Grading Fibrinolysis Resistance in Sepsis: A Bedside Tool That Identifies the Highest-Mortality ICU Endotype

Summary of a Letter | American Journal of Respiratory and Critical Care Medicine 2026 (advance article) | Coupland LA, Frost SA, Lin J, Pham N, Self M, Crispin PJ, Rabbolini DJ, Keragala CB, Medcalf RL, Aneman A.

Why this paper matters to Haemoview

This peer-reviewed letter in **AJRCCM** — the leading critical care journal — establishes the first **point-of-care grading system for fibrinolysis resistance in sepsis**, built entirely on the **ClotPro® TPA-test®** (Haemoview Diagnostics). In 116 septic ICU patients across 428 sequential assays, three distinct fibrinolysis resistance endotypes (Grades 1–3) were identified that align with disease severity, organ failure, plasma fibrinolysis marker profiles and 28-day mortality. Grade 3 patients had a **3.9-fold increased hazard for death** versus Grade 1. A companion preprint on medRxiv contains the full mechanistic dataset, including ex vivo reversibility data not present in the published Letter.

Study at a glance

Item	Detail
Article type	Peer-reviewed Letter to the Editor (AJRCCM advance article); companion preprint on medRxiv with full methods, tables and reversibility sub-study
Authors	Coupland LA, Aneman A, et al. — Liverpool Hospital ICU, Ingham Institute, UNSW Medicine, Monash Australian Centre for Blood Diseases, ANU, University of Sydney
Journal	Am J Respir Crit Care Med 2026; DOI: 10.1093/ajrccm/aamag281. Preprint: medRxiv 2026.03.25.26349336
Clinical scope	Adult ICU patients with sepsis or septic shock (Sepsis-3 criteria); 116 patients, 428 sequential tPA-VET assays
Core finding	The TPA-LT/FIBA10 ratio (sec/mm) defines three fibrinolysis resistance grades. Grade 3 carries a 3.9-fold hazard for 28-day mortality. Dynamic improvement in grade tracks favourable outcomes.
ClotPro link	The ClotPro® TPA-test® (650 ng/mL tPA) is named in the Methods as the assay enabling the grading system; the FIB-test® provides the fibrin-clot amplitude (FIBA10) for normalisation

The clinical gap this paper closes

The authors state plainly: *"The degrees and dynamics of [fibrinolysis] resistance that associate with mortality in acute sepsis are unknown, and a simple tool to aid clinician interpretation of fibrinolysis measurements is lacking."* Until now, fibrinolysis resistance has been measured inconsistently, at single time points, and without a clinical interpretive framework. This study provides exactly that — a data-driven, three-tier grading system derived from a parameter already produced by every ClotPro TPA-test.

Key message: *"Grading of fibrinolysis resistance in sepsis enables rapid identification of patients at greatest mortality risk, with any dynamic improvement corresponding to favourable clinical outcomes."*

Key findings in detail

1 | A simple bedside ratio defines three fibrinolysis resistance endotypes

The TPA-LT (clot lysis time) is influenced by the amount of fibrin substrate present (FIBA10). The **TPA-LT/FIBA10 ratio (sec/mm)** normalises for this and produced three reproducible clusters by Gaussian Mixture Modelling:

Grade	TPA-LT/FIBA10	Interpretation	28-day mortality
Grade 1	< 13 sec/mm	Preserved fibrinolysis; correlation with FIBA10 like non-septic controls (r=0.85). 34% of septic patients.	**15%**
Grade 2	13 – <26 sec/mm	Moderate resistance; partial loss of TPA-LT ↔ FIBA10 correlation (r=0.41). Intermediate inhibitory marker profile.	**24%**
Grade 3	≥ 26 sec/mm	Severe resistance; correlation lost (r=0.15, ns). High PAI-1, low plasminogen, raised α2AP/plasminogen.	**42%**

2 | Grade 3 identifies a high-mortality, organ-failure phenotype

On admission, Grade 3 patients had the highest APACHE III (86 [80–122] vs 69 [57–82] in Grade 1, p<0.001) and SOFA scores (15 [11–19] vs 10 [6–12], p<0.001). All Grade 3 patients required vasopressors/inotropes, 90% required mechanical ventilation, and 58% required renal replacement — versus 36%, 65% and 18% in Grade 1. The hazard ratio for 28-day ICU mortality in Grade 3 was **3.9 (95% CI 1.4–11)** versus Grade 1.

