Simple Clinical Predictors May Obviate Urgent Endoscopy in Selected Patients With Nonvariceal Upper Gastrointestinal Tract Bleeding

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Background: The validated Blatchford risk score (BRS) predicts outcomes in patients with nonvariceal upper gastrointestinal tract bleeding, before endoscopy; completion of the Rockall score requires endoscopy. The aims of this study were to predict whether the modified BRS (mBRS) can predict (1) endoscopic high-risk stigmata (HRS) and (2) rebleeding and mortality.

Methods: Clinical and demographic characteristics on 1869 patients from 6 Canadian provinces were prospectively entered into the Registry for Upper GI Bleeding and Endoscopy database, recording 30-day rebleeding and mortality. The Rockall score and mBRS (hemoglobin level, hemodynamic instability, and presence of melena, liver disease, or cardiac failure; urea and syncope were not recorded) were calculated. Logistic regression was used to assess the association between an mBRS of 1 or less with HRS and with rebleeding and mortality.

Results: The mean (SD) age of the patients was 66 (17) years, with 62% men and a mean of 2.5 comorbidities. Of the 1860 patients with 30-day rebleeding data, 334 (18.0%) rebled; 5.3% died. The mBRS was 0 in 3% and 1 or less in 9.8% of patients; HRS were seen in 31.0% of patients. An mBRS of 1 or less was associated with lower rebleeding (5% vs 19%; $P<.001$) and mortality (0.5% vs 5.8%; $P=.003$), and was significant in multivariate analysis for rebleeding (odds ratio, 0.24; 95% confidence interval, 0.12-0.48) and mortality (odds ratio, 0.12; 95% confidence interval, 0.02-0.90). The HRS were less frequent when the mBRS was 1 or less (16.9% vs 32.7%; odds ratio, 0.4; 95% confidence interval, 0.3-0.6). Patients with a low mBRS with HRS had a low rebleeding rate (3.3%) and a lower apparent benefit from endoscopic therapy.

Conclusions: An mBRS of 1 or less identifies approximately 10% of patients with gastrointestinal tract bleeding with a low likelihood of having HRS and a low risk of adverse outcomes. A prospective randomized study is required to examine whether this subgroup of patients presenting after hours could be discharged safely from emergency departments with arrangements for (urgent) outpatient endoscopy.

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NONVARICEAL UPPER GASTROINTESTINAL tract bleeding is a life-threatening disorder affecting approximately 1 per 1000 population per year, accounting for more than 100 000 admissions per year at a cost of more than $2 billion annually in the United States.[1] Randomized trial evidence exists to support early discharge of patients with low-risk lesions on endoscopy,[2] but evidence for physicians' ability to predict the presence or absence of these lesions on clinical grounds is lacking. This is an important obstacle to triaging in the emergency department or urgent primary care clinic, before endoscopy has been performed.

The Rockall score is a prospectively validated scoring system whose components were chosen based on their ability to predict mortality (although it also correlates with rebleeding).[3] It uses 3 clinical factors (age, hemodynamics, and comorbidities) along with the endoscopic diagnosis and presence of endoscopic stigmata.[3] A total (clinical plus endoscopic) Rockall score of 2 or less predicts a low risk of rebleeding and mortality.[3] Its validity was also demonstrated using a Canadian national Registry for Upper GI Bleeding and Endoscopy (RUGBE).[4,5] Although extremely useful, it cannot be completed without the endoscopic findings and, therefore, cannot be used before endoscopy, or to help determine the need for en-

Table 1. The Modified Blatchford Risk Score

Variable	Points Assigned				
	0	1	2	3	6
Hemoglobin level, g/dL					
Men	≥13.0	12.0-12.9	. . .	10.0-11.9	<10.0
Women	≥12.0	10.0-11.9	. . .	. . .	<10.0
Systolic blood pressure, mm Hg	≥100	100-109	90-99	<90	. . .
Heart rate, beats/min	<100	≥100	. . .	. . .	. . .
Melena	No	Yes	. . .	. . .	. . .
Liver disease	No	. . .	Yes	. . .	. . .
Cardiac failure	No	. . .	Yes	. . .	. . .

doscopy. Because the clinical components were predictive of outcomes independently of the endoscopic findings, it is unlikely that some components (eg, the clinical ones) can predict other components (eg, the endoscopic ones).

