Upper gastrointestinal bleeding and factors affecting the rebleeding risk

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Abstract

Introduction: Identifying high risk patients is crucial to prevent rebleeding in UGIB. Early detection of patients who are at risk of rebleeding can be useful to reduce morbidity and mortality.

Aim: To summarize the risk factors of rebleeding in UGIB.

Method: Articles and studies were acquired from PubMed. Keywords used were: ‘rebleeding’, ‘upper gastrointestinal bleeding’, ‘risk factors’.

Result: Several studies have found that prognostic factors in UGIB may indicate a higher risk of rebleeding in UGIB. Those factors being shock at admission, PRC transfusion, low hemoglobin levels, low albumin levels, high creatinine levels, active bleeding at endoscopy, and need for endoscopic therapy. Scoring systems can also be useful to predict rebleeding, mainly GBS and Complete Rockall score.

Conclusion: Shock at admission, PRC trasnfusion, low hemoglobin levels, low albumin levels, high creatinine levels, active bleeding at endoscopy, and need for endoscopic therapy are risk factors of rebleeding in UGIB.

Keywords: Rebleeding; upper gastrointestinal bleeding; risk factor

1. Introduction

Upper gastrointestinal bleeding (UGIB) remains as one of the most common causes of hospitalisations[1], with an estimated incidence rate of 80 to 150 cases per 100,000 people annually worldwide[2]. Despite therapeutic advances in the treatment of UGIB including endsocopic hemostasis modalities and use of proton pump inhibitors (PPI)[3], incidence of rebleeding remains relatively high at 7-16% and increases mortality in UGIB patients[4]. Several studies have analysed various factors associated with increased risk of rebleeding in UGIB. The aim of this study is to summarize the risk factors of rebleeding in UGIB according to the current findings.

2. Materials and Methods

This is a literature review on the current knowledge and findings regarding UGIB and rebleeding. Literatures and articles were searched via PubMed. Keywords used were: 'rebleeding', 'upper gastrointestinal bleeding', 'risk factors'. Textbooks were also included for theoretical references in this review.

3. Result and Discussion

3.1. UGIB and Rebleeding

3.1.1 Definition

Upper gastrointestinal bleeding (UGIB) is defined as hemorrhage that occurs in the gastrointestinal tract proximal to the ligament of Treitz[2,5]. There is still no certain definition of rebleeding itself. Jiménez-Rosales et al. defined rebleeding as the presence of fresh hematemesis and/or melena associated with the development of shock or a reduction in the hemoglobin concentration of more than 2 g/dl over 24 hours[1], but other studies have mentioned different definitions of rebleeding. In a previous retrospective study by Lazăr, Ursoniu, and Goldiș, rebleeding was defined as the recurrence of active digestive hemorrhage (hematemesis, melena or hematochezia), hemodynamic instability, or a decrease in the hemoglobin level of more than 2 g/dL within 24 h of the first endoscopic procedure associated with the endoscopic visualization of active bleeding at the site of the previously treated lesion[3]. Nam et al. defined rebleeding as hematemesis, significant decreased in blood pressure (<80 mmHg or 25% decreased in baseline blood pressure), >20% increase in heart rate, >2 g/dL of hemoglobin decrease within 7 days after successful endoscopic therapy and had to be confirmed by second endoscopic examination[6]. In a guideline for nonvariceal upper gastrointestinal bleeding (NVUGIB) diagnosis and management, the European Society of Gastrointestinal Endoscopy (ESGE) recommended a definition for recurrent bleeding as bleeding following initial successful endoscopic hemostasis[7].

3.1.2 Epidemiology

The incidence of UGIB varies from 80 to 150 cases per 100,000 individuals annually[2]. UGIB contributes to 300,000 hospitalisations annually in the United States[5]. In the recent times, majority of UGIB patients are older and present with multiple comorbidities[3]. Rebleeding occurs in 10-20% of UGIB cases [1], but multiple studies have reported higher incidence rates of rebleeding. A retrospective analysis by Nam et al. showed that rebleeding occurred in 41 (20.7%) out of 198 patients[6]. In another retrospective study, Uysal and Acar stated that rebleeding occurred in 77 (32%) out of 241 patients[8].

