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International Normalized Ratio as an Effect Modifier of the Heparin-Mortality Association in Sepsis: A Retrospective Cohort Study

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Abstract

Heparin is widely used in sepsis, but whether baseline coagulation status modifies its association with mortality is unknown. In 38,431 septic ICU patients from MIMIC-IV, we modeled the international normalized ratio (INR) as a continuous effect modifier of the heparin-mortality association using restricted cubic splines in Cox models, with inverse probability of treatment weighting, propensity score matching, and competing-risk models for robustness, and negative-control exposures to assess severity confounding. INR significantly modified the heparin-mortality association ($p<0.001$), with a crossover from harm to benefit at INR ≈ 2.8: associations were adverse at INR ≤ 2.4 (adjusted absolute risk increase ≈ 5.7%) and favorable at INR ≥ 3.4 (absolute risk reduction ≈ 5.0%). Negative-control exposures without antithrombotic mechanisms showed INR-dependent interactions (renal replacement therapy: $p=0.035$; corticosteroids: $p=0.078$), formally demonstrating severity-of-illness confounding, and therapeutic heparin was almost never administered to high-INR patients in external cohorts. Observational data therefore cannot resolve whether heparin benefits or harms coagulopathic patients with sepsis. We propose a three-tier INR-based prognostic enrichment hypothesis as a design blueprint for an INR-enriched randomized trial rather than for clinical decisions.

Introduction

Heparin is the most widely used anticoagulant in intensive care, primarily for venous thromboembolism prophylaxis. In sepsis, the rationale extends further: heparin has anti-inflammatory properties [1], inhibits thrombin-mediated endothelial activation, and may attenuate the microvascular thrombosis driving organ dysfunction [2–4]. Yet evidence for a survival benefit is inconsistent: meta-analyses of randomized trials suggest only a small, population-undefined mortality reduction with therapeutic-dose heparin [5–7]. Patients with normal coagulation may experience net harm (predominantly bleeding), whereas those with sepsis-induced coagulopathy—consumptive depletion of platelets and clotting factors with elevated INR—may benefit from interrupting the thrombo-inflammatory cycle.

Previous studies have suggested interactions between coagulation parameters and heparin outcomes [8], but none has characterized how the heparin-mortality association varies continuously across the INR spectrum. Crucially, this question may be unanswerable with observational data: clinicians are reluctant to anticoagulate patients with elevated INR, creating channeling bias and sparse exposure precisely where benefit might exist. We therefore had dual aims: (i) to characterize INR as a continuous effect modifier of the heparin-mortality association; and (ii) to formally assess whether observational data can answer this question, via negative controls and quantification of real-world exposure.

Results

Cohort Characteristics

The cohort comprised 38,431 septic ICU stays, with 6,572 (17.1%) 28-day deaths; 15,890 patients (41.3%) received heparin and 22,541 (58.7%) did not; 7,685 (20.0%) had consumptive coagulopathy. Baseline characteristics are in Table 1: heparin-exposed patients had higher platelet counts, lower INR, and less consumptive coagulopathy (largest SMD, platelet count 0.325), and nine variables showed SMD > 0.1, justifying propensity adjustment.

Table 1
Baseline characteristics of the MIMIC-IV sepsis cohort by heparin exposure

Variable	Overall (N = 38,431)	No heparin (n = 22,541)	Heparin (n = 15,890)	SMD
Age, years	68.0 [57.0–78.0]	67.0 [57.0–78.0]	68.0 [56.0–79.0]	0.021
Male sex	22,440 (58.4)	13,453 (59.7)	8,987 (56.6)	0.063
SOFA (excl. coagulation)	5.0 [3.0–7.0]	5.0 [3.0–7.0]	5.0 [3.0–8.0]	0.049
Platelet count, ×10⁹/L	161.0 [107.0–231.0]	147.0 [97.0–214.0]	181.0 [125.0–251.0]	0.325
INR	1.4 [1.2–1.7]	1.4 [1.2–1.8]	1.3 [1.2–1.6]	0.183
Consumptive coagulopathy	7,685 (20.0)	5,428 (24.1)	2,257 (14.2)	0.253
Creatinine, mg/dL	1.2 [0.9–2.1]	1.2 [0.8–2.0]	1.3 [0.9–2.2]	0.054
Total bilirubin, mg/dL[a]	0.8 [0.4–1.8]	0.8 [0.5–2.1]	0.7 [0.4–1.5]	0.209
Lactate, mmol/L[a]	2.3 [1.5–3.8]	2.4 [1.6–4.0]	2.1 [1.4–3.7]	0.148
Hemoglobin nadir, g/dL	9.4 [8.0–11.0]	9.1 [7.7–10.8]	9.8 [8.3–11.4]	0.273
Diabetes	12,776 (33.2)	7,238 (32.1)	5,538 (34.9)	0.058
Cirrhosis	6,846 (17.8)	4,400 (19.5)	2,446 (15.4)	0.109
Active cancer	6,036 (15.7)	3,575 (15.9)	2,461 (15.5)	0.010
Chronic kidney disease	10,353 (26.9)	5,875 (26.1)	4,478 (28.2)	0.048
Mechanical ventilation	23,272 (60.6)	13,270 (58.9)	10,002 (62.9)	0.084
Vasopressor use	18,418 (47.9)	10,259 (45.5)	8,159 (51.3)	0.117
Renal replacement therapy	2,908 (7.6)	1,685 (7.5)	1,223 (7.7)	0.008
FFP transfusion	3,739 (9.7)	2,523 (11.2)	1,216 (7.7)	0.121
28-day mortality	6,572 (17.1)	3,974 (17.6)	2,598 (16.3)	0.034
Major bleeding (ICD)	11,820 (30.8)	8,029 (35.6)	3,791 (23.9)	0.259

Continuous variables are median [IQR]; categorical variables are n (%). Heparin = any heparin (therapeutic IV or prophylactic) during the ICU stay. SMD = standardized mean difference (heparin vs no heparin); nine variables exceeded SMD > 0.1 (platelet count, INR, consumptive coagulopathy, total bilirubin, lactate, hemoglobin nadir, cirrhosis, vasopressor use, FFP transfusion). [a]Total bilirubin missing in 34.0% and lactate in 27.0%; medians shown are from available data (see Methods for missing data handling).

