Am J Transl Res 2026;18(10):9553-9563
www.ajtr.org /ISSN:1943-8141/AJTR0175231

Original Article

Endoscopy timing and rebleeding in acute upper gastrointestinal bleeding: independent and interactive effects of hemodynamic stability

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Received July 7, 2026; Accepted September 3, 2026; Epub October 15, 2026; Published October 30, 2026

Abstract: Objectives: To explore the independent and interactive effects of endoscopy timing and admission hemodynamic status on 30-day post-hemostasis rebleeding in patients with acute upper gastrointestinal bleeding (AUGIB). Methods: In this retrospective single-center cohort study, we enrolled 208 AUGIB patients. Patients were divided into ultra-early (< 6 h), early (6-24 h), delayed (> 24 h) endoscopy groups, and hemodynamically stable/unstable subgroups. Multivariable logistic regression was applied to identify independent predictors. Multiplicative and additive interaction analyses were performed, and a sensitivity analysis restricted to non-variceal bleeding was conducted. A temporal validation cohort of 47 consecutive patients was additionally analyzed to evaluate the clinical applicability and generalizability of the prediction model. Results: Overall 30-day rebleeding rate reached 16.83%. After covariate adjustment, delayed endoscopy (adjusted OR = 4.94, 95% CI 1.85-13.16, P = 0.001) and hemodynamic instability (adjusted OR = 2.45, 95% CI 1.08-5.55, P = 0.032) independently elevated rebleeding risk. In the temporal validation cohort, the model achieved an AUC of 0.85 (95% CI: 0.72-0.97), with good calibration (Hosmer-Lemeshow P = 0.973), supporting the model's robustness and clinical utility. Subgroup analysis showed that the difference in rebleeding rates was minimal among stable patients, while unstable patients with delayed endoscopy had a 55.0% rebleeding rate. Delayed endoscopy × hemodynamic instability showed borderline multiplicative interaction (OR = 6.22, P = 0.081) and significant additive synergism (RERI = 7.83, AP = 0.84). Sensitivity analysis reproduced consistent trend without statistical significance. Conclusions: Delayed endoscopy and hemodynamic instability are independent rebleeding risk factors. Their synergistic interaction mainly exists in additive scale. Hemodynamically unstable AUGIB patients should receive endoscopic hemostasis within 24 h to reduce recurrent bleeding risk.

Keywords: Acute upper gastrointestinal bleeding, endoscopy timing, hemodynamic stability, rebleeding, interaction effect

Introduction

Acute upper gastrointestinal bleeding (AUGIB) remains one of the most common and life-threatening emergencies encountered in gastroenterology and emergency medicine [1]. Its clinical course is notoriously unpredictable: a patient who presents as stable at triage may deteriorate rapidly, while another with significant hematemesis may stabilize with timely resuscitation [2]. With an estimated annual incidence ranging from 15 to 172 per 100,000 population and a rising trend attributed to population aging, AUGIB places a substantial burden on healthcare systems worldwide [3]. Endoscopy currently serves as the cornerstone of both diagnosis and treatment, offering the dual advantage of identifying the bleeding source and delivering targeted hemostasis in a single procedure [4, 5]. Yet, despite advances in endoscopic techniques and peri-procedural care, rebleeding within 30 days after initial hemostasis remains a devastating complication that independently predicts mortality and prolonged hospitalization [6, 7]. Identifying modifiable risk factors for rebleeding and refining treatment strategies accordingly have therefore become pressing clinical priorities.

https://doi.org/10.62347/WMRK1756

The timing of endoscopic treatment is a key controllable factor influencing the hemostasis effect and prognosis of patients, but the clinical benefits of this approach remain controversial and inconclusive [8, 9]. Existing studies have confirmed that early endoscopic intervention can quickly control bleeding and shorten the length of hospital stay [10]. However, some studies have suggested that performing emergency endoscopic procedures does not improve the clinical outcomes of patients and may even increase the risk of complications [11, 12]. The hemodynamic status serves as a crucial indicator for assessing the severity of a patient's condition, directly reflecting the body's ability to maintain circulatory compensation [13]. Patients with unstable hemodynamics often have higher systemic stress responses and coagulation dysfunction [14]. At present, most clinical studies focus solely on the impact of endoscopic timing or hemodynamic status on prognosis, and rarely pay attention to the combined effect and interaction between the two.

The limitations of current research have led to a lack of individualized endoscopic timing decision-making basis in clinical practice, making it impossible to formulate precise treatment plans for patients with different hemodynamic conditions. Based on this, this study selected patients with AUGIB as the research subjects, aiming to explore the independent association between the timing of endoscopic treatment and the risk of postoperative rebleeding. It further conducted stratified analysis of the differences in efficacy between stable and unstable hemodynamic populations, and verified whether there was an interaction between the two. The results of this study aim to supplement clinical evidence, provide scientific references for the individualized timing of endoscopic intervention for patients with different severity of conditions, reduce the incidence of postoperative rebleeding, and improve the clinical prognosis of patients.

