

Clinical Courses after Acute Decompensation of Cirrhosis: How the PREDICT Trajectories should be Interpreted

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Abstract: Patients admitted with acute decompensation of cirrhosis often look similar at presentation but do not remain clinically similar. During the following weeks, some develop acute-on-chronic liver failure (ACLF), some return repeatedly with portal-hypertension-related complications, and others enter a period of relative stability. The PREDICT study described these courses as pre-ACLF, unstable decompensated cirrhosis (UDC), and stable decompensated cirrhosis (SDC). This framework is clinically attractive because it shifts attention from the admission event to the subsequent direction of disease. Its use, however, requires caution. The three groups were defined by outcomes observed over 90 days and are not yet diagnoses that can be assigned reliably when the patient first arrives. In this review, we examine the evidence behind the trajectories and discuss how they may inform care without overstating their present predictive value. Progressive inflammation and declining organ function are most relevant to the pre-ACLF course, whereas UDC is more often associated with recurrent complications in the setting of severe portal hypertension. SDC carries a lower short-term risk, but stability does not necessarily imply recompensation. For current practice, the principal value of the framework is to encourage serial assessment, careful discharge planning, prevention of recurrent decompensation, and timely consideration of transplantation. Prospective models and trajectory-specific trials are still required before these categories can support standardized treatment pathways.

Keywords: Acute Decompensation, Cirrhosis, Acute-on-Chronic Liver Failure, Clinical Course, Portal Hypertension, Recompensation

1. Introduction

An admission for ascites, variceal bleeding, hepatic encephalopathy, infection, or jaundice is usually taken to mark decompensated cirrhosis. That label is prognostically important, but it conceals a wide range of subsequent outcomes. Natural-history studies describe a series of transitions—from first decompensation to recurrent events, ACLF, transplantation, and death—rather than a single, uniform stage of disease [1,2,3]. The contrast is familiar in practice: two patients may be admitted with the same complication and respond similarly during the first few days, yet their courses after discharge may diverge markedly. In China, where HBV infection remains a major etiology, the applicability of these Western-derived trajectories requires particular scrutiny [4].

The PREDICT study addressed this heterogeneity by following patients admitted with acute decompensation and identifying three courses over the next 90 days: development of ACLF (pre-ACLF), readmission without ACLF (UDC), and neither readmission nor ACLF (SDC) [4]. The proposal was important because it introduced time into a classification that had largely been based on the presence or absence of decompensating events. It also complemented the broader argument that decompensated cirrhosis should be described as a dynamic state, with the possibility of both further deterioration and recovery [5].

ACLF occupies the severe end of this spectrum but should not be used as a synonym for acute decompensation. In the EASL-CLIF framework, ACLF is defined by acute deterioration, organ failure,

and a high risk of short-term death [6,7]. Prognosis is not fixed at diagnosis: early improvement, persistence, or progression of organ failure changes outcome substantially [8]. Standard guidance for decompensated cirrhosis remains the foundation of treatment [9], while external validation studies suggest that the broad PREDICT courses are reproducible outside the original cohort [10,11].

A difficulty arises when the trajectory labels are used as though they were admission diagnoses. In the original study, “pre-ACLF” became known only when ACLF occurred during follow-up; UDC and SDC were likewise assigned from subsequent events. The framework therefore describes what happened, whereas clinicians need to know what is likely to happen. In our view, this distinction is the starting point for interpreting the literature. The trajectories are useful clinical concepts, but their prospective prediction remains an unresolved problem.

2. Scope and Literature Search

A focused PubMed search was undertaken and updated in July 2026. Search terms included cirrhosis, acute decompensation, ACLF, pre-ACLF, unstable decompensation, stable decompensation, recompensation, systemic inflammation, portal hypertension, infection, frailty, readmission, prognostic score, and liver transplantation. We reviewed the PREDICT report and its external validation first, then examined relevant cohort studies, randomized trials, consensus statements, practice guidelines, and recent reviews. Reference lists were searched for additional studies that informed mechanism, prognosis, or management. The purpose was to provide a critical narrative synthesis; no formal systematic-review protocol or quantitative meta-analysis was used.

