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REVIEW ARTICLE

Acute-on-Chronic Liver Failure: Diagnosis to Liver Transplantation

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Abstract: Introduction: Patients with acute-on-chronic liver failure (ACLF) have different characteristics from those presented by non-ACLF patients with liver diseases. The degree of ACLF impacts the outcome with or without transplantation, with divergences in the literature, especially regarding post-transplant prognosis. **Objectives:** To review the different aspects of patients with ACLF, including the concepts of the syndrome adopted by various institutions, the treatment of complications, and to describe the knowledge about the outcomes with or without transplantation of patients with the syndrome reported in the literature. **Methods:** Twenty-two articles were included in the PubMed, MEDLINE and the Scientific Electronic Library Online (SciELO) databases with the descriptors "ACLF definitions" and "Liver transplantation ACLF." The concepts and data from the selected texts were compared and used as a basis for writing this article. **Results:** There are some differences in the definition of the syndrome, varying especially between Western and Eastern countries. ACLF patients awaiting liver transplantation have characteristics distinct from those presented by non-ACLF patients. The degree of ACLF also impacts the outcome with or without transplantation, with divergences in the literature especially regarding the post-transplant prognosis of ACLF-3 patients, with an increasing trend in the indication of transplantation even for these patients. **Conclusions:** Outcomes vary among ACLF patients according to the degree of the disease. Liver transplantation has been more frequently indicated in ACLF-3, with waiting time impacting outcomes. Further studies are needed to define which subgroups of patients benefit most from liver transplantation.

Keywords: Acute Chronic Liver Failure; Critical Care; Decision Making; Liver Failure; Liver Transplantation; Survival.

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a condition characterized by acute decompensation of cirrhosis associated with organ failure, with high short-term mortality.[1,2] Several societies on different continents have sought to establish a definition for the syndrome, based on aspects such as organ failure and precipitating factors of the disease.

Literature data indicate that between 24 and 40% of cirrhotic patients admitted to hospitals present ACLF.[3] Generally, the syndrome has a precipitating factor, most often bacterial infection, followed by active alcoholism and acute reactivation of hepatitis B[2]; however, the cause is not identified in 40 to 50% of the time.[2,3] In the West, most patients who develop ACLF have cirrhosis secondary to alcohol use or hepatitis C virus as the cause of the liver disease. Its mortality was described as 33% by the Canonic study, but found in the literature as between 15 and 80% within

28 days, depending on the degree of disease.[4] Even in patients who recover from ACLF without transplantation, the estimated mortality over the next six months is estimated to be between 40 and 60%.[5]

This article addresses different aspects of patients in ACLF, covering the concepts of the syndrome adopted by different institutions, the management of complications, and the summary of knowledge about the outcomes with or without transplantation in patients with the syndrome.

METHODS

Research Strategy

We conducted a nonsystematic review study that aimed to review the different aspects of patients in ACLF. The search for articles was conducted by PubMed, MEDLINE and the Scientific Electronic Library Online (SciELO) databases using the descriptors "ACLF definitions" and "Liver transplantation ACLF," conducted between September 2021 and January 2022. The search encompassed 469 articles. Among them, 22 were selected according to their abstract and title presenting the information most objectively consistent with the intent of our study and most dense that allowed a review of aspects of the syndrome of patients in ACLF, their diagnosis, treatment, and experience in liver transplantation for this population.

Articles published before 2012 were excluded. All included articles were published in English. The concepts and data noted in the selected texts were compared and used as a basis for writing this article (Figure 1).

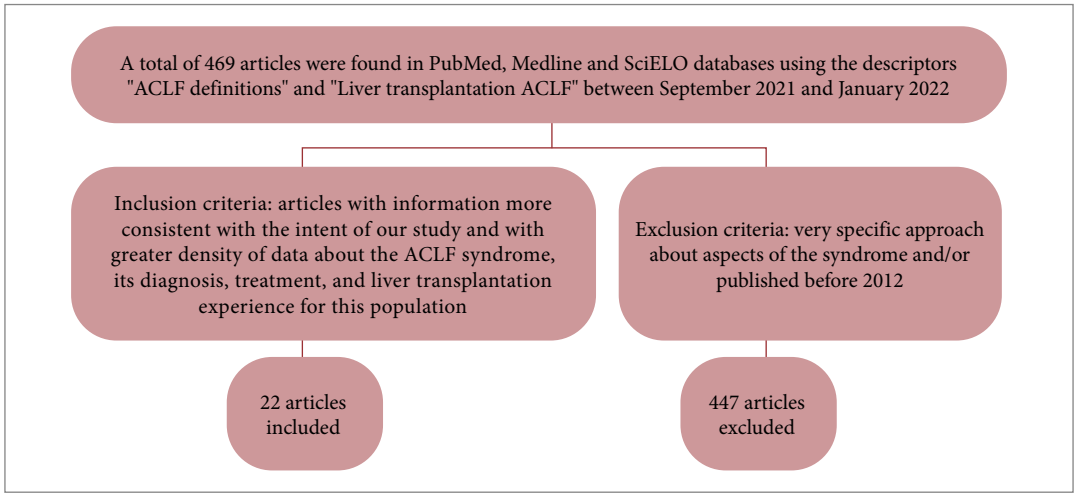

Figure 1. Flowchart of the research methodology of the articles included in this study.

