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GUIDELINES

The Global ACLF Consensus : the 'Istanbul Document'

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Abstract

The Kyoto Consensus introduced a key conceptual shift in characterizing acute-on-chronic liver failure (ACLF) patients into Type-A and Type-B phenotypes. A day-long meeting was convened at Istanbul during APASL 2026 to assess the real-world applicability of Type-A and Type-B ACLF across continents. The objective was that physicians could recognize ACLF as a unified disease entity, and quality research and new therapeutic options with defined end-points could be undertaken. Data from APASL ACLF Research Consortium (AARC), EASL-CLIF and NACSELD were assessed and discussed in detail. While the applicability of Type-A and Type-B varied across cohorts, the definition required to be appended. The experts unanimously agreed that 'liver failure' as identified by serum bilirubin of ≥ 5 mg/dl and INR ≥ 1.5 should be the 'core' for both Type-A and Type-B ACLF. Type-A ACLF is considered when "a patient with compensated advanced chronic liver disease or compensated cirrhosis presents with index decompensation as liver failure followed by development of ascites and/or hepatic encephalopathy within 4 weeks." Type-B ACLF is considered when "a patient with prior or concurrent decompensated cirrhosis presents with acute decompensation as liver failure accompanied by one or more extrahepatic organ failures." New definitions of organ dysfunction and failure, as well as endpoints for clinical trials, were also deliberated and finalized. The "Istanbul Report", presents a milestone evidence based consensus document carrying harmonization of various aspects of ACLF, incorporating current evidence, critically analyzed unanimous recommendations, and key areas for future studies.

Keywords Cirrhosis · Chronic liver disease · Liver failure · Type-A ACLF · Type-B ACLF · Decompensation · Organ failure · Harmonization · Organ dysfunction · Jaundice · Ascites

Extended author information available on the last page of the article

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Introduction

Acute-on-chronic liver failure (ACLF) is increasingly recognized as a common entity associated with high short-term mortality [1]. There have been several definitions of this disease since 2009 [2, 3]. The disease has been noted to be challenging to manage with a frequent need for organ support systems to bridge individuals with ACLF to liver transplant. In Asia, plasma exchange has been frequently used for these patients but without a definitive survival benefit [4]. Therapies to prolong the survival in ACLF include but not limited to early identification and management of infections, prevention of acute kidney injury through judicious use of diuretics for ascites control and use of albumin for modest volume paracentesis, midodrine with albumin for prevention of recurrent paracentesis, immunonutrition through omega 3 fatty acid lipid emulsions, prevention of variceal bleeding with beta blockers, and lastly bridge the individual to liver transplant timely before futility ensues [4, 5]. Liver transplant in Asia and worldwide has been increasingly used for ACLF but with challenges of infections and kidney injury post-transplant and suboptimal quality of life. The unmet need in ACLF is early identification of the disease and prevention of progression from organ dysfunction to extrahepatic organ failures. While liver failure is the central insult culminating in organ failures, the differing definitions across continents have made the research progression in ACLF tardy, despite increasing number of publications [6]. Therefore, a uniform definition of ACLF is required to ensure appropriate research for improving the outcomes and invite industry to invest in this acutely fatal disease and improve the transplant free survival. Building on the previous Kyoto consensus statements, this "Istanbul Report" aimed at understanding the harmonization of definition, its applicability, prognostication and organ allocation and to refine further understanding of ACLF. Several experts and leaders representing various societies were included and the data from each continent was discussed. Each section had moderators from different continents and speakers presented data from literature, and in the absence of published data, existing datasets (from APASL ACLF Research Consortium-AARC, EASL-CLIF, and NACSELD) were assessed and presented at the Istanbul AARC meeting, and deliberations were made on statements. The level of evidence and grade of recommendations were based on the GRADE system [7, 8]. A modified Delphi methodology was conducted in accordance with the CREDES recommendations and reported following the ACCORD reporting guideline [9, 10]. Panelists (Appendix I) rated each statement on a 5-point Likert scale (strongly disagree, disagree, neutral, agree, strongly agree). Consensus was predefined as ≥ 80% of panelists selecting either "agree" or "strongly agree" for consensus agreement, or "disagree" or "strongly disagree" for consensus disagreement.

Type-A and Type-B ACLF-Rationale for global harmonization

The fragmented research in ACLF due to various definitions being used regionally has reached a critical impasse and prevented scientists from enthusiastically participating in the research. Apart from ensuring education at primary care to identify ACLF early there is a need for harmonized definition. In recent years the gap between Eastern and Western hepatologists regarding the definition of ACLF has now significantly decreased, making possible the harmonization of this definition across the world. There are several reasons for harmonization of definition. Most patients present to primary health care and harmonization clears the confusion for them to identify ACLF, prognosticate and plan early referral for liver transplant center. Harmonization by Type-A and Type-B clarifies distinct established phenotypes (with already proven mechanistic pathways) preserving the research done in this area for the past two decades. The aim to reach a uniformity in research goals and facilitate multicenter multinational studies and merge the existing data sets of more than 11,800 population each from AARC, EASL-CLIF and NACSELD. Also, the representatives of EASL-CLIF reported the results of a survey that physicians across Europe had expressed a willingness to harmonize the definition and re-analyze the very large cohort of European and Latin American patient data with cirrhosis and acute decompensation collected by the European and Latin American patients data with cirrhosis and acute decompensation collected by the European Foundation for the Study of Chronic Liver Failure (EF-CLIF) and suggested that liver failure should be the core of the definition. This also goes in line with the Baveno VII definition, where acute decompensation (AD) does not include jaundice as a primary manifestation [11]. Hence, a patient with pre-existing decompensated cirrhosis presenting with AD and jaundice would qualify to be called ACLF.