3. From a Decompensating Event to a Clinical Course

3.1. What a Trajectory Adds to a Prognostic Score

Severity scores and clinical trajectories answer related but different questions. MELD-Na and MELD 3.0 estimate risk from variables measured at a particular time [12,13]. CLIF-C AD was developed for hospitalized patients with acute decompensation who do not have ACLF, whereas CLIF-C ACLF is used after organ failure has emerged [14,15]. These scores are valuable, but a score obtained on admission cannot describe whether renal function will recover, inflammation will subside, or a patient will return with recurrent ascites two weeks later. Reviews of prognostic tools increasingly emphasize repeated measurement and selection of a score appropriate to the patient’s current state [16].

PREDICT placed this temporal information at the centre of risk assessment. The biological findings suggested two overlapping axes. Patients who later developed ACLF had the most pronounced and progressive systemic inflammation. Patients with UDC showed greater evidence of portal hypertension together with persistent, lower-grade inflammation, while inflammatory markers generally improved in SDC [4]. This division is not absolute, but it offers a useful way to understand why the same initial complication can lead to organ failure in one patient and recurrent non-ACLF admissions in another [17,18].

3.2. Inflammation, Immune Paresis, and Organ Failure

Inflammation in decompensated cirrhosis is sustained by several processes that occur simultaneously. Increased intestinal permeability and dysbiosis expose the liver and systemic circulation to microbial products [19]. Damage-associated signals released from injured tissue add to this stimulus. At the same time, cirrhosis-associated immune dysfunction limits effective antimicrobial responses [20]. The result is not simply “too much” or “too little” immunity, but a combination of inflammatory injury and impaired host defence. This helps explain both the high incidence of infection and the marked clinical deterioration that infection can precipitate [21,22].

Changes in adaptive immunity and myeloid-cell function may precede overt organ failure [23,24]. Other studies have linked outcome to the balance between macrophage migration inhibitory factor and soluble CD74, or to metabolic disturbances such as palmitoylcarnitine-mediated immune-cell dysfunction [25,26]. These observations are biologically coherent and may eventually improve risk prediction. For the moment, however, they remain mechanistic or exploratory findings; none has displaced routine clinical assessment.

3.3. Portal Hypertension as a Driver of Repeated Decompensation

Portal hypertension contributes to decompensation through more than increased portal pressure. Intrahepatic resistance, endothelial dysfunction, splanchnic vasodilation, and altered circulatory responses promote sodium retention, ascites, renal hypoperfusion, and variceal complications [18]. Repeated events can therefore occur even when formal organ-failure criteria are not met, a pattern that is especially relevant to UDC. The balance is fragile: infection, bleeding, or kidney injury may amplify systemic inflammation and shift a patient from recurrent decompensation towards ACLF [27]. The main features and prognostic implications of the three trajectories are summarized in Table 1.

Table 1: The three outcome-defined courses described in the PREDICT study.

Trajectory	Definition over 90 days	n (%)	Main biological signal	Mortality	Clinical reading
Pre-ACLF	ACLF developed during follow-up	218 (20.4%)	Progressive, high-grade systemic inflammation	53.7% at 3 months; 67.4% at 1 year	A rapidly deteriorating course with impending organ failure
UDC	At least one readmission for acute decompensation, without ACLF	233 (21.8%)	Severe portal hypertension with persistent low-grade inflammation	21.0% at 3 months; 35.6% at 1 year	Recurrent complications and substantial intermediate-term risk
SDC	Neither readmission nor ACLF during follow-up	620 (57.9%)	Lower-grade inflammation that declined over time	9.5% at 1 year	Relative stability, although ongoing surveillance remains necessary

Note: Classification was based on events observed during 90-day follow-up; the categories should not be read as diagnoses available at admission. Data from Trebicka et al. [4].

