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CLINICAL REVIEWS

CME

Systematic Review of the Predictors of Recurrent Hemorrhage After Endoscopic Hemostatic Therapy for Bleeding Peptic Ulcers

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BACKGROUND: An increased knowledge regarding the predictors of rebleeding after endoscopic therapy for bleeding ulcers should improve clinical management and outcomes. The aim of this systematic review was to identify the strongest and most consistent predictors of rebleeding to assist in the development of tools to stratify and appropriately manage patients after endoscopic therapy.

METHODS: Bibliographic database searches for prospective studies assessing rebleeding after endoscopic therapy for bleeding ulcers were performed. Relevant studies were identified, and data were abstracted in a duplicate and independent fashion. The primary outcomes sought were significant independent predictors of rebleeding by multivariable analyses in ≥2 studies.

RESULTS: Ten articles met the prespecified inclusion criteria. The pooled rate of rebleeding after endoscopic therapy was 16.4%. The independent pre-endoscopic predictors of rebleeding were hemodynamic instability (significant in 5 of 5 studies; summary odds ratio [OR] 2.75, 95% confidence interval [CI] 1.99–3.51) and comorbid illness (significant in 2 of 7 studies; insufficient data to calculate summary OR or report OR range). The independent endoscopic predictors of rebleeding were active bleeding at endoscopy (significant in 5 of 8 studies; summary OR 1.93, 95% CI 1.30–2.55), large ulcer size (significant in 4 of 5 studies; summary OR 2.01, 95% CI 1.21–2.80), posterior duodenal ulcer (significant in 2 of 3 studies; insufficient data to calculate summary OR or report OR range), and lesser gastric curvature ulcer (significant in 2 of 2 studies; insufficient data to calculate summary OR or report OR range).

CONCLUSIONS: The independent predictors of recurrent hemorrhage after endoscopic therapy, particularly those that are the strongest and most consistent in the literature, may be used to select patients who are most likely to benefit from aggressive post-hemostasis care, including intensive care unit (ICU) observation and second-look endoscopy. Prospective studies designed to formally assess the relative utilities of these factors in predicting rebleeding and dictating management are needed.

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INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is a serious clinical problem that accounts for over 300,000 hospitalizations in the United States annually (1) and has a mortality rate of ~5–10% (2–4). Bleeding peptic ulcer is the most common cause of UGIB (5). Endoscopic hemostatic therapy is the treatment of choice for patients with high-risk bleeding peptic ulcers as it has been shown to significantly reduce rebleeding and improve survival in this patient population (6, 7). Initial hemostasis can be achieved in over 90% of patients, although approximately 20% will experience clinically relevant rebleeding.

As recurrent hemorrhage is probably the most important predictor of death from UGIB (8, 9) and influences other important end points such as transfusion requirement, need for surgery, and length of hospital stay, identifying patients who are likely to rebleed is a critical component of effectively managing patients with bleeding peptic ulcers. Triaging these patients to higher levels of care and managing them more aggressively may improve clinical outcomes.

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Multiple prospective clinical trials have evaluated the risk factors for rebleeding after endoscopic hemostasis (10–21). In this systematic review, we summarize these predictors of rebleeding in a clinically relevant fashion. The goals of this review are to identify the most consistent and powerful predictors of rebleeding after endoscopic hemostasis, to suggest how these risk factors can be utilized in the risk stratification process, and to propose future directions in research pertaining to this topic.

METHODS

The systematic review was conducted according to standard guidelines (22). A computer-assisted search with the OVID (Ovid Technologies, Inc. New York, NY) interface to Medline and Embase was conducted to identify potentially relevant articles. A search of these databases from January 1, 1950 to January 1, 2008, was performed using the exploded (exp) medical subject heading (MESH) terms: "exp peptic ulcer hemorrhage" AND "exp risk assessment" OR "exp risk" OR "exp risk factors." Manual searches of reference lists from potentially relevant articles were performed to identify any additional studies that may have been missed using the computer-assisted strategy.

