients with ACLF included small numbers of patients. Although its effect on mortality varies in studies, evidence that it improves shock status is generally more prominent [51, 52]. It should be remembered that adrenal insufficiency may occur in cirrhotic patients with refractory shock. In this case, hydrocortisone 50 mg i.v. every 6 hours or 200 mg infusion can be tried empirically for 7 days or until discharge from the ICU [12].

Management of respiratory failure

Transthoracic echocardiography is a guide in the management of cardiopulmonary complications. Hepatic hydrothorax may exacerbate disorders of gas exchange in the critically ill patient with cirrhosis. Intermittent therapeutic thoracentesis forms the basis of treatment. The presence of tense ascites may also compromise respiratory function by reducing chest wall compliance and may require therapeutic paracentesis. Since further hepatic decompensation may develop in these patients, TIPS is often contraindicated [12].

Pulmonary vasodilator therapy (inhaled NO, epoprostenol) may be considered to optimize in selected cases. Noninvasive ventilation (NIV) should be considered early in patients with AD or ACLF and should be closely monitored for lack of response to treatment [12]. High-flow nasal cannula therapy may be considered as an alternative to NIV. It has advantages over NIV in terms of increased patient comfort, potentially reduced risk of aspiration in the event of HE, and less impairment of venous return caused by the lower positive end-expiratory pressure (PEEP) effect. However, the response to treatment should be closely monitored as it may cause delayed intubation due to gradually worsening hypoxemic respiratory failure [12, 53]. In mechanical ventilation practice, lung protective ventilation and spontaneous breathing whenever possible are advocated. Endotracheal intubation is mandatory in patients with HE grades 3–4 [10]. In patients with AD and/or ACLF who require mechanical ventilation for reasons other than ALI, a lung protective strategy including low tidal volume (6 mL/kg PBW) and low plateau pressure (< 30 cm H_2O) is recommended to prevent ventilator-induced lung injury. During mechanical ventilation for mild ALI (PaO_2/FiO_2, 200–300 mmHg) in ACLF, a low PEEP strategy should be considered. In moderate-severe ALI (PaO_2/FiO_2, < 200 mmHg), a high PEEP strategy may be necessary [12]. In patients with ventilation-dependent cirrhosis, prophylactic antibiotic use is not recommended to reduce mortality or duration of mechanical ventilation. The risk of ventilation-related pneumonia can be reduced by elevating the head 30 to 45 degrees and subglottic suction. It is recommended to use prophylactic PPI in cirrhosis patients receiving mechanical ventilation [10]. Pre-LT intubation increases the incidence of postoperative pneumonia as well as post-LT mortality [8]. Today, in most LT centers, severe pulmonary hypertension (mean pulmonary artery pressure > 45 mmHg) is considered a contraindication for LT [54].

Management of nutrition

Preventing malnutrition and sarcopenia in cirrhotic patients is important in reducing mortality. For patients with cirrhosis and/or ACLF, an objective assessment of nutritional status and risk (NUTRIC) score should be performed at the time of admission to the ICU. Energy and protein requirements should be

measured and targeted at 12–25 kcal/kg. The main energy target is 30–35 kcal/kg/day (or 1–1.4 times the estimated energy expenditure). It should evolve towards higher target goals as the clinical course improves. In addition, a calorie target of 25–35 kcal/kg is recommended to support obese cirrhotic patients during the catabolic state. Nutritional support should be carried out multidisciplinaryly, especially in patients with ACLF hospitalized in the ICU [1, 8, 12]. Protein restriction should not be done, on the contrary, higher protein supplementation should be encouraged (1.2–2.0 g/kg/day) in malnourished patients with ACLF. Enteral nutrition should be preferred in patients undergoing invasive ventilation unless there are contraindications. If oral intake is not possible, enteral feeding should be attempted, ideally using a naso-jejunal tube. However, caution is recommended when using enteral nutritional support in patients with a high risk of aspiration, such as the presence of HE [10]. Nutritional support should be started slowly at 5–10 kcal/kg for the first 24 hours, and serum electrolytes should be monitored both before starting feeding and at least every 12 hours for the first 3 days. To avoid cardiac dysrhythmias, aggressive electrolyte supplementation and cardiorespiratory monitoring are recommended [12].

In patients fasting for more than 12 hours, 2–3 g/kg/day i.v. glucose may be recommended [1]. It should be kept in mind that hyperglycemia may frequently develop in patients receiving nutritional support. It is recommended to target blood sugar levels at 140–180 mg/dL and avoid long-term hypoglycemia. Studies show that tighter glucose control (target blood sugar 80–110 mg/dL) does not lead to a decrease in mortality, and even increases mortality by causing hypoglycemia attacks [12]. Micronutrients should be supplemented when necessary. The development of refeeding syndrome should not be overlooked and patients should be closely monitored for this condition. Enteral nutrition should be started as soon as possible in patients with variceal bleeding. Appropriate assessment of frailty and malnutrition using validated tools is recommended in all patients with ACLF [1].

