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ORIGINAL ARTICLE

Severe Upper Gastrointestinal Hemorrhage Caused by Reflux Esophagitis

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Abstract

Background There are few reports about reflux esophagitis (RE) as a cause of severe upper gastrointestinal bleeding (UGIB).
Aims This study aims to evaluate (1) changes in its prevalence over the last three decades and (2) clinical and endoscopic characteristics and 30-day outcomes among RE patients with and without focal esophageal ulcers (EUs) and stigmata of recent hemorrhage (SRH).
Methods A retrospective study of prospectively collected data of esophagitis patients hospitalized with severe UGIB between 1992 and 2020. Descriptive analysis and statistical comparisons were performed.
Results Of 114 RE patients, the mean age was 61.1 years and 76.3% were males. 38.6% had prior gastroesophageal reflux disease (GERD) symptoms; overall 36% were on acid suppressants. Over three consecutive decades, the prevalence of RE as a cause of severe UGIB increased significantly from 3.8 to 16.7%. 30-day rebleeding and all-cause mortality rates were 11.4% and 6.1%. RE patients with focal EUs and SRH ($n=23$) had worse esophagitis than those with diffuse RE ($n=91$) ($p=0.012$). There were no differences in 30-day outcomes between RE patients with and without EUs and SRH.
Conclusions For patients with severe UGIB caused by RE, (1) the prevalence has increased significantly over the past three decades, (2) the reasons for this increase and preventive strategies warrant further study, (3) most patients lacked GERD symptoms and did not take acid suppressants, and (4) those with focal ulcers and SRH had more severe esophagitis and were treated endoscopically.

Keywords Upper gastrointestinal bleeding · Reflux esophagitis · Esophageal ulcer · Outcomes · Endoscopy

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Introduction

Gastroesophageal reflux esophagitis (RE) as a cause of severe nonvariceal upper gastrointestinal (UGI) hemorrhage in adults has a reported prevalence of 5–12%, compared with peptic ulcers which account for 20–50% [1–4]. In contrast to this complication of gastroesophageal reflux disease (GERD), the prevalence of symptomatic GERD is variably reported ranging from 3 to 33% of the population worldwide and is especially higher in Western countries [5]. In spite of the widespread use of proton pump inhibitors (PPIs), the prevalence of GERD has not been decreasing, nor has its mortality [6, 7]. For complicated GERD such as strictures or bleeding, risk factors are increased age and more severe grades of esophagitis [8]. In a Japanese study of GERD and its complications, approximately 5% presented with upper gastrointestinal bleeding (UGIB); 3% with esophageal stricture; and 1% with both presentations [8].

The disease-specific mortality rate of RE is extremely low [7]. With PPIs and other peptic disorder medications for a GERD diagnosis, severe complications such as bleeding should be preventable [9]. With a better understanding of risk factors of severe GERD as a cause of severe UGIB, the rates of UGIB and hospitalization for RE could also potentially be reduced.

The aims of this study were to: (1) assess the change in prevalence of RE as a cause of severe UGI hemorrhage over the last three decades and (2) report clinical and endoscopic features and 30-day outcomes of patients with RE with and without focal esophageal ulcers (EUs) and stigmata of recent hemorrhage (SRH).

Materials and Methods

Study Design and Patients

This is a retrospective study of prospectively collected data of patients from two academic institutions who were hospitalized with severe UGI hemorrhage and had a diagnosis of RE. Patients were identified through the Center for Ulcer Research and Education (CURE) Hemostasis Research Unit databases using the diagnosis codes of inpatient status and UGI hemorrhage, esophagitis, and EUs. Data analyzed in this study were collected from March 1992 to April 2020. All patients had been enrolled in Institutional Review Board (IRB)-approved prospective cohort or randomized studies of severe UGI hemorrhage.

Besides the database findings, data sources varied by hospital. The endoscopic software used included EndoWorks (Olympus, Tokyo, Japan) for the endoscopic procedures performed prior to March 2018 and EndoVault (EndoSoft LLC, NY, USA) for the procedures performed after that. Any missing data were retrieved from electronic medical records at each center including Epic electronic record systems (Epic Systems Corporation, WI, USA) and Computerized Patient Record System—CPRS (Department of Veterans Affairs, USA).

All studies were performed in accordance with the ethical standards as laid down in the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Inclusion and Exclusion Criteria

Inclusion criteria were adult patients aged 18 years old or older who were hospitalized due to severe UGI hemorrhage and had a final endoscopic diagnosis of RE with or without focal EUs and SRH as the cause of the bleeding. Patients were excluded if they had another source of UGIB from non-GERD-related causes of esophagitis, Cameron ulcers, post-rubber band ligation (RBL) ulcers, esophageal or gastric varices, gastric or duodenal ulcers, UGI malignancy, Mallory–Weiss tears, or angiomas.

Patients with nonreflux-related esophagitis such as infectious esophagitis (e.g. Candida or Herpes simplex virus), pill-induced esophagitis, or immune-mediated esophagitis such as Stevens–Johnson syndrome with esophageal involvement were excluded for the primary analysis.

Severity of Bleeding and Diagnosis of Esophagitis

Severe UGIB was defined as having clinical signs of overt bleeding (hematemesis, hematochezia, and/or melena); a decrease in hemoglobin from baseline $\geq$ 2 g/dL; and transfusion of two or more units of red blood cells (RBCs) [10].

