

Coagulopathy subphenotypes and mortality in critically ill patients with sepsis: a multicentre retrospective cohort study using MIMIC-IV and SICdb

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Article

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Abstract

Background

Sepsis-induced coagulopathy is common and carries a substantial mortality burden, yet its clinical presentation is heterogeneous. Existing coagulopathy subphenotype studies are confined to single-country databases, and none have applied consensus clustering with cross-national external validation.

Methods

In this multicentre retrospective cohort study, we analysed adult septic patients with complete baseline coagulation profiles (international normalised ratio [INR], activated partial thromboplastin time [aPTT], fibrinogen, and platelet count) from MIMIC-IV v2.2 (derivation cohort, $n = 5,115$) and SICdb v1.0.6 (external validation cohort, $n = 622$). Consensus clustering (500 bootstrap resampling iterations, 80% item subsampling, 1 – Pearson correlation distance, average linkage) was applied to log-transformed, z-standardised coagulation variables. The primary outcome was 28-day all-cause mortality, analysed with Kaplan–Meier curves, log-rank tests, and sequential multivariable Cox models adjusted for demographics and illness severity (excluding the coagulation component of SOFA to avoid overadjustment).

Results

Three reproducible subphenotypes were identified: coagulation-preserved (Phenotype 1, 56.8%), isolated aPTT prolongation (Phenotype 2, 10.0%), and pan-coagulopathy (Phenotype 3, 33.2%). In MIMIC-IV, 28-day mortality was 9.4%, 10.5%, and 13.0%, respectively (log-rank $P = 5.2 \times 10^{-4}$); after full adjustment, Phenotype 3 versus 1 showed a hazard ratio (HR) of 1.25 (95% CI 1.04–1.51), whereas Phenotype 2 showed no excess risk (HR 1.01, 0.75–1.35). In SICdb, the phenotype distribution differed markedly (74.1%/19.3%/6.6%), but phenotypes were strongly associated with mortality (28-day mortality 16.9%, 35.0%, and 34.1%; log-rank $P = 2.9 \times 10^{-6}$). Notably, Phenotype 2—prognostically neutral in MIMIC-IV—carried a two-fold adjusted mortality risk in SICdb (HR 2.01, 95% CI 1.34–2.99; 90-day HR 2.32, 1.65–3.27), indicating context-dependent prognostic heterogeneity. Sepsis-induced coagulopathy (SIC) scores were complementary: among patients meeting SIC criteria, Phenotype 2 was associated with increased mortality (HR 1.60, 1.02–2.51), whereas among SIC-negative patients no such association was observed.

Conclusions

Consensus clustering identified three biologically interpretable coagulopathy subphenotypes with cross-national reproducibility. Pan-coagulopathy conferred consistent excess mortality, whereas isolated aPTT

prolongation identified a high-risk subgroup only in the surgical ICU setting and among SIC-positive patients. These findings support phenotype-informed stratification of septic coagulopathy for prognostication and future anticoagulant trial design.

Introduction

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, remains a leading cause of in-hospital mortality worldwide, accounting for an estimated 11 million deaths annually [1, 2]. Among the myriad derangements that characterise the septic host response, coagulation abnormalities occupy a central position: sepsis-induced coagulopathy spans a continuum from subclinical platelet activation and consumption to overt disseminated intravascular coagulation (DIC), and affects more than half of critically ill septic patients [3, 4]. Thrombocytopenia, prolongation of clotting times, and hypofibrinogenaemia are each independently associated with mortality, and their co-occurrence defines the consumptive phenotype that carries the worst prognosis [3, 4].

In 2019, the International Society on Thrombosis and Haemostasis (ISTH) introduced the sepsis-induced coagulopathy (SIC) score to identify the compensated phase of DIC in sepsis, combining platelet count, prothrombin time–international normalised ratio (PT-INR), and the total SOFA score [5]. A SIC score of ≥ 4 delineates a population with mortality exceeding 30% and has been proposed as an entry criterion for anticoagulant trials [5, 6]. However, threshold-based scores compress the multidimensional coagulation disturbance into a single ordinal scale, and thereby cannot distinguish qualitatively different—and potentially therapeutically relevant—patterns of haemostatic failure. This limitation may partly explain why large randomised trials of anticoagulant agents in broadly defined sepsis-associated coagulopathy, including recombinant activated protein C and recombinant soluble thrombomodulin, have yielded consistently negative results [7–9]: heterogeneous enrolment may dilute any treatment effect confined to a specific subpopulation.

Unsupervised subphenotyping offers a data-driven alternative. Latent class and cluster analyses have identified reproducible subphenotypes of sepsis and acute respiratory distress syndrome (ARDS) with divergent outcomes and, importantly, differential treatment responses to fluid management and supportive strategies [10–13]. Two studies have applied this paradigm specifically to coagulation markers: Kudo and colleagues derived four coagulation phenotypes from three Japanese registries and found that recombinant thrombomodulin was associated with survival benefit only in the severe-coagulopathy phenotype [14]; Cai and colleagues applied latent class analysis to SIC patients in MIMIC-IV and reported phenotype-specific heparin effects [15]. Both studies were, however, restricted to a single country and healthcare system, and relied on k-means or latent class methods that are sensitive to outliers and distributional assumptions. Consensus clustering, which assesses cluster stability through repeated resampling, is the reference standard for robust class discovery in oncology [16, 17] but has not been applied to sepsis coagulopathy subphenotyping.

We therefore conducted a multicentre retrospective cohort study to (i) identify coagulopathy subphenotypes among critically ill septic patients using consensus clustering on four routinely measured coagulation variables in MIMIC-IV; (ii) validate the subphenotypes and their mortality associations in an external cohort of a different nationality, care structure, and case-mix (SICdb, an Austrian surgical ICU database); and (iii) examine whether the subphenotypes complement the SIC score in risk stratification.

Methods

Study design and data sources

This retrospective cohort study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [18]. The derivation cohort was drawn from MIMIC-IV version 2.2, a publicly available critical care database containing de-identified records of patients admitted to intensive care units (ICUs) of Beth Israel Deaconess Medical Center (Boston, MA, USA) between 2008 and 2019 [19]. The validation cohort was drawn from SICdb version 1.0.6, a comprehensive open dataset from the surgical ICU of the University Hospital Salzburg (Salzburg, Austria) covering 2013–2020 [20]. Both databases were released under data use agreements after de-identification, and the original data collection was approved by the respective institutional review boards with a waiver of informed consent; the present secondary analysis therefore required no additional ethical approval.

