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ORIGINAL ARTICLE

Upper Gastrointestinal Bleeding Caused by Severe Esophagitis: A Unique Clinical Syndrome

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Abstract
Background We have recognized a unique clinical syndrome in patients with upper gastrointestinal bleeding who are found to have severe esophagitis.
Aim We aimed to more clearly describe the clinical entity of upper gastrointestinal bleeding in patients with severe esophagitis.
Methods We conducted a retrospective matched case–control study designed to investigate clinical features in patients with carefully defined upper gastrointestinal bleeding and severe esophagitis. Patient data were captured prospectively via a Gastrointestinal Bleeding Healthcare Registry, which collects data on all patients admitted with gastrointestinal bleeding. Patients with endoscopically documented esophagitis (cases) were matched with randomly selected controls that had upper gastrointestinal bleeding caused by other lesions.
Results Epidemiologic features in patients with esophagitis were similar to those with other causes of upper gastrointestinal bleeding. However, hematemesis was more common in patients with esophagitis 86 % (102/119) than in controls 55 % (196/357) ($p < 0.0001$), while melena was less common in patients with esophagitis 38 % (45/119) than in controls 68 % (244/357) ($p < 0.0001$). Additionally, the more severe the esophagitis, the more frequent was melena. Patients with esophagitis had less abnormal vital signs, lesser decreases in hematocrit, and lesser increases in BUN. Both pre- and postRockall scores were lower in patients with esophagitis compared with controls ($p = 0.01$, and $p < 0.0001$, respectively). Length of hospital stay ($p = 0.002$), rebleeding rate at 42 days ($p = 0.0007$), and mortality were less in patients with esophagitis than controls. Finally, analysis of patients with esophagitis and cirrhosis suggested that this group of patients had more severe bleeding than those without cirrhosis.
Conclusions We have described a unique clinical syndrome in patients with upper gastrointestinal bleeding who have erosive esophagitis. This syndrome is manifest by typical clinical features and is associated with favorable outcomes.

Keywords Hemorrhage · Esophagus · Proton pump inhibitor · Nonvariceal upper gastrointestinal bleeding · Outcome

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Introduction

Acute upper gastrointestinal bleeding is one of the most common emergencies leading to hospital admission. It is typically manifest clinically by hematemesis and melena. Other important clinical features of upper gastrointestinal bleeding include changes in vital signs, a drop in hemoglobin/hematocrit value, and an elevated BUN, the latter of which signifies the presence of blood in the gastrointestinal tract [1].

The causes of upper gastrointestinal bleeding are highly varied and include disorders involving the esophagus, stomach, and upper small bowel [1, 2]. The most common causes of upper gastrointestinal bleeding are gastroduodenal ulcers and esophageal varices. Esophagitis has been recognized as a cause of upper gastrointestinal pathology and bleeding, but details about patients with bleeding from this diagnosis have received little attention [3–6]. We have recognized a clinical syndrome that includes patients with upper gastrointestinal bleeding who are found to have erosive esophagitis. We show here that these patients appear to not only present with unique clinical features, but also have a comparatively benign clinical course.