Materials and methods

Study design and patient population

This retrospective cohort study was conducted at our hospital using data from the electronic medical record (EMR) system. Between January 2024 and December 2025, consecutive adult patients admitted with a diagnosis of AUGIB were screened for eligibility. The diagnosis of AUGIB was based on clinical features such as hematemesis, coffee-ground emesis, melena, or endoscopic evidence of upper GI bleeding (UGIB) [15]. Final analysis included a total of 208 eligible patients. Based on hemodynamic status at admission, patients were categorized as hemodynamically stable (n = 152) and unstable (n = 56). To further evaluate the model's clinical utility and generalizability over time, an independent temporal validation cohort was established by consecutively screening patients who met the same inclusion and exclusion criteria during the subsequent period from January 2026 to March 2026. A total of 47 eligible patients were finally included in the temporal validation cohort. This research strictly adhered to the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University (approval No. 1871). Given the retrospective nature of this study, the requirement for written informed consent was waived by the ethics committee.

Inclusion and exclusion criteria

Inclusion criteria: patients aged ≥ 18 years who had a confirmatory diagnosis of AUGIB; underwent upper GI endoscopy with therapeutic intent during the index hospitalization; complete clinical, laboratory, endoscopic, and follow-up records available. Exclusion criteria: lower gastrointestinal bleeding; obscure gastrointestinal bleeding; gastrointestinal diseases; hemorrhage due to prior gastrointestinal surgery that significantly modified the upper gastrointestinal anatomy; absence of complete key clinical information; death before endoscopy; or repeated admission for the same bleeding episode. For patients with multiple hospitalizations, only the first admission was included in the analysis.

Definitions and measurements

Hemodynamic instability was defined as either systolic blood pressure < 90 mmHg and/or heart rate > 100 beats per minute at presentation, or the need for fluid resuscitation to maintain circulatory stability [16]. Based on the interval between hospital admission and endoscopic intervention, patients were categorized into three groups: ultra-early endoscopy (within

6 hours after admission), early endoscopy (in 6-24 hours after admission), and delayed endoscopy (performed more than 24 hours after admission) [9]. The primary outcome was rebleeding within 30 days after successful initial endoscopic hemostasis [17]. Rebleeding was defined as recurrent hematemesis or melena after initial stabilization, a decrease in hemoglobin level of at least 20 g/L without another identifiable cause, hemodynamic deterioration attributable to recurrent gastrointestinal bleeding, or endoscopic confirmation of recurrent bleeding requiring repeat hemostatic intervention. The occurrence of rebleeding was determined through review of inpatient medical records, nursing documentation, endoscopy reports, discharge records, emergency revisit records, and outpatient follow-up records documented within 30 days after treatment.

Data collection and study variables

All study data were retrospectively collected from the hospital electronic medical record system, laboratory information system, endoscopy database, nursing records, and discharge summaries. Demographic and baseline clinical characteristics included age, sex, body mass index (BMI), smoking status, alcohol abuse history, hypertension, diabetes mellitus, cardiovascular disease, chronic kidney disease, and anticoagulant use. Clinical presentation variables included hematemesis, melena, Glasgow-Blatchford Score (GBS) [18], and hemodynamic status at admission. Endoscopic data included the timing of endoscopy and the etiology of bleeding, which was classified as peptic ulcer bleeding, gastroesophageal variceal bleeding, acute erosive gastritis, or other causes. Laboratory parameters measured at admission included hemoglobin, platelet count, blood urea nitrogen, serum creatinine, serum albumin, and alanine aminotransferase. All laboratory analyses were performed in the hospital central laboratory according to standardized institutional protocols.

Outcomes

The study's main outcome was rebleeding within 30 days of index endoscopic treatment. Rebleeding was defined as recurrent hematemesis or melena after initial stabilization, a decrease in hemoglobin level of at least 20 g/L without another identifiable cause, hemodynamic deterioration attributable to recurrent gastrointestinal bleeding, or endoscopic confirmation of recurrent bleeding requiring repeat hemostatic intervention. To ensure complete and unbiased ascertainment of the primary outcome, a comprehensive follow-up strategy was implemented. For in-hospital events, occurrence of rebleeding was determined through daily review of electronic medical records, nursing documentation, and laboratory results. For patients discharged before the 30-day endpoint, follow-up was conducted via standardized telephone interviews 30 days post-endoscopy by trained research nurses blinded to the patients' endoscopic timing and hemodynamic grouping. In addition, the hospital's electronic medical record system and readmission database were searched to capture any unplanned emergency visits or rehospitalizations for recurrent bleeding at our center. For rebleeding events suspected to have occurred at outside facilities, patients or their families were asked to provide medical records, endoscopic reports, or discharge summaries from the external hospital; these documents were independently reviewed by two senior gastroenterologists who were blinded to the study grouping, and adjudication was reached by consensus in cases of disagreement. The follow-up was successfully completed in 208 of the 219 patients (94.98%), with 11 patients (5.02%) lost to follow-up despite at least three telephone contact attempts on different days and times. Given the low proportion of missing outcome data, patients with incomplete follow-up were excluded from the final analysis without imputation, as this was considered unlikely to introduce substantial bias.

