

Antithrombotic Profile and Mortality Predictors of Non-Traumatic Bleeding at Emergency Department: A Prospective Observational Study

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Abstract

Objective: This prospective observational study evaluated the clinical profile of adults presenting to the emergency department (ED) with non-traumatic bleeding and examined whether bleeding severity, antithrombotic use, and physiological/laboratory parameters were associated with in-hospital and 30-day mortality.

Materials and Methods: Demographic data, comorbidities, medication exposure, bleeding site, vital signs, laboratory variables, and clinical outcomes were recorded using a standardized data collection form. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria. Group comparisons were performed using appropriate parametric or non-parametric tests, and variables associated with mortality were evaluated using multivariable logistic regression.

Results: Among 310 patients screened, 297 adults were included after exclusion of 13 patients with cirrhosis-related complications. Gastrointestinal bleeding was the most common presentation (48.1%), and 55.9% of patients were using at least one antithrombotic agent. Major bleeding was more frequent in older patients, males, patients with comorbidities, and those with central nervous system (CNS) or gastrointestinal bleeding. In-hospital mortality was 8.1%, and 30-day mortality was 12.1%. In the final multivariable model, major bleeding (OR=7.223, 95% CI: 2.268–23.005, p=0.001) and lower oxygen saturation (OR=0.757, 95% CI: 0.665–0.860, p<0.001) were independently associated with in-hospital mortality. CNS bleeding, hypertension, higher blood urea nitrogen, higher pulse rate, and lower oxygen saturation were independently associated with 30-day mortality.

Conclusion: In adults presenting to the ED with non-traumatic bleeding, mortality appeared to cluster around bleeding severity and markers of physiological compromise rather than antithrombotic exposure alone. Early risk stratification using bleeding site, ISTH major bleeding criteria, oxygen saturation, pulse rate, and renal function markers may help identify patients requiring closer monitoring and more aggressive management.

Keywords: Antithrombotic agents, emergency department, major bleeding, mortality, non-traumatic bleeding, risk stratification

Introduction

Non-traumatic bleeding is a frequent but clinically heterogeneous reason for emergency department (ED) presentation. In contemporary ED practice, the initial evaluation of these patients is increasingly complicated by population aging, multimorbidity, chronic kidney disease, cardiovascular disease, and exposure to multiple drugs that may alter hemostasis. Therefore, the clinical

question is no longer limited to identifying the anatomical source of bleeding; ED physicians must also rapidly determine whether the patient has a potentially fatal bleeding phenotype, whether antithrombotic therapy contributes to bleeding severity, and which physiological markers should trigger closer monitoring or early escalation of care [1–3]. Antithrombotic therapy is central to the prevention of thromboembolic events, but it also creates a major



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challenge at the point of acute care. Antiplatelet agents, vitamin K antagonists, and direct oral anticoagulants (DOACs) are commonly prescribed in older patients who already have a high baseline risk of bleeding because of comorbidity and polypharmacy. In addition, concomitant use of antiplatelet agents, anticoagulants, or non-steroidal anti-inflammatory drugs (NSAIDs) may increase bleeding risk through different mechanisms, including impaired platelet activation, reduced coagulation factor activity, and gastrointestinal mucosal injury [4–7]. The concept of “major bleeding” is not used uniformly across the literature. Definitions vary according to study population, anatomical bleeding site, hemodynamic instability, transfusion requirement, hemoglobin decrease, need for intervention, or involvement of a critical organ or compartment. This variability limits comparison between studies and may be particularly problematic in ED cohorts, where gastrointestinal bleeding, central nervous system (CNS) bleeding, epistaxis, hematuria, hemoptysis, and gynecological bleeding are evaluated within the same clinical workflow [1]. In the present study, the International Society on Thrombosis and Haemostasis (ISTH) criteria were selected to define major bleeding because they combine clinically meaningful outcomes with objective criteria that can be applied across heterogeneous bleeding presentations. The ISTH definition captures fatal bleeding, critical-site bleeding, substantial hemoglobin decline, and transfusion requirement, thereby providing a pragmatic framework for ED risk stratification rather than a bleeding-site-specific classification alone [8]. Although previous studies have examined specific bleeding subgroups such as gastrointestinal bleeding, intracerebral hemorrhage, epistaxis, hematuria, or hemoptysis, fewer studies have evaluated the overall ED profile of non-traumatic bleeding patients while simultaneously considering antithrombotic exposure, bleeding severity, physiological compromise, and short-term mortality. This gap is clinically important because ED disposition decisions are often made before definitive source control, endoscopic intervention, surgical management, or specialist follow-up is completed [1,9–11]. We therefore hypothesized that, among adults presenting to the ED with non-traumatic bleeding, mortality would be associated more strongly with bleeding severity, bleeding site, and markers of acute physiological compromise than with antithrombotic exposure alone. The aim of this study was to describe the clinical and antithrombotic profile of ED patients with non-traumatic bleeding and to identify factors associated with in-hospital and 30-day mortality using a prospective observational cohort.

