



Optimal Timing of Prophylactic Anticoagulation in Traumatic Brain Injury: A Target Trial Emulation



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Introduction

ICU patients following traumatic brain injury (TBI) face competing risks of intracranial hemorrhage expansion and venous thromboembolism (VTE), where prevention of one may increase likelihood of the other. These risks are time-dependent: bleeding risk predominates acutely, transitioning toward thrombotic risk by days 3–4 due to immobility and trauma-related coagulopathy. Recent meta-analyses suggest prophylaxis within 72 hours is safe, but evidence for 24- and 48-hour windows remains limited. TBI heterogeneity including injury severity, age, comorbidities, and concomitant injuries further complicates identifying optimal timing. We believe some patients may benefit from early anticoagulation and thus emulated a target trial using the National Trauma Data Bank to estimate mortality-minimizing prophylaxis timing and identify patient trajectory phenotypes that may benefit from early anticoagulation.

Methods

Design: Target trial emulation using NTDB (2019–2021)
Inclusion: Age ≥ 18 , LMWH within first week, AIS-defined TBI, hospital LOS > 24 hours
Causal estimand: Per-protocol effect of VTE prophylaxis initiation at 24, 48, or 72 hours on 14-day in-hospital mortality
Approach: Clone-censor-weight (CCW) method with stabilized inverse-probability treatment weights (IPTW) and censoring weights (IPCW); weights truncated at 1st/99th percentiles
Covariates: Age, sex, ISS, AIS-Head, GCS, admission vitals, comorbidities (hypertension, coagulopathy, prior anticoagulation), mechanism of injury, trauma level, neurosurgical indicators
Phenotyping: K-means clustering on 0–24 hour trajectories using cubic B-spline basis expansions; optimal k selected via silhouette coefficient; variable selection via LASSO with cross-validated λ

