Predictors of positive endoscopic findings in hospitalized patients with occult gastrointestinal bleeding

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Abstract

Anemia with occult gastrointestinal bleeding (OGIB) is a common reason for inpatient gastroenterology consultation and endoscopy. However, the utility of inpatient endoscopy in this setting is unclear. The aim of this paper is to determine variables that predict positive endoscopic examinations for inpatients presenting with anemia and OGIB. We performed a prospective observational study of consecutive hospitalized patients between March 2013 and April 2014 with anemia and OGIB. For patients undergoing inpatient endoscopic evaluation, logistic regression was used to determine which variables were associated with detecting etiology of OGIB. An occult bleeding score (OBS) was created using receiver operating characteristics and area under the curve (AUC) analysis to predict detection of bleeding source and need for endoscopic intervention. Of the 74 patients identified, 55 (74%) underwent endoscopic evaluation, of whom 28 patients had a source of OGIB identified. Patients with malignancy (OR 7.25, 95%CI 1.06-144) were more likely to have a bleeding source identified on endoscopy, whereas patients with higher admission hemoglobin levels were less likely to have a detected source (OR 0.62, 95%CI 0.41-0.86). The OBS was constructed by assigning a point each for malignancy and admission hemoglobin <8.2 g/dL. The OBS predicted detection of etiology of bleeding and endoscopic intervention with an AUC of 0.79 and 0.75. The yield of endoscopy in determining a bleeding source in patients with OGIB is significant particularly in patients with malignancy or a low hemoglobin level. A simple score can assist in determining whether inpatient endoscopy is warranted in this population.

Introduction

Occult gastrointestinal bleeding (GIB) refers to the clinical presentation of a positive

stool fecal occult blood test (FOBT) with or without iron deficiency anemia in the absence of overt bleeding.¹ Although only recommended in the context of colon cancer screening,² FOBT is frequently ordered in the inpatient setting due to anemia,³ and is a common reason for inpatient gastroenterology consultation.⁴ Because of its false positive results, inpatient guaiac testing commonly leads to negative endoscopic testing,^{4,5} and has been shown to have little beneficial impact on inpatient clinical management.⁶ In fact, despite endoscopic evaluation with upper esophagogastroduodenoscopy (EGD) and colonoscopy, the source of bleeding can remain undetected in patients with occult GIB in up to 52% of patients.⁷

In such cases where initial endoscopic evaluation is unrevealing, current guidelines recommend consideration of further studies such as capsule endoscopy and enteroscopy.^{2,8,9} However, although occult GIB is a common clinical scenario in the hospital, there is limited data regarding which risk factors predict either detecting the bleeding source on inpatient endoscopy, or the need for endoscopic intervention. In addition, recent data have described risk factors for increased 30-day hospital readmissions and rebleeding for patients with overt GIB.¹⁰ There is limited data on whether patients with occult bleeding have increased hospital readmission and rebleeding rates, and whether endoscopic intervention or localization during index hospitalization can reduce these rates.

Our primary aims were to determine the yield of endoscopy in patients with anemia and occult GIB and whether clinical or laboratory parameters on admission could predict patients who were high or low risk for having either a source of occult GIB detected on endoscopic evaluation, or require endoscopic intervention. Other aims were to report all-cause 30-day hospital readmissions and rebleeding in a population of hospitalized patients with anemia and occult GIB.

Materials and Methods

As described elsewhere,^{10,11} we performed a prospective observational cohort study of consecutive patients admitted with or developing GIB in the hospital. Data were collected on a total of 750 patients admitted to Beth Israel Deaconess Medical Center (BIDMC, Boston, MA, USA) from March 2013 to April 2014. Patients were included in this study if the gastroenterology service was consulted for anemia and occult GIB, as defined by a positive stool guaiac test in the setting of anemia. Patients with overt GIB ($n=676$) as defined by presence of hematemesis, coffee ground eme-

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sis, melena, or hematochezia were excluded from this study.

