Acute on chronic gastrointestinal bleeding: a unique clinical entity

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ABSTRACT

Gastrointestinal bleeding is defined in temporal–spatial terms—as acute or chronic, and/or by its location in the gastrointestinal tract. Here, we define a distinct type of bleeding, which we have coined 'acute on chronic' gastrointestinal bleeding. We prospectively identified all patients who underwent endoscopic evaluation for any form of gastrointestinal bleeding at a University Hospital. Acute on chronic bleeding was defined as the presence of new symptoms or signs of acute bleeding in the setting of chronic bleeding, documented as iron deficiency anemia. Bleeding lesions were categorized using previously established criteria. We identified a total of 776, 254, and 430 patients with acute, chronic, or acute on chronic bleeding, respectively. In patients with acute on chronic gastrointestinal bleeding, lesions were most commonly identified in esophagus (28%), colon and rectum (27%), and stomach (21%) ($p<0.0001$ vs locations for acute or chronic bleeding). In those specifically with acute on chronic upper gastrointestinal bleeding (n=260), bleeding was most commonly due to portal hypertensive lesions, identified in 47% of subjects compared with 29% of acute and 25% of chronic bleeders, ($p<0.001$). In all patients with acute on chronic bleeding, 30-day mortality was less than that after acute bleeding alone (2% (10/430) vs 7% (54/776), respectively, $p<0.001$). Acute on chronic gastrointestinal bleeding is common, and in patients with upper gastrointestinal bleeding was most often a result of portal hypertensive upper gastrointestinal tract pathology. Reduced mortality in patients with acute on chronic gastrointestinal bleeding compared with those with acute bleeding raises the possibility of an adaptive response.

Significance of this study

What is already known about this subject?

- There is extensive information on acute gastrointestinal (GI) bleeding as well as chronic GI bleeding. Each of these in their own right has a specific differential diagnosis, management algorithm, and outcome.
- However, to the best of our knowledge, there is no previous information on the topic of chronic gastrointestinal bleeding.

What are the new findings?

- Acute on chronic bleeding is a unique clinical syndrome characterized by a typical presentation with acute bleeding (hematemesis, melena, or hematochezia), and also by the presence of chronic GI bleeding manifested by iron deficiency anemia.
- These patients have different clinical characteristics than those with typical acute or chronic GI bleeding.
- While virtually any lesion may cause acute on chronic bleeding, portal hypertensive lesions of the upper GI tract (with portal hypertensive enteropathy/gastropathy causing chronic bleeding, and varices causing acute bleeding) were the most common causes of this type of bleeding.

How might these results change the focus of research or clinical practice?

- When confronted with patients that have acute on chronic bleeding, clinicians should be aware of the association of this presentation with cirrhosis and portal hypertension. This knowledge will influence differential diagnosis, and approach to evaluation.

INTRODUCTION

Gastrointestinal (GI) bleeding encompasses a multitude of clinical scenarios. It can vary widely in severity, ranging from clinically insignificant to life threatening, and can originate from anywhere in the GI tract. It has traditionally been divided into temporal–spatial categories based on the acuity and location of the bleeding; acute bleeding is typically associated with witnessed or reported hematemesis, melenemesis, melena, and/or hematochezia. Bleeding is also usually assigned to a specific location in the GI tract—upper, lower, or unknown (typically known as obscure bleeding).[1]

Acute GI bleeding can be caused by a lesion found anywhere in the GI tract.[2] It is a common problem, with upper GI hemorrhage alone accounting for ~300 000 admissions per year in the USA.[3 4] A wide variety of upper GI tract lesions can bleed acutely; peptic ulcer disease and esophagogastric varices have been reported to account for ~70% of identified

acute upper GI bleeding lesions, while the remaining 30% of patients reportedly bleed from arteriovenous malformations, Mallory-Weiss tears, tumors, erosions, and Dieulafoy's lesions.[5–7] Common causes of acute lower GI bleeding include diverticulosis, ischemia, neoplasia, angiodysplasia, inflammatory bowel disease, and anorectal causes.[8] Chronic GI bleeding is often occult[2 9] and an important form is manifest clinically as iron deficiency anemia.[10] Chronic, occult bleeding can originate from any part of the GI tract, and is commonly caused by carcinoma or inflammation-associated mucosal injury (eg, erosive esophagitis or gastritis or colitis).[2]

We have recognized that patients with lesions that are typically associated with iron deficiency anemia and chronic bleeding may present with symptoms and signs of acute bleeding including melena, hematemesis, or hematochezia. This syndrome is characterized clinically by acute GI bleeding in the context of evidence of chronic blood loss, typically with documented iron deficiency anemia. We propose a new designation for these patients, termed 'acute on chronic gastrointestinal bleeding'.