RESULTS

Definitions for ACLF

There are more than 10 definitions for ACLF. The first one was proposed by the Asian-Pacific Association for the Study of the Liver (APASL). After expert consensus, positive and negative criteria for the diagnosis of the syndrome were proposed, updated in 2014 and 2019 after analysis of data collected from 1,402 and 3,300 patients, respectively.[6] According to this definition, to confirm the diagnosis of ACLF, previous chronic liver disease should be present (with or without cirrhosis, excluding steatosis), with a precipitating event causing acute liver failure (exclusively in this classification, always an intrahepatic cause). As exclusion criteria, presence of a previous ascites episode or extrahepatic factor triggering decompensation, such as bacterial infection.[6,7] Thus, liver failure is the core of this definition, and may be associated with hepatic encephalopathy and dysfunction or failure of other organs as a consequence, but these are not criteria involved in the definition itself. Also, according to this classification, acute liver failure is defined by jaundice (serum total bilirubin level greater than or equal to 5 mg/dL) and coagulopathy (International Normalized Ratio [INR] greater than or equal to 1.5 or prothrombin activity less than 40%) associated with a four-week course of ascites and/or hepatic encephalopathy.[6]

The definition of ACLF proposed by APASL has not proven adequate for the Western population, most of which patients with liver disease have decompensation linked to bacterial infection (mainly spontaneous bacterial peritonitis) or active alcoholism.

With the purposes of defining the concept of ACLS, evaluating the prevalence, and improving the accuracy of the prognostic criteria of the syndrome, in 2009, the European Association for the Study of Chronic Liver Failure (EASL-CLIF) Consortium

conducted a large observational study in several European centers, the Canonic study, which included 1,343 patients hospitalized with decompensated cirrhosis in 12 European countries.[7] According to the findings of this study, the diagnosis of ACLF was defined by the presence of acute decompensation of cirrhosis associated with failure of one or more organs—by their presence, number and types of organ affected—and high short-term mortality (≥ 15% at 28 days).[3,6] As per the established definition, patients with previous decompensation of cirrhosis can also be characterized as in ACLF. Disease severity was classified into grades 1, 2, and 3, depending on the number of organs affected, with the mortality outcomes quite different.[3,7]

The EASL-CLIF turned out to be the definition that best predicts the prognosis of patients in ACLF.[7] Widely used in the evaluation of critically ill patients, the SOFA score (which includes evaluation of liver, kidney, brain, coagulation, circulation and respiratory function) was adapted to contemplate relevant characteristics of cirrhotic patients, receiving the name of CLIF-SOFA and later simplified to CLIF Consortium Organ Failure (CLIF-C OF) score, being the specific score to predict the prognosis of patients in ACLF.[3] This score evaluates six systems: liver, kidneys, brain, coagulation, circulation, and respiration.

Derived from the CLIF-C OF, the CLIF-C ACLF score was developed, also seeking to estimate more accurately the mortality of ACLF patients at 28 days. CLIF-C ACLF was indicated as having the ability to predict mortality with an accuracy of up to 25% more than the referred models, especially when applied to ACLF patients grade 3. Studies have already validated its superiority in this regard when compared to the model for end-stage liver disease (MELD), MELD-Na, and Child-Pugh. The CLIF-C ACLF included the patient's white blood cell count and age, proving to be a very good predictor of mortality. It ranks patients on a linear scale from 0 to 100, with the severity increasing as the score increases.

The analysis of the outcomes of patients with CLIF-C ACLF values greater than 64 led to the questioning of the futility of indicating transplantation in these patients, since at 65 points the mortality rate was noted to be greater than 80% within 28 days.[5,8] Analyses derived from the Canonic study also pointed out that ACLF patients with more than four organ failure or CLIF-C ACLF greater than or equal to 64 between days 3 and 7 of ACLF diagnosis had a 28-day mortality rate of 100%.

A study by Correlius demonstrated that with a score greater than or equal to 55, the 28-day mortality rates are 80%, and with a score greater than or equal to 70, they are 100%, making intensive support or listing for HT futile.[8] In the Canonic study, most patients had cirrhosis as a result of alcohol and hepatitis C virus, and the main ACLF triggering events observed were alcohol hepatitis and bacterial infection and/or gastrointestinal bleeding.[6]

In America, the definition of ACLF given by the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) was proposed in the publication of their observational study that included 507 patients with cirrhosis admitted to 18 hospitals in the United States and Canada, whose data were collected prospectively.[6] Similar to the EASL definition, it also considered patients with or without episodes of prior decompensation. The main cause of ACLF precipitation found was (extrahepatic) infectious. It is characterized by the failure of two to four systems, as it excludes hepatic and coagulation causes (it considers four systems: kidneys, brain, circulatory, and respiratory).