Study population

Adults (aged ≥ 18 years) with sepsis were eligible. In MIMIC-IV, sepsis was defined according to the Sepsis-3 criteria (suspected infection with an acute increase in SOFA score ≥ 2), yielding 12,124 septic ICU encounters. In SICdb, we used the dataset's curated sepsis cohort ($n = 704$). We restricted the analysis to patients with a complete baseline coagulation panel—INR, aPTT, fibrinogen, and platelet count measured within the first ICU day—because these four variables were the only coagulation assays captured completely and harmoniously in both databases. D-dimer and thrombin time were excluded a priori because of $> 97\%$ missingness in both cohorts. Patients with any missing value among the four index variables were excluded (MIMIC-IV, $n = 7,009$; SICdb, $n = 82$), leaving a derivation cohort of 5,115 and a validation cohort of 622 patients (Fig. 1).

Data quality and variable harmonisation

Before analysis, we implemented database-specific quality control. In MIMIC-IV, laboratory records with a unit field of "0" represent placeholder fills rather than measured values (e.g., fibrinogen = 312.31 mg/dL in 7,005 encounters); these were treated as missing. In SICdb, prothrombin time is reported as Quick percentage, which is inversely correlated with INR (Spearman $\rho = -0.66$ in our data); to avoid redundancy

and unit incompatibility, the clustering variables were restricted to INR. The four index variables were thus identical in both cohorts. Comorbid burden was quantified with the Charlson comorbidity index [21]; illness severity with the total SOFA score, its haemostasis (coagulation) subcomponent, and the Acute Physiology and Health Evaluation (APACHE) III score [22, 23]. For the validation cohort, where derived severity scores were largely unavailable, we used the first-day vital parameters (heart rate, peripheral oxygen saturation, temperature) and routine laboratory values (white blood cell count, C-reactive protein, haemoglobin), together with documented heparin exposure, as adjustment covariates.

Consensus clustering

The four coagulation variables were log2-transformed (to reduce right skewness) and z-standardised. Consensus clustering was then performed in the derivation cohort following the principles of ConsensusClusterPlus [17]: 500 bootstrap iterations, each drawing a random 80% subsample of patients; hierarchical clustering with average linkage and one-minus-Pearson-correlation distance; and accumulation of pairwise co-membership across resamples to build consensus matrices for candidate cluster numbers $k = 2-5$. Cluster count selection considered (i) the proportion of ambiguous clustering (PAC)—the fraction of sample pairs with consensus values in the ambiguous interval 0.1–0.9, where lower values indicate more stable clustering [24]; (ii) the average silhouette width [25]; (iii) the stability of individual clusters across increasing k ; and (iv) biological interpretability. Phenotypes were labelled descriptively after inspection of the underlying coagulation profiles.

External validation by nearest-centroid assignment

To assign subphenotypes in SICdb, we computed each phenotype's centroid as the median of the log-transformed index variables among derivation-cohort members. Centroids and SICdb patients were z-standardised within the SICdb sample space (to accommodate between-database distributional shifts, such as the markedly higher fibrinogen levels in the post-operative Austrian cohort), and each patient was assigned to the nearest centroid by Euclidean distance [26].

Outcomes

The primary outcome was 28-day all-cause mortality, measured from ICU admission. The secondary outcome was 90-day all-cause mortality.

Statistical analysis

Baseline characteristics are presented as medians (interquartile ranges) or counts (percentages) and compared across subphenotypes using Kruskal–Wallis or χ^2 tests. Survival across subphenotypes was compared with Kaplan–Meier estimates and log-rank tests, and quantified with Cox proportional hazards models [27] using Phenotype 1 as the reference. Three sequential models were fitted: Model 1 (unadjusted); Model 2 (adjusted for age, sex, and Charlson index); and Model 3 (further adjusted for

illness severity—non-coagulation SOFA, APACHE III, white cell count, haemoglobin, mechanical ventilation, and renal replacement therapy in the derivation cohort; and vital parameters, C-reactive protein, and heparin exposure in the validation cohort). The coagulation subcomponent of the SOFA score was deliberately excluded from adjustment because it is constructed from the same variables that define the subphenotypes; adjusting for it would induce overadjustment bias. The SIC score was computed for each derivation-cohort patient according to ISTH criteria [5], and phenotype–mortality associations were examined separately among SIC-positive (score ≥ 4) and SIC-negative patients. In SICdb, an exploratory analysis tested phenotype-by-heparin interaction. As sensitivity analyses, we repeated the survival analysis with $k = 2$ and examined C-statistics of the phenotypes, SIC score, and SOFA for 28-day mortality. Complete-case analysis was used throughout; missing data in adjustment covariates were minimal ($< 3\%$). All analyses were two-sided with $\alpha = 0.05$ and performed in Python 3.11 (lifelines, SciPy, scikit-learn, pandas).

Results

Cohort characteristics

The derivation cohort (MIMIC-IV) comprised 5,115 patients with a median age of 64 years (IQR 54–74), 65.3% men, median SOFA score 7 (5–10), and median Charlson index 4 (2–6); 28-day and 90-day mortality were 10.7% (549/5,115) and 14.5% (741/5,115), respectively. The validation cohort (SICdb) comprised 622 older patients (median age 70, IQR 60–80), 57.6% men, with higher crude mortality (28-day 21.5%; 90-day 28.9%), reflecting the surgical ICU case-mix and the strong acute-phase response typical of post-operative patients (median fibrinogen 483 mg/dL versus 244 mg/dL in MIMIC-IV). Patient flow is summarised in Fig. 1.

Consensus clustering identifies three coagulopathy subphenotypes

The PAC decreased monotonically with increasing k (0.62 at $k = 2$, 0.56 at $k = 3$, 0.50 at $k = 4$, 0.43 at $k = 5$), whereas the average silhouette width was highest at $k = 2$ (0.52) and attenuated progressively (0.41 at $k = 3$). However, the $k = 2$ solution merely separated “coagulation-preserved” from “coagulation-impaired” patients and carried no prognostic information in sensitivity analysis (adjusted HR 1.08, 95% CI 0.91–1.28; $P = 0.36$). Crucially, the cluster that emerged at $k = 3$ —characterised by isolated aPTT prolongation—remained entirely stable at $k = 4$ and $k = 5$, whereas additional clusters beyond three arose solely from subdivision of the two other phenotypes without improving the silhouette. We therefore adopted the three-cluster solution as the most informative and parsimonious (Fig. 2).

The three subphenotypes showed sharply distinct coagulation profiles (Table 1, Fig. 3):

Phenotype 1—coagulation-preserved (n = 2,903; 56.8%)

near-normal haemostasis (INR 1.30, aPTT 29.5 s, fibrinogen 317 mg/dL, platelets $191 \times 10^9/L$) despite comparable overall illness severity.

Phenotype 2—isolated aPTT prolongation (n = 513; 10.0%)

marked prolongation of the intrinsic pathway (aPTT 53.9 s, IQR 39.3–99.6; nearly double the Phenotype 1 median) with only mildly deranged extrinsic pathway (INR 1.40) and moderate reductions of fibrinogen (187 mg/dL) and platelets ($145 \times 10^9/L$); total SOFA (7, IQR 6–10) was similar to Phenotype 1.

