

BLEEDING PEPTIC ULCER – TERTIARY CENTER EXPERIENCE: EPIDEMIOLOGY, TREATMENT AND PROGNOSIS

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SUMMARY – The aim of this study was to demonstrate epidemiological, clinical and endoscopic characteristics of acute upper gastrointestinal bleeding (UGIB) with special reference to peptic ulcer bleeding (PUB). The study included 2198 consecutive patients referred to our emergency department due to acute UGIB from January 2008 to December 2012. All patients underwent urgent upper GI endoscopy within 24 hours of admission, and 842 patients diagnosed with PUB were enrolled and prospectively followed-up. The cumulative incidence of UGIB was 126/100,000 in the 5-year period. Two out of five patients had a bleeding peptic ulcer; in total, 440 (52.3%) had bleeding gastric ulcer, 356 (42.3%) had bleeding duodenal ulcer, 17 (2%) had both bleeding gastric and duodenal ulcers, and 29 (3.5%) patients had bleeding ulcers on gastroenteric anastomoses. PUB was more common in men. The mean patient age was 65.9 years. The majority of patients (57%) with PUB were taking agents that attenuate the cytoprotective function of gastric and duodenal mucosa. Rebleeding occurred in 77 (9.7%) patients and 47 (5.9%) patients required surgical intervention. The 30-day mortality was 5.2% and 10% of patients died from uncontrolled bleeding and concomitant diseases. In conclusion, PUB is the main cause of UGIB, characterized by a significant rebleeding rate and mortality.

Key words: *Gastrointestinal hemorrhage – epidemiology; Gastrointestinal hemorrhage – therapy; Peptic ulcer hemorrhage – epidemiology; Peptic ulcer hemorrhage – therapy; Endoscopy, gastrointestinal; Prognosis; Tertiary care centers; Croatia*

Introduction

Upper gastrointestinal bleeding (UGIB) is a common medical emergency and accounts for 5% of emergency department presentations *per year* and 2% to 3% of hospital admissions in developed countries¹. The incidence rate of UGIB varies from 48 to 160 cases *per 100,000 population*, with consistent reports of higher

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incidence among men and the elderly². The most common cause of acute UGIB is non-variceal, where peptic ulcer bleeding (PUB) accounts for 28% to 59% of cases²⁻⁴.

Endoscopy has become the standard of care in the diagnosis and treatment of UGIB. Most national and international guidelines recommend performing upper endoscopy within 24 hours of presentation in patients with UGIB⁵⁻⁷. Despite major advances in diagnostic and therapeutic approaches, PUB remains a significant problem and an important cause of morbidity and mortality. Rebleeding after initial hemostasis occurs in 10% to 30% of patients with PUB⁸⁻¹¹. The reported PUB mortality rates in various countries across Europe range from 3.4% to 14%, and the reason for this difference remains unknown¹²⁻¹⁵.

The aim of this prospective study was to determine the epidemiological, clinical and endoscopic characteristics of UGIB with a focus on the treatment and prognosis of PUB in a tertiary care center.

Patients and Methods

This prospective study was conducted in a tertiary care center in the City of Zagreb, Croatia, which covers a population of approximately 300,000 people. All consecutive patients presenting with UGIB (hematemesis, melena, hematochezia or blood admixture upon nasogastric aspiration) to the Emergency Internal Medicine Unit, Sestre milosrdnice University Hospital Center between January 2008 and December 2012 were included. These patients were then, if necessary, hospitalized in the Interventional Gastroenterology Unit of the same hospital. If the same patient was hospitalized more than once during the study period, only the first episode was counted as the incident case, irrespective of previous or subsequent episodes of PUB.

Upper gastrointestinal endoscopy was performed in all patients within 24 hours of hospital admission. Only patients with PUB confirmed by endoscopy were prospectively followed-up for 30 days. After initial endoscopic examination, patients in whom endoscopic therapy had been performed were hospitalized. All patients received high-dose acid suppression therapy (pantoprazole or esomeprazole 80 mg intravenously as an initial bolus followed by 40 mg intravenously and/or oral 3 times *per day* for at least 48 hours, followed by 40 mg daily *per os*).