There is also a definition for ACLF unique to patients with hepatitis B, with or without cirrhosis, developed by the Chinese Group on the Study of Severe Hepatitis B (COSSH), published in a prospective, observational study that included 1,322 patients with cirrhosis or liver failure due to hepatitis B virus admitted to 13 hospitals in China. These patients had chronic liver disease with or without cirrhosis, with acute decompensation.[6] The main causes of decompensation seen in them were hepatitis B virus reactivation and/or (bacterial) infection. It also evaluates six systems or organs for its definition: liver, kidneys, brain, coagulation, circulation, and respiratory.[6]

Concepts about the ACLF syndrome have been constantly revised. The identification of ACLF shows that precipitating events of cirrhosis decompensation associated with organ failure are responsible for a large proportion of deaths and hospitalizations of liver disease patients. Interestingly, ACLF occurs in patients with present cirrhosis, or in its absence, but with underlying liver disease.[3]

ACLF Grades

APASL

The severity proposed by the APASL definition was given according to the APASL ACLF Research Consortium (AARC) score, updated in 2014, whereby the classification is given by scoring according to serum bilirubin level, hepatic encephalopathy, INR, serum lactate and creatinine levels.

Table 1. Acute-on-Chronic Liver Failure Research Consortium (AARC)* APASL score.

Points	Total bilirubin (mg/dL)	Encephalopathy grade	International Normalized Ratio	Lactate (mmol/dL)	Creatinine (mg/dL)
1	< 15	0	< 1.8	< 1.5	< 0.7
2	15-25	I-II	1.8-2.5	1.5-2.5	0.7-1.5
3	> 25	III-IV	> 2.5	> 2.5	> 1.5

*AARC-ACLF grade according to the scores indicated: grade 1: sum of 5-7 points; grade 2: sum of 8-10 points; grade 3: sum of 11-15 points.

EASL-CLIF

The classification criteria proposed by the EASL-CLIF also classify the ACLF patient in grades 1, 2 and 3, but depending on the number of organs involved, with very different mortality outcomes. [3,7] ACLF grade 1 includes three subgroups:

- patients with renal failure only;
- patients with failure of only one of the systems—hepatic, coagulation, circulation or pulmonary—associated with an increase in the serum creatinine level of 1.5 to 1.9 mg/dL, or hepatic encephalopathy grade I or II, or both;
- patients with neurological failure with a serum creatinine level of 1.5 to 1.9 mg/dL;

ACLF grade 2 covers patients with failure of two organs (or systems), and ACLF grade 3, patients with failure of three or more organs (or systems).

NACSELD

Patients are also classified by NACSELD's definition of ACLF according to the number of systems affected: failure of two, three, or four organs or systems.

The following items are definers of failure:

- renal: need for dialysis or other form of renal replacement;
- brain: hepatic encephalopathy grade III or IV (West Haven criteria);
- circulation: mean arterial pressure < 60 mmHg or 40 mmHg reduction in systolic pressure from baseline, despite adequate fluid supply and cardiac output management;
- respiratory: need for mechanical ventilation.

COSSH

The definition for ACLF unique to patients with hepatitis B developed by COSSH uses the CLIF-C OF score to establish organ failure and resembles the EASL classification, also classifying patients into three grades according to severity: ACLF grade 1 is subdivided into:

- patient with renal failure only;
- patient solely with renal failure associated with INR > 1.5 or more, or serum creatinine of 1.5 to 1.9 mg/dL, or encephalopathy grade I or II, or any combination of these changes;
- patient with single system failure—coagulation, respiratory, circulatory—associated with serum creatinine between 1.5 and 1.9 mg/dL or hepatic encephalopathy grade I or II, or both;
- patient with brain failure associated with a serum creatinine level of 1.5 to 1.9 mg/dL.

ACLF grade 2 includes patients with failure of two organ systems, and ACLF grade 3 those with failure of three or more.[6]

More recently, a score has been proposed by NACSELD to predict 30-day survival in ACLF patients. By NACSELD, the diagnosis of ACLF is made by the failure of two or more extrahepatic organs. In a 2018 study, the ability to predict 30-day mortality in ACLF patients was evaluated at several centers in North America, looking at 2,675 patients. This score considers patient age, MELD value, white blood cell count, serum albumin on admission, and presence of infection. It was observed that the main predictor of mortality was the presence of active infection, regardless of the MELD value, white blood cell count, and albumin value at admission. However, in a study conducted in Europe, the NACSELD-ACLF score was shown to underestimate the diagnosis of ACLF patients when compared to EASL-CLIF.[2,22]

The World Gastroenterology Organization proposes a classification based on the underlying liver disease of patients with ACLS:[3]

- type A ACLF: patients with underlying liver disease, without cirrhosis;
- type B ACLF: patients with compensated prior cirrhosis;
- type C ACLF: patients with previous decompensated cirrhosis. This classification is not covered in the definition of ACLF adopted by the APASL, in which the main negative criterion for diagnosis is the presence of a previous episode of ascites.

Paradoxically, patients in group C, that is, who have had previous decompensation of cirrhosis, have better outcomes when with ACLS. The mechanism is not yet known, but it seems to be related to adaptation to the hyperinflammatory state of the disease.[3]

Decompensated cirrhosis vs. ACLF

Cirrhosis is a chronic and progressive liver disease characterized by replacement of the liver parenchyma by fibrosis, with destruction of the architecture and parenchyma, as the end result of chronic liver diseases of various etiologies. The disease progresses without evident symptoms during the first 10 years of its evolution, a period known as compensated cirrhosis. After that, changes in blood flow and liver metabolism lead to the accumulation of ascites, a period called decompensated cirrhosis, associated with a survival of 3 to 5 years.[7] This phase is also characterized by the onset of coagulopathy, encephalopathy, recurrent infections, and digestive bleeding, requiring hospitalization.[9]

It is known that when the cause is treated, it is possible to revert the state from decompensated to compensated cirrhosis, with improvement in the patient's status. Thus, it is indicated that, in alcohol cirrhosis, the patient should stop drinking, and, among those with hepatitis B or hepatitis C virus, have the virus treated,[7] thus preventing the process of continuous necrosis and destructuring of the liver parenchyma architecture, which increases resistance to venous flow and, consequently, portal hypertension.