We obtained baseline demographic information and the following clinical data via medical record review during hospitalization: comorbidities, home medications, and initial laboratory studies. Baseline hemoglobin values were recorded by review of prior clinic notes. We recorded the details of in-hospital management, transfusion requirements, endoscopic procedures and interventions, and etiology of bleeding. Inpatients were classified as having iron deficiency, if the transferrin saturation was less than 20%, or if the ferritin levels were less than 40 ng/mL. For all etiologies, the bleeding source was defined based on the presence of stigmata of hemorrhage on endoscopic evaluation. Endoscopic interventions included the use of endoclips, electrocautery, epinephrine, or argon plasma coagulation. The timing of initial procedure and choice of endoscopic therapy was left to the discretion of the attending gastroenterologist, as there was no structured protocol for evaluation and management of these patients.

Discharge data included hospital length of stay (LOS), and discharge medications. Patients were mailed a letter to inform them of the study and the plan to contact them by telephone to complete a survey. An investigator (NS, JDF, VRP) contacted all patients via telephone at 30 days after discharge to determine

all interval emergency department (ED) visits and hospital readmissions. Rebleeding events as well as the reason for interval readmissions were confirmed via review of our online medical record. Deaths occurring in follow up were confirmed by reviewing the medical record and online death registries.¹²

The study was approved by the BIDMC Institutional Review Board.

Statistical analysis

Categorical variables are reported as percentages, and continuous variables are reported as medians (interquartile ranges). Comparisons between groups for categorical data were made with Fisher's exact test. Continuous data were compared using the 2-sample t test for normally distributed variables and Wilcoxon rank-sum test for non-normally distributed variables. Univariable and multivariable logistic regression were used to determine associations of variables to localizing a

source of occult GIB. An occult bleeding score (OBS) was constructed using admission hemoglobin and presence of active malignancy. The optimal hemoglobin cutoff was determined by the receiver operating characteristic curve (ROC). The ability of the OBS to predict localization of bleeding and endoscopic intervention was assessed by area under the curve (AUC) analysis. Univariable logistic regression was used to report associations between clinical variables and both 30-day readmissions and rebleeding. All analyses were performed using JMP Pro 10.0 (SAS Institute, Cary, NC, USA).

Results

Of the 750 patients who the GI service was consulted on for GIB during the study period, seventy-four inpatients were identified who

were admitted with or developed anemia and occult GIB. Seventy-four percent (n=55) underwent an inpatient endoscopic procedure and 19 (26%) were managed conservatively without endoscopic evaluation. None of the patients who were managed conservatively developed overt GIB during hospitalization. Patients who underwent an endoscopic procedure had a higher difference between their previous baseline hemoglobin prior to hospitalization, and their nadir hemoglobin during hospitalization (3.2 g/dL vs 2.2 g/dL, P=0.03). Patients on systemic anticoagulation were not more likely to have an inpatient endoscopic evaluation for occult GIB and anemia (40%, n=22/55 vs 32%, n=6/19; P=0.59). Sixty-two percent (n=46/74) of the cohort had no identified source of bleeding during the hospitalization. One patient died during hospitalization due to septic shock who did not undergo endoscopic evaluation. This patient did not develop overt GIB. The median age of the cohort was 74

Table 1. Baseline demographics.

