

Coagulation Trajectory Subphenotypes Identify High-Risk Sepsis Patients Missed by the Sepsis-Induced Coagulopathy Score: A Retrospective Cohort Study with External Validation

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Abstract

Background

The Sepsis-Induced Coagulopathy (SIC) score assesses coagulation at a single time point and may miss patients whose coagulation profile is deteriorating over the first days of sepsis.

Methods

We conducted a retrospective cohort study of adult sepsis patients (Sepsis-3 criteria, first ICU stay ≥ 72 h) in MIMIC-IV (2008–2022) to determine whether 72-h trajectories of routine coagulation markers identify prognostic subphenotypes that static scoring misses. Platelet count, INR, and PTT were summarized over the first 72 ICU hours in nine 8-h windows (platelet nadir; INR and PTT peaks) and clustered with Gaussian mixture models; the primary outcome was hospital mortality. External validation used eICU-CRD ($n = 12,828$) with independent refitting.

Results

Among 3,138 patients, three reproducible subphenotypes emerged: Low ($n = 1,814$; 16.2% mortality), Moderate ($n = 633$; 17.7%), and High ($n = 691$; 27.8%; $p < 0.001$). The High group—persistently elevated INR and PTT—had higher mortality after SOFA adjustment (hazard ratio [HR] 1.62, 95% CI 1.35–1.96). 81.9% of High-group patients (566/691) did not meet SIC criteria (score ≥ 4 with a platelet-plus-INR subtotal > 2) yet carried 26.3% mortality—1.7 times that of SIC-negative Low patients (15.8%); the mortality gradient persisted among all 2,908 SIC-negative patients (15.8%–26.3%, $p < 0.001$). Adding the trajectory cluster to SOFA plus age improved the AUC modestly (0.645 to 0.656; $\Delta\text{AUC} + 0.011$). eICU-CRD independently reproduced the SIC-negative gradient (15.4%–23.4%; $\chi^2=97.0$, $p < 0.001$).

Conclusions

Trajectories of routine coagulation markers over the first 72 ICU hours identify a high-mortality subphenotype that the SIC score fails to flag in over 80% of cases. Serial laboratory measurements already collected in routine care should be interpreted dynamically, and incorporating the direction of change into coagulopathy screening warrants prospective evaluation.

Trial Registration

Not applicable. This retrospective observational cohort study of de-identified data does not require registration as a clinical trial.

Introduction

Sepsis [1, 2] is among the leading causes of death worldwide, with an estimated 48.9 million cases and roughly 11 million deaths annually [3]. In the organ-failure cascade of sepsis, coagulation is central, spanning subclinical clotting activation to overt disseminated intravascular coagulation (DIC) [1, 4, 5]. Convergent mechanisms—tissue factor upregulation on monocytes and endothelium, neutrophil extracellular traps, and endothelial injury—drive coagulation while endogenous anticoagulants (antithrombin, protein C, tissue factor pathway inhibitor) are suppressed [4, 6, 7]. Generated thrombin amplifies inflammation via protease-activated receptors on platelets, endothelium, and leukocytes, so hemostasis both mirrors and aggravates infection severity [5, 6]. Organ dysfunction and death track with platelet consumption, microvascular thrombosis, and coagulation-factor depletion [7, 8], so coagulation status is closely tied to outcome.

Sepsis-associated coagulopathy is common and strongly predicts mortality [8]. Yet the tools used to evaluate it rest on a single laboratory assessment at one time point. The SOFA coagulation component uses the admission platelet count [9]; the SIC score pools platelet count, INR, and SOFA into one cross-sectional threshold [10]; the ISTH overt DIC criteria use platelet count, fibrin-related markers, prothrombin time, and fibrinogen, likewise a single assessment [11]. Even the most recent ISTH update, which acknowledges the dynamic nature of DIC, still scores it from a single time point [12]. None captures how the state is changing: a patient with a falling platelet count or rising INR is managed identically to one with stable values when the two match at measurement, despite divergent courses. SIC, proposed in 2017, is a pragmatic early-screen aligned with Sepsis-3 [10]; ISTH overt DIC targets established DIC and needs assays beyond the routine panel [11].

The limitation of snapshot scoring is recognized in other critical-care domains. Temperature trajectories identified four sepsis subphenotypes with distinct mortality and host response [13]; latent class analysis of routine variables defined four clinical phenotypes differing in organ dysfunction, inflammation, and treatment response [14]; organ-dysfunction trajectories across the first ICU week defined outcome-distinct subphenotypes [15]. In each case, temporal dynamics of a continuously measured signal carried prognostic information invisible to single-time-point assessment, without high-frequency monitoring. Whether the same applies to bedside coagulation scores—SIC, ISTH DIC, SOFA coagulation—has not been systematically examined, even though serial coagulation testing is routine and the direction of change (falling platelets, rising INR) is visible on the flowsheet yet absent from every current instrument.

In parallel, data-driven approaches have been applied directly to SIC. Supervised machine-learning models have been developed to predict SIC dynamically during critical illness [16], to identify SIC early from routinely collected data [17], and to predict 28-day mortality in patients who already meet SIC criteria [18]. These models take SIC status or a downstream outcome as the supervised label and ask how accurately individual risk can be forecast. They do not, however, ask whether the SIC construct itself—applied as an admission snapshot—systematically misses a subgroup of patients whose coagulopathy declares itself through the trajectory of serial measurements rather than through baseline values.

Answering that question requires the complementary unsupervised perspective taken here, in which subgroups are defined by the joint evolution of routine coagulation markers before any comparison with an existing score.

In this study we asked whether the joint evolution of platelet count, INR, and PTT over the first 72 ICU hours identifies sepsis patients at high risk of hospital death whom the SIC score—a pragmatic early screening instrument [10]—classifies as low risk. We used Gaussian mixture models [19] to derive trajectory-defined subgroups in MIMIC-IV [20] and validated them by independent refitting in eICU-CRD [21], following prior trajectory-phenotyping frameworks [13, 14]. Our hypothesis was narrow: that a clinically meaningful share of high-risk coagulopathy in sepsis is missed by static screening because its risk emerges from the trajectory of serial measurements. We did not claim trajectory analysis is methodologically superior to existing scores. Anticoagulant therapy for SIC remains contested: heparin trials reported divergent, inconclusive findings [22–24], and guidelines do not recommend routine anticoagulation [25]. Whether trajectory-defined subgroups differ in response to early heparin—and could identify patients most likely to benefit—is unknown.