The differentiation between decompensated cirrhosis and ACLF is the presence of organ failure—and not just associated dysfunction.[7] While in ACLF we observe intense systemic inflammatory process and organ failure with high 28-day mortality, in acute decompensated cirrhosis the inflammatory state is moderate and the 28-day mortality is low (2%, according to the Canonic study).

The Predict study, conducted in 2017 by EASL, aimed to identify the factors enrolled in acute decompensation of cirrhosis that predict the onset of ACLF after following 1,071 patients admitted with acute decompensation of cirrhosis in 48 hospitals in Europe. Of these patients, 218 developed ACLF within 90 days. Among the most striking features of the group were the presence of organ dysfunction and severe systemic inflammation, with several episodes of bacterial infection, and progression to ACLF syndrome, closely linked to these episodes, with onset in a short period of time.[9] Patients who progress to ACLF have a higher prevalence of liver dysfunction or failure, encephalopathy, renal dysfunction, and ascites. Despite the identification of these factors, the study did not develop a tool or scale that could better predict progression to ACLF than CLIF-C-AD and MELD-Na.[9]

Although contradictory, some studies reviewed in our work describe that up to 40% of patients who develop ACLF do not have an identified precipitating factor. On the Asian continent, reactivation of hepatitis B virus in chronic infection, hepatitis A and E infection, acute alcoholic hepatitis, and acute bacterial infection are most described as precipitating triggers of ACLF. In the West, the most common causes are bacterial infections and active alcoholism.[7]

Sepsis is the major complication of cirrhosis and the most common cause of ACLF precipitation, being recognized in 30% of cases.[7] It arises from multiple immune deficiencies and is often a cause of death or removal from the transplant list.[1,2] Increased permeability of the intestinal walls predisposes to spontaneous bacterial peritonitis, a major cause of sepsis.

The pathophysiology of patients with ACLF is strictly correlated to a state of inflammation, with increased levels of interleukins, inflammation factors (especially IL-6, IL-1β, IL-8, and polymerase chain reaction [PCR]), and leukocytosis in these patients, even when no active focus of infection is identified. The worse the organ dysfunction, the higher these markers, usually evidencing worsening inflammation.[2,7] The elevation of these elements causes collateral tissue damage and contributes to organ failure. The role of molecules expressed by microorganisms known as pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP) is well described in the activation of the systemic inflammatory state. PAMPs are recognized by cellular pattern-recognition receptors (PRR) of the innate immune system, producing an intracellular signaling cascade that precipitates the synthesis of proinflammatory factors. High serum levels of PAMPs are observed, for example, in cases of bacterial translocation that occurs in the intestinal lumen because of the increased permeability of the intestinal mucosa, bacterial overgrowth, and worsening of the immune system seen in cirrhotic patients.[6]

As already mentioned, the inflammatory state in ACLS occurs even in the absence of infection and is linked to the presence of DAMP release by the death or damage of PRR-related cells. Several forms of liver injury leading to DAMP release have been described, such as alcohol hepatitis and ischemia-reperfusion liver damage.[6]

The state of systemic inflammation culminates in tissue hypoperfusion, largely caused by increased nitric oxide release, whose synthesis is also stimulated by PAMPs. By increasing nitric oxide, we have splanchnic vasodilation and, as a response, renal hypoperfusion, which culminates in acute renal failure or hepatorenal syndrome.[1,6]

Tissue damage due to leukocytosis and infiltration of defense cells into the capillaries generates a cycle of cellular injury, emergence of microthrombi and apoptosis, as well as release of DAMPs and progression of inflammation.[6] Enrolled in organ failure, mitochondrial dysfunction has also been observed in ACLF patients, with deficient adenosine triphosphate production and oxidative phosphorylation observed.[6]

Treatment

ACLF Patient Management

Treatment of ACLF patients aims at prompt identification of the cause (when identified) and management of the organ failure that accompanies the syndrome. The most common of the observed dysfunctions is renal, followed by coagulopathy and encephalopathy. Intensive care unit (ICU) care is essential, and these patients must be transferred to specialized centers that offer liver transplantation.

