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REVIEW

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Acute-on-chronic liver failure and immune dysregulation: Systemic inflammation and immunoparesis paradox

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Abstract

Acute-on-chronic liver failure (ACLF) is a severe clinical syndrome characterized by abrupt hepatic decompensation and systemic inflammation in patients with underlying chronic liver disease, frequently progressing to multi-organ failure and high short-term mortality. Although ACLF is increasingly recognized as a distinct clinical entity, its pathogenesis remains incompletely understood, and diagnostic criteria vary across international guidelines. Central to ACLF is immune dysregulation, driven by systemic inflammation triggered by bacterial translocation, pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs), alongside immunoparesis resulting from sustained immune activation. This review synthesizes current preclinical and clinical evidence on ACLF's classification, underlying mechanisms, and the dynamic interplay between hepatic injury, immune dysfunction, and organ failure. In addition, we highlight emerging biomarkers and the therapeutic strategies aimed at improving diagnostic accuracy and patient outcomes.

Abbreviations: AARC, APASL-ACLF Research Consortium; AASLD, American Association for the Study of Liver Diseases; ACLF, acute-on-chronic liver failure; AD, acute decompensation; ADC, acute decompensation of cirrhosis; AGA, American Gastroenterological Association; APAP, acetaminophen; APASL, Asian Pacific Association for the Study of the Liver; APP, acute-phase proteins; BDL, bile duct ligation; CARS, compensatory anti-inflammatory response syndrome; CCl_4, carbon tetrachloride; CK18, cytokeratin 18; CLD, chronic liver disease; CLIF-C OF, CLIF Consortium Organ Failure; CLIF-SOFA, Chronic Liver Failure–Sequential Organ Failure Assessment; CLP, cecal ligation and puncture; COSSH, Chinese Group on the Study of Severe Hepatitis B; CRP, C-reactive protein; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DAMPs, damage-associated molecular patterns; D-GalN, D-galactosamine; DILI, drug-induced liver injury; EASL-CLIF, European Association for the Study of the Liver—Chronic Liver Failure; ECLS, extracorporeal liver support; ESR, erythrocyte sedimentation rate; G-CSF, granulocyte colony-stimulating factor; HE, hepatic encephalopathy; HLA-DR, human leukocyte antigen DR isotype; HMGB1, high-mobility group box 1; IFN-γ, interferon-γ; IL-1β, interleukin-1β; IL-1ra, interleukin-1 receptor antagonist; IL-6, interleukin-6; IL-8, interleukin-8; IL-12, interleukin-12; IL-22BP, interleukin-22 binding protein; IL-22Fc, interleukin-22 fused with an Fc domain; IL-33, interleukin-33; INR, International Normalized Ratio; JAK-STAT, Janus kinase–signal transducer and activator of transcription; KC, Kupffer cell; LBP, lipopolysaccharide-binding protein; LPS, lipopolysaccharide; LT, liver transplantation; LTA, lipoteichoic acid; LTE_4, leukotriene E_4; LXA_5, lipoxin A_5; MAP, mean arterial pressure; MAPK, mitogen-activated protein kinase; MARS, Molecular Adsorbent Recirculating System; MCP-1, monocyte chemoattractant protein 1; MDSC, myeloid-derived suppressor cell; MERTK, MER receptor tyrosine kinase; MHN, massive hepatic necrosis; M-MDSC, monocytic myeloid-derived suppressor cell; MOF, multiorgan failure; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; NET, neutrophil extracellular trap; NF-κB, nuclear factor κB; NLR, neutrophil-to-lymphocyte ratio; NLRs, NOD-like receptors; PAMPs, pathogen-associated molecular patterns; PCT, procalcitonin; PD-1, programmed cell death protein 1; PGE_2, prostaglandin E_2; $PGF_2\alpha$, prostaglandin $F_2\alpha$; PRR, pattern recognition receptor; PS, porcine serum; PV, plasma viscosity; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; RRT, renal replacement therapy; SBP, spontaneous bacterial peritonitis; sFasL, soluble Fas ligand; SIRS, systemic inflammatory response syndrome; SMHN, submassive hepatic necrosis; SPMs, specialized pro-resolving mediators; sST2, soluble ST2; STAT1, signal transducer and activator of transcription 1; STAT3, signal transducer and activator of transcription 3; TAA, thioacetamide; TEG, thromboelastography; TIM-3, T-cell immunoglobulin and mucin domain-containing protein 3; TIPS, transjugular intrahepatic portosystemic shunt; TLR4, Toll-like receptor 4; TLRs, Toll-like receptors; TNF-α, tumor necrosis factor-α; TPPM, Tongji Prognostic Predictor Model; Tregs, regulatory T cells; WBC, white blood cell.

Keywords: acute-on-chronic liver injury, chronic liver disease, damage-associated molecular patterns (DAMPs), immune paralysis, immunoparesis, multi-organ failure, pathogen-associated molecular patterns (PAMPs)

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a distinct, multifaceted, and life-threatening clinical syndrome characterized by the sudden onset of systemic inflammation and rapid deterioration of liver function in individuals with pre-existing chronic liver disease (CLD).[1–3] This sudden decline frequently culminates in multi-organ failure (MOF) and is associated with high short-term mortality.[1]

Although ACLF is increasingly recognized as a distinct clinical entity, its pathogenesis remains incompletely understood, and its *definitions vary considerably across international guidelines*.[4] Such variability has fueled an ongoing debate regarding its classification and underscores the need for a unified framework to guide diagnosis and therapeutic strategies.

The pathophysiological cascade of ACLF typically begins with hepatic inflammation driven by hepatocyte injury. This localized inflammation progresses to systemic inflammation, which is marked by immune activation and immunoparesis (also referred to as immune cell paralysis), reflecting profound immune dysregulation. Systemic inflammation is often triggered by bacterial translocation or the release of damage-associated molecular patterns (DAMPs), whereas immunoparesis arises from persistent immune cell activation. Together, these processes contribute to extrahepatic organ dysfunction, heightened susceptibility to infection, and ultimately MOF and death.

In this review, we aimed to provide a comprehensive overview of ACLF, emphasizing its classification, underlying mechanisms, and the central role of immune dysregulation, particularly the interplay between systemic inflammation and immunoparesis. By integrating evidence from both preclinical and clinical studies, we explored the complex interactions between hepatic injury, immune dysfunction, and organ failure. Our goal is to clarify emerging concepts, support refinement of diagnostic criteria, and highlight potential biomarkers and therapeutic strategies to improve patient outcomes.

ACLF: CLINICAL DEFINITIONS

The American Association for the Study of Liver Diseases (AASLD, 2024) defines ACLF as a clinical syndrome characterized by sudden hepatic failure in patients with pre-existing chronic liver disease (CLD), often accompanied by extrahepatic organ failure and associated with high short-term mortality.[2] This rapid deterioration frequently necessitates intensive care and may progress to MOF.

A major challenge in *identifying* and *managing* ACLF is the lack of a universally accepted definition, as clinical guidelines vary significantly across regions.[5] Differential definition of ACLF reflecting variations in pathophysiological emphasis and clinical practice have been developed by several international consortia—(1) The Asian Pacific Association for the Study of the Liver (APASL, 2009/2014); (2) the European Association for the Study of the Liver—Chronic Liver Failure Consortium (EASL-CLIF, 2013); (3) The North American Consortium for the Study of End-Stage Liver Disease (NACSELD, 2018); (4) The Chinese Group on the Study of Severe Hepatitis B (COSSH); and (5) Kyoto Consensus 2025 (Table 1).

The Asian Pacific Association for the Study of the Liver (APASL) defines ACLF as an acute hepatic insult in individuals with CLD (with or without cirrhosis) but without prior decompensation. Common triggers include hepatitis B virus reactivation and acute alcoholic hepatitis. Diagnostic criteria require jaundice (serum bilirubin ≥ 5 mg/dL) and coagulopathy (INR ≥ 1.5 or prothrombin activity $< 40\%$), progressing within 4 weeks to ascites and/or hepatic encephalopathy (HE).[6] The APASL definition is fundamentally *liver-centric*, emphasizing hepatic dysfunction as the core feature and *excluding patients with previous decompensation or acutely decompensated cirrhosis*. Extrahepatic insults such as sepsis or gastrointestinal bleeding are considered complications rather than precipitating factors, and extrahepatic organ failures are viewed as consequences of progressive ACLF or secondary infections, not as diagnostic criteria. This approach underscores the APASL focus on primary hepatic injury as the defining element of ACLF. The limitation of this definition is in excluding patients with prior decompensation, as well as not including organ failure, aside from cerebral and hepatic, in the core diagnostic criteria. The inclusion or exclusion of prior decompensation was determined to require further prospective studies before adjusting APASL guidelines.[6] In contrast, the exclusion of extrahepatic organ failure was intentional as the definition of ACLF intends to diagnose primary liver failure and identify the clinical syndrome before extrahepatic organ failure develops. Cerebral failure, or HE, is included in this definition as it is the early and direct sequelae of primary metabolic dysfunction of the liver.

In contrast, the European Association for the Study of the Liver—Chronic Liver Failure (EASL-CLIF) Consortium defines ACLF as a systemic syndrome occurring in patients with acutely decompensated cirrhosis, characterized by failure of one or more vital organ systems and associated with high short-term mortality, estimated at 20%–40% within 28 days.[1,3,12] This definition, derived from the landmark CANONIC study of 1343 consecutive patients hospitalized for acute decompensation (AD), emphasizes that ACLF is not limited to hepatic failure but reflects a multi-organ dysfunction state triggered by acute deterioration in a cirrhotic substrate.[1] Diagnostic assessment under this framework evaluates 6 organ systems: *liver*, *kidney*, *brain*, *coagulation*, *circulation*, and *respiration*. Organ failure is determined using the Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score, adapted from the original SOFA system to reflect cirrhosis-specific physiology.[1] Coagulation is included as an organ system because severe impairment of hemostasis (eg, INR ≥ 2.5 or platelet count $< 20{,}000/mm^3$) reflects profound synthetic dysfunction and correlates with poor prognosis, making it a surrogate marker of systemic failure rather than an isolated laboratory abnormality. ACLF severity is graded based on the number of organ failures: grade 0 refers to patients with AD but no organ failure (high risk of progression if systemic inflammation is present); grade 1 includes single organ failure (typically kidney) or a combination of mild renal dysfunction and grades I–II HE; grade 2 denotes 2 organ failures; and grade 3 represents 3 or more organ failures, associated with the highest mortality. This grading system underscores the systemic nature of ACLF, where prognosis worsens exponentially with each additional organ failure, highlighting the need for early recognition and aggressive management. Although liver failure is not universally present under the CLIF concept, the term ACLF remains valid because the syndrome occurs exclusively in patients with CLD and represents an acute deterioration leading to MOF within a liver-specific context. Furthermore, the CLIF score was designed for clinical prognostication, and the fact remains that a higher number of organ failures in the context of liver disease raises mortality. This conceptualization resolves the apparent contradiction: ACLF is not defined by isolated hepatic failure but by systemic pathophysiology superimposed on chronic liver dysfunction. ACLF should be understood as a systemic inflammatory and immune dysregulation syndrome triggered by AD in cirrhosis, rather than a purely hepatic event. This perspective shifts the focus from liver-centric definitions to models that capture multi-organ involvement and dynamic systemic processes. Recognizing ACLF as a systemic syndrome supports the use of organ failure-based prognostic models such as CLIF-C ACLF and NACSELD, which outperform liver-specific scores in predicting short-term mortality. This distinction also underpins therapeutic strategies that prioritize multi-organ support, infection control, and timely transplant evaluation, rather than interventions targeting hepatic function alone. Despite its strengths, the EASL-CLIF definition may fail to identify early stages of ACLF where extrahepatic organ failure has not yet occurred. While the definition demonstrates high sensitivity and negative predictive value,[13] no longitudinal study has conclusively linked these characteristics to improved survival compared with alternative definitions. Furthermore, the CLIF-SOFA score has been shown to be inferior to the APASL-ACLF Research Consortium (AARC) score in predicting mortality, with an area under the receiver operating characteristic curve of 0.80.[14]

The North American Consortium for the Study of End-Stage Liver Disease (NACSELD) adopts a pragmatic approach, defining ACLF by the presence of 2 or more extrahepatic organ failures: shock, grades III–IV HE, renal failure requiring dialysis, or respiratory failure requiring mechanical ventilation.[8] This simplified model was designed to facilitate rapid clinical assessment and predict short-term outcomes, particularly 30-day mortality, in hospitalized patients with cirrhosis. Unlike other definitions, NACSELD does not incorporate liver-specific parameters or coagulation status, emphasizing instead the systemic nature of ACLF and the prognostic impact of MOF. By prioritizing extrahepatic dysfunction, NACSELD offers a practical tool for clinicians managing critically ill cirrhotic patients in intensive care settings.[8,15] This definition is more accurate in predicting 28-day mortality as compared with the EASL-CLIF guideline due to the inclusivity and sensitivity of EASL-CLIF diagnostic criteria.[13] Although the strict emphasis on severe organ failure aligns with predicting short-term mortality, it misses many patients who do not reach the MOF diagnostic requirement. Similarly, in not strictly mentioning liver failure, this definition does not account for hepatic-centric cases of ACLF.