METHODS

This prospective cohort study evaluated all patients who underwent endoscopy (including esophagogastroduodenoscopy (EGD), enteroscopy, sigmoidoscopy, and/or colonoscopy) to investigate GI bleeding at Parkland Memorial Hospital (Dallas, Texas, USA) between 1 January 2006 and 31 December 2011. Patient data was captured prospectively via a Gastrointestinal Bleeding Healthcare Registry, which collects data on patients admitted with any form of GI bleeding. For this registry, patients with all forms of GI bleeding are identified, and data pertaining to the hospital admission abstracted and entered prospectively into a dedicated GI bleeding database (Microsoft Access, Microsoft Corporation, Redmond, Washington, USA). Data captured includes multiple clinical and historical features, American Society of Anesthesiologists (ASA) score, medications, laboratory, and endoscopic data (endoscopic diagnosis, stigmata of recent or active hemorrhage, and therapies). The study was approved by the Institutional Review Board at the University of Texas Southwestern Medical Center and met all criteria for good clinical research.[11]

All patients with symptoms or signs of acute or chronic GI bleeding, aged 18 and older, who underwent endoscopy were included. Patients who presented with GI bleeding but who did not undergo endoscopy and patients with repeated GI bleeding encounters were excluded. Patients with known GI bleeding within the previous 12 months for any reason or who did not undergo endoscopy were excluded.

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 bleeding lesion, the latter is considered a secondary lesion. Primary bleeding lesions are assigned to one of the following based on identification of the lesion endoscopically: esophageal varices, erosive esophagitis, esophageal ulcers, Mallory-Weiss tear, gastric varices, portal hypertensive gastropathy (PHG), 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 three-member panel adjudicates the bleeding lesion (in a blinded fashion).

Iron studies were routinely obtained and included in the database. In-hospital mortality and 30-day mortality as an outcome were captured for all patients.

DEFINITIONS

Based on previous literature and clinical practice,[12] for the purposes of inclusion into the Gastrointestinal Bleeding Healthcare Registry, we consider acute GI bleeding to have occurred in the setting new onset of hematemesis, melena, or hematochezia (witnessed or reported), in addition to a drop of hematocrit of at least 4 percentage points below baseline or below the lower limit of normal. We also required bleeding to have occurred within 7 days prior to diagnostic endoscopy. Both of these criteria were used to ensure that bleeding was acute. Chronic bleeding was defined as documented iron deficiency anemia (based on the WHO classification, which includes a hematocrit <39.6% for men and <36.8% for women[13] with a serum ferritin level ≤45 ng/mL),[14] without a history of blood loss from another source. Acute on chronic GI bleeding was defined specifically as a combination of these clinical scenarios.

A history of cirrhosis was established by imaging findings consistent with portal hypertension (splenomegaly, varices), liver biopsy, endoscopic evidence of varies, or documented clinical complications of cirrhosis including ascites, hepatic hydrothorax, or hepatic encephalopathy. Previous peptic ulcer disease was defined as having a previous prior endoscopic finding of peptic ulcer, or patient report of previous ulcer disease.

Lesions consistent with chronic blood loss were defined as previously described.[10] In brief, lesions considered to be consistent with chronic, occult blood loss included the following. In the upper GI tract—gastroduodenal or esophageal ulcers >1 cm in size, or more than two different and distinct ulcers, vascular ectasias >8 mm in size, erosive esophagitis (greater than Los Angeles grade 2),[10] severe gastritis,[15] severe PHG[16] (characterized by red lesions, with or without mosaic-like pattern lesions on endoscopy),[17] mass lesions >2 cm in size, gastric vascular ectasia (GAVE), and Cameron lesions as described.[2 18] In the colon—polyps >2 cm, ulcers and mass lesions as above, vascular ectasias >8 mm in size, colitis secondary to inflammatory bowel disease, ischemia, or infections,[10] and medium-to-large (grade 2–3) internal hemorrhoids[19] were considered to be sources consistent with chronic bleeding.