Phenotype 3—pan-coagulopathy (n = 1,699; 33.2%)

global derangement across all four axes (INR 1.70, IQR 1.50–2.20; aPTT 35.6 s; fibrinogen 186 mg/dL; platelets $105 \times 10^9/L$), accompanied by greater illness severity (SOFA 9, IQR 7–12), higher APACHE III scores, and more frequent renal replacement therapy (12.5% versus 7.5% in Phenotype 1).

Table 1

Baseline characteristics of the derivation cohort (MIMIC-IV) by coagulopathy subphenotype. Data are median (interquartile range) or n (%). P values from Kruskal–Wallis tests (continuous variables) or χ^2 tests (categorical variables). SOFA: Sequential Organ Failure Assessment; APS III: Acute Physiology and Health Evaluation III score; SIC: sepsis-induced coagulopathy.

Variable	Phenotype 1 Coagulation- preserved (n = 2,903)	Phenotype 2 Isolated aPTT prolongation (n = 513)	Phenotype 3 Pan- coagulopathy (n = 1,699)	P
Age, years	64 (54–74)	67 (57–76)	64 (54–74)	0.002
Male sex	1,888 (65.0%)	333 (64.9%)	1,118 (65.8%)	0.86
INR	1.30 (1.20–1.40)	1.40 (1.20–1.50)	1.70 (1.50–2.20)	< 0.001
aPTT, seconds	29.5 (26.5–33.4)	53.9 (39.3–99.6)	35.6 (30.8–44.5)	< 0.001
Fibrinogen, mg/dL	317 (219–500)	187 (141–269)	186 (147–245)	< 0.001
Platelets, $\times 10^9/L$	191 (150–248)	145 (124–189)	105 (76.5–133)	< 0.001
White blood cells, $\times 10^9/L$	13.0 (9.4–17.5)	11.6 (8.4–15.3)	11.0 (7.7–15.1)	< 0.001
Haemoglobin, g/dL	10.5 (9.0–12.2)	10.3 (8.7–12.1)	9.3 (8.0–10.9)	< 0.001
SOFA score (total)	7 (5–9)	7 (6–10)	9 (7–12)	< 0.001
SOFA haemostasis subcomponent	0 (0–1)	1 (0–2)	2 (1–3)	< 0.001
APS III score	43 (31–60)	41 (28–62)	49 (33–70)	< 0.001
SAPS II	37 (29–47)	38 (31–48)	40 (32–50)	< 0.001
Charlson comorbidity index	4 (2–6)	4 (3–6)	4 (3–6)	< 0.001
Mechanical ventilation	2,716 (93.6%)	487 (94.9%)	1,562 (91.9%)	0.027
Renal replacement therapy	218 (7.5%)	45 (8.8%)	213 (12.5%)	< 0.001
SIC score ≥ 4	247 (8.5%)	135 (26.3%)	1,267 (74.6%)	< 0.001

Variable	Phenotype 1 Coagulation- preserved (n = 2,903)	Phenotype 2 Isolated aPTT prolongation (n = 513)	Phenotype 3 Pan- coagulopathy (n = 1,699)	P
28-day mortality	274 (9.4%)	54 (10.5%)	221 (13.0%)	< 0.001
90-day mortality	380 (13.1%)	68 (13.3%)	293 (17.2%)	< 0.001

Subphenotypes and mortality in the derivation cohort

Subphenotypes discriminated 28-day survival (log-rank $P = 5.2 \times 10^{-4}$; 90-day $P = 2.5 \times 10^{-4}$) (Fig. 4). In unadjusted analysis, Phenotype 3 had a 42% higher hazard of 28-day death than Phenotype 1 (HR 1.42, 95% CI 1.19–1.69), which attenuated modestly but remained significant after full adjustment (HR 1.25, 95% CI 1.04–1.51; $P = 0.017$); the corresponding 90-day estimate was HR 1.21 (1.03–1.42; $P = 0.021$). By contrast, Phenotype 2 was not associated with excess mortality in any model (fully adjusted 28-day HR 1.01, 95% CI 0.75–1.35; $P = 0.97$) (Table 2, Fig. 5). The association of Phenotype 3 was thus independent of demographics, comorbidity, and non-haemostatic illness severity, indicating that the prognostic information of the pan-coagulopathy pattern is not a mere reflection of overall disease severity.

Table 2

Association between subphenotypes and mortality in the derivation cohort (MIMIC-IV, n = 5,115). Cox proportional hazards models with Phenotype 1 (coagulation-preserved) as the reference. Model 1: unadjusted. Model 2: adjusted for age, sex, and Charlson comorbidity index. Model 3: additionally adjusted for non-coagulation SOFA score, APS III, white blood cell count, haemoglobin, mechanical ventilation, and renal replacement therapy. HR: hazard ratio; CI: confidence interval.

Outcome / Model	Phenotype 2 vs 1 HR (95% CI)	P	Phenotype 3 vs 1 HR (95% CI)	P
28-day mortality				
Model 1 (unadjusted)	1.14 (0.85–1.52)	0.39	1.42 (1.19–1.69)	< 0.001
Model 2 (+ demographics)	1.14 (0.85–1.53)	0.38	1.37 (1.14–1.63)	< 0.001
Model 3 (+ severity)	1.01 (0.75–1.35)	0.97	1.25 (1.04–1.51)	0.017
90-day mortality				
Model 1 (unadjusted)	1.03 (0.80–1.33)	0.82	1.36 (1.17–1.59)	< 0.001
Model 2 (+ demographics)	1.03 (0.79–1.33)	0.83	1.31 (1.13–1.53)	< 0.001
Model 3 (+ severity)	0.93 (0.72–1.20)	0.58	1.21 (1.03–1.42)	0.021

External validation in SICdb

The three subphenotypes were reproducible in the Austrian surgical ICU cohort, with identical qualitative gradients in all four coagulation variables (Supplementary Table S1): Phenotype 1 (n = 461; 74.1%) again showed preserved haemostasis (INR 1.20, aPTT 37 s, fibrinogen 525 mg/dL, platelets 209 × 10⁹/L); Phenotype 2 (n = 120; 19.3%) showed isolated aPTT prolongation (57 s) with INR 1.55; and Phenotype 3 (n = 41; 6.6%) showed pan-coagulopathy (INR 1.80, fibrinogen 324 mg/dL, platelets 95 × 10⁹/L). The between-cohort difference in phenotype distribution (notably, the scarcity of Phenotype 3 in SICdb) is consistent with the higher baseline fibrinogen of post-operative patients, which shifts the centroid-based boundaries.

