

Predictors of early rebleeding after endoscopic therapy in patients with nonvariceal upper gastrointestinal bleeding secondary to high-risk lesions

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BACKGROUND: In an era of increasingly shortened admissions, data regarding predictors of early rebleeding among patients with nonvariceal upper gastrointestinal bleeding (NVUGIB) exhibiting high-risk stigmata (HRS) having undergone endoscopic hemostasis are lacking.

OBJECTIVES: To determine predictors of early rebleeding, defined as rebleeding before completion of recommended 72 h intravenous proton pump inhibitor infusion postendoscopic hemostasis.

METHODS: Data from a national registry of patients with upper gastrointestinal bleeding (the REASON registry) were accessed. Univariable and multivariable analyses were sequentially performed to identify significant independent predictors among a comprehensive list of clinical and laboratory characteristics.

RESULTS: Overall, 393 patients underwent endoscopic hemostasis for NVUGIB with HRS. Forty patients rebled ≤ 72 h thereafter (32.5% female, mean [\pm SD] age 70.2 ± 11.8 years, 2.88 ± 2.11 comorbidities), while 21 rebled later (38.1% female, mean 70.5 ± 14.1 years of age, 2.62 ± 2.06 comorbidities). Hematemesis or bright red blood per nasogastric tube aspirate was identified as the sole independent significant predictor of early rebleeding versus later among both NVUGIB and, more specifically, patients with peptic ulcer bleeding (OR 7.94 [95% CI 1.80 to 35.01]; $P < 0.01$, and OR 8.41 [95% CI 1.54 to 46.10]; $P = 0.014$, respectively).

CONCLUSIONS: When attempting to determine the optimal duration of pharmacotherapy and timing of discharge for patients following endoscopic hemostasis for NVUGIB with HRS, it is noteworthy that individuals who present with hematemesis or bright red blood per nasogastric tube aspirate are at particularly high risk for rebleeding within the first 72 h.

Key Words: Bleeding; Endoscopic therapy; Hemostasis; High-risk stigmata; Nonvariceal; Upper gastrointestinal tract

Acute upper gastrointestinal bleeding (UGIB) remains an important clinical problem accounting for high rates of morbidity and mortality, while peptic ulcer disease remains the most common cause of UGIB (1).

A systematic review of prospective trials performed by Elmunzer et al (2), who assessed rebleeding after endoscopic therapy in peptic ulcer bleeding (PUB), attempted to identify the strongest and most consistent predictors of rebleeding; however, there was no assessment regarding the timing of rebleeding. Identification of such predictors could help refine the triage of patients presenting with UGIB to their

Les prédicteurs d'une reprise rapide des saignements après un traitement endoscopique chez des patients ayant des saignements gastro-intestinaux non variqueux en raison de lésions à haut risque

HISTORIQUE : À une époque d'hospitalisations toujours plus courtes, on possède peu de données sur les prédicteurs de reprise rapide des saignements chez les patients ayant des saignements non variqueux des voies digestives supérieures (SNVDS) présentant des stigmates à haut risque (SHR) qui ont subi une hémostase endoscopique.

OBJECTIFS : Déterminer les prédicteurs de reprise rapide des saignements, définis comme la reprise des saignements avant la fin de l'infusion d'inhibiteurs de la pompe à protons recommandée pendant 72 heures après une hémostase postendoscopique.

MÉTHODOLOGIE : Les chercheurs ont consulté les données d'un registre national de patients ayant des saignements de voies digestives supérieures (le registre REASON). Ils ont effectué des analyses univariable et multivariables équentielles pour déterminer les prédicteurs indépendants importants dans une liste détaillée de caractéristiques cliniques et de laboratoire.

RÉSULTATS : Dans l'ensemble, 393 patients ont subi une hémostase endoscopique en raison de SNVDS présentant des SHR. Quarante patients ont saigné de nouveau dans les 72 heures suivantes (32,5 % de femmes, âge moyen [\pm ÉT] de $70,2 \pm 11,8$ ans, $2,88 \pm 2,11$ comorbidités), tandis que 21 ont saigné plus tard (38,1 % de femmes, âge moyen de $70,5 \pm 14,1$ ans, $2,62 \pm 2,06$ comorbidités). Les chercheurs ont établi qu'une hématomèse ou du sang rouge vif dans l'aspirat de la sonde nasogastrique étaient les seuls prédicteurs indépendants d'importance d'une reprise rapide des saignements plutôt que de saignements plus tardifs chez des patients qui avaient des SNVDS et, plus précisément, des saignements causés par un ulcère gastroduodénal (RRR 7,94 [95 % IC 1,80 à 35,01]; $P < 0,01$, et RRR 8,41 [95 % IC 1,54 à 46,10]; $P = 0,014$), respectivement).