The Chinese Group on the Study of Severe Hepatitis B (COSSH) focuses on hepatitis B virus (HBV)-related ACLF, incorporating patients with prior decompensation and systemic inflammation. Its prognostic scoring system (COSSH-ACLF) uses 6 variables, including INR, HE, neutrophil count, bilirubin, serum urea, and age, in order to predict short-term mortality, offering a tailored approach for HBV-endemic regions.[10,16] Neutrophil count is utilized as a more specific inflammatory marker to the alternative of white blood cells, while serum urea replaced creatinine from the previous COSSH-ACLF scoring due to a higher sub-hazard ratio.[16] This definition lacks generalizability as it is not validated outside the HBV-related ACLF cohort.

Finally, the Kyoto Consensus seeks to unify these definitions, framing ACLF as a dynamic syndrome of acute hepatic deterioration on CLD, frequently associated with systemic inflammation and multi-organ dysfunction. By integrating elements from APASL, EASL-CLIF, NACSELD, and COSSH, the Kyoto Consensus aims to standardize diagnostic criteria globally and improve comparability across research and clinical practice.[11] The Kyoto Consensus proposes 2 types of ACLF: type A and type B. Type A ACLF encompasses APASL, COSSH, Japanese, and Mexican definitions of ACLF. It "includes patients with a first-time acute insult resulting in features of liver failure in a patient with underlying CLD or cirrhosis. It does not include patients with previous decompensation or extrahepatic insults. It can be reversible and considers infection as a consequence more often than a precipitant of ACLF and is associated with high (30%–40%) 28-day mortality." Type B ACLF includes patients with type A ACLF, with the addition of patients with previous decompensation and organ failure caused by both hepatic and extrahepatic insults, including infection. This is associated with high (40%–50%) 28-day mortality.[10] This encompasses the EASL-CLIF and NACSELD definitions.

Overall, ACLF definitions differ in their emphasis on hepatic versus systemic failure, inclusion of prior decompensation, and organ failure criteria. APASL is liver-centric, EASL-CLIF and NACSELD prioritize systemic dysfunction, COSSH addresses HBV-specific contexts, and Kyoto Consensus offers a unified framework. These variations impact patient selection, prognostication, and therapeutic strategies.

Clinical and research implications

The absence of a unified definition of ACLF, including its diagnostic criteria, acute precipitants, and etiology of underlying CLD, poses significant challenges for both clinical practice and research.[17] Although all major definitions agree that ACLF is associated with poor prognosis and high short-term mortality,[5] the lack of consensus introduces variability that affects patient care and slows scientific progress.

Clinical implications

Divergent definitions create heterogeneity in timely patient identification, risk stratification, and management recommendations. The APASL definition, with its hepatic-centric focus, facilitates early liver-directed interventions in first decompensation but may fail to capture patients with severe extrahepatic organ failure.[6] Conversely, the EASL-CLIF multi-organ framework offers superior prognostic accuracy and informs ICU admission, organ support, and transplant prioritization, yet requires comprehensive organ failure assessment that may be resource-intensive.[3] The NACSELD's binary approach, emphasizing extrahepatic organ failures, enables rapid bedside decision-making and predicts 30-day mortality effectively, but may overlook earlier hepatic-predominant ACLF phenotypes.[9] The COSSH criteria, tailored for HBV-endemic regions, refines prognostication and supports timely interventions and bridge-to-transplant strategies.[10] These discrepancies influence transplant candidacy, timing of escalation, and allocation of critical care resources, ultimately impacting patient outcomes. Inconsistent diagnostic criteria can also delay or misguide treatment, compromising survival.

Research implications

Lack of harmonization impairs comparability and reproducibility across studies, limiting meta-analyses and delaying consensus guidelines. Clinical trials often enroll heterogeneous cohorts due to variable inclusion criteria, reducing external validity and complicating endpoint interpretation. Biomarker discovery and mechanistic studies are constrained by inconsistent thresholds for organ failure, hindering the generalization of prognostic models such as CLIF-C ACLF,[18] or COSSH-ACLF.[10] Large registries face difficulties harmonizing datasets across regions with differing etiologies and diagnostic constructs. Terminological inconsistencies—where terms like acute liver decompensation, acute liver failure, and ACLF are used interchangeably—further contribute to misclassification, affecting patient management and trial eligibility. The American Gastroenterological Association (AGA) has attempted to bridge these gaps by proposing a more inclusive definition: ACLF as a potentially reversible condition in patients with CLD, with or without cirrhosis, carrying a high risk of MOF and mortality within 3 months if untreated.[5] However, global adoption remains limited.

Need for harmonization

The current fragmentation in clinical identification of ACLF underscores the urgent need for a unified global framework. In this context, a multi-society group of experts has issued a consensus statement defining organ failures in cirrhosis to standardize clinical outcomes in ACLF.[19] A forthcoming standard ACLF definition based on such consensus would expand sample sizes and statistical power in existing cohorts, improve diagnostic accuracy, enable timely interventions, and optimize resource allocation. Critically, a harmonized definition should facilitate early diagnosis

TABLE 1 Comparison of ACLF definitions by international consortia

Consortium	Core criteria	Organ systems considered	Grading/severity	Key features	Clinical implications	Reference
APASL	Acute hepatic insult in CLD (± cirrhosis), jaundice (bilirubin ≥ 5 mg/dL), coagulopathy (INR ≥ 1.5 or prothrombin activity < 40%), progression to ascites/HE within 4 weeks	Hepatic focus	No formal grading	Liver-centric; often first decompensation; extrahepatic failures considered complications	Early hepatic-failure identification; strong utility in HBV/alcoholic hepatitis; limited capture of MOF	[6,7]
EASL-CLIF	Acute decompensation of cirrhosis + ≥ 1 organ failure	Liver, kidney, brain, coagulation, circulation, respiration	Grades 0–3 by number/severity of failures (CLIF-SOFA)	Derived from CANONIC (n = 1343); includes coagulation owing to prognostic impact	Robust prognostication guides ICU triage and transplant prioritization; identifies high-risk cohorts	[1,3]
NACSELD	≥ 2 extrahepatic organ failures	Shock, HE III–IV, renal dialysis, respiratory ventilation	Binary	Simple bedside tool; excludes liver-specific parameters	Rapid risk stratification and 30-day mortality prediction in ICU settings; MOF is predictive of poor survival	[8,9]
COSSH	HBV-related ACLF; acute insult ± prior decompensation; systemic inflammation	Multi-organ involvement	Prognostic score (COSSH-ACLF, COSSH-ACLF II)	Six predictors (INR, HE grades, neutrophils, bilirubin, urea, age)	Tailored for HBV-endemic regions; improves early prognosis and intervention planning	[10]
Kyoto Consensus	Unified, dynamic definition: acute hepatic deterioration + systemic inflammation ± multi-organ dysfunction	Integrative (hepatic + extrahepatic)	Proposed dynamic severity model	Seeks harmonization across regions/etiologies	Enables global comparability; supports registry science and collaborative trials	[11]

Abbreviations: ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; CLD, chronic liver disease; CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment; COSSH, Chinese Group on the Study of Severe Hepatitis B; EASL-CLIF, European Association for the Study of the Liver—Chronic Liver Failure; HBV, hepatitis B virus; HE, hepatic encephalopathy; ICU, intensive care unit; INR, international normalized ratio; MOF, multi-organ failure; NACSELD, North American Consortium for the Study of End-Stage Liver Disease.

within a "golden window," when reversibility of ACLF is possible, thereby improving survival and accelerating evidence-based therapy development. The Kyoto Consensus[11] represents a pivotal step toward integrating hepatic and extrahepatic components across diverse etiologies, offering a pathway to harmonize definitions and elevate both clinical care and scientific discovery in ACLF.

Prognostic scoring and timing of treatment

Clinical decision-making in ACLF is primarily guided by the extent of organ dysfunction and prognostic severity scores such as MELD, CLIF-SOFA, CLIF-C, and NACSELD ACLF. These scoring systems are critical for identifying high-risk patients and determining the optimal timing for interventions. For example, a CLIF-C score ≥ 64 between days 3 and 7 predicts nearly 100% 28-day mortality, underscoring the need for urgent liver transplant evaluation.[20] Failure of this score to improve within 3–7 days despite appropriate supportive care suggests irreversible disease and potential futility of continued intensive therapy.[18] Liver transplantation remains the only potentially curative treatment for ACLF, irrespective of etiology,[21] yet it is feasible in fewer than one-fourth of patients, with a 5-year survival exceeding 80%.[22,23] Transplantation is contraindicated in several clinical scenarios, including uncontrolled sepsis, severe cardiopulmonary disease, extrahepatic malignancy, and fulminant hepatic failure with sustained intracranial pressure >50 mm Hg or cerebral perfusion pressure <40 mm Hg.[24] Given the dynamic nature of ACLF, sequential assessment at days 0, 3, 7, and 14 is recommended to guide ICU resource allocation, renal replacement therapy, vasopressor use, and transplant eligibility.[11]

In comparative evaluations, the Kyoto Consensus identifies the AARC score as more accurate than MELD, CLIF-SOFA, and SOFA, except in HBV-related ACLF, where the Tongji Prognostic Predictor Model (TPPM) may offer superior predictive value.[25] All scoring systems require ongoing validation and refinement. Beyond transplantation, severity scores also inform selection for immune-modulating and investigational therapies. Patients with higher scores, often ineligible for transplant, exhibit severe systemic inflammation and immune dysregulation, making them candidates for interventions targeting pro-inflammatory pathways and promoting hepatic regeneration, such as granulocyte colony-stimulating factor (G-CSF), toll-like receptor 4 (TLR4) antagonists, or plasma exchange with albumin. In summary, ACLF severity scores are indispensable for assessing disease trajectory, determining transplant timing and eligibility, guiding therapeutic intensity, and identifying candidates for clinical trials.

DEFINING ACLF THROUGH THE LENS OF LIVER DISEASE PROGRESSION

To understand ACLF, it is essential to first distinguish it from CLD, compensated (non-decompensated), and decompensated cirrhosis, as these stages represent the continuum of CLD progression.

CLD and its stages

CLD refers to the progressive deterioration of liver function lasting more than 6 months. It involves ongoing damage to the liver tissue, which can lead to fibrosis (scarring), cirrhosis (advanced scarring), and eventually liver failure. This progression impairs the ability of the liver to perform vital functions, such as detoxification of blood, production of bile, and synthesis of essential proteins. CLD typically advances through the following stages: (i) Liver injury—initial damage caused by factors such as viral hepatitis, alcohol use, or metabolic disorders. (ii) Inflammation (hepatitis)—the liver becomes inflamed as it responds to injury. (iii) Fibrosis scar tissue begins to replace healthy liver tissue. Fibrosis was graded from F0 (no fibrosis) to F4 (severe fibrosis/cirrhosis). (iv) Cirrhosis—extensive scarring disrupts liver architecture and function. Cirrhosis is classified as compensated or decompensated (see below for details). In compensated cirrhosis, the liver is heavily scarred but still performs most of its functions. Hence, compensated patients with cirrhosis may be asymptomatic. In decompensated cirrhosis, the liver can no longer function properly, leading to complications such as ascites, jaundice, variceal bleeding, and HE. (v) End-Stage Liver Disease/ACLF—This is the most severe phase, where liver failure occurs, often requiring liver transplantation (schematic Figure 1).