Methods

We conducted a retrospective age matched case–control study designed to investigate clinical features in patients with upper gastrointestinal bleeding and erosive esophagitis. The study included patients admitted to Parkland Memorial Hospital (Dallas, TX), a University of Texas Southwestern teaching hospital, from January 1, 2007 through July 15, 2011. Patient data were captured prospectively via a Gastrointestinal Healthcare Registry, which collects data on patients admitted with any form of gastrointestinal bleeding. Patients with all forms of gastrointestinal bleeding are identified, and data pertaining to the hospital admission abstracted and entered prospectively into the registry database (Microsoft Access, Microsoft Corporation, Redmond, WA). Data captured included multiple clinical and historical features and American Society of Anesthesiologists (ASA) score on physical status (1–3 = normal to severe; 4–5 = life threatening to moribund), medications, laboratory, and endoscopic data (endoscopic diagnosis, stigmata of recent or active hemorrhage, and therapies). Primary hemostasis rates, treatment failures, and 30-day rebleeding events are also collected. Rebleeding is defined as visualization of vomited red blood, a drop in hematocrit of $\geq$9 points (or hemoglobin 3 g/dL) after endoscopy or by development of hypotension (SBP $\leq$ 90) more than 2 h after endoscopy. By design, a bleeding lesion or a lesion with stigmata of recent bleeding in any given case is designated as the primary diagnosis. When more than one lesion/diagnosis is present in addition to a primary lesion, it is considered a secondary lesion, but not deemed to be the cause of hemorrhage. Primary bleeding lesions are assigned to one of the following lesions: esophageal varices, erosive esophagitis, esophageal ulcers, Mallory–Weiss tear, gastric varices, portal hypertensive gastropathy, gastric ulcer, erosive gastritis, duodenal ulcer, erosive duodenitis, Dieulafoy (any location), vascular ectasias (any location), neoplasia (any location), other, or no source identified. The etiology of bleeding is routinely assigned by the attending physician responsible for the procedure. In situations in which there is disagreement between such assignment and the study team, a 3-panel group adjudicates the bleeding lesion (in a blinded fashion). Causes of death for all patients are classified into 8 different groups, which included the following: gastrointestinal bleeding, cardiorespiratory failure, renal failure, liver failure, sepsis, multiorgan system dysfunction, malignancy, unknown, or other. The study team adjudicates the cause of death in a blinded fashion. Death was considered to be due to bleeding when the patient either died while actively bleeding, when the bleeding event led to subsequent event that caused death (i.e., surgery), or when the bleeding event was judged to lead to one of the complications highlighted above. Data entry into the database was double key entered.

Upper gastrointestinal hemorrhage was defined as reported or witnessed melena, hematemesis, coffee ground emesis, or hematochezia (in patients with hematochezia, upper gastrointestinal hemorrhage is considered to be present only in the setting of a concomitant documented upper gastrointestinal tract lesion) in the setting of at least a 4-point drop in hematocrit from baseline or normal.

All patients meeting the above specified criteria for upper gastrointestinal bleeding were considered. Cases included patients with upper gastrointestinal bleeding, who were found to have esophagitis at the time of endoscopy, and in whom did not have another lesion. Patients with a gastric ulcer, duodenal ulcer, portal hypertensive gastropathy, Mallory–Weiss tear, esophageal varices, gastric cancer, or a primary source of bleeding not from the esophagus were excluded. The severity of erosive esophagitis was determined based on Los Angeles Classification as described previously [7–10]. It is standard practice for patients in our medical center with upper gastrointestinal bleeding to receive standard PPI therapy (bolus therapy followed by continuous infusion) until the time of endoscopy. The study protocol was approved by the UT Southwestern IRB, and the study met all criteria for Good Clinical Practice research.

Statistics

We matched each case with three controls, i.e., subjects were randomly selected from the total cohort of patients with upper gastrointestinal bleeding, but in whom no evidence of esophagitis was noted. Control subjects were randomly selected from the total cohort of patients with upper gastrointestinal bleeding, but in whom no evidence of esophagitis was noted. Comparisons between cases and controls were made using student's *t* test for means and chi-square test for comparison of proportions. In the

