

PREDICTORS OF 30-DAY REBLEEDING AFTER SUCCESSFUL ENDOSCOPIC HEMOSTASIS FOR PEPTIC ULCERS: A SYSTEMATIC REVIEW AND EXPLORATORY META-ANALYSIS

S.R. Aliev^{1*}, V.M. Kadyrova¹, T.Kh. Tairov¹, M.S. Musaev¹, A.Kh. Yusupalieva¹, R.R. Akhatova¹ and D.G. Izmailova²

¹Faculty of General Medicine, Astrakhan State Medical University, Ministry of Health of the Russian Federation, Astrakhan, Russia

²Faculty of Pediatrics, Astrakhan State Medical University, Ministry of Health of the Russian Federation, Astrakhan, Russia

*Corresponding Author: Said R. Aliev, Email: said.aliev.1337@gmail.com; ORCID: 0000-0003-1181-2242.

Said R. Aliev: 0000-0003-1181-2242

Viloriya M. Kadyrova: 0009-0000-4967-467X

Tagir Kh. Tairov: 0009-0002-6027-6845

Malik S. Musaev: 0009-0009-4808-2360

Aliya Kh. Yusupalieva: 0009-0006-5487-4637

Ramilla R. Akhatova: 0009-0007-3436-3706

Dilyafuz G. Izmailova: 0009-0005-1498-7744

ABSTRACT

Rebleeding after successful endoscopic hemostasis remains a clinically important complication of peptic ulcer bleeding. We assessed prognostic factors for clinically confirmed rebleeding within 30 days and pooled effects only when predictor definitions, outcome timing, and effect measures were sufficiently comparable. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement. Two reviewers independently screened 1,523 deduplicated records, assessed the available full texts, extracted prognostic estimates, checked cohort overlap, and evaluated risk of bias with the Quality In Prognosis Studies tool. The primary synthesis prioritized adjusted odds ratios from independent cohorts reporting a 30-day outcome; random-effects pooling was prespecified only for genuinely comparable studies. Four independent contemporary cohorts contributed 10 verified adjusted associations, but no identically defined adjusted predictor was reproduced in at least two independent cohorts. The strongest individual associations were reported for shock (adjusted odds ratio, 12.691; 95% confidence interval, 5.129–31.399), estimated glomerular filtration rate <30 mL/min/1.73 m² (adjusted odds ratio, 4.770; 95% confidence interval, 1.168–18.211), higher Rockall risk, and procedure duration >13.5 minutes (adjusted odds ratio, 2.899; 95% confidence interval, 1.768–4.754). Contemporary studies identify several clinically relevant risk signals, but heterogeneity in predictor definitions and multivariable models precludes a reliable pooled adjusted estimate. Future prognostic studies should use standardized definitions and a uniform 30-day outcome.

KEYWORDS: Peptic ulcer; Gastrointestinal hemorrhage; Hemostasis, endoscopic; Recurrence; Prognosis

INTRODUCTION

Rebleeding after technically successful endoscopic hemostasis is clinically distinct from persistent bleeding and primary failure of hemostasis, earlier systematic reviews repeatedly associated recurrent hemorrhage with hemodynamic instability, active bleeding, large ulcers, and anatomically unfavorable ulcer location (Elmunzer et al., 2008; García-Iglesias et al., 2011), although much of this evidence predates routine high-dose proton pump inhibitor therapy and the widespread use of contemporary mechanical or combination endoscopic techniques.

Interpretation of newer prognostic studies is complicated by marked variation in patient selection, endoscopic treatment, predictor definitions, model construction, and follow-up windows; variables carrying the same label may therefore represent different clinical contrasts, while adjusted estimates may not be comparable when covariate structures or effect measures differ, we restricted the review to rebleeding within 30 days after successful primary endoscopic hemostasis, kept adjusted and unadjusted evidence separate, examined possible cohort overlap, and reserved quantitative synthesis for predictor contrasts reproduced in independent populations. Our aim was to identify and critically appraise prognostic factors associated with clinically confirmed 30-day rebleeding after successful endoscopic hemostasis for peptic ulcer bleeding and to determine whether contemporary studies provide sufficiently comparable adjusted estimates for quantitative pooling.