Liver transplantation

The main reason for the success of LT is correct patient selection. Currently, the MELD system is used in LT listing in many countries. In patients with AD or ACLF, there may be patients whose MELD score does not increase as much as expected. While this does not indicate that the disease is not serious, it may also cause the patient's need for early LT to be overlooked. For this reason, it may lead to various discussions in patients without living donors or in centers where LT with living donors is not performed. Although various scores other than MELD scores have been recommended for predicting post-LT outcomes, their performance is inconsistent [12]. The MELD score does not include cerebral, circulatory, and/or respiratory deficiencies, so it does not prioritize patients with ACLF. Early prediction of transplant-free survival and decision-making for LT before sepsis or multiorgan failure occurs may help improve the outcomes of these patients [4]. In addition to the opinions stating that the APASL-AARC model is better in selecting patients for the LT decision because it detects patients before OF develops [4], the NACSELD-ACLF score can help to determine the patients who need palliative care (> 2 OFs) or LT (≤ 2 OFs). There are also opinions stating that it can save resources when used in this way [11]. In the presence of an initial MELD score > 28, AARC score > 10, HE grades 3–4 with not accompanied by multiorgan failure, or in the absence of overt sepsis, early LT should be considered for patients to increase survival by up to 80% at five years [4, 8].

LT is the only curative treatment option, especially in suitable patients with ACLF. The patient should be evaluated very carefully when deciding on LT. It is vital that the LT time is not too early or too late. For this reason, the "Golden Window" at ACLF is very important. All patients with ACLF-2 and ACLF-3 should be evaluated early if suitability for LT. Patients determined to be suitable in this patient group benefit significantly from LT [1, 6]. There are also studies showing that survival with LT is over 90% in patients with HBV reactivation [4]. On the contrary, meta-analyses have been published showing that post-LT survival is lower in patients with ACLF than in those without ACLF [55]. EASL recommended applying the ACLF-LT program when deciding on LT in ACLF patients [1].

Conditions considered contraindicated for LT have been identified [4, 10, 12]:

- Severe frailty (clinical frailty scale ≥ 7) in critically ill patients with cirrhosis in the ICU
- Sepsis with ≥ 2 OFs or uncontrolled sepsis (MDR, persistent fever, and antibiotic use < 72 hours)
- Severe ARDS (PaO_2/FiO_2 < 150)
- Need for high and progressive doses of norepinephrine (> 3 mg/hour)
- Lactate levels over 9 mmol/L
- HE with requiring ventilator support for > 72 hours
- Active GI bleeding
- Hemodynamic instability
- Advanced azotemia (serum Cr > 4 mg/dL or 300% increase in Cr level compared to baseline or need for RRT)
- ≥ 4 OFs at any given time

Active alcoholism is also a contraindication for LT. However, it is still controversial in the case of severe alcoholic hepatitis. In acute alcoholic hepatitis, especially in steroid-unresponsive patients, LT is becoming a salvage option to improve survival, and it is stated that selected patients should be prioritized for LT [4, 56].

Mortality was found to be approximately 67% of ACLF patients on the LT waiting list, and it has been shown that the factors causing mortality in these patients are mostly caused by sepsis, requiring mechanical ventilation, severe hypotension, and need for RRT [4]. It is stated that due to the significantly high mortality rate in the ACLF-3 clinic, case-based LT decisions should be made without delay, expanded donor criteria/living donor LT should be established for suitable patients and globally futile LT criteria should be established for patients who are thought to not benefit from LT [1]. In the absence of an LT option, these patients may be offered early bridge treatments and liver dialysis [4].

Bridge treatments

Artificial extracorporeal liver support systems are simple dialysis systems. They are able to the removal of water-soluble and albumin-bound toxins from the patient's plasma. Liver support devices and hepatocyte transplantation can theoretically take over some functions of the liver. They are options that can be applied as bridge therapy in patients with ALF and ACLF until recovery or LT. However, although extracorporeal liver support systems provide improvement in biochemical, HE, HRS, and circulatory and immune dysfunction; the expected effectiveness on mortality has not been demonstrated [4, 22]. Hepatocyte transplantation with liver progenitor cells is the other bridge treatment being studied. But there is a lack of long-term effects in this treatment. Other cell-based therapies, enhancement of hepatic regeneration, and intestinal modulation via fecal microbiota transplantation are being attempted. However, they are still far from an alternative to transplantation [8].