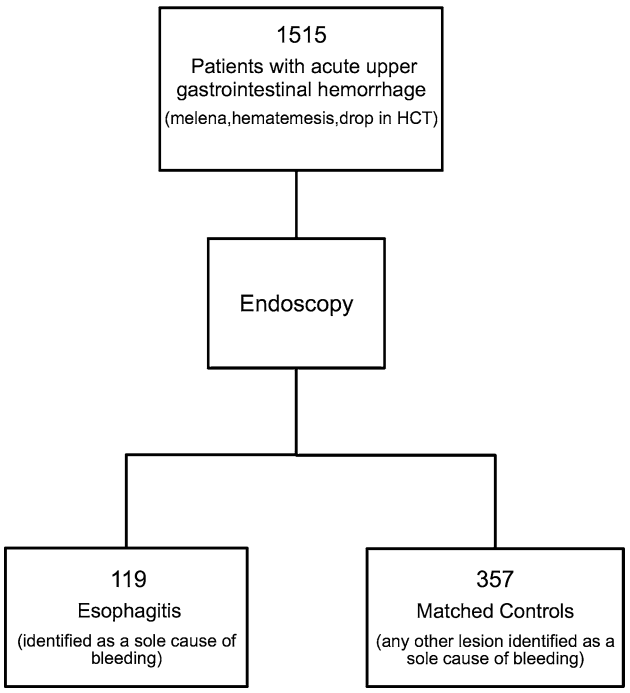

Fig. 1 Study patients. A total of 1,515 patients with upper gastrointestinal hemorrhage, defined by witnessed or reported hematemesis or melena and at least a four-point drop in hematocrit (compared with baseline or from normal) that underwent endoscopy, were identified. Patients with endoscopic evidence of esophagitis were compared with a random group of age- and gender-matched patients with upper gastrointestinal bleeding

presence of significantly different variances, Satterthwaite *t* test *p* values are reported. For variables whose distribution was not normal such as LOS, group comparisons were made using the Kruskal–Wallis nonparametric test. All reported *p* values are unadjusted and two-sided.

Comparisons among clinical variables within a table were performed using Bonferroni correction (note, when multiple significance tests are reported within a table, marginally statistically significantly different results should be interpreted in light of a Bonferroni adjustment for multiple tests). Odds ratios were estimated using logistic probability models. *P* values are based on likelihood ratio comparisons and 95 % confidence intervals are based on Wald confidence limits. All analyses were performed using SAS version 9.3 (SAS institute, Inc., Cary, NC, USA).

Results

A total of 1,515 patients with upper gastrointestinal bleeding were identified during the study period; 119 patients with esophagitis and no other potential cause of bleeding were identified (Fig. 1). Demographics are described in table (Table 1). The groups appeared to be well matched in terms of age, gender, and race. ASA scores were 2.4 ± 0.6 for cases and 2.5 ± 0.7 for controls (not statistically different). There was a borderline difference in age ($p = 0.04$) for the 2 groups, but no statistically significant difference in gender or race (of note, in light of the use of Bonferroni adjustment, the difference in age was viewed to be not significant).

Table 1 Demographics

	Esophagitis (cases $n = 119$)	No esophagitis (controls $n = 357$)	p value
Age	49 ± 14	53 ± 14	0.04
Gender			0.17
Male	87 (73 %)	235 (66 %)	
Female	32 (27 %)	122 (34 %)	
Ethnicity			0.08
Caucasian	36 (30 %)	90 (25 %)	
Hispanic	47 (40 %)	143 (40 %)	
African American	34 (29 %)	106 (30 %)	
Other	2 (2 %)	18 (5 %)	

The most common presenting symptom in patients with esophagitis was hematemesis (Table 2). Hematemesis was a presenting symptom in the vast majority of esophagitis patients (102/119) and was common in the control group (55 % of patients, 196/357); hematemesis was the only clinical indicator of active bleeding in 62 % of esophagitis and 32 % of control patients. Melena was less common in patients with esophagitis, found in 38 % (45/119) of patients, while melena was present in slightly over two-thirds of controls (68 % of patients, 244/357) ($p < 0.0001$). Melena only was uncommon in both groups (14 and 17 %, respectively), while both hematemesis and melena were present much more often in controls than in esophagitis patients (51 vs. 24 %, respectively). A past history of GERD was present in 23 % of patients with esophagitis and 9 % of those with other causes of upper gastrointestinal bleeding ($p < 0.0001$). Systolic ($p = 0.001$) and diastolic blood pressure ($p < 0.0001$) was higher in patients with esophagitis than in patients with other causes of upper gastrointestinal bleeding.

