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ORIGINAL RESEARCH

Early Antiplatelet Therapy in Upper Gastrointestinal Bleeding with Coronary Artery Disease: A Landmark Analysis of MIMIC-IV and eICU-CRD Databases

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Abstract: **Introduction:** The safety of early antiplatelet administration versus withholding in patients with concurrent upper gastrointestinal bleeding (UGIB) and coronary artery disease (CAD) or myocardial infarction (MI) remains unresolved. This study aimed to evaluate the association between early antiplatelet therapy timing and mortality in this population.
Methods: This retrospective cohort study included 3,422 adults with UGIB and concurrent CAD or MI from the Medical Information Mart for Intensive Care IV (MIMIC-IV) dataset (2008-2019). Patients were classified as having antiplatelet therapy ordered within 24 hours (AP-24h; n=1,530), between 24 and 72 hours (AP-24-72h; n=368), or no antiplatelet therapy within 72 hours (No-AP; n=1,524; reference). This study quantified immortal time bias using 72-hour mortality distributions, applied landmark analysis to eliminate this bias, and externally validated findings using the eICU Collaborative Research Database (eICU-CRD). After excluding 87 patients dying within 72 hours, the MIMIC-IV landmark cohort comprised 3,335 patients. The primary outcome was 1-year all-cause mortality from the 72-hour landmark point. eICU-CRD external validation applied the same phenotype and exposure timing; after excluding 137 early deaths, the validation cohort included 2,657 patients. The eICU-CRD outcome was post-landmark hospital mortality.
Results: Landmark analysis demonstrated a 72-hour mortality rate of 3.7% in No-AP versus 1.8% in AP-24h, confirming misclassification of early critically ill patients into the reference group. Adjusted landmark Cox regression showed no significant difference in 1-year all-cause mortality for AP-24h (hazard ratio (HR): 0.910, 95% confidence interval (CI): 0.806-1.027, p=0.125) or AP-24-72h (HR: 0.884, 95% CI: 0.733-1.066, p=0.197) compared with No-AP. In-hospital mortality was similar across groups (8.7-9.8%); adjusted logistic regression showed no significant differences for AP-24h (OR: 1.056, 95% CI: 0.786-1.419, p=0.718) or AP-24-72h (OR: 1.007, 95% CI: 0.646-1.568, p=0.976). Thirty-day mortality was also similar for AP-24h (HR: 0.934, 95% CI: 0.780-1.118, p=0.455) and AP-24-72h (HR: 1.027, 95% CI: 0.785-1.343, p=0.847). In the eICU-CRD validation cohort, post-landmark hospital mortality was 8.69%, 5.07%, and 8.00% for AP-24h, AP-24-72h, and No-AP, respectively. Fully adjusted validation models showed no increased in-hospital mortality for AP-24h (OR: 0.97, 95% CI: 0.62-1.53, p=0.895) or AP-24-72h (OR: 0.74, 95% CI: 0.32-1.69, p=0.469).
Conclusion: After correcting for immortal time bias using landmark analysis, early antiplatelet administration in UGIB patients with CAD or MI was not associated with increased 1-year all-cause mortality or in-hospital mortality in the MIMIC-IV dataset, and this finding was externally supported in the eICU-CRD dataset.

Keywords: Upper gastrointestinal tract; Gastrointestinal hemorrhage; Platelet aggregation inhibitors; coronary artery disease; Validation study

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1. Introduction

Upper gastrointestinal bleeding (UGIB) affects approximately 40–150 per 100,000 adults annually (1, 2) and carries an in-hospital mortality of 2–15% (3). A growing proportion of patients with UGIB are concurrently receiving antiplatelet therapy for coronary artery disease (CAD) or myocardial infarction (MI), creating an acute management dilemma: continuing therapy risks hemorrhage escalation, yet interruption risks stent thrombosis (4) or recurrent MI (5).

Current guidelines from major gastroenterology and cardiovascular societies (6-9) offer divergent recommendations on timing, leaving clinicians without reliable, actionable evidence. Prior observational studies in this area have been limited by small sample sizes and most critically immortal time bias (10, 11), a methodologic flaw rarely quantified or corrected in the UGIB–antiplatelet literature.

Immortal time bias arises when the exposure definition window overlaps with the survival follow-up period (10). Patients who die before receiving antiplatelet therapy are automatically classified as No-AP, artificially inflating reference group mortality and overstating the apparent benefit of early antiplatelet administration (10, 11).

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In this study, the primary aim was to establish the safety boundary of early antiplatelet administration in UGIB patients with concomitant CAD or MI, using a methodologically rigorous approach validated across two independent critical care datasets. Several previous studies using MIMIC-IV and eICU-CRD datasets have adopted exposure-window restriction combined with landmark-analysis approaches to mitigate immortal time bias. However, to the author's knowledge, no prior study in this clinical context has directly quantified the magnitude of immortal time bias by comparing corrected and uncorrected effect estimates.

This study aimed to evaluate the association between early antiplatelet therapy timing and mortality in patients with concurrent UGIB and CAD or MI using landmark analysis on MIMIC-IV dataset and validated the findings on eICU-CRD dataset.

2. Methods

2.1. Study design and data source

A retrospective cohort study was conducted on patients with concurrent UGIB and CAD or MI using the MIMIC-IV version 2.2 dataset, a de-identified electronic health record database from Beth Israel Deaconess Medical Center (2008-2019), accessed through PhysioNet credentialing (12, 13). External validation used eICU-CRD version 2.0, a de-identified multicenter intensive care unit (ICU) database from the United States (2014-2015) (14). Institutional Review Board (IRB) review was not required for fully de-identified data.

