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Guidelines for the diagnosis and treatment of acute-on-chronic liver failure (2025)

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Acute-on-chronic liver failure (ACLF) is an acute decompensation of liver function in patients with chronic liver disease, characterized by high short-term mortality and recognized as a leading cause of death in this population.[1] It requires refined clinical classification to achieve precise diagnosis, targeted treatment, and stratified management. Currently, multiple definitions of ACLF exist worldwide with notable discrepancies, hindering the comparability of research data and creating confusion in clinical diagnosis, treatment, and management.[2,3] To standardize ACLF clinical practice in China, the Severe Liver Disease and Artificial Liver Group and the Nutrition and Regeneration in End-Stage Liver Disease Group of the Chinese Society of Hepatology, Chinese Medical Association, have organized a panel of Chinese experts to develop China's first clinical guideline for ACLF diagnosis and management.[4] This guideline integrates the latest advances in global research and clinical practice, aiming to harmonize ACLF diagnostic criteria across regions while ensuring precision and comprehensiveness. By incorporating the characteristics of the Chinese population with ACLF, accumulated clinical experience, and robust medical evidence, we propose a unified ACLF definition and provide authoritative recommendations for its diagnosis, treatment, and clinical management.

Recommendation Strength and Level of Evidence

The strength of each recommendation was determined using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. Based on current evidence-based medical data, this guideline aims to provide standardized recommendations for the diagnosis and management of ACLF, thereby supporting clinicians in making informed decisions. It is important to note that these guidelines are not mandatory and do not encompass all clinical scenarios. Physicians should individualize the treatment plans according to each patient's condition, preferences, professional judgment, and available healthcare resources. Considering the rapid progress in ACLF research, these guidelines will be continuously updated to incorporate the latest scientific evidence (full-length version of the consensus can be found in the Supplementary File, http://links.lww.com/CM9/C718).

Recommendations: Diagnosis of ACLF

Early diagnosis is crucial for a timely intervention. While emphasizing that high mortality rates can improve diagnostic specificity, it is equally important to maintain sensitivity to better identify patients with potentially reversible conditions. Synthesizing the existing global definitions of ACLF and aligning them with China's clinical needs, this guideline defines ACLF as follows: ACLF is an acute deterioration of liver function in patients with chronic liver disease (including non-cirrhosis, compensated cirrhosis, or decompensated cirrhosis), characterized by hyperbilirubinemia and coagulopathy (with or without extrahepatic organ failure), and is associated with high short-term mortality (Grade 1A).

Based on clinical presentation at onset, ACLF can be classified into two types [Supplementary Figure 1, http://links.lww.com/CM9/C718].

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ACLF type I: Acute severe liver injury occurring in patients with chronic liver disease (primarily chronic hepatitis or compensated cirrhosis), meeting both of the following criteria: total bilirubin (TBil) ≥12 mg/dL (205.2 μmol/L) or a daily increase of ≥1 mg/dL (17.1 μmol/L), and coagulopathy indicated by an International Normalized Ratio (INR) ≥1.5 or prothrombin activity (PTA) ≤40%, with no extrahepatic organ failure present at diagnosis; although complications such as infection, hepatic encephalopathy (HE), ascites, gastrointestinal bleeding, acute kidney injury (AKI), or subsequent progression to extrahepatic organ failure may develop during the disease course.

Staging of ACLF type I (disease severity classification):

Early stage: Severe gastrointestinal symptoms (e.g., profound fatigue, anorexia, persistent vomiting, abdominal distension), elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels accompanied by progressive hyperbilirubinemia (TBil ≥12 mg/dL [205.2 μmol/L] or daily increment ≥1 mg/dL [17.1 μmol/L]), and incipient coagulopathy (30% <PTA ≤40% or 1.5 ≤INR <1.9).

Intermediate stage: Worsening hyperbilirubinemia, aggravated coagulopathy (20% <PTA ≤30% or 1.9 ≤INR <2.5), and progressive clinical deterioration from early-stage features.

Advanced stage: Critical coagulopathy (PTA ≤20% or INR ≥2.5) and/or life-threatening complications, including severe hemorrhagic diathesis, grade 3–4 HE (West Haven criteria), acute renal failure, and other similar complications.

Pre-ACLF diagnosis: Patients who do not yet meet the full criteria for ACLF type I but present with the following features should be classified as pre-ACLF and managed proactively: severe gastrointestinal symptoms (e.g., profound anorexia, persistent vomiting, and abdominal distension), markedly elevated ALT and/or AST levels with progressive hyperbilirubinemia (TBil 5–12 mg/dL [85.5–205.2 μmol/L]), and progressive coagulopathy, defined as declining prothrombin activity (PTA >40% but decreasing) and INR <1.5. Such patients require immediate clinical vigilance and early intervention to prevent the progression to definitive ACLF.