INR as Continuous Effect Modifier of the Heparin-Mortality Association

In the primary restricted cubic spline (RCS) model (5 knots, 4 df), INR significantly modified the heparin-mortality association (likelihood ratio test [LRT] χ^2=64.31, df = 4, p < 0.001). The heparin HR decreased monotonically with increasing INR (Fig. 1): at INR 1.0 the adjusted HR was 1.57 (1.20–2.06, p = 0.001), declining to 1.09 (0.99–1.19) at INR 2.5, crossing 1.0 at INR ≈ 2.8, and reaching 0.66 (0.55–0.80, p < 0.001) at INR 5.0. The association was significantly adverse (CI lower bound > 1.0) for INR 0.9–2.45, neutral for INR 2.5–3.3, and significantly favorable (CI upper bound < 1.0) for INR 3.35–5.0. The crossover was stable across spline specifications (2-df spline ≈ 2.85; 3-df ≈ 2.80; 4-df ≈ 2.78), consistent with a transition zone rather than a precise threshold.

INR versus Platelet Count: Relative Contribution

With INR and platelet count entered as mutually adjusted 4-knot RCS interaction terms, INR remained a highly significant modifier (LRT χ^2=59.79, df = 4, p < 0.001), while platelet count independently but more weakly modified the effect (LRT χ^2=11.03, p = 0.027). The ≈ 5.4-fold ratio of LRT statistics establishes INR as the dominant contributor, with platelet count playing a secondary role.

Binary Interaction Confirmation

The binary analysis confirmed the pattern (Table 2, Fig. 2): interaction HR 0.736 (0.639–0.848, p < 0.001) in the multivariable Cox model, with IPTW, propensity score matching, Fine–Gray, complete-case, and MICE analyses all directionally consistent (Table 2; Supplement S1, S2). Heparin was associated with higher adjusted hazard in non-coagulopathic patients (HR = 1.41 [1.31–1.52], p < 0.001) but neutral in consumptive patients (median INR 2.0, IQR 1.7–2.7; HR = 1.03 [0.91–1.16], p = 0.67)—averaging across the adverse, transition, and favorable zones (Fig. 1). Kaplan-Meier curves confirmed the favorable association at INR > 2.7 (log-rank p < 0.001).

Table 2
Heparin × consumptive coagulopathy interaction across analytical approaches (MIMIC-IV)

Analysis	N	Interaction HR (95% CI)	p value
Multivariable Cox regression (primary)	38,431	0.736 (0.639–0.848)	< 0.001
Inverse probability of treatment weighting	18,584	0.670 (0.572–0.786)	< 0.001
Propensity score matching	6,754	0.806 (0.657–0.988)	0.038
Fine–Gray subdistribution hazard model	38,431	0.695 (0.603–0.802)	< 0.001
Cause-specific hazard model	38,431	0.695 (0.604–0.800)	< 0.001
Complete-case analysis	18,584	0.743 (0.634–0.870)	< 0.001
Multiple imputation (MICE, 20 imputations)	38,431	0.736 (0.639–0.848)	< 0.001

Interaction HR = hazard ratio for the heparin × consumptive coagulopathy interaction term. N for propensity score matching = matched sample size; IPTW restricted to complete cases. The Fine–Gray and cause-specific models treat bleeding without death as a competing event (Supplement S1); multiple imputation details in Supplement S2.

Absolute Risk and Illustrative Sample-Size Anchors

All ARDs are IPTW-standardized (ATT) unless specified as crude (Table 3): +5.7% at INR ≤ 2.4 (crude + 8.4%), + 0.6% in the neutral zone, and − 5.0% at INR ≥ 3.4 (95% CI − 9.8% to + 0.4%; crude − 5.1 percentage points, p = 0.06)—an illustrative sample-size anchor, not a clinical risk-benefit estimate (see Methods).

Table 3
Crude and IPTW-standardized 28-day mortality and absolute risk difference by INR stratum (MIMIC-IV)

INR stratum	Crude mortality, no heparin	Crude mortality, heparin	IPTW ARD (95% CI)*
≤ 2.4 (adverse zone)	13.6%	22.1%	+ 5.7% (+ 4.5% to + 6.9%)
2.5–3.3 (neutral zone)	32.2%	33.5%	+ 0.6% (− 5.4% to + 6.6%)
≥ 3.4 (favorable zone)	36.8%	31.7%	−5.0% (− 9.8% to + 0.4%)

*ARD = IPTW-standardized (ATT) absolute 28-day mortality risk difference (heparin minus no heparin); negative favors heparin; 95% CIs from 200-replicate bootstrap. Crude differences: +8.4% (≤ 2.4), + 1.3% (2.5–3.3), − 5.1% (≥ 3.4), computed from unrounded rates. Stratum definitions match the enrichment score (Supplement S7).

Treatment Dimension

The interaction pattern was consistent across dose categories (Fig. 3a): therapeutic IV heparin (N = 5,500) interaction HR 0.736 ($p < 0.001$), any anticoagulant 0.741 ($p < 0.001$), prophylactic-only 0.816 ($p = 0.008$), IV low dose (< 800 U/h) 0.749 ($p = 0.061$), and IV high dose (≥ 800 U/h) 0.803 ($p = 0.020$)—consistently < 1.0 regardless of dose or route, indicating a more favorable heparin association in consumptive coagulopathy across anticoagulant types.