Statistical analysis

Continuous variables were first tested for normality using the Shapiro-Wilk test. Variables conforming to a normal distribution ($P > 0.05$) were presented as mean ± standard deviation (SD) and compared between two groups using Student's t-test or among three groups using one-way analysis of variance (ANOVA). Variables with a non-normal distribution ($P \leq 0.05$) were presented as median (interquartile range, IQR) and compared using the Mann-Whitney U test for two-group comparisons or the Kruskal-Wallis H test for three-group comparisons. Categorical variables were shown as frequencies and percentages and compared using the

chi-square test or Fisher's exact test, as appropriate. The independent predictors of rebleeding after 30 days were analyzed using multivariable logistic regression, with adjusted odds ratios (ORs) and their 95% confidence interval (CI) calculated. Variables considered clinically relevant or showing potential association in univariate analysis were included in the multivariable model. To see if endoscopy timing effects were modified by hemodynamic status, we added multiplicative interaction terms for endoscopy timing and hemodynamic instability into the logistic regression models. The Wald statistic and likelihood ratio tests were performed on multiplicative interactions. The relative excess risk due to interaction, attributable proportion due to interaction, and synergy index were recurrently calculated to evaluate the additive interaction further. The relative excess risk due to interaction (RERI), attributable proportion (AP), and synergy index (S) were calculated to evaluate the additive interaction between endoscopy timing and hemodynamic instability. All three additive interaction metrics were estimated using the method proposed by Hosmer and Lemeshow, which derives these measures from the coefficients of a logistic regression model that includes the two main effect terms and their product term. The 95% confidence intervals for RERI, AP, and S were estimated using the bootstrap method with 1,000 resamples, as the bootstrap approach does not rely on distributional assumptions and provides more robust interval estimates for these nonlinear combinations of regression coefficients. We performed a sensitivity analysis that limited the sample to patients with non-variceal upper gastrointestinal bleeding to test the robustness of the findings. Model discrimination was assessed using the concordance index (C-index), while evaluation of calibration took place using the Hosmer-Lemeshow goodness-of-fit test. Statistical analyses were performed with SPSS and R software and a two-sided *P* value < 0.05 was considered statistically significant.

Results

Baseline characteristics according to hemodynamic status

The study sample comprised 208 patients with upper gastrointestinal (GI) bleeding, 152 (73.1%) were hemodynamically stable and 56 (26.9%) were hemodynamically unstable at presentation. As shown in **Table 1**, there were no significant differences between the two groups regarding age, sex distribution, BMI, current smoking status, alcohol abuse, hypertension, diabetes mellitus, cardiovascular disease, chronic kidney disease, use of anticoagulants, bleeding etiology, and timing of endoscopy (all P > 0.05). Hemodynamically unstable patients were more likely to present with hematemesis (69.6% vs 55.9% P = 0.074). Glasgow-Blatchford score was slightly lower in unstable patients as compared to the stable group (9.39 ± 1.87 vs 9.86 ± 1.52 P = 0.069). The two groups were generally balanced in demographic and clinical characteristics. No significant differences were observed between stable and unstable patients with respect to hemoglobin level [95.70 (IQR 84.55-109.12) vs. 93.36 (IQR 78.67-108.39) g/L, Z = -0.98, P = 0.325], platelet count [191.50 (IQR 132.00-259.25) vs. 161.55 (IQR 94.00-259.50) × 10^9/L, Z = -1.45, P = 0.148], blood urea nitrogen [10.90 (IQR 7.40-15.17) vs. 12.85 (IQR 6.88-17.28) mmol/L, Z = -1.17, P = 0.244], serum creatinine [83.50 (IQR 57.00-113.00) vs. 84.00 (IQR 72.27-117.90) μmol/L, Z = -1.42, P = 0.155], serum albumin (36.16 ± 6.83 vs. 36.49 ± 6.20 g/L, P = 0.750), or alanine aminotransferase levels [39.00 (IQR 24.00-72.00) vs. 42.00 (IQR 16.75-71.00) U/L, Z = -0.18, P = 0.860].

Rebleeding rates stratified by endoscopy timing and hemodynamic status

The rebleeding rates stratified by endoscopic timing and hemodynamic status are shown in **Figure 1**. Among patients with stable hemodynamics, the rebleeding rate was the lowest in the early endoscopic group (8.00%), higher in the delayed group (14.58%), and highest in the ultra-early group (20.69%). Similar patterns were observed in patients with unstable hemodynamics. It is worth noting that the rebleeding rate among unstable patients who received delayed endoscopy was the highest across all subgroups (55.0%), while among unstable patients, the rebleeding rate for those who received early endoscopy was 9.1%, and for those who received ultra-early endoscopy it was 21.4%. In contrast, the rebleeding rate for stable patients remained at a relatively low level regardless of the timing of endoscopy.