Admission laboratory data were remarkable in patients with esophagitis; the hemoglobin and hematocrit (Table 2; Fig. 2) were significantly higher in patients with esophagitis than in patients with other causes of upper gastrointestinal bleeding ($p < 0.0001$). The BUN at the time of gastroenterology team consultation ($p < 0.05$) and the initial PT-INR were also lower ($p < 0.01$) in patients with esophagitis.

The Rockall score (17–22), either preendoscopy or postendoscopy, was significantly lower in patients with esophagitis compared with those with upper gastrointestinal bleeding (Fig. 3) ($p < 0.001$).

Table 2 Clinical features

	Erosive esophagitis (cases $n = 119$)	No esophagitis (controls $n = 357$)	Odds ratio (95 % CI)	p value
Hematemesis	102 (86 %)	196 (55 %)	4.92 (2.83–8.57)	<0.0001
Melena	45 (38 %)	244 (68 %)	0.28 (0.18–0.43)	<0.0001
Vital signs				
Systolic (mm Hg)	132 ± 26	123 ± 25	1.01 (1.00–1.02)	0.001
Diastolic (mm Hg)	83 ± 59	69 ± 16	1.03 (1.02–1.04)	<0.0001
Pulse	94 ± 21	91 ± 20	1 (0.99–1.01)	0.17
Laboratory values				
Hemoglobin	11 ± 3	9 ± 2	1.59 (1.43–1.76)	<0.0001
Hematocrit	34 ± 8	27 ± 6	1.17 (1.13–1.21)	<0.0001
Platelets	222 ± 106	195 ± 127	1 (1.000–1.0003)	0.03
BUN	26 ± 24	32 ± 31	0.99 (0.98–1.00)	0.05
Creatinine	1.9 ± 2.9	1.6 ± 2.6	1 (0.95–1.10)	0.43
INR	1.1 ± 0.3	1.4 ± 1.1	0.2 (0.11–0.53)	0.0005

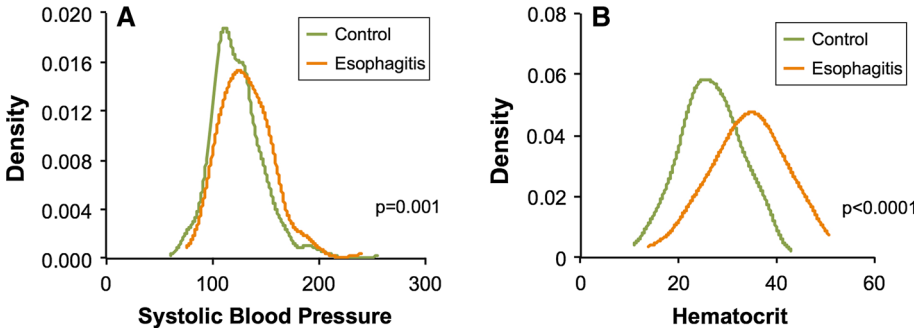

Fig. 2 Clinical features in esophagitis and control patients. In **a/b,** are shown Kernel density plots for systolic blood pressure (**a**) and hematocrit (**b**), of esophagitis and control patients