A diagnosis of erosive or ulcerative esophagitis was made during the initial upper endoscopy. The severity of esophagitis was graded according to the Los Angeles (LA) Classification of GERD [11]. LA grades A and B have only longitudinal mucosal breaks that do not extend beyond two mucosal folds, with the grade B defined as mucosal breaks longer than 5 mm. LA grades C and D have both longitudinal and circumferential mucosal breaks with grade D involving at least 75% of esophageal circumference. Focal EUs were defined as an ulcer at or above the gastroesophageal junction (GEJ) with a minimum size of 5 mm and more than 1 mm in depth as determined by biopsy forceps or accessory of known dimensions.

SRH include active arterial bleeding, oozing bleeding, nonbleeding visible vessel, adherent clot, and flat spot, similar to peptic ulcer bleeding (PUB) [10]. LA classification and SRH were reported by the same group of endoscopists, and endoscopic pictures were retrospectively reviewed to

confirm the LA grade by DJ, TW, and UK. A diagnosis for infectious esophagitis was confirmed by histopathology and culture of endoscopic brushings and/or biopsies.

Definition of Rebleeding, Medical Treatment, and Endoscopic Hemostasis

Rebleeding was diagnosed when patients had clinical symptoms and signs of further bleeding 12 or more hours after the index upper endoscopy and met the same criteria of severity as the index bleed. All-cause 30-day mortality was reported. Mortality from UGIB was defined as patients dying of gastrointestinal (GI) bleeding or a complication from GI bleeding.

All patients with esophagitis were treated with oral or intravenous (IV) PPIs, antireflux measures (thorax elevation with a wedge while sleeping, avoidance of straining and heavy lifting, avoidance of foods that aggravate the patient's GERD symptoms, and avoidance of eating or drinking within 2 h of lying down), correction of severe coagulopathies and blood product transfusions if indicated. Patients with EUs and major SRH (active arterial bleeding, visible vessels, or adherent clots) had endoscopic hemostasis and subsequently received IV PPI infusion for 72 h. After they began eating, all RE patients received oral twice-daily PPIs.

Data Collection and Management

All patient study charts were reviewed including endoscopic reports and pictures, histopathology and culture reports, admission notes, GI consult notes, discharge summaries, and follow-up visit notes within 30 days. Baseline variables reported were demographics, comorbidities and risk scores, bleeding-related medications (e.g. aspirin, antiplatelet drugs, anticoagulants), nonsteroidal anti-inflammatory drugs—NSAIDs, alcohol consumption, smoking history, GERD history, and a history of prior UGIB [10]. Other data recorded were laboratory results, endoscopic findings (grade of esophagitis, ulcer size, SRH, and other nonbleeding UGI lesions), type of endoscopic hemostasis (if performed), rebleeding events, readmissions, and death. All medications that the patients were taking were obtained from the study chart which included over-the-counter medications such as aspirin and NSAIDs. Any missing information was retrieved from the electronic medical records.

Outcome Measures and Comparisons

The first outcome determined was the change in RE prevalence as a cause of severe UGIB over the last three decades. Initially for comparisons of potential risk factors, we divided the patients into two cohorts—the first half (1992–2006) and second half (2007–2020). To further study the increase in prevalence, we also looked at three cohorts. According to their study entry date, the first was 1992–2000, the second was 2001–2010, and the third was 2011–2020. Another outcome was 30-day rebleeding rates for patients with and without focal EUs and SRH. We also reported overall 30-day rates of rebleeding, reintervention, readmission, complications, and mortality rates. We also compared baseline characteristics, units of red blood cell (RBC) transfused, and length of hospital stays of patients with and without focal EUs and SRH. To assess potential risk factors, we also assessed the past medical history (GERD, size and presence of hiatal hernia, obesity, and other comorbidities).

Statistical Analysis

Descriptive statistics were used to analyze and compare patient demographics and 30-day outcomes. Patients with diffuse esophagitis without EUs were compared to those with EUs and SRH using Student's *t* test, Mann–Whitney *U* test, and Chi-square tests. Continuous variables were reported as either mean and standard deviation (SD) for normal distribution or median and interquartile range (IQR) for nonnormal distribution, while categorical variables are reported by the number of patients and percentages. A p value of less than 0.05 was considered to be statistically significant. Data collection was performed using Microsoft Excel (Microsoft Corp., WA, USA). All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

All Patients with Severe UGIB and Those Identified as Esophagitis

In total, 2703 patients with clinically and endoscopically documented UGIB were identified from CURE Hemostasis databases from 1992 to 2020. Of these, 114 patients were diagnosed as RE and eight others as non-GERD-related esophagitis (Fig. 1).

Prevalence of Reflux Esophagitis as a Cause of UGI Bleeding

In the first half of the study period from 1992 to 2006 (14 years duration), 1545 patients had UGIB and the prevalence of RE was 1.6% (25/1545). In the second half of the study from 2007 to 2020 (13 years), the prevalence of RE as a cause of severe UGIB was 7.7% (89/1,158). This was a significant increase in prevalence—$p < 0.001$.