Independent predictors of rebleeding

Multivariate logistic regression analysis adjusting for sex, Glasgow-Blatchford Score, bleeding

Table 1. Baseline characteristics of patients stratified by hemodynamic status

Variables	Total (n = 208)	Stable (n = 152)	Unstable (n = 56)	Statistic	*P*
Age, years, Mean ± SD	62.69 ± 11.59	62.26 ± 11.87	63.86 ± 10.80	t = -0.88	0.380
Male, n (%)	138 (66.35)	102 (67.11)	36 (64.29)	χ^2 = 0.15	0.703
BMI, kg/m^2, Mean ± SD	25.38 ± 4.30	25.68 ± 4.12	24.59 ± 4.69	t = 1.63	0.105
Smoking, n (%)	100 (48.08)	74 (48.68)	26 (46.43)	χ^2 = 0.08	0.773
Alcohol Abuse, n (%)	60 (28.85)	42 (27.63)	18 (32.14)	χ^2 = 0.41	0.524
Hypertension, n (%)	94 (45.19)	73 (48.03)	21 (37.50)	χ^2 = 1.83	0.176
Diabetes, n (%)	47 (22.60)	33 (21.71)	14 (25.00)	χ^2 = 0.25	0.615
Cardiovascular disease, n (%)	37 (17.79)	25 (16.45)	12 (21.43)	χ^2 = 0.69	0.405
Chronic kidney disease, n (%)	27 (12.98)	20 (13.16)	7 (12.50)	χ^2 = 0.02	0.900
Hematemesis, n (%)	124 (59.62)	85 (55.92)	39 (69.64)	χ^2 = 3.20	0.074
Melena, n (%)	152 (73.08)	113 (74.34)	39 (69.64)	χ^2 = 0.46	0.498
Glasgow Blatchford Score, Mean ± SD	9.73 ± 1.63	9.86 ± 1.52	9.39 ± 1.87	t = 1.83	0.069
Anticoagulant use, n (%)	76 (36.54)	53 (34.87)	23 (41.07)	χ^2 = 0.68	0.410
Etiology of bleeding, n (%)				χ^2 = 4.83	0.185
Peptic ulcer	125 (60.10)	98 (64.47)	27 (48.21)		
Gastroesophageal varices	54 (25.96)	36 (23.68)	18 (32.14)		
Acute erosive gastritis	22 (10.58)	14 (9.21)	8 (14.29)		
Others	7 (3.37)	4 (2.63)	3 (5.36)		
Timing of endoscopy, n (%)				χ^2 = 1.80	0.407
Early (6-24 h)	97 (46.63)	75 (49.34)	22 (39.29)		
Ultra-early (< 6 h)	43 (20.67)	29 (19.08)	14 (25.00)		
Delayed (> 24 h)	68 (32.69)	48 (31.58)	20 (35.71)		
Hemoglobin, g/L, Mean ± SD	94.92 (82.64, 109.12)	95.70 (84.55, 109.12)	93.36 (78.67, 108.39)	Z = -0.98	0.325
Platelet, × 10^9/L, Mean ± SD	187.00 (121.75, 259.25)	191.50 (132.00, 259.25)	161.55 (94.00, 259.50)	Z = -1.45	0.148
Blood urea nitrogen, mmol/L, Mean ± SD	11.20 (7.27, 16.20)	10.90 (7.40, 15.17)	12.85 (6.88, 17.28)	Z = -1.17	0.244
Creatinine, μmol/L, Mean ± SD	83.90 (64.00, 113.00)	83.50 (57.00, 113.00)	84.00 (72.27, 117.90)	Z = -1.42	0.155
Albumin, g/L, Mean ± SD	36.25 ± 6.65	36.16 ± 6.83	36.49 ± 6.20	t = -0.32	0.750
Alanine aminotransferase, U/L, Mean ± SD	39.00 (22.75, 71.25)	39.00 (24.00, 72.00)	42.00 (16.75, 71.00)	Z = -0.18	0.860

Note: Hemodynamic instability was defined as systolic blood pressure < 90 mmHg and/or heart rate > 100 beats per minute, or requiring fluid resuscitation. SD, standard deviation.