Two investigators (BJE, SY) independently reviewed titles and abstracts of all citations identified by the literature search. Potentially relevant studies were retrieved, and selection criteria were applied. The selection criteria were: (a) articles that evaluated predictors of rebleeding after endoscopic hemostatic therapy with a multivariate analysis, (b) studies in which data were collected prospectively, (c) studies in humans, (d) studies published in the English language, and (e) data not duplicated in another manuscript. Eligible articles were reviewed, and data were abstracted onto standardized data extraction forms in a duplicate and independent manner by two investigators (BJE, SY). The following data were abstracted for each included study: (a) date and location of the trial, (b) demographics of the study population, (c) definition of UGIB, (d) definition of rebleeding, (e) subject inclusion criteria, (f) subject exclusion criteria, (g) use of pharmacotherapy, (h) use of endoscopic hemostatic therapy, (i) number and proportion of patients achieving initial hemostasis, (j) number and proportion of patients experiencing rebleeding, (k) death rate, (l) predictors of rebleeding in a univariate analysis, (m) predictors of rebleeding in a multivariable analysis, (n) predictive value of each individual risk factor, and (o) risk factors that were found not to predict rebleeding. The agreement between the investigators was over 90%. Any discrepancies were resolved by consensus.

The methodological quality of each included study was assessed by one investigator (BJE) using the criteria set forth by the Third U.S. Preventive Services Task Force for cohort studies (23). These criteria rate the internal validity of a study as "good" (all criteria met), "fair" (not all criteria met, but no fatal flaws), or "poor" (fatal flaw in at least one of the criteria).

The following data are presented in the results section: (a) the clinical trials meeting the inclusion criteria, (b) the characteristics of each included trial, (c) composite rebleeding and death rates for the entire data set, (d) studied risk factors that did not predict recurrent bleeding by a multivariable analysis, and (e) independent predictors of recurrent hemorrhage with their odds ratios (OR) and confidence intervals (CI) (when available).

For predictors that were independently significant in two or more trials, the number of trials in which the predictor was positive is compared with the number of trials in which it was assessed but reported to be not significant. Further, the numbers and proportions of patients with each risk factor who suffered rebleeding are compared with the numbers and proportion of patients without the risk factor who rebled.

A weighted summary OR for recurrent hemorrhage for each predictor that was significant in two or more studies was calculated by a meta-analysis of the ORs and standard errors (calculated from the 95% CIs for the OR) provided in individual studies (Review Manager software, version 4.2.7; Cochrane Collaboration, Oxford, United Kingdom). These summary effect estimates should be interpreted with caution, however, because included studies generally did not report ORs for factors that were not significant predictors in the multivariable analysis. Therefore, a comprehensive summary estimate, including data from both positive and negative studies, could not be calculated, and the summary estimates may overestimate the potential risk.

RESULTS

A total of 304 titles were initially reviewed. Of these, 27 abstracts appeared pertinent, but the review of text resulted in 10 articles that met the criteria for this systematic review (11–20).

As per the inclusion criteria, all articles evaluated risk factors for rebleeding after endoscopic therapy as a primary end point. Seven of these clinical trials evaluated risk factors for overall failure of endoscopic therapy, which included both the failure to achieve initial hemostasis as well as recurrent hemorrhage. In these studies, however, initial hemostasis was achieved in over 90% of patients, making recurrent hemorrhage the dominant end point in the statistical analyses. The remaining three studies exclusively addressed risk factors for rebleeding after endoscopic hemostasis had been initially achieved. Whenever possible, results are presented to reflect rebleeding after initial hemostasis. If these data were unavailable, then the results indicate overall failure of hemostasis, rather than recurrent hemorrhage *per se*. The baseline patient characteristics, follow-up data, and clinical outcomes were collected prospectively in all included trials. It is not stated, however, in any of the studies whether the study design for the evaluation of prognostic factors predicting rebleeding was determined *a priori*. Eight studies assessed the predictors of rebleeding by a univariate analysis followed by

Table 1. Prospective Clinical Trials Evaluating Risk Factors for Recurrent Hemorrhage After Endoscopic Hemostatic Therapy