CONCLUSIONS : Lorsqu'on tente de déterminer la durée optimale de la pharmacothérapie et le moment du congé des patients après une hémostase endoscopique secondaire à des SNVDS accompagnés de SHR, il est bon de savoir que les personnes qui présentent une hématomèse ou du sang rouge vif dans l'aspirat de la sonde nasogastriques sont particulièrement vulnérables à la reprise des saignements dans les 72 heures.

appropriate level of care (ie, intensive care unit, monitored setting, ward, etc), while possibly guiding the route of administration and duration of subsequent acute pharmacotherapy.

Currently, it is recommended that patients with PUB secondary to high-risk lesions be hospitalized following endoscopic hemostasis for a minimum of 72 h while receiving a continuously infused proton pump inhibitor (PPI) drip as per existing guidelines (3). However, many centres appear to be discharging patients after only 48 h (4). The need for high-dose intravenous (IV) PPI regimens postendoscopic therapy as opposed to lower dosing regimens has also been recently questioned (5-9).

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Based on this information, the current study aimed to determine predictors of rebleeding before the completion of the recommended 72 h IV PPI infusion (versus later) following endoscopic hemostasis in patients with nonvariceal UGIB (NVUGIB) exhibiting high-risk stigmata (HRS).

METHODS

The REASON registry

The REgistry of patients undergoing endoscopic and/or Acid Suppression therapy and Outcomes analysis for upper gastrointestinal bleeding (REASON) registry, a national registry of patients presenting with suspected UGIB, was used in an effort to determine whether any predictors of early rebleeding (defined as within 72 h of presentation), among patients with NVUGIB and HRS and, more specifically, patients with PUB and HRS, could be identified. The REASON registry was constructed as a retrospective medical chart review conducted in 21 Canadian hospitals (both tertiary and community institutions) in 2004 to 2005 (10). Briefly, sites reviewed the charts of all hospitalized patients ≥ 18 years of age with a primary or secondary coded discharge diagnosis of UGIB. Patients initially assessed at another institution for the present episode of bleeding and subsequently transferred to the participating site were excluded, as were (for the purposes of the present analysis) all patients bleeding from variceal sources. A specialized web-based electronic data capture system was developed for this registry; study nurses and investigators received standardized training on the protocol and the specific data variables to be captured.

The entered data were reviewed centrally for internal logic of patient flow and biological plausibility. Data validation checks according to a predefined data validation scheme were conducted similar to those performed in previous registries by the current group of investigators (11). To further validate the abstracted information, 10% of all records were also audited by a second, independent study nurse.

Recorded information included demographics, historical data, physical examination findings and the yield of nasogastric (NG) aspirate, if performed, in addition to laboratory, management and outcomes data.

Several outcomes were collected using a priori standardized definitions: rebleeding was defined as overt hematemesis; passage of fresh blood from the rectum; a fall in hemoglobin concentration of >2 g/L within any 24 h period after the first 24 h following endoscopy hemostasis; shock (defined as a systolic blood pressure of ≤ 90 mmHg or a heart rate ≥ 110 beats/min) in the presence of continuing melena; or the presence of fresh blood in the stomach or duodenum, or both, at repeat endoscopy when further bleeding was suspected (11). Continued bleeding was defined as spurting or oozing arising from an artery on the initial endoscopic examination that did not respond to endoscopic therapy, or the persistence following initial endoscopy of: the presence of a bloody aspirate from NG tube (reinserted because of clinical suspicion); shock (defined as a systolic blood pressure ≤ 90 mmHg or a heart rate ≥ 110 beats/min); and/or the need for substantial replacement of blood and fluid volume (transfusion of ≥ 3 units of blood within 4 h) following endoscopic therapy (11). An a priori decision was made to group rebleeding and continued bleeding together for the purpose of all analyses as performed previously (11).

Information regarding rebleeding and its timing within 30 days of the patient's initial hospitalization was collected in addition to the timing of endoscopic hemostasis. A patient experiencing a subsequent bleed >30 days after the initial bleeding event was considered to have experienced a new bleeding episode.