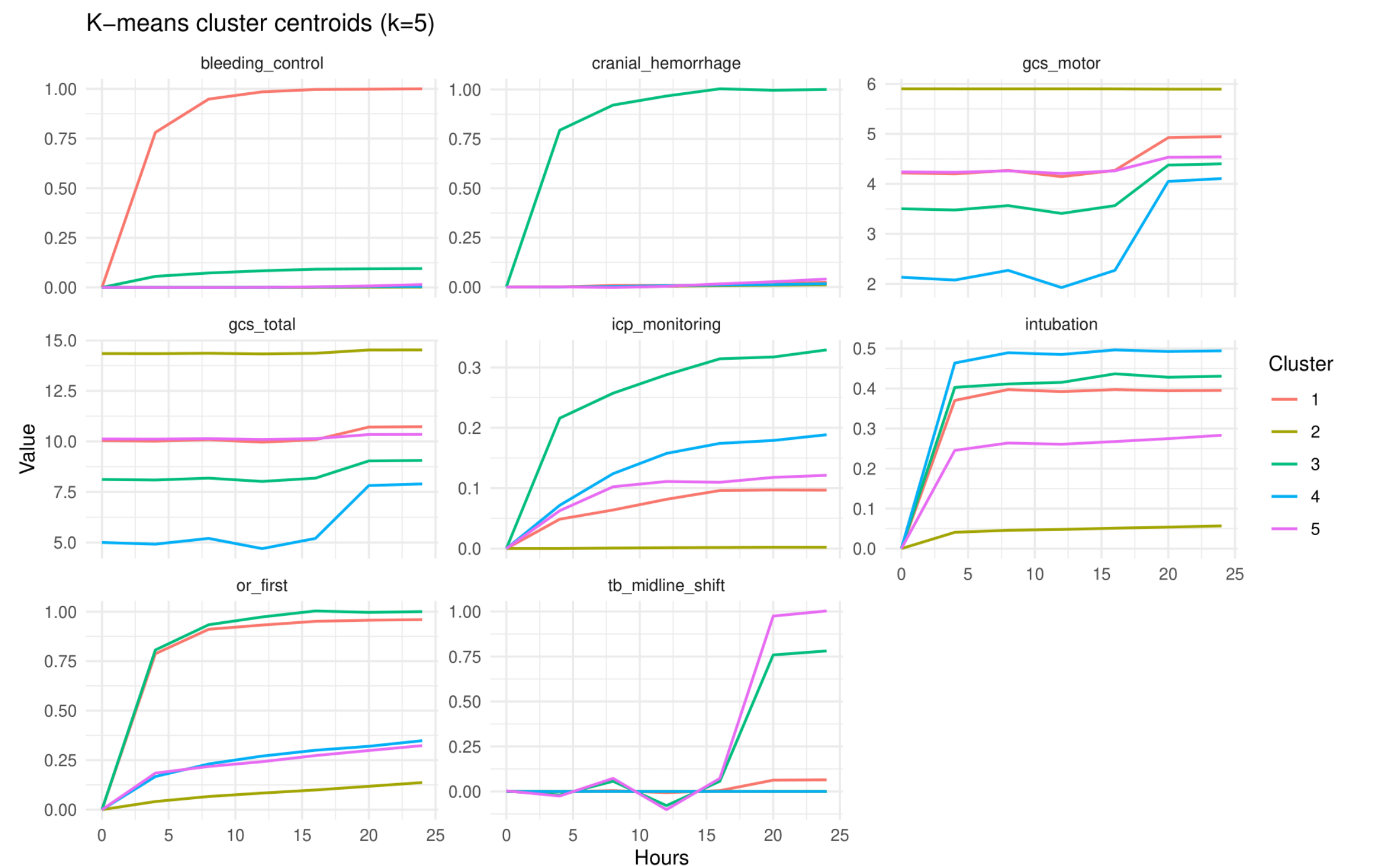