3 | Fibrinolysis resistance is dynamic — and that matters clinically

With sequential ClotPro TPA-test assays (median 3 per patient, separated by ~25 hours), patients frequently transitioned between grades during the first week in ICU. A reduction in grade was associated with a decreased risk of death, and an increase in grade was associated with worsening outcome. **This positions the TPA-LT/FIBA10 grade as a real-time treatment-response biomarker**, not a single-point prognostic label.

4 | Plasma marker profile validates the grading

A nested sub-study (n=40, 162 samples) confirmed the biological basis of the grades: Grade 3 was characterised by significantly higher **PAI-1 activity**, lower **plasminogen**, and elevated **PAI-1/tPA** and **α2-antiplasmin/plasminogen** ratios — a coherent inhibitory fibrinolysis signature.

5 | Ex vivo reversibility — the preprint signal worth knowing

The companion **medRxiv preprint** includes a reversibility sub-study not present in the AJRCCM Letter: doubling the tPA dose or adding an α2-antiplasmin inhibitory antibody reduced **100% of Grade 2 cases to Grade 1**, while **53% of Grade 3 cases remained refractory** even at doubled tPA. This separates a pharmacologically tractable endotype (Grade 2) from a refractory one (Grade 3) — direct implications for future profibrinolytic trial design.

6 | A research and clinical agenda — and where ClotPro belongs

- **Clinical use today:** bedside risk stratification, dynamic monitoring of treatment response, and identification of patients at greatest mortality risk.
- **Trial enrichment:** Grade 3 defines the high-mortality population profibrinolytic and anti-PAI-1 therapy trials need to enrol; Grade 2 may be the optimal pharmacological-responder population.
- **Validation pathway:** the authors call for confirmation in larger multicentre cohorts — positioning ClotPro as the de facto platform for that next phase of research.

Relevance to ClotPro® and Multiclot® users

This paper turns a research parameter — fibrinolysis resistance — into a structured, gradable clinical signal available from a single ClotPro assay panel (TPA-test + FIB-test). It directly strengthens the Haemoview clinical narrative for ICU customers managing sepsis and septic shock.

Paper finding	Relevance to ClotPro/Multiclot users
Three reproducible fibrinolysis resistance endotypes from one ClotPro panel	The TPA-LT/FIBA10 ratio is calculated from values every ClotPro user already generates. No new instrument, no new assay — a new interpretation framework that adds clinical value to existing workflows.
Grade 3 = 3.9-fold hazard for 28-day death	A bedside number that stratifies sepsis mortality risk independently of APACHE/SOFA. A powerful credibility point in ICU clinician conversations about why ClotPro deserves routine use beyond bleeding management.
Dynamic transitions track outcome	Serial ClotPro testing becomes a treatment-response monitor. Justifies repeat assays during the first week of ICU admission — increasing per-patient ClotPro utilisation in line with clinical benefit.
Biological validation by PAI-1, plasminogen, α2AP, ratios	The grading is not just statistical clustering — it reflects a coherent inhibitory fibrinolysis biology. This protects the narrative from 'arbitrary cut-off' criticism in scientific discussions.
Ex vivo reversibility data (preprint)	Provides direct rationale for profibrinolytic trial designs using ClotPro for patient enrichment. Positions Haemoview as a research partner of choice for the next generation of sepsis coagulopathy trials.
Authors call for larger multicentre validation	A clear roadmap: any ICU evaluating ClotPro for sepsis can contribute to the validation cohort. This is a strong door-opener for new sites and academic collaborations.

Suggested customer conversation points

- *"If your ICU already runs ClotPro for trauma or cardiac bleeding, you are minutes away from a peer-reviewed fibrinolysis grading system for sepsis — using data you already generate."*
- *"For the first time, ICU clinicians have a bedside number that tells them not just how sick their septic patient is, but whether their fibrinolysis is recoverable — and whether today's treatment is working."*
- *"Grade 3 patients are the trial-enrichment population profibrinolytic therapy has been waiting for. ClotPro is the platform that identifies them."*
- *"Serial ClotPro testing is not just monitoring — published evidence now shows grade transitions track clinical outcome in real time."*