3.1.3 Etiology and Pathogenesis

Peptic ulcer and variceal bleeding (which includes esophageal and gastric varices) are the most frequently found etiologies of UGIB. Peptic ulcer accounts for the most number of UGIB cases, but mortality rate is highest in UGIB caused by variceal bleeding and malignancies[4]. Data from the Center of Ulcer Research and Education (CURE) University of California, Los Angeles (UCLA) shows that the most common cause of severe UGIB is peptic ulcer, accounting for a total of 35.2%. Variceal bleeding, whether esophageal or gastic varices, was the second most frequent cause of severe UGIB at 21.9%. Other etiologies of severe UGIB include other lesions associated to portal hypertension (4.6%), esophagitis (4.6%), angioectasia (4%),

Mallory-Weiss tear (4%), Dieulafoy lesion (3.2%), neoplasm of the gastrointestinal tract (3.1%), epistaxis (2.2%), erosions (2.1%), and others.

Table 1. Causes of severe UGIB in the UCLA CURE database (n=968)

Cause	Frequency (%)
Peptic ulcer	35.2
Esophageal or gastric varices	21.9
Other portal hypertension-related lesions	4.6
Esophagitis	4.6
Angioectasia	4
Mallory-Weiss tear	4
Dieulafoy lesion	3.2
Upper gastrointestinal tract neoplasm	3.1
Epistaxis	2.2
Erosions	1.2
Others	8.8
No cause found	7.3

Peptic ulcers and erosive gastritis are caused by a decrease in the mucosal defense system due to Helicobacter pylori infection, use of Non-Steroidal Anti-Inflammatory Drugs (NSAID) or a combination of both. The majority of duodenal ulcers are caused by H. pylori infection which induce a diffuse antral gastritis. A number of patients chronically infected by H. pylori present with a gastritis where the inflammation predominantly involves the antrum portion of the stomach. This infection results in a decrease of somatostatin secretion in the antrum of the stomach which increases the secretion of gastrin by G cells of the stomach. This induces an increased amount of gastric acid secretion that usually cause duodenal ulcers. However most patient with H. pylori infection manifest as pan-gastritis which predisposes patients to gastric ulcer. Pan-gastritis involves both the fundus and antrum mucosa of the stomach, where somatostatin secretion is increased and gastrin secretion is reduced. Therefore, gastric ulcers are caused by damages to the mucosal defense system rather than hypersecretion of gastric acid[9].

NSAIDs disrupt the stomach's mucosal defense via inhibition of the Cyclooxygenase (COX) enzyme. There are two main forms of COX: COX-1 which is found in endothelium cells, gastric epithelium, platelets, and function constantly; and COX-2 which is only found in a number of tissues and mainly functions during inflammation. The mechanism of COX inhibition by NSAID, specifically gastrointestinal COX-1 inhibition reduces the synthesis of prostaglandin which reduces its protective function in the gastric mucosa and leads to gastritis or ulcers[9,10].

In variceal bleeding, varices formation is a result of portal hypertension due to liver cirrhosis. The portal vein system carries capillary blood from the esophagus, stomach, small intestine, large intestine, pancreas, gall bladder, and spleen to the liver. Under normal conditions, the portal vein system has a low resistance which can accommodate a large volume of blood flow. However, the rise of intrahepatic pressure in the condition of liver cirrhosis causes an increase in the portal vein pressure that exceeds the systemic blood pressure. This prevents blood from entering the liver via the portal vein system, which makes blood flow back to systemic circulation through portal-systemic circulations and forms varices. Varices that form in the distal

part of the esophagus and proximal part of the stomach causes esophageal varices or gastric varices. When these varices are ruptured, UGIB occurs.