2.2. Study population

Adult (age 18 years) patients admitted with UGIB, as a principal or significant secondary discharge diagnosis (ICD-9: 530.21, 531.xx–534.xx, 578.xx; ICD-10: K25–K28, K29.x, K92.0–K92.2), and concurrent CAD or MI were considered. Index time was the hospital admission date. To strengthen the UGIB phenotype, at least one of the following was required within 72 hours: endoscopy, blood transfusion, proton pump inhibitor (PPI) administration, or hemoglobin level <10 g/dL. Exclusion criteria: age <18, hospitalization <24 hours, lower gastrointestinal bleeding only, and repeat admissions (index admission retained).

Patients with liver cirrhosis, portal hypertension, or esophagogastric varices (ICD-9/10: K70.x, K74.x, I85.x, K76.6) were retained in the primary analysis but excluded in a prespecified liver-disease-excluded sensitivity analysis to address variceal-risk heterogeneity.

2.3. Exposure definition

Antiplatelet therapy (aspirin and/or P2Y12 inhibitors: clopidogrel, ticagrelor, prasugrel) was identified from inpatient medication orders (15). Because database medication records reflect hospital orders rather than pre-admission reconciliation or confirmed administrations, terminology reflects timing of inpatient antiplatelet orders:

- AP-24h: ordered within 24h (original n=1,530; Landmark cohort n=1,503)
- AP-24-72h: ordered 24–72h after admission (original n=368; Landmark cohort n=365)
- No-AP: no antiplatelet order within 72h as reference group (original n=1,524; Landmark cohort n=1,467)

2.4. Landmark analysis

To eliminate immortal time bias (10, 11, 16), hour 72 was designated as the Landmark time point. Patients dying within 72 hours (MIMIC-IV: n=87 (2.5%); eICU-CRD: n=137(4.9%)) were excluded. Survival times in MIMIC-IV were recalibrated from the Landmark. Dates of death in MIMIC-IV were censored at one year after the last hospital discharge; follow-up for 1-year all-cause mortality was available within this predefined window.

2.5. Outcomes

The primary outcome in the MIMIC-IV landmark analysis was 1-year all-cause mortality from the landmark point (Cox proportional hazards regression, hazard ratio (HR)). Secondary outcomes were in-hospital mortality (logistic regression, odds ratio (OR) with 95% confidence interval (CI) and p-value) and 30-day all-cause mortality (Cox HR).

The studied outcome in landmark analysis of eICU-CRD dataset (validation study) was hospital mortality because long-term mortality is unavailable in eICU.

2.6. Covariates

Seventeen prespecified covariates were included: age, sex, acute MI, prior MI, coronary stent history, coronary artery bypass grafting (CABG) history, heart failure, atrial fibrillation, diabetes mellitus, chronic kidney disease, liver disease, active malignancy (from admission ICD codes), proton-pump inhibitor (PPI) use, anticoagulant use, minimum hemoglobin, maximum creatinine, and vasopressor use (within 24h of admission). The 24-hour measurement window for laboratory and medication variables preceded the exposure window for the AP-24-72h group, avoiding post-baseline adjustment bias.

2.7. Statistical analysis

This study quantified immortal time bias using 72-hour mortality distributions, applied a Landmark analysis to eliminate this bias, and validated the findings using the eICU database. Continuous variables were presented as median (interquartile range (IQR); Kruskal-Wallis test) and categorical ones as n (%; chi-square).

Primary MIMIC-IV model was based on multivariable Cox regression in the Landmark cohort and secondary in-hospital mortality model was based on logistic regression.

Inverse probability of treatment weighting (IPTW) using multinomial propensity scores (17, 18), time-varying Cox regression (19, 20), liver-disease-excluded analysis, and propensity score matching were used for sensitivity analyses.

eICU-CRD validation study used logistic regression with No-AP as reference, reported as unadjusted, age/sex/Acute Physiology and Chronic Health Evaluation (APACHE)-adjusted, fully adjusted, and liver-disease-excluded models. The fully adjusted eICU-CRD model included age, sex, APACHE score, hemoglobin, creatinine, liver/variceal-risk diagnosis, PPI orders, anticoagulant orders, vasopressor use, and mechanical ventilation. Analyses were performed in R 4.3.2 and Python 3.11. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed (21).

3. Results

3.1. Baseline characteristics of studied patients

Of 3,422 patients, 87 (2.5%) died within 72 hours. Distribution was markedly unequal: No-AP 57/1,524 (3.7%), AP-24h 27/1,530 (1.8%), AP-24-72h 3/368 (0.8%). The 2.1 times higher 72-hour mortality rate in the reference group directly demonstrates the immortal time bias mechanism (10, 11): patients dying before receiving therapy were systematically classified as No-AP. All 87 were excluded from the Landmark analysis.

Table 1 presents the baseline characteristics of included participants from MIMIC-IV dataset for landmark analysis (n = 3,335). AP-24h patients had significantly higher rates of acute MI (33.9% vs. 19.4%, p<0.001) and stent history (33.1% vs. 20.1%, p<0.001) compared to No-AP group (4, 5). The No-AP group had higher rates of liver disease (15.4%) and malignancy (16.8%). Anticoagulant use was highest in AP-24h (64.8%), reflecting routine ICU prophylactic anticoagulation (12) in a group with higher ICU admission rates (46.8%).

3.2. Landmark analysis of MIMIC-IV dataset for studied outcomes

Tables 2 and 3 summarize the findings of MIMIC-IV dataset landmark analysis for studied outcomes.

3.2.1 One-year all-cause mortality

The crude 1-year mortality rate was 35.6% in AP-24h, 32.6% in AP-24-72h, and 37.1% in No-AP. Adjusted Landmark Cox (n=3,142 complete cases) analysis showed no significant difference for AP-24h (HR: 0.910, 95% CI: 0.806–1.027, p=0.125) or AP-24-72h (HR: 0.884, 95% CI: 0.733–1.066, p=0.197; Table 3). The standard Cox model on the original (pre-Landmark) cohort, fitted without complete-case restriction, yielded HR: 0.860 (p=0.021); the comparable complete-case adjusted model without landmark restriction (Table 1, row ii) yielded HR: 0.889 (p=0.050). Both pre-Landmark estimates were directionally more protective than the bias-corrected landmark estimate (HR: 0.910, p=0.125), demonstrating that immortal time bias inflated the apparent benefit of early antiplatelet therapy regardless of analytic sample (10, 11, 14). Landmark survival curves are shown in Figure 1.