ACLF type II: Acute hepatic decompensation occurring predominantly in patients with underlying cirrhosis (compensated or decompensated), characterized by significant hyperbilirubinemia and coagulopathy (INR ≥1.5 or PTA ≤40%), accompanied by rapid-onset renal dysfunction (serum creatinine 1.5–2.0 mg/dL [132.6–176.8 μmol/L]) within a short timeframe (typically ≤1 week) or extrahepatic organ failure (renal, cerebral, respiratory, or circulatory systems). The diagnostic criteria for organ failure were in accordance with the European Association for the Study of the Liver-Chronic Liver Failure Consortium (EASL-CLIF) Consortium standards.

Staging of ACLF type II (disease severity-based classification):

Early stage: Acute hepatic decompensation in cirrhosis with hyperbilirubinemia, coagulopathy (INR ≥1.5 or PTA ≤40%), and renal dysfunction (serum creatinine 1.5–2.0 mg/dL [132.6–176.8 μmol/L]) within a short timeframe (typically ≤1 week).

Intermediate stage: Acute decompensation in cirrhosis complicated by failure of one extrahepatic organ (renal, cerebral, respiratory, or circulatory), as defined by the EASL-CLIF Consortium criteria.

Advanced stage: Acute decompensation in cirrhosis with two or more extrahepatic organ failures, indicating a high-risk phenotype requiring intensive multidisciplinary intervention.

Recommendations: Prognostic Assessment in ACLF

Prognostic evaluation and early warning in ACLF require dynamic monitoring and should be incorporated throughout the management process. Patients with high-risk factors for disease progression, such as advanced age, underlying cirrhosis, or pre-ACLF stage, require heightened vigilance, timely risk stratification, and early intervention to prevent clinical deterioration.

For ACLF type I, which primarily manifests as hepatic organ failure at onset, an initial assessment should be performed using prognostic models such as the Model for End-Stage Liver Disease (MELD), MELD-Na, and Asian Pacific Association for the Study of the Liver ACLF Research Consortium (APASL-AARC) scores to determine disease severity and outcomes. If extrahepatic organ failure develops, the combined use of Chinese Group on Study of Severe Hepatitis B (COSSH)-ACLF II, chronic liver failure consortium (CLIF-C) ACLF, and North American Consortium of Study of End-stage Liver Disease (NACSELD) organ failure scores is recommended (Grade 1B).

ACLF type II, characterized by concurrent hepatic failure and extrahepatic organ dysfunction or failure at onset, requires a multiparametric prognostic assessment, including but not limited to the MELD, MELD-Na, COSSH-ACLF II, CLIF-C ACLF, and NACSELD organ failure scores (Grade 1B).

Dynamic reassessment of ACLF severity every 3–7 days is essential to guide therapeutic decision-making. Traditional prognostic models rely on single time-point outcomes (e.g., survival, mortality, or liver transplantation), whereas the emerging dynamic prognostic stratification incorporates stage-specific evaluations (4-week and 12-week intervals) and expanded outcome categories (recovery, death, liver transplantation, or persistent liver failure). This approach provides novel insights for developing precision-driven predictive models and represents an advanced framework for the prognostic assessment of ACLF (Grade 1B).

Recommendations: Treatment of ACLF

Early diagnosis and intervention: Etiology-specific treatment and comprehensive supportive care should be promptly initiated to stabilize organ function and mitigate complications.

Comprehensive medical management

General supportive care

These include bed rest, clinical monitoring, correction of hypoproteinemia, surveillance of laboratory parameters, and appropriate disinfection and isolation measures.

Nutritional assessment, supportive therapy, and follow-up management

Nutritional assessment

Recommendation: Standardized nutritional assessments should be performed in all patients with ACLF to determine the severity of malnutrition and develop individualized nutrition regimens (Grade 1A).

Implementation: A multidisciplinary nutritional support team (NST) comprising hepatologists, registered dietitians, specialized nurses, and clinical pharmacists should be established.

Nutritional support therapy

Nutritional targets should be progressively achieved at 1.2–1.3 times the resting energy expenditure (REE) or 30–35 kcal/kg per day, individualized according to disease status, baseline nutritional state, and gastrointestinal absorptive capacity. Oral feeding is the preferred route, with recommended daytime fractionated meals and nocturnal supplementation along with vitamin and micronutrient supplementation as needed (Grade 1A).

Management of patients with HE:

Grade ≤2 HE: Protein intake targets (1.2–1.5 g/kg per day) should be maintained and incrementally increased via fractionated feeding, adjusted to individual tolerance.