Other nonvariceal causes of UGIB include erosive esophagitis, a condition caused by gastroesophageal reflux disease (GERD)[9]. Esophagitis occurs when there is a reflux of gastric acid and pepsin from the stomach back to the esophagus. This triggers an inflammation in the esophagus mucosa that can cause microscopic and macroscopic lesions, including erosions and ulcerations. UGIB can also be caused by malignancies of the gastrointestinal tract. Several malignancies in the upper gastrointestinal tract include squamous cell carcinoma of the esophagus, esophageal adenocarcinoma, and gastric adenocarcinoma. Although symptoms of gastric and esophageal carcinoma may differ, both can cause bleeding which manifests as UGIB[11].

3.1.4 Diagnosis

History taking should include history of previous gastrointestinal bleeding, coagulopathy, use of antithrombotics, and NSAIDs in patients suspected of UGIB. History of liver diseases including cirrhosis, hepatitis, and alcohol consumption should also be inquired to evaluate the possibility of variceal bleeding[5]. Symptoms of UGIB include hematemesis or vomiting of dark colored gastric contents resembling “coffee-grounds”, and melena which is black colored stools with a typical odor[2]. Other symptoms also include abdominal pain or tenderness, dizziness, and syncope[5]. Hematemesis indicates that the source of bleeding is from the upper gastrointestinal tract, whereas melena indicates that blood has been in the gastrointestinal tract for ≥14 hours to 3-5 days. The more proximal the site of bleeding, the more likely melena is to occur. Hematochezia, which is defecation of fresh red colored blood, usually indicates a lower source of gastrointestinal bleeding. However, UGIB may manifest as hematochezia when the bleeding is profuse and blood exits before forming melena. Hematochezia can be associated with hemodynamic instability and reduced hemoglobin levels in UGIB[11]. Physical examination in UGIB should evaluate hemodynamic stability, presence of abdominal pain or tenderness, and stool color. Laboratory tests include complete blood count, basic metabolic panels, coagulation tests, and liver function test. Hemoglobin and hematocrit levels should be monitored and repeated according to the patient’s severity and clinical condition. A blood urea nitrogen (BUN)/creatinine ratio >36 can differentiate UGIB from lower gastrointestinal bleeding (LGIB)[5].

The gold standard for upper gastrointestinal mucosa examination is upper endoscopy or esophagogastroduodenoscopy (EGD)[11]. Aside from diagnosis, EGD can also stratify high risk and low risk stigmata of peptic ulcer bleeding. The standard endoscopy classification for peptic ulcer bleeding is the Forrest classification.

Table 2. Forrest Classification

Forrest Classification	Characteristic
Forrest Ia	Active spurting bleeding
Forrest Ib	Active oozing bleeding
Forrest IIa	Nonbleeding visible vessel
Forrest IIb	Adherent clot
Forrest IIc	Flat pigmented spot
Forrest III	Clean base ulcer

Several scoring systems have been constructed for risk stratification in UGIB patients which are the Glasgow-Blatchford Score (GBS), Rockall score, and AIMS65. Of these scoring systems, ESGE recommends the use of GBS in UGIB patients for risk stratification[7].

Table 3. Glasgow-Blatchford Score, high risk [≥6]/low risk [<6]

GBS	0	1	2	3	4	6
BUN (mg/dL)	<18,2		≥18,2 - <22,4	≥22,4 - <28	≥28 - <70	≥70
Hemoglobin, male (g/dL)	≥13	≥12 - <13		≥10 - <12		<10
Hemoglobin, female (g/dL)	≥12	≥10 - <12				<10
Systolic blood pressure(mmHg)	≥110	≥100 – 109	≥90 – 99	<90		
Other markers		Heart rate>100 bpm, melena	Syncope, liver disease, heart failure			

Table 4. AIMS65 scoring system, high risk [≥3]/low risk [<3]

AIMS65	Score
Albumin <3 g/dL	1
International Normalized Ratio (INR) >1,5	1
Altered mental status	1
Systolic blood pressure <90 mmHg	1
Age >65 years old	1

