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Research Article

Bleeding Peptic Ulcer: Epidemiology, Treatment and Prognosis

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Keywords GI bleeding; Peptic ulcer bleeding; Gastric ulcer; Duodenal ulcer; Endoscopic treatment

Abbreviations UGIB: Upper Gastrointestinal Bleeding; PUB: Peptic Ulcer Bleeding; *H. Pylori*: Helicobacter Pylori; HE: Hematoxylin-Eosin Stain; UBT: Urea Breath Test; PPI: Proton Pump Inhibitor; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

Abstract

Aims: The aim of this study was to demonstrate epidemiological, clinical and endoscopic characteristics of acute Upper Gi Bleeding (UGIB) with a focus on Peptic Ulcer Bleeding (PUB).

Methods: This study included 2198 consecutive patients that were referred to our emergency department due to acute Upper Gi Bleeding (UGIB) from January 2008 to December 2012. All patients under went urgent upper GI endoscopies within 24 hours of admission, and 842 patients diagnosed with PUB were enrolled and prospectively followed.

Results: The cumulative incidence of UIGB was 126/100000 for a 5-year period. Two out of five patients had a bleeding peptic ulcer, of which 440 (52.3%) patients had a bleeding gastric ulcer, 356 (42.3%) had a bleeding duodenal ulcer, 17 (2%) had both bleeding gastric and duodenal ulcers and 29 (3.5%) patients had bleeding ulcers on gastroenteric anastomosis. PUB was more common in men. Average patient age was 65.9 years. The majority of patients with PUB were taking agents that attenuate the cytoprotective function of the gastric and duodenal mucosa (57%).Half of the patients received a red blood cell transfusion, with a median of 2.2 units. Re-bleeding occurred in 77(9.7%) patients and 47 (5.9%) required surgical intervention. The thirty-day morality was 5.2%, and 10% of patients died from uncontrolled bleeding and concomitant diseases.

Conclusion: PUB is the main cause of UGIB, characterized by a significant re-bleeding rate and mortality.

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 countries [1]. The incidence rate of UGIB varies from 48 to 160 cases per 100000 populations, with consistent reports of higher incidence among men and the elderly [2]. The most common cause of acute UGIB is non-variceal, where peptic ulcer bleeding (PUB) accounts for 28 to 59% of cases [2-4].

Endoscopy has become the standard of care in the diagnosis and treatment of UGIB. Most national and international guidelines recommend performing upper endoscopy within 24hours of presentation in patients with UGIB [5-7]. Despite major advances in diagnostic and therapeutic approaches, PUB remains a significant problem and an important cause of morbidity and mortality. Re-bleeding after initial hemostasis occurs in 10 to 30% of patients with PUB [8-11]. The reported PUB mortality rates in various countries across Europe range from 3.4% to 14%, and the reason for this difference remains unknown [12-15].

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.

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. Between January 2008 and December 2012, all consecutive patients presenting to the Emergency Internal Medicine Unit in the Clinical hospital center "Sestre milosrdnice" with UGIB (hematemesis, melena, hematochesia or blood admixture upon nasogastric aspiration) 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 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, written informed consent was obtained from all patients or their relatives, which included possible risks, benefits, and treatment options during the procedure. In addition 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 was 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 cause of bleeding, presence of fresh blood/clots or stigmata of recent hemorrhage, endoscopic intervention, medical treatment, re-bleeding 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 mmHg or heart rate>100 beats/min.

The grading of overall health and co-morbidity 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; grade 4, life-threatening illness).Stigmata of recent hemorrhage was defined according to the 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, Forrest III- clean ulcer base) [16]. The size of an ulcer was classified as <2 cm or 2≥ cm. 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 histopathological examination of the specimens using Hematoxylin-Eosin (HE) stain. In all patients with gastric ulcers in whom recurrent bleeding was not observed, control endoscopy was performed four to five days after initial hemostasis and biopsy specimens were obtained from the margins and base of gastric ulcers to exclude malignancy. Control 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 control endoscopy with histology was performed 2 weeks after proton pump inhibitor (PPI) treatment was 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 re-bleeding rate, need for surgical intervention, need for blood transfusion, length of hospital stay, and 30-day mortality.