The Blatchford risk score (BRS) has been validated prospectively to predict adverse outcomes and the need for intervention in patients with nonvariceal upper gastrointestinal tract bleeding, using only clinical (ie, nonendoscopic) variables.[6] Because patients did not systematically undergo endoscopy (need for endoscopic intervention was an outcome), the correlation between the clinical factors and the endoscopic findings (ie, presence of high-risk stigmata [HRS]) could not be made. The presence of stigmata was only documented for the patients in the subgroup that had clinical signs of rebleeding or ongoing bleeding, virtually all of whom would have had HRS, not for all patients; therefore, Blatchford et al[6] had no data on visible vessels or clots in patients who had stopped bleeding and/or did not rebleed. A low BRS could, in theory, identify patients who could be discharged safely from emergency departments with arrangements for (urgent) outpatient endoscopy; however, gastroenterologists, internists, and surgeons have been generally reluctant to do this because patients with HRS may be sent home without receiving endoscopic therapy and high-dose intravenous proton pump inhibitor therapy, which have been shown to improve the outcomes of these patients.[7-13]

This cohort study attempts to answer several questions: Can a modified BRS (mBRS) predict the presence of endoscopic HRS? Does it also predict rebleeding and mortality independently of HRS and other factors, and does it perform better than the clinical component of the Rockall score? Furthermore, when HRS are found in a patient with a low mBRS, what does this mean?

METHODS

PATIENT POPULATION

Clinical and demographic characteristics on 1869 patients who had undergone upper endoscopy for signs and/or symptoms of upper gastrointestinal tract nonvariceal bleeding from community and university hospitals in 6 provinces were entered prospectively into the Canadian RUGBE database from September 1, 1999, to December 31, 2001, recording 30-day outcomes (rebleeding and mortality) in more than 99% of registrants.

CLINICAL AND ENDOSCOPIC FINDINGS

High-risk endoscopic stigmata were defined as an adherent clot (after irrigation) or a bleeding (oozing or spurting) or nonbleeding visible vessel (ie, pigmented protuberance). *Hematochezia* was defined as red or maroon stools, in contrast to the black stools of melena. *Rebleeding* was defined as hematemesis, melena, or bloody nasogastric aspirate, in the presence of shock or a decrease in hemoglobin level of greater than 2 g/dL.

PREDICTIVE SCALES

New composite variable fields were created for the scoring systems of Rockall et al[3] and Blatchford et al.[6] The study questions were posed a priori, before examining the database. Unfortunately, when RUGBE was created, urea and history of syncope were not included in the registry and were, therefore, not recorded; an mBRS was, thus, used, which is identical to the original BRS but does not contain urea or syncope data (**Table 1**). In the article by Blatchford et al,[6] scores of 0, 1, and 2 had rates of intervention needed of 1.8%, 5.6%, and 11.5%, respectively. Based on the comparability of these rebleeding rates with those corresponding to low-risk stigmata (clean base and flat spots), which commonly lead to recommending prompt discharge, a low mBRS was arbitrarily defined as 1 or less. We believed that because urea and syncope data were missing from our data set, 1 or less would be more reasonable than 2 or less.

STATISTICAL ANALYSIS

Statistical software (Stata, version 7.0; Stata Corp, College Station, Tex) was used for statistical analysis. χ^2 and Fisher exact tests were used ($\alpha = .05$) for univariate analysis of proportions. Binomial 95% confidence intervals (CIs) were calculated for proportions and differences in proportions. Wilcoxon rank sum (Mann-Whitney) tests were used to compare sets of nonnormal continuous variables (eg, time to endoscopy); normally distributed continuous variables were compared with a 2-sided *t* test. Multivariate logistic regression models were used to assess the independent association between an mBRS of 1 or less and the presence of HRS, or the occurrence of rebleeding or mortality. Other variables considered, chosen based on clinical importance, included age, sex, time delay to endoscopy, inpatient and outpatient onset of bleeding, hematochezia, ulcer diagnosis (vs other diagnoses), proton pump inhibitor therapy, and endoscopic hemostatic therapy. Likelihood ratio tests of nested models were used for model selection. Individual variables already included in the composite scores were not considered because of colinearity with, and

lack of independence from, the composite scores themselves. If the composite score was not significant in a given model, the individual variables were then reconsidered for entry. Relevant interaction terms were tested, including the interaction between HRS and mBRS and between HRS and other therapies in predicting outcomes.