The ACLF patient's condition is very dynamic, and rapid improvement or worsening can be observed. The first 3 to 7 days of evolution usually correlate better with prognosis than the severity exhibited at the onset of the condition.[6] According to the Canonic study, ACLF-3 patients, 3 to 7 days after diagnosis have the worst prognosis, which is directly linked to the number of organ failures.[6]

ACLF patients must be admitted to the ICU. They are immunodeficient and susceptible to infections, which, when installed, present potential severity. Already at admission, 37% of patients have some infection, and 46% of the remaining patients develop an infection in the following four weeks.[6] MELD and Child-Pugh scores may not adequately reflect the patient's organ dysfunction status.[22]

Combating infection and treating sepsis

Broad-spectrum microbial therapy is indicated, with active search for possible foci of infection. Being extremely immunosuppressed, sarcopenic, manipulated, and invaded, ACLF patients are very susceptible to fungal infections.[1] Antifungal therapy should also be considered, especially when there is no improvement after 48 h of antimicrobial therapy.[1]

Management of renal failure

It is known that pretransplant ACLF patients with acute renal failure are predisposed to worse post-transplant survival and increased rates of chronic kidney disease.[1] Albumin infusion seems to be a protective effect in renal failure stages I and II and in hepatorenal syndrome. Also in hepatorenal syndrome, vasopressors such as norepinephrine and terlipressin are the most important tool in fighting the disease.[6] Hemodialysis should be used whenever necessary, but early institution is advised to be avoided.[6] The United Network for Organ Sharing (Unos) in the United States guides simultaneous kidney and liver transplantation for patients with ACLF and glomerular filtration rate < 25 mL/min or who need dialysis for six or more weeks.[6]

Respiratory system protection

Orotracheal intubation is indicated for patients with sensory impairment (Glasgow score of 8 or less) and encephalopathy grade IV as airway protection. It is important to use ventilatory protection strategies. Prone position is advisable whenever possible. Drainage of ascites through paracentesis in case of a tense abdomen that restricts thoracic expansion is also generally indicated. Directly associated with hepatopathy are: portopulmonary hypertension, hepatopulmonary syndrome, hydrothorax. Patients on ACLF, however, may develop any of the pulmonary complications present in other critically ill patients.[1]

Hemodynamic control

To compensate for portal hypertension and splanchnic vasodilation, the ACLF patient remains in a hyperdynamic state. Added to this, the increased circulation of neurons as a result of the decreased circulating blood volume promotes sodium and water retention. Cardiac dysfunction, seen in up to 50% of patients in ACLF, can impair circulatory function, affecting the patient's ability to tolerate HT.[1] It is advised to maintain mean arterial pressure measurements > 65 mmHg; consider the use of 5% albumin for volume resuscitation, especially in cases of spontaneous bacterial peritonitis, acute renal failure, and drainage of bulky ascites during paracentesis; prefer noradrenaline as a vasopressor, followed by epinephrine and vasopressin; use intravenous hydrocortisone in case of refractory shock (norepinephrine > 0.5 mg/kg/min).[6]

Coagulation control

Fibrinogen and platelet replacement is advised in patients with severe deficiency (respectively, < 1 g/L and < 20,000 × 10^9/L) to undergo invasive procedures. Prophylaxis for deep vein thrombosis should be performed in patients without severe coagulopathy.[6]

Central nervous system

Traditional management of encephalopathy is advised, with enemas and lactulose. Avoid benzodiazepines and deep sedation. Refractory cases with normal serum ammonia levels should be submitted to an electroencephalogram and cranial imaging exam[1,6] to exclude other causes.

Overall, 38% of ACLF patients with encephalopathy respond to corticosteroids, although when of alcoholic etiology a worse response to its use is observed. However, for responders, it should be used, weighed against the risks of bacterial infections.[6]

While on the waiting list, ACLF candidates do not yet have proven effective liver function replacement therapies. Some studies have tried to evaluate the efficacy of extracorporeal liver support, but without showing an increase in survival. This therapy would replace three liver functions: detoxify, stimulate liver regeneration, and prevent progressive liver injury. Some systems have been studied, including the molecular adsorbent recirculating system, Prometheus and stem cells, all without changing mortality rates so far.[5]

Two European multicenter studies evaluated the benefit of extracorporeal therapy in ACLF and found no impact on survival, despite improving encephalopathy. More recently, the possibility of plasma exchange to remove toxins and inflammatory mediators has been discussed, with the use of albumin as a bridge to transplantation, but so far without conclusive results pointing to benefits.[6]

Transplantation in ACLF

Experience and knowledge of HT for the ACLF patient has been increasing worldwide. The main issue currently being explored addresses the identification of the best time for transplantation, which has been called the *golden window,* when the patient would

be in the most opportune clinical situation for the procedure. With the identification of the best time for the procedure, the identification of the patient with indication for the procedure also compounds the issue. Not all ACLF patients will have real benefit from transplantation, because it is known that some have extremely poor prognosis even if taken to HT. Thus, discriminating these patients becomes fundamental, given the scarcity of graft supply.

Patients in ACLF grade 1 have little difference in the prognostic outcome of transplantation when compared to those without ACLF undergoing liver transplantation, and there is consensus among all societies on the indication of HT at this stage of the disease. However, grade 3 patients have post-HT mortality at substantially higher rates.[6] While the survival rates after transplantation of patients with ACLF grades 1 and 2 are described as 82 to 90% after the first year, in cases of failure of three or more organs (ACLF-3), extreme patient impairment is observed, in which the survival rates or response to HT can approach up to 80% mortality, and in certain cases of extreme severity the act of HT may be considered a futile treatment.