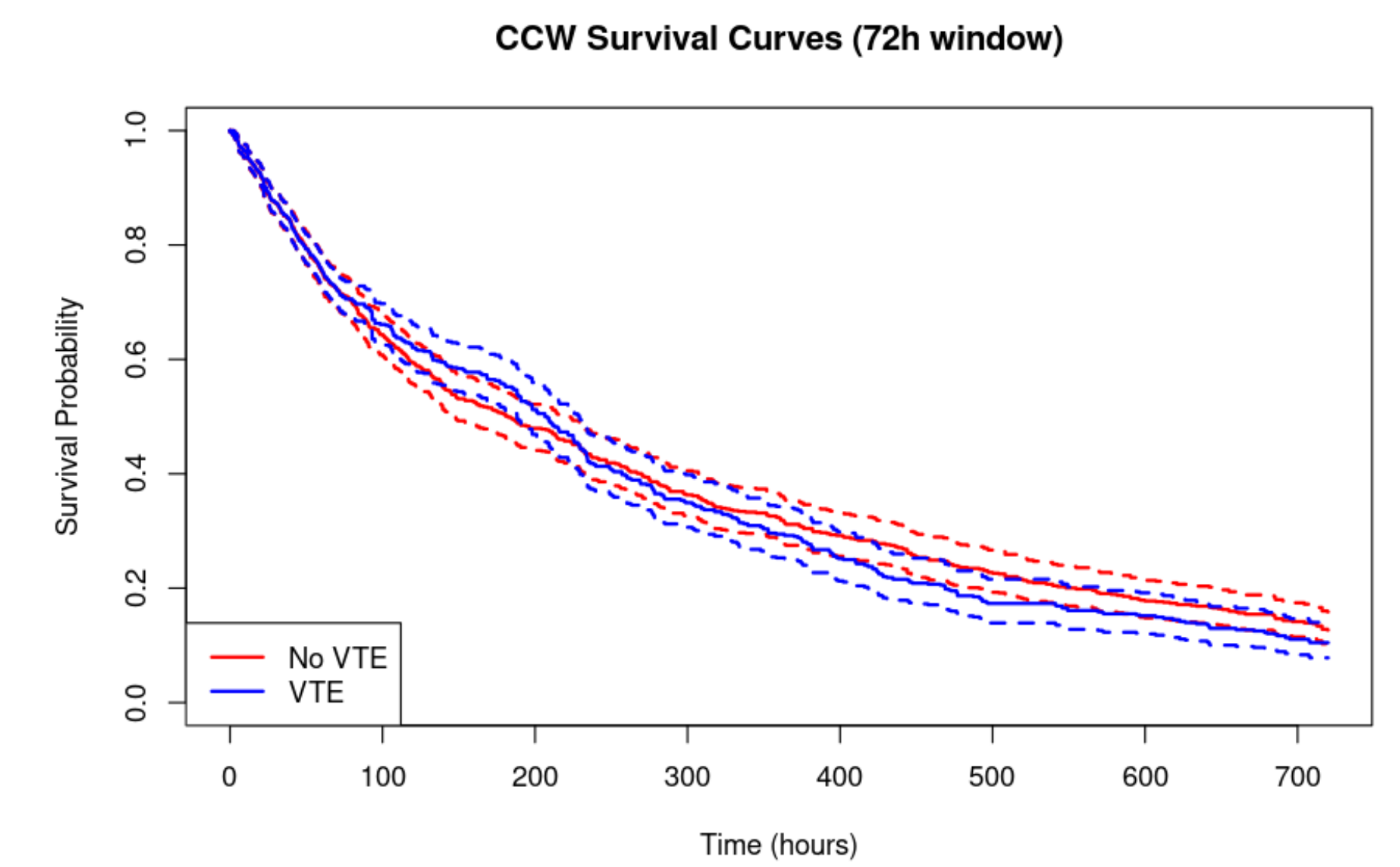
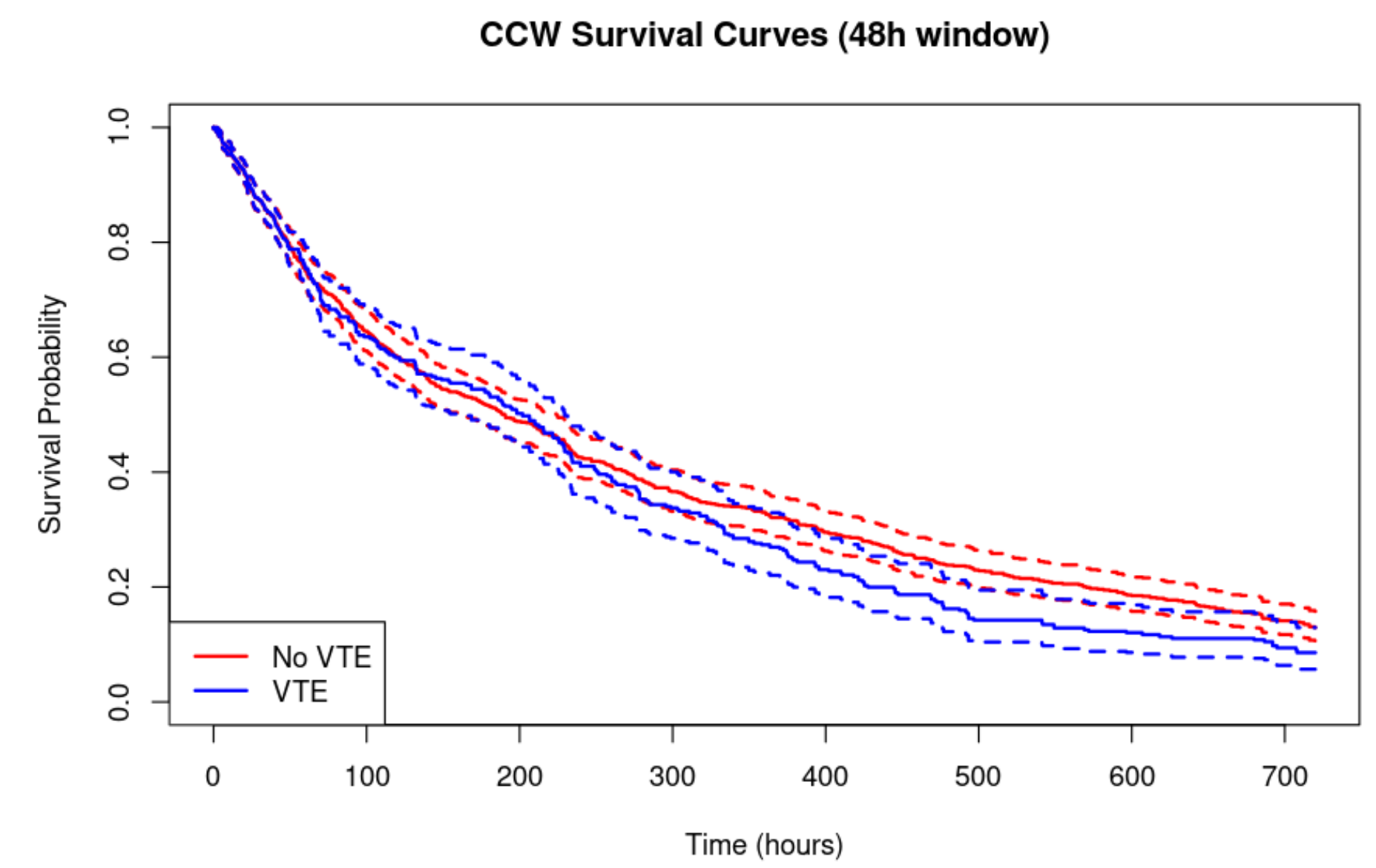