In clinical practice, hospitalized patients could be better characterized at presentation as either: Type-A ACLF, "a patient with compensated advanced chronic liver disease (cACLD) or compensated cirrhosis presents with index decompensation as liver failure followed by development of ascites and/or hepatic encephalopathy within 4 weeks." or Type-B ACLF, defined as "a patient with prior or concurrent decompensated cirrhosis presents with acute decompensation as liver failure accompanied by one or more extrahepatic organ failures. 'Liver failure,' as identified by serum bilirubin of ≥ 5 mg/dl and INR ≥ 1.5, should be the core for

both Type-A and Type-B ACLF. Type-A ACLF patients represent an earlier, potentially more reversible stage, whereas Type-B ACLF a relatively late stage of the disease. Type-A includes the Japanese, COSSH, AASLD, and Mexican definitions of ACLF, while Type-B resembles EASL-CLIF and NACSELD [12–17].

Statements

1.1 The gap between Eastern and Western perspectives on the definition of ACLF has substantially narrowed over the past two years, creating a strong foundation for the development of a globally harmonized and clinically applicable definition. (Consensus agreement: 94%).

1.2 The place of 'liver failure' in the harmonized definition of ACLF should be central (Level of Evidence: high; Recommendation: Strong) (Consensus agreement: 97%).

1.3 Classifying patients as Type-A ACLF (a patient with compensated advanced chronic liver disease (cACLD) or compensated cirrhosis presenting with index decompensation as liver failure followed by development of ascites and/or hepatic encephalopathy within 4 weeks, akin to Eastern criteria). Type-B ACLF (a patient with prior or concurrent decompensated cirrhosis presenting with acute decompensation as liver failure accompanied by one or more extrahepatic organ failures, akin to the Western criteria) is recommended. (Level of Evidence: high; Recommendation: Strong) (Consensus agreement: 87.5%).

1.4 Because blood levels of bilirubin and those of International Normalized Ratio (INR), respectively reflect different liver functions, we recommend using them simultaneously to define liver failure among patients with decompensated chronic liver diseases (Level of Evidence: high; Recommendation: Strong) (Consensus agreement: 92%).

Does Type-A and Type-B ACLF classifications include more real-world cases?

Definitions of ACLF had remained heterogeneous across continents, despite a shared understanding of its high short-term mortality. This heterogeneity has resulted in fragmented research, limited collaborative efforts, and persistently poor patient outcomes. Several studies showed that patients included in AARC definition were not included in the EASL-CLIF definition and vice versa. The primary distinction between the definitions lies in whether the acute insult develops in a patient with no prior decompensation and results in 'liver failure' as the first event [Eastern, APASL] or in a patient with or without prior decompensation and with or without liver failure at presentation [Western, EASL-CLIF/NACSELD].

A large Indian multicenter unpublished study of 966 non-electively hospitalized patients (alcohol as dominant etiology in 68%) evaluated the applicability of these definitions. There were 374 patients who presented first time with decompensation and 602 had prior decompensation. Approximately 76.5% (278/374) of patients who presented for the first time with decompensation (Type-A ACLF) satisfied APASL liver failure criteria (bilirubin > 5 mg/dl and INR > 1.5) and had a mortality of 31.3% at 30 days. Furthermore, of the 602 patients who had prior decompensation, 66.3% (399/602) met the APASL liver failure criteria (Type-B ACLF) and had a mortality of 44.1% at day 30.

Previously, liver or coagulation failure alone was not considered as ACLF as per EASL CLIF. However, analysis of the updated data from EASL-CLIF was discussed during the meeting. It was shown that single liver failure defined by both bilirubin ≥ 5 mg/dl and INR ≥ 1.5 and the absence of extrahepatic organ failures was associated with increased mortality at day 30 (17%) and 90 (31.4%) and crossed the critical requirement of 15% or more mortality at 28 days. The data from EASL-CLIF further showed that the mortality increased at day 30 and 90 with an increasing number of organ failures. Moreover, liver failure was found to be the dominant presentation in the EASL-CLIF cohort, driving the mortality. Based on these new analyses of the EASL-CLIF data, the experts suggested that Type-B ACLF is considered when "A patient with prior or concurrent decompensated cirrhosis presents with acute decompensation as liver failure accompanied by one or more extrahepatic organ failures." ACLF Type-B be classified as B1 (liver failure alone), B2 (liver failure with one extrahepatic organ failure) and B3 (liver failure with 2 or more extrahepatic organ failures) and it was unanimously agreed that liver failure should be the core of ACLF definition in both Type-A and Type-B." (Fig. 1).