Grade ≥3 HE: Protein intake should be temporarily reduced, and branched-chain amino acid (BCAA) formulations should be provided. Aspiration precautions (e.g., post-pyloric tube placement) should be implemented during enteral nutrition. Parenteral nutrition should be initiated if oral or enteral routes are contraindicated.

Symptomatic treatment

Use of anti-inflammatory and hepatoprotective agents

It is recommended that medications with anti-inflammatory, antioxidant, detoxifying, choleretic, or hepatocyte membrane-protective properties be administered, such as glycyrrhizic acid preparations (e.g., magnesium isoglycyrrhizinate), polyene phosphatidylcholine, reduced glutathione, and S-adenosylmethionine. However, the combined use of multiple agents with identical or similar mechanisms of action is not recommended (Grade 1B).

Application of microbiota-targeted therapy

Microecological modulators, including probiotics (such as *Bifidobacterium* and *Lactobacillus*), prebiotics (such as lactulose), and synbiotics (combinations of probiotics and prebiotics) may help restore the intestinal microecological balance in patients with liver failure, reduce secondary infections, and improve prognosis.

Use of immunomodulators

For ACLF associated with hepatitis B virus (HBV) infection, autoimmune hepatitis, alcohol-related liver disease, or drug-induced liver injury, glucocorticoid therapy may be considered in the absence of contraindications (Grade B1). In patients with pre-ACLF or early-stage ACLF type I with marked immunoinflammatory activity, short-term and low-dose glucocorticoids may be administered based on individualized treatment and active etiological therapy. Long-term use is not recommended, except in cases of autoimmune hepatitis or immune checkpoint inhibitor-related ACLF (Grade 1B). Before initiating therapy, factors such as patient age, cirrhosis stage, infection status, and bleeding risk should be carefully evaluated. During treatment, glucocorticoid-related adverse effects should be closely monitored, and treatment efficacy regularly assessed.

Etiological treatment

Identifying the underlying cause of liver failure is crucial for guiding treatment and determining prognosis. This requires the evaluation of both the primary disease and precipitating factors. In cases with an unclear chronic etiology, every effort should be made to establish the cause to enable targeted management. Precipitating factors, such as superimposed hepatotropic viral infections, physical or emotional stress, alcohol intake, fatigue, medication use, and bleeding, should be actively identified and eliminated.

Comprehensive medical management of complications

Targeted management should be implemented for complications, such as infections, ascites, cerebral edema, HE, AKI, gastrointestinal bleeding, hepatopulmonary syndrome, and portopulmonary hypertension. When appropriate, multidisciplinary consultations should be undertaken to develop individualized diagnostic and therapeutic plans.

Non-biological artificial liver support therapy

Artificial liver support should be considered based on a comprehensive assessment of the patient's ACLF classification (staging), disease progression rate, clinical presentation, laboratory findings, imaging results, complications, plasma availability, and principles and characteristics of the selected treatment modality. Therefore, the timing, modality, and frequency of the treatment must be determined accordingly (Grade 1A).

Liver transplantation

Liver transplantation is the definitive and effective treatment option for ACLF. In the absence of contraindications,

all patients with ACLF should be evaluated as potential candidates. Given the scarcity of donor organs, high costs, and the risk of postoperative complications, careful selection of suitable candidates is essential to optimize clinical outcomes.

For patients receiving comprehensive medical management and artificial liver support, a dynamic evaluation of the treatment response should be performed. Changes in prognostic scores during the clinical course should be used to identify optimal candidates for liver transplantation (Grade 1A).

For patients with ACLF type I, the MELD score can be used to assess transplant eligibility. For patients with disease progression and extrahepatic organ failure or ACLF type II, the CLIF-C ACLF score is recommended for a combined assessment (Grade 1A).

Patients whose condition is not effectively controlled or continues to deteriorate after 3–7 days of medical therapy but who have fewer than three organ failures or a CLIF-C ACLF score of <64 should be prioritized for liver transplantation. For those with three or more organ failures or a CLIF-C ACLF score ≥64, daily monitoring is recommended. If organ function improves or the score decreases (i.e., organ failures ≤3 or CLIF-C ACLF score <64), re-evaluation for liver transplantation should be undertaken (Grade 2B).

Caution is warranted when considering liver transplantation in patients with ACLF and acute respiratory distress syndrome or severe coronary artery disease with non-reconstructable vasculature (Grade 1A).

With advances in medical technology, the indications for liver transplantation have expanded, and some conditions previously regarded as absolute contraindications are no longer considered as such. A multidisciplinary approach to diagnosis and treatment allows for a more accurate identification of suitable candidates and a more rational allocation of medical resources.

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Conflicts of interest

None.

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