Both the Unos and European associations were able to show improvement in outcomes with the indication of HT for ACLF-3 patients.[5] In general, patients with ACLF grade 1 or 2, as long as they do not have uncontrolled infection, are considered to be in the *golden window, a* time that may end when they reach stage 3 of the disease, even when these patients have a low MELD-Na score.[1,10] Following the trend of most groups and studies today, according to the Canonic study, even patients with more than three organ failure or CLIF-C ACLF > 64, as well as critically ill patients who have shown improvement of their ACLF grade in the short term, should be indicated for transplantation, since they have a poor prognosis if not transplanted, with findings of relatively low post-HT complication rates.[8]

Mortality outcomes for ACLF-3 patients vary in the literature. Post-HT survival for these patients is sometimes described as low after the first year of transplantation; some centers report 50 to 80% survival at one year. In a study by Vinay that included 3,636 patients transplanted in ACLF, a significant benefit in one-year survival was demonstrated for patients with ACLF grade 3 who were able to switch to ACLF grade 2 undergoing HT, especially in cases of patients under 60 years of age, for whom the survival rate was estimated at 88% at one year. This same study was the first to point out that recovery from circulatory, respiratory, and neurological failure had the main impact on improving one-year survival in transplanted ACLF-3 patients. It also showed that patients older than 60 years had a survival rate below 75% at one year, but that when these same patients older than 60 years were able to improve their condition to ACLF-2, they had a survival rate of 82.7% at one year.[11]

Data from a meta-analysis indicated a significant difference between the survival of transplanted and nontransplanted ACLF patients: respectively, 85.3% vs. 28.2% at one year. The most important predictor in survival of ACLF patients was clearly pointed out as the degree of ACLF: the higher the number of organ failure, the worse the outcome, with ventilatory failure being the main negative predictor pointed out in this study. This meta-analysis also revealed that delay in transplantation, recipient age, graft quality, and the need for mechanical ventilation before transplantation were associated with worse outcomes. It also found that the length of hospital and ICU stay, as well as the consumption of hospital supplies, was higher in transplanted ACLF patients when compared to nontransplanted ACLF patients.[12]

Another important consideration is that ACLF patients with loss of renal function do not always recover it, with one study showing permanent mean glomerular filtration rate loss of 10 mL/min/1.73 m^2 more than non-ACLF patients after one year of HT. It also showed that the loss of function caused by acute tubular necrosis would be potentiated by the proinflammatory factors of the ACLF state and that failure to recover renal function after three months of HT appears to be the biggest predictor of long-term loss.[13]

Long-term (5-year) survival after HT in ACLF patients was noted to be 67.7% for ACLF-3 patients and 75 to 79% in ACLF-1 or ACLF-2 patients, and the most recurrent cause of death for ACLF patients was infection-related. For non-ACLF patients, infections and malignancy were the leading causes. For eligibility of patients for transplantation, the literature suggests accepting a minimum estimated survival of 50% for 5 years.[14] Even for ACLF-3 patients, the study indicated a 5-year survival of 67.7%, speaking in favor of indicating the procedure for these patients as well.

The use of the MELD (and MELD-Na) scale values for prioritizing patients on the list is associated with very critical patients, possibly already outside the ideal window for transplantation. It is necessary to think about a new classification in order to prioritize ACLF patients to take advantage of the most opportune moment for transplantation, avoiding the progression of the condition, when sometimes the patient becomes too severe for the procedure.

The MELD-Na score, initially without sodium level assessment (MELD), was proposed in 2000 for prognostic assessment of patients undergoing transjugular intrahepatic portosystemic shunt. In 2002, it was widely adopted to sort the list of patients waiting for HT. The MELD score had the benefit that, since it assesses biochemical characteristics, it cannot be easily manipulated or dependent on the assessor's gauging, as it was with the Child-Pugh model, whose parameters such as ascites and encephalopathy lacked precision in their measurement.

As a criticism of the MELD or MELD-Na model for sorting the graft waiting list, the scoring of some patients by this model may not reflect the severity of patients in ACLF, as in the case of encephalopathic, sarcopenic, those with refractory ascites, those with primary sclerosing cholangitis, hepatopulmonary syndrome, and hepatocellular carcinoma (HCC) (although HCC cases would

benefit from modifications in scoring). It can be stated that ACLF patients have distinct characteristics and do not always exhibit scores that are compatible with their severity status. Nor are important functions such as circulatory system, respiratory system, age, and white blood cell count, relevant factors that impact the prognosis of ACLF.[5]

Furthermore, a cohort study conducted in the United States also noted that the MELD-Na score was unable to predict the 90-day risk of death in ACLF patients,[15] and only a small proportion of these patients were able to score high enough to receive an organ offer, despite the high mortality rate, and were disadvantaged on the waiting list. This inability of the MELD-Na score to assess ACLF patients was more evident among patients with grade 1 than those with grade 2 or 3; only a minority of patients were able to score high enough to receive a liver offer. Still, for all ACLF patients, the MELD-Na score was the main factor in considering HT for patients. Many of them do not score high enough to have this therapeutic possibility contemplated.[15]