MATERIAL AND METHODS

Reporting standard and eligibility criteria

The review was prepared in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 (Page et al., 2021). We included studies of adults with gastric or duodenal ulcer bleeding in whom primary endoscopic hemostasis had been successful and defined the primary outcome as clinically confirmed rebleeding within 30 days, persistent bleeding, failure of initial hemostasis, non-ulcer sources, and mixed populations from which the target subgroup could not be isolated were excluded from the primary synthesis; candidate prognostic factors also had to be ascertainable by the end of the index hemostatic procedure, the protocol was not prospectively registered, and this limitation was retained in the interpretation, eligibility criteria were not broadened after inspection of study results to create additional pooled contrasts.

Information sources and search

The search was updated on October 3, 2026 and covered each database from inception. The working search file contained 1,496 records from PubMed and 950 from Europe PMC; PMID-based deduplication left 1,523 unique records for screening. Search concepts combined peptic or gastroduodenal ulcer bleeding with rebleeding or recurrent hemorrhage and terms related to prognosis, predictors, and risk factors, while reference lists of relevant reviews and eligible articles were checked for additional reports.

Study selection and verification

Two reviewers independently screened titles and abstracts before assessing the available full texts, resolving disagreements by discussion and consensus, with arbitration by a third reviewer prespecified if necessary. Data extraction, assessment of predictor and outcome compatibility, detection of potentially overlapping cohorts, and Quality In Prognosis Studies (QUIPS) evaluation were also performed independently and then reconciled; multiple publications arising from the same underlying cohort were linked and not counted as separate studies.

The archived selection files contained 65 publications that had progressed beyond title and abstract screening; documented full-text eligibility assessment was preserved for 26, whereas no such record remained for 39; the strict quantitative synthesis was therefore limited to the independently verified evidence set, and the incomplete archival documentation was treated as a major limitation rather than assumed to represent completed screening.

Data extraction and risk of bias

For each eligible publication, we recorded study design, setting, recruitment period, sample size, number of rebleeding events, definitions of successful hemostasis and rebleeding, timing of the outcome, ulcer characteristics, endoscopic and pharmacologic treatment, and all reported prognostic effects. Each estimate was documented together with its measure of association, 95% CI, unit or threshold, reference category, and covariates included in the adjusted model.

Risk of bias was assessed with the six-domain Quality In Prognosis Studies (QUIPS) framework without collapsing domain judgments into a numerical score (Hayden et al., 2013). Particular attention was given to data-driven covariate selection, the relation between event count and model complexity, missing data, simultaneous inclusion of composite scores and their components, residual confounding, and possible cohort overlap.

Statistical analysis

Primary pooling required at least two independent cohorts with the same predictor definition, the same 30-day outcome, and the same effect measure; odds ratios, risk ratios, and hazard ratios were not combined. When compatible cohorts were available, estimates were transformed to the logarithmic scale, between-study variance was estimated by restricted maximum likelihood, and 95% CIs were calculated with modified Hartung-Knapp inference. Unadjusted effects reconstructed from 2×2 tables were analyzed separately, no pooled estimate was produced for $k < 2$, and funnel plots or small-study tests were not planned for fewer than 10 studies per factor, consistent with methodological guidance for prognostic factor reviews (Riley et al., 2019).

RESULTS

Study verification and evidence set

Among 1,523 deduplicated records, 1,458 were excluded after title and abstract screening and 65 publications entered the archived eligibility stage. Full-text assessment documentation was available for 26 publications, of which 22 did not meet the strict criteria for the 30-day adjusted synthesis: eight used a different rebleeding window, six did not allow isolation of the target population after successful primary endoscopic hemostasis, five primarily evaluated treatment effects without an eligible baseline prognostic analysis, and three lacked an extractable compatible multivariable prognostic estimate. Four independent contemporary cohorts met all strict criteria: Lu et al., Hong et al., Ogiyama et al., and He et al. (Lu et al., 2012; Hong et al., 2014; Ogiyama et al., 2021; He et al., 2022).

