Systemic Inflammation, ACLF, and Coagulation Cross-Talk

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Disclosures

Founder: Yaqrit Ltd. · Hepyx Ltd. · Cyberliver Ltd. · Gigabiome Ltd.

Inventor: Ornithine Phenylacetate · DIALIVE · CARBALIVE · G-TAK · CirrhoCare · Alcochange

Speaker & Grant Reviewer: Grifols

Research Collaborator: Yaqrit Ltd.

Talk Overview

1. **Clinical characteristics of ACLF**

   and distinction from mere decompensated cirrhosis

2. **Evidence for severely deranged inflammation in ACLF**

   Clinical, biochemical, and molecular evidence

3. **Evidence of coagulation disturbance in ACLF**

   and its characteristics

4. **Systemic inflammation as a possible driver**

   of coagulation disturbance — a hypothesis

5. **Perspectives**

   Addressing coagulation disturbance in ACLF: testing and treatment

ACLF vs Decompensated Cirrhosis: A Critical Distinction

Acute Decompensation (AD)

- First or recurrent decompensation
- Ascites, HE grade 1–2, variceal bleed, SBP
- No organ failure by CLIF-OF criteria
- 3-month mortality: 10–15%
- Portal hypertension–driven pathophysiology
- ↑ inflammatory markers — but modest
- Generally responds to standard care

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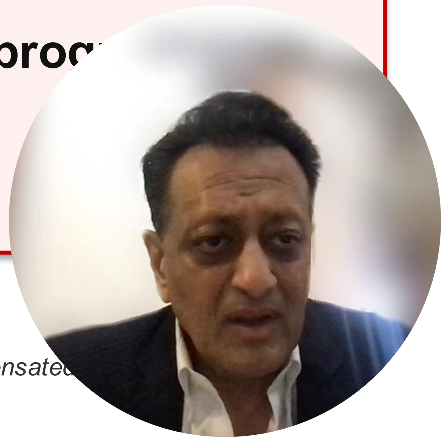
Acute-on-Chronic Liver Failure (ACLF)

- **Acute decompensation PLUS ≥1 organ failure**
- Organ failures: liver, kidney, brain, coagulation, circulation, respiratory
- Defined by EASL-CLIF criteria (CLIF-OF score)
- 28-day mortality: 22–90% (grade-dependent)
- Intense systemic inflammatory response (SIRS)
- Immune dysregulation (CAID)
- **A distinct syndrome: different pathophysiology, natural history, prog**



Arroyo V, Moreau R, Jalan R. N Engl J Med 2020;382:2137–45 | EASL Clinical Practice Guidelines on Decompensated

ACLF: Organ Failure Criteria and Epidemiology

Organ System	Failure Definition (CLIF-OF Score)	Prevalence in ACLF
Liver	Bilirubin ≥12 mg/dL (≥205 μmol/L)	Most common
Kidney	Creatinine ≥2.0 mg/dL OR RRT required	Common, ~50%
Brain	HE Grade 3–4 (West Haven criteria)	~30–40%
Coagulation	INR ≥2.5 OR Platelets ≤20×10³/μL	~30–50%
Circulation	Vasopressor use for septic shock	~25%
Respiratory	PaO_2/FiO_2 ≤200 OR SpO_2/FiO_2 ≤214	~25%

~100M
Global compensated cirrhosis burden

~10M/yr
Acute decompensation cases globally

>2M/yr
ACLF cases globally

41–
90-d
(gr

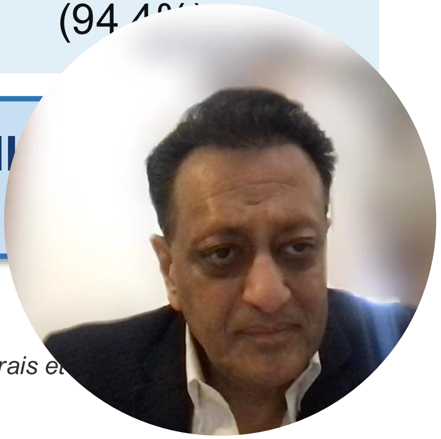
Arroyo V, Moreau R, Jalan R. N Engl J Med 2020;382:2137–45 | Jalan R et al. Development of CLIF-C ACLF score.