In the cohort of this study, although the mean score of ACLF patients was higher than that of non-ACLF patients (26 × 15, respectively), the 90-day death rates were 21% for non-ACLF patients and 40% for ACLF patients, being underestimated by MELD-Na in the latter. Thirty-five percent of ACLF patients who went on HT had a mean MELD-Na score higher than the mean score of non-ACLF patients (but when ACLF patients had a MELD-Na ≥ to 35, this proportion dropped to 9.1%, as patients benefited from Share-35, a resolution that prioritizes patients in such a score). Also, of the total ACLF patients studied, only 5% were considered for liver transplantation and less than 1% were ever listed.[15]

As cited, the mortality of ACLF-3 patients on the transplant waiting list is higher, even among those with lower MELD-Na. The literature suggests that ACLF-3 patients may have similar mortality to patients in acute liver failure.[15] For these, liver transplantation performed within less than 30 days of listing was associated with lower mortality, with survival rates described as high as 80% at one year. A 2019 study by Sundaram *et al*. pointed out that mortality on the transplant waiting list is higher for patients with ACLF grade 2 or 3 with MELD < 25 than for those without ACLF and with MELD ≥ 35.[10] It should be remembered here that systemic inflammation status is not covered by the MELD (or MELD-Na) score, although, as already mentioned, especially increased circulating cytokines correlate strongly with unfavorable outcome in ACLF.[1,5]

In the same article, the main factor associated with post-HT mortality or delisting of ACLF-3 patients was the need for mechanical ventilation, besides the use of a marginal liver (donor risk index [DRI] ≥ 1.7), which also decreased survival after the first year of transplantation. The analysis of ACLF-2 patients associated neurological and renal failure with delisting or death while waiting and mortality in the first year after transplantation, in this case also with the use of mechanical ventilation.[15]

Thinking about these uncertainties, an interesting study conducted with patients registered at Unos in 2021[16] tried to develop a Markov chain to maximize the survival of ACLF patients listed in the first 7 days. To do so, it divided 5,851 patients into six groups (younger or older than 60 years, number of failing organs [3 × 4-6], liver or extrahepatic failure), considered waiting time on list, and compared 1-year survival outcome regarding early organ receipt and graft quality (DRI ≤ 1.7 = optimal; or DRI ≥ 1.7 = marginal liver). For deciding the best time to accept the graft offer, risk of death without transplantation, post-HT survival, and uncertainty of the quality of grafts offered later were considered. The study found that, for all patients, considering the first 7 days on the waiting list, early transplantation was the main factor to positively impact survival, especially for patients > 60 years of age and those with 4-6 organ failure (among these, at any age). Also, by the results of the study, even with marginal grafting, delaying transplantation makes worse the survival chances of the ACLF-3 patient, given the high mortality risk day after day on the waiting list. This study further suggests that waiting for improvement of a system failure to perform transplantation is of little benefit, since the chances of recovery are low in these patients.[15]

The mortality of ACLF patients on the waiting list varies greatly between countries around the world, even within the same continent. A study in 20 HT centers in Europe showed a mortality rate of 7.6% in Spain versus 28% in the Netherlands, for example.[17] The main factors indicated as related to increased mortality after transplantation were serum lactate level > 4 mmol/L, need for renal replacement therapy, and multidrug-resistant germ infection while on the waiting list. The presence of multidrug-resistant germ infection was also associated with the most severe conditions before transplantation, usually in ACLF-3 patients on renal replacement therapy or in the ICU.[17]

This same study showed other important divergences on the practice of transplantation for ACLF patients, with significant differences in the rates of ACLF patients who end up being taken for transplantation, possibly linked to the difference in access to HT across regions, but that the survival rate of ACLF patients taken for transplantation after one year was over 80% and that 25% of patients died on the waiting list. The authors draw attention to the need to match organ supply for with ACLF-2 and 3 with parameters other than MELD score alone. It was also pointed out that the difference in the proportion of ACLF patients who are taken to HT is not explained by organ supply alone, since some countries with fewer offers were able to take more patients to the procedure.

There seems to be a greater association between the teams' perception of the outcomes of HT in ACLF patients and how these patients compete on the waiting list for supply with other patients. In the study, the mean number of days on the waiting list for HT in ACLF patients was 20, 8, and 5 days, respectively, for patients with ACLF grades 1, 2, and 3, and the death of patients who did not go to HT occurred on average on the seventh day, which allowed the authors to state that in these more severe patients,

death was possibly related to the absence of transplantation.[17] In view of better outcomes, the following should be considered in the allocation of the organ destined for the patient in ACLF: donor patient age, cold ischemia time, and transplant logistics.

Heise *et al.*[18] published a paper in 2018 suggesting an algorithm for decision making in the treatment of ACLF patients, according to which a daily reassessment between days 3 and 7 of the evolution of the condition would guide the decision whether to transplant the patient or not: if the patient presents with CLIF-C estimated mortality greater than 80%, probably listing to HT may not be a reasonable choice.

A report by Unos showed that specifically in ACLF-3 patients, post-HT survival when the procedure occurred within 30 days of diagnosis was 82%, and when it occurred thereafter, 79%. On the other hand, studies have shown that recovery or improvement of organ function prior to HT also improves survival outcomes. One of them, evaluating patients after one year of HT, showed that patients who went from ACLF-3 to ACLF-2 before the procedure had a survival rate of 88%, while those who remained in ACLF-3 at transplantation had rates of 82%.[5] Unfortunately, in the study, less than 25% of the patients listed in ACLF-3 were able to switch to ACLF-2.