Materials and Methods

Study Design, Setting, and Population

This single-center prospective observational study was conducted in the ED after approval by the Non-Invasive Ethics Committee of

Dokuz Eylül University (Protocol No: 2021/02-55). Consecutive adult patients presenting between January and June 2021 with symptoms related to non-traumatic bleeding were screened for eligibility. The study team did not interfere with diagnostic or therapeutic management, including transfusion, reversal therapy, endoscopy, surgical consultation, admission, discharge, or follow-up decisions.

Inclusion criteria were age 18 years or older, presentation to the ED with bleeding symptoms, and absence of trauma history. Exclusion criteria included end-stage cirrhotic liver disease, hemophilia A or B, von Willebrand disease, Bernard-Soulier syndrome, and Glanzmann thrombasthenia. Of 310 screened individuals, 13 were excluded because of cirrhosis-related complications, leaving 297 patients for analysis. Patients who died during ED follow-up were included in the in-hospital mortality analysis. Patients who left the ED before completing treatment were included in the outcome analyses if survival status could be verified. Survival status and, when applicable, date of death was confirmed through the hospital information management system, which is integrated with the national death notification/registry network and provides official death records regardless of the place of death (Fig. 1).

Data Collection and Medication Use Verification

Data were initially collected using a standardized study form. After written informed consent was obtained, data collection was performed by a physician member of the study team who was not the primary physician responsible for the patient's clinical care. The completed forms were subsequently transferred to a digital database and checked by another member of the study team for completeness and consistency.

Collected variables included age, sex, comorbidities, previous bleeding history, bleeding site, vital signs, physical examination findings, laboratory parameters, medication use, and clinical outcomes. Medication use included antiplatelet agents, anticoagulants, NSAIDs, drug combinations, specific drug names, and clinical indications when available.

Medication use was primarily assessed through patient or family interview and was cross-checked with previous electronic medical records and prescription information whenever available. This verification process was used to distinguish active medication use from medications that had only been prescribed previously but were not being taken at the time of ED presentation. For patients residing in nursing homes, medication information was additionally verified by contacting the nursing home staff or the responsible nurse.

Definition of Major Bleeding and Outcomes

Major bleeding was defined according to the ISTH criteria as one or more of the following: fatal bleeding; symptomatic bleeding

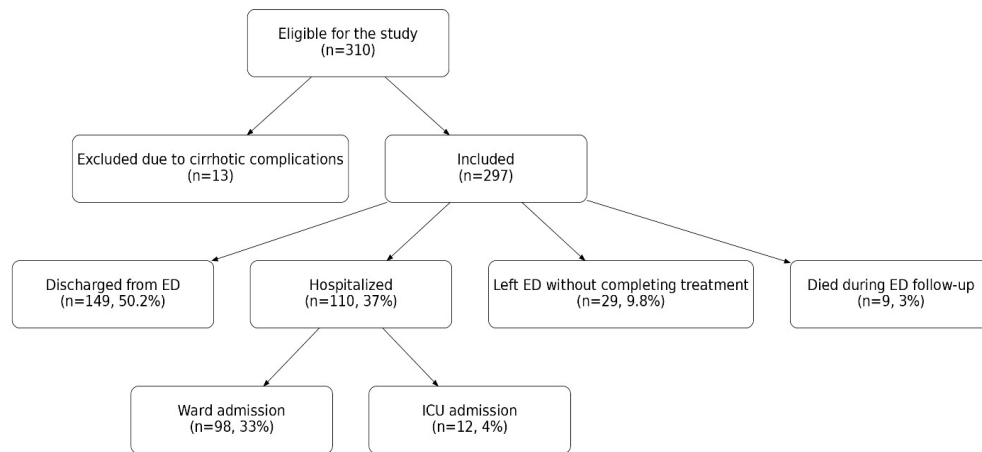


Figure 1. Flowchart of the study population.
Emergency Department (ED) Intensive Care Unit (ICU)

in a critical area or organ, including intracranial, intraspinal, retroperitoneal, intra-articular, pericardial, or intramuscular bleeding with compartment syndrome; a hemoglobin decrease of at least 2 g/dL attributable to bleeding; or transfusion of at least 2 units of blood products [8].

The primary outcomes were in-hospital mortality and 30-day mortality. In-hospital mortality was defined as death occurring during ED follow-up or subsequent hospitalization after admission from the ED. Thirty-day mortality was defined as death from any cause within 30 days after the index ED presentation. Survival status and, when applicable, date of death was verified primarily through the hospital information management system, which is integrated with the national death notification/registry network and provides official death records regardless of the place of death within Türkiye. When clarification was needed or electronic registry information was unavailable at the time of follow-up, patients or family members were contacted by telephone to confirm survival status.