Safety and Net Clinical Benefit

Crude bleeding rates with therapeutic IV heparin were lower than with no anticoagulation in both strata (Table 4; non-coagulopathic: 29.0% vs 31.8%, $\chi^2=15.14$, $p < 0.001$; consumptive: 43.5% vs 46.4%, $\chi^2=3.30$, $p = 0.069$)—most likely treatment selection, since heparin cannot plausibly reduce bleeding; these unadjusted comparisons are not causal.

Table 4
Crude major bleeding and blood product transfusion by anticoagulant exposure and coagulation status (MIMIC-IV)

Exposure	Bleeding, % (non-coag)	PRBC, % (non-coag)	FFP, % (non-coag)	Bleeding, % (consumptive)	PRBC, % (consumptive)	FFP, % (consumptive)
No anticoagulation	31.8	24.3	5.2	46.4	43.3	29.1
Prophylactic only	19.1	23.2	3.7	30.8	47.5	29.9
Therapeutic IV heparin	29.0	37.9	5.8	43.5	56.7	28.7

All values are crude (unadjusted) percentages. “No anticoagulation” = no heparin of any type (prophylactic or therapeutic) during the ICU stay. PRBC = packed red blood cell transfusion; FFP = fresh frozen plasma transfusion; non-coag = non-coagulopathic stratum; consumptive = consumptive coagulopathy stratum. Major bleeding was identified by ICD-9/10 codes for gastrointestinal, intracranial, or other major hemorrhage.

Exploratory mediation did not support bleeding as a mediator (proportion − 0.1%; Supplement S5; not causally interpretable). For net clinical benefit (death or major bleeding, Fig. 3b), the IV heparin interaction was consistent (HR_int = 0.855 [0.774–0.945], $p = 0.002$): higher hazard in non-coagulopathic patients (HR = 1.19 [1.13–1.25], $p < 0.001$), neutral in consumptive patients (HR = 0.98 [0.90–1.07], $p = 0.74$).

Robustness Analyses

E-value: 2.05 (point estimate) and 2.50 (CI boundary; Supplement S3): an unmeasured confounder associated with heparin receipt and mortality (risk ratio ≥ 2.05) could explain the interaction.

IPTW balance

all 13 propensity-model covariates achieved SMD < 0.1 after weighting (nine exceeded SMD > 0.1 before weighting; largest, vasopressor use 0.472).

Additive interaction

RERI = − 0.445 (bootstrap 95% CI − 0.645 to − 0.233)—sub-additive, i.e., predominantly multiplicative.

RCS knot sensitivity

crossover ≈ 2.78–2.85 across spline df (2–4) (see above)—a transition zone, not a precise cutoff.

External calibration

the MIMIC-IV-trained Cox model showed poor external discrimination (C-index 0.476–0.550; Supplement S4), reflecting cross-database risk differences; the goal is enrichment derivation, not absolute risk prediction.

Negative control exposures (Supplement S8)

None reproduced heparin's qualitative crossover (harm at low INR → benefit at high INR); for every negative control, stratum-specific HRs pointed in the same direction in both coagulation strata. However, renal replacement therapy (RRT) exhibited a significant quantitative INR-dependent interaction (LRT p = 0.035), corticosteroids a borderline one (LRT p = 0.078), and vasopressors none (LRT p = 0.254)—formal empirical evidence that severity-of-illness confounding is present in these data (see Discussion).

Exploratory Landmark Analysis: Day 4 INR Trajectory

In the exploratory Day-4 landmark analysis (N = 2,807 with baseline INR ≥ 2.7 and available Day-4 INR, excluding 39 who died or were censored before Day 4; Supplement S9), heparin was neutral among persistently coagulopathic patients (Day-4 INR ≥ 2.0, N = 1,419; HR = 0.97, 0.71–1.33, p = 0.86) and showed a non-significant adverse trend after INR normalization (N = 1,388; HR = 1.27, 0.95–1.70, p = 0.10); the trajectory×heparin interaction was not significant (LRT χ^2=1.79, p = 0.18). This analysis is limited by survivorship and collider stratification bias (Day-4 INR is influenced by Days 1–4 heparin) and modest power (165 heparin recipients in the persistent stratum); hypothesis-generating only.

Derivation of the Prognostic Enrichment Hypothesis

We derived a three-tier prognostic enrichment hypothesis mapping INR—a single routine laboratory value—to trial design categories (Supplement S7), from the RCS hazard ratios, significance zones, and IPTW-

adjusted ARDs. Favorable-zone (INR ≥ 3.4) ARDs have CIs including zero; they are illustrative anchors, not validated clinical decision tools.

Hypothetical Trial Design Projection

Because 88.2% of the cohort had INR ≤ 2.4—where heparin was associated with harm—the all-comers design yielded a net adverse association (weighted ARD − 4.9% [95% CI − 6.1% to − 3.8%]; benefit-positive convention, Supplement S10) and would be futile (**Supplement S10**; see Methods for caveats). Restricting enrollment to INR ≥ 2.7 reversed this to + 3.2% ARD (95% CI − 1.1% to + 7.4%), requiring 3,469 per arm for 80% power; a Score = 2 (INR ≥ 3.4) design gave + 4.3% ARD (95% CI − 1.1% to + 9.7%), requiring 1,905 per arm (70% power at 1,500 per arm). INR-guided enrichment thus converts a futile, harm-signaling all-comers trial into a potentially adequately powered trial enrolling only ≈ 6–10% of screened sepsis patients.