4. The Pre-ACLF Course

4.1. A High-Risk Course Defined in Retrospect

Pre-ACLF accounted for 20.4% of the PREDICT cohort. These patients had acute decompensation without ACLF at enrolment and developed ACLF within 90 days; mortality was 53.7% at 3 months and 67.4% at 1 year [4]. The magnitude of this risk makes the period before organ failure an obvious target for intervention. Yet the terminology contains an inherent tension: the group is clinically important precisely because clinicians would like to recognize it early, but it can be identified with certainty only after ACLF has occurred.

External validation has confirmed the adverse prognosis of this course [10], but no single baseline feature reliably separates patients who will develop ACLF from those who will follow another course. For now, describing a patient as “moving towards ACLF” is more defensible than stating that the patient “has pre-ACLF” on admission. This wording retains the clinical value of the concept without implying diagnostic certainty that the available evidence cannot support.

4.2. Bedside Clues, Not a Diagnostic Checklist

Concern should rise when abnormalities accumulate or fail to improve. Increasing bilirubin or INR, acute kidney injury, hyponatremia, new or worsening encephalopathy, circulatory instability, infection, leukocytosis, and a rising C-reactive protein concentration are all relevant. Their trajectory is often more informative than their absolute value. This is particularly true for serum creatinine: in cirrhosis, a modest increase may represent clinically important renal deterioration and should be staged and reassessed according to cirrhosis-specific criteria [28].

Prognostic scores can organize this information, but they do not remove uncertainty. MELD-Na, MELD 3.0, CLIF-C AD, and CLIF-C ACLF were built for different clinical settings [12,13,14,15]. Using the wrong score, or relying on a single calculation during a changing illness, may be falsely reassuring. Contemporary reviews recommend matching the score to the current syndrome and repeating it when the course remains unstable [29]. The Padua model 2.0, which incorporated presepsin with clinical scores,

is an example of an attempt to predict later ACLF, but it still requires wider external validation [30].

Reserve outside the liver also matters. Sarcopenia has been associated with subsequent ACLF [31], and the Liver Frailty Index provides an objective measure of physical vulnerability [32]. Six-minute walking distance and heart-rate variability have likewise been related to decompensation or mortality [33,34]. These measures are not specific enough to define a trajectory, but they can identify patients who have little capacity to tolerate another infection, procedure, or period of immobility.

4.3. Decisions That Should Not Wait for Organ Failure

The first priority is to identify and treat a reversible precipitant. Infection, gastrointestinal bleeding, alcohol-associated hepatitis, viral reactivation, drug toxicity, and volume- or medication-related kidney injury should be considered systematically rather than as a routine list. Local microbiology matters because infection patterns and resistance differ between hospitals and regions [21,22,27]. When infection is suspected, cultures and diagnostic paracentesis should be obtained promptly. Acute kidney injury requires a parallel review of volume status, nephrotoxic drugs, infection, and possible hepatorenal syndrome [7,28].

The response over the next 48–72 hours is often more revealing than the admission profile. Serial creatinine, bilirubin, INR, sodium, urine output, mental status, blood pressure, oxygen requirement, and infection markers help distinguish recovery from continuing deterioration. Lactate is useful in selected critically ill patients. Because early changes in ACLF grade strongly influence outcome [8], new organ dysfunction should prompt escalation of care and discussion with intensive-care and transplant teams. No single drug prevents ACLF across its different precipitants; timely treatment of the cause and meticulous supportive care remain central [7,17].

Transplant assessment should not be postponed until organ failure is clearly irreversible. The appropriate timing varies, particularly when infection, comorbidity, or frailty may be reversible. Recurrent decompensation, worsening renal function, or a persistently high-risk course should therefore lower the threshold for early referral.

5. Unstable Decompensated Cirrhosis

5.1. Recurrent Admission without ACLF

UDC was defined by at least one readmission for acute decompensation within 90 days in the absence of ACLF. It represented 21.8% of PREDICT, with mortality of 21.0% at 3 months and 35.6% at 1 year [4]. This intermediate position can be misleading. These patients do not meet the organ-failure definition of ACLF, but repeated hospitalizations carry cumulative consequences: loss of muscle and independence, disruption of caregiving arrangements, medication changes, procedures, and repeated exposure to infection.