Materials and Methods

Data Sources

We used two critical care databases. The derivation cohort was MIMIC-IV (v3.0) [20], ICU admissions at Beth Israel Deaconess Medical Center (2008–2022), spanning laboratory, vital-sign, and outcome modules linked through de-identified study identifiers; we obtained access via PhysioNet (data use agreement and human-subjects training). External validation used eICU-CRD (v2.0) [21], over 200,000 ICU admissions across 208 US hospitals (2014–2015); identical laboratory parameters and window definitions were applied. Both datasets are de-identified and released via PhysioNet. MIMIC-IV collection was approved by the BIDMC and MIT institutional review boards; this secondary analysis of de-identified data was exempt from additional review.

Study Population

We included adults (≥ 18 years) meeting Sepsis-3 criteria [26] (suspected or confirmed infection with an acute SOFA rise ≥ 2), limited to a first ICU stay of at least 72 hours, the shortest span that supports a meaningful trajectory while keeping early death or discharge from distorting the estimates. We excluded liver disease, metastatic cancer, traumatic brain injury, and major admission bleeding (Figure S1) to isolate sepsis-driven coagulopathy, since these independently alter coagulation profiles or indicate alternative causes.

Sepsis-Induced Coagulopathy (SIC) score. We computed the SIC score as an admission snapshot using the published weights [10] and the operational definition applied in recent MIMIC-based implementations [27]: platelet count ≥ 150 , 100–149, and $< 100 \times 10^9/L$ scored 0, 1, and 2 points; INR ≤ 1.2 , > 1.2 –1.4, and $>$

1.4 scored 0, 1, and 2 points; SOFA respiratory, cardiovascular, hepatic, and renal subscores (each 0→0, 1→1, $\geq 2 \rightarrow 2$, summed, capped at 2 per subscale). **Because MIMIC-IV provides a pre-computed SOFA coagulation subscore (platelet-based, range 0–4) rather than four individual organ subscores, we used the coagulation subscore as the SOFA component, consistent with the ISTH rule that caps each organ at 2 points.** SIC was defined as a total score ≥ 4 with the platelet-plus-INR subtotal exceeding 2 (i.e. ≥ 3) [27]. We used the platelet nadir and INR peak from the first 8 hours (the same window as trajectory extraction). This approach yields conservative SIC estimates: the coagulation subscore (max 4) is a lower bound on the four-organ sum (max 8), so patients near the threshold may be classified as negative when the full organ-score sum would reach ≥ 4 . The resulting sensitivity (11.2%) and specificity (93.6%) are consistent with prior MIMIC-based reports of the SIC score's screening performance.

Coagulation Trajectory Extraction

We extracted platelet count, INR, and PTT from the first 72 ICU hours—the core of routine coagulation monitoring and the most complete longitudinal data (D-dimer and fibrinogen were > 80% missing). The 72-hour window balances temporal resolution against retention, since longer windows progressively exclude early deaths/discharges. Each parameter was summarized into nine 8-hour windows (hours 0–8 through 64–72); within each we recorded platelet nadir and INR and PTT peaks—the standard clinical anchors. Implausible values were excluded (platelet < 5 or > 2000 $\times 10^9/L$; INR > 20; PTT > 200 s), yielding 27 features. We imputed missing windows with the cohort median as a conservative default. PTT was expressed as a patient-to-normal ratio (patient value divided by the upper reference limit of 35 s) to harmonize across laboratories; we restricted to these three parameters to stay aligned with existing scores (SIC and SOFA coagulation use platelet and INR; PTT is routine). Chart times permitted exact window placement.

Gaussian Mixture Model Clustering

All 27 features were z-score normalized. We fit a diagonal-covariance Gaussian mixture model [28] for $k = 2-6$ (BIC: $k = 2$, 124,174; $k = 3$, 43,383; $k = 4$, - 14,196; $k = 5$, - 27,855; $k = 6$, - 31,226). Diagonal covariance reduces parameters in 27-dimensional space and improved stability; we chose GMM over group-based trajectory modeling [29] because it captures the joint correlation of three parameters simultaneously. The 3-component solution was selected by (a) a monotonic mortality gradient (16.2%, 17.7%, 27.8%) with the largest High-versus-rest contrast; (b) minimum cluster size > 20% (633, 20.2%), whereas $k = 6$ yielded clusters as small as 181 (5.8%); and (c) interpretability of the Low–Moderate–High framework. BIC decreased monotonically through $k = 6$ and was not the sole criterion. We fit each model by expectation–maximization [28] from 20 random starts (up to 500 iterations) and assigned patients to the component with the highest posterior probability. Assignments were reproducible (adjusted Rand index 0.998–1.0; mean posterior 0.998; 99.7% of patients ≥ 0.7) and labeled Low, Moderate, High by ascending mortality. Because GMM is unsupervised, assignment is independent of the mortality outcome, so the cluster–mortality association is not circular.

Statistical Analysis

Primary outcome was hospital mortality per database flag. Continuous and categorical comparisons used ANOVA and chi-square. LASSO logistic regression on the 27 features—with L1 regularization and penalty strength chosen by 5-fold cross-validation maximizing the area under the receiver operating characteristic curve (AUC)—retained 24 of 27 (cross-validated AUC 0.610), confirming signal distributed across parameters and windows; leading features were late-window platelet nadir (plt_w6-8) and INR peaks (inr_w6-7). Survival time ran from ICU admission to death, censored at ICU discharge; groups were compared by Kaplan-Meier and log-rank. Cox regression assessed cluster–mortality association unadjusted and SOFA-adjusted, as both a per-step ordinal model and pairwise versus Low; proportional hazards held (Schoenfeld global $p = 0.94$). Discrimination used Harrell's C; 5-fold mortality-stratified cross-validation estimated optimism (full minus cross-validated C). Incremental value of SOFA + age versus SOFA + age+cluster was quantified by AUC, continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI), with bootstrap 95% confidence intervals and the DeLong test for AUC differences. Decision curve analysis assessed clinical utility. Screening performance of GMM (Moderate+High positive) was compared with the admission SIC definition (score ≥ 4 with platelet-plus-INR subtotal > 2) for mortality sensitivity, specificity, and predictive values. Shock was any vasopressor use. Analyses used Python 3.12 (scikit-learn, lifelines, statsmodels); two-sided $p < 0.05$. Per SAGER, sex (46.8% female) was reported descriptively; sex-stratified analyses were not performed given few events within subphenotypes.