Exploratory External Assessment in MIMIC-III and eICU

The enrichment score was applied unmodified to MIMIC-III and eICU (full results in Supplement S6). Both cohorts had extremely sparse heparin exposure in high-INR strata (MIMIC-III Score 2: n = 5 exposed; eICU Score 1: n = 0; Score 2: n = 1) and were therefore underpowered, able neither to confirm nor refute the hypothesis. In MIMIC-III, the 3-level score×heparin interaction was not significant (p = 0.083), and stratum-specific ARDs (Score 0: −4.2% [95% CI − 10.9% to − 1.0%]; Score 2: +12.5% [− 40.3% to + 46.3%]) did not reproduce the MIMIC-IV gradient. eICU was non-evaluable because therapeutic heparin was essentially never administered to coagulopathic patients (0 exposed at INR 2.5–3.3; 1 at INR ≥ 3.4)—sparsity that itself reveals prevailing practice and strengthens the case for randomization (see Discussion).

Discussion

INR continuously modifies the heparin-mortality association in sepsis: significantly adverse at INR ≤ 2.4, favorable at INR ≥ 3.4, neutral between, with a crossover at ≈ 2.8 robust to spline specification (2.78–2.85) and consistent across IPTW, PSM, and competing-risk analyses. INR dominated platelet count as the driver of the interaction (LRT ratio ≈ 5.4).

The binary phenotype (PLT < 150 AND INR > 1.5) captures the interaction (HR_int = 0.736) but functions largely as a proxy for high INR (median 2.0 vs 1.3 in non-consumptive patients). Its INR > 1.5 cutoff is suboptimal: heparin remains significantly adversely associated up to INR 2.4 and significantly favorably associated only at INR ≥ 3.4. The “neutral” binary result (HR = 1.03) averages across adverse, transition, and favorable zones—within which the adjusted HR reaches 0.66 (0.55–0.80) at INR 5.0—and should not be read as absence of effect.

The most important finding may be what the negative controls reveal. RRT and corticosteroids—exposures with no plausible INR-dependent mechanism—showed significant (RRT: LRT p = 0.035) and borderline (corticosteroids: p = 0.078) quantitative INR-dependent mortality associations, formally

demonstrating that severity-of-illness confounding is present. They did not reproduce heparin's qualitative crossover, but their interactions show that unmeasured severity drives part of the effect modification. If such confounding exists in MIMIC-IV—among the most carefully curated critical care databases, despite extensive adjustment—further observational calibration and any meta-analysis of observational studies are unlikely to resolve the fundamental problem.

The external cohorts tell the same story: therapeutic heparin was almost never administered to high-INR patients (eICU: 0 exposed at INR 2.5–3.3), so observational data will always be sparse exactly where benefit is hypothesized. Any observed "benefit" would be suspect (confounding by indication reversal); any "harm" could reflect channeling of the sickest patients to no-heparin care. Only a trial can break this impasse.

Several non-exclusive mechanisms may explain the association. First, confounding by indication and its reversal: therapeutic heparin may be given preferentially to sicker patients at low INR and to high-INR patients perceived at lower bleeding risk—producing spurious harm and benefit signals; IPTW/PSM balance only measured covariates, the E-value of 2.05 provides moderate protection, and the negative controls demonstrate such confounding is present. Second, interception of thrombo-inflammatory pathways: in sepsis-induced coagulopathy, heparin potentiates antithrombin III, interrupting the thrombin → inflammation → endothelial injury cycle [1, 4]—speculative, requiring prospective validation. Third, INR elevation also reflects endothelial dysfunction and hepatic synthetic impairment [9]; high-INR patients may carry greater heparin-responsive endothelial pathology. Bleeding did not mediate the interaction (proportion − 0.1%, Supplement S5; time-dependent bias).

Prophylactic-dose heparin showed favorable associations in both coagulopathic (HR = 0.61) and non-coagulopathic (HR = 0.74) patients, whereas therapeutic IV heparin was associated with higher hazard in non-coagulopathic patients (HR = 1.41) but neutral in consumptive patients (HR = 1.03). These conditional associations generate two trial-design hypotheses: (i) continued VTE prophylaxis regardless of INR; and (ii) therapeutic-dose heparin warrants testing specifically in the high-INR stratum, where the association was most favorable. These are testable hypotheses, not clinical recommendations.

This study adds three things to the field. First, the first continuous characterization of INR as an effect modifier of heparin in sepsis, revealing a gradient that binary subgroup analyses obscure. Second, quantification of INR's dominance over platelet count, suggesting INR alone may suffice for enrichment decisions. Third—and most importantly—formal empirical evidence, via negative controls, that severity confounding renders this question unanswerable with observational data, combined with real-world heparin exposure in the high-INR subgroup too sparse ever to resolve it. Collectively, a methodological argument for moving directly to a randomized trial, not merely a clinical hypothesis.

A pragmatic, INR-enriched randomized trial of therapeutic heparin in sepsis—with bleeding monitoring—is the logical next step. (i) **Enrichment**: enroll baseline INR ≥ 3.4 (Score = 2)—where the observed ARD ≈ 5.0% anchors sample size—as primary target; exclude INR ≤ 2.4 (adverse association); include INR 2.5–3.3 as exploratory. These are hypotheses, not validated criteria. (ii) **Continuous effect modification**:

model INR as a continuous modifier (RCS) in the primary analysis rather than a binary subgroup, which can mislabel the neutral mid-INR zone. (iii) **Stratified design**: stratify randomization by INR stratum (≤ 2.4 / 2.5–3.3 / ≥3.4), pre-specify dose-stratified analyses, with 28-day all-cause mortality as primary outcome. The three-tier score (Supplement S7) provides a ready-to-use framework.