Clinical variables	Cohort (n=74)	Procedure performed (n=55)	No procedure (n=19)	P value
Age, median (IQR)	74 (62-84)	74 (61-84)	71 (62-86)	0.84
Male sex, n (%)	41 (55)	31 (56)	10 (53)	0.80
Tobacco, n (%)	17 (23)	5 (26)	12 (22)	0.75
In-hospital GIB, n (%)	12 (16)	8 (42)	4 (7)	0.001
Number of comorbidities, median (IQR)	10 (8-13)	10 (8-13)	12 (7-16)	0.38
Comorbidities, n (%)				
Hypertension	58 (78)	43 (78)	15 (79)	1.0
Coronary artery disease	30 (41)	23 (42)	7 (37)	0.79
Atrial fibrillation	19 (26)	14 (25)	5 (26)	1.0
Congestive heart failure	20 (27)	13 (24)	7 (37)	0.37
Cerebrovascular disease	16 (22)	14 (25)	2 (11)	0.21
Renal failure	32 (43)	25 (45)	7 (37)	0.60
Active malignancy	10 (14)	6 (11)	4 (21)	0.27
Cirrhosis	10 (14)	8 (15)	2 (11)	1.0
History of GIB	30 (41)	24 (44)	6 (32)	0.42
Iron deficiency, n (%)	40 (54)	33 (60)	7 (37)	0.11
Home medications, n (%)				
Anticoagulants	28 (38)	22 (40)	6 (32)	0.59
Aspirin	41 (55)	28 (51)	13 (68)	0.28
Etiology, n (%)				
Arteriovenous malformation	7 (9)	7 (13)	N/A	N/A
Dieulafoy lesion	3 (4)	3 (5)	-	-
Diverticular	1 (1)	1 (2)	-	-
Variceal	1 (1)	1 (2)	-	-
Gastritis	2 (3)	2 (4)	-	-
GAVE	3 (4)	3 (5)	-	-
Portal gastropathy	3 (4)	3 (5)	-	-
Duodenal ulcer	2 (3)	2 (4)	-	-
Gastric ulcer	6 (8)	6 (11)	-	-
No source	46 (62)	27 (49)	19 (100)	-
Management, n (%)				
Endoscopic intervention	11 (15)	11 (20)	0 (0)	N/A
Blood transfusion	54 (73)	41 (75)	13 (68)	0.77
Fresh frozen plasma	7 (9)	7 (13)	0 (0)	0.18
Intensive unit care	19 (26)	14 (26)	5 (26)	1.0
Length of stay, median IQR	5 (3-9)	5 (3-9)	5 (3-10)	0.55
Nadir hemoglobin, g/dL	7.0 (6.4-7.6)	6.9 (6.4-7.6)	7.1 (6.6-7.8)	0.62
Difference between Baseline and Nadir Hgb, g/dL	2.8 (1.7-4.2)	3.2 (1.8-4.5)	2.2 (1.6-2.9)	0.03

IQR, interquartile range; GIB, gastrointestinal bleeding; GAVE, gastric antral vascular ectasias; Hgb, hemoglobin.

years (IQR 62-84). Fifty-four percent (n=40/74) of patients had evidence of iron deficiency at the time of hospitalization. Demographics and occult GIB etiology are summarized in Table 1.

Diagnostic procedures and their yields

The source of occult bleeding was detected in 36% (n=18/50) of patients undergoing inpatient EGD (n=50), whereas the source of bleeding was detected in only 12% (n=3/25) of patients undergoing colonoscopy after a non-diagnostic EGD. Median time to EGD was 48 hours (range 6-168 hours), and the median time to colonoscopy was 72 hours (range 24 to 168 hours). A source of bleeding was detected in an additional 3 patients undergoing capsule endoscopy (n=8) after non-diagnostic EGD and colonoscopy. Two of these three patients subsequently went on to having an enteroscopy, one of whom had a bleeding source confirmed on enteroscopy. Two additional patients underwent an enteroscopy without having a preceding capsule endoscopy, neither of whom had a positive source detected.

Localization of bleeding

For the 55 patients who had an endoscopic evaluation, logistic regression was performed to determine variables associated with detecting a bleeding source (Table 2). Patients with active malignancy at time of occult bleeding (OR 7.25, 95%CI 1.06-144, P=0.04), and patients requiring inpatient blood transfusion (OR 4.25, 95%CI 1.13-20.9, P=0.03) were more likely to have a bleeding source detected. Patients with higher admission hemoglobin levels (OR 0.62 per-unit, 95%CI 0.41-0.86, P=0.003) and nadir hemoglobin levels during hospitalization (OR 0.65 per-unit, 95%CI 0.41-

0.92, P=0.01) were less likely to have an identified bleeding source. Age and use of anticoagulation were not associated with detection of a bleeding source.

On multivariable logistic regression adjusting for presence of active malignancy and blood transfusion, higher admission hemoglobin values were associated with a decreased risk of detecting a bleeding source (OR 0.65, 95%CI 0.40-0.96, P=0.04).

Occult bleeding score

An occult bleeding score (OBS) was constructed for patients undergoing endoscopy by assigning a point each for active malignancy and admission hemoglobin levels less than 8.2 g/dL. The association between the OBS and localization of bleeding and endoscopic intervention is depicted in Figure 1. For patients with an OBS of 0, 6% (n=1/18) had a source of

occult bleeding detected. No patients with an OBS of 0 required endoscopic intervention. The OBS predicted detection of bleeding source with an AUC of 0.79 (95%CI 0.67-0.87), and endoscopic intervention with an AUC of 0.75 (95%CI 0.64-0.82).