Statements

2.1 Type-A and Type-B ACLF shall include 'liver failure' identified by elevation in bilirubin and INR as the core of the definition. (Level of Evidence: High; Recommendation: Strong) (Consensus agreement: 93%).

2.2 Type-A and Type-B ACLF classification identifies a substantially higher proportion of real-world cases and should be adopted in routine clinical practice (Level of Evidence: High; Recommendation: Strong) (Consensus agreement: 83%).

2.3 The Type-A and Type-B ACLF classification is simple and easy to use in clinical practice. It facilitates research prioritization and enables early identification of patients with higher potential for reversibility based on liver failure definitions. (Level of Evidence: Low; Recommendation: Strong) (Consensus agreement: 85%).

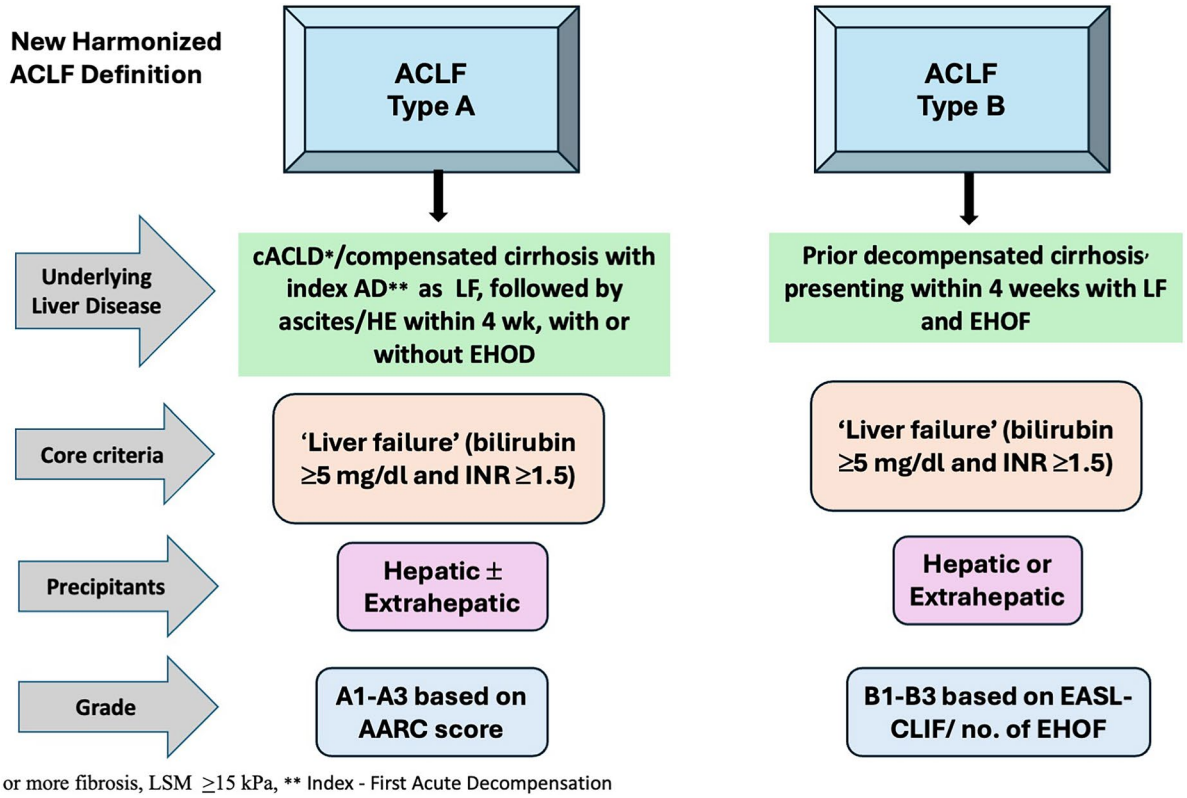


Fig. 1 ACLF definition background and core components

Can we reliably differentiate AD, NAD, ACLF-A, and ACLF-B?