Independent verification also clarified several study-level details. Hong et al. included 522 patients after successful endoscopic hemostasis, 93 of whom rebled within 30 days, and found that a procedure duration >13.5 minutes was independently associated with rebleeding (adjusted odds ratio [aOR], 2.899; 95% CI, 1.768–4.754) (Hong et al., 2014); in Lu et al., group labels in the abstract conflicted with the full-text tables, so the published full-text coefficients were used for 177 patients without and 43 with rebleeding (Lu et al., 2012).

Adjusted prognostic associations

The four independent cohorts contributed 10 verified adjusted associations (Table 1, Figure 1), yet no identically defined predictor contrast was reproduced in at least two independent cohorts with the same 30-day outcome, so a primary pooled adjusted odds ratio (OR) was not calculated. The largest individual association was reported for shock in He et al. (aOR, 12.691; 95% CI, 5.129–31.399) (He et al., 2022), while Ogiyama et al. found an association for severe renal dysfunction (estimated glomerular filtration rate [eGFR] <30 vs ≥30 mL/min/1.73 m²: aOR, 4.770; 95% CI, 1.168–18.211) (Ogiyama et al., 2021); higher Rockall risk and procedure duration >13.5 minutes were likewise positively associated with rebleeding (Lu et al., 2012; Hong et al., 2014; He et al., 2022).

Table 1. Independently verified adjusted associations with rebleeding within 30 days

Study	N/events	Predictor	aOR	95% CI	Main limitation
Lu 2012	220/43	Rockall ≥6 vs <6	3.215	1.324–7.808	Incomplete model adjustment; possible cohort overlap with Liang
Lu 2012	220/43	Creatinine, per 1 mg/dL	1.119	0.992–1.263	CI includes 1
Hong 2014	522/93	Procedure >13.5 min	2.899	1.768–4.754	Retrospective design; duration may reflect lesion complexity
Ogiyama 2021	274/17	eGFR <30 vs ≥30	4.770	1.168–18.211	Only 17 events; limited multivariable adjustment
Ogiyama 2021	274/17	BUN, per 1 mg/dL	1.010	0.995–1.026	Only 17 events; CI includes 1
He 2022	360/51	Shock	12.691	5.129–31.399	Epinephrine injection monotherapy; stepwise modeling
He 2022	360/51	Rockall, per 1 point	1.877	1.250–2.820	Composite score entered with component variables
He 2022	360/51	Heart rate >100/min	2.610	1.098–6.203	Epinephrine injection monotherapy
He 2022	360/51	Prothrombin time >13 s	2.387	1.019–5.588	Epinephrine injection monotherapy
He 2022	360/51	Gastric vs duodenal ulcer	2.258	1.003–5.084	Epinephrine injection monotherapy

aOR, adjusted odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen.