Heparin treatment-effect analysis. Because all patients survived to a 72-hour landmark, heparin effect was evaluated by target trial emulation, removing immortal-time bias from post–time-zero exposure [30]. Exposure was any subcutaneous or intravenous heparin charted in inpatientevents (itemid 225152 intravenous; 225975 subcutaneous) within 72 hours. Each patient was cloned into initiation and no-initiation arms; follow-up was censored at divergence from the assigned arm, and stabilized inverse-probability weights (trimmed 1st/99th percentiles) came from a logistic propensity model including age, sex, total SOFA, SOFA coagulation subscore, and peak lactate, vasopressor use, atrial fibrillation, venous thromboembolism, valvular disease, stroke, intracranial hemorrhage, chronic kidney disease, cancer, and bleeding. Within each subphenotype, weighted Cox models related heparin to 28-day mortality; treatment-by-subphenotype interaction was tested globally, with bootstrap 95% survival differences. Sensitivity analyses used subcutaneous-only and intravenous-only exposure.

Causal forest analysis. Treatment-effect heterogeneity was characterized with a causal forest (2,000 trees; honest splitting, out-of-bag predictions) [31] using trajectory subphenotype, age, sex, SOFA, lactate, baseline platelet/INR/PTT, and the comorbidity indicators above; exposure and outcome matched the target trial emulation. Variable importance and mean out-of-bag conditional average treatment effects (CATE) per subphenotype are reported in Supplementary Methods.

External Validation

External validation followed prior trajectory-phenotyping frameworks [13, 14]—independent refitting rather than direct transport, which does not preserve clustering across databases with different laboratory density and timing. eICU-CRD patients meeting the same criteria received an independent GMM fit ($k = 3$, diagonal covariance, 20 starts, 500 iterations); gradients were tested by chi-square. As a secondary check, direct transport of MIMIC scaler and parameters to eICU yielded poor discrimination ($C \approx 0.50$).

Results

Cohort Characteristics

The final cohort included 3,138 sepsis patients (age 61.9 ± 17.3 ; 46.8% female; median SOFA 3, IQR 2–4) drawn from > 50,000 ICU admissions (Figure S1). Hospital mortality was 19.0% (597 deaths); vasopressor use (shock) occurred in 838 (26.7%); heparin (subcutaneous or intravenous) within 72 hours in 1,571 (50.1%), concentrated in the High group. Baseline characteristics differed across subphenotypes: the High group was older (64.8 vs 61.7 years), with higher SOFA coagulation subscores (0.43 vs 0.22), a higher prevalence of shock (41.1% vs 21.8%), and more frequent heparin exposure (65.6% vs 47.3%) than Low; total SOFA was similar across groups (median 3.0, IQR 2.0–4.0, in Low and Moderate; 3.0, IQR 2.0–5.0, in High). Moderate, relative to Low, was younger (59.3 ± 18.2 years) with less heparin exposure (41.1% vs 47.3%), whereas its shock prevalence lay between Low and High (25.1%) (Table 1). A pre-planned heparin treatment-effect analysis (target trial emulation) appears below and in Table S1; sex-stratified analyses were not performed.

Table 1
Baseline characteristics of sepsis patients by coagulation trajectory subphenotype

Characteristic	Overall (n = 3,138)	Low (n = 1,814)	Moderate (n = 633)	High (n = 691)
Age, years	61.9 ± 17.3	61.7 ± 17.3	59.3 ± 18.2	64.8 ± 16.0
Female, n (%)	1,470 (46.8)	856 (47.2)	281 (44.4)	333 (48.2)
SOFA total, median [IQR]	3.0 [2.0–4.0]	3.0 [2.0–4.0]	3.0 [2.0–4.0]	3.0 [2.0–5.0]
SOFA coagulation	0.28 ± 0.66	0.22 ± 0.57	0.30 ± 0.68	0.43 ± 0.82
Shock, n (%)	838 (26.7)	395 (21.8)	159 (25.1)	284 (41.1)
Heparin (SC/IV) within 72 h, n (%)	1,571 (50.1)	858 (47.3)	260 (41.1)	453 (65.6)
Hospital mortality, n (%)	597 (19.0)	293 (16.2)	112 (17.7)	192 (27.8)
<i>Data presented as mean ± SD, median [IQR], or n (%). Right-skewed variables (e.g., SOFA total) are reported as median [IQR].</i>				

Coagulation Trajectory Subphenotypes

GMM identified three groups: Low ($n = 1,814$; 57.8%; 16.2% mortality), Moderate ($n = 633$; 20.2%; 17.7% mortality), and High ($n = 691$; 22.0%; 27.8% mortality). Cluster quality was high (mean posterior probability 0.998; 99.7% of patients ≥ 0.7) and assignments reproducible (adjusted Rand index 0.998–1.0). Trajectory patterns diverged clearly (Fig. 1): the High group showed persistently elevated INR (mean 1.73 at admission, declining to 1.38 by 72 h) and PTT ratio (1.44 to 1.28), whereas Low and Moderate remained near normal (INR 1.2–1.3; PTT ratio 0.86–0.94). Platelet trajectories overlapped substantially (72-h nadirs 171–192 $\times 10^9/L$), so separation was driven primarily by INR and PTT rather than platelet count; mean admission SOFA coagulation subscores were 0.22, 0.30, and 0.43. The Moderate group differed only marginally from Low in mortality (17.7% vs 16.2%, $p = 0.40$) and trajectory shape; the contrast was driven by High.