Post discharge outcomes

Twenty-five patients (34%) were either readmitted to a hospital or required an ED visit within 30 days of initial hospital discharge (21 patients with hospital readmissions and 4 with only ED visits). The most common reason for readmission or ED visit was recurrent gastrointestinal bleeding (n=9). Other common reasons for hospitalization or ED visits included flare of congestive heart failure (n=4), infection (n=3), and decompensated liver disease (n=2). Of the 9 patients with recurrent bleeding within 30 days, 4 patients presented

Table 2. Variables associated with localizing a source of occult bleeding for patients undergoing an inpatient endoscopic procedure (n=55).

Variables	Localized source of bleeding		
	OR	95%CI	P value
Age	1.04	0.99-1.08	0.09
Female sex	1.38	0.47-4.10	0.55
Systemic anticoagulation	1.36	0.46-4.06	0.58
Intensive unit care	1.22	0.36-4.21	0.75
Coronary artery disease	2.17	0.73-6.62	0.16
Iron deficiency	1.36	0.46-4.13	0.58
Active malignancy	7.25	1.06-144	0.04
Cirrhosis	2.25	0.49-12.0	0.30
Blood transfusion	4.25	1.13-20.9	0.03
Admit hemoglobin	0.62	0.41-0.86	0.003
Nadir hemoglobin	0.65	0.41-0.92	0.01

OR, odds ratio; CI, confidence interval.

Table 3. Post-hospital discharge outcomes for entire cohort on univariable logistic regression (n=74).

Variables	30-Day ED or readmission (n=25)			30-Day Rebleeding (n=9)		
	OR	95%CI	P value	OR	95%CI	P value
Age	0.99	0.95-1.03	0.57	0.99	0.95-1.05	0.86
Female sex	2.58	0.97-7.13	0.06	2.81	0.68-14.3	0.17
Systemic anticoagulation	0.89	0.32-2.38	0.82	1.37	0.31-5.65	0.66
Number of comorbidities	1.12	1.01-1.25	0.04	1.17	1.02-1.37	0.03
Coronary artery disease	2.62	0.98-7.22	0.05	3.42	0.83-17.4	0.09
Renal failure	1.34	0.50-3.56	0.56	3.00	0.72-15.2	0.14
Active malignancy	2.20	0.56-8.77	0.25	2.03	0.27-10.4	0.44
Aspirin use	5.33	1.82-18.2	0.002	3.19	0.71-22.5	0.14
Admission hemoglobin	0.93	0.72-1.17	0.53	0.81	0.54-1.14	0.24
Iron deficiency	1.13	0.43-3.01	0.81	0.64	0.15-2.65	0.54
Nadir Hemoglobin	0.90	0.67-1.18	0.46	0.74	0.44-1.14	0.19
Procedure performed	0.83	0.28-2.57	0.75	3.06	0.51-58.9	0.25
Diagnosis confirmed	1.34	0.50-3.73	0.53	1.56	0.36-6.49	0.54

ED, Emergency Department; OR, odds ratio; CI, confidence interval.

with new onset overt bleeding after initially presenting with occult GIB. Two of these patients presented with overt UGIB [one patient with hematemesis due to gastric antral vascular ectasias (GAVE) and one patient with melena due to a duodenal ulcer]. The patient with rebleeding due to a duodenal ulcer did not have an upper EGD during the index hospitalization, whereas the patient with GAVE was identified during EGD on index hospitalization. The other two patients had overt LGIB with subsequent negative colonoscopies. Of the 5 patients with recurrent occult GIB, 2 patients had a capsule endoscopy during the hospital readmission showing angioectasias in the jejunum with stigmata of hemorrhage. One patient without endoscopic evaluation during initial hospitalization was found to have severe gastritis on hospital readmission. One patient with known history of GAVE presented with recurrent anemia requiring repeat argon plasma coagulation. Finally, one patient had persistent obscure, occult GIB. On univariable logistic regression, an increased number of comorbidities (OR 1.12, 95%CI 1.01-1.25; $P=0.04$) were associated with increased risk of 30-day hospital readmissions. Other variables associated with 30-day readmissions are detailed in Table 3. Clinical variables associated with recurrent GIB are detailed in Table 3. Increased number of comorbidities were associated with increased risk of rebleeding (OR 1.17, 95%CI: 1.02-1.37, $P=0.03$). Having an inpatient endoscopic evaluation was not associated with a reduced risk of recurrent bleeding (OR 3.06, 95%CI 0.51-58.9, $P=0.25$). Use of systemic anticoagulation was not associated with an increased risk of recurrent bleeding (OR 1.37, 95%CI 0.31-5.65, $P=0.66$). Five patients (7%) died prior to the 30 day study call. Four patients died from metastatic cancer, and one patient died from septic shock.