Plasma exchange

Plasma exchange has been shown to improve survival in patients with ALF, but its effect on ACLF is not clearly known [10]. Plasma exchange appears to be a promising and effective bridge therapy in the process of LT or spontaneous regeneration in patients with ACLF, especially in combination with treatments that will enhance liver regeneration [4]. Apart from this, there is a short-term survival improvement in patients with HBV-ACLF by using plasma exchange, and the APASL-ACLF definition was used in this study [10].

Single-pass albumin dialysis

In single-pass albumin dialysis, the patient's blood is dialyzed against a dialysate containing albumin to remove unwanted toxins [10]. Patients with severe HE benefits from albumin dialysis, but there is no evidence that it improves the survival of patients with ACLF [1].

The molecular adsorbent recirculation system

The molecular adsorbent recirculation system (MARS) reduces serum Cr and bilirubin levels because it is a molecule removal function of the dialysis system that does not necessarily improve kidney or liver function. Contradictory results were observed in meta-analyses comparing MARS with standard medical treatment. While some of them have been shown to have no benefit in reducing mortality, some have been shown to reduce mortality by 33% [4].

Fractionated plasma separation and adsorption (Prometheus)

Fractionated plasma separation and adsorption (Prometheus); it's an artificial extracorporeal liver support system that the blood cells and large protein molecules are separated from the plasma and molecules smaller than 250 kD. The filtered plasma is then passed through 2 adsorbents, a neutral and an anion exchange resin before being combined with the blood cell filtrate. The blood cells and adsorbed plasma are then dialyzed with a high-flux dialyzer to remove water-soluble toxins. These systems can only perform the detoxification functions of the liver. Although it reduces bilirubin levels, there is no improvement on mortality [10].

It traditionally requires a cell source such as human or porcine hepatocytes. Although they look attractive, the technology is complex and requires a critical mass of cells. Also, there are concerns about xenotransmission [10].

Next-generation treatments

Granulocyte colony-stimulating factor

It is a potential treatment method due to its ability to stimulate the proliferation and differentiation of neutrophil progenitor cells, thus potentially reversing immunoparalysis, and stimulating hepatic regeneration in ACLF. It has been shown to have positive effects on survival in alcoholic cirrhosis and alcoholic steatohepatitis. Studies are showing that it improves liver functions and 3-month mortality in HBV-ACLF. However, no superiority in 90-day mortality has been demonstrated in all-cause ACLF patients. Currently, its routine use is not recommended in patients with AD or ACLF [1, 10, 26].

Mesenchymal stem cell transplantation

They are multipotent cells that can regenerate and differentiate into various cell types, including hepatocytes, and have immunomodulatory properties. There is evidence that it improves liver fibrosis and protects against fulminant liver failure. In HBV-ACLF, umbilical cord-derived mesenchymal stem cells (MSCs) have been shown to improve liver functions, leading to a decrease in MELD score and mortality. However, more and larger studies are required [10, 26].

Toll-like receptor 4 inhibition

Toll-like receptor (TLR)-mediated immune cell activation plays an important role in the innate immune response. It initiates inflammatory processes critical for host defense. Uncontrolled TLR-driven innate cell activation that occurs in cirrhosis is effective in determining the low- and high-grade inflammation characteristic of ACLF [26].

TAK-242

It inhibits TLR-4 activation. Studies are continuing in the trial phase [26].

Recombinant alkaline phosphatase

Lipopolysaccharide (LPS) is an endotoxin derived from the cell wall of gram-negative bacteria. High serum LPS levels are associated with an increased risk of mortality in patients with AD and ACLF. Recombinant alkaline phosphatase (recAP) LPSs can be made non-toxic by dephosphorylation [26].

gDNA and emricasan

In addition to PAMPs, products from necrotic and apoptotic hepatocyte death also trigger the development of SIRS in the pathogenesis of ACLF. End products of apoptotic pathways, such as gDNA (size-laddered low molecular weight DNA), are seen in patients with ACLF. The predominant method of cell death in ACLF is necrosis. Emricasan, a caspase inhibitor, blocks apoptosis. It has been shown to have a hepatoprotective effect on cholestatic and fatty liver disease in animal experiments. In addition, although a decrease in apoptotic markers was observed in ACLF, it did not lead to an improvement in the scores [26].

Mitofusin-2

Mitochondrial fusion protein 2 (Mfn2) has many biological functions, including vital effects on apoptosis and autophagy. Although necrosis is the dominant method of cell death in ACLF, apoptotic cell death also contributes to the clinical presentation. Mitofusin-2 may be part of future combination therapies in ACLF patients [26].