Subphenotypes were strongly associated with mortality in SICdb (Fig. 4): 28-day mortality was 16.9%, 35.0%, and 34.1% for Phenotypes 1–3 (log-rank P = 2.9 × 10⁻⁶); 90-day mortality was 22.6%, 48.3%, and 43.9% (P = 2.5 × 10⁻⁹). After full adjustment, Phenotype 2 carried a two-fold hazard of 28-day death (HR 2.01, 95% CI 1.34–2.99; P < 0.001) and an even stronger 90-day association (HR 2.32, 1.65–3.27; P < 0.001); Phenotype 3 showed a comparable point estimate (28-day HR 1.55) that did not reach significance, reflecting the small number of patients and events in this stratum (n = 41; 14 deaths within 28 days) (Table 3, Fig. 5).

Table 3

Association between subphenotypes and mortality in the external validation cohort (SICdb, n = 622). Cox proportional hazards models with Phenotype 1 as the reference. Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: additionally adjusted for heart rate, peripheral oxygen saturation, temperature, white blood cell count, C-reactive protein, haemoglobin, and heparin exposure (penalised estimation). HR: hazard ratio; CI: confidence interval.

Outcome / Model	Phenotype 2 vs 1 HR (95% CI)	P	Phenotype 3 vs 1 HR (95% CI)	P
28-day mortality				
Model 1 (unadjusted)	2.25 (1.55–3.25)	< 0.001	2.37 (1.35–4.17)	0.003
Model 2 (+ age, sex)	2.35 (1.62–3.40)	< 0.001	2.36 (1.34–4.16)	0.003
Model 3 (+ severity, heparin)	2.01 (1.34–2.99)	< 0.001	1.55 (0.85–2.82)	0.15
90-day mortality				
Model 1 (unadjusted)	2.47 (1.79–3.39)	< 0.001	2.35 (1.43–3.86)	< 0.001
Model 2 (+ age, sex)	2.59 (1.88–3.56)	< 0.001	2.35 (1.43–3.86)	< 0.001
Model 3 (+ severity, heparin)	2.32 (1.65–3.27)	< 0.001	1.72 (1.02–2.90)	0.041

Subphenotypes versus the SIC score: complementary stratification

The SIC score was strongly related to the subphenotypes (Kruskal–Wallis $P < 0.001$): SIC positivity (score ≥ 4) was present in 8.5% of Phenotype 1, 26.3% of Phenotype 2, and 74.6% of Phenotype 3, while overall SIC-positive patients had higher 28-day mortality than SIC-negative patients (16.0% vs 8.2%). The subphenotypes nevertheless added structure within SIC strata. Among SIC-positive patients ($n = 1,649$), Phenotype 2 was associated with a 60% higher adjusted mortality hazard (HR 1.60, 95% CI 1.02–2.51; $P = 0.040$) and Phenotype 3 showed a similar trend (HR 1.34, 0.96–1.87; $P = 0.09$). Conversely, among SIC-negative patients ($n = 3,466$), no phenotype carried excess risk (Phenotype 2 HR 0.63, 0.40–0.99; Phenotype 3 HR 1.11, 0.77–1.59). Thus, isolated aPTT prolongation becomes prognostically meaningful only when combined with concurrent SIC-level thrombocytopenia, INR elevation, or organ dysfunction—a pattern unresolvable by the SIC score alone, which does not incorporate aPTT. As expected for a descriptive (not optimised) classifier, the C-statistic of the phenotypes alone for 28-day mortality (0.543) was below that of the SIC score (0.611) and SOFA (0.694); the value of subphenotyping lies in qualitative risk structure rather than incremental prediction.

Exploratory analysis of heparin treatment in SICdb

Heparin exposure was common (Phenotype 1, 90.2%; Phenotype 2, 86.7%; Phenotype 3, 73.2%) and confounded by indication, precluding causal inference. In an interaction model adjusted for age and sex, phenotype-by-heparin interaction terms suggested—without reaching significance—a directionally greater heparin association with lower mortality within Phenotype 2 (interaction HR 0.51, 95% CI 0.24–1.09; $P = 0.083$) and Phenotype 3 (HR 0.66, 0.22–1.99; $P = 0.46$), consistent with previous phenotype-specific anticoagulant analyses [14, 15]. These exploratory findings are hypothesis-generating only (Supplementary Table S2).

Sensitivity analyses

Forcing a two-cluster solution abolished the prognostic signal (adjusted HR 1.08, 95% CI 0.91–1.28; $P = 0.36$), confirming that the three-subphenotype resolution carries information that a binary coagulopathy/no-coagulopathy split destroys. Findings were unchanged in 90-day analyses and across all adjustment levels (Tables 2–3).

Discussion

In this multicentre cohort study spanning two national ICU databases, consensus clustering of four routinely measured coagulation variables identified three reproducible subphenotypes of sepsis-associated coagulopathy: coagulation-preserved (57%), isolated aPTT prolongation (10%), and pan-coagulopathy (33%). The pan-coagulopathy subphenotype carried a consistent, severity-independent excess mortality in both cohorts. The most striking finding, however, was the context-dependent behaviour of the isolated aPTT prolongation subphenotype: prognostically neutral in the US medical ICU derivation cohort but associated with a two-fold adjusted mortality hazard in the Austrian surgical ICU validation cohort, and prognostically informative specifically among patients already meeting SIC criteria.

Our pan-coagulopathy subphenotype aligns closely with the severe-coagulopathy clusters reported by Kudo and colleagues (cluster dA, defined by high fibrin/fibrinogen degradation products and D-dimer with severe organ dysfunction) [14] and by Cai and colleagues (Class 2, characterised by prolonged PT/INR, multiple organ failure, and high lactate) [15]. The convergence of three different clustering methods (k-means, latent class analysis, and our consensus clustering), different variable sets, and different populations on a “global consumptive” phenotype provides strong evidence that this entity is a robust feature of sepsis coagulopathy across healthcare systems. Our contribution is to show that this phenotype can be captured with the minimal, universally available panel of INR, aPTT, fibrinogen, and platelets—no specialised assays required—and that its excess mortality (adjusted HR 1.25) persists after stringent adjustment for non-haemostatic illness severity.

The isolated aPTT prolongation subphenotype deserves particular attention. Isolated prolongation of aPTT with near-normal INR reflects derangement confined to the intrinsic (contact) pathway—a pattern observed with heparin contamination, lupus anticoagulants, factor XII deficiency, or early consumptive states. In the derivation cohort, this pattern was fully benign after adjustment, consistent with the notion that isolated aPTT prolongation in a predominantly medical ICU population frequently reflects transient or spurious causes. In SICdb, however, the same laboratory pattern carried a two-fold mortality hazard. Several non-exclusive explanations merit consideration. First, the surgical ICU setting (post-operative acute-phase state with baseline fibrinogen of 483 mg/dL) may render intrinsic-pathway prolongation a marker of more advanced consumptive coagulopathy: relative to the abundant fibrinogen of post-operative patients, the Phenotype 2 fibrinogen of 354 mg/dL represents a substantial relative deficit that the absolute value understates. Second, distribution shift between databases may alter centroid-assignment boundaries, although standardisation within the SICdb space mitigates this. Third, differences in aetiology, timing of sampling, and concurrent therapies may modify the meaning of aPTT prolongation. Regardless of mechanism, our results demonstrate—for the first time, to our knowledge—that the prognostic significance of a coagulopathy subphenotype is care-context-dependent, a caution of direct relevance to the design of multinational trials that assume phenotypes portend identical risk across settings.