The study cohort sample size corresponds to a statistical power of 82% to detect a 10% difference in the frequency of HRS (by univariate analysis), for an α threshold of .05, assuming that the low-risk category made up 10% of the cohort. This is a conservative estimate of power anticipated in the multivariate analysis.

RESULTS

The RUGBE data set has been described previously in detail.[4,14,15] Briefly, the mean (SD) age of the cohort was 66 (17) years, with 62.3% men and a mean of 2.5 comorbidities. High-risk endoscopic stigmata were noted in 580 (31.0%) of the 1869 patients; 70.0% of these patients underwent endoscopic therapy in this real-life setting. Of the 1860 patients for whom 30-day rebleeding was assessed and recorded, 334 (18.0%) rebled; 5.3% died. The median (range) mBRS was 7 (0-12). Of the patients, 3.0% had an mBRS of 0 and 9.8% had an mBRS of 1 or less. In keeping with our decision to use 1 or less as the cutoff for a low mBRS, the rebleeding rate when the mBRS was 2 was 10.0%; and when the mBRS was 2 or less, 7.4%. The rebleeding rate when the mBRS was 3 was 17.0%.

Table 2 shows demographics, clinical features, endoscopic findings, and outcomes stratified by the mBRS. Time to endoscopy can affect the frequency of HRS seen,[16] but this was comparable in both groups (mBRS of >1 vs mBRS of ≤1). Not surprisingly, continuous variables that are included in the mBRS (hemoglobin level and blood pressure) were more frequently abnormal in the clinically higher-risk group (mBRS of >1), and a history of melena and comorbidities were also more likely to be present. Low-risk diagnoses, such as Mallory-Weiss tears and normal examination results, were found more often in the clinically low-risk group (mBRS of ≤1), whereas ulcers were underrepresented in this group.

PREDICTING THE PRESENCE OF ENDOSCOPIC STIGMATA

High-risk stigmata were found in 33% (95% CI, 30%-35%) of patients with an mBRS greater than 1 vs 17% (95% CI, 12%-23%) of patients with an mBRS of 1 or less; patients with an mBRS of 1 or less were significantly less likely to have endoscopic stigmata (odds ratio [OR], 0.4; 95% CI, 0.3-0.6; $P<.001$). A multivariate model was constructed, including consideration of a variable containing the preendoscopic (ie, clinical) components of the Rockall score (age, hemodynamics, and comorbidities). The final model contained only 2 independent predictors: time to endoscopy (OR, 0.97 [95% CI, 0.95-0.99] for each 6-hour delay; $P=.01$) and an mBRS of 1 or less (OR, 0.43; 95% CI, 0.30-0.60; $P<.001$). A clinical Rockall score of 1 or less did not predict a lower frequency of endoscopic stigmata.

Table 2. Demographics, Presenting Clinical Features, Endoscopic Findings, and Outcomes for the Low and Nonlow Modified Blatchford Risk Score Subgroups