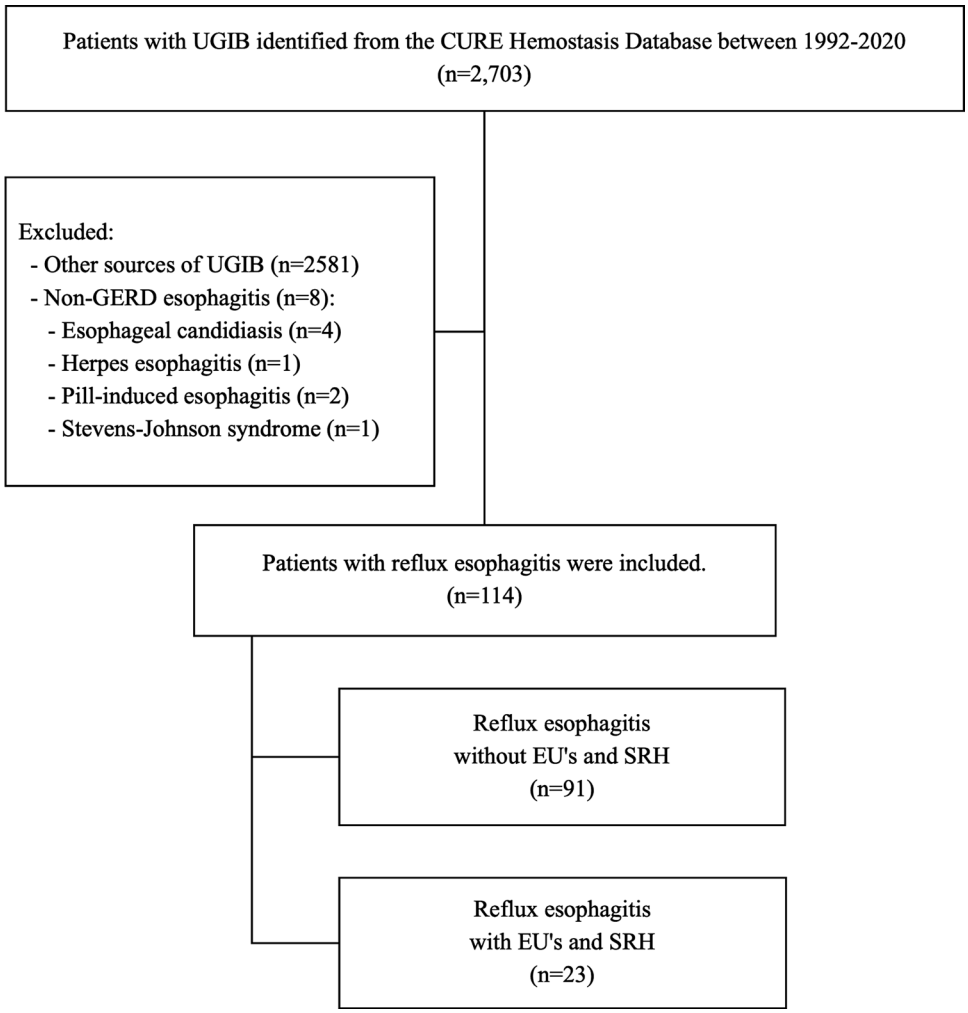

Fig. 1 Flowchart diagram showing eligible patients in the study. A total of 2703 patients hospitalized with severe UGIB from 1992 to 2020, 114 patients with reflux esophagitis were included

To better illustrate the changes in prevalence of RE as a cause of severe UGIH. Refer to Fig. 2. The prevalence increased from 3.83 to 8.55% and mostly recently to 16.7%.

For additional comparisons of risk factors, we divided the patients in half by study entry date. Patients in the second half of the study period had a significantly higher rate of hiatal hernia (78.7% vs. 36%, $p < 0.001$) than in the first half. However, a history of prior GERD diagnosis, age, antiplatelet, or anticoagulant drug use were not statistically different. BMI was not included in the comparison because the data were not available in the patients charts mostly in the first half.

Demographics of Patients with Reflux Esophagitis

Demographic data of all 114 RE patients are presented in Table 1. The majority of patients were Caucasian ($n = 66$, 57.9%), Hispanic ($n = 24$, 21.1%), African American ($n = 15$, 13.2%) and Asian ($n = 9$, 7.9%). Presenting signs and symptoms were hematemesis (75.4%), melena (55.3%), hypotension (21.1%), nonspecific abdominal pain (14%), and

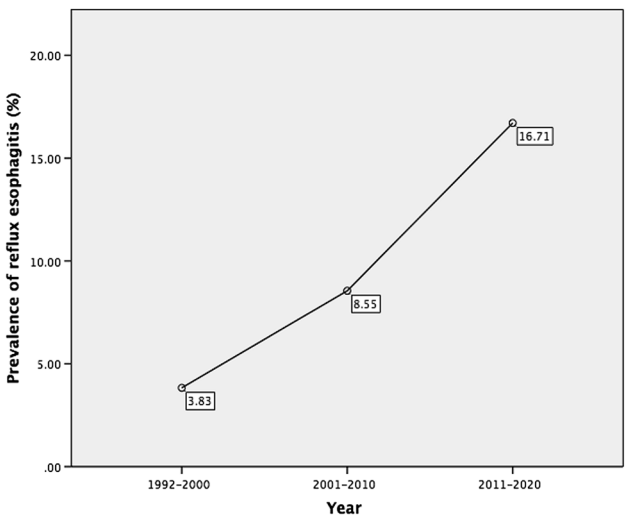

Fig. 2 Prevalence of patients with severe UGIB from reflux esophagitis in 3 decades (1992–2020)