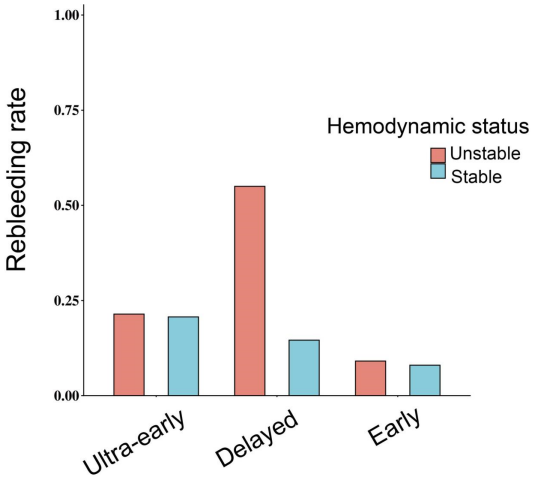


Figure 1. Rebleeding rates stratified by endoscopy timing and hemodynamic status.

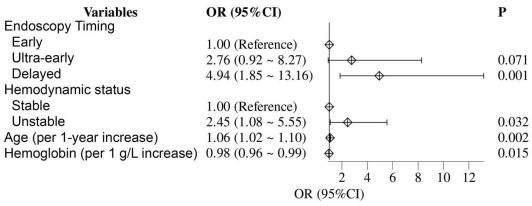


Figure 2. Forest plot of multivariate analysis. Adjusted for sex, Glasgow-Blatchford Score, bleeding etiology, and anticoagulant use.

etiology, and anticoagulant use was used to identify the independent influencing factors of rebleeding (**Figure 2**). Taking early endoscopy (within 6 to 24 hours) as the reference category, delayed endoscopy (> 24 hours) was significantly associated with an increased risk of rebleeding (adjusted OR 4.94, 95% CI 1.85-13.16, P = 0.001). The ultra-early endoscopy (< 6 hours) was associated with a trend toward increased risk (adjusted OR 2.76, 95% CI 0.92-8.27), but this did not reach statistical significance (P = 0.071). Hemodynamic instability was also observed as an independent predictor of rebleeding (adjusted OR 2.45, 95% CI 1.08-

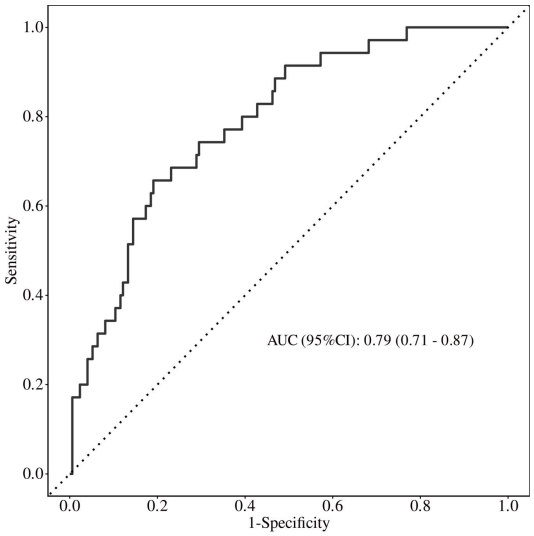


Figure 3. ROC of the multivariate logistic regression model.

5.55, P = 0.032). Additionally, increasing age was associated with an increased risk of rebleeding (adjusted OR per year 1.06, 95% CI 1.02-1.10, P = 0.002), while higher hemoglobin levels had a protective effect (adjusted OR 0.98/g/L, 95% CI 0.96-0.99, P = 0.015). The model had good discrimination (ROC = 0.79, **Figure 3**) and excellent calibration (Hosmer-Lemeshow P = 0.992, **Figure 4**).

Clinical validation of the multivariable prediction model

To further evaluate the clinical applicability and temporal generalizability of the multivariable prediction model, an independent time validation cohort comprising 47 consecutive patients admitted after completion of the derivation cohort was analyzed. The confusion matrix is presented in **Figure 5**.

Among the 47 patients, the model correctly identified 6 of the 9 patients who experienced 30-day rebleeding and correctly classified 32 of the 38 patients without rebleeding. Overall, the model achieved an accuracy of 80.85%, with a sensitivity of 66.67%, specificity of 84.21%, positive predictive value of 50.00%, and negative predictive value of 91.43%. The discriminative performance remained satisfactory in the temporal validation cohort, with an AUC of 0.85 (95% CI: 0.72-0.97). No statistically significant difference in discrimination was observed between the derivation and temporal validation cohorts according to the DeLong test (P = 0.560), indicating stable predictive performance across different enrollment periods. Furthermore, calibration remained excellent, as demonstrated by a Hosmer-Lemeshow goodness-of-fit test *P* value of 0.973, suggesting good agreement between predicted and observed probabilities. Overall, these findings support the robustness and potential clinical utility of the proposed multivariable prediction model in independent patients.

Multiplicative interaction between endoscopy timing and hemodynamic instability

To assess if the impact of endoscopy timing varied based on hemodynamic status, multiplicative interaction analyses were conducted (**Table 2**). No significant interaction was found between ultra-early endoscopy and hemodynamic instability (OR 0.91, 95% CI 0.09-8.98, *P* value = 0.935). Conversely, the interaction term of delayed endoscopy and hemodynamic instability had an estimated OR of 6.22 (95% CI 0.80-48.65), although this was not statistically significant (P = 0.081). The likelihood ratio test of the models with and without interaction terms suggested a trend towards improved model fit once interactions were included (χ^2 = 5.27, P = 0.072). The findings indicate that delayed endoscopy and hemodynamic instability may work together to elevate the risk of rebleeding.