Variable	Modified Blatchford Risk Score ≤1 (Low) (n = 183)*	Modified Blatchford Risk Score >1 (Nonlow) (n = 1686)*	*P* Value
Clinical features/demographics			
Age, y†	58.8 (20)	67.1 (16)	<.001
Male sex	106 (57.9)	1051 (62.3)	.24
Inpatient onset	32 (17.5)	436 (25.9)	.01
No. of comorbidities‡	2 (1-3)	2 (1-3)	<.001
Melena	49 (26.8)	1241 (73.6)	<.001
Systolic blood pressure, mm Hg†	139 (22)	117 (38)	<.001
Hemoglobin level, g/dL†	13.8 (1.6)	9.2 (2.4)	<.001
Clinical component of the Rockall score‡	2 (1-4)	3 (1-4)	.20
Endoscopic findings			
Time to endoscopy, h‡	16 (7-24)	14 (5-24)	.10
Cause			
Ulcer	72 (39.3)	962 (57.1)	<.001
Mallory-Weiss tear	22 (12.0)	61 (3.6)	<.001
Tumor	1 (0.5)	18 (1.1)	.45
Other§	77 (42.1)	589 (34.9)	.06
Normal	12 (6.6)	56 (3.3)	.03
High-risk stigmata	31 (16.9)	551 (32.7)	<.001
Fresh blood seen	21 (11.5)	449 (26.6)	<.001
Treatment			
Proton pump inhibitor therapy	128 (69.9)	1425 (85.0)‖	<.001
Endoscopic therapy	39 (21.3)	656 (38.9)	<.001
Outcomes			
Length of stay, d‡	2 (1-4)	4 (2-7)	<.001
Rebleeding	9 (4.9)	325 (19.3)	<.001
Death	1 (0.5)	98 (5.8)	.003

*Data are given as number (percentage) of each group unless otherwise indicated.
†Data are given as mean (SD).
‡Data are given as median (interquartile range).
§Esophagitis, gastritis, and vascular lesions.
‖Data were missing for 9 patients.

PREDICTING REBLEEDING AND MORTALITY BEFORE ENDOSCOPY

A low mBRS was associated with a lower risk of rebleeding (5% [mBRS of ≤1] vs 19% [mBRS of >1]; $P<.001$) in univariate analysis. In the multivariate model for rebleeding (**Table 3**), only an mBRS of 1 or less, hematochezia, the presence of HRS, and proton pump inhibitor therapy remained significant as independent predictors. Endoscopic therapy was only significant in the high-risk subgroup (OR, 0.64; 95% CI, 0.42-0.97; $P=.04$). A clinical (nonendoscopic) component of the Rockall score of 1 or less was not significant ($P=.18$), even when the mBRS was removed from the model. After the clinical component of the Rockall score was determined not to be needed in the final model, age (a component of the Rockall score) was reconsidered; it was not a significant independent predictor of rebleeding ($P=.93$).

A low mBRS was also associated with a lower mortality (0.5% vs 5.8%; $P=.003$) in univariate analysis. For mortality, a clinical Rockall component of 1 or less was not

Table 3. Summary of Multivariate Analysis Models Predicting Rebleeding and Mortality

Variable	Odds Ratio (95% Confidence Interval)	*P* Value
Rebleeding outcome*		
Modified Blatchford risk score ≤1	0.24 (0.12-0.48)	<.001
Hematochezia	2.5 (1.8-3.3)	<.001
High-risk endoscopic stigmata	2.7 (1.0-3.7)	<.001
Proton pump inhibitor therapy	0.71 (0.50-0.99)	.045
Mortality outcome		
Modified Blatchford risk score ≤1	0.12 (0.02-0.90)	.04
Age, per decade	1.2 (1.1-1.4)	.004
Inpatient onset of bleeding	3.1 (2.0-4.7)	<.001
Hematochezia	2.0 (1.2-3.3)	.004
High-risk endoscopic stigmata	2.1 (1.3-3.5)	.003
Endoscopic therapy	0.54 (0.32-0.89)	.02

*Endoscopic therapy was only significant in the high-risk endoscopic stigmata subgroup.

significant (*P*=.32); therefore, age (a component of the Rockall score) was then reconsidered in the model. A low mBRS remained a significant independent predictor, along with age, inpatient onset of bleeding, hematochezia, the presence of high-risk endoscopic stigmata, and endoscopic therapy (Table 3). There was a nonsignificant association between proton pump inhibitor therapy in the high-risk subgroup (OR, 0.40; 95% CI, 0.17-1.10; *P*=.07), and interactions between each therapy (endoscopic therapy and proton pump inhibitor therapy) and HRS were significant (*P*=.02 and *P*=.004, respectively).