First Author and Year	Location	Mean Age, % Female	Pharmacotherapy	Endotherapy
Guglielmi 2002	Italy	Mean age not reported, 34.8	Ranitidine IV, followed by omeprazole PO	Epinephrine and 1% polidocanol
Wong 2002	Hong Kong	62.5 yr, 30.5	Omeprazole PO	Epinephrine and heater probe
Chung 2001	Korea	55.2 yr, 13.3	Ranitidine IV	Hemoclip or hypertonic saline-epinephrine injection or both
Thomopolous 2001	Greece	58.6 yr, 19.7	Ranitidine IV	Epinephrine
Brullet 1996 (gastric ulcers)	Spain	65.9 yr, 32	Ranitidine IV, followed by PO	Epinephrine and 1% polidocanol
Brullet 1996 (duodenal ulcers)	Spain	61.7 yr, 22	Ranitidine IV, followed by PO	Epinephrine and 1% polidocanol
Park 1994	U.K.	64 yr, 41.7	Ranitidine IV	Epinephrine
Choudari 1994	U.K.	Demographics not reported	Ranitidine or cimetidine	Epinephrine and 5% ethanol or heater probe
Villanueva 1993	Spain	64.9 yr, 34	Ranitidine IV or PO	Epinephrine and polidocanol or epinephrine and thrombin
Saeed 1993	U.S.	61.8 yr, 0	Ranitidine IV, followed by PO	Epinephrine and 97% ethanol or epinephrine and heater probe

IV = intravenous; PO = oral.

a multivariate analysis, while two studies utilized the multivariate analysis alone. All studies were assessed as "good" or "fair" according to the US Preventive Services Task Force criteria for controlled cohort studies.

The specific characteristics of each clinical trial are listed in Table 1. Oral proton pump inhibitor (PPI) therapy was used in two studies: after intravenous (IV) histamine 2 receptor antagonist (H_2RA) infusion in one study (11) and as a monotherapy in the other (13). H_2RA therapy was used in nine studies (12, 14–20), followed by oral PPI in one study (11). None of the included studies report the use of "optimal" medical therapy involving an IV bolus of PPI followed by continuous infusion. Endoscopic hemostasis was achieved using a variety of techniques. Epinephrine injection monotherapy was administered in two studies (12, 18) and in one arm of another study (14). Epinephrine in combination with a second hemostatic method was administered in six studies (11, 13, 15, 16, 19, 20) and in one arm of two other trials (14, 17).

When pooling data from all the clinical trials, successful initial hemostasis was achieved in 92.3% of patients. Recurrent hemorrhage occurred in 16.4%. The pooled overall mortality was 6.4%, although the length of follow-up varied among studies from 72 h to 1 month.

The risk factors that independently predict rebleeding after endoscopic therapy based on the multivariable analyses in each included clinical trial are listed in Table 2. The ORs and CIs (when available) of risk factors that are significant in at least two studies are listed in Table 3, according to the study.

The independent pre-endoscopic predictors of rebleeding identified in multiple clinical trials are the presence of hemodynamic instability (significant in 5 of 5 studies; summary OR 2.75, 95% CI 1.99–3.51) and comorbid illness (significant in 2 of 7 studies; insufficient data to calculate summary OR or report OR range). The independent endoscopic predictors of rebleeding identified in multiple clinical trials are active bleeding at endoscopy (significant in 5 of 8 studies; summary OR 1.93, 95% CI 1.30–2.55), large ulcer size (significant in 4 of 5 studies: >2 cm [3 of 4 studies], >1 cm [1 of 1 study]; summary OR 2.01, 95% CI 1.21–2.80), posterior duodenal wall ulcer (significant in 2 of 3 studies; insufficient data to calculate summary OR; OR range 2.06–2.48), and lesser gastric curvature ulcer (significant in 2 of 2 studies; insufficient data to calculate summary OR or report OR range).

As endoscopic therapy with epinephrine alone is less effective than epinephrine followed by a second modality, we identified the independent predictors identified in the two trials that employed epinephrine monotherapy. The pre-endoscopic predictors were shock, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), history of ulcer bleed, an elevated heart rate, and obesity, while the endoscopic predictors were active bleeding and posterior duodenal, duodenal bulb, and lesser curve of stomach locations. The only predictors from these two studies not identified in other studies were the use of NSAIDs and obesity.