ACLF is Dynamic: Resolution Improves Survival

28-Day Transplant-Free Mortality (%)

Initial ACLF grade	Final grade one week after ACLF diagnosis			
	No ACLF (n = 376)	ACLF-1 (n = 179)	ACLF-2 (n = 132)	ACLF-3 (n = 147)
ACLF-1 (n = 483)	30/275 (10.9%)	24/134 (17.9%)	20/36 (55.6%)	33/38 (86.8%)
ACLF-2 (n = 252)	11/86 (12.8%)	9/33 (27.3%)	30/78 (38.5%)	43/55 (78.2%)
ACLF-3 (n = 99)	2/15 (13.3%)	2/12 (16.7%)	13/18 (72.2%)	51/54 (94[illegible]

Resolution of ACLF is achievable — and when it occurs, survival improves dramaticall[illegible] resolves to No ACLF: mortality falls from 94% → 13%.



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Evidence for Severely Deranged Inflammation in ACLF

Clinical & Biochemical Evidence

- Markedly elevated CRP (>50 mg/L in most ACLF)
- Procalcitonin elevation (bacterial / sterile sepsis)
- Leucocytosis / SIRS criteria met in majority
- Elevated IL-6, IL-8, TNF-α, IL-1β (>10× stable cirrhosis)
- Elevated HMGB1 and other alarmins (DAMPs)
- High-grade endotoxaemia (LPS)
- **Inflammatory profile grades with ACLF severity**

The Paradigm Shift in Understanding

Old paradigm:

Peripheral vasodilation → haemodynamic failure

New paradigm (Arroyo, Moreau, Jalan 2020):

Injury → Inflammation → Immune Dysregulation → Regeneration Failure → Organ Failure

Evidence:

- Gut-derived LPS activates systemic TLR4
- LPS levels and TLR4 expression correlate with ACLF grade
- TLR4 blockade prevents organ failure in experimenta
- Non-apoptotic cell death (pyroptosis, necroptosis

Arroyo V, Moreau R, Jalan R. N Engl J Med 2020;382:2137–45 | Engelmann C et al. J Hepatol 2021;74:102–12 | Kondo R et al. Cell D

Molecular Drivers: PAMPs, DAMPs, TLR4, and Immune Dysregulation

Microbial Triggers (PAMPs)

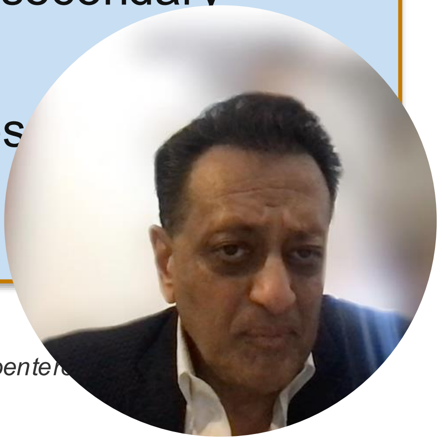
- LPS from bacteria
- Bacterial translocation
- Peptidoglycans, bacterial DNA, flagellin
- Activate TLR4, TLR2, TLR9
- LPS levels correlate with ACLF grade
- → NF-κB → TNF-α, IL-1β, IL-6, IL-8

Sterile Triggers (DAMPs)

- HMGB1, mitochondrial DNA, uric acid
- Released during hepatocyte necrosis
- Caspase-4-mediated PYROPTOSIS
- RIPK-1-mediated NECROPTOSIS
- Activate NLRP3 inflammasome
- → Self-amplifying inflammatory loop

Immune Dysregulation (CAID)

- Cirrhosis-associated immune dysfunction
- SIMULTANEOUS: SIRS + Immunoparesis
- ↓ Monocyte/neutrophil responsiveness
- ↑ IL-10, TGF-β immunosuppression
- Vulnerable to secondary infections
- → Perpetuates
resolution



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Coagulation Disturbance in ACLF: The Rebalanced Haemostasis Paradigm