In the Kyoto consensus, we defined acute decompensation (AD) as the acute development of complications of cirrhosis, like rapid development of ascites, gastrointestinal bleeding, and hepatic encephalopathy, within four weeks and requiring non-elective medical attention [18]. It is well-known that patients with AD or further decompensation have a high mortality in the absence of recovery or liver transplantation within 3 months. In contrast, non-acute decompensation (NAD) describes a more gradual form of decompensation, in which symptoms develop slowly, often without the need for immediate hospitalization. The natural course and outcome of patients with AD and ACLF do vary depending on the nature and severity of the precipitating event and the stage of underlying liver disease [19, 20]. AD is driven by acute portal hypertension-driven complications while NAD is slowly progressive portal hypertension dysfunction. Conversely, ACLF Type-A is a hepatic inflammation-driven liver failure and complications, and ACLF Type-B is more related to systemic response to infection and inflammation, leading to extrahepatic organ failures. Differentiating AD, NAD, ACLF Type-A and Type-B is crucial, as management differs for each. Table 1 highlights differences between AD, NAD, ACLF Type-A and Type-B. The differentiation between these is based more on clinical parameters. However, at present, differentiating AD, NAD, Type-A and Type-B ACLF on clinical grounds alone may not be precise, as a proportion of AD patients may have high bilirubin, but may not have high INR or vice versa at presentation. Identifying patients with AD who are likely to progress to ACLF remains a major unmet need. Severity scores such as the Child–Pugh score and the MELD score predict mortality but cannot identify the transition to ACLF. CLIF-C AD score of more than 60 has a higher risk of progression to ACLF and can be used to identify patients with AD who are at risk of progression [21]. The PREDICT study reported that patients with elevated inflammatory markers such as high white cell counts, CRP, and cytokines are at risk for progression to ACLF [22]. Finally, the COSSH onset ACLF score (consisting of ALT, INR, bilirubin and ferritin) at admission has also been reported to accurately identify individuals with hepatitis B at risk of developing ACLF at days 7, 14 and 28 [23].

There is, however, a paucity of biomarkers to differentiate between these clinical entities and further studies and documentation is needed. Management also differs as AD and NAD and is dependent on MELD scores. Type-A ACLF has higher chances of reversal with medical management. Timely liver transplant based on assessment by AARC, and

Table 1 Differences between AD, NAD, ACLF Type-A and Type-B

Feature	Acute decompensation (AD)	Non-acute decompensation (NAD)	ACLF-A	ACLF-B
Core concept	Acute development of decompensating events in cirrhosis	Gradual worsening of cirrhosis without abrupt acute insult	ACLF dominated by primary hepatic failure	ACLF dominated liver failure along with extrahepatic organ failures/systemic inflammation
Time to onset	Rapid (within ~ 4 weeks)	Slow/subacute progression (in 3 months)	acute hepatic deterioration in 4 weeks	Acute multiorgan deterioration including hepatic
Acute precipitating event	Usually, present	Often absent or subtle	Definite hepatic insult usually identifiable	Often infection, variceal bleed driven
Common precipitants	Infection, alcohol binge, bleeding, hepatitis flare	Progressive portal hypertension	Alcohol, HBV flare, DILI	Infections, alcohol,
Underlying liver disease	Cirrhosis	Established decompensated cirrhosis	cACLD/cirrhosis with preserved extrahepatic reserve	Cirrhosis/advanced decompensated cirrhosis
Dominant pathophysiology	Acute worsening of portal hypertensive complications	Progressive circulatory/portal hypertensive dysfunction	Hepatic inflammation with or without systemic inflammation	Systemic inflammation with immune dysregulation and EHOF
Hyperbilirubinemia	Variable	Mild–moderate	Marked hyperbilirubinemia	Moderate–severe
Coagulopathy	Mild–moderate	Chronic stable abnormality	Prominent	Moderate–severe
Extrahepatic organ failure	Usually absent	Absent	May occur later	Early and prominent
Renal dysfunction	Possible but limited	Chronic/recurrent	Secondary phenomenon	Common and often central
Infection burden	Variable	Lower	May be secondary	Major driver
Systemic inflammation	Mild–moderate	Low-grade	High	Very high
Hemodynamic instability	Uncommon	Rare	Variable	Common
Typical geography historically	Universal	Universal	More commonly described in Eastern cohorts	More commonly described in Western cohorts
Representative diseases	Ascites, HE, variceal bleed	Slowly progressive ascites/recurrent HE	HBV-ACLF, severe alcoholic hepatitis	Infection-triggered cirrhosis with liver failure with or without extrahepatic organ failures
Short-term mortality	Intermediate	Lower	Moderate	high
Potential for reversal	Moderate	Often possible/recompensation	Possible if hepatic insult controlled early	Less common
Main therapeutic focus	Treat precipitant and support	Chronic cirrhosis optimization	Liver-directed therapy ± early LT	Aggressive ICU care, sepsis control, organ support, LT
Scores	MELD, MELD NA, MELD 3.0, CTP score/Class	MELD, MELD NA, MELD 3.0, CTP score/Class	AARC score, AARC grade, MELD-lactate	CLIF-C ACLF, EASL CLIF grade
Transplant urgency	Selective	Usually elective	Early referral important	Immediate referral often needed

cACLD compensated advanced chronic liver disease, *HE* hepatic encephalopathy, *ACLF* acute-on-chronic liver failure, *MELD* model for end-stage liver disease, *AARC* APASL ACLF Research Consortium, *NA* sodium, *EASL CLIF* European Association for the Study of the Liver–Chronic Liver Failure Consortium

MELD-lactate score is life-saving in these patients. There is evidence to support the use of bridge therapies such as plasma exchange for both Type-A and Type-B ACLF, which is not for AD or NAD, as they are driven by portal hypertension [24, 25].