The number of studies in which each of the identified predictors was significant compared with the number of studies in which the predictors did not reach statistical significance is illustrated in Table 4. In addition, for each study in which the aforementioned predictors were significant, the number and percentage of patients with each predictor who experienced rebleeding, the number and percentage of patients without the predictor who experienced rebleeding, as well as the overall number and proportion of patients who rebled in the study are listed in Table 5.

Table 6 lists the risk factors that were not found to be independently predictive of recurrent hemorrhage in more than one study. These risk factors include, age, sex, anticoagulant or NSAID use, hematemesis, and pre-endoscopy transfusion requirement.

Table 2. Results of Prospective Clinical Trials Evaluating Risk Factors for Recurrent Hemorrhage After Endoscopic Hemostatic Therapy

First Author and Year	Total No. of Patients	No. of Patients With Initial Hemostasis	No. of Patients With Rebleeding	Independent Risk Factors for Rebleeding From Multivariable Analyses
Guglielmi 2002	447	429 (95.9%)	86 (20%)	Pre-endoscopic: systolic blood pressure ≤100, cirrhosis, recent surgery Endoscopic: Forrest 1a–2c (active or recent bleeding), ulcer >2 cm, location fundus, location body
Wong 2002	1,144	1,128 (98.6%)	94 (8.2%)	Pre-endoscopic: shock, hemoglobin <10 g/dL Endoscopic: Fresh blood in stomach, active bleeding, ulcer ≥2 cm
Chung 2001	143	139 (94.4%)	36 (25.2%)	Endoscopic: active spurting
Thomopolous 2001*	427	390 (91.3%)	86 (20%)	Pre-endoscopic: shock, use of NSAIDs, history of ulcer bleed Endoscopic: active bleeding, location posterior duodenum
Brullet 1996 (gastric ulcers)	178	175 (98.3%)	41 (23.4%)	Endoscopic: active bleeding, location high on lesser curve of stomach, ulcer >2 cm
Brullet 1996 (duodenal ulcers)	120	106 (88.3%)	18 (17%)	Pre-endoscopic: shock Endoscopic: ulcer >2 cm
Park 1994*	135	127 (94%)	25 (20%)	Pre-endoscopic: elevated heart rate, obesity Endoscopic: location duodenal bulb or lesser curve of stomach
Choudari 1994	326	308 (94.5%)	44 (14.3%)	None (age is the only predictor assessed by the multivariable analysis)
Villanueva 1993	233	217 (93%)	41 (18.9%)	Pre-endoscopic: presence of concurrent illness Endoscopic: location posterior duodenal bulb, location superior bulb, ulcer >1 cm
Saeed 1993	80	75 (93.8%)	8 (of 69) (12%)	Pre-endoscopic: ≥3 illnesses, life-threatening illness

*Independent risk factors for surgery (rather than rebleeding).
NSAIDs = nonsteroidal anti-inflammatory drugs.

Table 3. Odds Ratios for Independent Predictors of Rebleeding Based on Multivariable Analyses That Appear in Multiple Clinical Trials

Predictor	Study	Odds Ratio (95% CI)
Hemodynamic instability	Guglielmi *et al*., 2002	3.68 (1.99–6.81)
	Wong *et al*., 2002	2.21 (1.40–3.48)
	Thomopolous *et al*., 2001	2.31 (1.33–6.97)
	Brullet *et al*., 1996 (duodenal ulcers)	3.53 (1.27–4.10)
	Park *et al*., 1994	NR
Comorbid illness	Villanueva *et al*., 1993	NR
	Saeed *et al*., 1993	Likelihood ratio 7.63, $P = 0.005$
Active bleeding	Guglielmi *et al*., 2002	14.47 oozing*, 13.38 spurting**
	Wong *et al*., 2002	1.65 (1.07–2.56)
	Chung *et al*., 2001	6.48 (1.88–22.49)
	Thomopolous *et al*., 2001	2.45 (1.51–3.93)
	Brullet *et al*., 1996 (gastric ulcers)	2.98 (1.12–7.91)
Large ulcer size (≥2 cm)	Guglielmi *et al*., 2002	4.61 (2.20–9.64)
	Wong *et al*., 2002	1.80 (1.15–2.83)
	Brullet *et al*., 1996 (gastric ulcers)	3.64 (1.34–9.89)
	Brullet *et al*., 1996 (duodenal ulcers)	2.29 (1.13–10.9)
Large ulcer size (>1 cm)	Villanueva *et al*., 1993	NR
Posterior duodenal ulcer	Thomopolous *et al*., 2001	2.48 (1.37–7.01)
	Villanueva *et al*., 1993	NR
Lesser gastric curve ulcer	Brullet *et al*., 1996 (gastric ulcers)	2.79 (1.01–7.69)
	Park *et al*., 1994	NR