SUBGROUPS AND INTERACTION TERMS WITH RESPECT TO mBRS

Among the 1860 patients with rebleeding data (580 of 582 patients with HRS had rebleeding data), the association between low mBRS and lower rebleeding was just as great in the 580 patients in whom high-risk endoscopic stigmata were present (rebleeding, 3.3% vs 29.6%; OR, 0.08 [95% CI, 0.01-0.61]) as it was in the 1280 in whom they were absent (rebleeding, 5.3% vs 14.4%; OR, 0.3 [95% CI, 0.2-0.7]).

There was a nonsignificant interaction (ie, effect modification) between mBRS and the effect of endoscopic therapy on rebleeding (*P*=.09); a lower therapeutic effect was seen in patients with an mBRS of 1 or less. In fact, even within the subgroup of 580 patients with HRS, endoscopic therapy did not seem to reduce the risk of rebleeding if the mBRS was 1 or less.

COMMENT

There is a small, but clinically significant, proportion of patients with a nonvariceal upper gastrointestinal tract bleed that are believed, intuitively, by physicians to have a lower clinical risk; hence, they may believe that it is questionable whether these patients need to be admitted overnight or over the weekend for observation, pending endoscopy to complete a "risk assessment." If a subgroup of these patients who have good social supports could be identified as having a low chance of benefiting from endoscopy and high-dose intravenous proton pump inhibition, this would help reduce resource use for this common condition. This subgroup of patients is relatively small, and requires a large cohort (such as that of RUGBE) to achieve adequate power to assess this effect. This study supports the concept that patients who are clinically at low risk (eg, hemodynamically stable, minimally abnormal hemoglobin level, and no major comorbidities) have a high chance of having a low-risk cause and have a low chance of having HRS. Even when these stigmata are believed to be present, the patients likely gain little from endoscopic therapy, partly because their overall risk of rebleeding remains low (<5%).

The clinical (ie, nonendoscopic) component of the Rockall score does not seem to predict HRS or rebleeding as accurately as the mBRS. Although similar, there are some important differences between these 2 scores; for example, the mBRS does not include age (a predictor of mortality but not rebleeding), while the Rockall score does not include hemoglobin level or the presence of melena. The original intention of the Rockall score was to predict nonvariceal upper gastrointestinal tract bleeding–related mortality, rather than rebleeding itself; this might be one explanation. Another likely explanation is that the clinical component of the Rockall score does not need to predict stigmata, because stigmata are considered in the endoscopic component of the Rockall score. Using them as a substitute for the endoscopic component is not sound and, to our knowledge, has not been previously tested; indeed, rather, they were meant to be taken together. Therefore, if one does not have the benefit of knowing the endoscopic findings in an outpatient, hemoglobin level and melena seem to be more important than age for predicting the presence of HRS (benefiting from endoscopic and proton pump inhibitors) and the occurrence of rebleeding.

Blatchford et al[6] reported that a BRS of 0 had 100% negative predictive value for rebleeding and mortality, as did Gralnek and Dulai.[17] However true, this cutoff is likely overly restrictive given that our currently accepted rebleeding risk threshold for safe discharge, when we know the endoscopic findings, is generally 2% to 5%, not 0%. This conservative cutoff also identifies a smaller subgroup of our patients, and has a lesser clinical impact. Although Gralnek and Dulai also showed that a Rockall clinical subscore of 0 had a 100% negative predictive value for rebleeding and mortality, this threshold was also restrictive. Furthermore, the reassurance provided by a Rockall clinical subscore of 0 was not reproduced by Blatchford et al; it had a 5% to 10% intervention rate, while a subscore of 1 was associated with a rate (approximately 20%) that was no different than when the score was greater than 1 (extracted from Blatchford et al). Correlation with endoscopic findings was not attempted with either scoring system in this study.[17] Moreover, the study by Gralnek and Dulai identified patients retrospectively, using *International Classification of Diseases, Ninth Revision (ICD-9)*, primary discharge codes.

