Clinical predictors of outcome in acute upper gastro-intestinal bleeding

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Objective. Endoscopy has traditionally been used to risk-stratify patients with upper gastrointestinal bleeding (UGIB). This is problematic in resource-poor environments. The study aimed to identify patients who would not require urgent endoscopy by identifying clinical variables before endoscopy that predict uneventful recovery.

Design. Prospective, descriptive cross-sectional study.

Setting. Groote Schuur Hospital, Cape Town.

Subjects. Two hundred consecutive patients aged over 12 years, presenting with haematemesis and/or melaena.

Outcome measures. Good outcome, i.e. no blood transfusion, endotherapy or surgery, and alive at 1 month following presentation.

Results. Eighty patients (40%) had a good outcome. Haemoglobin > 10 g/dl (odds ratio (OR) 25.5, 95% confidence interval (CI): 8.9 - 74.8; $p < 0.001$), absence of melaena (OR 4.8, 95% CI: 1.79 - 12.94, $p = 0.002$) and absence of syncope (OR 4.0, 95% CI: 1.67 - 9.48; $p = 0.002$) were independent predictors of good outcome. The three variables combined as a positive test had the best association with good outcome when compared with a single variable or a combination of two variables. The three-variable model had sensitivity for good outcome of 34%, specificity of 98%, and likelihood ratio for a positive test of 13.5 and for a negative test of 0.68. Thirty patients (15%) had the combination for the prediction rule, i.e. haemoglobin > 10 g/dl, no melaena and no syncope; 3 (10%) had a poor outcome (required endotherapy).

Conclusion. The prediction rule accurately excluded poor outcome, a priority in the clinical context, but did not predict good outcome. Clinical implications are a 15% reduction in unnecessary urgent endoscopies, with less than 5% of patients with poor outcome not undergoing urgent endoscopy. These findings may have particular clinical relevance in under-resourced health care environments.

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Acute upper gastrointestinal bleeding (UGIB) is a common cause of emergency hospital admission and is associated with substantial health expenditure.[1] The condition is also not uncommon among already-hospitalised patients.

Despite improved technology in the management of UGIB, mortality has remained high. This has been attributed to the increase in the population of elderly people who tend to have other underlying diseases leading to the high mortality rate. According to international literature, mortality varies from 4% to 10%.[2,3] The bulk of severe morbidity and mortality occurs in patients with recurrent bleeding or significant co-morbid illness.[4]

The use of non-steroidal anti-inflammatory drugs (NSAIDs), common in the elderly, more than doubles mortality associated with peptic ulcer complications.[5]

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Endoscopy has traditionally been used to risk-stratify patients with UGIB.[6] This approach may be inappropriate in large areas of South Africa where endoscopy is not readily available. Ideally, to avoid waste of limited resources and time, it would be helpful to identify patients in whom endoscopy could be delayed without deleterious outcome, reserving emergency endoscopy for patients at highest risk for both re-bleeding, morbidity and mortality. In this class of patients endoscopy is used not only for diagnosis but also for endoscopic treatment to control massive ulcer bleeding.

From the time that research and debate on factors influencing the outcome of acute upper gastro-intestinal haemorrhage began, age, co-morbidity, shock, admission haemoglobin values, presentation (either with haematemesis, melaena or both), ulcer type, ulcer size, stigmata of recent haemorrhage (visible vessel in an ulcer bed, ooze, fresh clot) and transfusion requirement have all been described as significant risk factors for further haemorrhage and death.[7] However, there is no universal agreement on a set of risk factors as researchers have emphasised different factors according to their experience and have used different endpoints.[2]

Until recently, no study had attempted to devise a simple and therefore clinically useful risk scoring system that would

be readily available to the clinician for categorising patients by risk. Of the studies that have investigated predictors of outcome, a large number have looked at predictors of adverse outcome (re-bleed, death and surgery). Very few studies have looked at predictors of good outcome. Even then, most of these studies have included endoscopic findings in their decision criteria.[6,8]

Does a predictor of good outcome equal the absence of a predictor of poor outcome? It is not possible to implement the opposite of predictors of adverse outcome as being predictors of good outcome, as endpoints in the studies would be different. For example, factors that predict mortality, such as age and co-morbidity, are not necessarily predictive of persistent or recurrent bleeding.[9]

Of principal concern is the safety of patients who would be discharged from primary and secondary health care facilities for deferred endoscopy examination. There is a need to isolate those predictors of good outcome able to classify patients who could be safely discharged on medical therapy without prior endoscopy and recover without any adverse event. The decision rule would be used only to delay (urgent) endoscopy; a diagnostic endoscopy would still be done. Diagnostic endoscopy without a therapeutic procedure does not alter mortality, although in most cases it provides information on the source of bleeding.