*95% CI = 3.27–64.05.
**95% CI = 2.69–66.66.
NR = not reported; CI = confidence intervals; Hg = hemoglobin.

Table 4. Comparison of Positive and Negative Studies for Each Predictor of Rebleeding After Endoscopic Therapy That Reached Statistical Significance in Multivariable Analyses in At Least Two Clinical Trials

Predictor	No. of Studies in Which Predictor Was Independently Significant	No. of Studies in Which Risk Factor Did Not Reach Significance
Hemodynamic instability	5	0
Comorbid illness	2	5
Active bleeding	5	3
Large ulcer size	4	1
Posterior duodenal ulcer	2	1
Lesser gastric curvature ulcer	2	0

DISCUSSION

The independent predictors of rebleeding in this systematic review help identify patients at high risk for recurrent hemorrhage after endoscopic therapy for bleeding peptic ulcers. The independent pre-endoscopic predictors of rebleeding that are significant in at least two separate studies are hemodynamic instability and comorbid illness. The independent endoscopic predictors of rebleeding that are significant in at least two separate studies are active bleeding at endoscopy, large ulcer size, posterior duodenal location, and lesser gastric curve location. Of these, on the basis of consistency and statistical strength, hemodynamic instability, active bleeding, large ulcer size, and posterior duodenal location appear to be the most important predictors of rebleeding. The presence of these factors merits clinical concern and consideration of a more aggressive post-hemostasis care strategy.

An area of particular interest is the use of second-look endoscopy after the initial control of hemorrhage. This strategy has been shown to modestly decrease the risk of rebleeding (24), but remains controversial due to conflicting data (25), high costs, and the fact that published studies did not employ intensive IV PPI therapy after endoscopic hemostasis. Given the relatively low risk of rebleeding after therapy, a policy of routine second-look endoscopy would lead to a large number of unnecessary procedures. On this basis, the international Nonvariceal UGI Bleeding Consensus Group in 2003 concluded that second-look endoscopy would be of statistical benefit only in select high-risk patients, although this patient subset is not clearly defined (26). Performing risk stratification based on information available after the index endoscopy could select patients that are most likely to benefit from second-look endoscopy, improving clinical outcomes while limiting costs. Prospective clinical trials are necessary to determine if the risk factors identified in this systematic review can select patients most likely to benefit from second-look endoscopy.

Another matter of interest is the intensive care unit (ICU) observation of patients with UGIB, an area of limited clinical research (27, 28). Experts have recommended that patients with high-risk peptic ulcers should be monitored in the ICU after endoscopic therapy (29). The large majority of these patients, however, will not suffer rebleeding. Identification of patients at particularly high risk for rebleeding and

Table 5. Proportion of Patients With and Without Independent Predictors Who Experienced Rebleeding After Endoscopic Therapy