Survival Analysis and Comparison with Static Scores

Mortality differed significantly across groups ($p < 0.001$; Table 2). Kaplan-Meier analysis confirmed early and sustained separation (log-rank $\chi^2=36.5$, $p < 0.001$; Fig. 3); Low vs High and Moderate vs High both $p < 0.001$, whereas Low vs Moderate did not ($p = 0.25$). Unadjusted Cox regression per one-step increase in cluster severity gave HR 1.31 (95% CI 1.19–1.43, $p < 0.001$); after SOFA adjustment the HR was 1.27 (95% CI 1.15–1.39, $p < 0.001$), with C-statistics of 0.557 and 0.581 for the unadjusted and adjusted models, respectively (Figure S4). Versus Low, High had independently higher mortality (SOFA-adjusted HR 1.62, 95% CI 1.35–1.96, $p < 0.001$) whereas Moderate did not (HR 1.12, 95% CI 0.90–1.40, $p = 0.29$). The mortality gradient held within both strata: in shock ($n = 838$), mortality was 20.8% (82/395), 20.1% (32/159), and 32.7% (93/284) for Low, Moderate, and High ($\chi^2=15.0$, $p = 0.001$), and in non-shock ($n = 2,300$), 14.9% (211/1,419), 16.9% (80/474), and 24.3% (99/407) ($\chi^2=20.1$, $p < 0.001$; Figure S3, Table 2). Shock raised mortality within Low ($\chi^2=7.5$, $p = 0.006$) and High ($\chi^2=5.5$, $p = 0.019$) but not Moderate ($\chi^2=0.7$, $p = 0.42$). Using the admission SIC definition [10, 27], 230 patients (7.3%) met SIC criteria (score ≥ 4 with platelet-plus-INR subtotal > 2). Among the 2,908 SIC-negative patients (1,754 Low, 588 Moderate, 566 High), GMM maintained the gradient: 15.8%, 17.7%, 26.3% ($p < 0.001$; Fig. 2). For mortality prediction, GMM (Moderate+High) had sensitivity 50.9%/specificity 59.9% versus SIC 11.2%/93.6%; PPV/NPV were 23.0%/83.8% and 29.1%/81.8%. Within the High group, SIC-negative patients retained substantial mortality (26.3%), lower than SIC-positive patients (34.4%; $p = 0.084$). Adding clusters to SOFA + age improved the logistic discrimination AUC (0.645 to 0.656, $p < 0.001$; continuous NRI 20.3%, IDI 0.77%; Figure S5), with net benefit gains at $\geq 25\%$ thresholds (Figure S6). Cross-validation was stable (cluster-only C 0.564 full, 0.563 ± 0.020 ; optimism 0.001). The High group had higher mean SOFA coagulation subscore than Low (0.43 vs 0.22, ANOVA $p < 0.001$), yet 81.9% of High patients (566/691) were SIC-negative and still carried 26.3% mortality. ICU length of stay was similar across groups (median 6.3, 6.5, and 6.4 days; Kruskal–Wallis $p = 0.90$).

Table 2
Hospital mortality by subphenotype stratified by shock status

Subphenotype	Non-shock (n = 2,300)	Shock (n = 838)	p-value
Low	14.9% (211/1419)	20.8% (82/395)	0.006
Moderate	16.9% (80/474)	20.1% (32/159)	0.42
High	24.3% (99/407)	32.7% (93/284)	0.019
p-value	< 0.001	0.001	
Additional file 1: Supplementary Materials comprising the Supplementary Methods (target trial emulation and causal-forest details), Figures S1–S7, and Table S1.			

External Validation

Using the framework of prior trajectory-based phenotyping studies [13, 14], we refit the GMM independently on eICU-CRD (n = 12,828). The three-group gradient was reproduced: Low 15.6%, Moderate 21.5%, High 24.7% ($\chi^2=134.2$, $p < 0.001$; Figure S2), cluster sizes 8,165, 1,510, 3,153, with similar incremental AUC (+ 0.013; 0.624 to 0.637). The eICU cohort spanned community, academic, and rural hospitals—a more heterogeneous case mix than the single-center derivation. Direct model transport (MIMIC scaler and parameters applied to eICU) showed poor discrimination ($C \approx 0.50$), best explained by systematic between-database INR/PTT distribution differences. Independent refitting preserved the gradient in both databases. Applying the same admission SIC definition to eICU-CRD, 1,046 patients (8.2%) met SIC criteria (score ≥ 4 with platelet-plus-INR subtotal > 2) and 11,782 (91.8%) were SIC-negative. The trajectory mortality gradient persisted among SIC-negative patients (Low 15.4%, Moderate 20.8%, High 23.4%; $\chi^2=97.0$, $p < 0.001$), and 2,722 of 3,153 High-group patients (86.3%) were SIC-negative despite 23.4% mortality—a blind spot at least as large as in the derivation cohort. Screening performance was comparable (SIC sensitivity 11.3%/specificity 92.6% vs GMM 46.4%/65.9%).

Heparin treatment effect by trajectory subphenotype. All patients were alive at the 72-hour landmark, enabling a target trial emulation of early heparin that avoids immortal-time bias [30]. Using cloning, censoring, and inverse-probability weighting (stabilized, truncated 1st/99th percentiles), heparin (subcutaneous or intravenous) within 72 hours was associated with lower 28-day mortality in the High group (adjusted HR 0.67, 95% CI 0.51–0.89, $p = 0.006$; weighted 28-day survival difference + 20.9 percentage points, 95% CI 3.8–36.0; Fig. 4, Table S1). The association was weaker and non-significant in Moderate (HR 0.72, 95% CI 0.49–1.05, $p = 0.09$) and absent in Low (HR 0.95, 95% CI 0.76–1.19, $p = 0.68$); the global treatment-by-subphenotype interaction was non-significant ($p = 0.49$). In a causal forest [31] (2,000 trees; out-of-bag honest estimates), High showed the largest estimated benefit (mean out-of-bag CATE – 5.7 vs – 3.2 percentage points in Low; $p < 0.001$), with older age and lower peak lactate the strongest continuous modifiers; 88% of patients had directionally favorable effects and the overall out-of-bag effect was – 3.9 percentage points (Figure S7).