Table 5. Complete Rockall Score

Rockall Score	0	1	2	3
Age	<60	60 – 79	≥80	
Heart rate (bpm)	<100	≥100		
Systolic blood pressure(mmHg)	≥100	≥100	<100	
Comorbidity	None		Ischemic heart disease, heart failure, other major comorbidities	Kidney or liver failure, disseminated malignancy
Diagnosis	Mallory-Weiss or no lesion and no stigmata	Other diagnosis	Malignant lesion	
Stigmata of bleeding	No stigmata or dark spot ulcer		Blood in upper gastrointestinal tract, adherent clot, visible vessel/spurting	

3.1.5 Management

Patients with hemodynamic instability should receive fluid resuscitation using crystalloid fluids in order to correct hypovolemia, restore tissue perfusion, and prevent multiorgan failure. Packed red cell (PRC)

transfusion should be given when hemoglobin levels are ≤7 g/dL for patients without history of cardiovascular disease, and ≤8 g/dL for patients with a history of cardiovascular disease. UGIB patients should be given high dose PPI immediately to decrease the prevalence of high risk stigmata bleeding and reduce the need for endoscopic therapy. After initial resuscitation and stabilization, early endoscopy (≤24 hours from patient presentation) is recommended in patients with acute UGIB.

Endoscopic hemostasis is superior compared to pharmacotherapy alone in peptic ulcer bleeding. Endoscopic therapy include injection, thermal, and/or mechanical modalities. Injection using epinephrine is effective in achieving initial hemostasis, but compared to other monotherapy or combination therapy, epinephrine injection is inferior in preventing rebleeding. Therefore, epinephrine injection should only be used as a combination therapy with a second endoscopic modality for peptic ulcer treatment[7].

Standard management of variceal bleeding include vasoconstrictor administration and endoscopic therapy. The three recommended intravenous vasoconstrictor agents are terlipressin, somatostatin, and octreotide. Intravenous vasoconstrictor decreases portal vein pressure by reducing blood flow to the portal vein system, and should be given immediately and maintained for 2-5 days. Following endoscopic examination, a combination therapy of intravenous vasoconstrictor and endoscopic variceal ligation (EVL) is recommended as standard therapy. In cases of standard therapy failure, transjugular intrahepatic portosystemic shunt (TIPS) can be performed by connecting the hypertensive portal vein to a normotensive systemic vein (inferior vena cava) to normalize portal vein pressure[12].

3.2. Risk Factors Associated with Rebleeding in UGIB

3.2.1 Risk Factors

A number of studies have found possible risk factors related to rebleeding in UGIB. In a prospective cohort study with a total of five hundred and seven patients with UGIB, Jiménez-Rosales et al. analysed multiple factors that were possibly related to rebleeding. Univariate analysis showed that low systolic blood pressure, history of cirrhosis, tachycardia, high creatinine levels, low hemoglobin levels, low albumin levels, need for endoscopic therapy, and number of PRC units transfused were related to rebleeding. A multivariate analysis was also performed using variables that were significant in the univariate analysis. The results show that tachycardia and high creatinine levels were independent risk factors of rebleeding in UGIB, whilst albumin was an independent protective factor from rebleeding[1]. Similarly, in a retrospective study by Lazăr, Ursoniu, and Goldiş which consists of one thousand five hundred and eighty one NVUGIB patients, presence of hemodynamic instability or shock (systolic blood pressure <100 mmHg and/or pulse rate >100 beats per minute) at admission were significantly related to rebleeding. Multivariate analysis also showed that Rockall score, need for endoscopic therapy, number of blood transfusions, and sepsis increased the risk of rebleeding[3]. In a large meta-analysis study that analysed factors associated with rebleeding in peptic ulcer bleeding, hemodynamic instability was an independent risk factor for rebleeding. The variable was analysed in 13 out of 14 studies and was significant in 9 of them. Low hemoglobin levels and transfusion were also independent risk factors, which were significant in 2 out of 10 studies and 2 of 6 studies respectively. Active bleeding during endoscopy was also found significant in 6 of 12 studies[13]. According to a retrospective observational study by Uysal and Acar which analysed two hundred and forty one UGIB patients, high urea levels, low hematocrit levels, positive H. pylori test, and PRC transfusion were significantly related to rebleeding in UGIB[8]. A systematic review and meta-analysis study examined the association of hemodynamic instability with poor prognosis in acute gastrointestinal bleeding. The results show that hemodynamic instability was associated with a fourfold increase of rebleeding UGIB[14].