Table 1 Demographics of all patients with severe reflux esophagitis and 30-day outcomes

Baseline characteristics of patients with severe esophagitis ($n=114$)	
Age, years old, mean (SD)	61.1 (15.9)
Male, *n* (%)	87 (76.3)
CURE Prognosis Score, median (IQR)	3 (1)
Glasgow–Blatchford Bleeding Score, median (IQR)	10 (6.5)
Age-adjusted Charlson Comorbidity Index, median (IQR)	5 (4.3)
ASA Classification, *n* (%)	
Class I	2 (1.7)
Class II	26 (22.6)
Class III	54 (47.4)
Class IV	30 (26.1)
Class V	2 (1.7)
Prior UGI bleeding, *n* (%)	41 (36)
Chronic anemia, *n* (%)	48 (42.1)
Iron deficiency anemia, *n* (%)	6 (5.3)
Prior GERD diagnosis, *n* (%)	44 (38.6)
Medications for peptic disorder, *n* (%)	
Proton pump inhibitors	35 (30.7)
Antacid	1 (0.9)
Histamine type 2 receptor antagonist	3 (2.6)
Sucralfate	2 (1.8)
Comorbidities, *n* (%)	
Cirrhosis and other chronic liver diseases	39 (34.2)
Diabetes mellitus	37 (32.5)
Prior cardiovascular accident	17 (14.9)
Bleed medications, *n* (%)	
Aspirin	39 (34.2)
Anticoagulants	20 (17.5)
Antiplatelet drugs	10 (8.8)
NSAIDs	22 (19.3)
Alcohol consumption, *n* (%)	27 (23.7)
Smoking history, *n* (%)	
Former smoker	25 (21.9)
Current smoker	22 (19.3)
Inpatient start of UGIB, *n* (%)	37 (32.5)

n number of patients, *SD* standard deviation, *IQR* interquartile range, *CURE* Center of Ulcer Research and Education, *ASA Classification* American Society of Anesthesiologists Classification, *GERD* gastroesophageal reflux disease, *NSAIDs* nonsteroidal anti-inflammatory drugs, *UGI* upper gastrointestinal, *UGIB* upper gastrointestinal bleeding

hematochezia (8.8%). 3.5% of patients were nursing home residents prior to hospitalization for UGIB. Two (1.8%) patients were bedridden and five (4.4%) patients had recent nasogastric tubes. The median body mass index (BMI) was 25.9 (IQR 8.48, range 16.0–44.3) kg/m^2. Chronic anemia was diagnosed in 42.1% (48/114) of patients, whereas chronic iron deficiency was a pre-admission diagnosis in 5.3% (6/114) of other patients (Figs. 3, 4).

Forty-one patients had a history of prior UGIB. Peptic ulcer disease was the most common cause of all prior UGIB events (26.7%), followed by esophagitis (15%), Mallory-Weiss tear (8.3%), esophageal varices (6.7%), and Dieulafoy's lesion (2.3%). However, forty percent of prior UGIB events were unknown causes. Thirty-four percent of patients ($n=39$) had cirrhosis or chronic liver disease. Their Child–Pugh Classes were A in 1 (2.6%); Class B in 10 (25.6%); Class C in 21 (53.8%); and unknown in 7 (17.9%). The median model for end-stage liver disease (MELD) score (IQR) was 21 (17).

All patients had acute anemia with a mean hemoglobin (SD) of 8.4 (2.9) g/dL on admission after IV fluid resuscitation. The mean platelet counts and coagulation tests were within normal limits. The median blood urea nitrogen (BUN) level was higher than normal (31.5, IQR 38.3 mg/

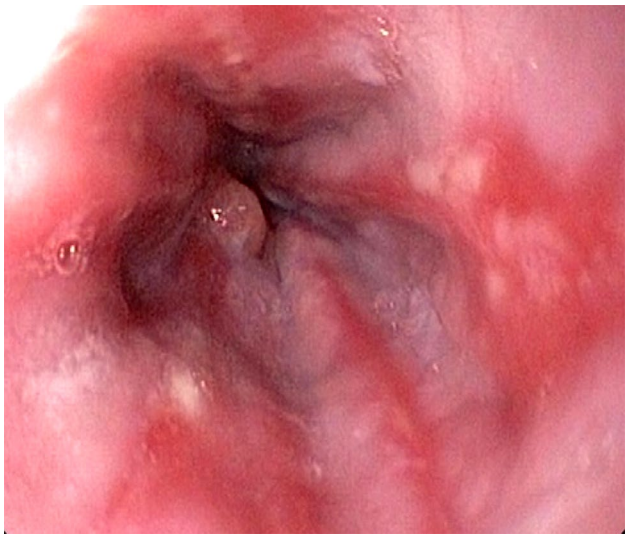

Fig. 3 Los Angeles grade C reflux esophagitis (diffuse), without focal esophageal ulcers and stigmata of recent hemorrhage

dL), and median serum creatinine was high normal (1.1, IQR 1.2 mg/dL).