Discussion

The main finding of this study is that a reproducible high-mortality subphenotype, defined by the joint 72-hour trajectories of routine coagulation markers, escapes the SIC score in more than 80% of cases. The High group—persistently elevated INR and PTT—had nearly double the mortality of the Low group (27.8% vs 16.2%; SOFA-adjusted HR 1.62, 95% CI 1.35–1.96). The SIC definition (score ≥ 4 with a platelet-plus-INR subtotal > 2) flagged only 7.3% of patients; among the remaining 92.7% who were SIC-negative, the trajectory gradient persisted (15.8%–26.3%), and 566 of 691 High-group patients (81.9%) were SIC-negative at admission despite 26.3% mortality—1.7 times the mortality of SIC-negative Low patients (15.8%). The pattern replicated across two databases spanning 208 hospitals. The SIC blind spot replicated in eICU-CRD: 86.3% of High-group patients were SIC-negative yet carried 23.4% mortality across 208 hospitals, confirming the screening gap beyond the derivation cohort.

One negative result merits attention: the Moderate group did not differ significantly from Low in mortality (17.7% vs 16.2%, $p = 0.40$) or SOFA-adjusted Cox (HR 1.12, 95% CI 0.90–1.40). The informative contrast lay between High and the rest; no clean three-tier gradient emerged. This is consistent with the data—Moderate's INR/PTT trajectories were near-normal, resembling Low—so clustering effectively separated a high-risk INR/PTT-elevated subphenotype from the rest. We report this without imposing a three-tier narrative. Because Moderate was statistically indistinguishable from Low on both mortality ($p = 0.40$) and trajectory shape, the clinically actionable partition reduces to High versus non-High; all reported subgroup contrasts are unchanged when Moderate is grouped with Low.

The modest discrimination increment ($\Delta\text{AUC} + 0.011$) should not obscure the study's primary contribution: trajectories flag a substantial high-risk subgroup that static scores misclassify as low risk. The advance is a screening gap defined at the bedside; the discrimination metrics above quantify the incremental information carried by trajectory shape beyond a single assessment, and the method yields no standalone deployable prediction model.

Our approach complements, rather than competes with, supervised prediction models for SIC. Recent machine-learning studies have targeted SIC directly: dynamic prediction of SIC during critical illness [16], early identification of SIC from the MIMIC-IV database [17], and early prediction of 28-day mortality among patients with established SIC [18]. Because those models optimize prediction of a label derived from the SIC framework, their discrimination metrics are not directly comparable with the incremental AUC reported here; the two literatures answer different questions. The present study asks whether the screening instrument itself has a structural blind spot for trajectory-defined risk—a question that cannot be answered by models that treat the SIC score as ground truth. Mechanistically, SIC is now understood as an early, potentially reversible stage on the continuum from sepsis-associated coagulopathy to overt DIC [32]; capturing its evolution therefore requires serial assessment, which is precisely the information an admission snapshot discards.

The High group illustrates the blind spot most clearly. Its mean admission SOFA coagulation subscore (0.43) exceeded Low (0.22, $p < 0.001$), yet SIC still failed to flag 81.9% of High patients (566/691); these

unflagged patients carried 26.3% mortality—1.7 times that of SIC-negative Low patients (15.8%). Although the High group's admission INR was already elevated (1.73), most remained SIC-negative, and the trajectory retained independent prognostic information beyond SOFA (adjusted HR 1.62, 95% CI 1.35–1.96); the temporal pattern is therefore not redundant with a single admission INR. For identifying deaths, SIC had sensitivity 11.2%/specificity 93.6% versus GMM (Moderate+High) 50.9%/59.9%. GMM trades specificity for higher sensitivity—acceptable in screening, where missing high-risk patients outweighs extra monitoring. At the bedside, persistent elevation of INR and PTT—even with normal platelet counts—warrants more attention than a single admission SIC suggests. The discordance is mechanical. Because SIC requires a platelet-plus-INR subtotal above 2 and a total score of at least 4, patients whose admission INR is already elevated but whose platelet count remains $\geq 150 \times 10^9/L$ (subtotal ≤ 2) cannot meet the criteria regardless of organ failure; those with milder INR elevation or limited respiratory, cardiovascular, hepatic, and renal failure fall below the total of 4. These are exactly the patients whose platelet count then falls and whose INR and PTT continue to rise over the first 72 hours—the pattern a trajectory view catches.

Clinically, repeated coagulation assessment over 72 hours—measurements already present on routine ICU flowsheets—may carry prognostic value beyond initial SIC/ISTH DIC screening [8]. Whether trajectory subgroups respond differently to anticoagulation warrants study: heparin trials in sepsis showed heterogeneous, inconclusive results [22–24], and 2021 SSC guidelines do not address anticoagulation for SIC [25]. Our target trial emulation found the heparin–mortality association strongest in High (HR 0.67, 95% CI 0.51–0.89, $p = 0.006$; Table S1), but the formal interaction test was non-significant ($p = 0.49$), so this is an effect gradient, not proof of differential benefit; causal forest pointed the same direction, with largest benefit in High [31]. Trajectory-defined subgroups are a plausible enrichment stratum for future anticoagulant trials in SIC.

Limitations: the ≥ 72 -hour ICU stay requirement introduced survivor bias, excluding early deaths/discharges, so findings apply to patients surviving initial 72 hours. As retrospective data, unmeasured confounding may influence associations. Bleeding was defined by ICD codes rather than chart-confirmed bleeding [33], risking misclassification. Coagulation labs are not drawn on fixed schedules, creating trajectory-density variation; missing windows were filled with cohort medians (conservative, but may attenuate separation). GMM on discretized windows differs from GBTM [13, 29]; direct MIMIC→eICU transport showed poor discrimination ($C \approx 0.50$), so external validation used independent refitting, which reproduced the gradient but yields no single deployable model. We excluded liver disease and metastatic cancer; findings may not extend to those populations.