Clinically, CLD is defined as early-stage CLD that includes liver injury to fibrosis stages F0–F2, whereas advanced CLD encompasses fibrosis stages F3–F4, including both compensated and decompensated cirrhosis. A recent guideline published by the AASLD defines ACLF as a rapid deterioration in liver function in patients with pre-existing CLD with or without cirrhosis, often triggered by an acute insult.[2]

Compensated cirrhosis

It is also known as non-decompensated cirrhosis and is marked by preserved liver function despite structural liver damage. Patients are often asymptomatic or exhibit mild signs of liver dysfunction. Laboratory values, such as serum albumin and INR, are typically within normal ranges, and there are no clinical signs of liver failure (eg, jaundice, ascites, and variceal

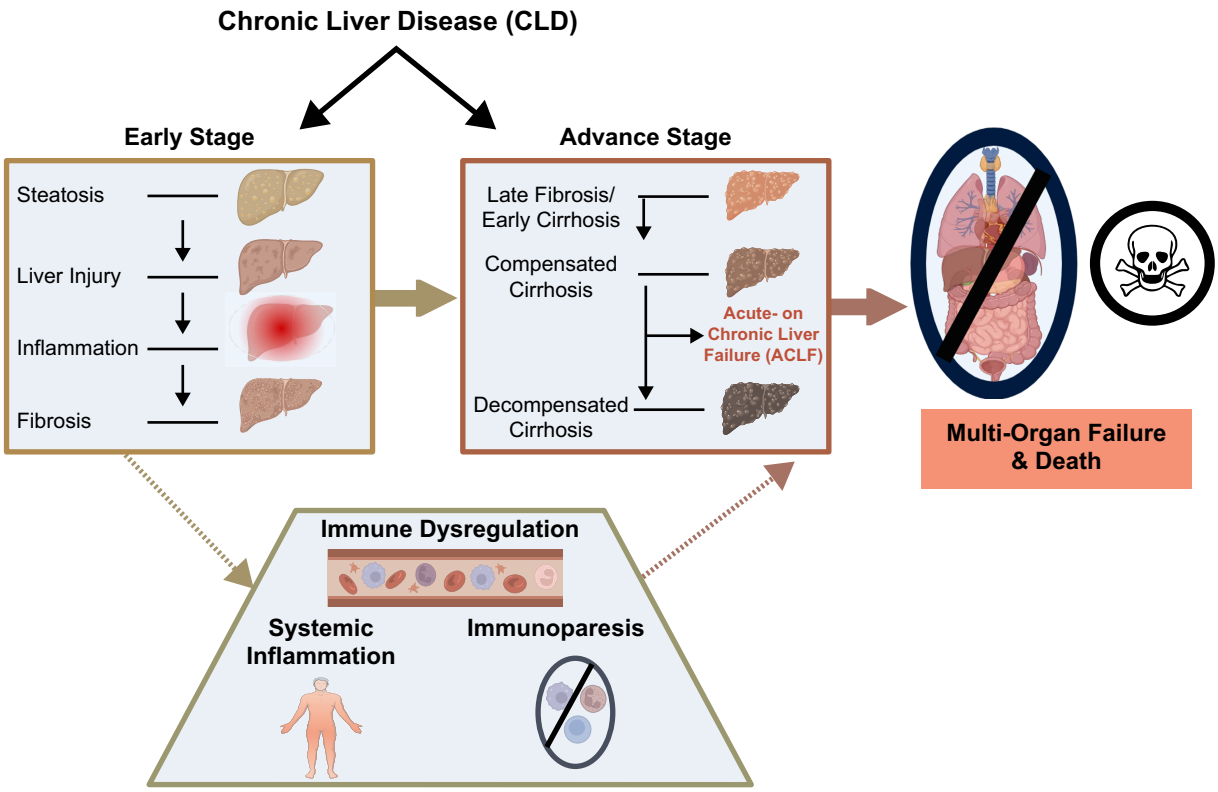

FIGURE 1 Progression of chronic liver disease (CLD) and associated immune dysregulation. CLD evolves from early stages—characterized by steatosis, hepatocellular injury, inflammation, and mild fibrosis—to advanced stages, including late fibrosis, compensated cirrhosis, and decompensated cirrhosis. Acute-on-chronic liver failure (ACLF) typically arises in the advanced stage following an acute insult. Throughout this progression, immune dysregulation plays a central role: systemic inflammation (SI) begins at low levels in early CLD and intensifies with disease advancement, while immunoparesis emerges predominantly in later stages. Together, SI and immunoparesis drive susceptibility to infection, multi-organ failure (MOF), and ultimately death.

bleeding). Individuals can remain stable for up to 12 years, although they remain at risk of progression if liver injury continues.[26]

Decompensated cirrhosis

This stage involves a significant decline in liver function with complications such as ascites, variceal hemorrhage, HE, and spontaneous bacterial peritonitis (SBP). Laboratory findings often include elevated bilirubin levels, low albumin levels, and a prolonged INR. Portal hypertension contributes to the development of varices and splenomegaly. Decompensated cirrhosis carries a markedly higher mortality risk, particularly within 2 years of onset.[26,27] Cirrhosis is traditionally staged from 1 to 4, with stages 1–2 being compensated and stages 3–4 being decompensated.[26]

ACLF: A distinct clinical syndrome

ACLF represents a sudden and severe deterioration in liver function in patients with pre-existing CLD, typically progressing rapidly over days to weeks. This syndrome is typically triggered by an *acute insult* (or injury) (also known as an *acute precipitating event*) such as bacterial infections, alcohol binge, or drug-induced liver injury (DILI), although in up to 40% of cases, no clear precipitant is identified.[1,28] Clinically, ACLF is characterized by jaundice, coagulopathy, HE, and multi-organ dysfunction, particularly involving the kidneys, cardiovascular system, and brain, which are hallmark features.[1,29]

Historically, ACLF has been conceptualized within the PIRO framework (Predisposition, Insult, Response, Organ Failure), reflecting its overlap with sepsis pathophysiology in cirrhotic patients.[1] While ACLF and sepsis share features such as systemic inflammation, immune dysregulation, and MOF, they remain distinct entities. Infection is the most frequent precipitant of ACLF in Western cohorts, reinforcing this overlap; however, ACLF can also result from non-infectious triggers, including alcohol binge, gastrointestinal bleeding, DILI, or HBV reactivation. Unlike sepsis, which is defined by infection and a dysregulated host response, ACLF occurs exclusively in patients with CLD and often involves sterile inflammation driven by

DAMPs. Diagnostic frameworks further differentiate the 2: ACLF is identified using organ failure-based scores (eg, CLIF-C ACLF, NACSELD, COSSH) regardless of infection status, whereas sepsis requires suspected or confirmed infection plus an increase in SOFA score. Therapeutically, ACLF management integrates liver-specific strategies such as transplant evaluation, immunomodulation, bioartificial liver support, and precipitant control, while sepsis care focuses on infection source control and antimicrobial therapy. These distinctions underscore ACLF as a unique systemic syndrome with its own natural history, prognostic models, and transplant implications.

Etiologies of ACLF

ACLF develops when an acute precipitating event is superimposed on a background of CLD, leading to rapid clinical deterioration and organ failure.[30] Common acute triggers include bacterial infections, gastrointestinal bleeding, alcohol binge drinking, and viral reactivation.[28] The underlying CLD most often results from alcohol-associated cirrhosis, chronic hepatitis B or C, and nonalcoholic steatohepatitis (NASH).[28] Geographic variation is notable: in Western populations, alcohol consumption, bacterial infections, and DILI predominate, whereas HBV reactivation and superimposed viral hepatitis are more frequent in Asia.[29] Other recognized precipitants include systemic sepsis, major surgery, and chemotherapy-related hepatic injury.[31] Importantly, up to 40% of ACLF cases occur without an identifiable trigger, underscoring its multifactorial nature.[32]

The interaction between precipitating events and underlying etiology shapes clinical trajectories and outcomes. For example, *alcohol-associated cirrhosis* often presents with severe systemic inflammation and higher risk of MOF when triggered by infections or continued alcohol intake, resulting in poorer short-term survival.[33,34] In contrast, *HBV-related ACLF* may exhibit abrupt hepatic necrosis and profound jaundice following viral reactivation, but these patients often respond favorably to antiviral therapy if initiated early, improving prognosis.[35,36] Similarly, *NASH-related ACLF* tends to occur in older patients with metabolic comorbidities, predisposing them to cardiovascular and renal complications, which significantly influence mortality risk.[35,36] These pathophysiological differences explain why ACLF is not a uniform syndrome but a spectrum of clinical courses, ranging from reversible organ dysfunction to rapid progression toward death.

Pathological features of ACLF

ACLF exhibits a distinctive histopathological profile combining acute and chronic liver injury. The defining feature is *massive hepatocyte loss*, manifesting as *massive hepatic necrosis (MHN)* or *submassive hepatic necrosis (SMHN)*, accompanied by extensive inflammatory cell infiltration, collapse of hepatic architecture, cholestasis, and frequent microvascular thrombosis.[1] These acute changes coexist with chronic features such as fibrosis or cirrhosis, creating a dual pattern of injury. From a clinical standpoint, liver failure and HE (brain failure) are the most consistent pathological correlates across current ACLF diagnostic frameworks.

Etiology-specific variations are notable. *Alcohol-related ACLF* typically exhibits steatohepatitis with neutrophilic infiltration and Mallory–Denk bodies, whereas *HBV-related ACLF* often shows widespread hepatocyte dropout and interface hepatitis.[30] Early studies established MHN and SMHN as hallmark features of ACLF associated with HBV infection and autoimmune hepatitis.[34,37,38] In contrast, SMHN is generally absent in ACLF linked to HCV infection or alcohol abuse.[39] This distinction is clinically relevant because the landmark CANONIC study, which defined the European criteria for ACLF, was based predominantly on cases related to alcoholic hepatitis and HCV infection.[1] Consequently, SMHN-driven ACLF exhibits pathophysiological features that differ significantly from those observed in alcoholic hepatitis- or HCV-related ACLF.

Extrahepatic involvement is common and reflects the systemic nature of ACLF. Kidneys frequently demonstrate *acute tubular necrosis*, lungs exhibit *diffuse alveolar damage and pulmonary edema*, and the brain may develop *cerebral edema* in severe HE.[29] These systemic manifestations are driven by persistent inflammation and immune dysregulation, which also predispose patients to infections and worsen prognosis.[28]

Pathophysiology of ACLF

The pathophysiology of ACLF is driven by a complex interplay of systemic inflammation, immune dysfunction (see next section), and MOF. An acute hepatic or extrahepatic insult triggers an exaggerated inflammatory response, characterized by massive release of cytokines such as IL-6, TNF-α, and IL-1β, leading to a "cytokine storm" that accelerates tissue injury and organ dysfunction.[4,30] Activation of innate immune cells, including neutrophils and monocytes, promotes oxidative stress and endothelial damage, amplifying systemic inflammation.[31] A critical mechanism underlying this response is the activation of *pattern recognition receptors (PRRs)* by *pathogen-associated molecular patterns (PAMPs)*—derived from microbial components during infections—and *DAMPs*—released from injured hepatocytes, such as HMGB1 and mitochondrial DNA.[40] These signals initiate NF-κB

and inflammasome activation, driving pro-inflammatory cytokine release and linking infection and sterile hepatic injury to systemic inflammation (see section "DAMPS and PAMPS as mediators of Systemic inflammation" for details).

Concurrently, ACLF is marked by immune paralysis, with reduced monocyte HLA-DR expression and impaired adaptive immunity, predisposing patients to severe infections and sepsis.[31] This dual state of hyperinflammation and immunosuppression creates a vicious cycle that accelerates organ failure. Hepatic injury is compounded by impaired regeneration and mitochondrial dysfunction, while extrahepatic organs—particularly kidneys and lungs—succumb to circulatory collapse and microvascular dysfunction.[1] Dysregulated coagulation, gut microbiome alterations, and bacterial translocation further perpetuate systemic inflammation and MOF.[29] Overall, ACLF is a systemic syndrome or organ failures predisposed by liver failure, where immune dysregulation and systemic inflammation are central drivers of mortality.[28]

IMMUNE DYSREGULATION–SYSTEMIC INFLAMMATION AND IMMUNOPARESIS

ACLF pathogenesis involves a complex and paradoxical interplay between *systemic inflammation* and *immunoparesis*.[4,41,42] The severity of systemic inflammation and immunoparesis is strongly correlated with mortality and poor outcomes in ACLF patients.[43] Next, we discuss the role of systemic inflammation and immunoparesis in the pathogenesis of ACLF within the context of CLD and cirrhosis. These processes are intricately linked to progression from CLD and cirrhosis to ACLF.

Systemic inflammation in general

Systemic inflammation refers to a body-wide immune response involving activation of immune pathways across multiple organs and tissues. It is characterized by the release of pro-inflammatory cytokines, recruitment and activation of immune cells, and measurable changes in blood and tissue markers. Broadly, systemic inflammation can be classified into 2 forms. *Acute systemic inflammation* represents a short-term, controlled response to infection, trauma, or tissue injury. This phase is marked by transient activation of the innate immune system, coordinated cytokine release, and mobilization of inflammatory cells to facilitate tissue repair, restore homeostasis, and defend against pathogens. Resolution occurs through a switch to anti-inflammatory signaling and macrophage-mediated clearance of cellular debris.[44] When dysregulated, however, acute inflammation can lead to severe pathological states such as septic shock. In contrast, *chronic systemic inflammation* is a persistent, low-grade process characterized by sustained activation of both innate and adaptive immune systems. This maladaptive response drives progressive tissue damage through oxidative stress, continuous cytokine production, and endothelial dysfunction, ultimately resulting in organ injury. Chronic systemic inflammation underlies the pathogenesis of numerous conditions, including cardiovascular disease, type 2 diabetes, cancer, and autoimmune disorders.[45]

Technically, systemic inflammation can be defined as a multi-syndrome, phase-specific pathological process initiated by systemic damage and characterized by inflammatory activity within blood vessels, plasma, immune cells, and connective tissue, culminating in microcirculatory dysfunction in vital organs.