Additive interaction analysis

Table 3 depicts the additive interaction analyses. Ultra-early endoscopy and hemodynamic instability exhibited no evidence of positive additive interaction; both RERI and AP have negative values in this case. In contrast, there was substantial positive additive interaction between delayed endoscopy and hemodynamic instability. The RERI was 7.83 (95% CI 1.86-30.28) suggesting that the excess risk due to concurrent exposure was greater than the sum of their individual effects. The attributable proportion due to interaction was 0.84 (95% CI 0.45-1.00), signifying that approximately 84% of their joint effect is due to interaction. The value of the synergy index (15.34) proved its strong synergism. Overall, this shows that delayed endoscopy and hemodynamic instability work together to increase the risk of rebleeding.

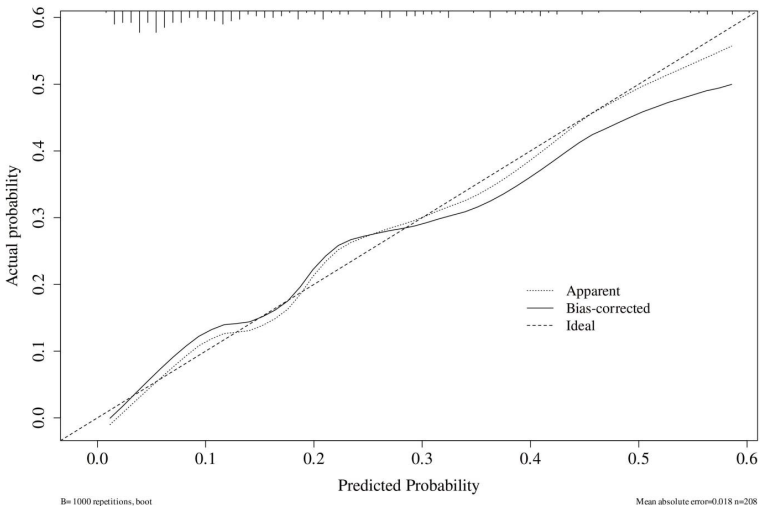


Figure 4. Calibration curve of the multivariate logistic regression model.

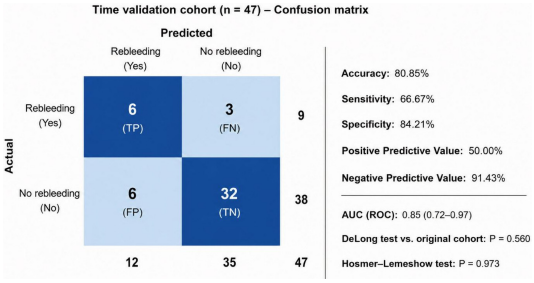


Figure 5. Confusion matrix and clinical validation performance of the multivariable prediction model in the temporal validation cohort.

Table 2. Multiplicative interaction analysis

Interaction term	Multiplicative interaction OR (95% CI)	P*
Ultra-early × Unstable	0.91 (0.09-8.98)	0.935
Delayed × Unstable	6.22 (0.80-48.65)	0.081
Model comparison		
Likelihood ratio test χ^2	5.27	0.072

Note: OR, odds ratio; CI, confidence interval. *P-values were derived from Wald tests. OR > 1 suggests a synergistic effect; OR < 1 suggests an antagonistic effect.

Sensitivity analysis in patients with non-variceal bleeding

The strength of the findings was evaluated using sensitivity analyses excluding patients with gastroesophageal variceal bleeding (**Table 4**). Despite the smaller sample size dulling statistical significance, the interaction estimates retained a significant degree of agreement in their direction and magnitude with previous findings in the primary analysis. In particular, the association between delayed endoscopy and hemodynamic instability was positive on multiplicative and additive scales. The multiplicative interaction OR was 5.78 (95% CI 0.44-75.52) whereas, the RERI and AP were 6.36 and 0.75, respectively. Though the confidence intervals widened and overlapped the null value, likely due to low statistical power, the main result that delayed endoscopy may cause a disproportionally increased risk of rebleeding in hemodynamically unstable patients still holds true. Calibration of the model remained acceptable, as demonstrated by a Hosmer-Lemeshow test *P* value of 0.42.