STATISTICAL ANALYSIS

Statistical analyses were performed using SAS (V.9.2). χ^2 analyses were used for group comparisons of each of the categorical measurements and one-way analysis of variance to compare three groups for the numerical measurements. Stepwise multiple logistic regression models were used to determine which demographic and risk factors were statistically related to the group prediction. The model entry criteria were selected at 5%. The Hosmer-Lemeshow technique was used to assess the model fit.

RESULTS

We identified 1460 patients with acute, chronic, or acute on chronic bleeding (as defined in Methods) who underwent endoscopy during the study period (figure 1). They had a mean age of 53±14 years, 38% were women (table 1). A history of cirrhosis was relatively common in patients with acute or acute on chronic bleeding, while a history of peptic ulcer disease was uncommon in all groups. As expected, patients in all groups were anemic, and patients in the chronic and acute on chronic groups had low ferritin levels.

Clinical location of bleeding

The clinical location of bleeding was evaluated in the different bleeding diagnostic groups, and was found to be statistically significantly different (p=0.001, table 2). Endoscopic lesions consistent with GI bleeding as defined were identified in 85% of all patients, most commonly in the upper GI tract. Upper GI tract lesions were the most prominent sources of acute on chronic GI bleeding (52%), while lesions in the colon and rectum were identified in 27% of patients. In contrast, in patients with acute GI bleeding, the proportion of upper GI tract lesions was higher (59%) and the proportion in the colon and rectum, lower (16%) (p<0.001 for each). The small bowel was an uncommon source of bleeding in all groups, comprising only 11% of total bleeding cases. In the chronic bleeding group, upper GI tract lesions were found in 40% of patients, while a lesion was identified in the colon and rectum in 22% of patients (p<0.001 for acute on chronic vs acute bleeding and p<0.001 for acute on chronic vs chronic bleeding).

Character of bleeding

In patients with acute on chronic bleeding, 70% of patients had hematemesis or melena, suggestive of a possible upper GI tract source of bleeding, while 79% of those with acute bleeding had hematemesis or melena (p=<0.001). Thirty percent of patients with acute on chronic bleeding had lower GI tract bleeding symptoms (hematochezia), and 21% of patients with acute bleeding had lower GI tract bleeding symptoms.

Specific types and location of lesions

Overall, inflammatory lesions (esophageal ulcer, gastric ulcer, duodenal ulcer, severe esophagitis, gastritis, and duodenitis) of the upper GI tract were by far the most common cause of bleeding, accounting for over 32% (468/1460) of all lesions (table 3). Gastroesophageal varices were slightly more than half as common. However, in patients with acute on chronic bleeding, gastroesophageal varices were the most common lesion identified overall (43%) and varices were significantly more common than in those with chronic or acute bleeding only (table 3). Further, in patients with acute bleeding, inflammatory lesions were by far the most common lesions accounting for 58% (310/537) of patients in this group (table 4). Peptic ulcer disease (duodenal ulcer and gastric ulcer together) was also an important source of upper GI bleeding, and was found to be more common in patients with acute (32%) than acute on chronic (28%) or chronic bleeding (21%) (p<0.001) (table 3). By definition esophageal varices did not cause chronic bleeding, but inflammatory lesions of the upper GI tract were prominent (table 3). Esophageal varices were much more common than gastric varices, on average in a 15:1 ratio. Sixteen patients (6%) with chronic GI bleeding were found to have varices as well as PHG; 13 patients were found to have PHG without gastroesophageal varices.

In the colon, the most common cause of bleeding overall was colitis, although colon cancer and polyps were prominent (table 3). Lesions in the small bowel were most commonly angioectasias (table 3).

We also assessed upper GI tract lesions separately based on their pathophysiologic cause (table 4). In this group, portal hypertensive lesions were most prominent in patients with acute on chronic bleeding (47% of patients with acute on chronic bleeding had portal hypertensive lesions), while inflammatory lesions were most common in patients with acute GI bleeding (58% of patients with acute bleeding had inflammatory lesions), and malignancy was more common in patients with chronic bleeding (16% of patients with chronic bleeding had a neoplastic lesion). The types of bleeding were evaluated in the different bleeding diagnostic