Predictor	Study	% Rebleeding in Patients With Predictor	% Rebleeding in Patients Without Predictor	% Rebleeding in Entire Study Population
Hemodynamic instability	Guglielmi *et al*., 2002	41.1 (30/73)	14.8 (54/366)	20 (86/429)
	Wong *et al*., 2002*	19.2 (35/182)	6 (59/946)	8.3 (94/1,128)
	Thomopolous *et al*., 2001*	47.1 (24/51)	16 (54/339)	22 (86/390)
	Brullet *et al*., 1996* (DU)	32.0 (8/25)	12.3 (10/81)	16.7 (17/102)
	Park *et al*., 1994	NR	NR	20 (25/127)
Comorbid illness	Villanueva *et al*., 1993	36.5 (42/115)	12.7 (15/118)	24.5 (57/233)
	Saeed *et al*., 1993	NR	NR	12 (8/69)
Active bleeding	Guglielmi *et al*., 2002	20.3 (39/192)	18 (45/247)	20 (86/829)
	Wong *et al*., 2002*	12.1 (71/587)	4.2 (23/541)	8.3 (94/1,128)
	Chung *et al*., 2001	NR	NR	25.2 (35/139)
	Thomopolous *et al*., 2001*	48.9 (46/94)	10.8 (32/296)	22 (86/390)
	Brullet *et al*., 1996* (GU)	26 (13/50)	8 (10/125)	13.1 (23/175)
Large ulcer size (≥2 cm)	Guglielmi *et al*., 2002	31.3 (40/128)	14.1 (44/311)	20 (86/429)
	Wong *et al*., 2002*	14.8 (36/244)	6.6 (58/884)	8.3 (94/1,128)
	Brullet *et al*., 1996* (GU)	23.9 (16/67)	6.5 (7/108)	13.1 (23/175)
	Brullet *et al*., 1996* (DU)	36.3 (8/22)	12 (10/84)	16.7 (17/102)
Large ulcer size (>1 cm)	Villanueva *et al*., 1993	42.0 (34/81)	15.1 (23/152)	24.5 (57/233)
Posterior duodenal ulcer	Thomopolous *et al*., 2001*	43.2 (16/37)	17.6 (62/353)	22 (86/390)
	Park *et al*., 1994	44 (11/25)	13.7 (14/102)	20 (25/127)
	Villanueva *et al*., 1993	57.1 (20/35)	18.7 (37/198)	24.5 (57/233)
Lesser gastric curve ulcer	Brullet *et al*., 1996* (GU)	22.9 (16/70)	6.7 (7/105)	13.1 (23/175)
	Park *et al*., 1994	35 (7/20)	16.8 (18/107)	20 (25/127)

*Percentage of patients experiencing rebleeding was not available. Percentage of patients experiencing overall failure (defined as the failure to achieve initial hemostasis and recurrent hemorrhage) is reported.
NR = not reported; DU = duodenal ulcer; GU = gastric ulcer.

Table 6. Factors Not Independently Predictive of Rebleeding After Endoscopic Therapy in More than One Study

Predictor	No. of Studies in Which Predictor Was Assessed	No. of Studies in Which Predictor Was Independently Predictive
Age	8	1
Sex	8	0
NSAID use	6	1
Anticoagulation	1	0
Smoking	2	0
EtOH abuse	2	0
Hx PUD	4	1
Hematemesis	4	0
Hemoglobin <10 g/dL	2	1
Transfusion requirement (pre-endoscopy)	2	0
Esoph lesion	2	0
DU (*vs* GU)	4	0
Fundic ulcer	2	1
Incisura ulcer	2	0
Antral ulcer	3	0
Pyloric ulcer	3	0
Ant duod ulcer	3	0
Sup duod ulcer	2	0
Inf duod ulcer	2	0
Anastamotic ulcer	1	0
Stoma ulcer	2	0
Volume of epi injection	2	0

PUD = peptic ulcer disease; DU = duodenal ulcer; GU = gastric ulcer; esoph = esophageal; duod = duodenal; ant = anterior; sup = superior; inf = inferior; epi = epinephrine; EtOH = alcohol; Hx = history.

subsequent appropriate triage to the ICU is likely to improve clinical outcomes. Prospective data will also be necessary to determine if the abovementioned risk factors can identify patients most likely to benefit from ICU observation, potentially in combination with second-look endoscopy.