3.2.2 In-hospital mortality

Post-landmark in-hospital mortality was 9.8% in AP-24h, 9.0% in AP-24-72h, and 8.7% in No-AP. Adjusted logistic regression showed no significant differences (AP-24h: OR: 1.056, 95% CI: 0.786-1.419, p=0.718; AP-24-72h: OR: 1.007, 95% CI: 0.646-1.568, p=0.976). Thirty-day mortality was likewise not significantly different for AP-24h (12.0%; HR: 0.934, 95% CI: 0.780-1.118, p=0.455) or AP-24-72h (13.4%; HR: 1.027, 95% CI: 0.785-1.343, p=0.847) compared with No-AP (12.7%).

3.3. Sensitivity analyses

The findings of sensitivity analysis are shown in table 4. To assess whether the primary findings were consistent across clinically distinct cardiac phenotypes, an exploratory subgroup analysis was performed stratifying the landmark analysis by presence of MI (acute or prior MI, n=1,629) versus CAD without an MI diagnosis (CAD without MI, n=1,706). This analysis was not prespecified in the original protocol but was added in response to reviewer feedback. Adjusted Cox models were fitted separately within each subgroup using the same complete-case covariate set as the primary Landmark Cox model (MI subgroup, n=1,555 complete cases; CAD without MI subgroup, n=1,587 complete cases), and interaction terms between antiplatelet timing and MI status were tested in the full Landmark cohort (n=3,142 complete cases) to assess effect modification (table 5).

IPTW (standardized mean difference (SMD) <0.02 for all covariates) (17, 18) demonstrated a possible protective trend for AP-24h (HR: 0.872, 95% CI: 0.767–0.991). Time-varying Cox regression (19, 20) gave HR: 0.914 (95% CI 0.819–1.020). Liver-disease-excluded analysis (n=2,914) remained directionally consistent (AP-24h HR: 0.942, 95% CI: 0.834–1.064; AP-24-72h HR: 0.928, 95% CI: 0.770–1.120).

3.4. External validation of landmark analysis finding in eICU-CRD dataset

In the eICU-CRD dataset, 2,794 adults with UGIB and CAD or MI were identified. After exclusion of 137 patients dying within 72 hours, the validation landmark analysis included 2,657 patients, including AP-24h n=518, AP-24-72h n=138, and No-AP n=2,001. Post-landmark hospital mortality was 8.69%, 5.07%, and 8.00%, respectively. In the fully adjusted validation model, AP-24h was not associated with increased hospital mortality compared with No-AP (OR: 0.97, 95% CI: 0.62-1.53, p=0.895); similar findings were observed for AP-24-72h (OR: 0.74, 95% CI: 0.32-1.69, p=0.469). Liver-disease-excluded validation remained directionally consistent (AP-24h OR: 1.06, 95% CI: 0.66-1.70; AP-24-72h OR: 0.82, 95% CI: 0.35-1.89). The eICU validation model estimates are shown in Table 4 and Figures 2 and 3.

4. Discussion

To the author's knowledge, this is among the first studies to directly quantify and correct immortal time bias in the upper gastrointestinal bleeding–antiplatelet literature and to externally validate the direction of findings in a multicenter ICU database. After a 72-hour landmark analysis,

early antiplatelet administration was not significantly associated with increased in-hospital or 1-year all-cause mortality in MIMIC-IV, and eICU-CRD validation showed no increase in post-landmark hospital mortality.

4.1. Immortal time bias and prior evidence

Immortal time bias is a well-established threat in pharmacoepidemiologic research (10, 11). This study demonstrated it concretely: 72-hour mortality was 3.7% in No-AP versus 1.8% in AP-24h, an approximately 2.1 times higher mortality rate arising entirely from misclassification of critically ill patients dying before therapy could be administered. This represents a previously underappreciated source of methodologic distortion in the prior observational literature on this clinical question. The one randomized trial in this area, Sung et al. (1), found aspirin continuation reduced 30-day cardiovascular events without significant rebleeding excess, broadly consistent with the bias-corrected findings (22).

To verify the novelty of the specific research question, a targeted literature search was conducted prior to this revision and did not identify any prior study examining antiplatelet management timing in upper gastrointestinal bleeding patients with concurrent coronary artery disease or myocardial infarction using MIMIC-IV and/or eICU. To the author's knowledge, the specific combination of (a) UGIB with concurrent CAD/MI, (b) immortal time bias quantification and landmark correction, and (c) two-database external validation has not previously been reported. Several studies using MIMIC-IV and eICU-CRD have addressed time-related exposure misclassification using alternative strategies. Wu et al. (23) examined beta-blocker use in sepsis-induced myocardial injury using MIMIC-IV and eICU, addressing potential immortal-time-related bias through sensitivity analyses restricting the exposure window to within 3 and 5 days of ICU admission, supplemented by a time-varying Cox model as a robustness check, an exposure-window-restriction approach. This study instead applies a formal 72-hour landmark analysis, which recalibrates the survival-time origin to the Landmark point and explicitly excludes patients who died before the exposure classification window closed, structurally separating the exposure-definition period from the survival analysis period. The analysis additionally directly quantified the magnitude of immortal time bias by comparing 72-hour mortality across exposure groups (Section 3.1) and by directly contrasting bias-corrected versus uncorrected hazard ratios (Table 1), an explicit quantification.

4.2. Safety implications for clinical practice

Post-landmark in-hospital mortality was 8.7–9.8% across groups (all adjusted $p > 0.7$), indicating early antiplatelet administration does not measurably increase immediate mortality. Current guidelines (6-9) recommend individualized reassessment after hemostasis; the data support prompt reassessment at 24–72 hours rather than prolonged empirical interruption. Patients within 30 days of percutaneous coronary intervention (4, 5) face asymmetrically severe consequences from interruption, making early reassessment especially critical.