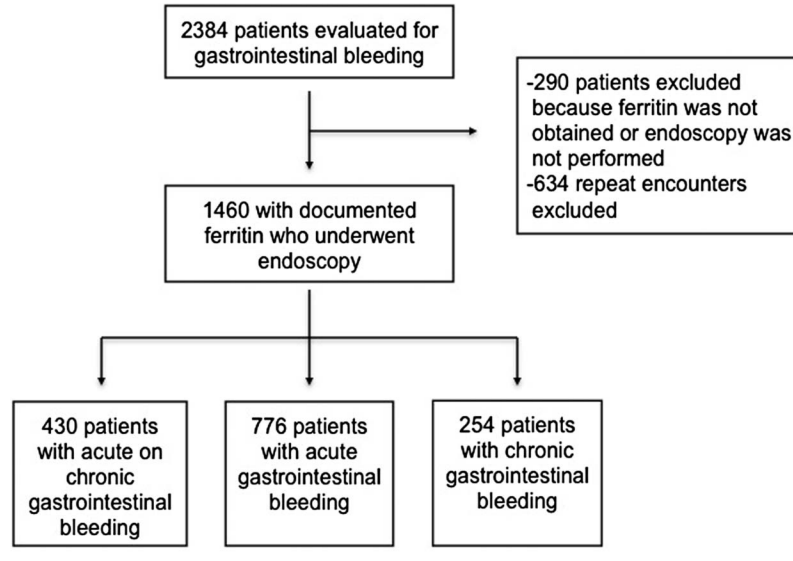

Figure 1 Inclusion flow chart. A total of 2384 patients were admitted to our institution with gastrointestinal bleeding in the study period. After excluding patients highlighted, 1460 patients made up the study groups.

Table 1 Patient characteristics

Characteristics	Total (n=1460) No. (%)	Acute on chronic (n=430) No. (%)	Acute (n=776) No. (%)	Chronic (n=254) No. (%)	p Value
Age*	53±14	52±15	53±13	55±13	0.020
Ethnicity					<0.001
Black	468 (32)	109 (25)	267 (34)	92 (36)	
Caucasian	333 (23)	95 (22)	192 (25)	46 (18)	
Hispanic	588 (40)	215 (50)	275 (35)	98 (39)	
Other	71 (5)	11 (3)	42 (5)	18 (7)	
Gender					<0.001
Female	561 (38)	168 (39)	258 (33)	135 (53)	
Medical history					
Cirrhosis	370 (25)	128 (30)	211 (27)	31 (12)	0.001
PUD	103 (7)	37 (9)	49 (6)	17 (7)	0.333
Alcohol abuse	770 (53)	239 (56)	416 (54)	115 (45)	0.027
Medications					
Aspirin and/or clopidogrel	316 (22)	81 (19)	171 (22)	64 (25)	0.139
Warfarin and/or enoxaparin	119 (8)	18 (4)	86 (11)	15 (6)	0.001
NSAIDs	227 (16)	77 (18)	111 (14)	39 (15)	0.261
Hematocrit*	27±6	26±6	28±7	26±5	<0.001
Platelets*	217±137	224±137	195±124	273±156	<0.001
INR*	1.3±0.8	1.3±0.6	1.4±1.0	1.2±0.6	<0.001
Ferritin*	273±787	19±12	500±1027	12±11	<0.001
30-day mortality	65 (4)	10 (2)	54 (7)	1 (0)	<0.001

*Mean±SD.
PUD, peptic ulcer disease.

Table 2 Lesion location

Lesion location	Total (n=1460) No. (%)	Acute on chronic (n=430) No. (%)	Acute (n=776) No. (%)	Chronic (n=254) No. (%)
Esophagus	382 (26)	120 (28)	248 (32)	14 (6)
Colon and rectum	298 (20)	115 (27)	127 (16)	56 (22)
Stomach	353 (24)	92 (21)	175 (23)	86 (34)
Unknown	223 (15)	48 (11)	96 (12)	79 (31)
Duodenal bulb	123 (8)	34 (8)	81 (10)	8 (3)
Esophagogastric junction	47 (3)	13 (3)	31 (4)	3 (1)
Small bowel	35 (2)	8 (2)	18 (2)	9 (4)
Total	1460 (100)	430 (100)	776 (100)	254 (100)

p <0.001 for differences among lesion locations for acute on chronic, acute, and chronic bleeding (by Chi square).

groups, and were found to be statistically significantly different (p=0.001, table 4).