38.6% ($n=44$) of patients had prior GERD symptoms. Of these, 65.9% ($n=29$) had a prior clinical/endoscopic diagnosis of GERD. 55.2% of these GERD patients were on acid suppression medications. Medications included PPIs in 41.4% ($n=12$), histamine type 2 receptor antagonists 10.3% ($n=3$), and antacids 3.4% ($n=1$). Of the 33 patients who had both prior GERD symptoms and prior UGIB, six (33%) patients were taking PPIs.

Of 70 patients without a history of GERD symptoms, 24 (34.3%) were on acid suppressants for other purposes such as prophylactic PPI therapy for aspirin or antiplatelet agents. Overall 36% (41/114) of patients with RE were on acid suppressants prior to hospitalization with severe UGIB.

Endoscopic Findings and Treatment for Reflux Esophagitis

Endoscopic findings are shown in Table 2. Of 114 RE patients, 23 (20.2%) had focal EUs with SRH. Half of the patients had LA class D esophagitis and the rest were grade B and C. Hiatal hernia was identified in 69.3%. The sizes of hiatal hernia were small in 26 (32.9%), medium in 24 (30.4%), and large in 23 (29.1%). Endoscopic hemostasis was utilized in only 17.5% of RE patients. A combination of epinephrine injection and hemoclips was the most common endoscopic treatment. All other patients without EUs were treated with medical therapy without endoscopic hemostasis.

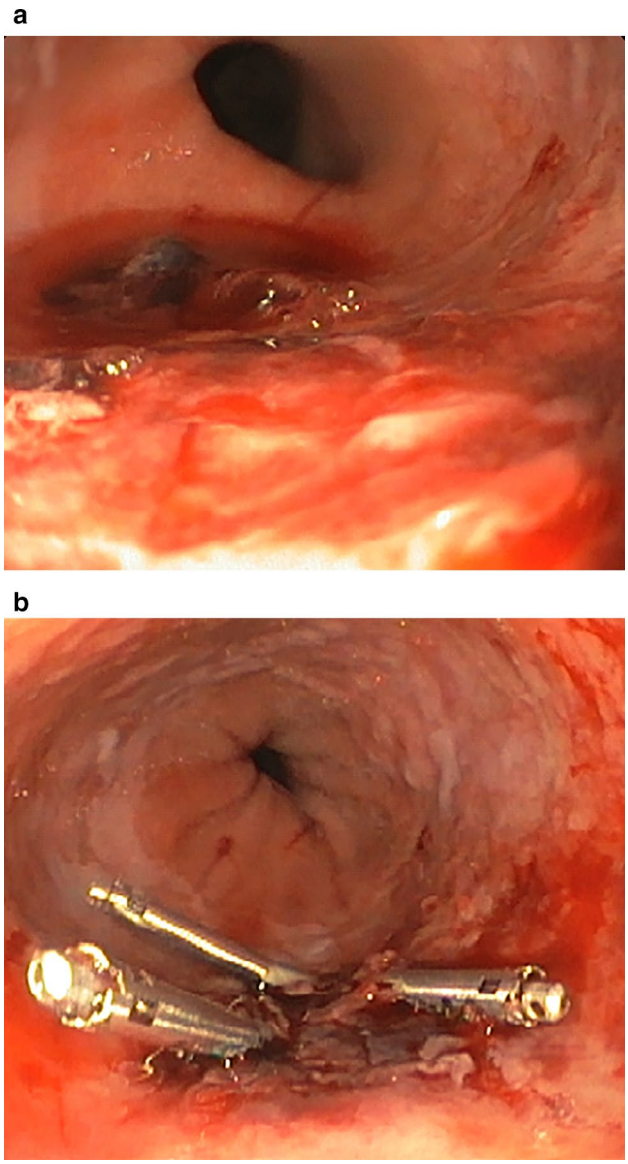

Fig. 4 Changes of focal esophageal ulcer with active bleeding after endoscopic hemostasis. **a** Esophageal ulcer before endoscopic hemostasis; **b** esophageal ulcer after endoscopic hemostasis with epinephrine injection and hemoclipping

30-Day Outcomes of All Reflux Esophagitis Patients

The 30-day outcomes are presented in Table 2. Data regarding PPI compliance within the 30-day period were available in 79 patients. Of these, 98.7% ($n=78$) were compliant, taking their PPIs daily. The rate of further bleeding from all causes was 11.4% ($n=13$). Of these, 46.2% ($n=6$) of patients rebled from RE—diffuse esophagitis or a focal EU. The other 53.8% ($n=7$) bled from non-RE causes including gastric ulcer ($n=1$, 7.7%), other GI causes (n = 3, 23.1%), and unknown causes ($n=3$, 23.1%). Six out of 13 patients had more than one

Table 2 Endoscopic findings and 30-day outcomes of all severe esophagitis patients