4.3. IPTW vs. Landmark Cox

The IPTW estimate (HR: 0.872) and Landmark Cox (HR: 0.910) differ in statistical significance but not clinical direction. Both fall within a narrow range (0.87–0.91). IPTW retains the full analytic sample through probabilistic reweighting, maximizing statistical efficiency (17, 18); Landmark Cox uses complete-case covariate adjustment. The time-varying Cox model (HR: 0.914) (19, 20) corroborates both. The totality of evidence indicates that early antiplatelet administration was not associated with mortality increase, with a possible modest protective trend that the primary analysis lacked power to confirm.

4.4. External validation and generalizability

The eICU validation cohort included 2,657 post-landmark patients from a multicenter ICU database and produced adjusted estimates centered near the null. Although eICU validation was restricted to hospital mortality and order-based medication exposure, the replication reduces concern that the MIMIC-IV findings are unique to a single institution or local practice pattern.

4.5. Variceal risk and exposure considerations

Excluding patients with liver disease (liver-disease-excluded variceal risk sensitivity, n=2,914) yielded directionally consistent results (AP-24h HR: 0.942). Because MIMIC-IV medication records reflect hospital orders rather than pre-admission reconciliation, it cannot be confirmed whether early inpatient antiplatelet ordering reflects reinitiation of pre-existing therapy or de novo initiation for acute coronary indications. Future studies incorporating medication reconciliation records would allow this distinction.

5. Limitations

This retrospective multi-database study cannot establish causality. Residual confounding from unmeasured variables, including endoscopic Forrest grade (6), hemorrhage severity scores (24, 25) and clinical gestalt, cannot be excluded. Cause-specific mortality is unavailable, precluding formal competing risk analysis. Laboratory covariates used 24-hour rather than 72-hour measurements. The 193 patients excluded from the primary MIMIC-IV Cox model due to missing laboratory values may introduce selection bias; IPTW analysis using the full landmark cohort mitigates this concern. The 87 patients excluded from the MIMIC-IV landmark analysis were the most critically ill; therefore, these findings should not be extrapolated to this high-risk subgroup. eICU validation was ICU-centered, limited to hospital mortality, and used medication orders rather than confirmed administrations; platelet count and International Normalized Ratio (INR) could not be reliably harmonized for validation

models. It was not possible to reliably distinguish emergency department from non-emergency department admission routes; therefore, extrapolation to strictly emergency department–origin presentations should be made cautiously, although the clinical dilemma remains relevant to early hospital and ICU care.

6. Conclusions

In a large, bias-corrected MIMIC-IV cohort of UGIB patients with CAD or MI, early antiplatelet administration within 72 hours was not associated with significantly increased in-hospital or 1-year all-cause mortality. External validation in eICU-CRD dataset similarly showed no increased post-landmark hospital mortality. These findings support timely antiplatelet reassessment after hemostasis rather than reflexive prolonged interruption, particularly in patients at high cardiovascular risk. Prospective trials with standardized endoscopic hemostasis grading and cause-specific mortality endpoints are needed to establish optimal reinitiation timing.

7. List of abbreviations

AP-24h: antiplatelet therapy ordered within 24 hours after hospital admission; AP-24-72h: antiplatelet therapy ordered 24 to 72 hours after hospital admission; APACHE: Acute Physiology and Chronic Health Evaluation; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CI: confidence interval; eICU: eICU Collaborative Research Database; HR: hazard ratio; ICD: International Classification of Diseases; ICU: intensive care unit; IPTW: inverse probability of treatment weighting; IQR: interquartile range; MI: myocardial infarction; MIMIC-IV: Medical Information Mart for Intensive Care IV; No-AP: no antiplatelet order within 72 hours; OR: odds ratio; PPI: proton-pump inhibitor; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; UGIB: upper gastrointestinal bleeding.

8. Declarations

8.1. Acknowledgments

Not applicable.

8.2. Authors' contributions

XZ conceived and designed the study, extracted and analyzed the data, interpreted the results, drafted and revised the manuscript, and approved the final submitted version.

8.3. Funding/Support

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8.4. Consent to publish

The author declares that he has no competing interests.

8.5. Availability of data and materials

The datasets analyzed during the current study are available through PhysioNet after completion of required training and data use agreements: MIMIC-IV v2.2 (https://physionet.org/content/mimiciv/2.2/) and eICU Collaborative Research Database v2.0 (https://physionet.org/content/eicu-crd/2.0/). The statistical code used for this secondary analysis is available from the corresponding author on reasonable request.

8.6. Conflict of interest

There is no conflict of interest.

8.7. Using artificial intelligence chatbots

None.

8.8. Ethics approval and consent to participate

This study used publicly available de-identified data from MIMIC-IV version 2.2 and the eICU Collaborative Research Database version 2.0, accessed through PhysioNet credentialing and required data use agreements. The original database releases were approved by the relevant institutional review boards, and informed consent was waived because the data are de-identified. The present secondary analysis did not involve direct contact with human participants.

8.9. Use of AI-assisted technologies

The author used AI-assisted tools for language polishing, formatting support, and editorial organization during manuscript preparation. The author verified all analyses, references, interpretations, and final manuscript content and takes full responsibility for the work.