Reviewing the literature, it is possible to notice an increasing trend of favorable opinion towards HT for ACLF-3 patients; however, the discrepancy between one-year survival outcomes in these patients points to the need for greater knowledge to identify which patients will benefit from the procedure and which present a poor prognosis and that, despite transplantation, will invariably evolve to death.

Aiming at the identification of ACLF-3 patients with benefit from HT, a study conducted in Europe proposed the Transplantation for ACLF-3 Model (TAM) score, a tool that can be applied at the bedside. Developed by analyzing outcomes of already transplanted patients, the TAM considers the main prognostic factors identified in the Liver Transplantation for Critically Ill Cirrhotic Patients study[19] on one-year post-HT mortality in ACLF-3 patients: recipient age $\geq$ 53 years, serum lactate level $\geq$ 4 mm/L, mechanical ventilation with PaO_2 /$FiO_2 \leq$ 200 mmHg, and WBC count $\leq$ 10 G/L. The presence of three or four negative factors would speak against the indication of HT, since the survival outcome found in the study population was 9.1% at one year. In contrast, patients with 0-1 risk factor had 84.5% survival after one year of HT.[19]

In a study recently conducted in France[20], the following predictors of 90-day post-HT mortality were identified: age, diagnosis at the time of listing (end-stage liver disease or hepatocarcinoma), infection in the month preceding transplantation, presence of ACLF at the time of transplantation, and donor gender (worse results with female donors). Patients with ACLF were 5.78 times more likely to die within 90 days post-HT, the condition with the greatest impact. The best results were shown in patients in acute liver failure. Age 57.2 years or older was associated with worse outcome.[20]

Evaluating the characteristics that were associated with the performance of HT, one study pointed out that the MELD-Na values and the serum lactate level were the predictive factors considered for the procedure. High serum lactate levels were associated with nontransplantation, reflecting the severity of the patients.[21] This same study pointed out that the incidence of complications, costs, and ICU stay, as well as the need for reinterventions, orotracheal intubation, and renal replacement therapy, were more frequent among ACLF-3 patients than among those with ACLF-1 and 2.

Considering the need for a more appropriate score to guide organ allocation for ACLF patients, a pilot project is being conducted in the UK and more recently in Spain and Argentina (the Chance study) in which ACLF-2 and ACLF-3 patients are listed for transplantation separately, and organ offers are prioritized to them. The project is a collaboration between the European Foundation for Chronic Liver Failure (EFCLF), the European Liver and Intestinal Transplant Association (ELITA), and the International Liver Transplantation Society (ILTS), and the project is likely to be adopted in other countries.

Possible contraindications to LT in ACLF

Because of the shortage of organ supply, HT can be considered when the patient's quality of life becomes worse after transplantation, given the consensus that the expected survival after LT should be at least 50% in 4 years.[5]

In the study by Trebicka *et al.*,[5] the question was raised about the contraindication of HT in active alcoholism, since the main factor associated with triggering ACLF in the West is alcoholism. Many countries consider the need for alcohol abstinence for 6 months for the indication of HT; however, in selected patients, improved survival rates of 77 to 97% of these patients were cited, and only 10–13% of these patients returned to alcoholism to harmful levels after being transplanted, even without the prior abstinence desired prior to the procedure. Sepsis, fungemia, or bacterial infection represent contraindications to HT, since the surgical procedure itself and the induced immunosuppression worsen the condition, but once controlled, HT should be indicated. An exception to the contraindication in the presence of infection is the presence of cholangitis in primary sclerosing cholangitis.

Untreated human immunodeficiency virus infection also contraindicates transplantation, as well as some cases of respiratory failure, especially if PaO_2/FiO_2 is below 150. Malignant disease also contraindicates transplantation, and the presence of cardiomyopathy, severe pulmonary hypertension, and severe malnutrition can be considered contraindications after detailed evaluation.

CONCLUSIONS

ACLF patients have distinct characteristics from other liver disease patients. Definitions of the syndrome vary mainly between Western and Eastern countries and differ regarding the precipitating factor. Outcomes with or without liver transplantation vary among ACLF patients according to the grade of the disease.

Increased knowledge and experience in case management have led to an increasing trend in the agreement to indicate transplantation, even for ACLF-3 patients, with the need for a prioritization system in the list that anticipates the chance of an early offer and, consequently, of better outcomes.

Still, it is known that in some extremely severe cases, with multiple organ failure, not even liver transplantation is able to reverse the outcome to death. It is hoped that future studies will achieve a clearer definition of which patients have real benefit when receiving an organ.

AUTHORS' CONTRIBUTION

Scientific and intellectual contribution to the study: Cronst J, Chedid MF; **Conception and design of the article:** Cronst J, Chedid MF, Pinto MA; **Technical production:** Cronst J, Chedid MF, Prediger L, Silva RK, Arruda S; **Data analysis and interpretation:** Cronst J, Chedid MF, Pinto MA; **Statistical analysis:** Cronst J, Chedid MF, Pinto MA; **Drafting of the manuscript:** Cronst J, Chedid MF, Pinto MA; **Revision:** Chedid MF; **Approval of the final article:** Cronst J, Chedid MF, Pinto MA.

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