The complementarity between subphenotypes and the SIC score carries practical implications. The SIC score omits aPTT and fibrinogen entirely; our analysis shows that among SIC-positive patients, the 31% who belong to Phenotype 2 face 60% higher adjusted mortality, while among SIC-negative patients the subphenotypes are inert. In pragmatic terms, a bedside clinician confronting a SIC-positive patient can use the four-variable pattern (rather than the scalar score) to grade risk: pan-coagulopathy and SIC-positive isolated aPTT prolongation identify the highest-risk configurations. Whether these configurations also identify patients most likely to benefit from anticoagulation remains unresolved. The negative phase III trials of broad-population anticoagulation in sepsis-associated coagulopathy [7–9], together with phenotype-specific post hoc analyses suggesting benefit confined to severe-coagulopathy subgroups [14, 15] and the directionally supportive heparin interaction in our validation cohort, collectively motivate phenotype-enriched rather than unselected trial designs. Our finding that Phenotype 3 comprises 74.6% of SIC-positive patients makes SIC positivity enriched for pan-coagulopathy—a

natural enrichment strategy already implicitly in place—whereas Phenotype 2, representing a quarter of SIC-positive patients, is currently invisible to trial eligibility criteria.

This study has several strengths. It is, to our knowledge, the first application of consensus clustering—the reference resampling-based class-discovery framework in oncology [16, 17]—to sepsis coagulopathy, providing explicit stability metrics (PAC, silhouette) rather than a single point solution. The two-cohort, two-country design with assignment rules fixed in the derivation cohort constitutes genuine external validation, not internal replication. Meticulous data harmonisation (placeholder-value exclusion in MIMIC-IV, Quick%-versus-INR reconciliation in SICdb) and the deliberate exclusion of the SOFA haemostasis subcomponent from adjustment models guard against artifactual or overadjusted estimates. We also transparently report the unstable and context-dependent results (Phenotype 2 heterogeneity, moderate PAC values), which we regard as findings of interest rather than nuisances.

Several limitations must be acknowledged. First, the observational design precludes causal inference, and the heparin analysis is subject to confounding by indication despite covariate adjustment. Second, requiring complete coagulation panels introduces selection bias: patients without coagulation testing may differ systematically from those tested, and the derivation cohort thus represents septic patients in whom clinicians measured coagulation—typically the more severely ill. Third, D-dimer, fibrin degradation products, antithrombin, and thrombin time were unavailable in both databases, so we could not capture the fibrinolytic and inhibitory dimensions that proved decisive in the Japanese phenotype analyses [14]; the derived phenotypes therefore reflect the “routinely measurable” coagulopathy space. Fourth, the validation cohort yielded only 41 Phenotype 3 patients, limiting precision (the 28-day point estimate of HR 1.55 was not statistically significant despite 90-day confirmation), and the penalised Cox models in SICdb trade some bias for stability. Fifth, phenotypes were defined at a single baseline time point; coagulopathy is dynamic, and trajectory-informed phenotyping may further improve resolution. Sixth, both databases are single-centre in origin (MIMIC-IV from one Boston hospital, SICdb from one Salzburg ICU), so “multicentre” here refers to the combination of two centres across two countries; generalisability to other settings requires further validation. Finally, cluster stability in this clinical dataset was moderate (PAC $\approx$ 0.56), a common occurrence when clustering correlated clinical laboratory variables, and underscores the need for the resampling-based transparency that consensus clustering provides.

Conclusions

Consensus clustering of four routine coagulation tests identified three biologically interpretable subphenotypes of sepsis-associated coagulopathy that were reproducible across two national ICU databases. Pan-coagulopathy—affecting one third of septic patients—conferred a consistent, severity-independent excess mortality and represents a natural candidate phenotype for enrichment in future anticoagulant trials. Isolated aPTT prolongation identified a high-risk subgroup only in the surgical ICU setting and among SIC-positive patients, demonstrating that the prognostic meaning of a coagulopathy pattern is context-dependent. Bedside integration of the four-variable coagulation profile with the SIC score offers a simple, cost-free refinement of risk stratification in septic coagulopathy.

Declarations

Ethics approval and consent to participate

Both MIMIC-IV and SICdb contain de-identified health records released under formal data use agreements; the original data collections were approved by the institutional review boards of Beth Israel Deaconess Medical Center and the University Hospital Salzburg, respectively, with waivers of informed consent. This secondary analysis of de-identified, publicly available data required no additional ethical approval.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Y.S.S., Q.Q.F. and H.B. performed the data curation and investigation. Y.S.S. carried out formal analysis, methodology and visualization and wrote the original manuscript. N.T. conceived the study, supervised the whole project and validated the analytical results. All authors reviewed and edited the manuscript and approved the final version of the article.

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Data Availability

MIMIC-IV (<https://physionet.org/content/mimiciv/2.2/>) and SICdb (<https://springernature.figshare.com>) are publicly available upon execution of data use agreements. Analysis code is available from the corresponding author on reasonable request.