Re-bleeding 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 2g/dL or 5% respectively over a 24-hour period after the primary bleeding was stopped. Patients that had unsuccessful initial endoscopic treatment or more than two successful re-treatments underwent emergency surgery.

Statistical Analysis

All analyses were performed with a statistical package [Statistica 11.0 (Statsoft, Inc., Tulsa, OK) for Windows]. The Mann-Whitney U-test and the 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 re-bleeding was studied in univariate analysis using Pearson chi-square 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 re-bleeding. A significance level α=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 a bleeding ulcer, while 57.2% had a non-ulcer bleeding (Mallory-Weis tear, angiomata, Dieulafoy's lesion, malignancy, acute erosive gastropathy, reflux oesophagitis, portal hypertensive gastropathy, arterial enteric fistula). In patients with bleeding ulcers, 94.6% of cases were attributed to gastric or duodenal ulcers, 2% from both gastric and duodenal ulcers, and 3.4%from an ulcer on previous gastroenteric anastomoses (Figure 1).

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

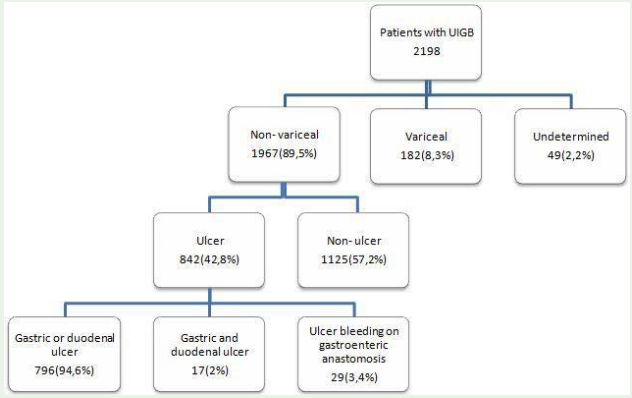

Figure 1: Patients with upper gastrointestinal bleeding (UGIB) from 2008 to 2012.

Table 1: Clinical and endoscopic characteristics of the patients at study entry n(%).

Age(y)	
<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)
H. pylori	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)

ASA, American Society of Anesthesiology, NSAIDs, non-steroidal anti-inflammatory drugs, H2, histamine 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% of patients had been taking gastro protective 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%) what was statistically significant (p<0.023) (Table 1).

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

Risk of re-bleeding was increased in patients with shock [OR 5,85 (CI 95% 3.01-11.37)], bleeding ulcer type Forrest Ia [OR 6.48 (CI 95% 3.12-13.48)] and ulcers >2 cm in diameter [OR 2.79(CI 95% 1.49-5.20)] (Figure 2).

Forty-seven patients (5.9%) were transferred to the Department of Surgery (5 due to successful endoscopic 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%. Risk of lethal outcome was increased in patients with shock [OR 2.74 (CI 95% 1.19-6.33)], reccurent bleeding [OR 3.54 (CI 95% 1.59-7.88)], ulcers >2cm 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)] (Figure 3).

Only 1/10 of patients died from bleed out and half of them were treated with red blood cell transfusions (Figure 4). The median volume of red blood cell transfusion was 2.2 (1-6) units and themedian hospital stay was 6 (1-45) days (Table 2).