Bias Reduction and Sample Size Considerations

To reduce selection bias, all eligible non-traumatic bleeding presentations during the predefined study period were screened using the same inclusion and exclusion criteria. Because this was a single-center ED cohort, the findings should be interpreted as reflecting the case-mix and clinical pathways of the study institution rather than the full national ED population.

No formal a priori sample size calculation was performed before enrollment. The final cohort size was determined by the number of eligible patients presenting during the study period. For transparency, the final analysis included 24 in-hospital deaths and 36 deaths within 30 days; therefore, the number of variables

entered multivariable models was restricted to reduce overfitting risk. Model results were interpreted as exploratory and hypothesis-generating rather than as definitive causal estimates.

Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY). Continuous variables are presented as mean±standard deviation or median and interquartile range according to distribution, and categorical variables are presented as number and percentage. Normality was evaluated using the Shapiro-Wilk test. Continuous variables were compared using the independent-samples t test or Mann-Whitney U test, as appropriate. Categorical variables were compared using the chi-square test, Fisher exact test, or Yates continuity correction, as appropriate.

Variables were first evaluated using univariable logistic regression analyses for each mortality outcome. Variables associated with mortality in univariable logistic regression at $p < 0.20$, together with clinically important variables identified a priori, were considered candidate variables for multivariable logistic regression models. Variables that were significant in group comparisons but did not show an independent association in univariable logistic regression, or that did not contribute to the final multivariable model, were not retained. Separate multivariable logistic regression models were constructed for in-hospital mortality and 30-day mortality. Backward stepwise elimination was applied within the multivariable models, with attention to clinical plausibility and the number of outcome events to minimize overfitting. Results are reported as odds ratios (ORs), 95% confidence intervals (CIs), and p values.

Age-adjusted logistic regression models were additionally constructed by adding age as a continuous covariate to the final

multivariable models. To assess potential effect modification, an interaction term between antithrombotic use and major bleeding was added to the logistic regression models. Because menometrorrhagia represents a clinically distinct, sex-specific bleeding subgroup that may differ from other bleeding presentations in terms of age and comorbidity profile, a sensitivity analysis was performed after excluding patients with menometrorrhagia.

Overall model performance was evaluated using the model chi-square statistic and Nagelkerke R^2 . Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test. Multicollinearity was evaluated using tolerance and variance inflation factor (VIF) values. A two-sided p value <0.05 was considered statistically significant.

A post-hoc power analysis was performed to evaluate the adequacy of the sample size ($n=297$) for the multivariable logistic regression models. For the primary outcome of in-hospital mortality (24 events out of 297 patients), a model with two independent predictors (major bleeding and SpO2) achieved a statistical power of 93.4% ($1-\beta=0.934$) to detect a significant association with an alpha level of 0.05. For the 30-day mortality outcome (36 events out of 297 patients), the multivariable model containing five independent predictors achieved a statistical power of 89.1% ($1-\beta=0.891$). These results indicate that the study cohort provided sufficient statistical power (well above the conventional 80% threshold) to identify independent risk factors for both in-hospital and 30-day mortality.

Results

A total of 297 adult patients met the inclusion criteria and were included in the final analysis. The cohort consisted of 152 male and 145 female patients. The mean age was 62.2 ± 18.9 years. Baseline laboratory findings reflected the heterogeneous clinical profile of the cohort. Overall, the mean hemoglobin level was 10.6 ± 3.0 g/dL, mean hematocrit was $32.3\pm8.6\%$, mean creatinine was 1.1 ± 1.1 mg/dL, mean BUN was 29.3 ± 24.3 mg/dL, and mean INR was 1.4 ± 1.2 . Patients with comorbidities had lower hematocrit levels and higher BUN and INR values, while patients with GI bleeding had lower hematocrit levels than those with other common bleeding sites.

The most frequent bleeding site was the gastrointestinal system (48.1%, $n=143$), followed by menometrorrhagia (13.8%, $n=41$), CNS bleeding (10.1%, $n=30$), epistaxis (9.8%, $n=29$), and hematuria (9.1%, $n=27$). Less frequent presentations included hemoptysis, oral cavity bleeding, intramuscular bleeding, cutaneous bleeding, subconjunctival hemorrhage, and dialysis fistula bleeding.

Almost half of the patients ($n=149$, 50.2%) were discharged from the ED. Ninety-eight patients (33.0%) were admitted to the ward, 12 patients (4.0%) were admitted to the intensive care unit, 29 patients (9.8%) left the ED before completing treatment, and 9 patients (3.0%) died during ED follow-up. Among admitted patients, 15 additional deaths occurred during ward or intensive care follow-up, resulting in total in-hospital mortality of 8.1% ($n=24$); (Fig. 1).