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Table 1: Baseline characteristics of included patients from MIMIC-IV dataset for landmark analysis (n=3,335)

Variable	AP-24h (n=1,503)	AP-24-72h (n=365)	No-AP (n=1,467)	p-value
Age (years)	72 (64–80)	73 (66–81)	73 (63–82)	0.015
Median (IQR)				
Sex	968 (64.4)	246 (67.4)	950 (64.8)	0.556
Male				
Cardiac history				
Acute MI	510 (33.9)	118 (32.3)	284 (19.4)	< 0.001
Prior MI	421 (28.0)	89 (24.4)	338 (23.0)	0.007
Coronary stent history	498 (33.1)	104 (28.5)	295 (20.1)	< 0.001
CABG history	358 (23.8)	87 (23.8)	281 (19.2)	0.005
Comorbidities				
Heart failure	849 (56.5)	183 (50.1)	632 (43.1)	< 0.001
Atrial fibrillation	621 (41.3)	154 (42.2)	559 (38.1)	0.134
Diabetes mellitus	736 (49.0)	166 (45.5)	609 (41.5)	< 0.001
Chronic kidney disease	725 (48.2)	151 (41.4)	554 (37.8)	< 0.001
Liver disease	156 (10.4)	39 (10.7)	226 (15.4)	< 0.001
Active malignancy	171 (11.4)	37 (10.1)	246 (16.8)	< 0.001
Treatment and procedures within 24 h of admission				
PPI use	1013 (67.4)	267 (73.2)	1121 (76.4)	< 0.001
Anticoagulant use†	974 (64.8)	155 (42.5)	574 (39.1)	< 0.001
Vasopressor use	153 (10.2)	68 (18.6)	212 (14.5)	< 0.001
ICU admission	703 (46.8)	233 (63.8)	729 (49.7)	< 0.001
Blood transfusion	412 (27.4)	148 (40.5)	459 (31.3)	< 0.001
Upper endoscopy	850 (56.6)	253 (69.3)	920 (62.7)	< 0.001
Laboratory values within 24 h of admission				
Minimum hemoglobin (g/dL), median (IQR)	8.9 (7.7–10.6)	9.0 (7.7–10.6)	8.7 (7.5–10.4)	0.003
Maximum creatinine (mg/dL), median (IQR)	1.4 (1.0–2.2)	1.3 (0.9–2.0)	1.2 (0.9–2.0)	< 0.001
Maximum INR, median (IQR)	1.3 (1.1–1.7)	1.3 (1.2–1.7)	1.3 (1.1–1.7)	0.455
Hospital LOS (days), median (IQR)	7.1 (3.8–14.4)	6.8 (3.9–13.0)	5.9 (3.0–11.7)	< 0.001

Data are presented as median (interquartile range (IQR)) or frequency (%). CABG: coronary artery bypass grafting; IQR: interquartile range; LOS: length of stay; MI: myocardial infarction; PPI: proton pump inhibitor; INR: International Normalized Ratio. Continuous variables: Kruskal-Wallis test. Categorical: chi-square. †Anticoagulant includes therapeutic (and prophylactice.g., deep vein thrombosis prophylaxis) agents; intensive care unit (ICU) patients routinely receive prophylactic anticoagulation. Group definitions: AP-24h: antiplatelet therapy ordered within 24 hours after admission; AP-24-72h: antiplatelet therapy ordered 24 to 72 hours after admission; No-AP: no antiplatelet order within 72 hours.

Table 2: Outcomes of patients with concurrent upper gastrointestinal bleeding and coronary artery disease or myocardial infarction selected from the MIMIC-IV dataset for 72-hour landmark analysis (n = 3,335)

Outcome	AP-24h (n=1,503)	AP-24-72h (n=365)	No-AP (n=1,467)	Adjusted HR or OR	p-value
1-year all-cause mortality	535 (35.6)	119 (32.6)	544 (37.1)	AP-24h: HR 0.910 (0.806–1.027) AP-24–72h: HR 0.884 (0.733–1.066)	0.125 0.197
In-hospital mortality	147 (9.8)	33 (9.0)	127 (8.7)	AP-24h: OR 1.056 (0.786–1.419) AP-24–72h: OR 1.007 (0.646–1.568)	0.718 0.976
30-day mortality	181 (12.0)	49 (13.4)	187 (12.7)	AP-24h: HR 0.934 (0.780–1.118) AP-24–72h: HR 1.027 (0.785–1.343)	0.455 0.847
Original analysis without landmark correction (reference)					
Standard Cox (n=3,422)	563 (36.8)	122 (33.2)	608 (39.7)	AP-24h: HR 0.860 (0.757–0.978) AP-24–72h: HR 0.785 (0.642–0.960)	0.021 0.018

Reference: No-AP group. All measures are presented with 95% confidence interval (CI). HR: hazard ratio (Landmark Cox, adjusted for 17 covariates); OR: odds ratio (logistic regression). Group definitions: AP-24h: antiplatelet therapy ordered within 24 hours after admission; AP-24-72h: antiplatelet therapy ordered 24 to 72 hours after admission; No-AP: no antiplatelet order within 72 hours.

Table 3: Comparing 1-year all-cause mortality in patients with concurrent upper gastrointestinal bleeding and coronary artery disease or myocardial infarction selected from MIMIC-IV dataset

Analysis	Number	AP-24h HR	AP-24-72h HR	P value
(i) Crude (unadjusted)	3,422	0.908 (0.810–1.019)	0.805 (0.663–0.979)	0.101
(ii) Adjusted (no landmark restriction)	3,223	0.889 (0.791–1.000)	0.825 (0.686–0.991)	0.050
(iii) Adjusted (72-h landmark analysis)	3,142	0.910 (0.806–1.027)	0.884 (0.733–1.066)	0.125

All measures are presented with 95% confidence interval (CI). i: no landmark, no covariate adjustment; ii: pre-bias-correction; and iii: bias-corrected, landmark analysis.
Comparison (i)→(ii)→(iii) illustrates how immortal time bias inflates the apparent protective association when the 72-hour exposure-classification window is not separated from the survival-analysis period (hazard ratio (HR) changes from 0.889, p=0.050 before correction, to 0.910, p=0.125 after Landmark correction).