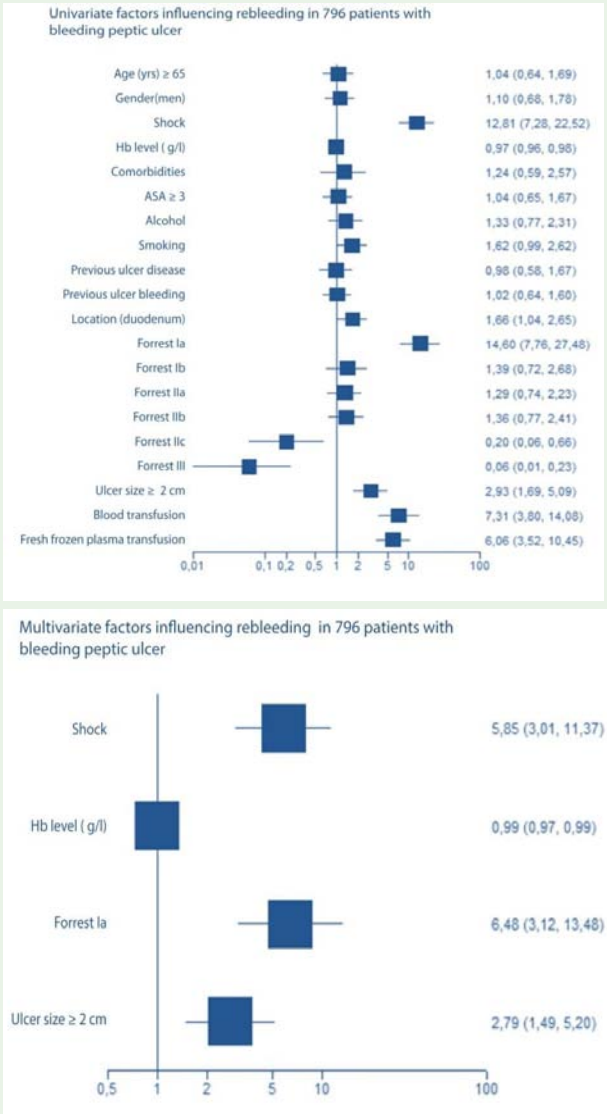

Figure 2: Univariate and multivariate factors influencing rebleeding in 796 patients with bleeding peptic ulcer.

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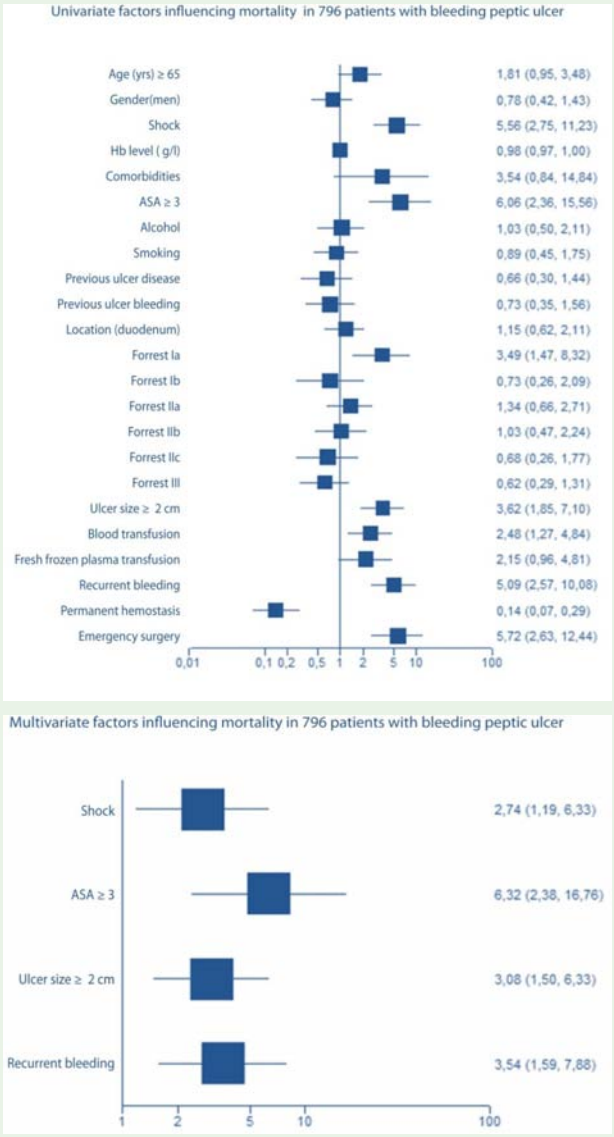

Figure 3: Univariate and multivariate factors influencing mortality in 796 patients with bleeding peptic ulcer.