A total of 166 patients (55.9%) were using at least one antithrombotic agent. Eighty-three patients (27.9%) were using a single antiplatelet agent, 21 (7.1%) were using dual antiplatelet therapy, and one patient (0.3%) was receiving triple antiplatelet therapy. NSAID use was reported in 26 patients (8.8%). A total of 131 patients (44.1%) were not using any antithrombotic medication, and 115 patients (38.7%) were not using antiplatelet, anticoagulant, or NSAID therapy (Fig. 2).

Antithrombotic use varied by bleeding site. Antiplatelet therapy was the most common medication group among patients with epistaxis, GI bleeding, hematuria, CNS bleeding, and hemoptysis (48.3%, 40.6%, 48.1%, 26.7%, and 43.8%, respectively), whereas anticoagulant use was most frequent in patients with menometrorrhagia (14.6%). Combined antiplatelet and anticoagulant therapy were observed in 9 patients (3.0%).

The frequency of major bleeding increased numerically with the number of antiplatelet agents, and an exploratory test for linear trend was statistically significant (linear-by-linear association, $p=0.033$). However, the overall exact association was

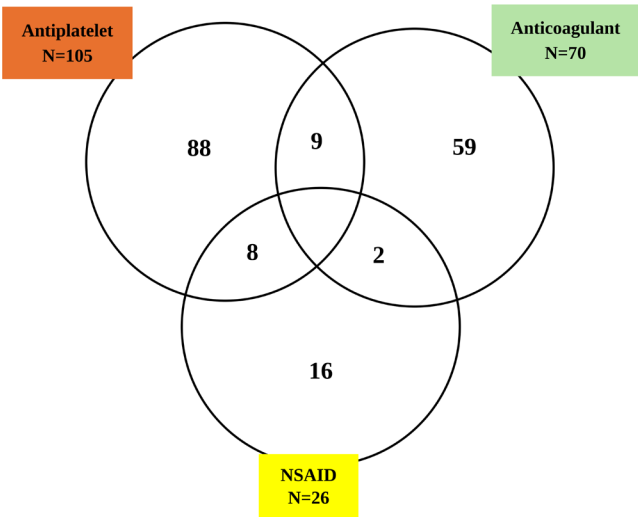


Figure 2. The distribution of antiplatelet, anticoagulant and non-steroidal anti-inflammatory drugs use according to medication combination among the study patients. Non-Steroidal Anti-Inflammatory Drugs (NSAID)

not statistically significant ($p=0.064$), and the finding should be interpreted cautiously because only one patient was receiving triple antiplatelet therapy.

Major bleeding was observed in 124 patients (41.8%). Patients with major bleeding were older than those without major bleeding (67.8 ± 16.6 vs. 58.2 ± 19.5 years, $p < 0.001$). Male sex and comorbidity were also associated with a higher frequency of major bleeding. All 30 patients with CNS bleeding fulfilled major bleeding criteria, which is expected because CNS bleeding is included among critical-site bleeding events in the ISTH definition.

In-hospital mortality was 8.1% ($n=24$). In univariable comparisons, in-hospital mortality was associated with older age, higher creatinine, higher BUN, higher INR, higher pulse rate, lower oxygen saturation, and major bleeding. In the final multivariable model, major bleeding (OR=7.223, 95% CI: 2.268-23.005, $p=0.001$) and lower oxygen saturation (OR=0.757, 95% CI: 0.665-0.860, $p < 0.001$) remained independently associated with in-hospital mortality. After adjustment for age, major bleeding and oxygen saturation remained statistically significant predictors of in-hospital mortality. Age itself was not independently associated with in-hospital mortality. Antithrombotic exposure did not significantly modify the association between major bleeding and mortality (Table 1-5).

The 30-day mortality rate was 12.1% ($n=36$). Thirty-day mortality was higher among patients with hypertension and among those with major bleeding. Patients who died within 30 days had lower hemoglobin and hematocrit values and higher BUN values. In the final multivariable model, CNS bleeding (OR=4.592, 95% CI: 1.553-13.578, $p=0.006$), hypertension (OR=2.239, 95% CI: 1.003-4.998, $p=0.049$), BUN (OR=1.024, 95% CI: 1.010-1.037, $p=0.001$), pulse rate (OR=1.024, 95% CI: 1.002-1.045, $p=0.029$), and oxygen saturation (OR=0.822, 95% CI: 0.734-0.920, $p=0.001$) were independently associated with 30-day mortality. After adjustment for age, the associations of CNS bleeding, BUN, pulse, and oxygen saturation with 30-day mortality remained largely unchanged. However, the association between hypertension and 30-day mortality was attenuated and no longer statistically significant. Age was not independently associated with 30-day mortality in the multivariable model (Table 4, Table 5).