Clinical markers of systemic inflammation

Clinical markers play a critical role in diagnosing systemic inflammation in patients with ACLF, assessing its severity, monitoring therapeutic response, and predicting outcomes.[46] These biomarkers are broadly classified into three categories: cellular markers, protein markers, and metabolic markers.

Cellular markers such as white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), erythrocyte sedimentation rate (ESR), plasma viscosity (PV), and monocyte HLA-DR expression are indicative of immune activation and dysregulation.[33] Elevated WBC and NLR are associated with heightened inflammatory responses,[33] while reduced HLA-DR expression on monocytes indicates immune paresis and increased infection risk (*see later*).[34]

Protein markers include acute-phase proteins like C-reactive protein (CRP), haptoglobin, procalcitonin (PCT), fibrinogen, and inflammatory cytokines such as IL-6, TNF-α, MCP-1, and IL-8.[30,33,34,47] These markers provide insight into the severity of systemic inflammation and correlate with disease progression and prognosis. Compared with patients without ACLF, those with ACLF exhibit significantly elevated levels of pro-inflammatory cytokines (eg, TNF-α and IL-6) and chemokines (IL-8 and MCP-1).[48] Among these, IL-6 and IL-8 show strong correlations with the clinical trajectory of ACLF; lower levels often signal recovery, whereas elevated levels are associated with worsening disease. IL-6 is particularly elevated in patients with bacterial infection–associated ACLF, whereas IL-8 serves as a distinguishing marker when active alcohol use is the precipitating factor. Notably, both cytokines parallel disease severity and are predictive of 28-day and 90-day mortality.[48]

Metabolic markers such as lactate, endotoxin, and lipopolysaccharide-binding proteins (LBPs) provide

additional insight into inflammatory burden and immune response. Elevated lactate reflects metabolic derangements and tissue hypoperfusion, while increased endotoxin and LBP levels indicate systemic inflammation and microbial translocation.

These markers are not specific to any particular disease, but their levels assist in assessing the overall systemic inflammatory state of the body. Elevated levels of systemic inflammatory markers indicate ongoing microbial infections, sterile infections, autoimmune conditions, and other inflammatory disorders.

From hepatic inflammation to systemic inflammation

Systemic inflammation in CLD often originates from persistent hepatic inflammation. Hepatic inflammation refers to the localized immune response within the liver tissue, triggered by various insults, such as alcohol, hepatotoxic drugs, ischemia, toxins, metabolic dysfunction, infections, or autoimmune conditions. Although this response is initially protective, chronic or severe hepatic inflammation can exacerbate liver injury and impair function.[49]

Although hepatic and systemic inflammation are distinct processes, they are closely interconnected. If sustained, hepatic inflammation can initiate or amplify systemic inflammation. In CLD, hepatocytes exposed to stressors such as viral infections, alcohol, xenobiotics, or a Western diet undergo cellular stress and may release hepatic stress signals. When this stress surpasses a critical threshold, hepatocytes undergo cell death, releasing intracellular contents known as DAMPs. These DAMPs activate the immune cells and trigger hepatic inflammation (*schematic* Figure 2).

As CLD progresses, inflammatory cells infiltrate the liver and perpetuate the inflammation (hepatitis). Initially localized, this inflammation can transition into systemic inflammation, particularly chronic inflammation. Persistent hepatic inflammation leads to the release of inflammatory mediators into circulation, contributing to the development of systemic inflammation, cardiovascular disease, and hepatorenal syndrome. A critical knowledge gap remains, while systemic inflammation is well documented in advanced CLD, both clinically and in preclinical models,[30] and the onset and progression of low-grade, chronic systemic inflammation during earlier stages of CLD remain poorly understood and underreported.

Hepatic inflammation begins with the innate immune cells activation in the liver

Hepatic inflammation is initiated by the activation of innate immune cells in response to pathogens, cellular injury, or danger signals. Kupffer cells (KCs) (resident hepatic macrophages) play a central role in recognizing PAMPs (from pathogens) or DAMPs (from damaged host cells) (*see details below in the next section*) through PRRs.

Upon PRR activation, KCs and other immune cells release pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β (Cytokine Production). These cytokines act locally and systemically, triggering intracellular signaling cascades, including the MAPK, NF-κB, and JAK-STAT pathways (Cytokine Signaling), which amplify the inflammatory response.

In some cases, PRR activation also leads to inflammasome activation, a complex that produces more inflammatory cytokines such as IL-1β. Inflammasome activation can lead to the release of more inflammatory cytokines, which further drives inflammation.

In addition, liver dysfunction in CLD can disrupt gut–liver axis homeostasis. Altered gut permeability and dysbiosis (microbiota imbalance) allow bacterial products such as lipopolysaccharide (LPS) to translocate into the portal circulation. These microbial components reach the liver and activate PRRs, exacerbating hepatic inflammation, which is a phenomenon known as gut-derived inflammation. This is particularly relevant in cirrhosis,[50] where a compromised gut barrier facilitates bacterial translocation and systemic immune activation.

Hepatic inflammation can also cause systemic effects via the acute-phase response

Hepatic inflammation also exerts systemic effects through an acute-phase response.[51,52] Inflammatory cytokines stimulate hepatocytes to produce acute-phase proteins (APPs) such as CRP, which modulate immune responses throughout the body.[52]

Moreover, hepatic cytokines can influence hematopoiesis and promote leukocytosis by stimulating white blood cell production in the bone marrow.[49]

In summary, hepatic inflammation initiates a cascade of immune responses that extends beyond the liver. Through cytokine release, signaling pathway activation, and gut–liver axis disruption, localized liver inflammation can evolve into systemic inflammation, contributing to the pathogenesis of ACLF and other CLD-related complications.

Systemic inflammation in the context of ACLF

ACLF is characterized by a high-grade systemic inflammatory response driven by excessive immune activation.[30] Hence, it has been hypothesized that an

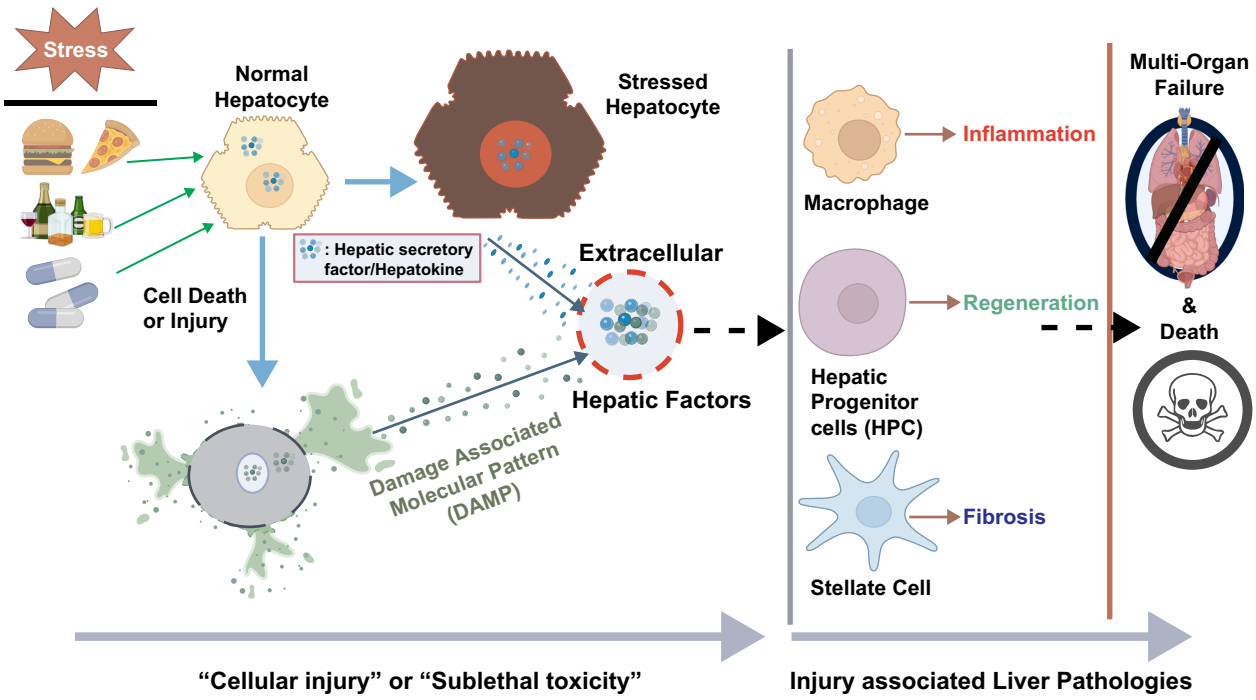

FIGURE 2 Conceptual framework of chronic liver disease (CLD) development and progression. Hepatocytes exposed to stressors—such as a Western diet, alcohol, or xenobiotics—undergo cellular stress, resulting in either sublethal toxicity or cell death. Injured hepatocytes release hepatic secretory factors (hepatokines) and damage-associated molecular patterns (DAMPs) into the extracellular space. These hepatic factors activate immune cells, particularly macrophages, driving inflammation, while also stimulating hepatic progenitor cells (HPC) for regeneration and hepatic stellate cells for fibrosis. This interplay establishes a continuum of injury-associated liver pathologies, which, when persistent, culminates in multi-organ failure (MOF) and death.

acute exacerbation of systemic inflammation in patients with CLD or cirrhosis-triggered by precipitating events such as active alcohol use or acute alcoholic hepatitis, bacterial infections, and certain drugs—initiates the development of ACLF.[30] This concept is strongly supported by findings from the CANONIC study, which, along with subsequent cytokine profiling, demonstrated strong correlations between elevated levels of inflammatory markers—such as TNF-α, IL-6, and lipopolysaccharide-binding protein (LBP)—and both the onset and severity of ACLF.[1,53,54] These observations underscore the central role of systemic inflammation in ACLF pathogenesis.

Further evidence indicates a direct relationship between the intensity of systemic inflammation and ACLF severity, with markedly higher concentrations of pro-inflammatory cytokines in ACLF patients compared with those with decompensated cirrhosis alone.[30] However, these conclusions are primarily based on correlative data, and no definitive study has established systemic inflammation as the causal driver of ACLF. Recently developed preclinical models of ACLF (*see below*) may provide critical tools to validate this causal link and elucidate underlying mechanisms.

The molecular triggers of this exaggerated inflammatory response remain incompletely understood. Proposed initiators include: (1) DAMPs released from necrotic or injured hepatocytes, and (2) bacterial translocation due to impaired intestinal barrier integrity, allowing PAMPs such as LPS to enter portal circulation and activate hepatic immune pathways. Despite these insights, targeted interventions against DAMPs or PAMPs have not yet been tested in preclinical models, nor have their systemic anti-inflammatory effects been validated clinically.

A key unresolved question is whether the high-grade systemic inflammation observed in ACLF represents a sudden escalation from the low-grade inflammation typical of CLD and cirrhosis. It is hypothesized that an acute insult superimposed on chronic liver dysfunction amplifies systemic inflammation, ultimately precipitating ACLF; however, this remains to be experimentally confirmed. Importantly, the severity of systemic inflammation is a strong predictor of mortality in ACLF,[43] with patients exhibiting intense inflammatory responses being significantly more likely to develop MOF and experience poor outcomes.[42] Moreover, components of the innate immune system appear disproportionately upregulated in ACLF compared with acute decompensation of cirrhosis (ADC), suggesting that innate immune dysregulation plays a pivotal role in the transition from ADC to ACLF.[30]

DAMPS and PAMPS as mediators of systemic inflammation

DAMPS

DAMPs, or damage-associated molecular patterns, also known as "danger signals" or "alarmins," are *endogenous* molecules released by damaged, dying, or stressed cells that activate the innate immune system and trigger inflammatory responses. In the context of liver disease, hepatocytes—which constitute ~80% of hepatic cell volume—are a major source of DAMPs during cellular injury. Other hepatic cell types can also contribute to DAMP release (see Table 2 *for known DAMPS in liver disease*). Immunogenic forms of cell death, such as necrosis, necroptosis, and pyroptosis, are prevalent in liver disease and significantly increase DAMP release.[63] Notably, ACLF is characterized predominantly by necroptosis, which amplifies this process.[64]

DAMPs function as "find me" and "eat me" signals, recruiting immune cells and promoting clearance of dying cells. These molecules are recognized by PRRs such as Toll-like receptors (TLRs), Receptor for Advanced Glycation End Products (RAGE), and NOD-like receptors (NLRs) expressed on immune cells, including macrophages (KCs in the liver), neutrophils, and dendritic cells. Engagement of these receptors initiates signaling cascades that culminate in the release of pro-inflammatory cytokines, perpetuating liver inflammation and tissue injury. Importantly, inflammation driven by DAMPs is classified as sterile inflammation—occurring in the absence of pathogens—which is a hallmark of ACLF in certain contexts, such as alcohol-associated hepatitis or HBV reactivation.[28,65,66]

While transient DAMP release can serve protective roles during acute injury, sustained release in CLD exacerbates inflammation, promoting fibrosis and ultimately contributing to liver failure.[67] DAMPs, including soluble ST2 (sST2), IL-33, HMGB1, and extracellular histones, have been reported to be elevated in ACLF.[55,76–80] However, their precise causal role in ACLF development and progression remains poorly defined. It is therefore critical to investigate the mechanistic relationship between DAMP signaling and ACLF pathogenesis using robust preclinical models (*see details below*). Such studies will clarify whether DAMPs act solely as biomarkers of tissue injury or actively drive immune dysregulation, cytokine storms, and MOF. Elucidating these pathways may reveal novel therapeutic targets to attenuate inflammatory damage and improve outcomes in ACLF patients.