Data analysis

Descriptive data were generated for the rebleeding rates and patient characteristics discussed above. All categorical data were expressed as proportions with 95% CIs determined using the normal approximation of the binomial distribution. Continuous data were expressed as mean \pm SD unless otherwise indicated.

Considering the natural history of the evolution of bleeding ulcers with HRS and its implications with regard to the duration of PPI infusion, as well as existing guidelines on acute pharmacological management of patients with NVUGIB, it was decided a priori to dichotomize the population according to early (≤ 72 h) or late rebled (>72 h) for the initial univariable analysis (3).

The possible clinical variables included in the multivariable analysis aimed at identifying predictors of rebleeding early within the first 72 h after endoscopic hemostasis were chosen based on possible predictors identified in the literature and guided by the univariable analysis. Multivariable analysis was performed using logistic regression modelling. The optimal model yielded the highest C coefficient score while being the most parsimonious. All analyses were performed using SAS software version 9.2 (SAS Institute, USA).

RESULTS

Patient population

The REASON database included a total of 1805 NVUGIB patients, of whom 393 demonstrated HRS on endoscopy and underwent endoscopic hemostasis and, of these, 61 rebled within the first 30 days. Although not significant, the proportion of female patients was greater in the group that rebled after 72 h (38.1%) compared with the group that bled within the first 72 h (32.5%). The mean ages and numbers of comorbid conditions were similar (rebleeding ≤ 72 h: 70.2 ± 11.8 years and 2.88 ± 2.11 comorbidities versus rebleeding >72 h: 70.5 ± 14.1 years and 2.62 ± 2.06 comorbidities) (Table 1). The rebleeding rate among patients exhibiting HRS overall was 15.5% (61 of 393). In comparison, the rebleeding rate for low-risk stigmata (Forrest IIc = flat pigmented spot and Forrest III = clean base ulcer) was 7.1% (18 of 255); 99.4% of patients received a PPI during their hospital stay.

Time to rebleed

Among 61 patients with HRS who rebled, the majority ($n=40$ [65.6%]) did so within the first 72 h. Of these, the mean time to rebleed was 1.38 ± 0.63 days (Figure 1). Figure 2 illustrates the breakdown of rebleeders among the patients who experienced this complicated course within the first 72 h.

Predictors of early rebleeding

Table 1 reports the results of the univariable analysis for possible predictors of early rebleeding in all NVUGIB patients with HRS: hematemesis or bright red blood per NG tube aspirate on initial presentation was the sole significant predictor of early rebleeding ($P=0.03$).

The best, most parsimonious logistic regression model is shown in Table 2 (C statistic = 0.764). The sole significant independent predictor of early rebleeding in all NVUGIB patients with HRS was hematemesis or bright red blood per NG tube aspirate on initial presentation (OR 7.94 [95% CI 1.80 to 35.01]; $P=0.0062$) (Table 2). An American Society of Anesthesiologists (ASA) score of 1 to 3 was associated with a trend toward earlier rebleeding in the first three days, as was an elevated presenting international normalized ratio (INR).

Multivariable analysis was similarly performed for the subgroup of patients with PUB and HRS. Within this group, the sole significant independent predictor of early rebleeding was also hematemesis or bright red blood per NG tube aspirate on initial presentation (OR 8.41 [95% CI 1.54 to 46.1]; $P=0.0149$) (Table 3).

DISCUSSION

NVUGIB accounts for a significant number of hospitalizations in North America (11), mainly due to PUB (12). Rebleeding in NVUGIB occurs in approximately 8% to 25% of patients, despite endoscopic therapy (13). Predictors of rebleeding have been previously identified in the literature (2,14-23). These include bedside (hemodynamic instability, comorbid illness and hemoglobin level at presentation) and endoscopic predictors (active bleeding at endoscopy, ulcer size and ulcer location).