The HEP-COVID randomized trial [10]—in high-D-dimer COVID-19 inpatients, a thrombo-inflammatory coagulopathy akin to sepsis-induced coagulopathy—demonstrated that therapeutic-dose heparin reduced thromboembolism and death in this subgroup. Post-hoc analyses of the SCARLET and KyberSept trials [11, 12] suggested selective benefit in sepsis-associated coagulopathy, though with different anticoagulant strategies. The ISTH SIC score uses both INR and platelet count [13], consistent with our finding that both independently modify the heparin effect; our data suggest INR alone captures most of the actionable signal, simplifying enrichment.

Strengths of this study include: (1) the continuous modifier approach (RCS) avoids arbitrary cutoffs and reveals the full gradient; (2) decomposition into INR and platelet contributions goes beyond a binary interaction; (3) six analytical methods (Cox, IPTW, PSM, Fine–Gray, additive interaction, RCS sensitivity) all confirm the interaction; (4) formal negative-control assessment—embraced as a key result—demonstrates that observational data cannot resolve this question; and (5) a ready-to-use three-tier enrichment framework.

Limitations: (1) Confounding by indication reversal cannot be excluded despite IPTW, PSM, and E-value analyses; the negative controls demonstrate residual severity confounding—no causal claims are made. (2) The crossover varies across spline specifications (2.78–2.85), a transition zone rather than a sharp threshold. (3) IV dose was approximated from mean infusion rate without weight adjustment; the low-dose subgroup (N = 747) was underpowered. (4) The external assessments were severely underpowered due to sparse exposure and do not constitute independent validation; we interpret the sparsity as revealing practice patterns. (5) A single baseline INR may not reflect coagulation status at heparin administration; trials should use repeated INR assessments. (6) Single-center derivation limits generalizability, and eICU sparsity suggests practice varies across centers. (7) The cohort is heterogeneous in infection source and severity; the interaction may differ by sepsis subtype. (8) The binary definition (PLT < 150 AND INR > 1.5) includes patients in the adverse range (INR 1.5–2.4), explaining the neutral subgroup association.

In summary, INR continuously modifies the heparin-mortality association in sepsis—adverse at INR ≤ 2.4, favorable at INR ≥ 3.4, crossover at ≈ 2.8—as conditional associations, not causal effects. Negative controls formally demonstrate severity-of-illness confounding (RRT: $p = 0.035$; corticosteroids: $p = 0.078$), and therapeutic heparin is almost never given to high-INR septic patients, so observational data will always be sparse where benefit is hypothesized. Traditional observational approaches—including any future meta-analysis—have therefore reached their limit. The three-tier enrichment hypothesis (enroll INR ≥ 3.4; exclude INR ≤ 2.4; include INR 2.5–3.3 as a secondary stratum; Supplement S7) provides a design blueprint for an INR-enriched randomized trial. Until such a trial is completed, prophylactic heparin should

continue per current VTE guidelines regardless of INR, therapeutic heparin use should remain guideline-directed, and these hypothesis-generating data should not alter current clinical practice.

Methods

Data Sources and Cohort Selection

This study used MIMIC-IV (v3.0) [14, 15], a publicly available ICU database from Beth Israel Deaconess Medical Center (2008–2022; 94,458 ICU stays), under PhysioNet credentialed access (data use agreement 1.5.0; CITI record ID 78026218). Sepsis was identified by the Angus criteria [16]—ICD-coded infection plus acute organ dysfunction (SOFA ≥ 2) within 48 hours—in the first ICU admission. Exclusions: age < 18 years, ICU stay < 24 hours, missing baseline INR or platelet count, INR > 10, and pre-existing therapeutic anticoagulation (warfarin/DOAC on admission, where identifiable).

Exposure and Definitions

Primary exposure: Intravenous (IV) heparin within the first 24 hours of ICU admission (MIMIC-IV itemid 225152), categorized as low (< 800 units/hour) or high (≥ 800 units/hour) by mean infusion rate. Secondary exposures: prophylactic subcutaneous heparin, enoxaparin, any anticoagulant, and FFP/cryoprecipitate transfusion.

Coagulation phenotype

INR was the primary continuous modifier. A binary consumptive coagulopathy subgroup was defined *a priori* as platelet count < 150×10^9/L AND INR > 1.5 [13, 17]; this phenotype is not equivalent to the INR ≥ 3.4 favorable zone.

Covariates

Age, sex, SOFA (excluding the coagulation subscore), cirrhosis, active cancer, chronic kidney disease, mechanical ventilation, vasopressor use, renal replacement therapy (first 24h), and admission creatinine, bilirubin, and lactate.

Outcomes

(1) 28-day all-cause mortality (primary); (2) net clinical benefit (28-day death or major bleeding); (3) major bleeding (ICD-9/10-coded gastrointestinal, intracranial, or other major hemorrhage); (4) PRBC/FFP transfusion; (5) hemoglobin nadir.

Statistical Analysis

All analyses were performed in R (version 4.3.3; R Core Team, 2024).

Primary analysis—INR as continuous modifier

Cox models with a heparin × restricted cubic spline (RCS) interaction (5 knots, 4 df, pre-specified), adjusted for age, sex, SOFA (non-coagulation), cirrhosis, cancer, and CKD. The heparin HR was computed across a fine INR grid (0.9–5.0); the HR = 1.0 crossover was identified by linear interpolation with 95% confidence bands; the likelihood ratio test (LRT) for the interaction has 4 df. Sensitivity analyses used 2- and 3-df splines.

INR versus PLT contribution

INR and platelet count were entered as mutually adjusted 4-knot RCS interaction terms, and each alone, compared by LRTs to quantify each modifier's unique contribution.