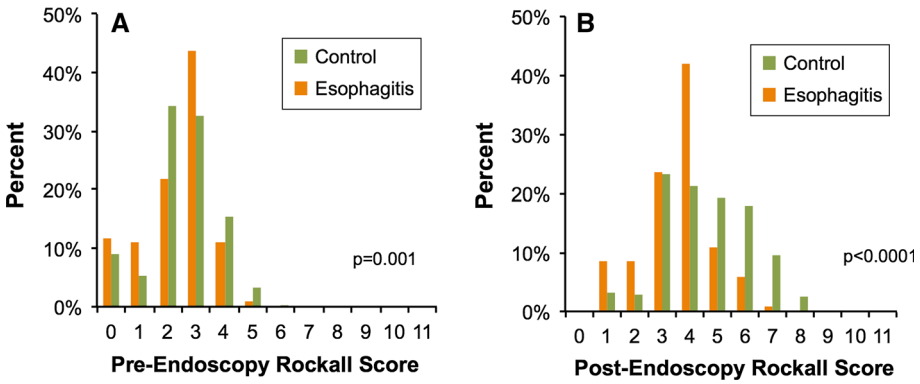

Fig. 3 Rockall scores. Graphs depicting the frequency of different Rockall scores (percent for each score) pre-endoscopy (**a**) and post-endoscopy (**b**) of esophagitis and control patients are shown

Additionally, total units of blood transfused ($p < 0.0001$), total units of platelets transfused ($p = 0.01$), and total units of FFP transfused ($p < 0.0001$) were less in patients with esophagitis than in patients with other causes of upper gastrointestinal bleeding.

Los Angeles (LA) grading of esophagitis revealed that the severity of endoscopic abnormality appeared to correlate with clinical symptoms (Table 3). Patients with lower LA grade disease appeared to more often present with hematemesis, while those with high LA grade disease, not only presented with hematemesis, but also had a higher frequency of melena, with nearly 50 % of patient in the LA grade D group having melena. In the 13 LA grade A patients and 22 LA grade B patients, 1 patient in each group had both hematemesis and melena. For 24 LA grade C patients, 7 had hematemesis and melena, and among 60 LA grade D patients, 19 had both hematemesis and melena. Endoscopic therapy was performed in 4/119 (3 %) patients, in whom ulceration with a visible vessel was identified. Specific therapy included endoscopic clipping in 2 patients,

Table 3 Severity of esophagitis and symptoms of bleeding

Esophagitis grade	LA grade A (total $n = 13$)	LA grade B (total $n = 13$)	LA grade C (total $n = 13$)	LA grade D (total $n = 13$)
Hematemesis	11/13	19/22	21/24	51/60
Melena	3/13	4/22	10/24	28/60

In all cases, other bleeding or potentially bleeding lesions were not present

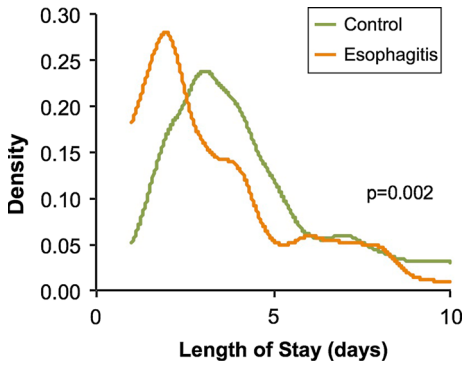

Fig. 4 Length of stay. A Kernel density plot for length of stay of esophagitis and control patients is shown

1 of whom had dual therapy with epinephrine followed by clipping; 1 patient had dual therapy with epinephrine and thermocoagulation.

Patients in the control group had typical causes of upper GI bleeding including gastric ($n = 77$ (22 %)) and duodenal ulcers ($n = 49$ (14 %)), esophageal varices ($n = 81$(23 %)), portal hypertensive gastropathy ($n = 16$ (9 %)), Mallory–Weiss tear ($n = 15$ (4 %)), vascular angioma ($n = 6$ (3 %)), malignancy ($n = 3$ (1 %)), erosive gastritis ($n = 46$ (13 %)), and others ($n = 64$ (18 %)). The average time from admittance to the ED to endoscopy was 23 ± 16 and 27 ± 22 h for cases and controls, respectively; the difference was not statistically significantly different in the two groups.

The length of stay was shorter in patients with esophagitis than controls ($p = 0.002$) than in controls (Fig. 4). Rebleeding within 42 days in patients with esophagitis was uncommon and was significantly less common than in patients with other causes of upper gastrointestinal bleeding ($p = 0.0007$) (Table 4). The overall mortality rate (6 %) at 42 days was the same for patients with esophagitis as for patients with other etiologies of upper gastrointestinal bleeding. However, no patient with esophagitis died as a result of upper gastrointestinal bleeding, while 4 of 357 patients with other causes of upper gastrointestinal bleeding died from bleeding.