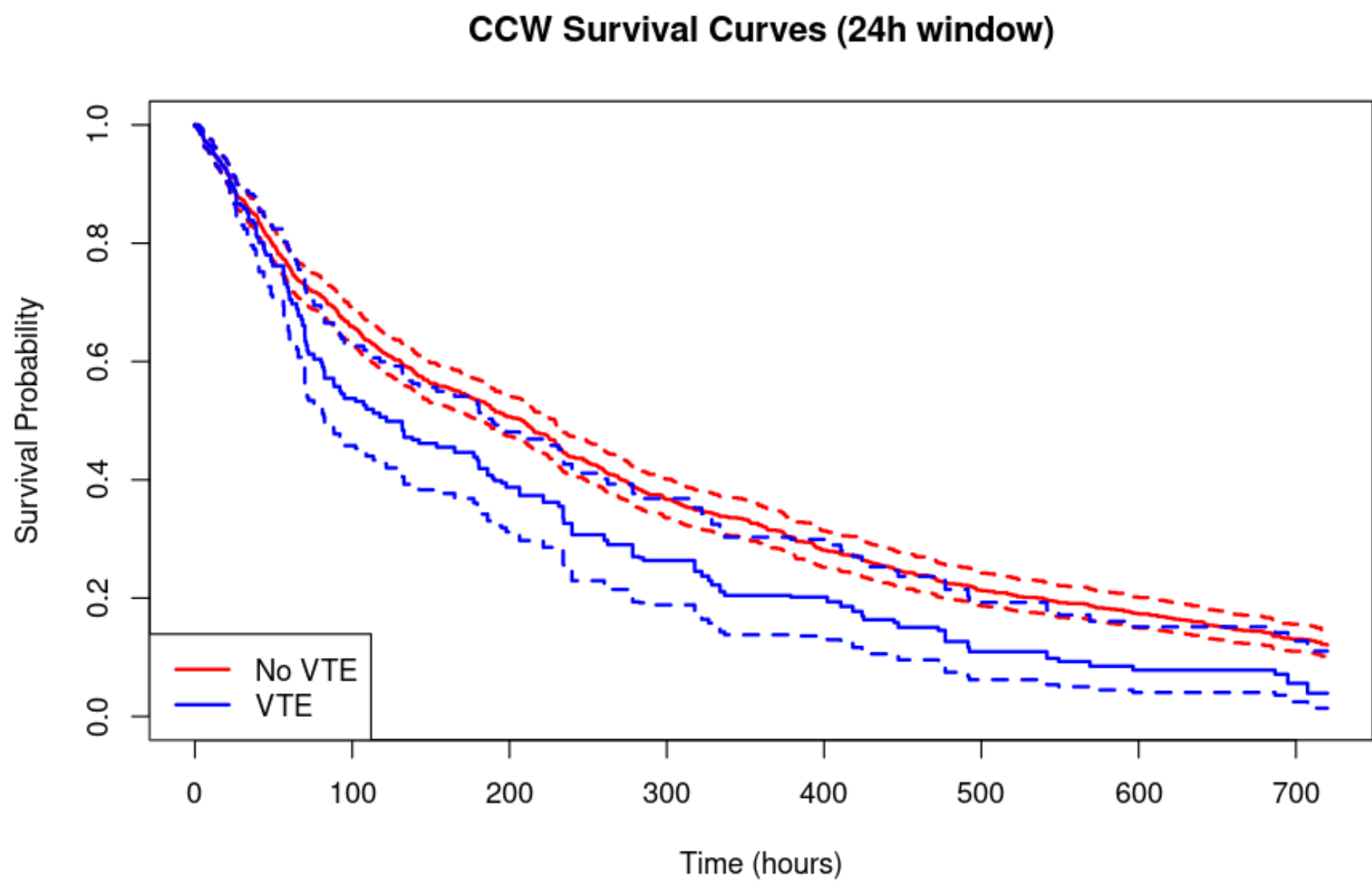