Table 6. Risk factors associated with rebleeding according to studies

Study	Risk Factor										
	Shock	Transfusion	Low Hgb	Low Hct	Low Alb	High Cr	High BUN	Hp	Endoscopy	Comorbidity	Other
(1)	✓	✓	✓		✓	✓	-	-	Need for therapy	Cirrhosis	
(3)	✓	✓	-		-	-	-	-	Need for therapy	Sepsis	-
(13)	✓	✓	✓		-	-	-	-	Active bleeding	-	-
(8)	-	✓	-	✓	-	-	✓	✓	-	-	-
(14)	✓	-	-	-	-	-	-	-	-	-	-

Hgb = hemoglobin, Hct = hematocrit, Alb = albumin, Cr = creatinine, BUN = Blood Urea Nitrogen, Hp = H. pylori

Hemodynamic instability or shock at admission is a prognostic factor in UGIB, where presence of shock at admission indicates a worse prognosis. Therefore, many studies have shown that shock at admission is significantly associated with rebleeding in UGIB. Low hemoglobin levels are also a similar prognostic factor in UGIB. However, a cut-off value for hemoglobin levels to predict rebleeding have not been determined. This suggests that PRC transfusion might be more useful to predict rebleeding as transfusion is a surrogate marker for low hemoglobin levels, usually below 7g/dL to 9 g/dL[13]. Other prognostic laboratory markers include high creatinine levels and low albumin levels which indicates a recent bleeding or presence of a severe comorbidity[1]. Endoscopic results such as active bleeding at endoscopy or need for therapy has also been associated with rebleeding in UGIB by several studies[1,3,13].

3.2.2 Scoring systems

Several studies also analysed the role of scoring systems for predicting rebleeding in UGIB. The Complete Rockall score is designed to combine information from initial assessment, clinical assessment, and endoscopic examination to stratify the risk in UGIB patients. According to a study by Bozkurt et al., UGIB patients with a Rockall score of 4 and 5 have significantly higher rate of mortality and rebleeding[15]. The study by Lazăr, Ursoniu, and Goldiş also showed that Rockall score was an independent risk factor for rebleeding in UGIB[3]. In a retrospective study by Uysal and Acar, analysis of rebleeding risk factors also included the GBS and AIMS65 scoring systems. Higher scores of both GBS and AIMS65 were associated with a higher risk of rebleeding in UGIB. Of the 2 scoring systems however, GBS showed a better performance and higher sensitivity in predicting rebleeding[8]. A cross-sectional observational study that assessed the performance of GBS showed that it had high sensitivity and specificity to predict rebleeding in UGIB. Whether variceal or non-variceal UGIB, GBS was shown to be a useful stratification system and a triage tool[16]. However, another study stated that Rockall score is superior compared to GBS regarding rebleeding prediction. The results of a prospective study by Tuncer et al. shows that Complete Rockall score had the highest effectiveness in predicting rebleeding in UGIB compared to GBS and Pre-endoscopic Rockall score (Complete Rockall score without endoscopic variables)[17]. This suggests that GBS might be more useful for initial risk stratification, whereas Complete Rockall score would be used for patients who have undergone endoscopic examination.

4. Conclusion

Presence of shock at admission, PRC trasnfusion, low hemoglobin levels, low albumin levels, high creatinine levels, active bleeding at endoscopy, and need for endoscopic therapy are risk factors of rebleeding

in UGIB. Other factors associated with rebleeding are low hematocrit, high urea levels, positive H. pylori test, and presence of comorbidities such as cirrhosis and sepsis. Scoring systems for risk stratification, specifically Complete Rockall score and GBS might also be useful for risk stratification and rebleeding prediction.

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