Prior to endoscopy, a written informed consent was obtained from all patients or their relatives, which included possible risks, benefits and treatment options during the procedure. In addition, a written informed consent was obtained from patients or their relatives before trial entry. The study was approved by the Ethics Committee of the hospital. Data were collected prospectively into a database, with patient details stored in a depersonalized manner to protect patient confidentiality.

Data collection

The following data were collected for each patient: demographic data, signs and characteristics of the bleeding episode, symptoms and history of ulcer or liver disease, coexisting illness, drug use, laboratory results, endoscopic diagnosis including the cause of bleeding, presence of fresh blood/clots or stigmata of recent hemorrhage, endoscopic intervention, medical treatment, rebleeding incidence, surgical therapy, duration of hospitalization and cause of death. Shock was defined as syncope or signs of shock upon physical examination, including systolic blood pressure <100 mm Hg or heart rate >100 beats/min.

Grading of overall health and comorbidity was performed according to the American Society of Anesthesiology (ASA) classification (grade 1, normal healthy patients; grade 2, mild systemic illness; grade 3, severe, but incapacitating systemic illness; and grade 4, life-threatening illness). Stigmata of recent hemorrhage were defined according to Forrest classification as follows: Forrest Ia, spurting bleeding; Forrest Ib, oozing bleeding; Forrest IIa, non-bleeding visible vessel; Forrest IIb, adherent clot; Forrest IIc, hematin on ulcer base; and Forrest III, clean ulcer base¹⁶. The size of ulcer was classified as <2 cm or ≥2 cm. The commonly used hemostatic procedures were epinephrine injections (1:10000 solution of epinephrine) and/or mechanical hemostasis with stainless steel hemoclips (Olympus, Japan) and/or thermocoagulation with a heater probe (Olympus, 7F, 20-30 joules).

Two biopsy specimens were obtained from the gastric antrum and body in all patients and the presence of *Helicobacter pylori* (*H. pylori*) infection was assessed by histopathologic examination of the specimens using hematoxylin-eosin (HE) stain. In all patients with gastric ulcers in whom recurrent bleeding was not observed, follow-up endoscopy was performed four to five days after initial hemostasis and biopsy specimens were ob-