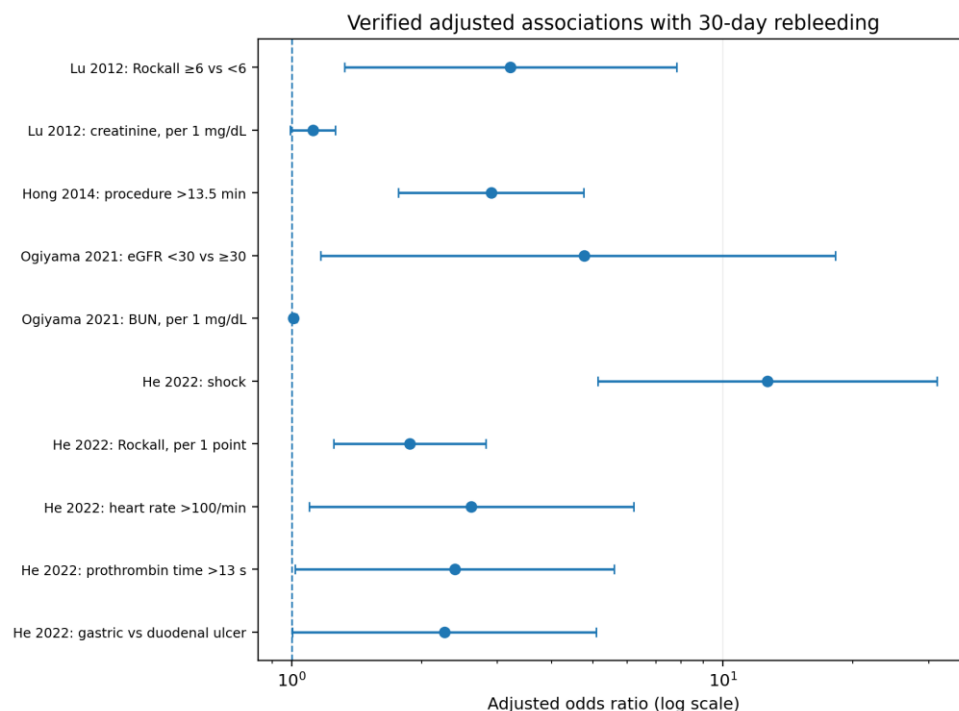


Figure 1. Independently verified adjusted associations with rebleeding within 30 days. Points represent published adjusted odds ratios and horizontal lines indicate 95% confidence intervals. The x-axis is logarithmic.

Exploratory unadjusted synthesis

Two independent cohorts with a 30-day outcome provided exact 2×2 data for five shared factors. Because these estimates were unadjusted and only two cohorts contributed to each comparison, pooling was treated as exploratory; the Hartung-Knapp intervals were extremely wide, did not permit stable inference, and were not used to define independent prognostic effects (Table 2).

Table 2. Exploratory pooled unadjusted associations with 30-day rebleeding

Factor	Pooled OR	95% CI	I ²	τ ²
Gastric vs duodenal ulcer	1.22	0.000118–1.26×10 ⁴	83.2%	0.885
Male sex	0.75	0.0145–39.3	0%	0
NSAID use	1.94	0.00801–470	0%	0
Liver cirrhosis	3.37	0.00279–4.07×10 ³	0%	0
Diabetes mellitus	1.11	0.00451–275	0%	0

OR, odds ratio; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug.

Historical benchmark

For context, we re-synthesized the adjusted ORs numerically reported by Elmunzer et al. as a historical benchmark (Elmunzer et al., 2008). That review mainly presented statistically significant estimates and combined follow-up periods ranging from 72 hours to 1 month, so its results were not treated as an updated primary meta-analysis; nevertheless, the direction of association remained consistent for hemodynamic instability, active bleeding, and ulcer size ≥2 cm (Table 3).

Table 3. Historical benchmark based on adjusted effects reported by Elmunzer et al

Factor	k	OR, REML+HK	95% CI	I ²
Hemodynamic instability	4	2.80	1.72–4.56	0%
Active bleeding	6	3.91	1.56–9.79	67.6%
Ulcer size ≥2 cm	4	2.73	1.17–6.34	42.6%

OR, odds ratio; REML, restricted maximum likelihood; HK, Hartung-Knapp; CI, confidence interval.

Risk of bias

The main sources of bias were residual confounding, few outcome events relative to model complexity, and treatment pathways that no longer fully reflect current endoscopic practice. Ogiyama et al. reported only 17 rebleeding events and used a multivariable model largely restricted to BUN and eGFR (Ogiyama et al., 2021); He et al. analyzed a single-center cohort treated with epinephrine injection monotherapy, where stepwise variable selection and simultaneous inclusion of Rockall score with several of its components increased the risk of overfitting and overadjustment (He et al., 2022). Lu et al. provided limited detail on model development and reported inconsistencies between the text and group counts (Lu et al., 2012), whereas in the retrospective study by Hong et al., procedure duration may have captured lesion severity, technical difficulty, and treatment choice rather than an isolated biological predictor (Hong et al., 2014).