Given the scarcity of information on the non-endoscopic triage of patients, a prospective study of patients with acute upper gastro-intestinal haemorrhage was undertaken to identify patients at low risk for an adverse outcome following acute UGIB at Groote Schuur Hospital in Cape Town.

Study population and methods

Consecutive patients over the age of 12 years presenting to the Emergency Unit with haematemesis and/or melaena between October 1997 and August 1998, were prospectively studied. Patients were excluded if: (*i*) their initial presentation was to another hospital that instituted resuscitative measures; (*ii*) they were known to have oesophageal varices or upper gastro-intestinal malignancy; (*iii*) they presented with anaemia without a clear history of UGIB; or (*iv*) if they developed UGIB during the course of hospitalisation for another problem.

Data were collected using a structured clerking sheet designed for the study, which included demographic characteristics; mode of presentation, i.e. haematemesis and/or melaena; history of pre-syncope (near fainting or extreme dizziness) or syncope (transient loss of consciousness with loss of postural tone); medication use, particularly non-steroidal anti-inflammatory drugs (NSAIDs), salicylates or warfarin; alcohol use; history of previous peptic ulcer disease; haemoglobin concentration; pulse; systolic blood pressure (SBP); postural hypotension; and co-morbidity. Each patient underwent endoscopic examination.

The criteria for a good outcome were: (*i*) non-performance of an endoscopic procedure (endotherapy) to control bleeding, a therapeutic surgical procedure, or a blood or blood product transfusion; and (*ii*) alive within 1 month of initial presentation. Patients were followed up at 1 month after hospital discharge.

Blood transfusion was taken to be a poor-outcome event because of the laboratory, medical and nursing expertise required in its administration, as well as being an indicator of significant bleeding. Endotherapy and surgery were regarded as poor-outcome criteria because these services require trained specialists who are only available at some secondary level hospitals and at no primary level hospitals. Hence all patients with UGIB requiring such interventions need to be referred to centres where these facilities are available. Death is the end-point that we all strive to reduce.

Data analysis

Data were entered into a standard spreadsheet (Excel), and univariate, bivariate and multivariate descriptive statistics were derived using Statistica Version 5.1 (1998) software. Bivariate analysis for individual predictive factors of good outcome was performed using the chi-square test. Continuous variables were compared using the unpaired *t*-test. To increase clinical relevance the continuous variables were converted into categorical variables using internationally acceptable ranges defining severity of an UGIB. Statistical significance was accepted at $p < 0.05$ (two-tailed).

Clinical predictors that showed significant association with good outcome on bivariate analysis were entered into a multiple logistical regression model. A final model was selected using stepwise multiple logistical regression analyses. Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio (LR) for a positive test and LR for a negative test were calculated individually and in combination for variables that were found to be independently associated with outcome.

LRs are measures of the accuracy with which a diagnostic test identifies its target disorder in an individual patient. They are regarded as the most useful indicators of test accuracy in a clinical context involving individual patients. The higher the ratio is above 1, the greater the change in probability in favour of the condition of interest; the lower the ratio below 1, the greater the change in probability against the condition of interest.[10]

The investigators pre-specified a predictive tool with a specificity of not less than 95% as an acceptable benchmark, i.e. no more than 5% of patients with poor outcome should miss urgent endoscopy.

Ethics approval

The study was approved by the Ethics and Research Committee of the Faculty of Health Sciences, University of Cape Town.

Results

Over the 10-month study period, a total of 306 patients were admitted to the Emergency Unit with a diagnosis of haematemesis and/or melaena. A total of 200 of these patients (65.4%) met the inclusion criteria and were included in the final analysis.

The median age of the 200 patients was 57.5 years (range 19 - 93 years). One hundred and twenty-two patients (61%) were males and 78 (39%) were females.