The usual clinical picture is recurrent ascites, episodic encephalopathy, portal hypertensive bleeding, infection, or fluctuating renal function. External cohorts support the existence of a recurrent, non-ACLF course [10,11]. Readmission studies also show that return to hospital is not explained by liver severity alone; medication problems, delayed follow-up, and gaps in transition-of-care arrangements contribute [35,36]. For this group, asking “what made another admission predictable?” is often more useful than simply recording the admitting diagnosis.

5.2. Why Instability Persists

Severe portal hypertension offers a plausible biological basis for UDC. Splanchnic vasodilation and reduced effective arterial volume favour sodium retention, recurrent ascites, hyponatremia, and renal vulnerability. The consequences of treatment can then feed back into the syndrome. Repeated paracentesis, restrictive diets, inactivity, and prolonged hospitalization may aggravate malnutrition and sarcopenia. Persistent low-grade inflammation provides a further source of fragility [17,18].

UDC should not be understood as a stable alternative to ACLF. Its boundaries are permeable. A patient with recurrent ascites may remain in a portal-hypertension-dominant course for months, yet infection or bleeding can rapidly produce organ failure. Management therefore has two aims that must be pursued together: reducing avoidable readmission and detecting a change in biological state before overt deterioration.

5.3. Preventing the Next Admission

Treatment is most effective when it is organized around the complication that repeatedly destabilizes the patient. For recurrent ascites, this includes feasible sodium advice, individualized diuretic dosing, large-volume paracentesis with albumin when indicated, prevention of spontaneous bacterial peritonitis, and consideration of TIPS in suitable candidates. Covered-stent TIPS improved transplant-free survival in selected patients with recurrent ascites, and early TIPS improved outcomes in selected high-risk variceal bleeding [37,38]. Broader management of portal hypertension should follow current consensus and practice guidance [39,40]. Nonselective beta-blockers often remain beneficial, although persistent hypotension or severe acute kidney injury may require dose reduction or temporary withdrawal [9]. In suspected hepatorenal syndrome-AKI, albumin and vasoconstrictor therapy should be considered only after careful evaluation, including respiratory and volume status [28,41].

The albumin literature is instructive because apparently conflicting trials studied different questions. Mechanistic work supports hemodynamic and anti-inflammatory effects in selected patients [42]. ANSWER reported a survival benefit with long-term outpatient albumin in patients with uncomplicated ascites [43]. ATTIRE, by contrast, found no benefit from targeted albumin infusions in hospitalized patients, while MACHT did not prevent complications with the tested midodrine–albumin regimen in transplant candidates [44,45]. These results do not support a simple conclusion that albumin “works” or “does not work.” The indication, setting, dose, duration, and patient population determine what the evidence means.

Recurrent encephalopathy exposes similar practical issues. Lactulose is effective only when patients understand how to adjust it and can tolerate the resulting bowel pattern. Rifaximin reduces recurrent overt encephalopathy and related hospitalization in appropriately selected patients [46,47]. Caregivers often notice altered sleep, attention, bowel habits, or medication adherence before a clear episode develops [48]. Their observations should be incorporated into the follow-up plan. After every unplanned admission, the team should reconsider transplant referral, symptom burden, palliative-care needs, and whether the current model of outpatient care is adequate.

6. Stable Decompensated Cirrhosis

6.1. A Lower-Risk Course with Residual Risk

SDC was the most frequent PREDICT course. Patients had neither ACLF nor readmission during the 90 days after the index admission; 1-year mortality was 9.5% [4]. The figure is substantially lower than that of pre-ACLF or UDC, but it should not be interpreted as recovery. Prior decompensation still confers risk of recurrent ascites, encephalopathy, bleeding, infection, hepatocellular carcinoma, and later transition to a less favourable course.