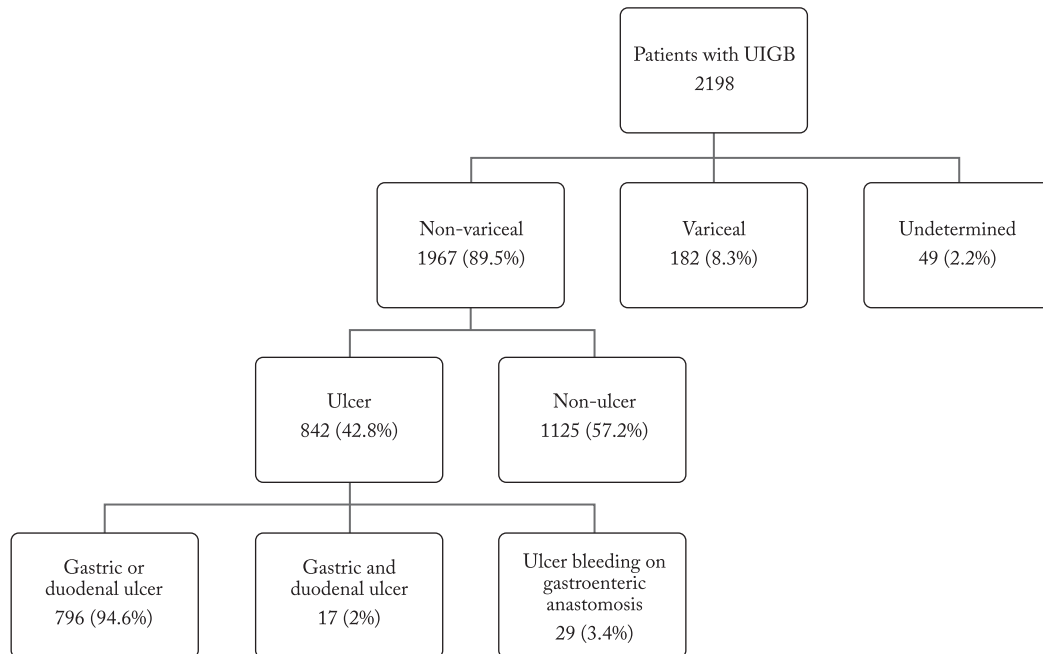


Fig. 1. Patients with upper gastrointestinal bleeding (UGIB) from 2008 to 2012.

tained from the margins and base of gastric ulcers to exclude malignancy. Follow-up endoscopy with histology was planned in all patients with gastric ulcers. In all patients with negative histology for *H. pylori* at index endoscopy, urea breath test (UBT) or follow-up endoscopy with histology was performed 2 weeks after proton pump inhibitor (PPI) treatment had been discontinued. Patients were considered positive for *H. pylori* infection in case of positive histology or positive UBT.

Clinical outcomes of PUB were analyzed according to the rebleeding rate, need for surgical intervention, need for blood transfusion, length of hospital stay, and 30-day mortality.

Rebleeding was defined as one or more signs of ongoing bleeding, including fresh hematemesis or melena, hematochezia, aspiration of fresh blood *via* nasogastric tube, instability of vital signs, and reduction of hemoglobin or hematocrit levels by more than 2 g/dL or 5%, respectively, over a 24-hour period after primary bleeding was stopped. Patients that had unsuccessful initial endoscopic treatment or more than two successful re-treatments underwent emergency surgery.

Statistics

All analyses were performed with the Statistica 11.0 (Statsoft, Inc., Tulsa, OK) for Windows statistical

package. The Mann-Whitney U-test and Kruskal-Wallis ANOVA test were used as nonparametric tests where appropriate, and a p-value <0.05 was considered significant. The predictive value of qualitative variables on mortality and rebleeding was studied in univariate analysis using Pearson χ^2 -test, when appropriate. Multivariate analysis was conducted using a forward elimination logistic regression model to identify a final set of variables independently associated with either mortality or rebleeding. A significance level $\alpha=0.05$ was used to retain variables in the multivariate model. All results were presented as odds ratios (ORs) with the associated 95% confidence intervals (95% CIs).

Results

From January 2008 to December 2012, 2198 patients with UGIB were analyzed; 89.5% of patients had non-variceal bleeding, 8.3% had variceal bleeding, and in 2.2% the source was not identified.

In the group of patients with non-variceal bleeding, 42.8% had bleeding ulcer, while 57.2% had non-ulcer bleeding (Mallory-Weiss tear, angiomata, Dieulafoy's lesion, malignancy, acute erosive gastropathy, reflux esophagitis, portal hypertensive gastropathy, arterial enteric fistula). In patients with bleeding ulcers,

Table 1. Clinical and endoscopic characteristics of patients at study entry

	n (%)
Age (yrs)	
<65	358 (45)
65-80	300 (37.7)
>80	138 (17.3)
Gender (male/female), n (%)	501 (62.9)/295 (37.1)
Hb level median (range), g/L	93.9 (26-182)
Findings at endoscopy	
Gastric ulcers	440 (55.3)
Duodenal ulcers	356 (44.7)
High-risk ulcers (Forrest Ia-IIb)	414 (52)
Low- risk ulcers (Forrest IIc-III)	382 (48)
Ulcer size, n (%)	
<2cm	696 (87.4)
≥2cm	100 (12.6)
Shock	77 (9.7)
<i>Helicobacter pylori</i>	220/531 (41.4)
Comorbidity (ASA class)	
ASA I	110 (13.9)
ASA II	225 (28.2)
ASA III-IV	461 (57.9)
Medication	
NSAIDs	225 (28.3)
Acetylsalicylic acid	162 (20.3)
Antiaggregation therapy	21 (2.6)
Anticoagulant therapy	46 (5.8)
Proton pump inhibitors or H2 blockers	73 (9.2)