Statements

3.1 Harmonization of ACLF definitions is critical as without a clear, unified diagnostic criteria, differentiating these groups remains a significant challenge in clinical practice. (Level of evidence: Low; Recommendation: Strong) (Consensus agreement: 94%).

3.2 Management of AD, NAD, Type-A and Type-B ACLF is different with respect to medical therapies and bridging therapies. (Recommendation: strong, Level of evidence: high) (Consensus agreement: 84%).

3.3 Severity scores and optimal timing of liver transplantation differ across disease categories, including AD, NAD, ACLF Type-A, and ACLF Type-B. (Level of evidence: High; Recommendation: Strong) (Consensus agreement: 94%).

Can reversal of ACLF be predicted early and reliably using Type-A and Type-B?

The Kyoto consensus defined reversal of ACLF as reversal of parameters used for defining ACLF within a time frame of 6 months and those achieving reversal within 90 days are considered as early reversers [18]. Reversal of ACLF is akin to recompensation in decompensated cirrhosis which is associated with improved survival and is an important therapeutic goal for delisting a patient [26]. Patients with HBV-related ACLF who achieve reversal of ACLF remain stable for up to 5 years [27]. A multicenter study including 346 patients with ACLF reported complete reversal of ACLF among 47% of patients with placebo compared to 73% who received beta blockers [28]. The mean time to reversal was 2.3–2.66 months [28]. Another multicenter study including 344 patients with ALD reported recompensation in 30% patients with alcohol-associated hepatitis while only 15.7% achieved recompensation in alcohol-associated hepatitis who presented as ACLF [29]. From the AARC database, about 70% of the survivors achieved a reversal of ACLF by day 90, which was maintained for 1 year. The median time to reversal of syndrome, i.e., jaundice and coagulopathy, was 30 days. Baseline albumin, AARC score, and transient elastography predicted long-term reversibility. Early reversal is possible in Type-A ACLF, especially with complete abstinence (for alcohol-ACLF), nutrition (etiology agnostic), non-selective beta blocker therapy and appropriate antivirals. ACLF may resolve in 55% of patients with ACLF-1, 35% with ACLF-2, and 15% with ACLF-3 [30]. Recently, bioartificial liver support systems have been reported to reverse Type-B ACLF, while there are no human trials reporting reversal of Type-B ACLF [31]. This also highlights that Type-B-ACLF is driven by infection and inflammation, and reversal of ACLF with bioartificial liver (BAL) using granulocyte and monocyte/macrophage apheresis again validates the previously published role of granulocyte colony-stimulating factor (G-CSF) as a regenerative therapy for ACLF [32]. Therefore, reversal of ACLF is possible in both Type-A and Type-B, which have liver failure as the core of definition; however, the data is still emerging, and the time for reversal needs to be evaluated further.

Statements

4.1 The reversal of ACLF is dependent on the definition of reversibility, etiology, and timeframe (Level of Evidence: Moderate; Grade of recommendation: Strong) (Consensus agreement: 90%).

4.2 Reversal of Type-A ACLF can occur in a variable percentage (40–70%) of patients. (Level of Evidence: Moderate; Grade of Recommendation: Strong) (Consensus agreement: 81%).

4.3 Reversal of Type-A ACLF can be predicted early based on baseline severity (AARC score) and other parameters, first week trend of liver functions (Bilirubin, INR). (Level of Evidence: Low, Grade of recommendation: Weak) (Consensus agreement: 83%).

Can transplant need and timing be better stratified using Type-A and Type-B ACLF?

ACLF remains a dynamic syndrome, and timing of transplant is crucial, and the decision is dynamic. The data to support liver transplant are robust for Type-A (APASL) and Type-B (EASL-CLIF [33–35]. A major challenge is to determine and differentiate utility and futility in this sick population. In our daily clinical practice, the key question is when a patient crosses from reversibility into rescue-only/salvage territory. Further questions remain particularly relevant in the living donor liver transplantation (LDLT) setting, including the definition of futile LDLT, the identification of a borderline patient category, and whether a harmonized decision-making algorithm integrating recipient severity with graft characteristics can be developed; equally important is defining the ethical boundaries within which such decisions should be made. We re-analyzed 30 consecutive LDLT performed for ACLF at Bahçeşehir University / Medical Park Göztepe Hospital between August 2022 and December 2025. Median recipient age was 46.5 years, median MELD-3 was 27.5, and median CLIF-C ACLF score

was 41. Six patients required preoperative ICU bridging. APASL grades I/II/III were 12/13/5, while AARC phenotype Type-A and Type-B distribution was 18 and 12, respectively. Overall Kaplan–Meier survival after LDLT was 81.5% at 30 days, with subsequent plateauing of the curve. Additional phenotype analysis showed superior outcomes in Type-A versus Type-B patients: 30-day and 1-year survival were 88.2% versus 70.0%, respectively. Exploratory analyses suggested directionally worse outcomes in Type-B phenotype, APASL grade III disease, CLIF-C $\geq$ 45, and MELD-3 $\geq$ 30.