Discussion

In this study, we examined the associations of endoscopy timing and hemodynamic status with 30-day rebleeding in AUGIB. Three main findings emerged. First, delayed endoscopy performed more than 24 hours after admission was associated with an independent significantly increased odds of rebleeding. Conversely, endoscopy conducted six to twenty-four hours after admission was associated with the most favorable outcomes. Second, hemodynamic instability at presentation was an independent risk factor for rebleeding, serving as a useful marker of severity. The third and most crucial point was that both the multiplicative and additive interaction analyses indicated that the adverse effect of delayed endoscopy was significantly amplified in the presence of hemodynamic instability. Sensitivity analyses confined to non-variceal bleeding reflected a similar trend, reinforcing the robustness of the findings. According to these findings, the prognostic implications of endoscopy timing may vary among patients. In addition, hemodynamic status may act as an important effect modifier in the association between treatment timing and rebleeding.

Despite decades of research, the optimal timing of endoscopy for AUGIB remains a subject

Table 3. Additive interaction analysis

Endoscopy timing	RERI (95% CI)	AP (95% CI)	S (95% CI)
Ultra-early (< 6 h)	-2.69 (-10.08 to 3.22)	-1.17 (-2.50 to 0.48)	0.33 (-0.34 to 2.43)
Delayed (> 24 h)	7.83 (1.86 to 30.28)	0.84 (0.45 to 1.00)	15.34 (-126.83 to 141.17)

Note: RERI, relative excess risk due to interaction; AP, attributable proportion; S, synergy index. RERI > 0, AP > 0, and S > 1 indicate positive additive interaction (synergy).

Table 4. Sensitivity analysis restricted to non-variceal bleeding patients (n = 154)

Analysis	Interaction term	Effect estimate (95% CI)	P
Multiplicative interaction			
Multiplicative OR	Ultra-early × Unstable	2.04 (0.10-41.57)	0.642
Multiplicative OR	Delayed × Unstable	5.78 (0.44-75.52)	0.181
Likelihood ratio test χ^2		2.29	0.318
Additive interaction			
RERI	Ultra-early × Unstable	-1.12 (-8.34 to 7.29)	-
RERI	Delayed × Unstable	6.36 (-0.04 to 32.04)	-
AP	Ultra-early × Unstable	-0.47 (-2.50 to 0.79)	-
AP	Delayed × Unstable	0.75 (-0.01 to 0.99)	-
S	Ultra-early × Unstable	0.55 (-3.18 to 12.38)	-
S	Delayed × Unstable	6.55 (-45.62 to 73.77)	-

Note: OR, odds ratio; CI, confidence interval; RERI, relative excess risk due to interaction; AP, attributable proportion; S, synergy index. OR > 1 suggests a synergistic effect; OR < 1 suggests an antagonistic effect. RERI > 0, AP > 0, and S > 1 indicate positive additive interaction (synergy).

of debate. The current guidelines generally recommend performing endoscopy within 24 hours after the visit, but whether earlier intervention leads to better outcomes remains uncertain [19]. Recent observational and systematic evidence has challenged the traditional assumption that "the sooner, the better". Studies like Guo et al. [9] state that endoscopy within 6 hours was not better than a procedure performed in 6-24 hours range in terms of clinical results. Moreover, for certain patients, it was worse. Lau et al. [20] came to comparable conclusions and determined that there's no evidence for widespread immediate endoscopy benefit over carefully timed intervention. According to the report by Mackiewicz-Pracka et al. [21], outcomes of emergency endoscopy were more strongly influenced by baseline patient characteristics and physiological condition than by timing alone. More recently, Eid et al. [22] demonstrated that the effect of endoscopy timing was significantly different across patient subgroups and bleeding causes recently. In totality, these studies suggest chronological timing alone may be an oversimplified determinant of prognosis.

Our results are very much in line with this idea. The rebleeding rates were lowest when endoscopy was performed within 6-24 hours. Moreover, ultra-early and delayed endoscopies had worse outcomes. One explanation could be that hemostasis effectiveness requires adequate physiological preparation in addition to skilled endoscopic technique [23]. Patients facing a heavy blood loss often need fluid resuscitation, blood transfusion, coagulopathy management, airway protection, and circulatory status optimization before endoscopy performed in an optimal condition [24]. For this reason, procedures performed too early may be done before stabilization is achieved and may therefore impair visualization and efficacy of the procedure. On the other hand, a long delay can cause bleeding to continue, destabilizing clots. When combined, these observations support the notion of a "therapeutic window" in AUGIB, in which the effectiveness of endoscopic intervention depends on an appropriate balance in the urgency and Physiological Optimization and not as early endoscopic intervention in every patient [25]. Although the adjusted odds ratios for age (1.06 per year) and hemoglobin (0.98 per g/L) appeared modest, these effect sizes become clinically meaningful when interpreted in larger increments. A 10-year increase in age corresponds to an approxi-

mately 79% higher rebleeding risk (OR ≈ 1.79), consistent with the well-recognized vulnerability of older patients with diminished physiological reserve [6, 10]. Likewise, each 10 g/L decrement in admission hemoglobin confers an approximately 18% increase in risk (OR ≈ 0.82 per 10 g/L), a magnitude that aligns with clinically relevant thresholds used in transfusion guidelines and the Glasgow-Blatchford Score [18]. Thus, rather than being marginal, these estimates underscore the clinical utility of baseline patient characteristics in individualized risk assessment.