The median total SOFA of 3 indicates a low-acuity cohort versus many sepsis studies, limiting generalizability to higher-acuity populations. The heparin analysis is observational: subcutaneous prophylaxis dominated exposure, and unmeasured confounding from indication and contemporaneous care (e.g., fluid resuscitation, anticoagulation regimens) cannot be excluded; the non-significant interaction means the gradient is hypothesis-generating, not causal. GMM yields no simple bedside rule, limiting immediate uptake, and conclusions about Moderate remain provisional given few events; future

work should validate in prospective cohorts, compare GMM with GBTM on the same data, and test whether trajectory-informed screening changes outcomes. More broadly, the 2025 ISTH revision of the DIC definition—which separates thrombotic from hemorrhagic phenotypes and acknowledges the SIC score as a detector of early-phase DIC [12]—reinforces that coagulation risk in sepsis is dynamic and phenotype-specific; trajectory-based views such as ours may inform future scoring revisions that incorporate the direction of laboratory change.

Conclusions

Coagulation trajectories over the first 72 ICU hours identify a high-mortality subphenotype that static SIC screening misses: 81.9% of High-group patients were SIC-negative, yet their mortality (26.3%) was 1.7 times that of SIC-negative Low patients (15.8%). The pattern was validated across two independent cohorts covering 208 hospitals. For practice, the implication is direct: serial coagulation measurements—already collected as part of routine care—should be interpreted as a dynamic process. Future refinement of sepsis-associated coagulopathy definitions, including the SIC score, should incorporate temporal dynamics—for example, the direction and rate of change of platelet count, INR, and PTT—which single-threshold snapshot scoring cannot capture. Such an approach would require no new measurements and could, in principle, be implemented within existing electronic health records after prospective validation.

Abbreviations

AUC, area under the receiver operating characteristic curve; BIC, Bayesian information criterion; CATE, conditional average treatment effect; CI, confidence interval; DIC, disseminated intravascular coagulation; GMM, Gaussian mixture model; HR, hazard ratio; IDI, integrated discrimination improvement; INR, international normalized ratio; IPTW, inverse probability of treatment weighting; IQR, interquartile range; ISTH, International Society on Thrombosis and Haemostasis; IV, intravenous; LASSO, least absolute shrinkage and selection operator; LOS, length of stay; MIMIC, Medical Information Mart for Intensive Care; NPV, negative predictive value; NRI, net reclassification improvement; PPV, positive predictive value; PTT, partial thromboplastin time; SC, subcutaneous; SD, standard deviation; SIC, Sepsis-Induced Coagulopathy; SOFA, Sequential Organ Failure Assessment.

Declarations

Acknowledgements

Not applicable.

Ethics Approval and Consent to Participate

This study used de-identified data from MIMIC-IV and eICU-CRD databases. The use of MIMIC-IV was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center. As a secondary

analysis of de-identified publicly available data, this study was exempt from additional ethics approval. eICU-CRD was accessed under the same PhysioNet data-use agreement covering MIMIC-IV. Consent to participate was not applicable because all data were de-identified.

Consent for Publication

Not applicable.

Availability of Data and Materials

MIMIC-IV and eICU-CRD are publicly available through PhysioNet (<https://physionet.org>) upon completion of data use agreements. Analysis code is available from the corresponding author upon reasonable request.

Authors' Contributions

Xueshu Yu: Conceptualization, Methodology, Formal analysis, Validation, Writing – original draft.

Wen Xu: Conceptualization, Formal analysis, Writing – original draft.

Yincai Ye: Data curation.

Luwei Xu: Data curation, Validation.

Jingye Pan: Supervision, Writing – review & editing.

Competing Interests

The authors report there are no competing interests to declare.

Declaration of Generative AI and AI-Assisted Technologies

During the preparation of this work the authors used large language model-based tools to assist with statistical analysis, drafting, and language editing. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Figures

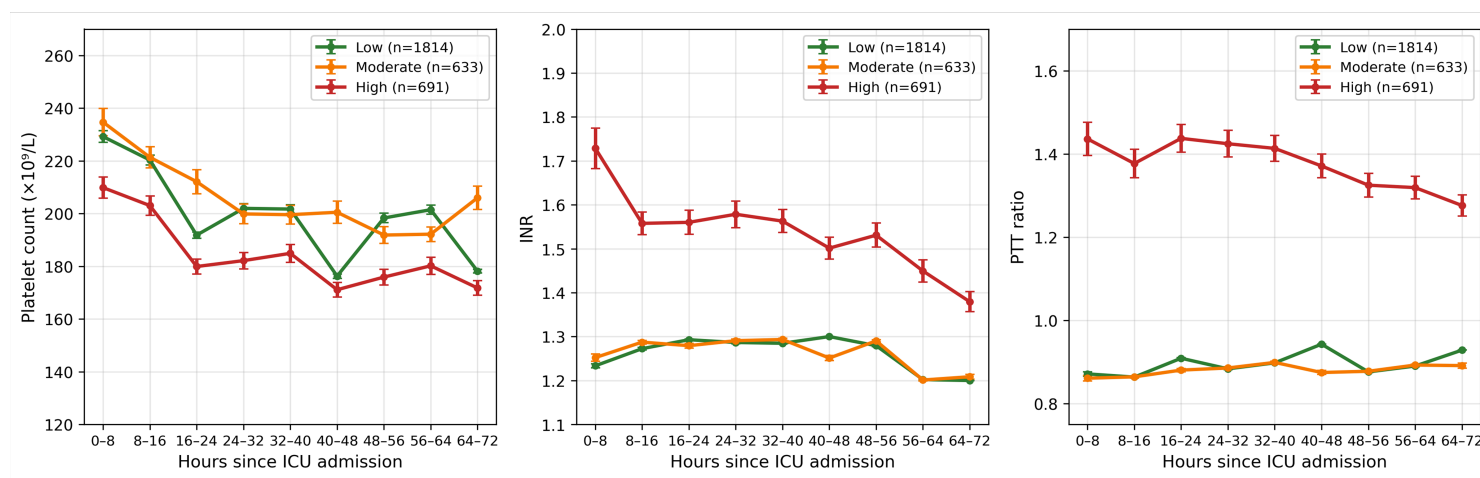


Figure 1

Coagulation trajectory subphenotypes over the first 72 ICU hours. Gaussian mixture model ($k=3$) identified three subgroups based on joint patterns of platelet count, INR, and PTT. Left panel: platelet count ($\times 10^9/L$). Middle panel: INR. Right panel: PTT ratio (patient value divided by the upper reference limit of 35 s). Green: Low ($n=1,814$; 16.2% mortality). Orange: Moderate ($n=633$; 17.7% mortality). Red: High ($n=691$; 27.8% mortality). The High group showed persistently elevated INR and PTT; platelet trajectories overlapped across groups. Solid lines denote mean values; shaded bands denote 95% CI.