TABLE 1
Study population characteristics at initial presentation including historical, physical examination and laboratory value variables (univariable analysis)

Characteristic	Rebleeding postendoscopic hemostasis		P
	≤3 days (n=40)	>3 days (n=21)	
Female sex	32.5 (7.3–47.7)	38.1 (15.4–60.8)	0.6621
Age, years, mean ± SD	70.2±11.8	70.5±14.1	0.9097
Number of comorbid conditions, mean ± SD	2.88±2.11	2.62±2.06	0.8005
Baseline ASA score* 1 to 3	85.0 (73.4–96.6)	71.4 (50.4–92.5)	0.2052
Hemodynamic instability	50.0 (33.8–66.2)	28.6 (7.5–49.6)	0.1078
Inpatient	25.0 (11.0–39.0)	28.6 (7.5–49.6)	0.7632
Rectal bleeding	7.5 (0.0–16.0)	14.3 (0.0–30.6)	0.3978
Hematemesis or bright red blood per nasogastric tube aspirate on initial presentation	47.5 (31.3–63.7)	19.1 (0.7–37.4)	0.0294
Epinephrine injection alone	40.0 (24.1–55.9)	23.8 (3.9–43.7)	0.2060
Hemoglobin on presentation, g/L, mean ± SD	90.4±25.7	89.9±34.4	0.5661
Presenting international normalized ratio†, mean ± SD	1.52±0.68	1.35±0.58	0.3514

Data presented as % (95% CI) unless otherwise indicated. All patients received intravenous proton pump inhibitors during the hospital admission, pre/post endoscopy. *American Society of Anesthesiologists (ASA) score refers to classification of a patient's severity and acuity of disease index; †Rebled ≤3 days (n=36), rebled >3 days (n=19)

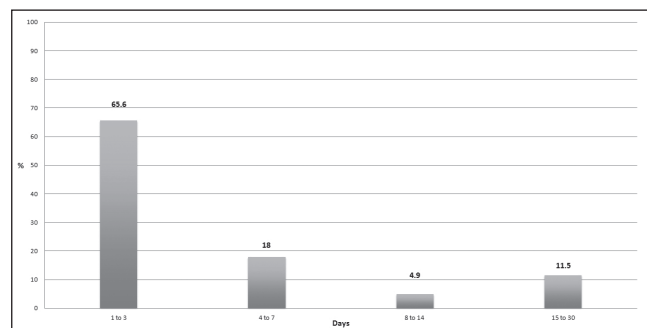


Figure 1 Distribution of patients with rebleeding from nonvariceal upper gastrointestinal bleeding with high-risk stigmata within the first 30 days

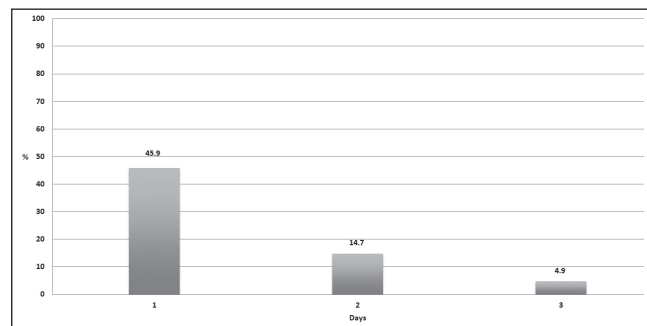


Figure 2 Distribution of patients with rebleeding from nonvariceal upper gastrointestinal bleeding with high-risk stigmata within the first 72 h

A study by Lau et al (24) demonstrated the natural evolution of stigmata of recent hemorrhage by performing serial endoscopy and found that the majority of these lesions evolved into clean-based ulcers within three days following endoscopic hemostasis. Based on clinical observations, consensus groups have stated that the majority of rebleeding occurs within the first three days after endoscopic therapy (3). This is why high-dose IV PPI infusion is currently recommended for a full 72 h after hemostasis (3,25), with confirmation of efficacy in a Cochrane meta-analysis update (26). However, some centres have begun selectively discharging such patients before completing the full 72 h of IV PPI therapy (4), with wide variations in the implementation of practice guidelines (8). Because of these potentially important disparities in practice, we sought to better define predictors of early rebleeding and, more specifically, within the first 72 h of endoscopic therapy, using nationally collected registry data.

TABLE 2
Independent predictors of early rebleeding in multivariable analysis in all nonvariceal upper gastrointestinal bleeding

Effect	OR (95% CI)	P
Hematemesis or bright red blood per nasogastric tube aspirate on initial presentation	7.94 (1.80–35.01)	0.0062
Baseline ASA class 1 to 3*	4.33 (0.74–24.91)	0.1004
Presenting INR†	2.74 (0.81–9.28)	0.1048

*American Society of Anesthesiologists (ASA) score refers to the classification of a patient's severity and acuity of disease index; †INR International normalized ratio, rebled ≤3 days (n=36), rebled >3 days (n=19)

TABLE 3
Independent predictors of early rebleeding in multivariable analysis in peptic ulcer disease bleeding only