In examining colonic lesions, tumors and polyps were found to be an important etiology of lower GI bleeding in all groups, and were shown to be much more prevalent in the group with chronic bleeding (71% (40/56)) when compared with those with acute on chronic (20% (23/115)) or acute bleeding (22% (28/127)) (p<0.001).

The role of antiplatelet agents, NSAIDs, and anticoagulants

Medications taken were evaluated in the different bleeding diagnostic groups, and were found to be statistically significantly different (p=0.001, table 5). A substantial proportion of patients included in our study (45%) were taking anticoagulants, antiplatelet agents, or NSAIDs. While the prevalence of NSAID and antiplatelet use was similar across all three groups (p=0.261 and p=0.139, respectively), anticoagulant (warfarin and enoxaparin) use was shown to be most common in the acute GI bleeding group (p=0.001) (table 1). Of the patients on anticoagulation, 72% (86/368) had acute GI bleeding, while only 15% (18/176) had acute on chronic GI bleeding and 13% (15/118) had chronic GI bleeding (table 5).

Features associated with acute on chronic bleeding

Multivariable stepwise logistic regression analyses were performed in order to identify clinical variables specifically associated with acute on chronic GI bleeding. A portal hypertensive lesion or a lesion in the colon and rectum was found to be more frequently associated with this syndrome (table 6). While the hematocrit and MCV levels were statistically associated less frequently with acute on chronic bleeding, the strength of this association was weak. However, a medication history of heparin, warfarin, or plavix was nearly twofold less frequently associated with acute on chronic GI bleeding (table 6).

Outcomes

We performed an additional analysis to specifically examine clinical covariates, including hemodynamics and blood transfusion. We examined these variables in each of the three groups, including acute, acute on chronic, and chronic. The mean systolic blood pressure (SBP) (±SD) for the three groups was 123±22, 126±26, and 133±22,

Table 3 Lesion location

Diagnosis	Total (n=1460) No. (%)	Acute on Chronic (n=430) No. (%)	Acute (n=776) No. (%)	Chronic (n=254) No. (%)
Upper GI Tract				
Gastroesophageal Varices	265 (29)	112 (43%)	137 (26%)	0 (0%)
Gastric ulcer	162 (18)	44 (17%)	101 (19%)	17 (16%)
Esophagitis	126 (14)	19 (7%)	96 (18%)	11 (10%)
Duodenal ulcer	102 (11)	29 (11%)	68 (13%)	5 (5%)
Severe gastritis	45 (5)	5 (2%)	22 (4%)	18 (17%)
PHG	44 (5)	11 (4%)	20 (4%)	29 (27%)
MWT	31 (3)	3 (1%)	28 (5%)	0 (0%)
Tumor	25 (3)	10 (4%)	11 (2%)	4 (4%)
Angioectasia	22 (2)	8 (3%)	3 (1%)	11 (10%)
Polyp	15 (2)	5 (2%)	4 (1%)	6 (6%)
Other	68 (8)	14 (5%)	47 (9%)	7 (3%)
Total (%)	**905** (100, 62)	**260** (100, 60)	**537** (100, 69)	**108** (100, 43)
Lower GI Tract				
Colitis	85 (29)	38 (33%)	42 (33%)	5 (9%)
Tumor	49 (16)	14 (12%)	15 (12%)	20 (36%)
Hemorrhoids	46 (16)	22 (19%)	16 (13%)	8 (14%)
Diverticular bleed	42 (14)	19 (17%)	23 (18%)	0 (0%)
Polyp	42 (14)	9 (8%)	13 (10%)	20 (36%)
Anastomotic Ulcer	16 (5)	6 (5%)	9 (7%)	1 (2%)
Angioectasia	8 (3)	4 (4%)	2 (2%)	2 (4%)
Other	9 (3)	2 (3%)	7 (6%)	0 (0%)
Total (%)	**297** (100, 20)	**114** (100, 27)	**127** (100, 16)	**56** (100, 22)
Small Bowel				
Angioectasia	13 (37)	6 (75%)	2 (13%)	5 (45%)
Tumor	5 (14)	1 (13%)	1 (6%)	3 (27%)
Dieulafoy	7 (20)	1 (13%)	6 (38%)	0 (0%)
Anastomotic Ulcer	6 (17)	0 (0%)	5 (31%)	1 (9%)
Other	4 (11)	0 (0%)	2 (13%)	2 (18%)
Total (%)	**35** (100, 2)	**8** (100, 2)	**16** (100, 2)	**11** (100, 4)
Unknown				
No lesion	223 (15)	48 (11)	96 (12)	79 (31)

GI, gastrointestinal; MWT, Mallory-Weiss tears; PHG, portal hypertensive gastropathy.