Oxysterol sulfates

Oxysterol sulfates (25-hydroxycholesterol 3-sulfate) are a new class of anti-inflammatory drugs under clinical evaluation and play an important role in lipid metabolism, inflammatory response, and cell survival through epigenetic modification [26].

Statin

Studies are still ongoing to investigate its effectiveness in preventing the development of ACLF in cirrhotic patients, as it shows hepatoprotective and anti-inflammatory properties and causes a decrease in portal pressure. Early results are promising [26].

N-acetylcysteine

NAC is a glutathione precursor that has long been applied in the treatment of paracetamol-induced ALF patients. It has the properties of scavenging free radicals, preventing mitochondrial dysfunction, and supporting the repair of hepatocytes. Studies are showing that it improves intrahepatic cholestasis, coagulation function, and liver biochemistry in HBV-ACLF [26].

Survival

It has been reported that the 28-day survival after NACSELD-ACLF evaluation in patients with hospitalized cirrhosis is as low as 3% [57]. An EASL-ACLF score > 70 at admission or on day 3 is associated with a 90-day mortality rate of approximately 90% [58]. The mortality rate in patients with persistent ACLF-3 after the first week of intensive care support is very high due to potentially limited regenerative capacity [9]. It is known that in patients with a significant increase in survival with LT, ACLF syndrome is reversed in approximately 70% of patients if 90-day transplant-free survival is achieved. However, approximately 1/3 of these patients experience ACLF recurrence within 1 year. Higher platelet count, lower WBC counts, and absence of HE are additional independent predictors of reversibility. Admission AARC grade, or evaluation of transient elastography at admission or follow-up, can identify patients who are likely to regress [4]. HE is associated with increased mortality at all severities and independently of other OFs and is present in approximately one-third of ACLF patients. Mortality increases as the degree of HE increases [4].

The prognosis for patients with ACLF should be determined after 3–7 days of full organ support following ICU admission. 3-7 days after diagnosis in ACLF-3 patients without LT option. It has been shown that the 28- and 90-day mortality of patients who still have ≥ 4 OFs on days or an EASL-ACLF score > 70 is 90% and 100%, respectively [12, 59]. There are opinions that care may be abandoned in these patients. Decisions regarding the futility of care should be based on the feasibility of LT and the potential reversibility of ACLF [1, 10, 12, 60].

Conclusions

The severity of AD is reflected by the degree of SI, while the degree of acute-chronic liver failure is defined by the number of OFs. Identifying and treating triggering factors is the most important step in prevention.

The type of underlying chronic liver disease may also affect mortality, possibly due to extrahepatic factors. While the definitions of AD and ACLF are so detailed, the treatment approach only depends on the decision of moderate or aggressive treatment for the current. In the future, it is expected that early diagnosis, possible triggering factors, and inflammatory markers will be determined and treatment plans will be developed to reverse OF. Early diagnosis and treatment are key to survival. Management currently relies largely on early diagnosis and provision of LT. Determining which patients with AD are most likely to transition to ACLF will allow for simplifying the current "identification soup".

Abbreviations

AARC: APASL-ACLF research consortium

ACLF: acute-on-chronic liver failure

AD: acute decompensation

AKI: acute kidney injury

ALI: acute lung injury

APASL: Asian Pacific Association for the Study of the Liver

CLIF-SOFA: Chronic Liver Failure-sepsis-related organ failure assessment

Cr: creatinine

CRP: C-reactive protein

CTP: Child Turcotte Pugh

DAMPs: damage-associated molecular proteins

DILI: drug-induced liver injury

EASL: European Association for the Study of the Liver

GI: gastrointestinal

HE: hepatic encephalopathy (West-Haven criteria)

HRS: hepatorenal syndrome

i.v.: intravenously

INR: international normalized ratio

LPS: lipopolysaccharide

LT: liver transplantation

MAP: mean arterial pressure

MDR: multidrug resistant

MELD: Model of the End Liver Disease

NACSELD: North American Consortium for the Study of End-Stage Liver Disease

NIV: noninvasive ventilation

NO: nitric oxide

OF: organ failure

PAMPs: pathogen-associated molecular patterns

PEEP: pozitif ekspirasyon sonu basıncı

PICD: paracentesis-induced circulatory dysfunction

PT: prothrombin

RAAS: renin-angiotensin-aldosterone system

RRT: renal replacement therapy

SBP: spontaneous bacterial peritonitis

SDC: stable decompensated cirrhosis

SI: systemic inflammation

SIRS: systemic inflammatory response syndrome

TIPS: transjuguler intrahepatik portosistemik shunt

TLR: Toll-like receptor

WBC: white blood cell

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