In PREDICT, SDC was associated with lower-grade inflammation that improved over time and fewer markers of severe portal hypertension than UDC [4]. External validation supports its more favourable prognosis [10]. A stable interval is therefore clinically valuable, not because surveillance can be relaxed, but because there is time to address the cause of liver injury, restore nutritional and physical reserve, review medications, and determine whether improvement is durable.

6.2. Stability, Recompensation, and the Gap between Them

Baveno VII made the distinction explicit. Recompensation requires control or removal of the etiological factor, resolution of previous decompensating events without continued use of the therapies that controlled them, and sustained improvement in liver function [39]. Patients with hepatitis B-related decompensated cirrhosis who meet these criteria have better outcomes than those who remain decompensated [49]. Even after clinical improvement, however, portal hypertension may persist [50,51]. This explains why a patient can appear well and still remain vulnerable.

Etiological treatment makes recompensation biologically plausible. Viral suppression or eradication, sustained alcohol abstinence, control of metabolic injury, and treatment of autoimmune or cholestatic disease can improve hepatic reserve. In HBV-related disease, a sustained complication-free period during antiviral therapy predicts more stable recompensation [52]. SDC is therefore a therapeutic opportunity rather than an endpoint.

6.3. Making Use of the Stable Interval

Follow-up should cover more than liver tests. Renal function, serum sodium, ascites, cognition, nutrition, frailty, medication safety, and adherence require periodic review alongside portal-hypertension management and hepatocellular carcinoma surveillance [2,3]. Routine protein restriction should be avoided; adequate energy and protein intake, including a late-evening meal or snack where appropriate, is recommended [53]. Exercise advice needs to be realistic. A generic instruction to “exercise more” is unlikely to help a patient with poor balance, severe sarcopenia, or frequent falls; supervised or individualized resistance training is preferable when available.

Digital monitoring may help patients report weight change, symptoms, cognitive difficulty, and medication use between visits [54]. Its benefit depends less on the device than on the pathway around it. Data must reach a team that can interpret them, contact the patient, and act on deterioration. Limited digital access, alert fatigue, and poorly defined escalation rules can otherwise turn monitoring into an additional burden.

7. Using the Trajectory Framework in Practice

7.1. Estimating a Course Prospectively

At the bedside, trajectory assignment is necessarily probabilistic. The clinician begins with the admission phenotype and then updates the estimate as treatment proceeds. Baseline liver and renal function, the precipitating event, inflammatory activity, portal-hypertension burden, previous admissions, frailty, nutrition, and early response all contribute. The relative weight of these factors changes over time; no isolated variable captures the whole course.

A practical assessment can be organized around three questions. Is organ function improving or deteriorating? Is the main unresolved problem systemic inflammation or a recurrent portal-hypertension-related complication? And does the patient have enough physiological and social reserve to remain stable after discharge? Documenting the answers at admission, during hospitalization, and before discharge is more informative than applying a trajectory label once and leaving it unchanged.

Table 2: Clinical priorities suggested by the dominant trajectory risk.

Clinical issue	Possible pre-ACLF course	Possible UDC course	Possible SDC course	Common question
Immediate concern	New organ dysfunction and early death	Another decompensation-related admission	Loss of stability or failure to recompensate	Has the precipitating cause been treated?
Monitoring emphasis	Frequent reassessment of organ function and infection	Early review of weight, renal function, ascites, cognition, and infection	Scheduled laboratory, functional, HCC, and portal-hypertension surveillance	What finding should trigger escalation?
Treatment emphasis	Precipitant control, organ support, and early transplant discussion	Prevention of recurrent ascites, bleeding, and encephalopathy; selected TIPS or albumin strategies	Etiological therapy, nutrition, exercise, and medication review	Could treatment itself cause kidney injury, hypotension, or sedation?
Discharge approach	Discharge only after objective stability and a rapid follow-up plan	Medication reconciliation, caregiver training, and contact within days	Structured long-term follow-up and self-management support	Does the patient have a written, feasible plan?
Research gap	Prediction before ACLF develops	Interventions that prevent readmission	Predictors of durable recompensation and relapse	Will findings generalize across regions and etiologies?