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Figures

Study flow diagram

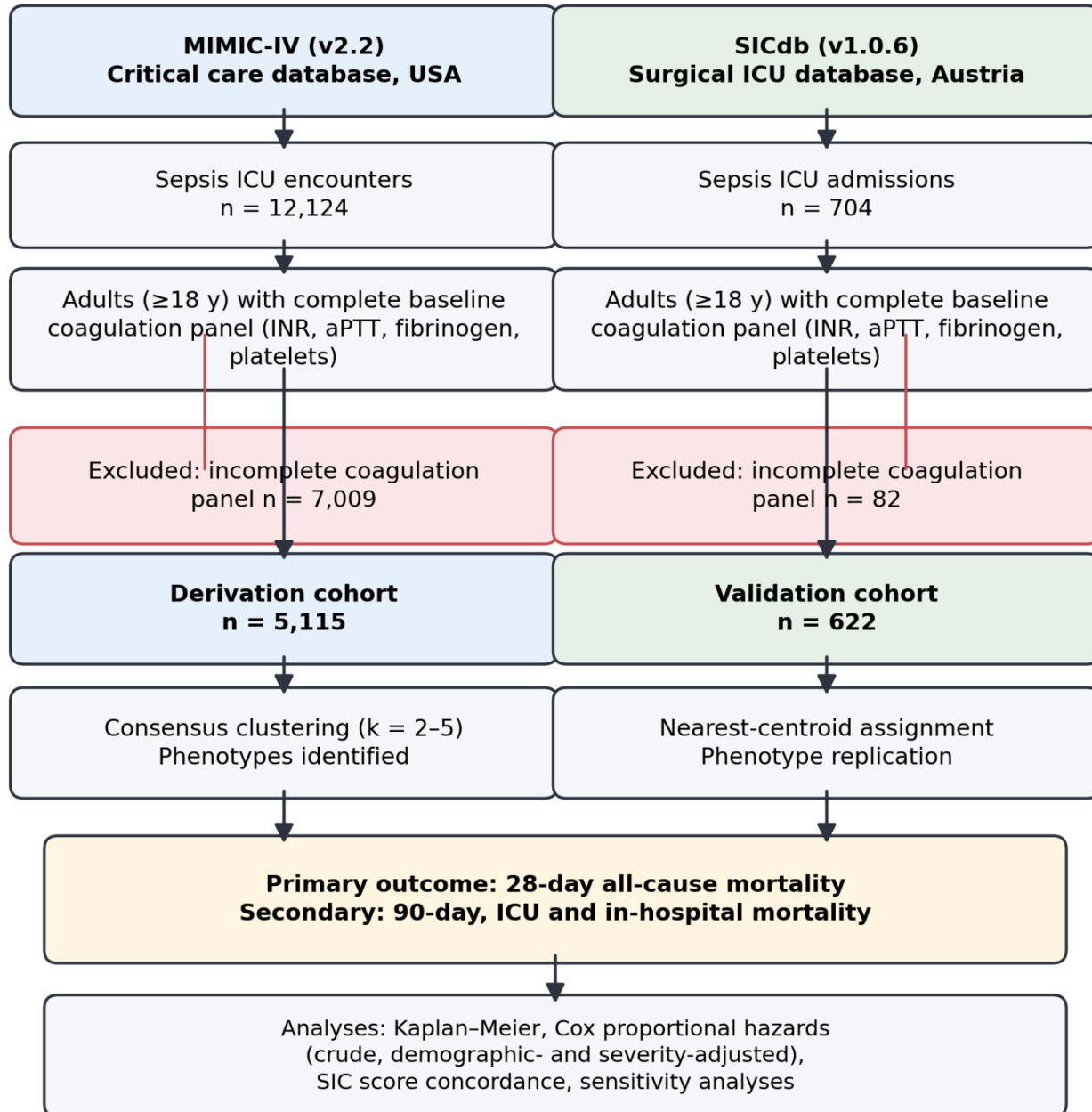


Figure 1

Study flow diagram. Adult septic ICU encounters from MIMIC-IV (v2.2, USA) and SICdb (v1.0.6, Austria) were screened for a complete baseline coagulation panel (INR, aPTT, fibrinogen, platelet count). MIMIC-IV served as the derivation cohort for consensus clustering and SICdb as the external validation cohort for nearest-centroid phenotype assignment.

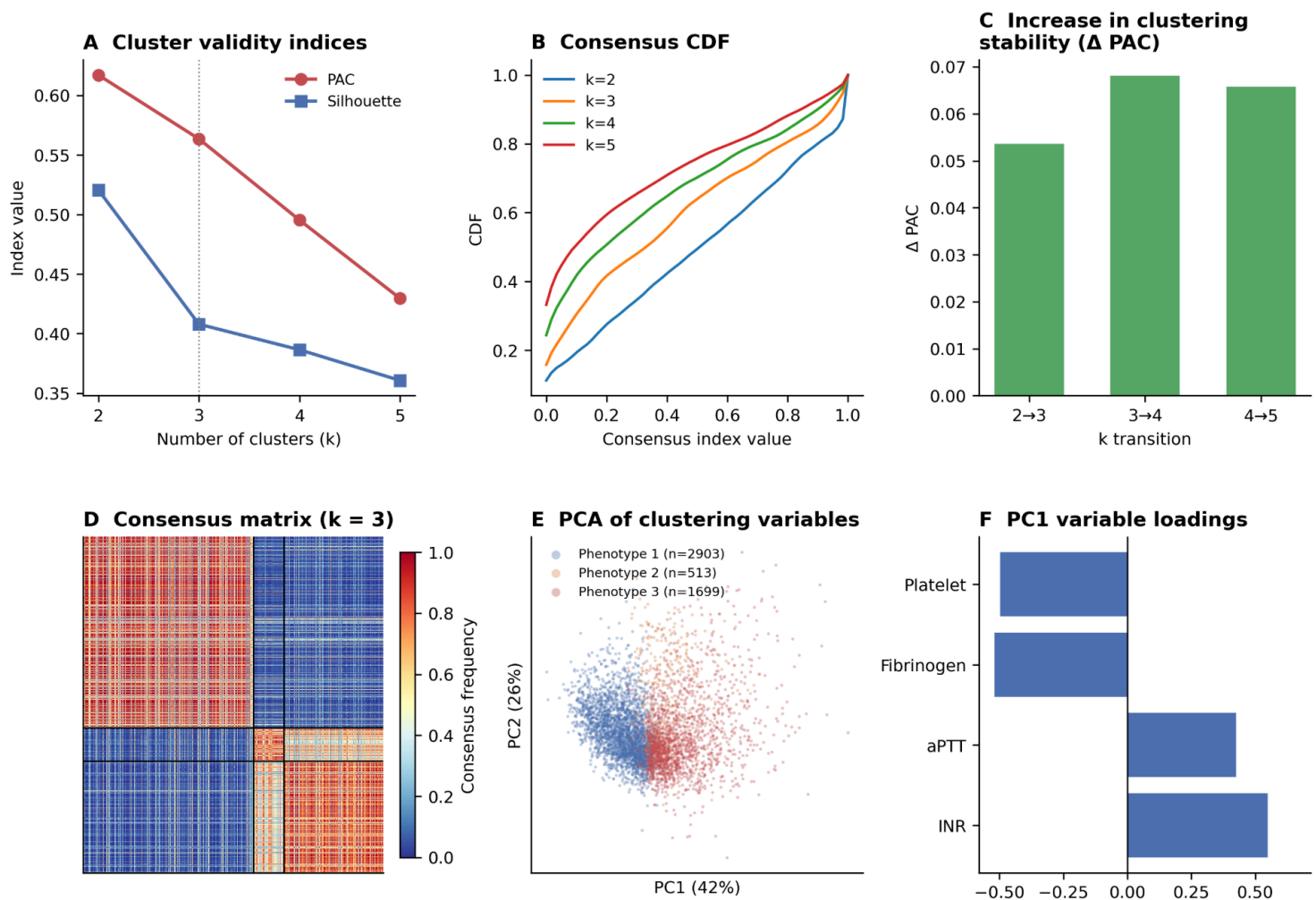


Figure 2

Consensus clustering diagnostics. (A) Cluster validity indices across candidate cluster numbers $k = 2-5$: proportion of ambiguous clustering (PAC, lower is better) and average silhouette width (higher is better). (B) Empirical cumulative distribution of consensus index values for each k . (C) Increase in clustering stability (Δ PAC) across k transitions. (D) Consensus matrix heat map for the selected $k = 3$, revealing three coherent blocks with a distinct intermediate-risk subpopulation. (E) Cluster sizes across k , demonstrating stability of the isolated-aPTT cluster ($n = 513$) from $k = 3$ onwards.