Table 3. ICU TBI Outcomes by Anticoagulation Initiation Window

Phenotype	Start window	14-day Relative Risk (%)	OR vs 0–24 h (95% CI)
Hemorrhage-control	24–48 h	6.4	1.13 (0.88–1.54)
	48–72 h	5.6	1.07 (0.85–1.49)
	72–96 h	6.7	1.12 (0.78–1.69)
	96–168 h	6.5	1.18 (0.83–1.72)
Low Trauma	24–48 h	5.4	0.94 (0.92–1.05)
	48–72 h	4.3	0.85 (0.76–0.99)
	72–96 h	3.8	0.81 (0.70–0.89)
	96–168 h	3.2	0.73 (0.69–0.79)
Moderate Trauma	24–48 h	6.3	0.98 (0.88–1.19)
	48–72 h	5.8	0.95 (0.85–1.17)
	72–96 h	5.0	0.85 (0.78–0.96)
	96–168 h	4.0	0.70 (0.60–0.89)
Severe ICH/mass effect	24–48 h	12.0	0.86 (0.75–1.18)
	48–72 h	12.0	0.86 (0.82–1.20)
	72–96 h	12.0	0.87 (0.77–1.31)
	96–168 h	10.0	0.68 (0.59–1.12)
Severe TBI (ICP+OR)	24–48 h	15.0	1.01 (0.88–1.21)
	48–72 h	15.0	1.03 (0.89–1.26)
	72–96 h	13.0	0.87 (0.73–1.10)
	96–168 h	11.0	0.72 (0.62–0.94)

Table 3. T = 0 is relative to ED entrance. Summary of clone–censor–weight analysis by clinical phenotype. Columns report phenotype, anticoagulation start window, 14-day risk (%), and odds ratios (95% CI) versus ≤ 24 h and 24–48 h reference windows where estimated.

Results

Among 1,039,147 TBI patients (431,210 ICU-admitted), median time to prophylaxis was 48.4 hours. At the population level, earlier initiation was associated with increased hazard (HR 1.36 at 24h, 1.15 at 48h, 1.08 at 72h), with protection emerging around 72–96 hours. Clustering of 0–24 hour clinical trajectories identified five distinct phenotypes with divergent optimal timing windows.

Lower-severity injuries (n = 108,422): Protection observed as early as 48–72h after 24-hour CT reassessment
Moderate polytrauma and **severe TBI with early ICP/OR**: Protection at 72–96h (HR 0.85 and 0.72, respectively)
Hemorrhage-control pathway and **mass-effect ICH**: No protective window identified

Discussion & Conclusion

Anticoagulation initiated at 72–96 hours was associated with lower 14-day hazard at the population level, while < 48 hours showed no clear benefit. Trajectory-based phenotyping revealed clinically meaningful heterogeneity: lower-severity patients demonstrated protection immediately after 24-hour CT reassessment, supporting initiation soon after radiographic stability. Moderate polytrauma and severe TBI with early ICP/OR showed protection at 72–96 hours. No protective window emerged for hemorrhage-control pathways or mass-effect ICH. These findings align with meta-analyses supporting "early" prophylaxis while clarifying that optimal timing varies by clinical phenotype.