One hundred and two of the patients (51%) had blood transfusions with 11 (5.5%) requiring more than five units of blood. Thirty-five (17.5%) had endoscopic therapy, and 8 (4%) underwent surgery. There were 13 deaths (6.5%), of which 8 deaths were related to gastrointestinal haemorrhage, while 5 were related to other underlying co-morbidity. Bleeding-related mortality was 4% and mortality due to underlying co-morbidity was 2.5%. Of the 200 patients, 80 (40%) had a good outcome (no transfusion, endotherapy or surgery, and alive at 1 month after presentation).

On bivariate analysis, age, pulse, SBP, haemoglobin, history of pre-syncope or syncope (syncope), anticoagulant use, presentation with either melaena or haematemesis, and co-morbidity were significant predictors of outcome. Variables not associated with outcome were use of NSAIDs, salicylates, alcohol and history of previous peptic ulcer disease (Table I).

Table I. Predictors of good outcome (no transfusion, endoscopic therapy or surgery, and alive at 1 month) (bivariate logistical regression analysis)

	RR	95% CI for RR	*P*-value
Age < 60 years	1.58	1.10 - 2.28	0.01
Pulse < 100 beats/min	1.76	1.18 - 2.60	0.003
SBP >100 mmHg	4.58	1.20 - 17.30	0.002
Hb > 10 g/dl	10.50	4.80 - 23.0	< 0.001
Syncope	0.43	0.29 - 0.62	< 0.0001
Warfarin	1.67	1.28 - 2.19	0.006
Co-morbidity	0.67	0.48 - 0.94	0.02
Haematemesis	1.72	1.14 - 2.59	0.005
Melaena	0.58	0.39 - 0.88	0.005
NSAIDs/salicylates	0.82	0.58 - 1.17	0.26
Alcohol	1.27	0.86 - 1.88	0.25
Previous PUD	0.90	0.62 - 1.32	0.59

RR = relative risk; CI = confidence interval; SBP = systolic blood pressure; Hb = haemoglobin; NSAIDs = non-steroidal anti-inflammatories; PUD = peptic ulcer disease.

Although not predictive of outcome, current intake of salicylates or NSAIDs was significantly associated with the diagnosis of peptic ulcer disease on endoscopy (relative risk (RR) 1.79, 95% confidence interval (CI): 1.33 - 2.40, $p < 0.001$).

On multiple logistical regression analysis, absence of melaena, absence of history of pre-syncope or syncope, and haemoglobin value greater that 10 g/dl were independent predictors of good outcome (Table II). These three variables were included in the final model selected (Table III).

Table II. Predictors of good outcome (no transfusion, endoscopic therapy or surgery, and alive at 1 month) (multiple logistical regression analysis)

	Odds ratio (OR)	95% CI for OR	*P*-value
No melaena	5.21	1.36 - 19.93	0.01
No haematemesis	0.96	0.29 - 3.10	0.95
No syncope	3.80	1.44 - 10.09	0.006
No warfarin	0.76	0.11 - 5.25	0.78
Hb >10 g/dl	22.97	6.85 - 76.98	< 0.0001
Pulse < 100 beats/min	2.37	0.78 - 7.10	0.12
SBP >100 mmHg	2.48	0.34 - 18.01	0.36
Age < 60 years	1.09	0.36 - 3.35	0.87
No co-morbidity	1.03	0.34 - 3.14	0.95

CI = confidence interval; Hb = haemoglobin; SBP= systolic blood pressure.

Table III. Final model — predictors of good outcome

	Odds ratio	95% CI for OR	*P*-value
No melaena	4.8	1.79 - 12.94	0.002
Hb >10g/dl	25.8	8.9 - 74.8	< 0.0001
No syncope	3.98	1.67 - 9.48	0.002

CI = confidence interval; Hb = haemoglobin.

The selected model had sensitivity for good outcome of 34% (95% CI: 27 - 40%), specificity of 98% (95 - 100%), positive predictive value of 90% (86 - 94%) and negative predictive value of 69% (62 - 75%). The likelihood ratio for a positive (LR+) test was 13.5 (5.3 - 54.0) and the likelihood ratio for a negative (LR–) test was 0.68 (0.57 - 0.79). In this study, using this model, 72% of patients were correctly classified.