These predictors might also be useful in determining the necessity of high-dose IV PPI therapy after endoscopic hemostasis. The current data support the use of IV bolus plus continuous infusion PPI in patients receiving endoscopic therapy for high-risk bleeding ulcers (30–36), with decisions based solely on endoscopic criteria (active bleeding, nonbleeding visible vessel, and adherent clot). Future studies may be useful in determining whether predictive factors can identify certain patients that derive a greater benefit (or inversely are unlikely to derive additional benefit) from the use of bolus plus continuous infusion of PPIs after endoscopic therapy. However, because continuous infusion PPI therapy has become the standard therapy and will presumably be used in future studies of ulcer rebleeding after endoscopic therapy, such an assessment may be difficult to perform.

The studies included in this systematic review evaluated patients with high-risk bleeding ulcers requiring endoscopic hemostatic therapy. The current evidence supports hospital admission for all such patients (37, 38). There are limited data, however, that do suggest that outpatient management of selected patients with nonbleeding visible vessels and favorable prognostic indicators may be safe and cost-effective (39), and a recent study demonstrated that very frequent oral PPI therapy achieves pH control similar to continuous IV infusion (40). Therefore, a set of predictors that could reliably identify patients with a risk of rebleeding near zero after endoscopic treatment (and oral PPI therapy) could allow for the outpatient management of certain patients, potentially conserving valuable resources.

Although substantial data have been published on the topic of risk stratification in UGIB, evidence-based guidelines for managing patients after initial hemostasis do not exist. This systematic review serves to identify risk factors for recurrent bleeding after endoscopic therapy that can be integrated and prospectively tested to validate their predictive ability. Based on such studies, strategies in which these risk factors are used to guide clinical management can be developed. The suggested areas of future investigation in UGIB risk stratification are: (a) a reappraisal of the predictors of rebleeding in patients receiving "optimal" medical and endoscopic management, (b) a prospective validation of a composite scoring system that contains some or all of the predictors identified in this systematic review, (c) an evaluation of the clinical benefit and cost-effectiveness of performing second-look endoscopy in patients with predictors identified in this systematic review, (d) an evaluation of the clinical benefit and cost-effectiveness of ICU observation in patients with predictors identified in this systematic review, and (e) an evaluation of the role of the identified predictors in selecting patients for oral PPI therapy and outpatient management after endoscopic therapy.

This systematic review has several important limitations that may affect the clinical applicability. First, what is currently considered as "optimal" medical therapy for high-risk bleeding ulcers, consisting of IV PPI bolus followed by continuous infusion, was not delivered in any of the component clinical trials. The risk factors identified in these trials might be affected in either a mitigating or an accentuating fashion by high-dose PPI therapy, and as such, a reappraisal of these predictors in prospective studies that utilize current optimal pharmacologic therapy is important. Second, epinephrine monotherapy, which is documented to be inferior to epinephrine plus a second modality such as thermal therapy or injection of sclerosant (41), was used in two trials and in a study arm of a third trial. The predictors from studies employing "suboptimal" therapy may not be generalizable to patients receiving standard endoscopic therapy, defined as epinephrine followed by a second modality. However, we did note that the independent predictors from the studies employing epinephrine alone were generally similar to those from the other studies in which dual endoscopic therapy was applied.

Also, as mentioned, the included studies generally did not report ORs for negative predictors in the multivariable analysis, preventing the calculation of a comprehensive summary OR that includes data from both positive and negative studies for each predictor. Therefore, the reported summary ORs are likely to be an overestimation of the effect. Moreover, due to significant disparity among trials regarding design,

statistical analysis, and end points, a clinical scoring system could not be devised. While these limitations should be taken into account when considering the clinical applicability of this systematic review, we do not believe that they substantially detract from the conclusions, particularly pertaining to the identification of future areas of research.

In summary, several clinical, laboratory, and endoscopic factors have been shown to independently predict recurrent hemorrhage after successful endoscopic treatment of high-risk bleeding peptic ulcers. The presence of these factors can identify patients at particularly high risk for rebleeding, a subgroup that may be most likely to benefit from an aggressive post-therapy care, including ICU monitoring and scheduled second-look endoscopy. Prospective studies designed to formally assess the relative utilities of these factors in predicting rebleeding and dictating management are needed.

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CONFLICT OF INTEREST

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