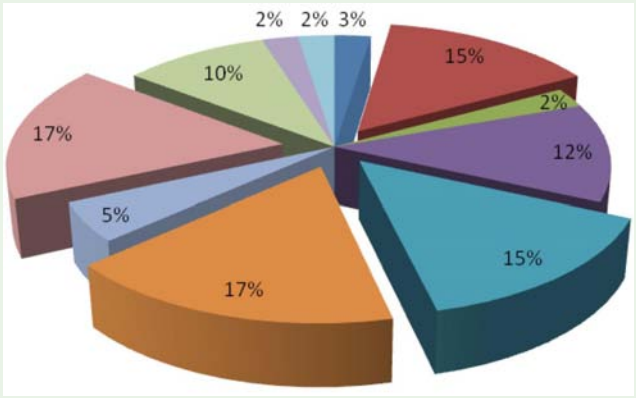

Figure 4: Causes of mortality in patients with peptic ulcer bleeding.

Table 2: Endoscopic therapy and clinical outcomes n(%).

Treatment	
Endoscopic therapy	465 (58.4)
Initial haemostasis411(51.6)	
Types of initial haemostasis	
Epinephrine	164 (39.9)
Endoclips	81 (19.7)
Epinephrine + endoclips	142 (34.6)
Heaterprobe	17 (4,1%)
Heaterprobe+ 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(day) (range)	6 (0-45)

Discussion

There has been a significant decline in the incidence of PUB and its complications following 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 Netherlands found a decline from 61/100,000 to 48/100,000 per year from 1993 to 2000 [17]. In Germany and the United Kingdom the incidence of PUB has remained unchanged, but the average patient age has increased [18,19]. In the county of Zagreb, 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 the gastric mucosa (NSAIDs and acetylsalicylic acid), which has also been shown in other studies [20]. The average patient age in this study was higher than 65 years. Van Leerdam found in one study that 70% of patients with UGIB were older than 60 years and 40% had several life-threatening diseases, and in another that about 50% of patients with PUB were taking NSAIDs and acetylsalicylic acid, with only 12% of them taking PPI as protection [4,17]. *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,IIb) [22]. In a study by Bratanic et al. around 30% of patients were described as high-risk [23]. In our study, PUB represented about 40% of all non-variceal UGIB, and bleeding gastric ulcers were found more frequently than bleeding duodenal ulcers. Re-bleeding after endoscopic treatment with endoclips or endoclips/diluted epinephrine occurred in 10% of patients and 5.9% of them required surgical intervention. Risk for recurrent bleeding was increased in patients with shock, actively bleeding ulcers, and ulcers larger than

2cm in diameter. Our results are in concurrence with results from other tertiary centers, and despite all available endoscopic methods for hemostasis, 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 bleed out, while others died from other comorbidities. Mortality was increased in patients with: shock, recurrent bleeding ulcers larger than 2cm 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. reported a PUB mortality rate of 4 to 5% in one prospective study [26]. Van Leerdam showed that 40% of patients that died because of UIGB had one or several life-threatening comorbidities. Marmo et al. showed that in the first 24 hours of hospitalization less than 30% of all patients died [17,26]. Villauneva et al. compared the efficacy of a restrictive transfusion strategy (target hemoglobin to 7-9 g/dL) with those 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 group [27]. 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.

Limitations of this study include a diverse medical staff that was 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.

Conclusion

In conclusion, the incidence of UGIB and PUB remained unchanged in the observed time period from 2008 to 2012, but we observed an increase in the average patient age with PUB. 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.

Acknowledgment

All authors made substantial contributions to all of the following: the conception and design of the study, acquisition of data, analysis and interpretation of data. All authors have made substantial contributions to drafting the article and revising it critically for important intellectual content. The study was designed by IB and SS. Data was acquired by IB, MN, AB, DK, SB, ZB, MZ, LSK and IB jr. IB analyzed the data, IB and SS wrote the manuscript. All authors have made substantial contributions to the final approval of the version to be submitted. The manuscript, including related data, figures and tables has not been previously published and is not under consideration elsewhere.

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