Endoscopic findings and treatment ($n=114$)	
LA Grade, *n* (%)	
B	24 (21.1)
C	28 (24.6)
D	62 (54.4)
Focal esophageal ulcers with SRH, *n* (%)	23 (20.2)
Stigmata of recent hemorrhage, *n* (%)	
Active bleeding	24 (21.1)
Oozing	18 (15.8)
Moderate pumping	6 (5.3)
Nonbleeding adherent clot	7 (6.1)
Visible vessel	5 (4.4)
Spot	3 (2.6)
Other nonbleeding UGI findings, *n* (%)	
Hiatal Hernia	79 (69.3)
Portal gastropathy	9 (7.9)
Barrett's esophagus	10 (8.8)
Polyps	4 (3.5)
Esophageal varices	6 (5.3)
Gastropathy	9 (7.9)
Duodenitis	6 (5.3)
Angiodysplasia	2 (1.8)
Endoscopic hemostasis performed, *n* (%)	20 (17.5)
Overall 30-day outcome parameters	
Length of stay, days, median (IQR)	5 (15.3)
Length of ICU stay, days, median (IQR)	1 (3)
Further bleeding, *n* (%)	13 (11.4)
RBC transfusion for rebleed, units, median (IQR)	4 (7)
Readmission, *n* (%)	14 (12.3)
Reintervention (EGD), *n* (%)	8 (7)
All-cause mortality, *n* (%)	7 (6.1)

n number of patients, *SD* standard deviation, *IQR* interquartile range, *LA Grade* Los Angeles Classification of Gastroesophageal Reflux Disease, *UGI* upper gastrointestinal, *ICU* intensive care unit, *RBC* red blood cell, *EGD* esophagogastroduodenoscopy, *SRH* stigmata of recent hemorrhage

episode of rebleeding including one from EUs, one from esophagitis, and four from other sources. Of 14 patients who were readmitted to the hospital within 30 days, only two had recurrent GI bleeding and the rest were for non-UGI-related illnesses (i.e. sepsis, cirrhosis-related complications, pneumonia, and other causes). The most common cause of all-cause mortality was sepsis ($n=4$). Other causes in three patients were sudden cardiac death, congestive heart failure, and end-stage malignancy. None of the deaths was caused by UGIB.

Of eight patients who had repeat EGD within 30 days, six were performed for rebleeding and two patients underwent evaluation for esophagitis healing.

There were no differences in the 30-day outcomes based on LA grades of esophagitis and among patients at either center (Supplement Tables 1, 2).

Comparison of Severe Reflux Esophagitis Patients With and Without Focal EUs and SRH

Table 3 shows baseline characteristics and 30-day outcomes of patients with severe esophagitis with and without EUs and SRH. There were no statistically significant differences in age (mean 60.87, SD 17 vs. mean 61.2, SD 15.7), gender (male, $n=18$, 78.3% vs. $n=69$, 75.8%), or race between the two groups. The comorbidities were similar in both groups. No statistical differences were found between the two groups in medications or laboratory results. However, the BUN was significantly higher in those with ulcers (median 47 vs. 29, IQR 44 vs. 37.5 mg/dL, $p=0.039$).

For endoscopic findings and treatment (Table 3), the majority of patients without ulcers had diffuse esophagitis, while those with ulcers had active bleeding as the most common SRH. The proportion of grades C and D RE was significantly higher in the group with focal ulcers.

Doppler endoscopic probe (DEP) was performed in eight patients with EUs and SRH. 75% (6/8) had arterial blood flow detected. All patients with positive DEP were treated endoscopically. One of eight patients (12.5%) rebled from unknown sources, since repeat esophagogastroduodenoscopy (EGD) was not performed to confirm the diagnosis. In 15 patients treated endoscopically without DEP guidance, 26.7% rebled, three from esophageal ulcers and one from an unknown source.

The 30-day outcome comparisons are also presented in Table 3. The rates of further bleeding, reintervention, and readmission were arithmetically higher in patients with ulcers. Rebleeding occurred in 13 patients. The diagnoses in those with focal EUs and SRH included esophagitis ($n=1$), esophageal ulcer ($n=2$), and unknown sources ($n=2$). For patients with diffuse esophagitis without focal ulcers, causes were esophagitis ($n=3$), esophageal varices ($n=1$), Dieulafoy's lesion ($n=1$), diverticulosis ($n=1$), gastric ulcer ($n=1$), and an unknown source ($n=1$).

Discussion

Reflux esophagitis as a cause of severe UGIB has significantly increased in prevalence from 3.8 to 16.7% over three consecutive decades in our two academic medical centers. Only 38.6% of patients had prior GERD symptoms. For all RE patients presented with UGIB, only 36% were taking acid suppressant medications for GERD or other indications prior to presenting with severe UGI hemorrhage. On endoscopy, most RE patients had diffuse esophagitis and lacked

Table 3 Comparison of patients with severe reflux esophagitis with and without focal EUs and SRH