PAMPS

PAMPs are conserved microbial molecules derived from bacteria, viruses, fungi, or parasites that elicit immune responses upon recognition by the host. In liver disease, PAMPs primarily originate from the gut, often as a consequence of gut microbiota dysbiosis and increased intestinal permeability (see Table 3 *for known PAMPS in liver disease*). This translocation of microbial products into the portal circulation delivers PAMPs to the liver, where they interact with PRRs expressed on hepatic immune cells such as KCs and monocytes, as well as non-immune cells, including hepatocytes and endothelial cells. Upon engagement with PRRs, PAMPs initiate signaling cascades that result in the production of pro-inflammatory mediators, including cytokines and chemokines, thereby amplifying hepatic inflammation and tissue injury. Importantly, PAMPs and DAMPs can synergistically activate the inflammasome—a multiprotein complex central to innate immunity—leading to the maturation and release of potent inflammatory cytokines such as

TABLE 2 DAMPs indicated in ACLF and CLD

DAMP	Stimulus	Function
High-mobility group box 1 (HMGB1)	Hepatocyte necrosis	Sterile inflammation trigger[55–57]
Cytokeratin-18 (CK18)	Hepatocyte necrosis and apoptosis	Intermediate filament protein[58]
Soluble Fas-ligand (sFasL)	Exposure to PAMP, phagocytosis of apoptotic cells	Apoptosis induction[56]
Interleukin-6 (IL-6)	Damage to mitochondria, activation of TLR4, cGAS–STING pathway	Inflammation and tissue repair via the STAT3 signaling pathway[59]
Cytochrome C (cyt C)	Hepatocyte necrosis and apoptosis	Macrophage activation and recruitment of immune cells[56]
Peroxiredoxin-1 (Prdx1)	Oxidative stress and cellular damage	Macrophage activation by TLR2 and TLR4, activating NF-κB and NLRP3 inflammasome signaling pathway[60,61]
Heat shock protein-70 (HSP-70)	Hepatic injury	Functions through TLR2 and TLR4 to activate macrophages, activating NF-κB and NLRP3[62]

Abbreviations: ACLF, acute-on-chronic liver failure; CLD, chronic liver disease; DAMPs, Damage-associated molecular patterns.

TABLE 3 PAMPs indicated in ACLF and CLD

PAMP	Stimulus	Function
Lipopolysaccharide (LPS)	Translocation of LPS from the gut into the systemic circulation	Activates TLR4 on Kupffer cells, leading to pro-inflammatory cytokine production[46,73]
Peptidoglycan	Bacterial products in systemic circulation and damage to liver cells	Activates NF-κB, leading to pro-inflammatory cytokine production[74,75]
Flagellin	Recognized by TLR5 on the cell surface of liver immune cells	Activates TLR5, leading to pro-inflammatory cytokine production and hepatic fibrogenesis[76]
Bacterial DNA (CpG motifs)	Recognized by TLR9, bacterial products in systemic circulation	Activation of immune cells and pro-inflammatory cytokine production[77]
Lipoteichoic acid (LTA)	Recognized by TLR2 on the cell surface of liver immune cells	Activates TLR2, leading to pro-inflammatory cytokine production[78]
Fungal beta-glucans	Translocation of fungal components from the gut into the systemic circulation	Activates NF-κB, leading to pro-inflammatory cytokine production[79,80]

Abbreviations: ACLF, acute-on-chronic liver failure; CLD, chronic liver disease; PAMPs, pathogen-associated molecular patterns.

interleukin-1β (IL-1β). This process contributes significantly to the progression of liver disease. PAMP-driven inflammation is particularly relevant in conditions associated with gut–liver axis dysfunction, such as cirrhosis, which can lead to ACLF, where microbial translocation and intestinal barrier impairment are common. Thus, PAMPs represent a critical link between gut dysbiosis, cirrhosis progression, and the severe inflammatory phenotype observed in ACLF.

DAMPs and PAMPs: Independent and synergistic drivers of systemic inflammation in ACLF

In ACLF, both DAMPs and PAMPs serve as critical mediators of systemic inflammation. While each class of molecules can independently activate immune responses, their interaction often creates a synergistic inflammatory loop that accelerates disease progression and contributes to multi-organ dysfunction. A key distinction between these 2 classes of molecules lies in their *origin* and *timing* of action. DAMPs, released from necrotic or injured hepatocytes, fuel sterile inflammation and are central to the development of systemic inflammatory response syndrome (SIRS) and MOF—a major determinant of mortality in ACLF.[81,82] In contrast, PAMPs, derived from microbial components such as LPS, primarily drive infection-related immune activation.

In advanced CLD, particularly ACLF, DAMPs, and PAMPs frequently converge, amplifying immune activation and precipitating a cytokine storm, characterized by excessive release of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. The downstream consequences include: (1) extensive hepatocellular injury and necrosis, (2) extrahepatic tissue damage, and (3) progression of CLD or cirrhosis to liver failure and multi-organ dysfunction.

Importantly, this hyperinflammatory state often triggers a compensatory anti-inflammatory response syndrome (CARS), aimed at restoring homeostasis. CARS is characterized by increased production of anti-inflammatory cytokines (eg, IL-10), expansion of regulatory immune cells, and suppression of pro-inflammatory signaling. While initially protective, prolonged, or exaggerated CARS can lead to immunoparesis (also known as immunoparalysis)—a pathological state marked by impaired pathogen clearance, reduced antigen presentation, and lymphocyte exhaustion. Immunoparesis significantly heightens susceptibility to secondary infections and worsens clinical outcomes in ACLF. Thus, CARS represents a regulatory phase, whereas immunoparesis reflects its maladaptive consequence (*see below for details*).

The relative contributions of DAMPs and PAMPs vary by etiology, shaping inflammatory phenotypes and clinical trajectories. HBV-related or autoimmune hepatitis-related ACLF following massive hepatocyte loss (SMHN/MHN) is predominantly DAMP-driven, with massive hepatocyte loss generating robust sterile inflammatory signals that propagate SIRS and organ injury.[34,37,38] DAMP release may originate not only from hepatic sources but also from failing extrahepatic organs such as the kidney, brain, circulatory system, and lungs, underscoring that the “battlefield” location—liver versus extrahepatic organs—shapes clinical outcomes. The combination of hepatic and extrahepatic DAMPs may further exacerbate systemic inflammation and worsen prognosis. Thus, even among chronic HBV patients, intrahepatic versus extrahepatic (kidney and other organs) ACLF phenotypes can influence prognosis.[65]

Conversely, alcoholic hepatitis-related ACLF typically exhibits a mixed PAMP–DAMP response: gut barrier dysfunction promotes bacterial translocation and LPS exposure (PAMPs), while ongoing alcohol-induced hepatocyte injury releases DAMPs. These

differences influence cytokine profiles (eg, IL-6, TNF-α, IL-1β), immune cell activation patterns, and therapeutic responsiveness, including differential benefits from infection control measures, albumin-based extracorporeal therapies, and immune-modulating strategies.

In summary, DAMPs and PAMPs are distinct yet complementary drivers of systemic inflammation in ACLF. DAMPs fuel sterile inflammation and SIRS, whereas PAMPs predominantly mediate infection-related immune responses. Together, they amplify systemic inflammation, precipitate cytokine storms, and drive organ failure and profound immune dysregulation (Figure 3). Etiology-specific patterns—such as DAMP-dominant HBV-ACLF following SMHN/MHN versus mixed PAMP–DAMP alcoholic hepatitis-related ACFL—underscore the need for tailored mechanistic investigation and personalized therapeutic algorithms.

IMMUNOPARESIS: THE PARADOX IN ACLF

ACLF presents a unique and paradoxical immune profile characterized by the coexistence of high-grade systemic inflammation with profound immune suppression, a state termed immunoparesis or immune paralysis. This duality is a defining feature of ACLF and is central to its clinical course, contributing to increased susceptibility to infections and poor clinical outcomes.

Immunoparesis describes a condition in which immune cells are present but functionally impaired. Although systemic inflammation in ACLF has been well documented, the development and molecular mechanisms driving concurrent immunosuppression remain incompletely understood in both preclinical and clinical contexts. Emerging evidence suggests that persistent systemic inflammation may induce immune exhaustion, ultimately leading to this immunosuppressive state. Both innate and adaptive immune compartments are affected.[83] This phenomenon is thought to represent an adaptive response aimed at limiting tissue damage caused by sustained inflammation. However, this protective mechanism comes at a significant cost—impaired pathogen clearance and heightened vulnerability to secondary infections (see section "Consequences of immune dysregulation/immunoparesis and chronic infection/sepsis"), which are major determinants of morbidity and mortality in ACLF.

Mechanisms of immunoparesis in ACLF

Immunoparesis in ACLF is characterized by immune cell populations that are numerically preserved or increased yet functionally impaired, resulting in heightened infection risk, organ failure, and poor outcomes.[84] The following 4 mechanistic models—ranging from regulatory cell differentiation defects and pro-inflammatory/anti-inflammatory imbalance to effector-cell dysfunction and cell-intrinsic inhibitory programs—provide an integrated framework to explain the pathogenesis of immunoparesis in ACLF.

Model 1: Differentiation defects in regulatory cells

One proposed mechanism involves impaired differentiation and function of regulatory immune cells—notably regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Tregs ($CD4^+CD25^+FOXP3^+$) expand and suppress innate and adaptive responses through IL-10/TGF-β and inhibitory checkpoints (eg, CTLA-4), fostering a tolerogenic milieu that blunts effector T-cell activity.

Similarly, MDSCs—especially monocytic MDSCs (M-MDSCs)—are markedly elevated versus healthy controls and stable cirrhosis.[85] These cells exhibit broad TLR hyporesponsiveness, reduced pathogen clearance, and are linked to infectious complications. Monocytes from ACLF also show diminished TNF-α/IL-6 production after TLR2/TLR4/TLR9 stimulation, and M-MDSCs are more impaired than classical $CD14^+HLA\text{-}DR^+$ monocytes.[85] Elevated plasma levels of S100A8/A9, predominantly produced by M-MDSCs, further reflect their expansion and immunosuppressive activity.[85]

Model 2: Pro-inflammatory/anti-inflammatory imbalance

A second proposed mechanism contributing to immunosuppression in ACLF centers on a dysregulated balance between pro-inflammatory and anti-inflammatory/pro-resolving programs. ACLF unfolds as a two-phase, dysregulated host response. The early phase features innate overactivation and a cytokine storm, with DAMP/PAMP signaling via pattern recognition receptors driving tissue injury and MOF.[86] In counter-regulation, the body initiates compensatory anti-inflammatory response syndrome (CARS), which leads to systemic immune deactivation. A central mediator of this response is interleukin-10 (IL-10), which suppresses nuclear factor kappa B (NF-κB) activity and downregulates the production of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8, and IL-12. IL-10 also reduces the generation of reactive oxygen species, platelet-activating factors, and chemokines. Elevated IL-10 levels on hospital admission have been associated with poor clinical outcomes.[86]

One major mediator of immunosuppression is prostaglandin E2 (PGE2), produced by circulating