A model taking any two of the three variables as a positive test had lower specificity of 83% (78 - 88%), and lower LR+ of 4.4.

Discussion

This prospective study was undertaken to define predictors of good outcome (i.e. no transfusion, endotherapy or surgery, and

alive at 1 month) in patients presenting with acute UGIB, with a view to identifying criteria for the selection of patients who would recover uneventfully without need for urgent endoscopy.

Eighty of the patients (40%) had a good outcome. One hundred and two (51%) had blood transfusion, 35 (17.5%) had endotherapy and 8 (4%) underwent surgery. The total mortality of 6.5% was within the range of most other studies. The main finding of the study was that absence of melaena, the absence of syncope and haemoglobin greater than 10 g/dl were predictors of good outcome, as pre-defined.

Some of the findings warrant comment:

1. The role of co-morbidity as a predictor of outcome has been confirmed in other studies.[3,11] In the present study, although co-morbidity was a predictor of poor outcome (Table I), this association was lost on multivariate analysis.

2. It is surprising that age, like co-morbidity, was a predictor of outcome on bivariate but not on multivariate analysis. Advanced age has been associated with adverse outcome in many other studies. The findings of this study were similar to findings of some previous studies that identified low-risk patients with UGIB.[7] The lack of association after adjustment in the multivariate model indicates that in this sample, haemoglobin greater than 10 g/dl and the absence of melaena or syncope were associated with a younger age and better predicted outcome.

3. Current intake of salicylates/NSAIDs was associated with an increased risk of peptic ulcer disease at endoscopy (RR 1.79, 95% CI: 1.33 - 2.40, $p < 0.001$) but was not significantly associated with outcome (Table I). The use of these drugs has been associated with increased risk of peptic ulcer occurrence, ulcer complication (haemorrhage or perforation) and death.[12]

Case control studies have found the increased risk of UGIB in patients taking NSAIDs to have a linear dose-response relationship.[12] The correlation between risk of peptic ulcer disease and dosage was not explored in this study. The inclusion of patients taking minimal doses of NSAIDs could have impacted on its association with outcome.

4. On bivariate analysis, presentation with haematemesis alone was associated with good outcome, while presentation with melaena alone was associated with poor outcome (Table I). This is unlike findings in most studies where haematemesis is associated with an adverse outcome.[3,13] The difficulty in comparing these studies with our study is that these studies included patients with varices who tend to present with haematemesis and are at high risk of a poor outcome. The other factor is that endpoints differ in different studies. The perceived need for blood transfusion as part of the outcome measures was included because of the perceived lack of expertise required for its administration at primary health care centres. We hypothesise that patients presenting with melaena alone may present late to hospital, as the bleeding is less brisk and less alarming. Therefore, they may present with much lower haemoglobin levels and require blood transfusion.

5. Syncope is correlated with rapidity of blood loss. This variable has been incorporated as a predictor of outcome in very few studies. Those studies that included syncope as a predictor variable found it not to be a predictor of mortality.[3,4] Nevertheless, we cannot compare our findings with these studies, as their endpoint was mortality. In the American Society for Gastrointestinal Endoscopy survey,[3] syncope was associated with blood transfusion of more than five units.

6. Haemoglobin, pulse and SBP are all measures of severity of the bleed. These variables have been used in many studies as predictors of outcome. On bivariate analysis, using internationally accepted cut-off levels for low risk of adverse outcome,[14] haemoglobin greater than 10 g/dl, pulse rate less than 100 beats/minute and SBP greater than 100 mmHg were significantly associated with a good outcome. However, on multivariate analysis, pulse rate and blood pressure lost statistical significance. This is probably due to the association between pulse rate, blood pressure levels and haemoglobin value that was adjusted for in the multivariate model.

On multiple logistical regression analysis, in the final model, absence of melaena, absence of syncope and haemoglobin greater than 10 g/dl were the predictors of good outcome (Table III). A combination of all three variables significantly improved the association. The improved specificity, predictive values and LRs of the combined variables demonstrate this.

Increasing the number of variables in the model (results not shown) did not improve its prediction of the outcome, and sensitivity decreased further, making the prediction rule worthless in selecting anyone for management without urgent endoscopy.

The specificity for the predictor model of 98% and 95% CI of 95 - 100% meet our predetermined requirement that a predictive tool should not have specificity of less than 95%.