Table 4 Upper gastrointestinal tract diagnoses by pathogenic cause

Diagnosis classification	Total (n=905) No. (%)	Acute on chronic (n=260) No. (%)	Acute (n=537) No. (%)	Chronic (n=108) No. (%)
Portal hypertensive lesion*	309 (34)	123 (47)	157 (29)	29 (25)
Inflammatory†	468 (52)	105 (40)	310 (58)	53 (45)
Neoplastic‡	40 (4)	15 (6)	15 (3)	10 (9)
Vascular§	36 (4)	12 (5)	11 (2)	13 (11)
Other	52 (6)	5 (2)	44 (8)	3 (3)

p <0.001 for differences among diagnosis classifications for acute on chronic, acute, and chronic bleeding (by Chi square).
*Portal hypertensive lesion includes esophageal varices and portal hypertensive gastropathy.
†Inflammatory lesions include esophageal ulcers, gastric ulcers, duodenal ulcers, esophagitis, severe gastritis, and duodenitis.
‡Neoplastic lesions include tumors and polyps.
§Vascular lesions include angioectasias, Dieulafoy's lesions, and gastric antral vascular ectasia.

respectively (diastolic blood pressures were 71±18, 71±15, and 74±16, respectively). The number of units of blood transfused (mean±SD) in the three groups (as above) was 2.6±4.7, 2.3±2.8, and 2.1±2.3, respectively. Differences in mean SBP in the acute versus chronic, and acute on chronic versus chronic groups were statistically significantly different ($p<0.05$). These data raise the possibility that the decline in blood volume was greater in acute bleeding patients than in the other groups.

The overall 30-day mortality (all cause) in the entire cohort was 4% (65/1480). Mortality was lowest in patients with chronic bleeding (1/254). Importantly, in patients with acute on chronic bleeding, 30-day mortality was less than that after acute bleeding alone (2% (10/430) vs 7% (54/776), respectively, $p<0.001$).

DISCUSSION

Here, we report a unique clinical syndrome that we have coined acute on chronic gastrointestinal bleeding. Such

Table 5 Patients taking anticoagulants, antiplatelet agents, or NSAIDs

Medication	Total (n=662)	Acute on chronic (n=176)	Acute (n=368)	Chronic (n=118)
Aspirin and/or Clopidogrel (No. %)	316	81 (26%)	171 (54%)	64 (20%)
Coumadin and/or Enoxaparin (No. %)	119	18 (15%)	86 (72%)	15 (13%)
NSAIDs (No. %)	227	77 (34%)	111 (49%)	39 (17%)

p <0.001 for differences among medications for acute on chronic, acute, and chronic bleeding (by Chi square).

Table 6 Clinical predictors of acute on chronic bleeding

Variable	OR	95% CI
Portal hypertensive lesion	2.200	1.635 to 2.960
Lesion location in colon or rectum	2.196	1.620 to 2.958
Hispanic ethnicity	2.043	1.542 to 2.708
White ethnicity	1.734	1.242 to 2.421
Hematocrit	0.966	0.947 to 0.985
MCV	0.962	0.951 to 0.973

bleeding is characterized by typical presentation with acute bleeding (hematemesis, melena, or hematochezia), and also by the presence of chronic GI bleeding manifested by iron deficiency anemia. Analysis of these patients revealed notable differences in clinical characteristics, diagnosis, lesion location, and mortality when compared with patients with typical acute or chronic GI bleeding. Lesions of the upper GI tract, particularly portal hypertension-related disorders were the most common cause of acute on chronic bleeding. Additionally, patients with acute on chronic bleeding had a lower mortality rate than those with acute bleeding alone.