Hb = hemoglobin; ASA = American Society of Anesthesiology; NSAIDs = nonsteroidal anti-inflammatory drugs

94.6% of cases were attributed to gastric or duodenal ulcers, 2% to both gastric and duodenal ulcers, and 3.4% to ulcer on previous gastroenteric anastomoses (Fig. 1).

The cumulative incidence of UGIB in the observed 5-year period was 126/100,000. In the group of 796 patients that were carefully followed-up, 55.3% had bleeding from gastric ulcers and 44.7% from duodenal ulcers. The mean patient age was 65.9 years and men

Table 2. Endoscopic therapy and clinical outcomes

	n (%)
Treatment	
Endoscopic therapy	465 (58.4)
Initial hemostasis	411 (51.6)
Types of initial hemostasis	
Epinephrine	164 (39.9)
Endoclips	81 (19.7)
Epinephrine + endoclips	142 (34.6)
Heater probe	17 (4.1%)
Heater probe + epinephrine	7 (1.7%)
Outcome	
Rebleeding	77 (9.7)
30-day mortality	41 (5.2)
Blood transfusion	394 (49.5)
Surgery	47 (5.9)
Median hospital stay (days, range)	6 (0-45)

had a higher incidence of bleeding (62.9% *vs.* 37.1%; $p < 0.001$). High risk ulcers (Forrest Ia-IIb) were verified in 52% of patients, most ulcers were >2 cm in diameter, 9.7% of patients presented with shock, and 57.9% of patients had moderate to severe comorbidities. When analyzed according to medication usage, 28.3% of patients with peptic ulcers had been taking non-steroidal anti-inflammatory drugs (NSAIDs), 20.3% acetylsalicylic acid, 2.6% anti-aggregation medication, 5.8% anti-coagulation therapy, and 9.2% gastroprotective medication (histamine 2 blockers or PPI). *H. pylori* testing was performed in 531 (66.7%) patients of which 220 (41.4%) tested positive. The presence of *H. pylori* infection was more common in patients with duodenal peptic ulcer (46.7% *vs.* 36.9%), which was statistically significant ($p < 0.023$) (Table 1).

Endoscopic treatment was performed in 456 (58.4%) patients; in 54.3% of cases hemostasis was achieved with hemoclips or with a combination of hemoclips and diluted epinephrine infiltration. Rebleeding occurred in 9.7% of patients (Table 2).

The risk of rebleeding was increased in patients with shock [OR 5.85 (CI 95% 3.01-11.37)], bleeding ulcer Forrest Ia type [OR 6.48 (CI 95% 3.12-13.48)] and ulcers >2 cm in diameter [OR 2.79 (CI 95% 1.49-5.20)] (Fig. 2).

Forty-seven (5.9%) patients were transferred to the Department of Surgery (5 due to successful endoscop-