Of the 200 patients in the study, 30 (15%) satisfied the prediction rule (haemoglobin greater than 10 g/dl, no melaena and no syncope). These patients would have been sent home without undergoing urgent endoscopy. However, 3 had been misclassified as they had a poor outcome. These 3 patients, who were false-positives according to the test criteria, required sclerotherapy to control haemorrhage. They did not have blood transfusion or surgery and were alive at 1 month. The clinical implications of these findings are that the test would result in a moderate impact on the reduction of unnecessary endoscopies (15% of admissions) with 5% or less of the patients with poor outcome being sent home without urgent endoscopy.

The prediction rule could be easily applied even in poorly resourced health centres, as it does not involve sophisticated equipment. It should be noted that these criteria help identify those who will get better anyway, regardless of endoscopy. It does not necessarily identify those who do not require

endoscopy for diagnostic purposes.

However, a clinical decision rule is 'data driven' in that it is derived from a specific sample of patients. The test may not perform as well in different populations and therefore needs to be validated.[15] Patients included in the study are not representative of our general population. Patients presenting to private hospitals with UGIB may be different at presentation from the study population in that they may present earlier or might have different degrees of exposure to risk factors for UGIB. Their outcome may differ due to different management strategies such as transfusion practices. For this reason, a validation study is required before the decision rule is considered for application in clinical practice.

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References

1. Gostout CJ. Outpatient management of upper gastrointestinal bleeding: Has the time finally arrived? *Gastrointest Endosc* 1998; **47:** 311-313.
2. Katschinski B, Logan R, Davies J, Faulkner G, Pearson J, Langman M. Prognostic factors in upper gastrointestinal bleeding. *Dig Dis Sci* 1994; **39:** 706-712.
3. Silverstein FC, Gilbert DA, Tedesco FJ, Buenger NK, Persing J and members of the ASGE survey on upper gastrointestinal bleeding II: Clinical prognostic factors. *Gastrointest Endosc* 1981; **27**(2): 80-93.
4. Zimmerman J, Siguencia J, Tsvang E, Beri R, Arnon R. Predictors of mortality in patients admitted to hospital for acute upper gastrointestinal haemorrhage. *Scand J Gastroenterol* 1995; **30:** 327-331.
5. Armstrong CP, Blower AL. Non-steroidal anti-inflammatory drugs and life threatening complications of peptic ulceration. *Gut* 1987; **28:** 527-532.
6. Rockall TA, Logan RFA, Devlin HB, Northfield TC. Selection of patients for early discharge or outpatient care after acute upper gastrointestinal haemorrhage. *Lancet* 1996; **347:** 1138-1140.
7. Rockall TA, Logan RFA, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996; **38:** 316-321.
8. Longstreth GF, Feitelberg SP. Successful outpatient management of acute upper gastrointestinal haemorrhage: use of practice guidelines in a large patient series. *Gastrointest Endosc* 1998; **47:** 219-222.
9. Castell DO, Blankenbaker RG, Bozymski EM, *et al*. Consensus statement on therapeutic endoscopy and bleeding ulcers. *Gastrointest Endosc* 1990; **36:** suppl 5, S62-S65.
10. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patient? The evidence-based medicine working group. *JAMA* 1994; **271:** 703-707.
11. Kollef MH, O'Brien JD, Zuckerman GR, Shannon W. BLEED: A classification tool to predict outcomes in patients with acute upper and lower gastrointestinal haemorrhage. *Crit Care Med* 1997; **25:** 1125-1132.
12. Henry D, Dobson A, Turner C. Variability in the risk of major gastrointestinal complications from nonaspirin non-steroidal anti-inflammatory drugs. *Gastroenterology* 1993; **105:** 1078-1088.
13. Terdiman JP, Ostroff JW. Risk of persistent or recurrent and intractable upper gastrointestinal bleeding in the era of therapeutic endoscopy. *Am J Gastroenterol* 1997; **92:** 1805-1811.
14. Hussain H, Lapin S, Cappell MS. Clinical scoring systems for determining the prognosis of gastrointestinal bleeding. *Gastroenterol Clin North Am* 2000; **29:** 445-464.
15. Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Application of methodological standards. *N Engl J Med*. 1985; **313:** 793-979.

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