The most novel finding of this study is a potential interaction between delayed endoscopy and hemodynamic instability. While hemodynamic instability has been known to predict adverse outcomes for quite a time, earlier studies have mainly evaluated it as independent prognostic. According to findings by Obeidat et al. [13] approximately twenty-five percent of patients develop shock and/or hemodynamic instability with gastrointestinal bleeding, and it has a significant influence on outcomes. Likewise, hemodynamic instability was reported to be associated with a higher chance of mortality through a retrospective study by Pham et al. [26]. Yet, not much attention has been paid to whether hemodynamic status modifies treatment timing's effect. Surprisingly, according to an international survey of clinicians by Obeidat et al. [27], practitioners globally already regard hemodynamic status as one of the principal determinants that they consider when determining the urgency of endoscopy, although the evidence is scant. Our findings provide quantitative evidence that may help explain this clinical intuition. The highest rebleeding rate was observed in patients who were both hemodynamically unstable and received delayed endoscopy. Additive interaction analyses suggested that a large proportion of excess risk is attributable to the interaction itself. From a biological point of view, it seems reasonable since hemodynamic instability reflects significant blood loss, poor tissue perfusion, activation of inflammatory cascades, platelet dysfunction and coagulation abnormalities [28]. Delays in achieving definitive hemostasis in such situations may have disproportionately deleterious effects. Even though the multiplicative interaction was marginally nonsignificant, the fact that the findings are robust across interaction models and sensitivity analyses suggests a plausible biological interaction may exist. Should this find confirmation in future studies, it will help explain the studies' heterogeneity around optimal endoscopy timing. It also supports the premise that timing decisions should be made according to physiological severity [29].

Our findings advocate the need for risk-stratified and precision-based management of AUGIB from a clinical perspective. Traditionally, management algorithms operate under fixed temporal thresholds. However, increasing evidence suggests individualized assessment. Numerous prediction models of late have shown satisfactory performance in predicting high-risk rebleeders and unfavorable outcomes [30, 31]. Zhuang et al. [32] created a clinically applicable predictive model for AUGIB rebleeding. Zang et al. [33] presented a risk stratification framework based on available clinical indicators. In addition, artificial intelligence and machine learning strategies are creating new opportunities for real-time risk assessment and dynamic clinical decision-making [3, 28]. In this sense, applying hemodynamic assessment on top of recognized risk prediction tools may offer a tangible strategy for refining the timing of endoscopy. Nevertheless, the present findings should be interpreted cautiously and considered hypothesis-generating rather than practice-changing.

It must be acknowledged that several limitations in this work exist. To begin with, this was a retrospective single-center study and therefore subject to the inherent selection bias, information bias, and residual confounding. Following that, the rather modest sample size could have limited the statistical power of interaction analyses and contributed to some estimates' wide confidence intervals. Third, the single measure of hemodynamic status at admission is likely unable to fully capture dynamic physiological changes during hospitalization. The fourth aspect is that while sensitivity analyses supported the robustness of the findings, the heterogeneity attributable to bleeding etiology and treatment strategies cannot be fully excluded. In the end, we were unable to include various potentially relevant variables in our analysis such as transfusion requirements, specific endoscopic hemostatic techniques, vasoactive medications and the detailed coagulation parameters. Further multicenter prospective studies with larger sample sizes are needed to

validate our findings. Specifically, future work should consider propensity score matching to mitigate confounding by indication, as endoscopy timing decisions are inherently influenced by baseline severity. Defining timing from symptom onset rather than hospital admission may better reflect the true bleeding duration, as pre-hospital delays vary considerably. In addition, incorporating dynamic rather than single-admission hemodynamic assessment could enable more nuanced, real-time decision-making. Finally, integrating machine-learning approaches with traditional risk scores holds promise for developing personalized endoscopy timing algorithms.

Conclusion

In this retrospective cohort study, the rebleeding risk in patients with AUGIB was independently associated with a delay to endoscopy of > 24 h and hemodynamic instability at admission. Most important of all, we identified a significant synergism between those two factors so that hemodynamically unstable patients with delayed endoscopy had a disproportionately higher rebleeding rate than the sum of their individual effects. In this context, the timing of endoscopy must be individualized according to the hemodynamic status and the decision to delay beyond 24 hours must be avoided as much as possible, especially in unstable patients. While our findings suggest there is a "therapeutic window" rather than a general "sooner-is-better" paradigm, they need confirmation in larger, prospective, multicenter cohorts. Future work should investigate whether the inclusion of hemodynamic assessment improves upon emerging machine-learning based risk models to optimize personalized timing of endoscopy and clinical outcomes.

Disclosure of conflict of interest

None.

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