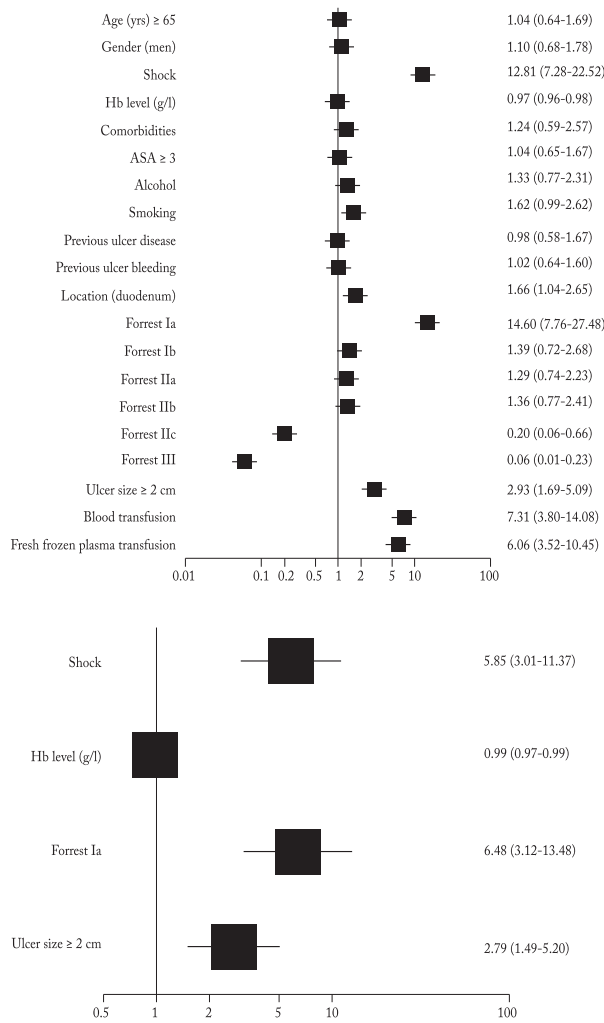


Fig. 2. Univariate and multivariate factors influencing rebleeding in 796 patients with bleeding peptic ulcer.

ic hemostasis, 1 due to perforation during the procedure, and 41 due to recurrent bleeding). Most of the transferred patients had bleeding from the posterior wall of the duodenum, posterior proximal third of the gastric corpus, and from the small gastric curvature. The most common surgical procedure performed was mechanical hemostasis (ligation) and gastric resection. The total 30-day mortality was 5.2%. The risk of lethal outcome was increased in patients with shock [OR 2.74 (CI 95% 1.19-6.33)], recurrent bleeding [OR 3.54 (CI 95% 1.59-7.88)], ulcers >2 cm in diameter [OR 3.08 (CI 95% 1.50-6.33)] and moderate to severe comorbidities (ASA ≥3) [OR 6.32 (CI 95% 2.38-16.7)] (Fig. 3).