Table 4: Sensitivity analysis of MIMIC-IV dataset for 1 year mortality and eICU-CRD dataset for in-hospital mortality of patients with concurrent upper gastrointestinal bleeding and coronary artery disease or myocardial infarction

Method	Analytic sample	AP-24h effect	AP-24–72h effect	*P*-value
MIMIC-IV 72-h landmark analysis for 1-year mortality (n=3,335)				
Landmark Cox (primary)§	3,142 complete cases	HR 0.910 (0.806–1.027)	HR 0.884 (0.733–1.066)	0.125
IPTW Cox (post-weighting SMD < 0.02)	3,335	HR 0.872 (0.767–0.991)	HR 0.872 (0.707–1.075)	0.036
Time-varying Cox (full cohort)	5,015 person-rows	HR 0.914 (0.819–1.020)	—	0.109
Liver-disease-excluded	2,914	HR 0.942 (0.834–1.064)	HR 0.928 (0.770–1.120)	0.336
eICU-CRD 72-h landmark analysis for in-hospital mortality (external validation; n=2,657)				
Unadjusted logistic regression	2,657	OR 1.09 (0.77–1.55)	OR 0.61 (0.28–1.34)	0.608
Age/sex/APACHE-adjusted logistic regression	2,363	OR 1.12 (0.76–1.66)	OR 0.74 (0.33–1.65)	0.559
Fully adjusted logistic regression	2,045	OR 0.97 (0.62–1.53)	OR 0.74 (0.32–1.69)	0.895
Liver-disease-excluded validation	1,890	OR 1.06 (0.66–1.70)	OR 0.82 (0.35–1.89)	0.802
Original MIMIC-IV biased analyses for 1-year mortality (for comparison only)				
Standard multivariable Cox	2,532	HR 0.860 (0.757–0.978)	HR 0.785 (0.642–0.960)	0.021
Propensity score-matched Cox	509/233 pairs	HR 0.969 (0.804–1.167)	HR 0.821 (0.629–1.071)	0.739

§ Primary Landmark Cox: 3,142 of 3,335 patients with complete covariate data; 193 excluded due to missing laboratory values.
MIMIC-IV estimates are hazard ratios (HRs) from Cox models unless otherwise stated; eICU estimates are odds ratios (ORs) from logistic regression models. eICU fully adjusted model included age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) score, hemoglobin, creatinine, liver/variceal-risk diagnosis, proton-pump inhibitor (PPI)orders, anticoagulant orders, vasopressor use, and mechanical ventilation. IPTW: inverse probability of treatment weighting. Standard Cox and PSM Cox shown for comparison only; both affected by immortal time bias. Bias magnitude: 0.050 HR units (0.910 0.860) for AP-24h.
Group definitions: AP-24h: antiplatelet therapy ordered within 24 hours after admission; AP-24-72h: antiplatelet therapy ordered 24 to 72 hours after admission; No-AP: no antiplatelet order within 72 hours.

Table 5: Subgroup analysis by myocardial infarction (MI) status versus coronary artery disease (CAD) without myocardial infarction

Subgroup	Number*	AP-24h HR; P value	AP-24-72h HR; P value
MI subgroup (acute or prior MI)	1,555	0.892 (0.766–1.039); p = 0.143	0.846 (0.669–1.071); p = 0.164
CAD without MI subgroup (no MI diagnosis)	1,587	0.965 (0.819–1.138); p = 0.674	1.002 (0.773–1.300); p = 0.987

All measures are presented with 95% confidence interval (CI). P for interaction values were 0.524 for AP-24h × MI status and 0.410 for AP-24-72h × MI status, tested in the full landmark cohort (n=3,142 complete cases) using interaction terms between antiplatelet timing and MI status. Point estimates were directionally consistent with the primary analysis in both subgroups, with no significant mortality difference for either antiplatelet timing category. The MI subgroup showed a numerically larger point estimate for protective association than the CAD without MI subgroup, consistent with a plausible higher absolute benefit of antiplatelet therapy in patients with established myocardial injury. No statistically significant effect modification by MI status was observed. Because this subgroup analysis was exploratory and some strata had limited event numbers, these findings should be interpreted as hypothesis-generating rather than confirmatory. HR: hazard ratio.*: complete-case analytic sample. Group definitions: AP-24h: antiplatelet therapy ordered within 24 hours after admission; AP-24-72h: antiplatelet therapy ordered 24 to 72 hours after admission; No-AP: no antiplatelet order within 72 hours.