↓ Pro-haemostatic pathways

- ↓ Coagulation factors II, V, VII, IX, X, XI, XIII
- ↓ Fibrinogen: mean 139 mg/dL (vs 258 in controls)
- **Fibrinogen <90 mg/dL → predicts 3-month mortality**
- Thrombocytopenia in 67–90% of ACLF patients
- Structurally weaker fibrin clots (↑ permeability)
- INR ≥2.5 in 0% ACLF-1, 49.5% ACLF-2, 70% ACLF-3

FRAGILE BALANCE

↓ Anti-haemostatic pathways (also)

- ↓ Antithrombin, Protein C, Protein S — proportional fall
- ↑ Factor VIII: endothelial source, rises with ACLF severity (driven by inflammation)
- ↑ VWF: 5–7× above normal; ↓ ADAMTS13 (54% of normal)
- VWF/ADAMTS13 imbalance partially compensates for thrombocytopenia
- **Net thrombin generation: PRESERVED or ↑ even at elevated INR**

⚠ INR reflects disease severity — NO haemostatic capacity

Ferdinande K et al. Liver Int 2025;45:e70378 | Fisher C, Patel VC et al.

Haemostatic Changes Across the Severity Spectrum

Ferdinande K et al. Liver Int 2025;45:e70378 | Fisher C, Patel VC et al. J Crit Care 2018;43:54–60

Parameter	Stable Cirrhosis	Acute Decompensation	ACLF Grade 1–2	ACLF Grade 3
INR	~1.2	1.4–2.0	2.0–2.5	≥2.5 (70% of pts)
Platelet count	~120 K	↓	↓↓	↓↓↓ 67–90% severe
Fibrinogen	~258 mg/dL	↓	↓↓	~139 mg/dL
Thrombin gen.	↑	↑↑	↑ or ~N	~Normal or mildly ↓
Factor VIII	↑	↑↑	↑↑↑	↑↑↑↑
VWF	↑	↑↑	↑↑↑	↑↑↑↑ (5–7× N)
ADAMTS13	↓	↓↓	↓↓↓	~54[illegible]
VET (ROTEM/TEG)	Normal	Variable	Hypo-coagulable >50%	[illegible]

Key insight: Thrombin generation is PRESERVED despite markedly abnormal INR — because an[illegible] pathways fall in parallel.

Fibrinolysis and the Bleeding–Thrombosis Paradox

Fibrinolysis in ACLF: Mixed Phenotypes

MIXED fibrinolytic phenotypes

- Hyperfibrinolysis — in minority (↑ tPA from endothelium)
- Balanced fibrinolysis — in some patients
- **HYPOFIBRINOLYSIS — in patients with sepsis**

- Hypofibrinolysis due to↑ PAI-1 (inflammation-induced)
- **Prolonged clot lysis time = independent predictor of 30-day mortality**

- **Proposed mechanism**: impaired microthrombi clearance → organ ischaemia

Bleeding prevalence: 7–67%

- Minor: ecchymoses, epistaxis (~49% of episodes)
- Major: GI haemorrhage (12–17% of ACLF patients)
- Intracranial haemorrhage: 23% in HE grade III

Thrombotic prevalence: 5–20%

- Portal vein thrombosis: most common macrovascular event
- **Intraorgan microthrombi: key mechanism of organ failure**
- VTE: DVT/PE in hospitalised ACLF patients

Both bleeding AND thrombosis occur in ACLF — sometimes simultaneously in the same patient. discriminate between these risks.

Blasi A et al. Hepatology 2020;71:1381–90 | Ferdinande K et al. Liver Int 2025;45:e70378 | Fisher C, Patel VC et al.

The Hypothesis: Systemic Inflammation Drives Coagulation Disturbance

"In ACLF, the intense systemic inflammatory response is the primary driver of haemostatic disturbance — through tissue factor upregulation, anticoagulant suppression, endothelial activation, PAI-1-driven hypofibrinolysis, and NETs-mediated immunothrombosis — creating a vicious cycle that propagates organ failure."