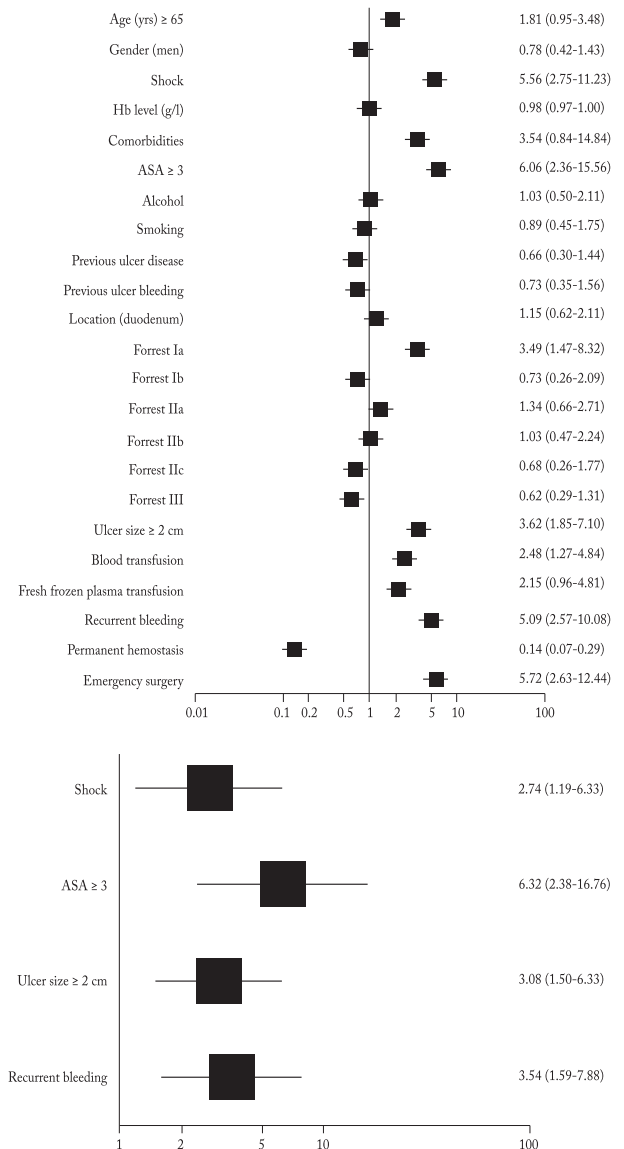


Fig. 3. Univariate and multivariate factors influencing mortality in 796 patients with bleeding peptic ulcer.

Only 1/10 patients died from bleeding out and half of them were treated with red blood cell transfusions. The median volume of red blood cell transfusion was 2.2 (1-6) units and the median hospital stay was 6 (1-45) days (Table 2).

Discussion

There has been a significant decline in the incidence of PUB and its complications since the introduction of PPIs and *H. pylori* eradication therapy. A

lower incidence was observed in Sweden from 1987 to 2004 in both men and women, and one study conducted in the Netherlands found a decline from 61/100,000 to 48/100,000 *per year* from 1993 to 2000¹⁷. In Germany and the United Kingdom, the incidence of PUB has remained unchanged, but the average patient age has increased^{18,19}. In the Zagreb County, Croatia, the incidence of UGIB and PUB did not significantly change from 2008 to 2012. This can be explained by the lower prevalence of *H. pylori* infection and increased use of drugs that affect the cytoprotective function of gastric mucosa (NSAIDs and acetylsalicylic acid), which has also been shown in other studies²⁰. The average patient age in this study was higher than 65 years. In one study, Van Leerdam found that 70% of patients with UGIB were older than 60 years and 40% had several life-threatening diseases⁴, and in another one Van Leerdam *et al.* report that about 50% of patients with PUB were taking NSAIDs and acetylsalicylic acid, with only 12% of them taking PPI as protection¹⁷. *H. pylori* infection was diagnosed in 40% of patients and was found more frequently in patients with bleeding duodenal ulcers. In one prospective study conducted in the Netherlands, *H. pylori* testing was performed in 65% of patients with 43% having positive findings, while a German study found that 56% of patients with PUB were *H. pylori* positive^{18,21}. Gralnek *et al.* found that PUB made up 28% to 59% of all UGIB. Half of the patients were categorized as high-risk ulcer patients (Forrest Ia, Ib, IIa and IIb)²². In a study by Bratanic *et al.*, around 30% of patients were described as high-risk²³. In our study, PUB represented about 40% of all non-variceal UGIB, and bleeding gastric ulcers were found more frequently than bleeding duodenal ulcers. Rebleeding after endoscopic treatment with endoclips or endoclips/diluted epinephrine occurred in 10% of patients and 5.9% of them required surgical intervention. The risk of recurrent bleeding was increased in patients with shock, actively bleeding ulcers, and ulcers larger than 2 cm in diameter. Our results are consistent with the results from other tertiary centers, and despite all endoscopic methods for hemostasis available, acute recurrent hemorrhage is still common, occurring in 10% to 28% of cases^{24,25}. We report a total 30-day mortality of 5.2%. Only 10% of patients died because of bleeding out, while others died from other comorbidities. Mortality was increased in patients with shock, recurrent bleeding ulcers larger than 2 cm in diameter, and moderate