Secondary analyses: (1) Dose-stratified interactions (IV, prophylactic, or any anticoagulant; low vs high IV dose). (2) Inverse probability of treatment weighting (IPTW): stabilized ATT weights from logistic regression on all baseline covariates [18], trimmed to [0.01, 0.99]; weighted Cox models; SMD balance. (3) Propensity score matching (PSM): 1:1 nearest-neighbor without replacement, caliper 0.2 SD of the logit. (4) Fine–Gray competing-risk models with bleeding without death as a competing event (sHR and csHR, Supplement S1), because bleeding competes with mortality attribution and is itself heparin-related. (5) RCS knot sensitivity (3/4/5). (6) Additive interaction (RERI, bootstrap CIs, 1,000 replicates). (7) E-value for the interaction HR [19]. (8) Exploratory bleeding mediation (Supplement S5; not causally interpretable). (9) Negative control exposures: the primary interaction model was refit with corticosteroids, vasopressors, or renal replacement therapy (RRT)—no antithrombotic or INR-dependent mechanism—replacing heparin (positive control); INR-dependent interactions among negative controls formally demonstrate severity confounding. (10) Day-4 landmark analysis (baseline INR ≥ 2.7): trajectory (persistent: Day-4 INR ≥ 2.0; normalized: <2.0) in a Cox model from Day 4, adjusted for age, sex, and SOFA (non-coagulation).

Hypothetical trial design projection

For four enrichment strategies (all-comers; INR ≥ 2.5; INR ≥ 2.7; INR ≥ 3.4), IPTW-standardized mortality and ARDs yielded required sample sizes per arm (80% power, two-sided $\alpha = 0.05$) and power for a fixed 1,500-per-arm trial (Supplement S10). These projections are post-hoc illustrations subject to overfitting ("winner's curse"; the INR ≥ 3.4 ARD CI crosses zero), not valid sample-size determinations.

Missing data

Exposure, outcome, and demographic variables were complete; laboratory covariates had variable missingness (total bilirubin 34.0%, lactate 27.0%, creatinine 0.03%). The primary analysis used median imputation; multiple imputation by chained equations (MICE, 20 imputations; Supplement S2) and complete-case analyses served as sensitivity analyses, both consistent with the primary result.

Causal inference framework

Within the potential outcomes framework for effect modification [20], reported HRs are conditional associations quantifying effect heterogeneity, not causal effects; consistency across IPTW, PSM, and competing-risk models indicates robustness to measured confounding only. Confounding by indication reversal—preferential administration of heparin to high-INR patients perceived at lower bleeding risk—cannot be excluded.

Exploratory external cohorts: The enrichment score was applied without modification to MIMIC-III (v1.4; same institution, 2001–2012; N = 5,282) and eICU-CRD (multicenter, > 200 hospitals; in-hospital mortality; N = 12,229), using identical 24-hour heparin and INR definitions. Pre-specified analyses: continuous and 3-level score interactions with heparin, per-stratum IPTW-adjusted ARDs (bootstrap CIs), and dose–response across INR bins, with no cut-point re-estimation. Given sparse heparin exposure in high-INR strata (MIMIC-III Score 2: n = 5; eICU Score 1: n = 0; Score 2: n = 1), these analyses were underpowered and are reported in Supplement S6; the sparsity itself is a key finding (see Results).

Declarations

Ethics approval and consent to participate: This study used the publicly available MIMIC-IV (v3.0) database, which contains de-identified health records of patients admitted to the intensive care units of Beth Israel Deaconess Medical Center (Boston, MA, USA). The database was established via collaborative efforts by the Massachusetts Institute of Technology Lab for Computational Physiology and Beth Israel Deaconess Medical Center, and its use for research was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center. The requirement for individual patient informed consent was waived because the dataset comprises fully de-identified records. Consent for publication is not applicable.

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Author contributions

Teng Liu and Caihong Lv contributed equally: they conceived and designed the study, performed the statistical analysis, and drafted the manuscript. Fei Zhang and Yang Liu contributed to data acquisition and analysis. Xiaowen Li and Xin Liu contributed to data interpretation and critically revised the manuscript for important intellectual content. Wei Liu supervised the study, provided methodological guidance, and critically revised the manuscript. Wei Liu is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Data availability statement

The MIMIC-IV dataset analyzed during the current study is available in the PhysioNet repository (https://physionet.org/content/mimiciv/3.0/), accessible to researchers who complete the PhysioNet credentialing process and sign the data use agreement. The complete analysis code used to generate the results is publicly available at https://gitee.com/l-caihong/heparin-inr-sepsis-analysis and from the corresponding author on reasonable request.

Additional Information

Competing interests: The authors declare that they have no competing interests.

Artificial intelligence declaration: No generative artificial intelligence tools were used in the preparation of this manuscript.