In the multivariable model for in-hospital mortality, major bleeding and lower oxygen saturation remained independently associated with mortality. The model was statistically significant, $\chi^2(2)=38.826$, $p < 0.001$, Nagelkerke $R^2=0.285$, and showed acceptable calibration, Hosmer-Lemeshow $\chi^2(5)=6.384$, $p=0.271$. Multicollinearity was not detected (VIF=1.027 for both variables). In the multivariable model for 30-day mortality, CNS bleeding,

Table 1. Demographic and clinical characteristics according to major bleeding status

Characteristic	Major bleeding (n=124)	No major bleeding (n=173)	p
Age, years	67.8±16.6	58.2±19.5	<0.001
Sex			0.007
Female	49 (33.8)	96 (66.2)	
Male	75 (49.3)	77 (50.7)	
Previous bleeding history			0.715
Yes	39 (43.3)	51 (56.7)	
No	85 (41.1)	122 (58.9)	
Any comorbidity			0.009
Yes	97 (46.6)	111 (53.4)	
No	27 (30.3)	62 (69.7)	
Bleeding site			<0.001
Central nervous system	30 (100.0)	0 (0.0)	
Gastrointestinal	75 (52.4)	68 (47.6)	
Epistaxis	4 (13.8)	25 (86.2)	
Hematuria	4 (14.8)	23 (85.2)	
Hemoptysis	4 (25.0)	12 (75.0)	
Menometrorrhagia	5 (12.2)	36 (87.8)	
Other	2 (18.2)	9 (81.8)	

Continuous variables are presented as mean $\pm$ standard deviation. Categorical variables are presented as n (%); percentages are calculated across major bleeding status within each row. p values were obtained using the appropriate two-group or overall categorical comparison. CNS bleeding is classified as major bleeding under the ISTH critical-site criterion.

hypertension, higher BUN, higher pulse rate, and lower oxygen saturation remained independently associated with mortality. The model was statistically significant, $\chi^2(5)=46.939$, $p < 0.001$, Nagelkerke $R^2=0.280$, and showed good calibration, Hosmer-Lemeshow $\chi^2(8)=2.138$, $p=0.976$. No problematic multicollinearity was observed (VIF range: 1.032–1.126). After excluding patients with menometrorrhagia, the results remained largely consistent with the main analyses, with no material change in the direction or interpretation of the main associations.

Discussion

The present study suggests that mortality among ED patients with non-traumatic bleeding is driven primarily by bleeding severity, critical-site involvement, and early physiological compromise rather than antithrombotic exposure alone. This distinction is clinically important. In the ED, medication exposure is often

Table 2. Antithrombotic and NSAID exposure profile and observed clinical outcomes

Panel A. Mutually exclusive medication categories				
Medication category	Total, n (%)	Major bleeding, n (%)	In-hospital mortality, n (%)	30-day mortality, n (%)
No antiplatelet, anticoagulant, or NSAID use	115 (38.7)	42 (36.5)	9 (7.8)	12 (10.4)
Antiplatelet only	88 (29.6)	39 (44.3)	7 (8.0)	9 (10.2)
Anticoagulant only	59 (19.9)	27 (45.8)	5 (8.5)	10 (16.9)
NSAID only	16 (5.4)	5 (31.3)	0 (0.0)	2 (12.5)
Antiplatelet + NSAID	8 (2.7)	5 (62.5)	2 (25.0)	2 (25.0)
Anticoagulant + NSAID	2 (0.7)	1 (50.0)	0 (0.0)	0 (0.0)
Antiplatelet + anticoagulant	9 (3.0)	5 (55.6)	1 (11.1)	1 (11.1)
Total	297 (100.0)	124 (41.8)	24 (8.1)	36 (12.1)
Panel B. Major bleeding according to the number of concurrent antiplatelet agents				
Number of antiplatelet agents	Total, n (%)	Major bleeding, n (%)	p	
0	192 (64.6)	75 (39.1)	0.033	
1	83 (27.9)	34 (41.0)		
2	21 (7.1)	14 (66.7)		
3	1 (0.3)	1 (100.0)		

In Panel A, percentages in the Total column were calculated using the full cohort as the denominator, whereas outcome percentages were calculated within each medication category. In Panel B, the overall association across antiplatelet-count categories was assessed using the Fisher–Freeman–Halton exact test ($p=0.064$), and the linear trend across the ordered categories was evaluated using the linear-by-linear association test (P for trend =0.033). The observed trend should be interpreted cautiously because only one patient was receiving three antiplatelet agents. NSAID, non-steroidal anti-inflammatory drug.

immediately visible and may dominate the initial assessment; however, our findings suggest that risk stratification should prioritize the patient's current clinical state, the anatomical consequences of bleeding, and evidence of systemic vulnerability.