While Type-A and Type-B ACLF categorization needs further validation, our analysis supports the need for a practical harmonization framework in which ACLF timing, trajectory, and phenotype may better guide transplant urgency than static scoring systems alone. In regions with established LDLT programs, immediate donor availability may permit intervention during the golden rescue window before irreversible systemic collapse develops in ACLF. APASL AARC initiative has made a critical attempt to fill the gap in this field. MELD-based allocation may not be most appropriate for ACLF, as these patients require multidisciplinary involvement of a hepatologist, surgeon, nephrologist, intensivist, nutritionist, and physiotherapist to identify a patient as fit for surgery and to prevent futile efforts. Type-A and Type-B classification must be used as a complementary tool alongside established tools like AARC and CLIF-C ACLF. Transplant allocation in ACLF should move beyond static severity scores toward a phenotype-based dynamic model integrating ACLF subtype, trajectory of organ failure, inflammatory burden, reversibility, and donor-graft characteristics. There may be need for separate dynamic scoring systems for Type-A and Type-B ACLF with respect to liver transplantation and further data and agreement. (Table 2, Fig. 2).

Statements

5.1 Early discussion and referral to a liver transplant center optimizes the time and improves outcomes for patients with ACLF irrespective of stratification into Type-A or Type-B. (Level of Evidence: Low; Recommendation: Strong) (Consensus agreement: 92%).

5.2 The need for liver transplantation should be considered early (within 3–5 days) in the context of dynamic changes in the patient's status rather than rigid allocation rules. (Level of Evidence: Low; Recommendation: Strong) (Consensus agreement: 81%).

5.3 Harmonization of ACLF terminology is likely to lead to the development of a liver transplant algorithm that will improve patient outcomes. (Level of Evidence: Low; Recommendation: Strong) (Consensus agreement: 89%).

Are we better at guiding therapy decisions using Type-A and Type-B classification?

Treatment decisions in ACLF need to be individualized and are dependent on timing of presentation, severity of organ failures, availability of extracorporeal therapies, infrastructure and expertise. Common indications for ICU care include septic shock, hemorrhagic shock (due to gastrointestinal bleeding), altered sensorium (due to hepatic encephalopathy, uremic encephalopathy, alcohol intoxication or withdrawal), renal failure, and respiratory failure [36]. Point of

Table 2 Liver transplant for Type-A and Type-B ACLF

Domain	Type-A ACLF	Type-B ACLF
Harmonization theme	Liver failure is at core	Liver failure is at core
Dominant pathology	Hepatic failure	Extrahepatic organ failure/inflammation
Best transplant window	Early	After stabilization/organ failure improvement
Response to LT	Often dramatic	Variable
Graft quality requirement	Moderate-high	Highest quality needed
Marginal graft tolerance	Possible	Poor
LDLT suitability	High	Selective
Relevant data from	Asia (LDLT dominant)	West (DDLT dominant)
Current allocation system	AARC, MELD, MELD-lactate	MELD, MELD 3.0, MELD NA
Ethical boundaries	+ + +	+ +
Data	Robust	Robust
Need for SLKT	Rare	Frequent
Futility threshold	Higher tolerance	Lower tolerance
Allocation urgency	Immediate	Conditional

ACLF acute-on-chronic liver failure, *LDLT* living donor liver transplantation, *DDLT* deceased donor liver transplantation, *MELD* model for end-stage liver disease, *AARC* APASL–ACLF Research Consortium, *Na* sodium