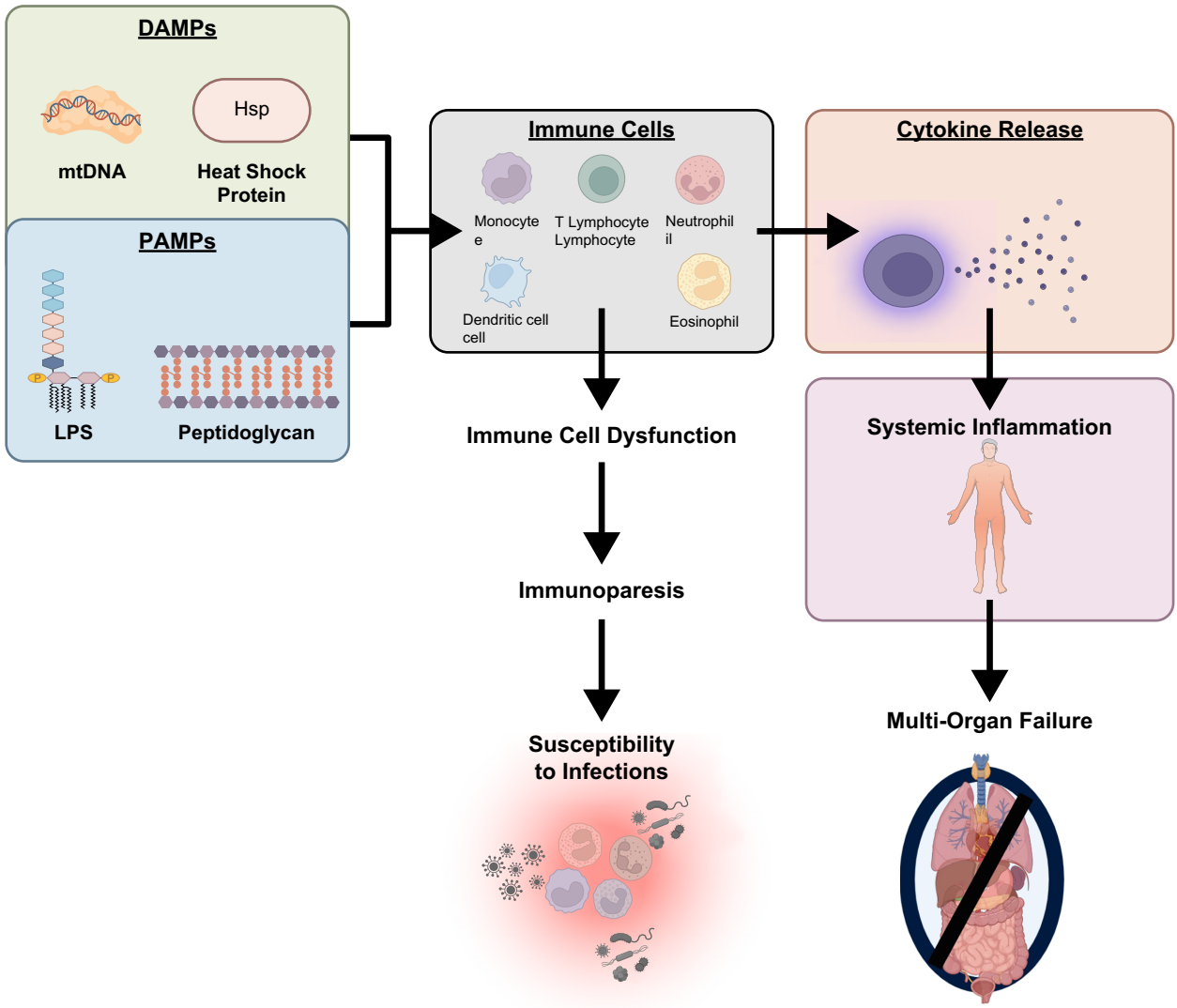

FIGURE 3 Role of DAMPs and PAMPs in immune dysregulation during ACLF. Damage-associated molecular patterns (DAMPs), such as mitochondrial DNA (mtDNA) and heat shock proteins (Hsp), and pathogen-associated molecular patterns (PAMPs), including lipopolysaccharide (LPS) and peptidoglycan, activate immune cells (monocytes, T lymphocytes, neutrophils, dendritic cells, and eosinophils). Persistent activation leads to immune cell dysfunction and immunoparesis, increasing susceptibility to infections. Concurrently, excessive cytokine release drives systemic inflammation, which, together with immunoparesis, contributes to multi-organ failure and death.

monocytes and tissue-resident macrophages.[87] PGE2 suppresses immune function by inhibiting NADPH oxidase-mediated bacterial death. Its levels are elevated in ACLF, partly because of impaired hepatic albumin synthesis. Notably, albumin infusion has been shown to reduce circulating PGE2 levels, offering a potential therapeutic strategy.[88]

Lipid mediator profiling in ACLF patients has revealed elevated levels of pro-inflammatory and vasoconstrictive eicosanoids, such as leukotriene E4 (LTE4) and prostaglandin F2α (PGF2α), along with reduced levels of specialized pro-resolving mediators (SPMs), such as lipoxin A5 (LXA5). LTE4 levels are positively correlated with IL-8 and the hepatocyte injury marker keratin-18 (K18), whereas LXA5 levels are inversely associated with inflammation and cell death. Furthermore, linoleic acid-derived lipid mediators such as 9(10)-EpOME and 12(13)-EpOME—linked to effective bactericidal activity—are significantly suppressed in ACLF patients.[84]

In addition, anti-inflammatory cytokines such as IL-10 and interleukin-1 receptor antagonist (IL-1ra) are elevated during the later stages of ACLF.[30] These cytokines, which are produced by monocytes and other immune cells, suppress the production of pro-inflammatory cytokines and contribute to the immunosuppressive environment.

Collectively, failure to maintain homeostasis between injury-driven inflammation and counter-regulation entrenches immunoparesis.

Model 3: Effector cells—neutrophils, monocytes, and T cells dysfunction in ACLF

Immune cell dysfunction is a hallmark of ACLF, with neutrophils, monocytes, and T cells exhibiting impaired functionality, which drives immune dysregulation, increased susceptibility to infections, and poor clinical outcomes.

Neutrophils, key effectors of the innate immune response, are often elevated in ACLF patients, partly due to increased circulating G-CSF levels. However, their functional capacity is markedly compromised.[84] Defective phagocytosis and impaired respiratory burst correlate strongly with organ failure and mortality. The NLR, an easily measurable biomarker, is significantly higher in ACLF compared with AD and predicts poor survival.

Unlike stable cirrhosis, which is frequently associated with neutropenia, ACLF patients typically exhibit increased absolute neutrophil counts. These neutrophils display high expression of activation markers such as CD11b, promoting endothelial adhesion. Despite this activated phenotype, they demonstrate impaired oxidative burst, defective degranulation, and reduced transendothelial migration—hallmarks of chronic intravascular activation and functional exhaustion.

In ACLF associated with alcoholic hepatitis, neutrophil dysfunction is further aggravated by reduced interferon-gamma (IFN-γ) production by T cells, driven by elevated IL-10 levels.[89] Although baseline reactive oxygen species (ROS) levels are high, indicating a primed state, stimulated ROS generation is diminished. This defect may reflect impaired intracellular signaling, including mTOR-dependent translational machinery dysfunction and degradation of the NADPH oxidase subunit gp91^{phox}/NOX2 by plasma elastase, an enzyme elevated in advanced cirrhosis. In addition, neutrophils in ACLF overexpress IL-8 receptors (CXCR1 and CXCR2), which may amplify systemic inflammation and contribute to hepatocyte injury. Collectively, these dysfunctional neutrophils fail to control infections and may exacerbate tissue damage, worsening disease progression.

T cells in ACLF patients exhibit features of exhaustion, characterized by increased expression of inhibitory receptors such as PD-1, TIM-3, and BTLA.[90–92] These changes impair T-cell effector functions and contribute to immune suppression.

Monocytes also display significant dysfunction, including impaired oxidative burst due to reduced NADPH oxidase expression and decreased HLA-DR surface expression—both recognized markers of immunoparesis.[93,94] Hepatic and extrahepatic macrophages undergo phenotypic shifts toward immune tolerance, accumulate in lymphoid tissues, and express inhibitory molecules, further increasing the risk of secondary infections and mortality.

Together, these findings underscore the multifaceted immune dysfunction in ACLF, where neutrophils, monocytes, and T cells are present but fail to perform their protective roles. This immunoparesis contributes to the high burden of infections and organ failure observed in ACLF and highlights the urgent need for targeted immunomodulatory therapies.

Model 4: Immune cell-intrinsic alterations

Beyond cytokine-driven dysregulation, cell-intrinsic alterations critically shape the immunosuppressive phenotype in ACLF. These changes impair pathogen recognition and clearance, reinforcing systemic immune dysfunction.

One well-characterized alteration is the upregulation of MER receptor tyrosine kinase (MERTK) in monocytes and macrophages. MERTK acts as a negative regulator of inflammation by suppressing TLR signaling and cytokine production. In ACLF, MERTK expression is significantly increased in circulating, hepatic, and lymph node-resident monocytes and macrophages compared with stable cirrhosis or healthy controls.[30,95,96] This upregulation correlates with impaired innate immune responses and reduced pathogen clearance. Importantly, pharmacological inhibition of MERTK in vitro restores pro-inflammatory cytokine production, suggesting that MERTK blockade may represent a promising therapeutic strategy to reverse immunoparesis.[96]

Similarly, $CD4^+$ T cells in ACLF exhibit increased expression of CD96, an immune checkpoint receptor that delivers inhibitory signals upon engagement with its ligand, CD155 (also known as PVR). This interaction contributes to T-cell dysfunction and suppresses adaptive immune responses.[97]

These models are mutually reinforcing. DAMP/PAMP-driven inflammation (model 2) expands regulatory suppressors (model 1), while effector-cell failure (model 3) and intrinsic checkpoints (model 4) lock in immunoparesis. The result is a paradoxical immune state of concurrent systemic inflammation and profound immunosuppression, underpinning secondary infections, organ failure, and poor outcomes in ACLF.[30,84–97]

Therapeutic implications

Understanding the unified pathogenesis of ACLF provides a foundation for targeted immunomodulatory strategies. Several approaches show promise in restoring immune balance. Albumin infusion can reduce circulating prostaglandin E_2 (PGE_2), thereby improving innate immune function and enhancing bacterial clearance (model 2).[88] Immune checkpoint modulation,

including blockade of PD-1, TIM-3, and CD96, offers a strategy to reverse T-cell exhaustion and restore adaptive immunity (models 3 and 4).[90–92,97] Similarly, targeting MERTK, a negative regulator of monocyte and macrophage activation, may reinstate pro-inflammatory signaling and improve pathogen clearance (model 4),[96] revive immune balance. Future clinical trials should adopt a biomarker-driven approach for patient stratification. Key indicators include the NLR, monocyte HLA-DR expression, S100A8/A9 levels, and lipid mediator profiles (eg, PGE_2, LTE_4, LXA_5). Such precision-based strategies could enable personalized immunotherapy, mitigating immunoparesis and improving clinical outcomes in ACLF.

CONSEQUENCES OF IMMUNE DYSREGULATION ON MOF

ACLF is defined as the presence of hepatic and/or extrahepatic organ failure, distinguishing it from the mere ADC. The development of MOF in ACLF is multifactorial and is driven by a combination of (1) intense systemic inflammation, (2) immune dysfunction, (3) tissue hypoperfusion, and (4) mitochondrial dysfunction and metabolic disturbances.

Intense systemic inflammation

Systemic inflammation is a hallmark of ACLF and plays a central role in organ failure. This leads to (a) direct immune-mediated tissue injury via activated immune cells (immunopathology) and (b) cytokine-induced dysfunction in organs, such as the kidneys (acute kidney injury), lungs (acute respiratory distress syndrome), and brain (HE).

Immune dysfunction

The immunosuppressive state of ACLF increases susceptibility to infections. The key contributors include bacterial translocation from the gut into the systemic circulation, even in the absence of overt infection and impaired pathogen clearance, which further fuels systemic inflammation and contributes to sepsis and organ failure.

Tissue/organ hypoperfusion

Severe systemic inflammation can cause vasoconstriction and reduce blood flow to the organs, leading to tissue hypoxia and dysfunction. Moreover, portal hypertension, a common complication of cirrhosis, can further impair blood flow to the liver and other organs and exacerbate tissue hypoperfusion. Tissue hypoxia contributes to cellular dysfunction and necrosis.

Mitochondrial dysfunction and metabolic disturbances

Inflammation-induced mitochondrial injury impairs cellular energy production: (a) Reduced ATP synthesis leads to energy failure in peripheral organs and (b) metabolic reprogramming favors glycolysis and amino acid catabolism over mitochondrial oxidative phosphorylation.[4,83] Recently, untargeted metabolomic profiling of ACLF patients has revealed a distinct metabolic signature, including increased proteolysis and lipolysis, enhanced glycolysis, pentose phosphate pathway, D-glucuronate metabolism, suppressed mitochondrial β-oxidation, and accumulation of metabotoxins from extra-mitochondrial amino acid metabolism. These changes reflect a peripheral organ energy crisis, in which immune and non-immune cells compete for limited energy resources, exacerbating organ dysfunction.[98]

Together, these mechanisms create a vicious cycle that drives MOF and contributes to the high morbidity and mortality observed in ACLF.