The predominance of gastrointestinal bleeding in this cohort is consistent with prior ED-based reports and supports the view that gastrointestinal hemorrhage remains the most common non-traumatic bleeding phenotype encountered in acute care. However, the prognostic meaning of bleeding site was not uniform. Gastrointestinal bleeding contributed substantially to case volume and anemia burden, whereas CNS bleeding carried disproportionate prognostic weight. These findings highlight that the prevalence of a bleeding site does not necessarily reflect its prognostic impact. Critical-site bleeding may be associated with death through direct organ injury, neurological deterioration, secondary pulmonary complications, aspiration, and reduced ability to compensate for physiological stress [1,10,12].

The use of ISTH criteria helped translate this heterogeneous clinical spectrum into a severity construct that was strongly associated with in-hospital mortality. The association between major bleeding and in-hospital death is biologically plausible because the ISTH definition captures events that already indicate

severe systemic or anatomical impact, including fatal bleeding, critical-site bleeding, substantial hemoglobin decrease, and transfusion requirement. The finding that all CNS bleeding events met major bleeding criteria should therefore be interpreted not as an unexpected statistical result, but as a consequence of the critical-site component of the ISTH definition [8].

A notable finding was that overall antithrombotic exposure was not independently associated with in-hospital or 30-day mortality after multivariable adjustment. This should not be interpreted as evidence that antithrombotic drugs are clinically irrelevant in bleeding presentations. Rather, several alternative explanations are possible. Antithrombotic use may increase the likelihood of bleeding presentation or major bleeding, but mortality after presentation may be driven more directly by bleeding site, physiological reserve, renal function, and early clinical deterioration. Additionally, patients known to be using anticoagulant or antiplatelet agents may be recognized earlier as high risk, monitored more closely, triaged more aggressively, or referred more rapidly for reversal, endoscopy, imaging, or specialist evaluation; this reverse surveillance bias could attenuate the independent association between medication exposure and mortality. Drug class, dosage, timing of the last dose, renal clearance, adherence, and reversal therapy could not be fully

Table 3. Demographic, clinical, and laboratory characteristics according to in-hospital mortality status

Characteristic	In-hospital death (n=24)	No in-hospital death (n=273)	p
Age, years	70.8±16.3	61.4±18.9	0.019
Sex			0.171
Female	8 (5.5)	137 (94.5)	
Male	16 (10.5)	136 (89.5)	
Previous bleeding history			0.916
Yes	8 (10.0)	82 (90.0)	
No	16 (7.7)	191 (92.3)	
Any comorbidity			0.086
Yes	21 (10.1)	187 (89.9)	
No	3 (3.4)	86 (96.6)	
Systolic blood pressure, mmHg	132.8±35.8	133.2±26.8	0.916
Diastolic blood pressure, mmHg	78.8±21.7	77.9±13.5	0.805
Pulse rate, beats/min	94.1±19.4	86.5±17.1	0.012
SpO ₂ , %	93.8±5.0	97.3±2.1	<0.001
Body temperature, °C	36.3±0.5	36.2±0.2	0.733
Respiratory rate, breaths/min	18.1±3.1	17.4±5.6	0.147
Hemoglobin, g/dL	9.9±3.3	10.7±2.9	0.308
Hematocrit, %	30.2±9.8	32.4±8.4	0.334
Platelet count, /μL	288,500±116,251	269,487±194,494	0.233
Creatinine, mg/dL	1.5±1.1	1.1±1.1	0.024
BUN, mg/dL	45.1±34.7	27.9±22.7	0.003
INR	1.7±1.6	1.4±1.2	0.044
aPTT, s	45.0±39.9	32.8±19.8	0.120
PT, s	21.9±24.9	17.7±20.0	0.103
Major bleeding			<0.001
Yes	20 (16.1)	104 (83.9)	
No	4 (2.3)	169 (97.7)	

Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as n (%); percentages are calculated across mortality status within each row. BUN: Blood urea nitrogen; INR: International normalized ratio; aPTT: Activated partial thromboplastin time; PT: Prothrombin time; SpO₂: Peripheral oxygen saturation.

captured by the broad medication categories used in this analysis [2,13,14].

The observed increase in major bleeding frequency with increasing number of antiplatelet agents is clinically meaningful, even though subgroup sizes were small. Combination antithrombotic therapy can impair hemostasis through multiple pathways, and previous studies have reported higher bleeding risk with dual or combined regimens [4,15]. In ED practice, these findings support careful medication reconciliation and a low threshold for identifying

patients receiving dual antiplatelet therapy or combined antiplatelet-anticoagulant therapy as potentially high-risk, even when the final mortality model does not retain antithrombotic exposure as an independent predictor [4,5].