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Figures

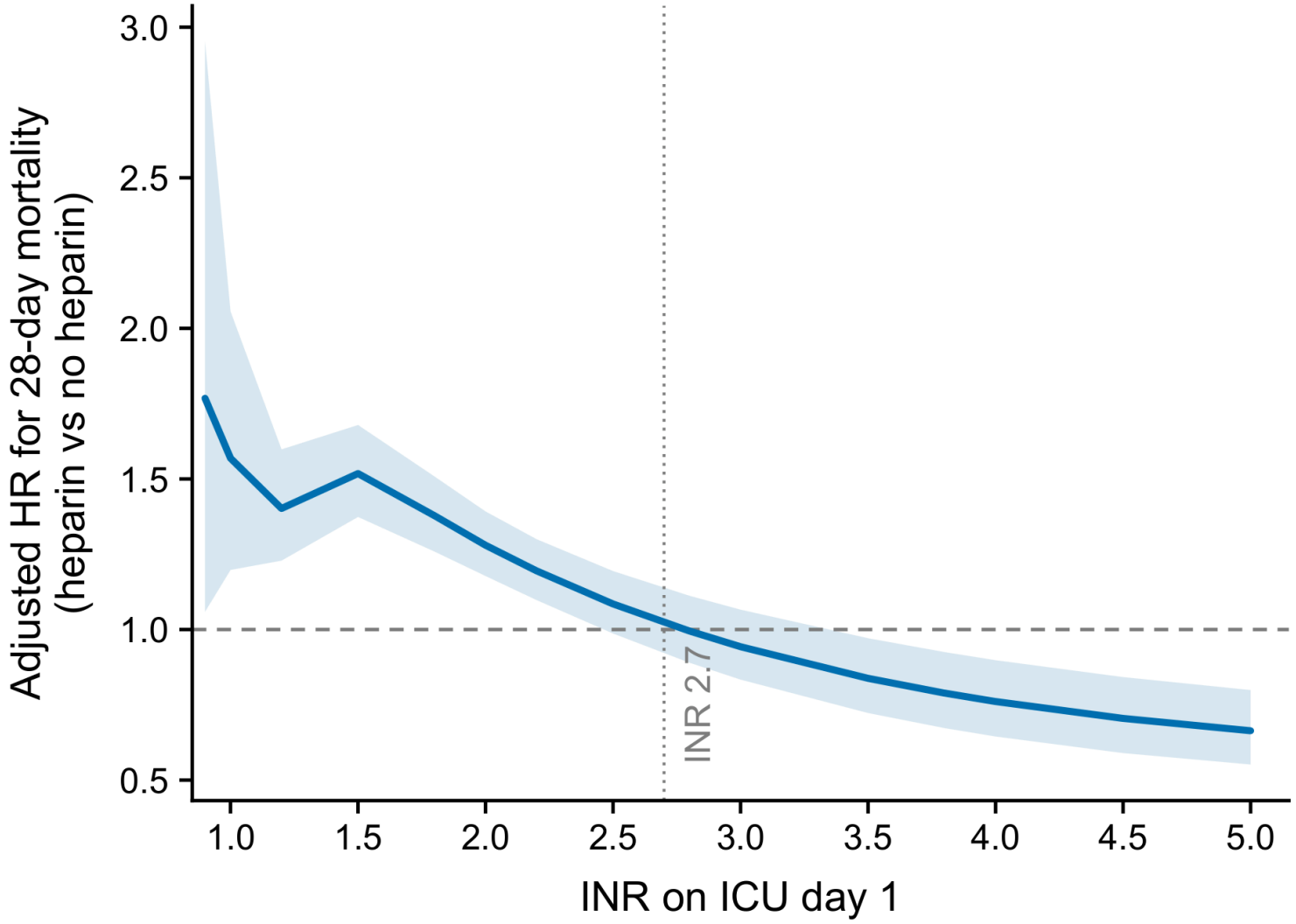


Figure 1

Restricted cubic spline dose-response curve showing the heparin hazard ratio as a function of the international normalized ratio (INR), with 95% confidence bands, the crossover point, and adverse/favorable zones. Red zone (INR ≤ 2.4): heparin associated with harm; yellow zone (INR 2.5–3.3): neutral; green zone (INR ≥ 3.4): heparin associated with benefit. The primary analysis used 5 knots (4 df); 2- and 3-df specifications were examined in sensitivity analyses (crossover range 2.78–2.85).