Discussion

Fecal occult blood testing in the setting of anemia is commonly performed in the inpatient setting, and frequently leads to gastroenterology consultation and inpatient diagnostic evaluation.^{6,13} Although there is data suggesting that advanced age and mean corpuscular volume may predict a positive endoscopic evaluation in patients with iron deficiency anemia,^{14,15} there is limited data on which hospitalized patients with anemia and a positive fecal occult blood test (FOBT) have either positive findings on endoscopic evaluation or need endoscopic intervention. In this prospective study, we demonstrate that hospitalized patients with concern for occult GIB who have active malignancy and lower admission hemoglobin levels are more likely to have a positive source of GIB detected on endoscopic evaluation. More importantly, a simple scoring tool was able to identify low risk patients with anemia and occult GIB who were unlikely to benefit from an endoscopic evaluation or need endoscopic intervention.

In a previous study of patients with iron deficiency anemia, patients with positive FOBT were more likely to have endoscopic lesions identified than those without.¹⁵ Rockey and colleagues studied patients with positive FOBT without iron deficiency.⁷ In that population, upper gastrointestinal lesions were identified more frequently than colonic lesions with 29% and 22% of cases being localized by EGD and colonoscopy respectively. We extend and add to the prior literature with a simple scoring system that could predict whether occult bleeding will be localized on endoscopy. In addition, as no patient with a score of 0 required an endoscopic intervention, our results suggest that stable inpatients with

occult GIB without transfusion requirements or active cancer may have their workup deferred to the outpatient setting, thereby decreasing healthcare costs. Notably, patients who were iron deficient at the time of positive FOBT results were not more likely to have a bleeding source detected on endoscopic evaluation.

Recent data have shown that 30-day readmission and rebleeding rates for patients hospitalized with overt lower GIB are 21% and 8% respectively.¹⁰ No prior studies have evaluated risk factors for either hospital readmissions or rebleeding in patients hospitalized with anemia and occult GIB. We demonstrate that the 30-day readmission rate for patients in our cohort was 28%, with a majority of readmissions being unrelated to GIB. This suggests that occult GIB may be a marker for chronic illness. More importantly, having either an inpatient endoscopic evaluation, or inpatient confirmation of bleeding source, was not associated with a reduced risk of rebleeding within 30 days. These results support that an inpatient endoscopic evaluation can be deferred to the outpatient setting in selected patients, given that they do not have an increased risk of recurrent bleeding.

These results must be interpreted in the context of the study design. As this was an observational study, there was no structured protocol for endoscopic evaluation or intervention. As FOBT testing is only recommended in the context of colon cancer screening and positive results require exclusion of colonic malignancy,² we cannot exclude the presence of colonic lesions in the patients who only underwent EGD. In addition, given the relatively small numbers of patients in our study, we were likely underpowered to detect significant associations between variables and both hospital readmissions and rebleeding. Given that we identified patients at the time of gastroenterology consultation, there is also a possibility of selection bias affecting our results as we were unable to capture patients with occult bleeding who did not require gastroenterology consultation. This was a small single-center study conducted at a tertiary care academic medical center thus limiting generalizability. Finally, the yield and utilization of post hospital discharge endoscopic evaluation was not available given that our primary interests were in reporting in-hospital procedure utilization and yields.

Conclusions

In summary, for hospitalized patients with anemia and occult GIB, those with active malignancy and lower admission hemoglobin values are more likely to have an identified

Figure 1. Association of occult bleeding score with: A) localization of bleeding source, and B) endoscopic intervention.

source of occult bleeding on endoscopy. An occult bleeding score based on admission hemoglobin and active malignancy can predict detection of occult bleeding and need for endoscopic intervention. Inpatient endoscopic evaluation or intervention is not associated with a reduced risk of recurrent bleeding.

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