We also performed an analysis of patients with esophagitis with and without cirrhosis and compared these

Table 4 Outcomes

	Esophagitis (cases $n = 119$)	No esophagitis (controls $n = 357$)	p value
Rockall score			
Preendoscopy	2.3 ± 1.2	2.5 ± 1.2	0.01
Postendoscopy	3.6 ± 1.3	4.6 ± 1.6	<0.0001
Transfusions			
RBC	0.8 ± 1.9	2.5 ± 3.5	<0.0001
Platelets	0.1 ± 0.5	0.1 ± 0.9	0.2
FFP	0.1 ± 0.5	0.3 ± 1.2	0.008
Length of stay (LOS)	3	11	0.002
Rebleed within 42 days	2 (2 %)	44 (12 %)	0.0007
Mortality within 42 days	7 (6 %)	26 (7 %)	0.3
GI bleeding	0 (0 %)	6 (2 %)	
Other	5 (4 %)	20 (6 %)	

patients with controls. In the esophagitis group, 12/119 (10 %) had cirrhosis, while in the control group, 116/357 (33 %) had cirrhosis (Table 5). There were no differences in outcomes in patients without cirrhosis (Table 5) compared with the larger group that included all patients (Table 4). However, there were several interesting findings in patients with and without cirrhosis. For example, Rockall scores were greater in patients with cirrhosis in both the esophagitis and control groups, and the amount of blood (in PRBC units) transfused in cirrhotics with esophagitis was greater than in any of the other groups. Rebleeding did not occur in any patient with esophagitis who did not have cirrhosis. Interestingly, mortality was greater in patients with cirrhosis and esophagitis than in any other group (Table 5).

Discussion

Here, we have described a unique clinical syndrome in patients with upper gastrointestinal bleeding and esophagitis. Specifically, we have shown that patients with esophagitis as the cause of clearly defined upper gastrointestinal bleeding frequently present with hematemesis, and often have hematemesis alone. They also presented with more stable vital signs, higher hemoglobin and hematocrit levels, and lower BUN levels than patients with other forms of upper gastrointestinal bleeding [11–13]. Finally, outcomes in these patients were better than patients with upper gastrointestinal bleeding caused by other lesions.

The literature focusing on esophagitis as a cause of upper gastrointestinal bleeding is limited [12, 14–18]; moreover, these studies did not highlight the unique clinical features identified here. We suspect that this is because here we have captured data prospectively on a large series

Table 5 Patients with cirrhosis

	Cirrhosis			No cirrhosis		
	Esophagitis $n = 12$	Controls $n = 116$	p value	Esophagitis $n = 107$	Controls $n = 241$	p value
Rockall score	3.9 ± 1.0	4.9 ± 1.3	0.008	3.6 ± 1.3	4.4 ± 1.7	<0.001
RBC transfused (# patients)	5 (42 %)	75 (65 %)	0.130	27 (25 %)	160 (66 %)	<0.001
Units	5.0 ± 3.3	4.0 ± 3.1	0.553	2.9 ± 2.1	3.8 ± 4.0	0.094
PLT transfused (# patients)	1 (8 %)	14 (12 %)	1.000	1 (1 %)	2 (1 %)	1.000
Units	5	3.1 ± 3.4	N/A[a]	3	3.0 ± 2.8	N/A[a]
FFP transfused (# patients)	1 (8 %)	20 (17 %)	1.000	4 (4 %)	17 (7 %)	0.330
Units	2	2.5 ± 1.2	N/A[a]	2.8 ± 1.5	4.2 ± 3.4	0.208
LOS (median)	4.5	4	0.488	3	4	0.001
Rebleed	2 (17 %)	18 (16 %)	1.000	0 (0 %)	26 (11 %)	<0.001
Mortality	4 (33 %)	12 (10 %)	0.044	3 (3 %)	14 (6 %)	0.290

[a] Statistical comparisons among groups were not possible because only 1 patient was included in one of the groups

of patients with upper gastrointestinal bleeding, and moreover, the prospective data capture provided for detailed and extensive collection of clinical data on these patients.