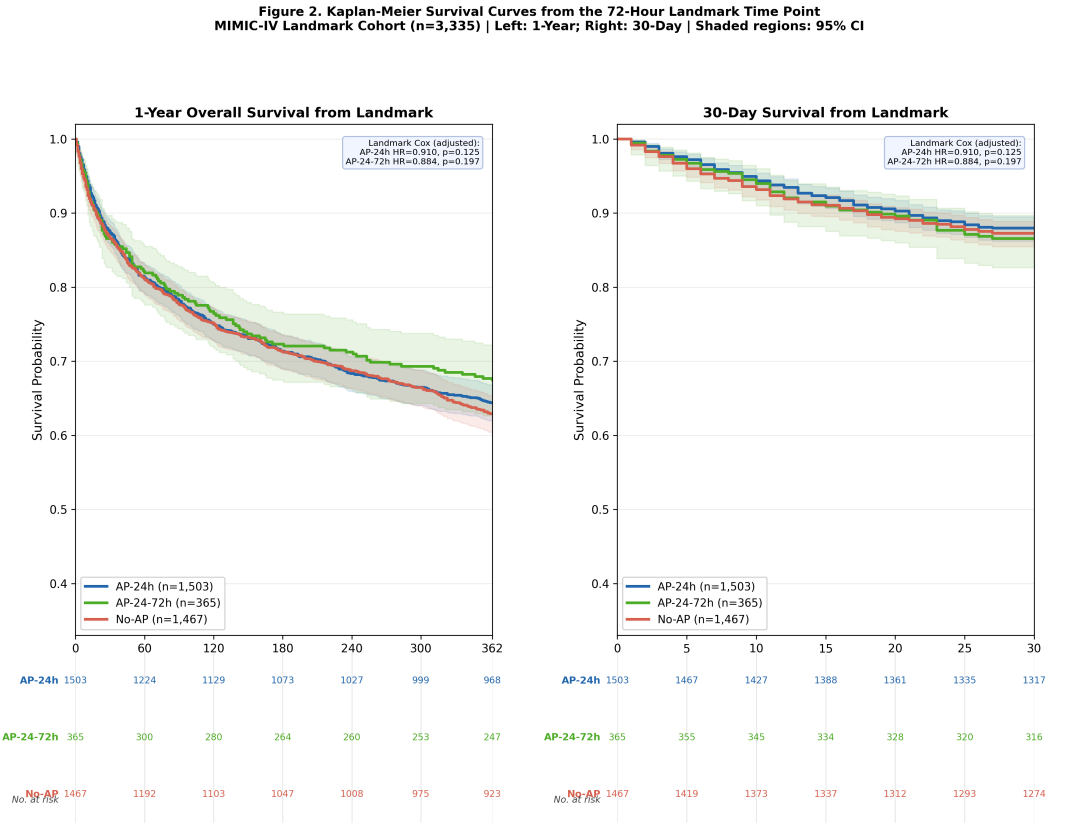

Figure 1: Kaplan-Meier survival curves of included patients from MIMIC-IV for landmark analysis. Curves display 1-year and 30-day survival from the 72-hour landmark point among 3,335 patients. Hazard ratios compare AP-24h and AP-24-72h with No-AP in adjusted Landmark Cox models. HR: hazard ratio. Group definitions: AP-24h: antiplatelet therapy ordered within 24 hours after admission; AP-24-72h: antiplatelet therapy ordered 24 to 72 hours after admission; No-AP: no antiplatelet order within 72 hours.

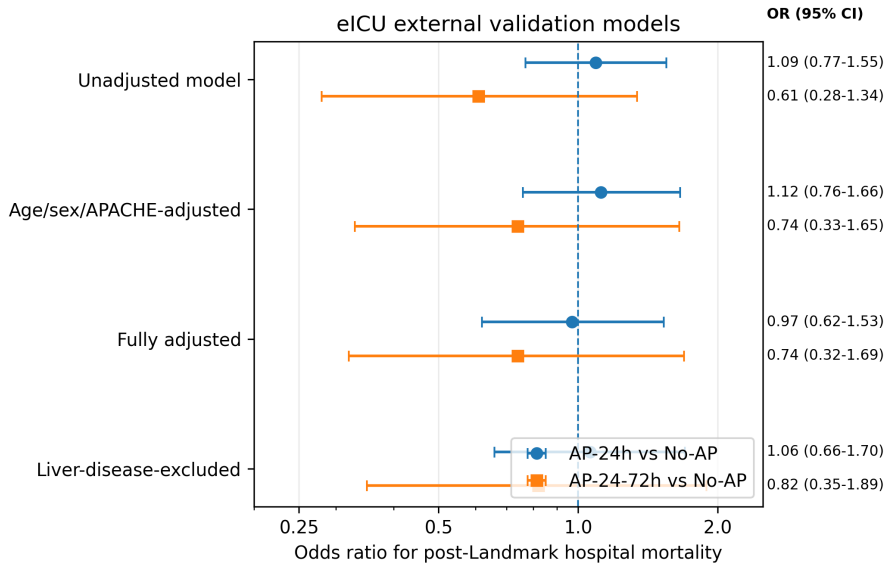

Figure 2: eICU-CRD dataset external validation models. Odds ratios (ORs) compare AP-24h and AP-24-72h with No-AP for landmark analysis of in-hospital mortality. The age/sex/APACHE-adjusted model adjusted for age, sex, and APACHE score; the fully adjusted model additionally included hemoglobin, creatinine, liver/variceal-risk diagnosis, proton-pump inhibitor orders, anticoagulant orders, vasopressor use, and mechanical ventilation. The liver-disease-excluded model excluded patients with liver or variceal-risk diagnoses. CI: confidence interval; APACHE: Acute Physiology and Chronic Health Evaluation. Group definitions: AP-24h: antiplatelet therapy ordered within 24 hours after admission; AP-24-72h: antiplatelet therapy ordered 24 to 72 hours after admission; No-AP: no antiplatelet order within 72 hours.