	Esophagitis and focal EUs and SRH ($n=23$)	Esophagitis without focal EUs and SRH ($n=91$)	p value
Presenting symptoms, *n* (%)			
Hematemesis	19 (82.6)	67 (73.6)	0.371
Melena	10 (43.5)	53 (58.2)	0.203
Hematochezia	2 (8.7)	8 (8.8)	0.988
Abdominal pain	4 (17.4)	12 (13.2)	0.604
Hypotension	8 (34.8)	16 (17.6)	0.071
Syncope	2 (8.7)	4 (4.4)	0.409
Transfusion for resuscitation, median (IQR)			
RBC, units	2 (2)	2 (2)	0.898
FFP, units	4 (2.3)	3 (3.5)	0.201
PLT, units	2 (10.3)	1 (4.5)	0.323
BMI, kg/m^2, median (IQR)	29.6 (5.2)	25.8 (8.4)	0.085
Chronic anemia, *n* (%)	7 (30.4)	41 (45.1)	0.205
Iron deficiency anemia, *n* (%)	0	6 (6.6)	0.206
Prior GERD diagnosis, *n* (%)	8 (34.8)	36 (39.6)	0.674
GERD or ulcer medications, *n* (%)	8 (34.8)	33 (36.3)	0.895
PPIs	6 (26.1)	29 (31.9)	
Histamine type 2 receptor antagonists	0	3 (3.3)	
Antacids	1 (4.3)	0	
Sucralfate	1 (4.3)	1 (4.3)	
Bleed drugs, *n* (%)			
Warfarin	3 (13)	8 (8.8)	0.537
Aspirin	7 (30.4)	32 (35.2)	0.669
NSAIDs	5 (21.7)	17 (18.7)	0.740
Endoscopic findings			
Stigmata of recent hemorrhage, *n* (%)			
Clean lesion	0	76 (83.5)	< 0.001
Adherent clot not removable	2 (8.7)	5 (5.5)	0.568
Active bleeding	14 (60.9)	10 (11)	< 0.001
Visible vessel	5 (21.7)	0	< 0.001
Spot	3 (13)	0	< 0.001
LA Grade, *n* (%)			0.012
B	0	22 (24.2)	
C	10 (43.5)	20 (22)	
D	13 (56.5)	49 (53.8)	
Size of hiatal hernia, *n* (%)			0.233
Absent/small	11 (47.8)	56 (61.5)	
Medium/large	12 (52.2)	35 (38.5)	
Endoscopic Doppler performed, *n* (%)	8 (34.8)	0	< 0.001
Positive	6 (26.1)	0	
Negative	2 (8.7)	0	
Endoscopic hemostasis performed, *n* (%)	20 (87)	0	< 0.001
Epi injection with hemoclips	10 (43.5)	0	
MPEC probe	4 (17.4)	0	
Epi injection with MPEC probe	2 (8.7)	0	
Hemoclips	2 (8.7)	0	
Epi injection alone	2 (8.7)	0	
30-day outcome parameters:			
Length of stay, days, median (IQR)	5 (27)	5 (14)	0.508

Table 3 (continued)

	Esophagitis and focal EUs and SRH ($n=23$)	Esophagitis without focal EUs and SRH ($n=91$)	p value
Length of ICU stay, days, median (IQR)	2 (14)	1 (3)	0.163
First rebleeding diagnoses, *n* (%)			
Esophagitis or EUs	3 (13)	3 (3.3)	0.061
Other sources	2 (8.7)	5 (5.5)	0.568
Units RBC transfused for rebleed, median (IQR)	3 (7)	8 (8)	0.310
Readmission, *n* (%)	2 (8.7)	12 (13.2)	0.558
Reintervention (EGD), *n* (%)	2 (8.7)	6 (6.6)	0.724
All-cause mortality, *n* (%)	1 (4.3)	6 (6.6)	0.689

n number of patients, *IQR* interquartile range, *RBC* red blood cell, *FFP* fresh frozen plasma, *PLT* platelet, *BMI* body mass index, *NSAIDs* non-steroidal anti-inflammatory drugs, *GERD* gastroesophageal reflux disease, *PPIs* proton pump inhibitors, *LA Grade* Los Angeles Classification of Gastroesophageal Reflux Disease, *EGD* esophagogastroduodenoscopy, *MPEC* multipolar electrocautery, *Epi* epinephrine, *ICU* intensive care unit, *EUs* esophageal ulcers, *Bleed drugs* antiplatelet or anti-coagulant drugs taken before UGIB

focal ulcers with SRH. Compared to patients with diffuse RE, the 30-day rebleeding, reintervention, and readmission rates were arithmetically higher than those with RE and focal EUs and SRH.

GERD is prevalent both in the USA and worldwide, but the prevalence of RE as a cause of severe UGIB varies [1, 12]. In a prospective French study of 219 UGIB patients by Costa et al., RE was the second most common cause, accounting for 8% of all UGIB [1]. Consistent with other reports, we observed that the prevalence of RE as a cause of UGIB has been increasing [13, 14]. Although in the USA, PUBs are the most common cause of UGIB [14, 15], the prevalence of bleeding RE increased from 2% in 1991 to 8% during 2005–2011 [14, 15].

Although there have been no clear-cut reasons reported for these trends, this is probably multifactorial. Potential risk factors for this are the increasing prevalences of obesity and GERD, the dramatic decrease in prevalence of *Helicobacter pylori* (*H. pylori*)-associated gastritis, and increasing age of the population. *H. pylori* causes atrophic gastritis which decreases acid secretion and results in a protective effect for development of GERD, as reported in a cohort of 10,102 patients with an odds ratio of 0.42 [16]. The prevalence of RE also increased after *H. pylori* was eradicated [17]. Similar results were also reported in other published studies [18, 19]. However, it is still a debate in Western countries [18–20]. One Spanish study reported that there was no association between *H. pylori* and GERD based upon both endoscopic findings and 24-h esophageal pH monitoring [20].