In entire cohort, inflammatory lesions (esophageal ulcer, gastric ulcer, duodenal ulcer, severe esophagitis, gastritis, and duodenitis) of the upper GI tract were by far the most common cause of bleeding, accounting for over 32% of all lesions (table 3) and over 50% of all upper GI tract lesions (table 4). In patients with acute bleeding, these lesions were responsible for some 58% (310/537) of lesions identified. In contrast, gastroesophageal variceal hemorrhage was the single most prevalent cause of acute on chronic upper GI bleeding, responsible for 43% of cases (table 3). Thus, while variceal hemorrhage overall was found to have a prevalence consistent with other GI bleeding populations,[20] it was most common in patients with acute on chronic bleeding. The clinical implications of these findings are twofold. First, while gastroesophageal varices and peptic ulcers are well-known causes of acute GI bleeding, and dictate specific therapy,[21] our data indicate that in patients with acute on chronic bleeding, it is important for clinicians to have a high index of suspicion for each of these disorders. Further, our findings raise the possibility of a specific pathogenesis for patients with acute on chronic bleeding. In particular, we speculate that patients most likely have a lesion that oozes chronically over time and then may bleed acutely, such as with an ulcer. Alternatively, in the case of portal hypertension, patients likely bleed from portal hypertensive gastropathy/enteropathy chronically, and then bleed from gastroesophageal varices acutely.

One of the most remarkable findings of this study was that the mortality in acute on chronic bleeding was found to be significantly less than in acute bleeding alone ($p<0.001$). On one hand, it might be predicted that the acutely bleeding group would have bleeding lesions often associated with a high mortality, such as gastroesophageal varices. However, patients with acute on chronic bleeding in fact had a greater prevalence of bleeding from gastroesophageal varices, which is known to have a higher mortality than non-variceal bleeding. There are several potential explanations for this finding. First, it is possible that patients with acute bleeding had more severe bleeding than the other groups. In fact, this is supported by our data which showed that patients with acute bleeding had lower SBP than in either of the other groups. Additionally, patients with acute bleeding had greater blood transfusion requirements. Second, we speculate that it is possible that patients with acute on chronic bleeding 'adapted' to a reduced hematocrit state. For example, patients with acute on chronic GI bleeding could have cardiovascular compensation from bleeding chronically such that an acute hemorrhage is associated with a less severe systemic circulatory effect. This possibility is supported by the finding that the cause of death in the setting of acute GI bleeding was more likely to be from non-bleeding causes than hemorrhage itself.[22] It is also possible that patients with acute on chronic GI bleeding have an earlier stage of cirrhosis; less advanced disease, especially when compared with patients with acute GI bleeding alone, would be associated with fewer liver disease complications and overall decreased mortality in the setting of acute GI bleeding. This possibility is supported by comparing mean INR levels, which was lower in patients with acute on chronic GI bleeding than those with acute GI bleeding alone (1.3 vs 1.4, respectively ($p<0.0001$)).

While this study's description of a distinctive syndrome, prospective collection of data, and its large sample size are all clear strengths, we recognize weaknesses that may potentially limit its generalizability. First, the study was conducted in a large urban inner city hospital, which was enriched for patients with GI bleeding, including those with cirrhosis. However, the frequency of variceal and non-variceal ulcer bleeding in this study was similar to that of other studies. While it could be argued that a high proportion of patients with gastroesophageal variceal bleeding could bias the study toward this lesion as a cause of acute bleeding, we believe that this demographic relationship is in fact a strength of the study. It has allowed us to emphasize that while gastroesophageal variceal bleeding has traditionally been thought of as a cause of acute bleeding, it was most common in patients in our cohort with acute on chronic bleeding, emphasizing this important association. While the relative proportions of patients with each acute, chronic, and acute on chronic bleeding may be different in other populations, our cohort was extremely diverse, which we also feel is an important strength, and furthermore consistent with the idea that the types of lesions identified here are typical of the general population. Finally, the use of ferritin as an inclusion criterion could have led to

potential bias. However, it should be emphasized that obtaining iron studies is part of routine local practice, and that the vast majority of patients in the cohort had a ferritin level obtained. Thus, we do not believe that excluding patients without a ferritin level is not a source of bias.

In conclusion, our findings suggest that many patients assessed for acute GI bleeding also have an underlying chronic component of bleeding that frequently goes unrecognized. Further, the findings have substantial implications in generating a differential diagnosis, in which identification of a chronic component of GI bleeding should focus the clinician toward specific disorders. Finally, given that patients with acute on chronic bleeding present with unique clinical features and have an improved outcome compared with patients with acute GI bleeding, practitioners should be aware of this clinical entity.

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Contributors DCR was involved in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, and oversight of the study. ACH was involved in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis. JSR was involved in analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis.

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