Inflammation Activates Coagulation

- ↑ Tissue Factor on monocytes/ endothelium (TNF-α, IL-1β, IL-6)
- ↓ Antithrombin (IL-6 suppresses hepatic synthesis)
- ↓ Protein C/S, ↓ Thrombomodulin
- ↑ PAI-1 → hypofibrinolysis
- NETs → FXII activation, platelet aggregation, microthrombi

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Coagulation Amplifies Inflammation

- Thrombin → PAR-1 / PAR-2 on leukocytes and endothelium
- PAR signalling → ↑ TNF-α, IL-6, IL-8
- Factor Xa → NF-κB activation
- Fibrin degradation products → macrophage activation
- Self-amplifying cycle of inflammation + thrombosis

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Microthrombi Drives Organ Failure

- Hypofibrinolysis → impaired microthrombi clearance
- Intraorgan thrombosis: renal, hepatic, cerebral, lung
- Organ ischaemia → DAMPs → further inflammation
- NETs deposit in liver
and peripheral mic
- Breaking this cy
therapeutic targe

Levi M, van der Poll T. Crit Care Med 2010;38(Suppl 2):S26–34 | Blasi A et al. Hepatology 2020;71:1381–90 | Ferdinande K et a

Evidence Supporting the Hypothesis

1. Factor VIII and VWF rise with ACLF severity

Both are markers of endothelial activation/inflammation — not of hepatic synthesis. Their progressive elevation correlates with systemic inflammatory burden, not with conventional liver function.

2. ADAMTS13 falls as ACLF severity increases

ADAMTS13 is a metalloproteinase suppressed by inflammatory cytokines. Its decrease (to ~54% of normal in ACLF) results in uncleaved ultra-large VWF multimers — promoting thrombosis.

3. PAI-1-driven hypofibrinolysis tracks with sepsis and organ failure

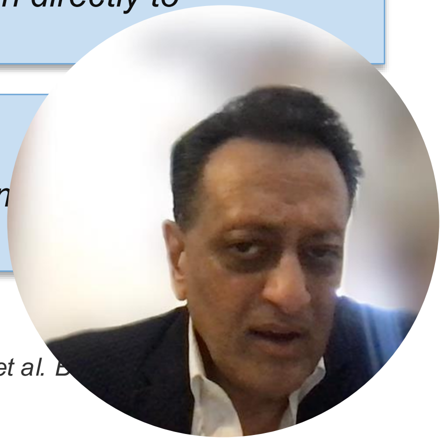
Prolonged clot lysis times (hypofibrinolysis) are specifically associated with sepsis and organ failure in ACLF — directly linking the inflammatory state to the fibrinolytic defect.

4. NETs are elevated in ACLF and predict mortality

NET biomarkers (MPO-DNA, cfDNA) are elevated in HBV-ACLF and predict 90-day mortality. NETs link neutrophilic inflammation directly to immunothrombosis and microthrombus formation.

5. Anti-inflammatory therapy improves haemostatic profile

DIALIVE reduces inflammatory mediators and albumin oxidation in ACLF — associated with resolution of organ failure. If inflamm coagulopathy, treating inflammation should restore haemostatic balance.



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NETs: The Bridge Between Neutrophilic Inflammation and Thrombosis

What Are NETs?

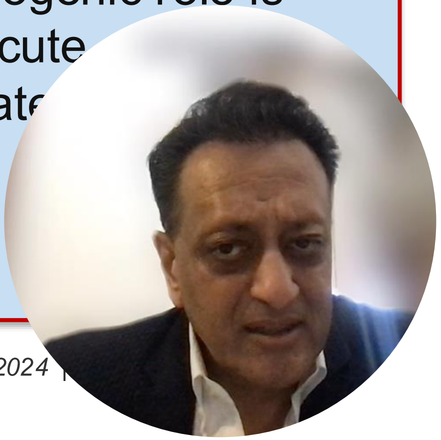
- Web-like DNA + histone + granular protein (MPO, elastase) structures
- Released by activated neutrophils
- Triggered by: LPS, cytokines, hypoxia, platelets
- Biomarkers: cfDNA, MPO-DNA complexes, citrullinated histone H3
- Generated in large quantities in ACLF

NETs Activate Coagulation

- Citrullinated histones activate Factor XII (contact pathway)
- DNA scaffold → platelet adhesion and aggregation
- Tissue factor expressed on NET surfaces
- → Platelet-rich microthrombi in sinusoids and microcirculation
- DNase disrupts NETs → reduces experimental thrombosis