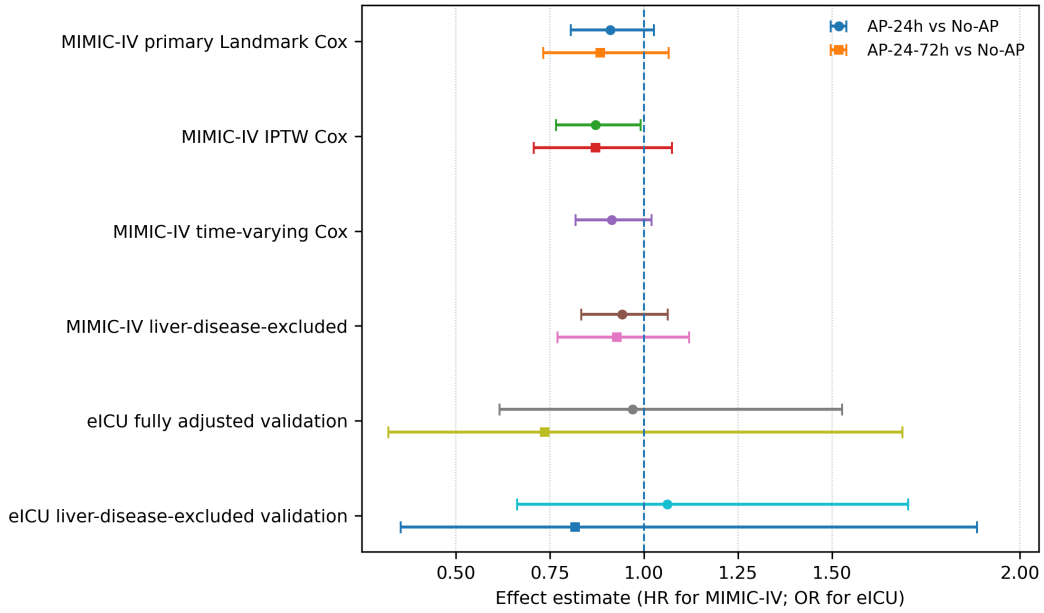

Figure 3: Forest plot of MIMIC-IV and eICU-CRD validation estimates. MIMIC-IV estimates are based on hazard ratios (HRs) from Cox models and eICU-CRD estimates are based on odds ratios (ORs) from logistic regression models. Circles indicate AP-24h versus No-AP; squares indicate AP-24-72h versus No-AP. Vertical dashed line indicates an effect estimate of 1.0. IPTW: Inverse probability of treatment weighting; Group definitions: AP-24h: antiplatelet therapy ordered within 24 hours after admission; AP-24-72h: antiplatelet therapy ordered 24 to 72 hours after admission; No-AP: no antiplatelet order within 72 hours.

Supplementary table 1: Search strategy in different databases

Scopus (n=106)
TITLE-ABS-KEY ("Spinal Cord Injury" OR "SCI" OR "acute spinal cord trauma" OR "spinal cord trauma") AND (TITLE-ABS-KEY ("Hypothermia, Induced" OR "therapeutic hypothermia" OR "systemic hypothermia" OR "local hypothermia" OR "cooling therapy" OR "targeted temperature management" OR "regional hypothermia")) OR INDEXTERMS ("hypothermia") AND (TITLE-ABS-KEY ("Recovery of Function" OR "neurological recovery" OR "motor recovery" OR "sensory recovery" OR "neuroprotection" OR "secondary injury" OR "inflammation" OR "decreasing second insult" OR "anti-inflammatory") OR INDEXTERMS ("recovery" OR "neuroprotection")) AND (TITLE-ABS-KEY ("acute" OR "early phase" OR "post-injury" OR "subacute"))
PubMed (n=9)
(("Spinal Cord Injury"[Mesh] OR "Spinal Cord Injuries"[Mesh] OR "SCI"[Title/Abstract] OR "acute spinal cord trauma"[Title/Abstract] OR "spinal cord trauma"[Title/Abstract]) AND ("Hypothermia, Induced"[Mesh] OR "therapeutic hypothermia"[Title/Abstract] OR "systemic hypothermia"[Title/Abstract] OR "local hypothermia"[Title/Abstract] OR "cooling therapy"[Title/Abstract] OR "targeted temperature management"[Title/Abstract] OR "regional hypothermia"[Title/Abstract] OR "hypothermia"[Mesh]) AND ("Recovery of Function"[Mesh] OR "neurological recovery"[Title/Abstract] OR "motor recovery"[Title/Abstract] OR "sensory recovery"[Title/Abstract] OR "neuroprotection"[Title/Abstract] OR "secondary injury"[Title/Abstract] OR "inflammation"[Title/Abstract] OR "decreasing second insult"[Title/Abstract] OR "anti-inflammatory"[Title/Abstract] OR "recovery"[Mesh] OR "neuroprotection"[Mesh]) AND ("acute"[Title/Abstract] OR "early phase"[Title/Abstract] OR "post-injury"[Title/Abstract] OR "subacute"[Title/Abstract]))
WOS (n=90)
TS=(("Spinal Cord Injury" OR "Spinal Cord Injuries" OR "SCI" OR "acute spinal cord trauma" OR "spinal cord trauma") AND ("Hypothermia, Induced" OR "therapeutic hypothermia" OR "systemic hypothermia" OR "local hypothermia" OR "cooling therapy" OR "targeted temperature management" OR "regional hypothermia" OR "hypothermia") AND ("Recovery of Function" OR "neurological recovery" OR "motor recovery" OR "sensory recovery" OR "neuroprotection" OR "secondary injury" OR "inflammation" OR "decreasing second insult" OR "anti-inflammatory" OR "recovery") AND ("acute" OR "early phase" OR "post-injury" OR "subacute"))
Embase (n=98):
('spinal cord injury'/exp OR 'spinal cord injury':ti,ab OR 'spinal cord injuries':ti,ab OR 'sci':ti,ab OR 'acute spinal cord trauma':ti,ab OR 'spinal cord trauma':ti,ab) AND ('induced hypothermia'/exp OR 'therapeutic hypothermia':ti,ab OR 'systemic hypothermia':ti,ab OR 'local hypothermia':ti,ab OR 'cooling therapy':ti,ab OR 'targeted temperature management':ti,ab OR 'regional hypothermia':ti,ab OR 'hypothermia'/exp) AND ('recovery of function'/exp OR 'neurological recovery':ti,ab OR 'motor recovery':ti,ab OR 'sensory recovery':ti,ab OR 'neuroprotection':ti,ab OR 'secondary injury':ti,ab OR 'inflammation':ti,ab OR 'decreasing second insult':ti,ab OR 'anti-inflammatory':ti,ab OR 'recovery'/exp OR 'neuroprotection'/exp) AND ('acute':ti,ab OR 'early phase':ti,ab OR 'post-injury':ti,ab OR 'subacute':ti,ab)
Cochrane (n=2):
(("Spinal Cord Injury" OR "Spinal Cord Injuries" OR "SCI" OR "acute spinal cord trauma" OR "spinal cord trauma") AND ("Hypothermia, Induced" OR "therapeutic hypothermia" OR "systemic hypothermia" OR "local hypothermia" OR "cooling therapy" OR "targeted temperature management" OR "regional hypothermia" OR "hypothermia") AND ("Recovery of Function" OR "neurological recovery" OR "motor recovery" OR "sensory recovery" OR "neuroprotection" OR "secondary injury" OR "inflammation" OR "decreasing second insult" OR "anti inflammatory" OR "recovery") AND ("acute" OR "early phase" OR "post-injury" OR "subacute"))