DISCUSSION

The contemporary literature supports several clinically plausible predictors of 30-day rebleeding after successful endoscopic hemostasis, but its chief weakness is lack of replication: no adjusted predictor contrast was reproduced in two independent contemporary cohorts using the same definition and outcome window. The absence of a pooled adjusted estimate should therefore be read as evidence of insufficient comparability and reproducibility, not as evidence that the examined factors lack prognostic value.

Shock had the largest individual adjusted association, although it was observed in a cohort managed with epinephrine injection monotherapy (He et al., 2022). Severe renal dysfunction was also associated with rebleeding, but eGFR measured during acute hemorrhage cannot be equated with established chronic kidney disease and adjustment for endoscopic severity was limited (Ogiyama et al., 2021); similarly, a procedure duration >13.5 minutes may capture technical difficulty and lesion complexity as much as any independent biological risk (Hong et al., 2014).

Earlier studies repeatedly linked hemodynamic instability, active bleeding, and large ulcer size with recurrent hemorrhage (Elmunzer et al., 2008; Hu et al., 2010; García-Iglesias et al., 2011), while more recent reports have continued to examine renal dysfunction and composite risk models (Ogiyama et al., 2021; He et al., 2022; Ito et al., 2024). The broad clinical consistency of these signals does not justify combining historical and contemporary estimates, because endoscopic devices, post-hemostasis acid suppression, rescue strategies, and outcome definitions have changed substantially across eras.

The evidence is most coherently interpreted in three layers: historically reproducible high-risk features, contemporary adjusted associations reported in individual cohorts, and exploratory pooled estimates derived from unadjusted data, keeping these layers separate prevents incompatible effect measures, predictor definitions, or follow-up windows from being treated as observations of a single underlying effect and follows the broader principle that prognostic estimates should be synthesized only when the construct, timing, and model are sufficiently comparable (Riley et al., 2019; Foroutan et al., 2020).

LIMITATIONS

Interpretation is limited by the absence of prospective protocol registration and by reliance on an archived search and eligibility audit rather than a prospectively deposited protocol. Several reports could not enter the strict quantitative synthesis because the outcome window, post-hemostasis target population, effect definition, or cohort independence could not be verified with sufficient confidence; contemporary cohorts also contained

relatively few rebleeding events, several models relied on data-driven variable selection, and endoscopic management ranged from epinephrine injection monotherapy to combination or mechanical therapy. Selective reporting of statistically significant coefficients in some earlier studies may have further inflated historical estimates.

Independent duplicate screening, extraction, and verification reduced the risk of transcription and selection errors but could not correct limitations of the primary studies or the incomplete archival full-text record. Because no predictor had two fully compatible adjusted 30-day estimates, neither formal assessment of small-study effects nor calculation of a pooled contemporary adjusted effect was methodologically informative.

CONCLUSIONS

Four independent contemporary cohorts yielded 10 verified adjusted associations with 30-day rebleeding after successful endoscopic hemostasis. Shock, severe renal dysfunction, higher Rockall risk, and prolonged hemostatic procedures showed notable individual associations, but no identically defined adjusted contrast was replicated in at least two independent contemporary cohorts, precluding a reliable pooled adjusted estimate. Future prognostic studies should use a standardized 30-day outcome, prespecified predictor definitions, adequately powered multivariable models, and complete reporting of adjusted estimates irrespective of statistical significance.

ETHICS STATEMENT

Not applicable. This systematic review used previously published aggregate data and involved no new intervention in humans or animals.

CONFLICTS OF INTEREST

The authors have no potential conflicts of interest.

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None.

AUTHOR CONTRIBUTIONS

Conceptualization: all authors; Data curation: all authors; Formal analysis: all authors; Investigation: all authors; Methodology: all authors; Project administration: SRA; Validation: all authors; Visualization: SRA, DGI; Writing-original draft: all authors; Writing-review & editing: all authors.

DATA AVAILABILITY

The study-level extraction matrix, analytic audit trail, and supplementary eligibility log are available from the corresponding author on reasonable request.

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