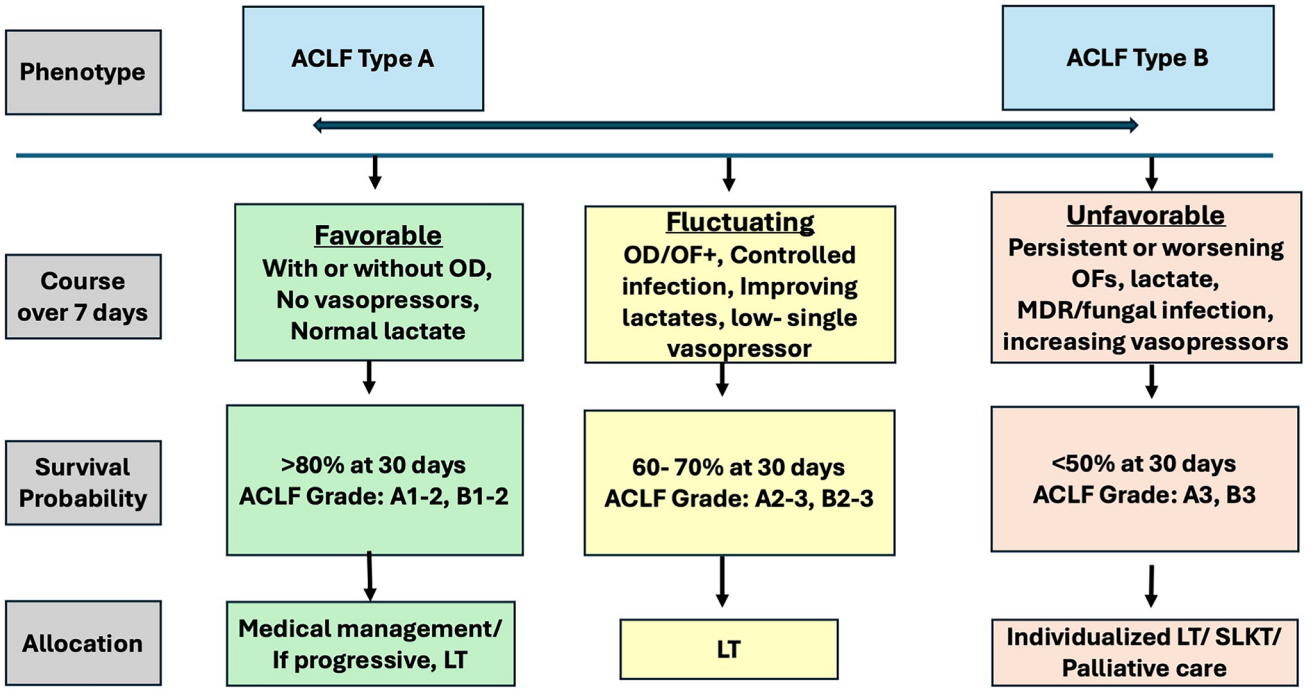


Fig. 2 Course of ACLF and transplant allocation in ACLF

care ultrasonography (POCUS) has been demonstrated to be useful in guiding fluid resuscitation in ACLF [37]. Patients with advanced ACLF grades therefore require prompt referral and appropriate ICU care to modify the course of the disease favorably [38]. Both Type-A and Type-B ACLF require adequate optimization prior, and the first seven days (golden window period) are critical in decision-making [30, 39]. Type-A ACLF patients with A2/A3 grade usually require ICU while those with B1–3 in Type-B require ICU care frequently and are dependent on organ failures. Therefore, classification of ACLF into Type-A and Type-B can aid in critical care management of patients.

Statements

6.1 Classifying ACLF into Type-A identifies a "golden window" for therapeutic interventions, during which extracorporeal liver support therapies or regenerative treatments may be utilized with the potential for syndrome reversibility. This period also allows time to arrange for a liver transplant prior to the onset of extrahepatic organ failures or sepsis. (Level of Evidence: Moderate, Recommendation: Strong) (Consensus agreement: 92%).

6.2 Classifying ACLF into Type-B, permits the use of extracorporeal liver support therapies as a bridge to liver transplantation, and also decisions regarding de-escalation or futility in cases where the syndrome progresses. (Level of Evidence: Moderate, Recommendation: Strong) (Consensus agreement: 83%).

6.3 When selecting patients with ACLF for liver transplantation in the context of organ failure, stratification should be based on the number and type of organ failures, the trajectory of these failures (progression, stability or resolution), and the presence of infection. (Level of Evidence: Moderate, Recommendation: Strong) (Consensus agreement: 100%).

What should change in practice, trials, and guidelines?

One of the major challenges in ACLF is the existence of multiple competing definitions, including those proposed by the APASL, EASL-CLIF and AASLD. These definitions arise from differing conceptual frameworks, particularly regarding whether organ failure is essential for the diagnosis of ACLF. Consequently, clinical trials become difficult to interpret because enrolled populations are heterogeneous and often biologically distinct, limiting comparability and pooling of data across studies. NACSELD defines ACLF primarily by the presence of ≥ 2 extrahepatic organ failures, whereas EASL-CLIF emphasizes systemic inflammation, multiorgan failure, and extrahepatic precipitants such as infection or sepsis [12, 40]. This heterogeneity complicates identification of patients most likely to benefit from a

therapy, reduces statistical power, and makes stratification and endpoint interpretation challenging.

Clinical trial design in ACLF is further complicated by the rapid progression and high short-term mortality of the syndrome, resulting in high dropout rates, difficulty in capturing meaningful clinical endpoints, and ethical concerns regarding placebo or control groups. In addition, ACLF is a highly dynamic condition in which patients may slowly improve but rapidly deteriorate, while validated surrogate endpoints remain limited. These factors contribute to inconsistent trial outcomes and difficulties in achieving regulatory approval.

Therapeutic options for ACLF remain limited, with liver transplantation representing the only definitive cure. This is mainly because of late patient selection and keeping survival as the end-point. There is indeed need to have simpler and more achievable end-points for therapeutic efficacy. However, the therapeutic window is often narrow, and several unresolved issues remain regarding transplant benefit versus futility, cost-effectiveness, and organ availability. Key unanswered questions include defining the optimal organ allocation strategy for ACLF, establishing objective criteria for futile liver transplantation, determining whether transplantation should await clinical stabilization, identifying donor graft characteristics associated with favorable post-transplant outcomes, understanding long-term survival and quality of life after transplantation, and assessing the broader implications for healthcare resource utilization. Important gaps remain, including the absence of clear ICU admission thresholds, explicit futility criteria, predictive models for liver transplant candidacy and futility, and protocolized pathways for assessment, management, and transplant evaluation of ACLF patients.