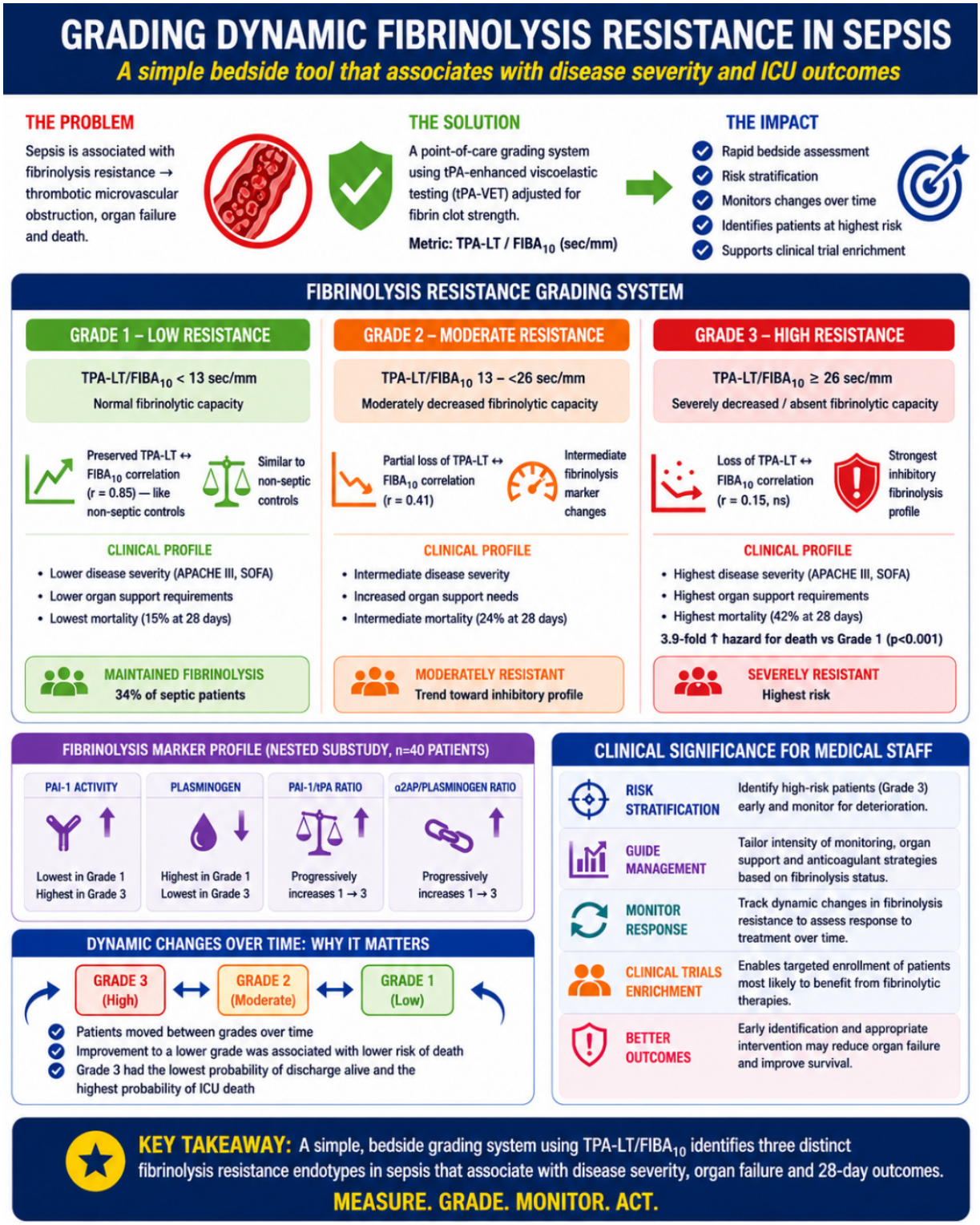
Sources

Coupland LA, Frost SA, Lin J, Pham N, Self M, Crispin PJ, Rabbolini DJ, Keragala CB, Medcalf RL, Aneman A. A grading system of dynamic fibrinolysis resistance in sepsis associates with ICU outcomes. *Am J Respir Crit Care Med* 2026 (advance article).
DOI: https://doi.org/10.1093/ajrccm/aamag281 | Open Access (CC BY-NC)
Related preprint with full methods, tables and ex vivo reversibility sub-study: medRxiv 2026.03.25.26349336 — https://doi.org/10.64898/2026.03.25.26349336

Disclaimer

Visual Summary — Infographic

The following infographic provides a visual overview of the key findings from Coupland et al. 2026, suitable for sharing with clinical colleagues.



Source: Coupland LA et al. Am J Respir Crit Care Med 2026 (advance article). DOI: 10.1093/ajrccm/aamag281.