7.2. The Discharge Interval Matters

For many patients, risk remains high after the acute problem appears to have settled. Discharge

planning should include medication reconciliation, clear instructions for diuretics, lactulose, and beta-blockers, review of renal function and sodium, nutrition advice, infection warning signs, caregiver education, and a follow-up appointment that the patient can realistically attend. Early readmission reflects both disease severity and the quality of transitions between inpatient and outpatient care [35,36]. Patients with persistent inflammatory or recurrent-decompensation signals generally need contact sooner than patients who have recovered without unresolved complications.

Functional decline may be evident before routine laboratory values change. Six-minute walking distance, the Liver Frailty Index, grip strength, or a caregiver's account of reduced activity can identify loss of reserve [31,32,33]. Heart-rate variability remains investigational but may provide additional prognostic information [34]. Such measures are worthwhile only when they lead to a response—nutrition support, rehabilitation, medication review, or closer follow-up.

7.3. What Prediction Tools Still Need to Do

A clinically useful model would provide updated probabilities of ACLF, readmission, stability, transplantation, and death rather than a single fixed label. Machine-learning approaches may help because they can incorporate nonlinear relations and repeated measurements. Current models are limited by modest sample sizes, missing data, local practice patterns, and insufficient external validation [55]. An impressive area under the receiver-operating-characteristic curve is not enough; calibration, interpretability, and evidence of clinical benefit are equally important.

Biomarker studies face the same test. A marker of inflammation or immune dysfunction may be statistically associated with outcome and still add little to bedside decision-making. New markers should be compared against strong clinical models, measured serially, and linked to an action that could plausibly improve outcome. Prediction without a clear management consequence has limited value.

8. Limitations and Priorities for Research

The principal limitation is built into the original design: the PREDICT groups were defined by outcomes over 90 days. Calling them baseline phenotypes risks circular reasoning. Generalizability is another concern. The original cohort was European and hospital based, while etiologies, precipitants, transplant access, antimicrobial resistance, and discharge practice vary widely. Readmission is influenced by the health system and family support as well as by liver biology. Mechanistic studies add further uncertainty because many are small and use different sampling times.

Future studies should treat acute decompensation as a sequence of changing states. Multicentre cohorts are needed to develop admission-time estimates and validate them across regions and etiologies. Models should allow movement between states rather than forcing patients into fixed categories. Biomarker studies require standardized sampling and analysis of clinical utility. Intervention trials could then test targeted strategies—for example, intensified infection surveillance in patients with a strong inflammatory signal, structured readmission-prevention programmes for recurrent decompensation, and etiological and rehabilitation programmes aimed at recompensation.

Recovery should be studied with the same care as deterioration. Some patients classified as SDC will eventually meet formal recompensation criteria; others remain clinically quiet but retain severe portal hypertension or frailty. Conversely, UDC may improve after effective etiological therapy, TIPS, or better coordinated outpatient care. Mortality and transplantation are essential outcomes, but quality of life, caregiver burden, functional independence, and cost should also be included. The practical framework in Table 2 is proposed for discussion and has not been prospectively validated.

9. Conclusions

The PREDICT study provided a useful language for the different courses that follow acute decompensation of cirrhosis. The pre-ACLF course carries the greatest risk and is associated with progressive inflammation and organ failure. UDC is characterized by recurrent decompensation and readmission, commonly in the setting of severe portal hypertension. SDC has the most favourable short-term prognosis and may, in some patients, precede recompensation. These distinctions are clinically meaningful, but they remain outcome-defined courses rather than prospectively validated diagnoses.

The immediate clinical lesson is modest but important: assessment should extend beyond how ill a

patient appears on one day. Direction of change, recurrent complications, functional reserve, and the safety of the post-discharge plan all matter. Serial organ assessment, prompt treatment of infection, careful management of portal hypertension, attention to nutrition and frailty, and timely transplant referral remain the practical response [56]. Whether the three trajectories can become a precision-treatment framework will depend on prospective prediction and trials showing that trajectory-informed care improves outcomes.

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