CONSEQUENCES OF IMMUNE DYSREGULATION/IMMUNOPARESIS AND CHRONIC INFECTION/SEPSIS

Patients with ACLF exhibit a compromised immune response, a condition known as immunoparesis, immunosuppression, or cellular immune depression, which significantly increases the risk of bacterial infection.[99] The CANONIC study demonstrated a stepwise increase in infection rates correlating with increasing ACLF grades, underscoring the clinical impact of immune dysfunction.[1]

Immunoparesis in ACLF is associated with impaired function of both innate and adaptive immune cells.[99,100] Importantly, signs of immune dysfunction begin to emerge in the early stages of cirrhosis, before the onset of ACLF.[100] This suggests that immunoparesis and systemic inflammation can coexist and, together, may contribute to the progression of ACLF. This dual immune state is characterized by several key features.

Impaired monocyte function

Circulating monocytes show reduced human leukocyte antigen-DR isotype (HLA-DR) expression. HLA-DR, an MHC class II molecule, plays a key role in the antigen

presentation process in monocytes. It displays peptides derived from ingested antigens to T-cell receptors, ultimately triggering T-cell activation and the immune response. Hence, reduced HLA-DR expression in circulating monocytes impairs antigen presentation and TNF-α production in response to LPS stimulation.[99] These monocytes also exhibit diminished phagocytic and oxidative burst capacities, compromising their ability to clear infections.[31] Thus, low HLA-DR expression is directly associated with poor survival in critically ill patients.[101]

Neutrophil dysfunction

Neutrophils have been reported to exhibit reduced phagocytosis and oxidative burst, particularly in alcoholic hepatitis-related ACLF. Moreover, they have high expression levels of CXCR1/CXCR2 receptors, which contribute to hepatocyte death through early apoptosis and necrosis and are associated with a greater risk of infection, organ failure, and mortality.[102]

T-lymphocyte exhaustion and suppression

T cells in ACLF patients express high levels of immune-inhibitory receptors, such as programmed cell death 1 (PD-1) and T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3, also known as hepatitis A virus cellular receptor 2), produce less IFN-gamma, and secrete more IL-10 due to chronic endotoxin exposure.[89] Notably, these effects can be reversed by blocking PD-1 and TIM-3, which restores the antimicrobial activity of T cells and neutrophils.[89] Profoundly reduced numbers of distinct adaptive immune cell populations have also been observed, even before ACLF development.[100] These changes were accompanied by parallel upregulation of co-stimulatory (eg, CD40L, OX40, CD69, GITR, TIM-1) and inhibitory immune checkpoints (eg, PDPN, PROCR, 2B4, TIGIT) on $CD4^+$ and CD8+ T cells.[100]

The imbalance between excessive systemic inflammation and immune paresis in ACLF significantly increases patients' vulnerability to infections, which frequently complicates their clinical course. Immunoparesis is believed to be a key contributor to increased infectious morbidity observed in these patients. Notably, the CANONIC study demonstrated a stepwise increase in the rate of bacterial infections with advancing ACLF grades.[1] Almost 50% of patients with ACLF without an initial infection develop one within 2 weeks. This highlights a shift toward an immunosuppressed phenotype, which not only increases susceptibility to infections but also worsens clinical outcomes.[99]

This immune dysregulation not only predisposes patients to infections but also worsens prognosis and contributes to the high mortality associated with ACLF.

IMMUNE DYSREGULATION AND THERAPEUTIC MANAGEMENT IN ACLF

ACLF is a complex syndrome characterized by profound immune dysregulation and MOF, necessitating a multifaceted therapeutic approach. The immune response in ACLF oscillates between hyperinflammatory and immunosuppressive phases, each critically influencing clinical outcomes and guiding personalized management strategies.

Hyperinflammatory states, identified by biomarkers such as elevated cytokines (IL-6, TNF-α), neutrophil-to-lymphocyte (N/L) ratio, and monocyte HLA-DR expression, are associated with systemic inflammation and rapid organ deterioration. In these patients, interventions such as plasma exchange, cytokine adsorption, or albumin dialysis may mitigate inflammatory cascades and prevent progression of organ failure. Conversely, immune paralysis—marked by reduced HLA-DR expression or increased PD-1/PD-L1 signaling—confers heightened susceptibility to infections, warranting prophylactic antibiotics, G-CSF, and immunostimulatory therapies.

Practical implementation of immune-guided care requires early and dynamic immune profiling integrated into routine clinical assessment. Measurement of inflammatory cytokines, leukocyte phenotyping, and soluble immune checkpoints at admission and during clinical deterioration enables risk stratification when combined with established prognostic scores such as CLIF-C ACLF. This approach facilitates identification of candidates for immunomodulatory interventions versus those requiring infection-prevention strategies. Continuous monitoring throughout hospitalization is essential to detect transitions between immune states, allowing timely therapeutic adjustments.

Despite growing mechanistic insights, translation of immune-based stratification into consistent clinical practice remains limited, in part due to the heterogeneity of ACLF definitions across international societies. These definitional inconsistencies—spanning diagnostic thresholds, organ failure criteria, and acute precipitants—continue to impede standardization of immune-guided management. Thus, while immune dysregulation is undeniably central to ACLF pathogenesis, its direct application to bedside decision-making remains constrained by variability in diagnostic frameworks. Nevertheless, these challenges underscore a crucial point: infections in ACLF must be identified as early as possible, and timely initiation of appropriate antibiotics or antifungal therapy is

essential, given the heightened risk of rapid deterioration in both hyperinflammatory and immune-paralysis states.

Therapeutic management of ACLF remains anchored in supportive care while incorporating pharmacologic and advanced interventions. The primary goal is to *stabilize the patient*, *address precipitating factors*, and *support failing organs* while evaluating candidates for *liver transplantation*. *Supportive care* includes prompt treatment of precipitating factors—such as infections and gastrointestinal bleeding—using early goal-directed therapy with broad-spectrum antibiotics within the first hour and intravascular volume resuscitation to maintain perfusion. ICU admission is often required for organ support, including mechanical ventilation for respiratory failure, vasopressors to maintain a mean arterial pressure ≥ 60 mm Hg, and renal replacement therapy for acute kidney injury.

Coagulation monitoring is critical for ACLF management. Thromboelastography (TEG) is used to assess clot formation and stability, detect hyperfibrinolysis, and guide targeted interventions.[35] Prophylactic transfusions and thrombopoietin agonists are generally discouraged owing to their limited benefits and potential risks, such as volume overload and thrombosis.

Pharmacologic interventions can include intravenous (i.v.) albumin infusion to manage circulatory dysfunction and hepatorenal syndrome, often in combination with vasoconstrictors such as terlipressin.[36] G-CSF has been investigated for its potential to enhance liver regeneration and improve immune function, although its clinical efficacy remains unclear.[37]

Liver transplantation (LT) is the definitive treatment for eligible patients, offering 1-year survival rates exceeding 80%, even in those with MOF.[37] Early identification of transplant candidates using prognostic scores and dynamic clinical assessment is critical to optimize timing.[37]

Additional interventions, such as *transjugular intrahepatic portosystemic shunt placement (TIPS)*, may be considered for refractory variceal bleeding or ascites.[36] However, its use in ACLF is controversial due to the risk of worsening encephalopathy and systemic inflammation.[34]

Extracorporeal liver support (ECLS), including Molecular Adsorbent Recirculating System (MARS) and Prometheus (fractionated plasma separation and adsorption), has shown promise in alleviating symptoms such as encephalopathy and may offer survival benefit; however, evidence remains limited and requires further validation.[38]

In summary, ACLF management is increasingly shaped by an evolving understanding of immune dysregulation, but the impact of this knowledge on routine practice continues to be hampered by definitional heterogeneity. Strengthening diagnostic harmonization while integrating early immune profiling and vigilant infection detection will be key to translating mechanistic insights into meaningful clinical benefit.

PRECLINICAL MODELS OF ACLF: BRIDGING MECHANISTIC GAPS AND THERAPEUTIC INSIGHTS

The complexity and heterogeneity of ACLF in humans have driven the need for robust preclinical models to elucidate its pathophysiology and progression.[103] However, the absence of an ideal experimental model remains a major obstacle to advancing both basic and translational research in this field. ACLF is a multifactorial syndrome characterized by diverse precipitants, variable disease phenotypes, and MOF. Its intricate nature makes it virtually impossible for a single animal model to replicate the entire clinical spectrum. Consequently, a range of complementary models is required to capture the most critical features of the disease. Despite these challenges, several preclinical models have been developed that successfully reproduce key hallmarks of ACLF-CLD, acute hepatic insult, systemic inflammation, and MOF using multi-hit strategies to closely mimic clinical conditions.

Multi-hit models of ACLF

Most preclinical ACLF models employ a two-step approach: (1) *Induction of CLD* and (2) *Induction of an acute insult/injury*. CLD is commonly induced using hepatotoxins such as carbon tetrachloride (CCl_4) or thioacetamide (TAA), which leads to progressive fibrosis and early cirrhosis. Alternative methods include bile duct ligation (BDL) to simulate cholestatic liver disease and repeated administration of porcine serum (PS) or human serum albumin to induce immune-mediated liver fibrosis.

The second step involves introducing an acute insult, typically through hepatotoxic agents alone or in combination with bacterial components such as LPS,[104,105] or via infection models such as *Klebsiella pneumoniae*[106] or cecal ligation and puncture (CLP).[107] These acute triggers generate DAMPs—released from necrotic hepatocytes—and PAMPs—derived from bacterial products or infections. Together, DAMPs and PAMPs activate innate immune pathways, amplify systemic inflammation, and precipitate multiorgan dysfunction, thereby closely mimicking the immunopathological cascade observed in human ACLF.

One widely used model is the CALP model (CCl_4/acetaminophen (APAP)/LPS), in which mice receive intraperitoneal CCl_4 for 8–10 weeks to induce CLD, followed by low-dose APAP and LPS challenge.[104] This model successfully reproduces key histological

and clinical features of human ACLF, including *hepatocyte ballooning*, *endothelial apoptosis*, *portal inflammation*, *vascular injury*, and *progressive necrosis*.[104] Mice also develop *ascites*, *acute tubular necrosis*, and *systemic inflammation*, which closely mirror the human disease phenotype. However, LPS administration alone does not fully replicate the complexity of the bacterial infections observed in clinical ACLF.

A more recent model combines chronic CCl_4-induced liver injury with an acute double-dose CCl_4 insult and intraperitoneal injection of *K. pneumoniae*.[106] This strategy more accurately reflects the clinical scenario of ACLF exacerbated by bacterial infection.

Another important model involves chronic liver injury induced by repeated CCl_4 administration, followed by an acute challenge with D-galactosamine (D-GalN).[105] D-GalN acts as a potent hepatotoxin by depleting uridine nucleotides, impairing RNA and protein synthesis, and sensitizing hepatocytes to necrosis and apoptosis. When administered after CCl_4-induced fibrosis, D-GalN triggers massive hepatocyte death, severe hepatic inflammation, and systemic complications, effectively mimicking AD in ACLF. This model is particularly useful for studying hepatocyte regeneration and immune-mediated injury, but requires careful dose optimization due to its high toxicity and mortality risk.

The CCl_4 + LPS model combines chronic CCl_4-induced fibrosis with an acute endotoxin challenge using LPS.[105] This approach induces a strong inflammatory response, KC activation, and cytokine storm, leading to systemic inflammation and multi-organ dysfunction. While this model effectively demonstrates the role of innate immunity and endotoxin-driven injury in ACLF, it does not fully replicate the complexity of polymicrobial infections seen in clinical settings.

An important advancement in ACLF research is the development of an optimized peritonitis-induced ACLF model that combines chronic CCl_4-induced cirrhosis with CLP to induce polymicrobial peritonitis.[108] This model successfully reproduces the full spectrum of extrahepatic organ failures observed in human ACLF, including renal, pulmonary, circulatory, coagulation, and neurological dysfunction. Key features include marked systemic inflammation with elevated IL-6 and TNF, bacterial translocation to multiple organs, and strong correlations between cytokine levels and organ impairment. Importantly, this model addresses a major limitation of earlier approaches by incorporating clinically relevant infection-driven immune activation. Its translational relevance is underscored by epidemiological data showing that bacterial infections are present in ~37% of ACLF patients at diagnosis, with SBP accounting for nearly 25% of these infections—data supported by a comprehensive Gut study.[109]

Alternative models of ACLF

Bile duct ligation

BDL is another method for inducing CLD, often followed by LPS to simulate ACLF.[110] However, due to the technical challenges of surgery in small animals, high risk of complications, and variability in disease progression, BDL has largely been supplanted by chemical models like CCl_4. Moreover, BDL-induced cholestatic injury does not elicit systemic inflammation as robustly as models using D-GalN, LPS, or CCl_4.[104,111]

Alcohol-induced models

Alcohol consumption is one of the most common precipitating factors for ACLF.[112] To replicate this clinical scenario, experimental models have incorporated alcohol as an acute trigger in the context of preexisting chronic liver injury.