Clinical Evidence in ACLF

- NET scores predict 90-day mortality in HBV-ACLF
- NETs linked to portal vein thrombosis
- Histological evidence: NETs + fibrin co-deposition in biopsies
- In clinically STABLE cirrhosis: NETs NOT independently linked
- → NETs pathogenic role is specific to the acute inflammatory stat



Huang T et al. Biomedicines 2024;12:2048 | Chen X et al. J Clin Transl Hepatol 2024 |

Perspectives: Assessing Coagulation in ACLF — Beyond the INR

⚠ INR in ACLF is a prognostic marker for disease severity — NOT a predictor of haemostatic capacity or bleeding risk. Prophylactic FFP/platelet correction based on INR alone is NOT recommended.

Conventional Coagulation Tests (CCTs)

PT/INR, APTT, platelet count, fibrinogen

- Widely available; required for ACLF diagnosis and scoring
- INR: hepatic synthetic function — NOT haemostatic predictor
- Fibrinogen <1.5 g/L: clinically significant; <0.9 g/L predicts mortality
- Cannot assess anticoagulant pathways; no platelet/VWF/fibrinolysis assessment
- Limitation: severely misleads if used to guide transfusion decisions

Thrombin Generation Assay (TGA)

Measures endogenous thrombin potential (ETP) ± thrombomodulin

- Best assessment of net haemostatic capacity in ACLF
- In ACLF: TG PRESERVED or ↑ vs healthy controls, despite elevated INR
- Confirms 'rebalanced' haemostasis — scientific basis for avoiding prophylactic FFP
- Thrombomodulin-modified TGA reflects Protein C pathway function
- Not yet widely available in clinical labs — research and specialist centres

Viscoelastic Testing (VET)

Whole-blood assessment of clot formation, strength and fibrinolysis

- >50% of ACLF patients hypocoagulable by VET (≥3 abnormal parameters)
- >70% hypocoagulable in multi-organ failure
- PREFERRED method for guiding blood product decisions in ACLF
- Guides: fibrinogen supplement (FIBTEM MCF <7 mm), p
- Mechanothromboela protocols reduce unn transfusions

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Perspectives: Treating Coagulation Disturbance in ACLF

Anti-Inflammatory Therapies

- DIALIVE (YAQRIT): removes inflammatory mediators → resolves ACLF faster
- TLR4 antagonists (Yaq005): reduce cytokine-driven coagulation activation
- RIPK-1 inhibitors: block necroptosis → reduce DAMP release
- IL-1β antagonists (Anakinra): reduce inflammasome
- G-CSF (GRAFT study): negative primary endpoint; further trials required

Blood Product Management

- Do NOT transfuse prophylactically based on INR
- VET-guided decisions: fibrinogen if FIBTEM MCF <7mm or Fbg <1.5 g/L
- Platelet transfusion: threshold <50K for procedures; <20K for spontaneous
- FFP: only for active bleeding with confirmed coagulation factor deficiency
- Avoid large-volume FFP — does not significantly change thrombin generation

Anticoagulation in ACLF

- LMWH: preferred agent for PVT prevention and treatment
- Direct oral anticoagulants (DOACs): CONTRAINDICATED in ACLF
- Mechanical thromboprophylaxis preferred over pharmacological where possible
- VET-guided anticoagulation: TEG/ROTEM can identify patients who would benefit
- Emerging: DNase therap NETs), PAR-1 antagonis thrombin-inflammation

Agarwal B et al. J Hepatol 2023;79:79–92 | Ferdinande K et al. Liver Int 2025;45:e70378 | Engelmann C et al. (GRAFT) J

Conclusions

1. ACLF is a distinct syndrome from decompensated cirrhosis

2. The systemic inflammatory response in ACLF is severe and qualitatively distinct

3. Haemostasis in ACLF is rebalanced but fragile

4. The INR is a prognostic marker — NOT a haemostatic test

5. The hypothesis: inflammation drives haemostatic disturbance in ACLF

6. Treating inflammation may be the key to restoring haemostatic balance

"The coagulation system in ACLF is not broken — it is overwhelmed by infla
Treat the inflammation to restore the balance."