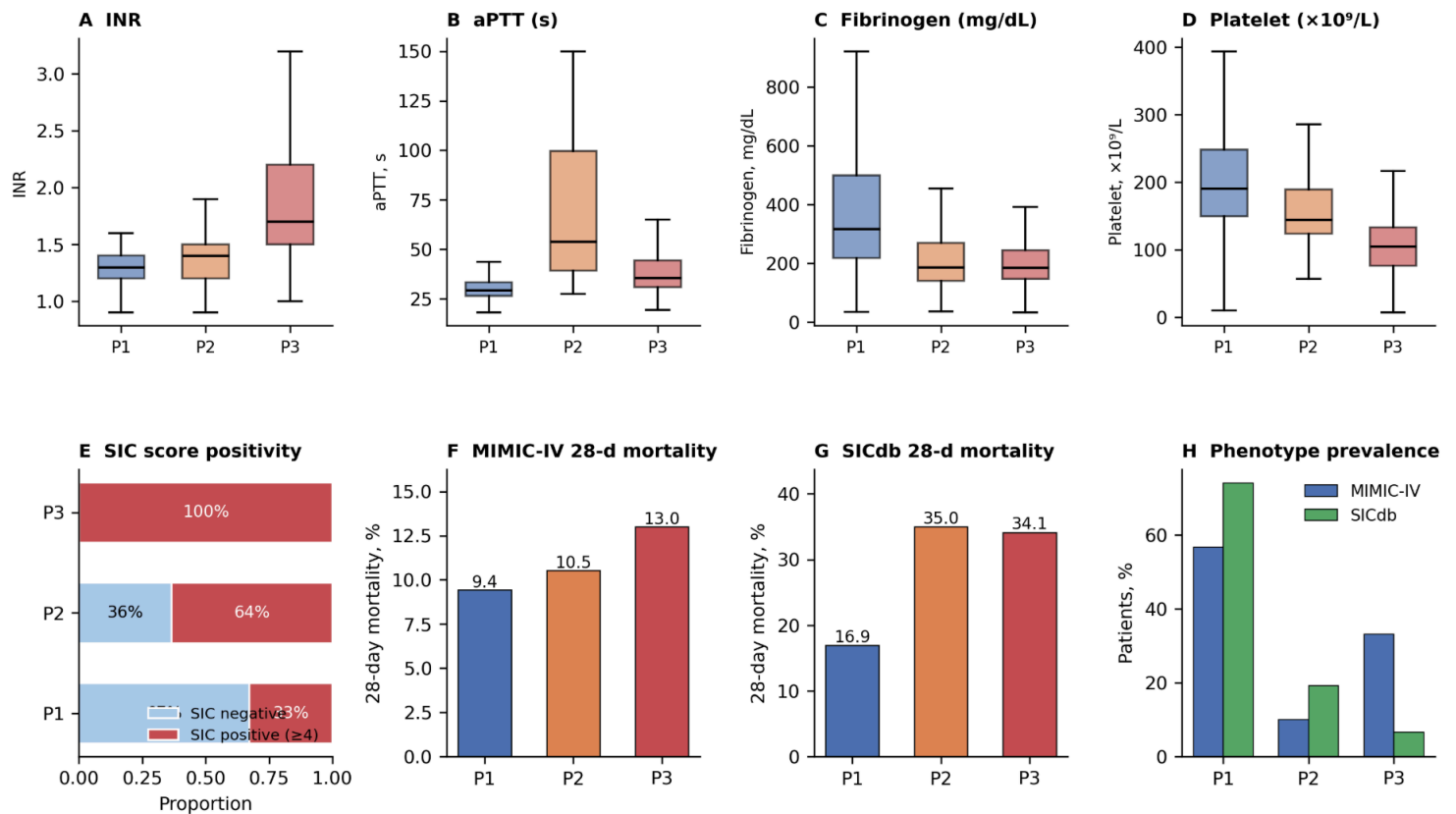


Figure 3

Coagulation profiles of the three subphenotypes. (A) Standardised (z-score) profiles of the four index variables by phenotype in the derivation cohort, illustrating the qualitatively distinct patterns of haemostatic derangement. (B) Corresponding profiles in the external validation cohort. (C) Distribution of the sepsis-induced coagulopathy (SIC) score by phenotype. (D) Two-dimensional projection (t-SNE) of the standardised coagulation variables, showing partial separation of the three subphenotypes.