Lower oxygen saturation was independently associated with both in-hospital and 30-day mortality. This variable may function as an early global marker of physiological decompensation rather than a bleeding-specific marker [16,17]. In patients with CNS bleeding, reduced consciousness, aspiration risk, impaired airway

Table 4. Demographic, clinical, and laboratory characteristics according to 30-day mortality status

Characteristic	Death within 30 days (n=36)	Alive at 30 days (n=261)	p
Age, years	70.4±14.5	61.1±19.1	<0.001
Sex			0.460
Female	15 (10.3)	130 (89.7)	
Male	21 (13.8)	131 (86.2)	
Previous bleeding history			0.538
Yes	13 (14.4)	77 (85.6)	
No	23 (11.1)	184 (88.9)	
Hypertension			0.012
Yes	22 (18.3)	98 (81.7)	
No	14 (7.9)	163 (92.1)	
Systolic blood pressure, mmHg	127.3±31.7	133.9±26.9	0.178
Diastolic blood pressure, mmHg	77.4±19.5	78.0±13.4	0.859
Pulse rate, beats/min	95.9±22.8	85.9±16.2	0.015
SpO ₂ , %	94.8±4.6	97.3±2.1	0.002
Body temperature, °C	36.2±0.4	36.2±0.2	0.394
Respiratory rate, breaths/min	18.1±3.0	17.4±5.7	0.483
Hemoglobin, g/dL	9.5±3.0	10.8±2.9	0.018
Hematocrit, %	29.1±8.9	32.7±8.4	0.017
Platelet count, /μL	271,277±120,675	270,988±103,387	0.988
Creatinine, mg/dL	1.4±1.0	1.1±1.1	0.099
BUN, mg/dL	45.9±34.1	27.0±21.7	<0.001
INR	1.8±1.6	1.3±1.5	0.140
aPTT, s	44.3±40.1	32.3±18.2	0.085
PT, s	23.3±27.6	17.3±19.2	0.210
Major bleeding			<0.001
Yes	26 (21.0)	98 (79.0)	
No	10 (5.8)	163 (94.2)	

Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as n (%); percentages are calculated across mortality status within each row. BUN: Blood urea nitrogen; INR: International normalized ratio; aPTT: Activated partial thromboplastin time; PT: Prothrombin time; SpO₂: Peripheral oxygen saturation.

reflexes, and neurogenic pulmonary edema may contribute to hypoxemia [18,19]. In patients with gastrointestinal bleeding or hemoptysis, hypoxemia may reflect aspiration, underlying cardiopulmonary disease, anemia-related oxygen delivery failure, or shock physiology [20]. Therefore, SpO₂ should be interpreted as an immediately available bedside warning signal that integrates respiratory, circulatory, and neurological risk.

Pulse rate and BUN were independently associated with 30-day mortality. Tachycardia may indicate sympathetic activation, blood

loss, pain, hypovolemia, infection, or cardiopulmonary stress, and may remain informative even when blood pressure is not significantly different between survivors and non-survivors. BUN elevation may represent renal hypoperfusion, chronic kidney disease, dehydration, protein load from upper gastrointestinal bleeding, or overall frailty [21–23]. The persistence of BUN in the 30-day mortality model suggests that renal and metabolic vulnerability may influence outcomes beyond the immediate bleeding episode.

Table 5. Final multivariable logistic regression models for in-hospital and 30-day mortality

Outcome and variable	Primary model OR (95% CI)	p	Age-adjusted model OR (95% CI)	p
In-hospital mortality				
Major bleeding (reference: no)	7.223 (2.268–23.005)	0.001	6.653 (2.055–21.543)	0.002
SpO ₂ , per 1 percent increase	0.757 (0.665–0.860)	<0.001	0.764 (0.672–0.869)	<0.001
Age, per 1-year increase	—	—	1.012 (0.981–1.043)	0.460
30-day mortality				
CNS bleeding (reference: no)	4.592 (1.553–13.578)	0.006	4.878 (1.631–14.588)	0.005
Hypertension (reference: no)	2.239 (1.003–4.998)	0.049	1.964 (0.861–4.478)	0.109
BUN, per 1 mg/dL increase	1.024 (1.010–1.037)	0.001	1.023 (1.009–1.037)	<0.001
Pulse rate, per 1 beat/min increase	1.024 (1.002–1.045)	0.029	1.025 (1.004–1.046)	0.021
SpO ₂ , per 1 percent increase	0.822 (0.734–0.920)	0.001	0.831 (0.743–0.930)	0.001
Age, per 1-year increase	—	—	1.017 (0.989–1.045)	0.239