The Static Score Blind Spot

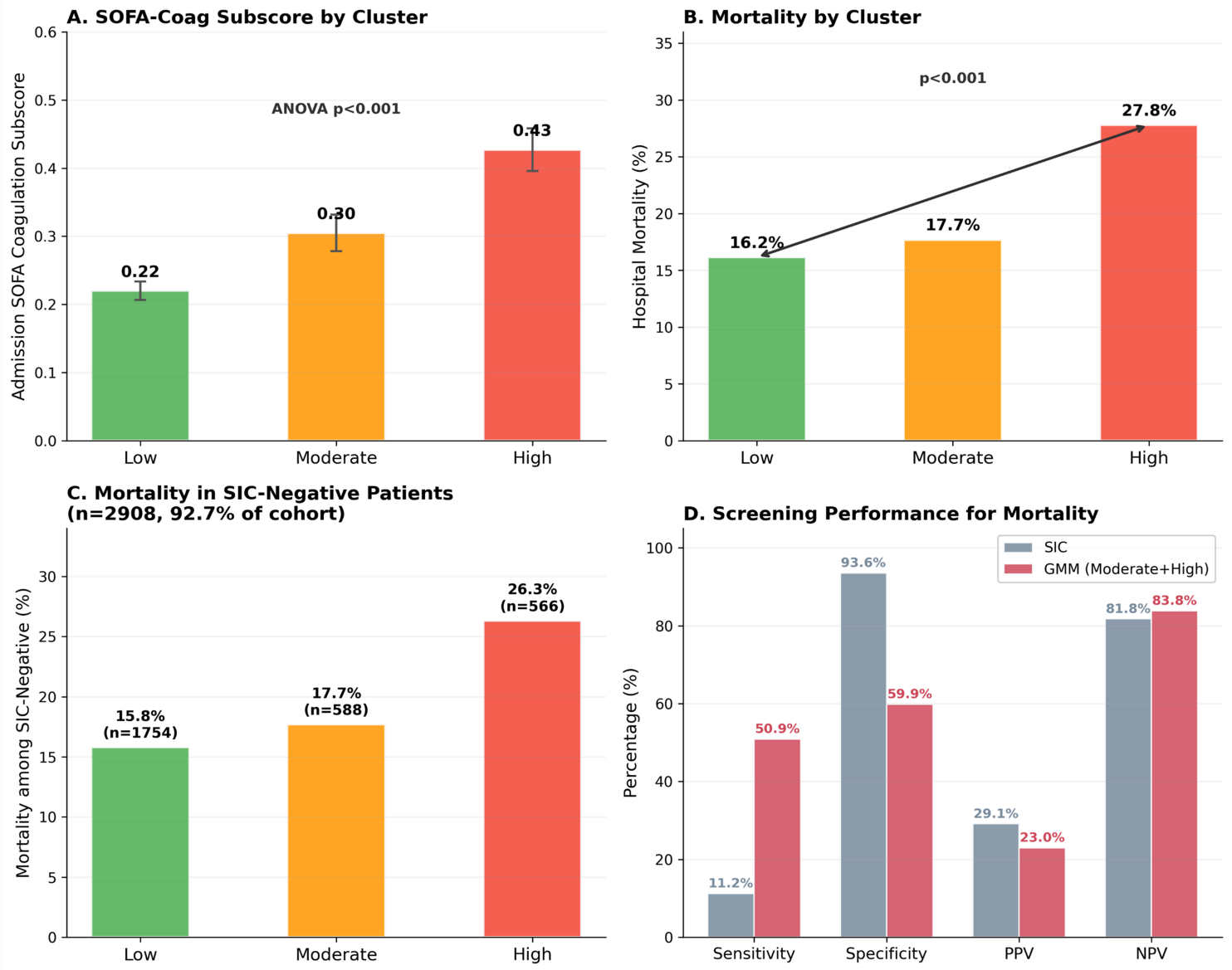


Figure 2

The Static Score Blind Spot. (A) Admission SOFA coagulation subscore by trajectory-defined cluster (Low 0.22, Moderate 0.30, High 0.43; ANOVA $p < 0.001$). (B) Hospital mortality by cluster (16.2%, 17.7%, 27.8%; $p < 0.001$). (C) Mortality gradient persisted among SIC-negative patients (n=2,908, 92.7% of the cohort): Low 15.8%, Moderate 17.7%, High 26.3% ($p < 0.001$). (D) Screening performance for mortality: SIC had sensitivity 11.2% and specificity 93.6%; GMM (Moderate+High combined) had sensitivity 50.9% and specificity 59.9%.