One approach involves administering a single high-dose alcohol binge (5 g/kg) in mice with BDL-induced fibrosis, simulating alcohol-associated AD.[113] In this model, cirrhosis develops as a consequence of cholestasis rather than chronic hepatotoxicity, which contrasts with CCl_4-based models where fibrosis results from prolonged toxic injury. Another widely referenced model combines chronic CCl_4 administration to induce fibrosis with an acute ethanol challenge via intragastric cannulation, producing features similar to human alcoholic hepatitis.[16,56,114,115] This combined insult triggers severe hepatic inflammation, hypoxia, opportunistic infections, and epigenetic alterations. While pathophysiologically relevant, the model is technically demanding and associated with high mortality, limiting reproducibility.

Immune-mediated models

Repeated injections of xenogeneic or allogeneic proteins such as porcine serum or human albumin can elicit a sustained immune response and lead to progressive hepatic fibrosis and cirrhosis. Following the establishment of fibrosis/cirrhosis, ACLF is typically precipitated by the administration of D-GalN in combination with LPS.[116,117] These models closely replicate the immunopathological mechanisms underlying immune-mediated liver injury; however, they are associated with considerable limitations, including high mortality rates and marked variability in immune responses among experimental subjects.[118] General strategies used in preclinical ACLF modeling are depicted in Figure 4.

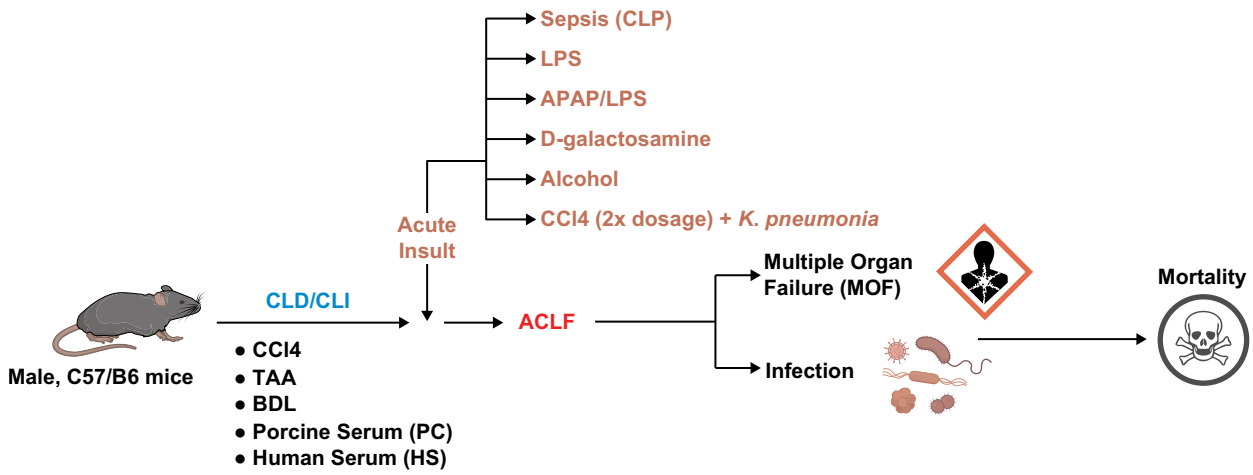

FIGURE 4 Experimental models for inducing acute-on-chronic liver failure (ACLF) in mice. Male C57BL/6 mice are first subjected to chronic liver disease or chronic liver injury (CLD/CLI) using agents such as carbon tetrachloride (CCl_4), thioacetamide (TAA), bile duct ligation (BDL), porcine serum (PC), or human serum (HS). An acute insult is then introduced to mimic ACLF, which may include sepsis (via cecal ligation and puncture, CLP), lipopolysaccharide (LPS), acetaminophen combined with LPS (APAP/LPS), D-galactosamine, alcohol, or high-dose CCl_4 combined with *Klebsiella pneumoniae* infection. These sequential hits lead to systemic inflammation, infection, and immune dysregulation, culminating in multiple organ failure (MOF) and high mortality.

Translational relevance and mechanistic insights

Preclinical models of ACLF have played a central role in advancing mechanistic understanding and guiding therapeutic development. These models consistently highlight 2 defining hallmarks of the syndrome: profound immune dysregulation and susceptibility to infection-driven exacerbation. Multi-hit experimental systems—typically combining chronic liver injury with acute secondary insults such as LPS exposure or polymicrobial infection—have revealed the critical contribution of innate immune activation, cytokine amplification, and impaired regenerative signaling to ACLF progression. Insights from these models have directly informed the design of therapeutic strategies aimed at modulating immune activation and reducing infection-related complications.

Despite inherent limitations, including species-specific immune responses, dosing variability, and challenges in reproducibility, chemically induced murine models continue to provide valuable mechanistic information.[118] A consistent observation across these models is the profound suppression of liver regeneration in ACLF. Mechanistically, this impairment arises from a shift away from pro-regenerative IL-6/STAT3 signaling toward dominant activation of the IFN-γ/STAT1 axis. Reduced IL-6 production by KCs, combined with heightened IFN-γ release during innate immune activation, leads to an imbalance that suppresses hepatocyte proliferation. Importantly, this mechanistic profile mirrors clinical observations: ACLF patients similarly exhibit elevated circulating IFN-γ and evidence of impaired hepatic regenerative capacity.[106]

These translational insights have fostered the development of immune-modulatory therapies aimed at restoring regenerative signaling while avoiding excessive immune stimulation. One notable example is IL-22Fc, a long-acting fusion protein that reactivates STAT3 signaling and enhances hepatocyte survival. IL-22Fc promotes expression of anti-apoptotic mediators such as BCL-2 and induces pro-proliferative molecules, including cyclin D1, leading to improved liver regeneration in preclinical ACLF models.[106,115] Because IL-22 receptors are restricted to epithelial cells rather than immune cells, IL-22-based therapies offer a unique advantage: they promote tissue repair while minimizing the risk of further immune activation—an essential consideration in ACLF.

Other mechanistic discoveries have shaped therapeutic approaches targeting infection-driven injury. In bile duct ligation/alcohol-induced ACLF models, neutrophil infiltration and neutrophil extracellular trap (NET) formation promote hepatocyte death through pyroptosis and necroptosis. This work identifies RIPK3 as a central mediator of cell death pathways.[113,119] Pharmacological inhibition of RIPK3 reduces NET formation, dampens inflammation, and attenuates multi-organ dysfunction.[113] Similarly, innate immune sensing through TLR4 plays a pivotal role in endotoxin-mediated injury; blockade of TLR4 with TAK-242 suppresses immune activation, reduces hepatocyte damage, and improves systemic inflammation in rodent models.[120] Combination therapy strategies are also emerging: for instance, co-administration of G-CSF, a promoter of hepatic regeneration, with TAK-242 demonstrates synergistic benefits by simultaneously augmenting regenerative capacity and limiting

TABLE 4 Ongoing clinical trials informed by current preclinical findings on ACLF

Trial name	Rationale	Study design	Outcome	Reference
A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Proof-of-Concept, Phase 2a Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Intravenous TAK-242 in Subjects With Acute Alcoholic Hepatitis Causing Decompensation of Alcohol-Related Cirrhosis and ACLF	TAK-242, a TLR4 inhibitor, has been affirmed via studies in vitro and in vivo as a therapeutic option for ACLF and ALF due to its reduction in the severity of organ injury and improvement in patient outcomes.	Phase 2a double-blind, randomized, placebo-controlled, multicenter, proof-of-concept study for adults with a history of alcohol-associated cirrhosis who continue to drink heavily, have a prior acute decompensating event, and have a clinically or histologically confirmed diagnosis of alcoholic hepatitis. Patients included possess a CLIF-C score between 35 and 64 and are graded 1 or 2 ACLF by CLIF-C score or by other indicated criteria.	Efficacy, safety, pharmacokinetics, and pharmacodynamics of TAK-242 in subjects with acute decompensation of alcohol-associated cirrhosis due to alcoholic hepatitis resulting in ACLF	https://clinicaltrials.gov/study/NCT04620148 NCT04620148[120]
Phase II, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of TAK-242 and (G-CSF) in Subjects With (sAH) and (ACLF)	This trial tests a new combination of drugs: TAK-242, a TLR4 antagonist that reduces inflammation, and G-CSF, which enhances liver regeneration. In preclinical data, this combination has prevented mortality in models of ACLF, indicating it as a therapeutic candidate for the treatment of ACLF.	Multicenter, randomized, double-blind, placebo-controlled trial in 78 hospitalized patients with severe alcoholic hepatitis and ACLF.	Safety and effect of TAK-242 alone and in combination with G-CSF (G-TAK) in patients with severe alcoholic hepatitis and ACLF	https://clinicaltrials.gov/study/NCT06890039[105]
F-652 (IL-22 Fusion Protein) in ACLF	F-652 is a novel dimeric IL-22: IgG2 fusion protein designed to promote hepatic regeneration via activation of pro-regenerative pathways and reversal of impaired regeneration observed in preclinical ACLF models. This and clinical use in related liver diseases support investigation as a therapeutic candidate for the treatment of ACLF.	Phase II design is ongoing. Approximately 60–80 patients with ACLF will be enrolled in a multicenter, randomized, double-blinded, placebo-controlled, phase II clinical study.	Safety, efficacy (liver function, survival), pharmacokinetics	https://www.evivebiotech.com/en/newsd/index?id=25&utm[106]

Abbreviations: ACLF, acute-on-chronic liver failure; ALF, acute liver failure; G-CSF, granulocyte colony-stimulating factor; TLR4, toll-like receptor 4.

inflammatory injury, ultimately improving survival.[105] These findings underscore the therapeutic potential of targeting both regenerative and inflammatory pathways, as well as infection control mechanisms. Major clinical trials based on these preclinical findings are summarized in Table 4.

Collectively, these preclinical models have become indispensable translational tools, shaping mechanistic understanding and informing clinical trial design, particularly in the domains of immune modulation, liver regeneration, and infection control. Their impact is highlighted by the recent 2025 consensus proposal, which incorporates immune dysregulation as an additional organ failure category in ACLF,[19] reflecting the shift toward recognizing systemic immune dysfunction as a core pathological component of the syndrome. Nonetheless, caution remains essential when extrapolating murine findings to human disease. Significant species-specific differences exist in immune responses, liver regenerative capacity, and systemic physiology. Continued refinement, standardization, and validation of preclinical models will be crucial for improving their translational relevance and ensuring the safe and effective application of preclinical discoveries to patient care.

CONCLUDING REMARKS, FUTURE DIRECTIONS, AND OPEN QUESTIONS

ACLF is a severe clinical condition marked by an acute decline in liver function in individuals with preexisting CLD, often triggered by a precipitating event. It is characterized by the failure of one or more extrahepatic organs and is associated with a high risk of short-term mortality. ACLF is recognized as a distinct clinical entity that requires specialized management strategies to address both hepatic and extrahepatic dysfunction. A defining feature of ACLF is significant immune dysregulation, presenting as a paradoxical state of intense systemic inflammation, followed by immunoparesis. DAMPs and PAMPs are critical for initiating and sustaining the immune response. These molecular signals activate immune cells via PRRs, leading to inflammatory signaling cascades and a cytokine storm, which results in tissue damage and MOF, which are key features of ACLF. Interestingly, this hyperinflammatory phase is often followed by immunoparesis, a maladaptive suppression of immune function. This immunosuppressive phase increases the risk of infection and sepsis, further exacerbating clinical outcomes. Consequently, ACLF pathogenesis involves a vicious cycle: PAMPs and DAMPs trigger systemic inflammation, leading to organ damage, immunosuppression, and subsequent infections, which drive further disease progression. Understanding the intricate balance between systemic inflammation and immune suppression is essential for developing effective therapeutic approaches. Future research should prioritize the following: (1) Identifying reliable biomarkers to differentiate between systemic inflammatory and immunosuppressive phases. (2) Developing targeted immunomodulatory therapies. (3) Improving preclinical models to more accurately reflect human ACLF. (4) Exploring personalized treatment strategies based on immune profiling. Key unanswered questions include the molecular mechanisms underlying the transition from systemic inflammation to immunoparesis, the role of the gut–liver axis, and the identification of early predictors of ACLF progression. Addressing these gaps is crucial to enhancing patient outcomes and guiding the development of innovative interventions.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this review were primarily derived from previously published studies, which are cited in the References section.

AUTHOR CONTRIBUTIONS

Abigail A. Drago, Sarah Yanofsky, and Bilon Khambu drafted the manuscript. Kamal Baral, Leah Spade, and Ramsey Rohner were responsible for figure design. Abigail A Drago, Sarah Yanofsky, Ramsey Rohner, Kamal Baral, Leah Spade, Peng-Sheng Ting, and Bilon Khambu contributed to the final discussion and the critical revision of the manuscript. All authors reviewed and approved the final version of the manuscript for submission.

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CONFLICTS OF INTEREST

The authors have no conflicts to report.

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