Primary models: in-hospital mortality—model $\chi^2(2) = 38.826$, $p < 0.001$; Nagelkerke $R^2 = 0.285$; Hosmer–Lemeshow $\chi^2(5) = 6.384$, $p = 0.271$; VIF = 1.027. Thirty-day mortality—model $\chi^2(5) = 46.939$, $p < 0.001$; Nagelkerke $R^2 = 0.280$; Hosmer–Lemeshow $\chi^2(8) = 2.138$, $p = 0.976$; VIF range = 1.032–1.126. Candidate variables were evaluated in univariable logistic regression; variables with $p < 0.20$ and clinically prespecified variables were considered for multivariable modelling, followed by backward elimination. Variables such as BUN and pulse rate were not retained in the final in-hospital model because they did not demonstrate an independent association after the prespecified variable-selection process. CNS, central nervous system; BUN, blood urea nitrogen; CI, confidence interval; OR, odds ratio; SpO₂, peripheral oxygen saturation; VIF, variance inflation factor.

Hypertension was associated with 30-day mortality in the main multivariable model, but its effect was attenuated after age adjustment. This suggests that hypertension may partly operate as a marker of older age and vascular comorbidity rather than as an isolated causal determinant of death in the overall cohort. Nevertheless, hypertension remains clinically relevant because of its established relationship with intracerebral hemorrhage, hematoma expansion, and other vascular bleeding phenotypes [12,24].

Limitations

Several limitations should be acknowledged. First, this was a single-center prospective observational cohort, and the findings may reflect the case-mix, referral patterns, triage thresholds, treatment pathways, and specialist availability of the study institution. Although consecutive eligible patients were screened during the predefined study period, external validity may be limited, and multicenter studies are needed before these findings can be generalized to other ED populations. Due to the observational nature of this cohort medication exposure was assessed through patient or family report and cross-checked with electronic medical records or prescription information when available. However, exact timing of the last dose, adherence, dose intensity, renal dose adjustment, over-the-counter NSAID use, and temporary discontinuation before ED presentation could not be fully verified in all patients. Therefore, misclassification of active medication exposure is possible.

Although the cohort was clinically heterogeneous, non-traumatic bleeding presentations included younger patients with menometrorrhagia, older patients with gastrointestinal bleeding, patients with CNS bleeding, and smaller subgroups such as hemoptysis, epistaxis, hematuria, and other bleeding sites. This heterogeneity reflects real ED practice, but it may also mask subgroup-specific mortality patterns. In particular, the relatively low risk menometrorrhagia subgroup may have diluted mortality estimates and attenuated associations between age, comorbidity, antithrombotic exposure, and outcomes. Although sensitivity analysis after excluding menometrorrhagia did not materially change the main interpretation, subgroup-specific estimates should still be interpreted cautiously.

Drug plasma levels, anti-factor Xa activity, thrombin time, DOAC-specific assays, platelet function tests, and other detailed hemostatic measurements were not routinely available. This limits the ability to distinguish between nominal medication exposure and clinically relevant anticoagulant or antiplatelet effect at the time of bleeding. As a result, the absence of an independent mortality association for antithrombotic exposure should not be interpreted as absence of pharmacological effect.

The analysis did not include detailed interventional variables that may influence mortality, such as timing of endoscopy, timing of surgery, timing and type of reversal therapy, use of prothrombin complex concentrate or specific antidotes, timing of transfusion,

timing of angiographic intervention, airway management, or intensive care interventions. These factors may act as mediators between bleeding severity and mortality or as confounders reflecting clinical severity. Their absence limits causal interpretation and prevents assessment of whether aggressive treatment modified mortality risk. Because of the observational design, causality cannot be established. The associations identified in this study may reflect direct effects of bleeding severity, underlying comorbidity, treatment decisions, unmeasured frailty, or residual confounding. The results should therefore be used to support ED risk stratification and future hypothesis generation rather than to infer causal relationships between antithrombotic exposure, bleeding severity, and mortality.

Conclusion

Taken together, these findings support a practical ED approach in which non-traumatic bleeding patients are not risk-stratified by antithrombotic use alone. A pragmatic first-pass assessment may include: (1) identification of critical-site bleeding, particularly CNS bleeding; (2) application of ISTH major bleeding criteria; (3) bedside assessment of oxygen saturation and pulse rate; (4) early review of renal function and BUN; and (5) structured medication reconciliation focusing on antiplatelet-anticoagulant combinations, NSAID exposure, and timing of last dose when available. Patients with critical-site bleeding, ISTH major bleeding, low SpO₂, tachycardia, or elevated BUN should be considered for closer monitoring, early senior review, and earlier involvement of relevant specialties.

Ethics

Ethics Committee Approval: This study was approved by the Dokuz Eylul University (Date: 18.01.2021, Decision no: 2021/02-55).

Informed Consent: Written informed consent was obtained.

Conflict of Interest: None declared.

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