Effect	OR (95% CI)	P
Hematemesis or bright red blood per nasogastric tube aspirate on initial presentation	8.41 (1.54–46.10)	0.0141
Presenting international normalized ratio	4.81 (0.75–30.84)	0.1048

In our analysis of the REASON database, hematemesis or bright red blood per NG aspirate at initial presentation was the sole significant independent predictor of rebleeding within the first 72 h after endoscopic hemostasis versus later. These characteristics may be a surrogate marker for the presence of a larger-calibre bleeding vessel, which may respond poorly to current therapeutic modalities or unfavourable physiological circumstances and, thereby, identify a patient at higher risk for earlier rebleeding.

These findings would appear to support the use of NG aspiration without lavage in initial prognostication (16) and risk stratification of patients with NVUGIB, especially in light of data suggesting extreme variations in its use (8), with progressively fewer patients undergoing NG tube insertion for sole sampling (27). Furthermore, it has also been suggested that patients with a bloody NG aspirate may represent a subgroup of patients in whom the administration of pre-endoscopic PPI is cost effective (28,29). In contrast, the performance of selectively complementing aspiration with NG lavage is gradually being replaced by the administration of prokinetics (30).

Current recommendations support the use of routine second-look endoscopy in certain high-risk patients (3,31). Whether patients presenting with hematemesis or bright red blood per NG tube represent

such a population in which a second-look endoscopy may be beneficial because they are at particularly high risk of rebleeding within the first three days requires further investigation.

In the best model we present, two additional prognosticators displayed strong trends toward rebleeding early within the first 72 h, albeit without achieving statistically significant discrimination, and warrant further discussion. It is well recognized that a higher ASA score is associated with increased rebleeding over the following 30 days (32). Our analysis also suggests that patients with an ASA score of 4 or 5 may be at increased risk for delayed rebleeding following endoscopic hemostasis; however, this finding did not attain statistical significance. Interestingly, a study by Cheng et al (33), which included a much greater proportion of patients with ASA scores of 4 or 5 (37.1%), also demonstrated a more delayed mean time to rebleeding (rebleeding within the first three days ranged from 11.3% to 15.4% and increased to 40.4% to 43.4% by day 28) (33). One explanation for this finding may be that sicker patients experience impaired wound healing, putting them at increased risk for delayed rebleeding. Cheng et al also found that patients with a low serum albumin level (eg, <30 g/L), had a cumulative rebleeding rate that increased significantly during days 4 to 14. The authors, thus, also suggested that the bioavailability of oral omeprazole may be affected by low serum albumin levels in sicker patients. Both mechanistic conclusions remain speculative and require further study. One also cannot rule out alternative methodological explanations for the association of delayed bleeding and increased ASA score. Bias may have occurred; for example, it may be that sicker patients are less likely to be rescoped early, with a decreased rebleeding detection rate in the presence of otherwise poorly interpretable clinical criteria. Finally, a type II error may also be present.

Regarding the trend noted with the presenting INR ratio value, although an elevated INR has been recently linked to increased mortality, its relationship with rebleeding remains controversial (3,34). Nonetheless, plausible physiological reasons linking an elevated INR to a possible rebleeding event within the first 72 h after endoscopic hemostasis exist and could explain the observed trend in our final model. Confounding factors may have included the cause of the INR elevation and varying degrees of aggressiveness in correcting, although, here too, a type II error cannot be ruled out.

The REASON database did not allow us to study some predictors of rebleeding after endoscopic treatment that have been identified in the literature. These include ulcer size and location (35); similarly, we had limited information regarding transfusional requirements that have recently also been proposed as possible predictors of rebleeding (36-38).

The observational nature of our data also limits our results and should be regarded as hypothesis-generating to better guide subsequent research in the area.

CONCLUSION

Hematemesis or bright red blood per NG aspirate was the sole independent significant predictor of rebleeding within the first 72 h versus later following endoscopic hemostasis among patients with NVUGIB endoscopically treated for HRS. When attempting to determine the optimal timing of discharge for such patients, it is important to realize that individuals who present with hematemesis or bright red blood per NG tube aspirate are at particularly high risk for earlier rebleeding within those critical first 72 h. These patients should be kept in hospital accordingly, and may further justify the current recommendations of administering an IV PPI for the full 72 h. Possible relationships between the timing of early rebleeding and both presenting ASA score and INR require further characterization.

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