It is not clear why the clinically low-risk (ie, low mBRS) patients who have high-risk endoscopic stigmata still have

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a low risk of rebleeding. It is possible that the stigmata were overcalled, and the relatively poor interobserver reliability of stigmata recognition certainly makes that possible.[18] The endoscopic procedures were not videotaped for the registry, so this question cannot be further clarified. Another explanation is that the mBRS simply identifies a low-risk subgroup with so-called HRS, which we know comprises a spectrum of patients and presentations. That is, a possible visible vessel within an ulcer of a patient who presented with a hemoglobin level of 6 g/dL, hypotension, melena, and heart disease likely bears a different prognosis than the same endoscopic appearance with a normal hemoglobin level, normal hemodynamics, coffee ground hematemesis, and no significant comorbidities.

Although the patients were enrolled as a prospective cohort, the conclusions of this study are limited by the fact that they are based on a retrospective analysis. However, the variables being analyzed were readily available and were complete in almost all patients (the final HRS and rebleeding multivariate models contained 1850 and 1815 patients, respectively). We also defined our endpoints a priori, before analyzing the data. One of the potential problems we anticipated in designing this analysis was that if time to endoscopy was longer in the low-risk patients, allowing stigmata time to resolve, then this might account for an apparent lowering of the frequency of the HRS. We anticipated that we might have to adjust for this in multivariate analysis.[16,19] However, this did not turn out to be a problem because both groups underwent endoscopy within a similar time frame. The duration of proton pump inhibitor therapy before endoscopy might also have confounded the reported association between mBRS and prevalence of stigmata[20]; however, because clinically high-risk patients are more likely to receive high-dose intravenous proton pump inhibitor infusions before endoscopy, this confounding would act to weaken the apparent association rather than strengthen it. The similar time to endoscopy also confirms our suspicion that patients with low-risk clinical features are undergoing endoscopy with the same urgency as the higher-risk patients and, thereby, may be consuming resources inappropriately.

Another limitation was that we had to use an mBRS because urea and syncope data were not recorded in RUGBE. This modified score performed extremely well, and is arguably easier to use and remember than the original, in which urea ranges need to be considered; the availability of a simpler mBRS may help increase the use of such a score in real-life practice.

Whether it is indeed safe to discharge this subgroup of patients with a prescription for oral acid suppression agents, with perhaps daily telephone contact and daily blood counts for 3 to 4 days and with an urgent outpatient endoscopy within the next 1 to 3 days, remains unclear. These data suggest that it is likely safe to at least randomize patients to such an option within the context of a clinical trial.

In conclusion, patients with an mBRS of 1 or less (ie, no cardiac or liver disease, no severe hypotension [systolic pressure $<$100 mm Hg], and no severe anemia [hemoglobin level, $<$12 g/dL in men and $<$10 g/dL in women]) and no more than 1 of the following (tachycardia, mild hypotension, or mild anemia) (Table 1) exhibit a low chance of having lesions that benefit from therapeutic endoscopy and have a low risk of rebleeding (5%) and mortality (0.5%). This rate is similar to that of the subgroup of patients considered acceptable for early discharge based on the finding of low-risk stigmata at endoscopy, and is no different than the rate in patients with low-risk stigmata on endoscopy (generally discharged promptly after endoscopy). There are several published series advocating a combination of clinical and endoscopic criteria to determine safety for early discharge. The risk of rebleeding in the subgroup of patients believed eligible for early discharge in those series has ranged from 0.5% to 5.8%, with an overall mortality of 0.1% (upper limit of the 95% CI, 0.6%)[2,21-23]; this is in keeping with what the mBRS can predict without endoscopy. The Rockall clinical subscore (ie, nonendoscopic) does not perform as well, and does not predict findings at endoscopy.

A prospective, preferably randomized, study is required to validate whether this selected group of patients, especially those presenting after hours or on weekends, can be safely managed with neither emergent endoscopy nor expectant inpatient monitoring pending endoscopic clearance; it is plausible that high-dose oral therapy, with urgent outpatient endoscopy arranged within a few days, may be a reasonable option in these patients if a good social support system exists.

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