Endpoints in clinical trials

Clinical trials in ACLF are limited as the hard endpoint of survival is rarely achieved. To date none of the therapies have been able to provide meaningful survival benefit except regenerative therapies in a controlled setting, fecal microbiota transplantation, and non-selective beta blockers in certain set of ACLF populations [28, 32, 41–43]. Prophylactic antibiotics, omega-3 fatty acid lipid emulsions, midodrine with albumin, plasma exchange and other such artificial liver support systems have all failed to provide significant survival benefit [24, 25, 44–48]. Nevertheless, these measures can provide some time for recovery and bridge the patients for transplant. More than 60% of patients with ACLF are ineligible for LT due to sepsis, organ failures, or being too sick to transplant, contributing to the high waitlist mortality [39]. Clinical improvement before LT is associated with better survival post-LT [49, 50]. It is well known that downgrading ACLF grade before LT improves survival post-LT [51]. Improvement in circulatory and brain failure, improving respiratory status, and eliminating the need for mechanical ventilation have been associated with reduced mortality post-LT [51]. Therefore, we believe that improvement in ACLF grade without development or worsening of extrahepatic organ failures and without development of infections should be considered as a feasible endpoint. A reduction in MELD score by 5 points with therapy at 1 month or 10 points at 3 months can also be considered as a relevant endpoint [52]. It is well known that MELD reduction prior to transplant is known to improve the outcomes of patients with ACLF [53]. These however are suggestions from the expert group and need to be assessed in clinical trial settings. Improvement in ACLF grade without new or worsening extrahepatic organ failures or development of infections should be considered a clinically meaningful endpoint. In addition, a reduction in MELD score by ≥ 5 points at 1 month or ≥ 10 points at 3 months may serve as relevant therapeutic endpoints. However, since the reduction in MELD score did not reach the desired consensus, there is need to have further studies.

Steps for education about Type-A and Type-B for primary care physicians

Physicians, GI and ICU fellows' education in ACLF should evolve from static definition-based teaching toward a dynamic phenotype-based framework integrating hepatic failure, systemic inflammation, organ failure trajectory, and transplant decision-making. Education regarding Type-A and Type-B ACLF should focus on shifting clinicians from a "single ACLF entity" mindset toward a phenotype-based framework that recognizes biological heterogeneity, differing mechanisms of organ failure, and distinct transplant implications with efforts to educate ACLF as a spectrum rather than a single syndrome: Type-A ACLF: hepatic failure–dominant phenotype; and Type-B ACLF: hepatic failure with or without extrahepatic organ failure/systemic inflammation–dominant phenotype.

This conceptual distinction helps clinicians better understand disease trajectory, reversibility, timing of transplantation, ICU management priorities, and futility assessment while emphasizing dynamic assessments. Integrating in ICU and hepatology training, developing visual algorithms, decision pathways, and linking phenotype to management strategy. Type-A: early identification, appropriate liver directed therapies, potential reversible and with dynamic early transplant evaluation and Type-B: stabilization with organ support, infection control, careful futility assessment and higher graft quality requirements after stabilization.

Next steps toward global consensus

Prospective data on Type-A and Type-B need to be collated across continents to validate previous findings, better understand the disease phenotype through basic science, and identify biomarkers to predict the development of ACLF. Some of the statements had low levels of evidence and require further studies. A society-driven education program for physicians and fellows at major society meetings should be developed, and an algorithmic approach to management should be created with experts from the West–East. Research should focus on preventing ACLF, modifying its course, and preventing progression from Type-A to Type-B and reversal from Type-B to Type-A. Vaccination strategies for infection, curbing alcohol use, adopting treat-all for hepatitis B, avoiding unnecessary medications, and adequate management of decompensation (ascites control, preventing variceal bleeding, preventing acute kidney injury, ensuring adequate nutrition, and preventing frailty) should be prioritized.

Conclusion

The prevalence of ACLF has increased exponentially in recent years due to the rising burden of alcohol misuse, multidrug-resistant bacterial infections, viral infections, and over-the-counter use of drugs and alternative medicines. The phenotypic classification of ACLF into Type-A and Type-B is easy to understand and use in clinical practice, and it guides decisions on management and prognostication, supported by robust mechanistic studies to date. Experts unanimously agreed that 'liver failure' should remain the defining feature of ACLF. Accordingly, Type-A ACLF develops in patients with cACLD or compensated cirrhosis, whereas Type-B ACLF develops in patients with prior decompensated cirrhosis and is characterized by concomitant extrahepatic organ failure(s). Further efforts should be invested in disseminating education, developing relevant models for organ allocation that consider ethical boundaries, and, lastly, preventing the development of ACLF.

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Declarations

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