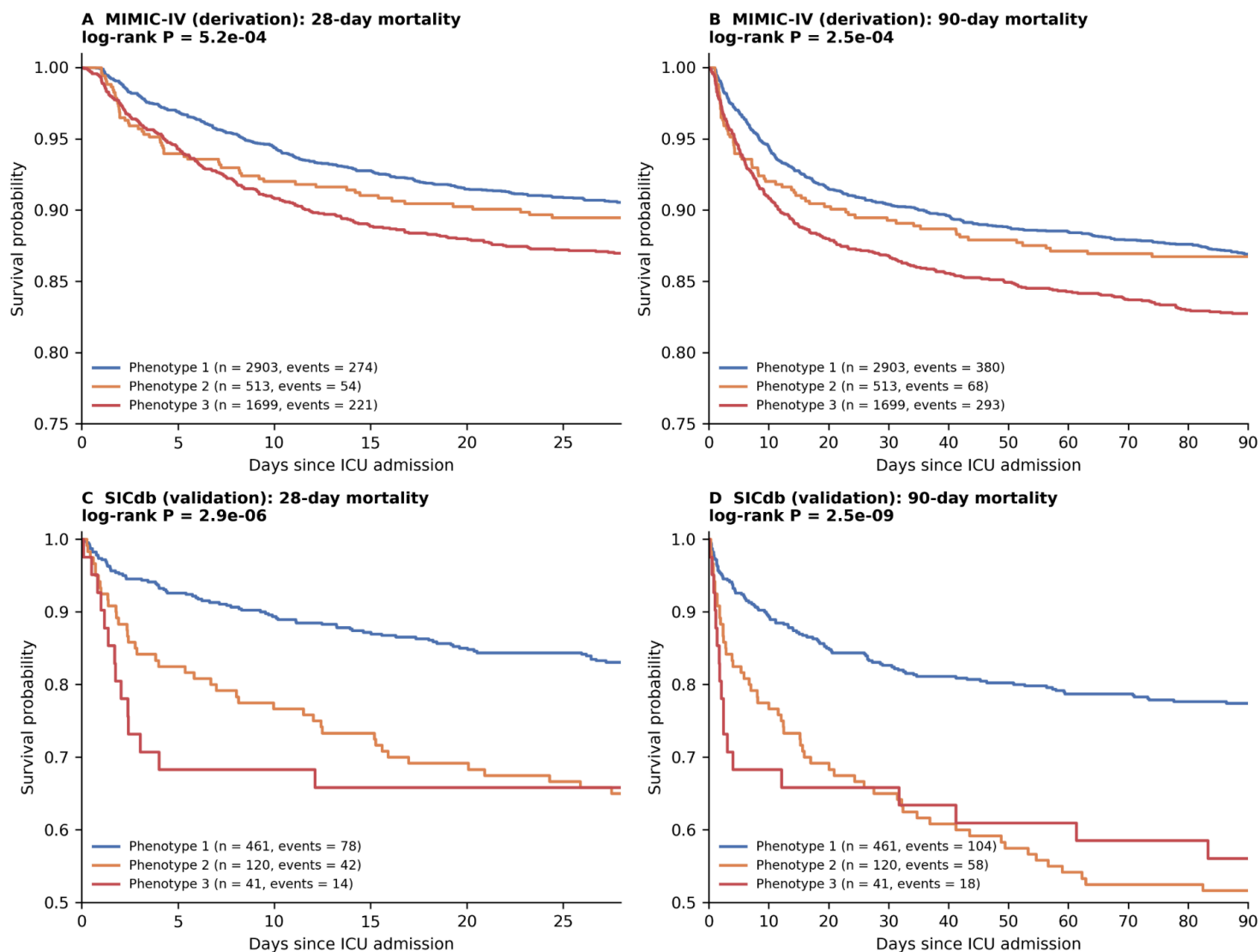


Figure 4

Kaplan–Meier survival estimates by coagulopathy subphenotype. (A) Derivation cohort (MIMIC-IV): 28-day all-cause mortality. (B) Derivation cohort: 90-day mortality. (C) External validation cohort (SICdb): 28-day mortality. (D) Validation cohort: 90-day mortality. P values from log-rank tests. In SICdb, both Phenotypes 2 and 3 show markedly worse survival than Phenotype 1, whereas in MIMIC-IV only Phenotype 3 separates from the reference.

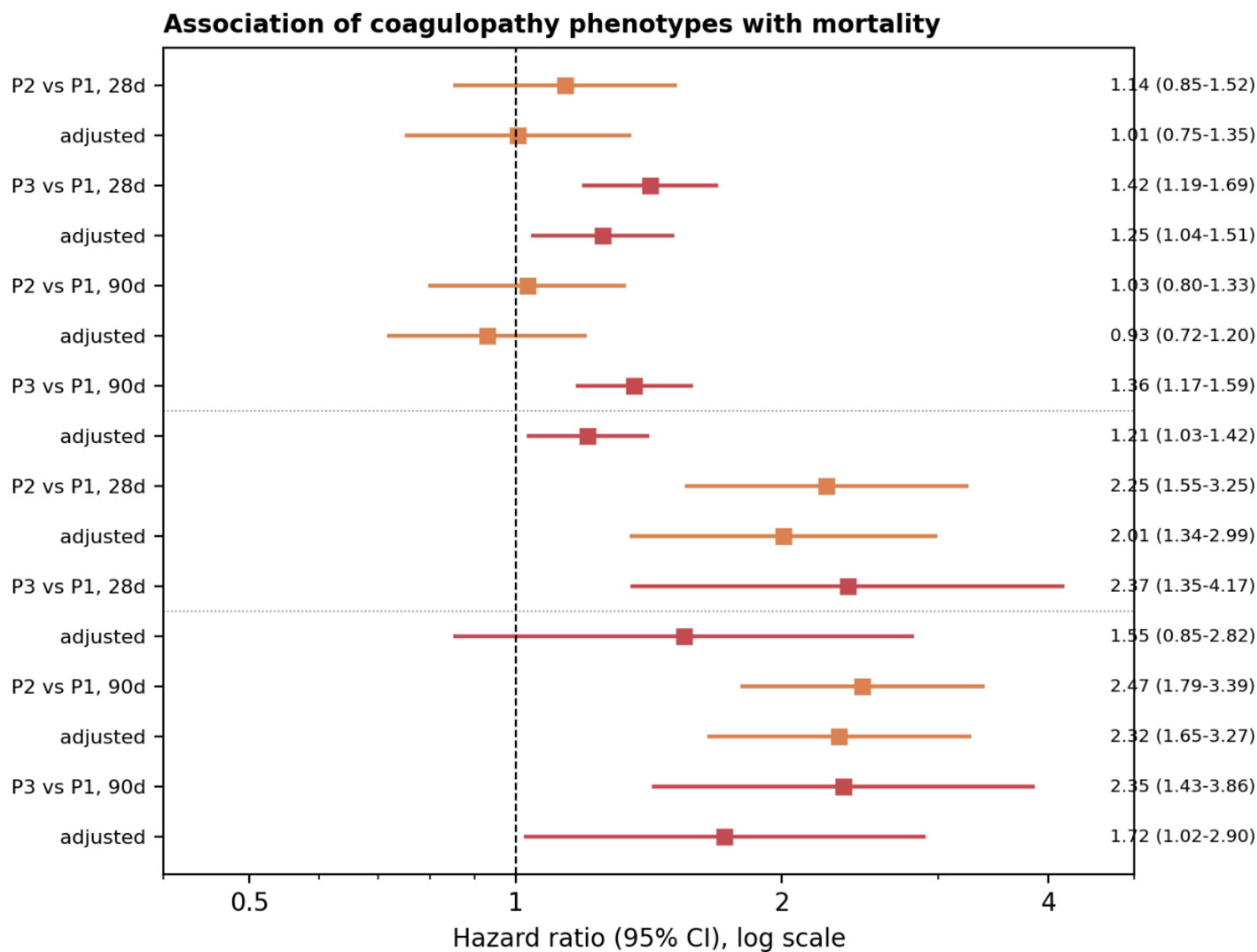


Figure 5

Forest plot of subphenotype–mortality associations across cohorts, outcomes, and adjustment levels. Squares denote hazard ratios; horizontal lines denote 95% confidence intervals; the vertical dashed line marks the null (HR = 1). Note the qualitative heterogeneity of Phenotype 2 (isolated aPTT prolongation) between the derivation cohort (neutral) and the external validation cohort (two-fold excess risk), in contrast to the consistent excess risk of Phenotype 3 (pan-coagulopathy).