to severe comorbidities (ASA ≥ 3). Almost 60% of patients with PUB presented with moderate to severe comorbidities (ASA III and IV). When considering other studies, Marmo *et al.* report a PUB mortality rate of 4% to 5% in one prospective study²⁶. Van Leerdam *et al.* showed that 40% of patients that died because of UGIB had one or several life-threatening comorbidities¹⁷. Marmo *et al.* showed that in the first 24 hours of hospitalization, less than 30% of all patients died²⁶. Villauneva *et al.* compared the efficacy of a restrictive transfusion strategy (target hemoglobin 7-9 g/dL) with that of a liberal transfusion strategy (target hemoglobin 9-11 g/dL) in patients with acute gastrointestinal bleeding, finding that the probability of survival at 6 weeks was higher in the restrictive-strategy group²⁷. This was also observed in a subgroup analysis of patients with PUB. Other authors also suggest better patient outcomes when the restrictive red blood cell transfusion strategy is used^{8,28-30}. In our study, half of the patients received red blood cell transfusions, with a median of 2.2 units.

The limitations of this study included diverse medical staff involved in endoscopic evaluation and treatment, resulting in inter-observer variability in endoscopic evaluation and treatment. Furthermore, this study had a short follow-up period of 30 days and was conducted in a tertiary center.

In conclusion, the incidence of UGIB and PUB remained unchanged in the observed period from 2008 to 2012, but we recorded an increase in the average age of PUB patients. Predictors of mortality in patients with PUB included shock, recurrent bleeding, ulcers larger than 2 cm in diameter, and moderate to severe comorbidities. Prevention of PUB, prompt intravascular volume replacement, early (≤ 24 hours) upper GI endoscopy, and a restrictive red blood cell transfusion strategy are important in the management of these patients.

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Sažetak

KRVARENJE IZ PEPTIČKOG VRIJEDA – ISKUSTVA TERCIJARNOG CENTRA:
EPIDEMIOLOGIJA, LIJEČENJE I PROGNOZA

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Cilj ove studije bio je prikazati epidemiološke, kliničke i endoskopske karakteristike akutnog krvarenja iz gornjeg probavnog sustava s naglaskom na krvarenje iz peptičkog vrieda. U studiju je bilo uključeno 2198 bolesnika koji su pregledani u hitnoj službi naše ustanove zbog akutnog krvarenja iz gornjeg probavnog sustava u razdoblju od siječnja 2009. do prosinca 2012. godine. Svim bolesnicima je učinjena hitna gastroskopija unutar 24 sata od prijma, a u 842 bolesnika kod kojih je dokazana peptička ulkusna bolest nastavljeno je kliničko praćenje. Kumulativna incidencija krvarenja je bila 126/100.000 u razdoblju od 5 godina. Dva od pet bolesnika su imali krvareći peptički vried; ukupno 440 (52,3%) bolesnika je imalo krvareći želučani vried, 356 (42,3%) duodenalni vried, 17 (2%) želučani i duodenalni vried, a 29 (3,5%) krvareći vried na gastroenteralnoj anastomozi. Srednja dob bolesnika je bila 65,9 godina. Većina bolesnika je uzimala lijekove koji suprimiraju citoprotektivne funkcije želučane i duodenalne sluznice (57%). Recidiv krvarenja zabilježen je u 77 (9,7%) bolesnika, a 47 (5,9%) je zahtijevalo kiruršku intervenciju. Smrtnost kroz 30 dana je bila 5,2%, a 10% bolesnika je umrlo zbog krvarenja i pratećih komorbiditeta. Krvarenje iz peptičkog vrieda je najčešći uzrok krvarenja iz gornjeg probavnog sustava, a obilježeno je značajnom stopom recidiva krvarenja i smrtnosti.

Ključne riječi: *Gastrointestinalno krvarenje – epidemiologija; Gastrointestinalno krvarenje – terapija; Peptički vried, krvarenje – epidemiologija; Peptički vried – terapija; Endoskopija, gastrointestinalna; Prognoza; Tercijarni zdravstveni centri; Hrvatska*