Obesity is another known major risk factor for GERD symptoms and is also associated with RE [21–23]. Based on a prospective study on 242 bariatric surgery candidates, RE was found in 34% [24]. GERD in obese patients is caused by a mechanical malfunction of lower esophageal sphincter along with increased intra-abdominal pressure and impaired gastric emptying [21].

An increase in the age of the population could be another contributor to the increase in prevalence of RE and silent bleeding. Since older patients have more comorbidities, especially cardiovascular and cerebral–vascular diseases, aspirin and antithrombotic medications are widely prescribed for both therapeutic and prophylactic purposes [25]. In our study, more than half of patients were on aspirin, anticoagulants, and other antiplatelet drugs before presenting with UGI bleeding. These medications increase the risk of GI bleeding [25].

Hiatal hernias, especially large ones, are also reported to be an independent risk factor for severe RE and also for symptomatic GERD [26, 27]. In our study, 69.3% of patients had hiatal hernias on endoscopy. However, the majority of them had no history of GERD symptoms. Nguyen et al. reported that most patients with severe esophagitis did not have a prior history of either hiatal hernia or GERD [28]. The prevalence of symptomatic GERD was reported to be lower in the elderly due to a reduction or absence of pain sensitivity to gastric acid [26, 29]. A silent presentation of UGIB without pain is similar to PUB patients, who often have no prior ulcer symptoms [30].

Previous studies reported that UGIB secondary to PUD was associated with significant morbidity and mortality. In the USA, the rebleeding and mortality rates were 17.7% and 7.2% [10], which were similar to rates in Canada [31]. For our study of RE patients, these rates were significantly lower at 11.4% and 6.1%, respectively. Guntapelli et al. also found that patients with RE as a cause of UGIB had more favorable clinical courses and outcomes than others with PUBs and other causes of UGIB [32].

PPIs are the mainstay of treatment for RE and other UGI peptic lesions [33]. However, the rates and roles of SRH and endoscopic hemostasis for patients with severe UGIB and RE are not well defined. Most patients with RE (79.8%) had diffuse esophagitis and no focal ulcers or SRH, and they

were treated medically with PPIs. Some rebled from diffuse RE or other causes. The minority of RE patients with UGIB (20.2%) had focal ulcers and SRH, and most of them were treated endoscopically. This was safe and effective—none rebled from the focal ulcers and no patient had a complication of the endoscopic treatment. In all, 87% (20/23) of our patients with focal EUs and SRH were treated with combination endoscopic hemostasis (epinephrine injection and hemoclips). Endoscopic hemostasis is known to improve outcomes in peptic ulcers with SRH [34]. Studies reported that combination treatment of epinephrine injection and either hemoclips or thermal therapy for PUB reduces the rates of rebleeding and emergency surgery [35, 36]. Currently, we found no guidelines for endoscopic hemostasis of RE with focal EUs and SRH. We utilized endoscopic DEP in risk stratification and treatment for some patients, which has not been previously reported. Results of DEP interrogation of EUs were similar to those of patients with PUB [37–39]. Only one RE patient with EUs and SRH who had DEP-guided endoscopic hemostasis had rebleeding.

This study has several limitations. First, due to its retrospective nature, some patients with RE may not have been included. Secondly, no long-term outcomes beyond 30 days are reported. Some patients with RE could have presented later with rebleeding. Third, this was not a study of RE healing and whether the time for healing is different from uncomplicated RE without UGIB is unknown. Lastly, as an academic and tertiary referral center, the endoscopic management of patients might not be applicable to the general population due to the different levels of expertise for accurate diagnosis and/or focal treatment.

Further research about earlier detection and treatment for silent RE is indicated. This could include evaluating patients with chronic anemia and GI blood loss by recommending earlier endoscopy for diagnosis and preemptive medical treatment. Also, careful monitoring and GI evaluation are recommended for both obese patients for RE and occult GI bleeding and also patients with severe comorbidities who are on chronic antithrombotic drugs or NSAIDs. As the population ages, more patients take antithrombotic drugs, and as the obesity prevalence increases, more patients are expected to present with severe UGI bleeding from RE without GERD symptoms.

Conclusions

The prevalence of severe reflux esophagitis as a cause of severe UGIB has significantly increased over the last three decades in our academic medical centers. The reasons for this increase are speculative but may relate to high prevalence of hiatal hernias; increase in comorbidities; more prevalent obesity; silent presentation of hemorrhage; and increased utilization of antithrombotic medications. The majority of RE patients lacked GERD symptoms and were not taking acid suppressants before presenting with UGIB. 79.8% of patients had diffuse esophagitis without focal ulcers or SRH. 20.2% had focal ulcers with SRH and most were treated endoscopically with combination hemostasis, which was safe and effective for definitive hemostasis. Further research is warranted about strategies to preemptively diagnose and treat patients with severe, asymptomatic RE before they develop severe UGIB.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest and no assistance in manuscript preparation.

Ethical approval All patients had been enrolled in Institutional Review Board (IRB)-approved prospective cohort or randomized studies of severe UGI hemorrhage at both VA Greater Los Angeles Healthcare System and University of California, Los Angeles. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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