Given the prevalence of upper gastrointestinal bleeding, the fact that esophagitis was a primary cause of bleeding in such a high proportion of all patients with upper gastrointestinal bleeding indicates that this disorder is clinically important and has several important implications. First, the fact that upper gastrointestinal bleeding is commonly caused by severe esophagitis indicates that this disease should be considered in the differential diagnosis of patients with upper gastrointestinal bleeding, and particularly in certain clinical situations, such as those highlighted here. Additionally, the high frequency of esophagitis as a cause of upper gastrointestinal bleeding suggests that the likely underlying pathophysiology leading to this disorder (GERD) is common and probably under-recognized. Moreover, if the majority of patients with upper gastrointestinal bleeding due to esophagitis have underlying GERD, this theoretically is treatable, and thus, bleeding may be preventable.

Although there is clearly some overlap in clinical presentation among patients with different etiologies of upper gastrointestinal bleeding, the relatively benign course of patients with esophagitis compared with other causes of upper gastrointestinal bleeding is noteworthy. Our data suggest that patients with esophagitis overall have a favorable course, with an excellent overall prognosis. In fact, the risk of rebleeding in patients with esophagitis was extremely low, and no patient with esophagitis died due to GI bleeding. Further, patients with esophagitis required significantly fewer blood products. These data therefore have several important implications. First, the data suggest that it is important to make a specific diagnosis (with endoscopy) in patients with upper gastrointestinal bleeding; those with a diagnosis of esophagitis can likely be handled differently than those with other causes of upper gastrointestinal bleeding [14, 17]. For example, patients with esophagitis probably do not require aggressive blood transfusion and moreover can likely be triaged toward early discharge once a definitive (endoscopic) diagnosis is made. Our findings also raise the possibility that the earlier a specific diagnosis of esophagitis is made, the faster patients can be appropriately triaged. Since the course of these patients is typically benign, in the absence of severe comorbidity, most patients can be triaged to less acute levels of care.

As might be predicted, bleeding appeared to be more severe in patients with cirrhosis than in those without cirrhosis (Table 5), with cirrhotics receiving more blood and blood products than those without cirrhosis. We also found that rebleeding was more common in patients with esophagitis and cirrhosis than those without cirrhosis. Further, length of stay was longer and mortality appeared to be greater in patients with esophagitis and cirrhosis compared with those without cirrhosis.

We recognize limitations of this study. First, the design was in part retrospective. However, this limitation is significantly mitigated by the fact that data for all patients with upper gastrointestinal bleeding are prospectively entered into the Gastrointestinal Healthcare Registry. Additionally, multiple aspects of the clinical picture in patients with GI bleeding are captured in this dataset, making it unlikely that features of gastrointestinal bleeding were not captured. We further recognize that we may have underestimated the prevalence of esophagitis causing upper gastrointestinal bleeding because we considered only patients undergoing endoscopy. While the number that could have been missed is likely to be low, this is relevant

because typically only patients with what is deemed clinically meaningful upper gastrointestinal bleeding are triaged to endoscopy. Thus, there may have been some patients with upper gastrointestinal bleeding caused by esophagitis that were not included in our analysis.

In summary, we have identified what appears to be a distinct clinical syndrome in patients with upper gastrointestinal bleeding. We have shown that overall, while severe esophagitis is a relatively common etiology of upper gastrointestinal bleeding, it causes a more benign form of this disorder.

Conflict of interest The authors certify that we have no financial arrangements (e.g., consultancies, stock ownership, equity interests, patent-licensing arrangements, research support, honoraria, etc.) with a company whose product figures prominently in this manuscript or with a company making a competing product.

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