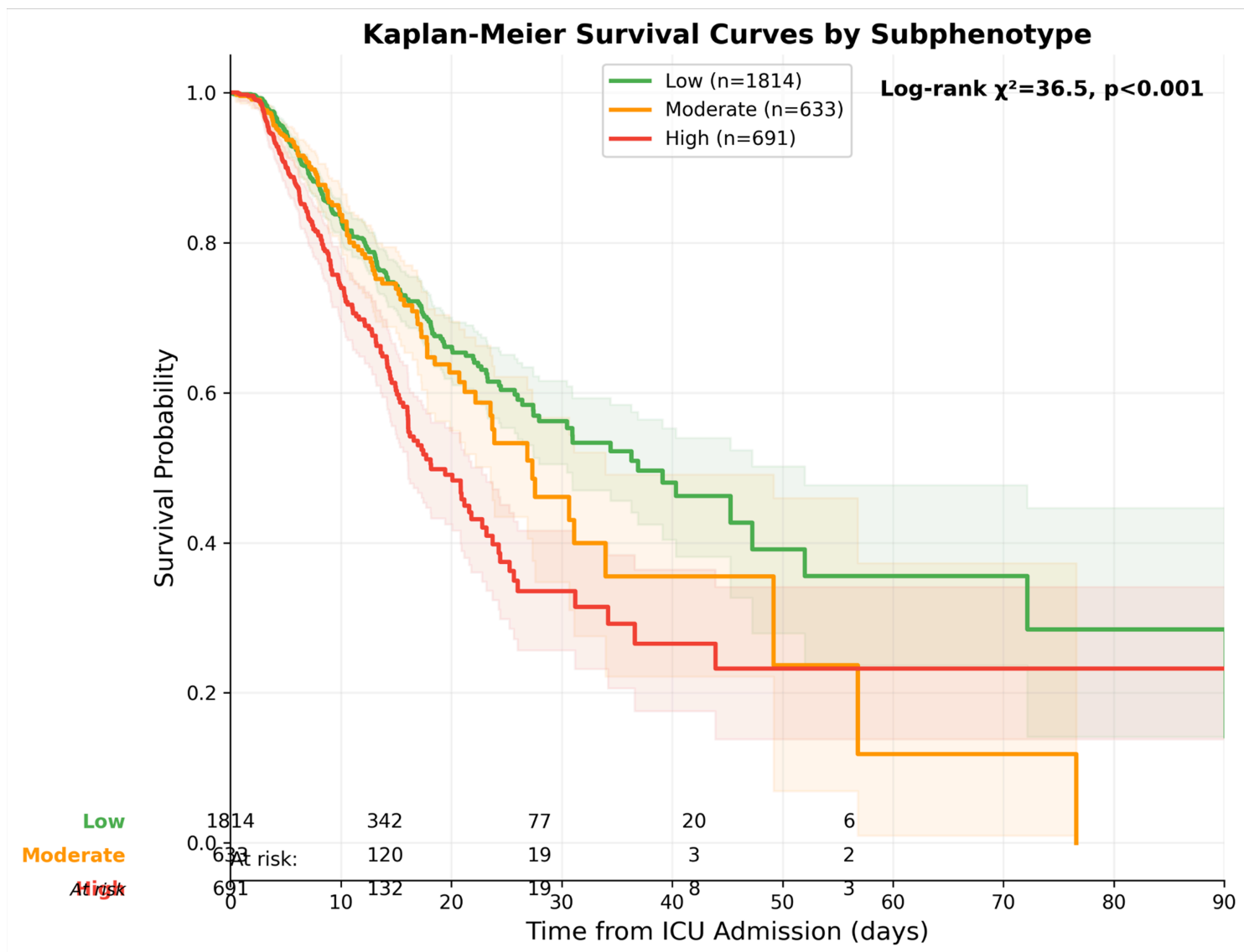


Figure 3

Kaplan-Meier survival curves of time to in-hospital death by coagulation trajectory subphenotype, censored at ICU discharge. Log-rank test: $\chi^2=36.5$, $p<0.001$. Shaded bands denote 95% confidence intervals.

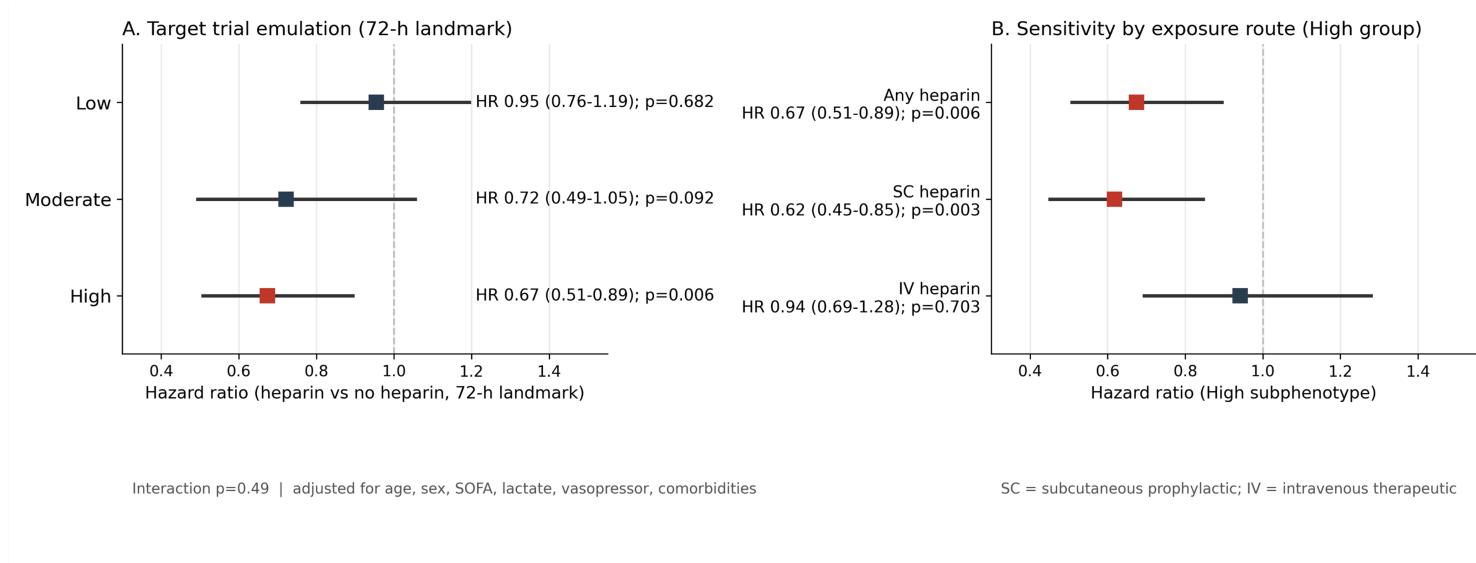


Figure 4

Heparin treatment effect by trajectory subphenotype. (A) Target trial emulation at a 72-hour landmark using cloning, censoring, and inverse-probability weighting: adjusted hazard ratios for 28-day mortality comparing heparin initiation (subcutaneous or intravenous) within the first 72 ICU hours versus no initiation, by trajectory subphenotype; horizontal lines show 95% confidence intervals and the global treatment-by-subphenotype interaction was non-significant (p=0.49). (B) Sensitivity analyses restricted to subcutaneous-only or intravenous-only heparin exposure in the High group. HR, hazard ratio.

Supplementary Files

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