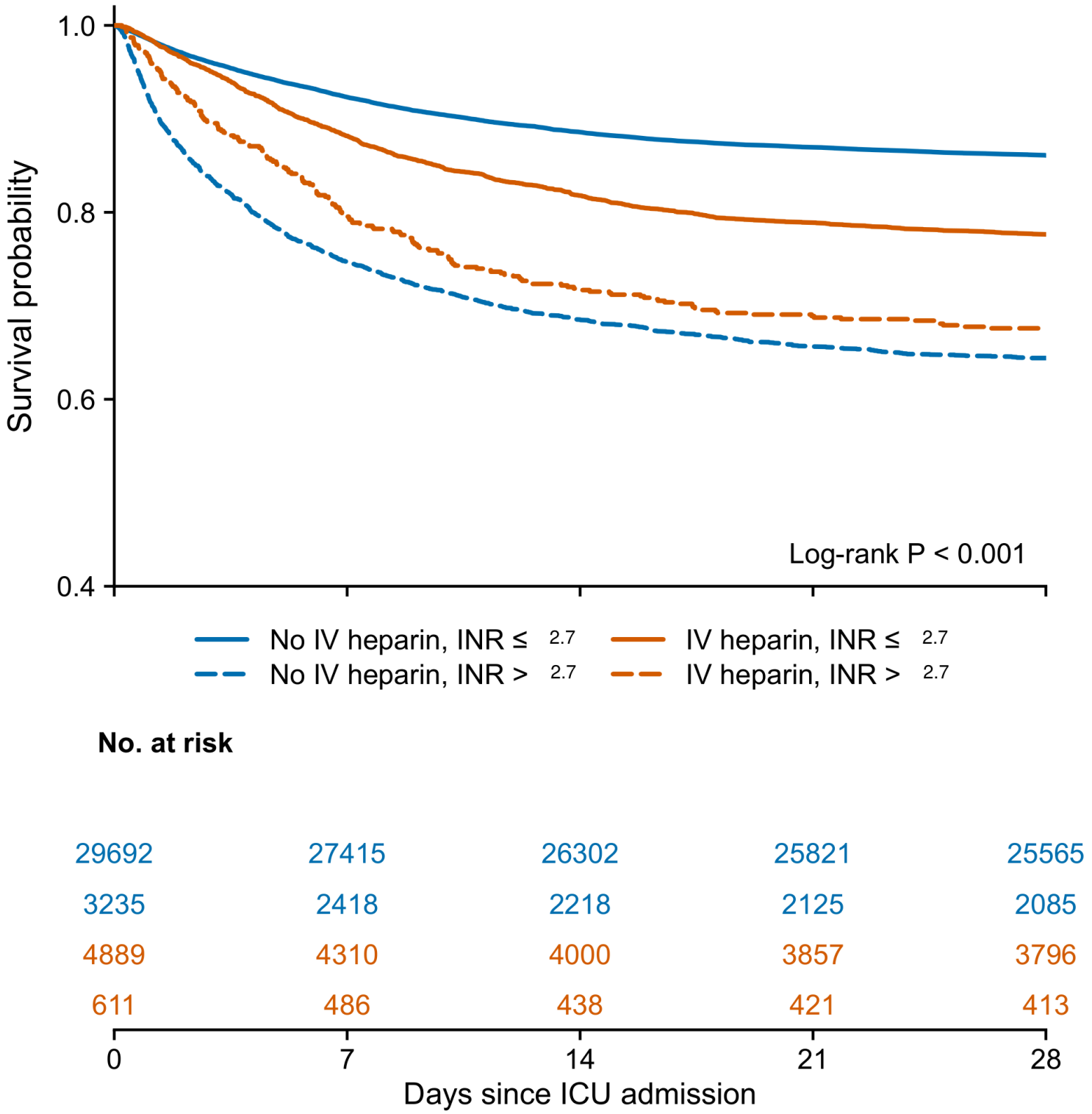


Figure 2

Kaplan-Meier survival curves for four groups (heparin vs no heparin, by INR high vs low using a cutoff of 2.7), with at-risk table and log-rank test.

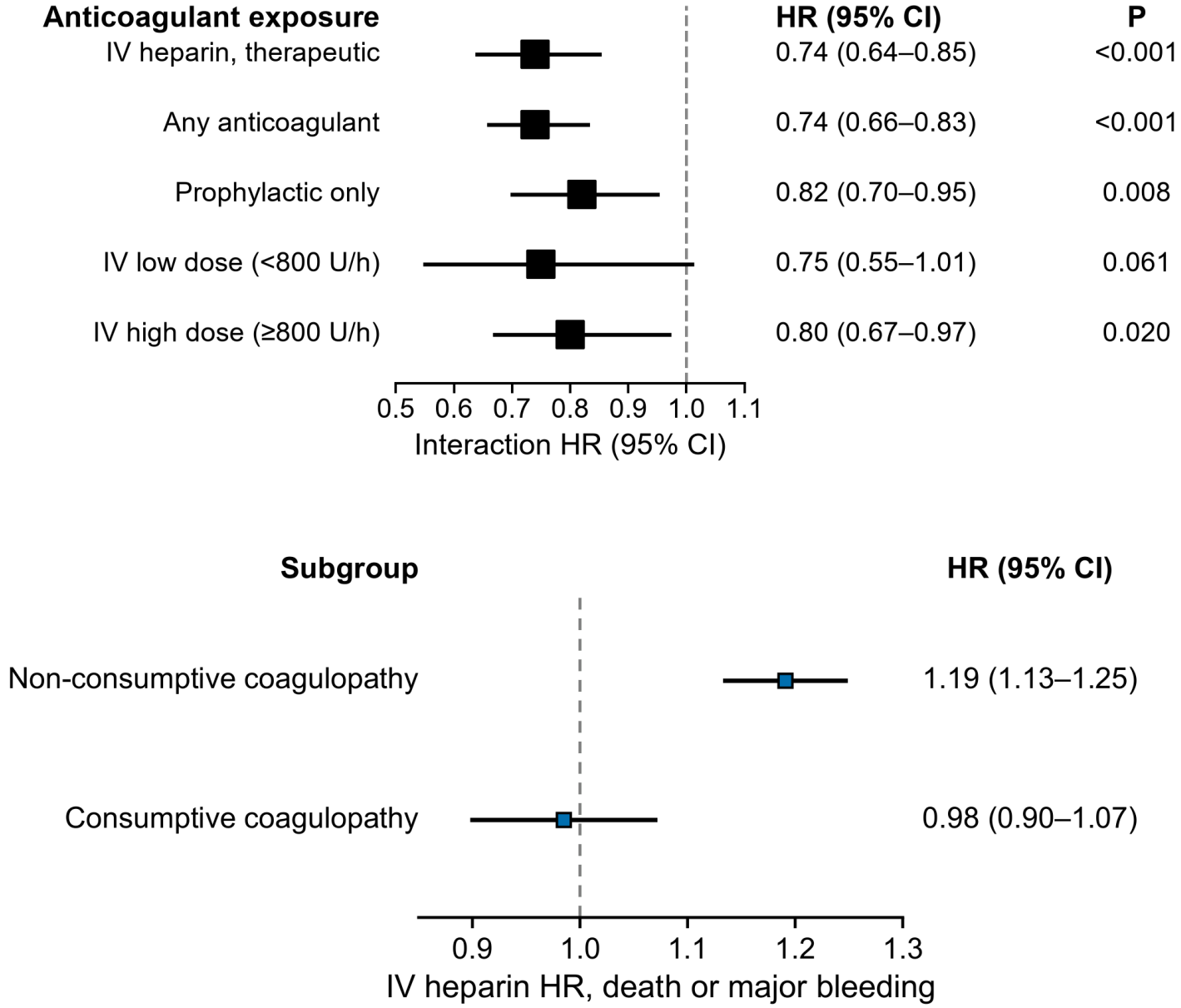


Figure 3

(a) Forest plot of interaction hazard ratios (95% CI) by anticoagulant type (therapeutic IV heparin, any anticoagulant, prophylactic only, IV low dose, IV high dose); the reference line at HR=1.0 indicates no interaction. (b) Forest plot of net clinical benefit (death or major bleeding) stratified by coagulopathy status for IV heparin exposure.

Supplementary Files

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- 04SupplementaryInformation.docx