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Comorbidity and risk of gastrointestinal bleeding

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Abstract
This analysis focuses on the acute GIT bleeding. It is one of the most urgent conditions in gastroenterological practice, with a total mortality rate of about 10%. It can present itself as bleeding from the upper and lower gastrointestinal tract. There are risk prognostic scales to assess the chance in the 30-day adverse risk events (e. g., mortality, rebleeding, and surgical intervention): Glasgow-Blatchford Bleeding Score, Rockall Score, AIMS65, Charlson Comorbidity Index CCI.
The Charlson Comorbidity Index is a method for categorizing a patient's comorbidities and predicting long-term mortality. A point system (from 0 to 6 points) is used for each category of comorbidity. It predicts in percentages the probability of whether or not the patient will survive in the next 10 years.
A study was conducted, based on existing literature, on the relationship between comorbidity, risk of GI bleeding, and long-term prognosis.
Comorbidities have been found to influence bleeding risks and long-term prognosis, but the Charlson index is unreliable and cannot be used alone as a predictor of bleeding outcome and its complications (conversion to surgery, persistent bleeding, and hemotransfusion).

Keywords: gastrointestinal bleeding, comorbidity, charlson comorbidity index, long-term prognosis and mortality

Introduction

Bleeding from the gastrointestinal tract is defined as bleeding from the upper GIT (above the ligamentum duodenum) and from the lower GIT (below the ligamentum Treitzi). Bleeding from the upper GIT is divided into variceal and nonvariceal. Acute bleeding is the most common emergency condition in gastroenterology practice, with an overall lethality of about 10%. Gastrointestinal bleeding may present itself with melena, hematochezia, or hematemesis. There are risk prediction scales to assess the risk of 30-day adverse events (mortality, rebleeding and surgical intervention): Glasgow - Blatchford Bleeding Score, Rockall Score, AIMS65, Charlson Comorbiditi index CCI Glasgow-Blatchford Bleeding score (Table 1) AIMS65 Index (Table 2).

The Charlson Comorbidity Index is a method for categorizing a patient's comorbidities and predicting long-term mortality. A scoring system (0 to 6 points) is used for each comorbidity category. It predicts in percentages the probability of whether or not the patient will survive into the next 10 years. For the calculation of the index it’s used (Table 3 and Table 4).

In Charlson's idex, patients are scored in percentages, with: 0 points give a positive forecast for the next 10 years in 98% of the cases (Table 5).

Globally, there is a growing ageing population with multiple co-morbidities, both acute and chronic.

Chronic Kidney Disease

Chronic kidney disease is a risk factor for gastrointestinal bleeding as it is associated with an increased risk of gastritis, peptic ulcer disease and angiodysplasia. Patients with gastrointestinal bleeding and comorbid CKD have a worse long-term prognosis than those with normal renal function and show a higher mortality rate than the general population. The risk of mortality increases with the progression of the underlying disease. The pathophysiology of GIT bleeding in these patients is multifactorial: uremic platelet dysfunction, drug-induced, ulcer disease, vascular malformations. Patients on extracorporeal dialysis are on anticoagulant and antiaggregant therapy which is a risk factor. The most common causes of upper GIT bleeding are ulcer disease, erosive gastritis or esophagitis, and vascular malformations. According to a study in which 727 patients participated, 60 of them had CKD and 10 of them were on hemodialysis (1. Evidence-based Review of Gastrointestinal Bleeding in the Chronic Kidney Disease Patient: Richard S. Kalman* and Marcos C. Pedrosa† *Section of Gastroenterology, Department of Medicine, Boston University Medical Center, Boston, Massachusetts, and †Section of Gastroenterology, Department of Medicine, VA Boston Healthcare System, Boston, Massachusetts) From the performed endoscopic studies, it was found that the most common cause of bleeding in CKD patients was ulcer disease (37%- gastric ulcer, 23%- duodenal ulcer). Angioectasias was the next most common cause of upper GIT bleeding (13%). This compares with an incidence of 1.3% in patients with normal renal function. Bleeding from esophageal varices was reported as a rare complication. Esophageal varices may develop as a complication in patients with a centripetal venous dialysis catheter as a result of occlusion of the vena cava superior and formation of collaterals. These "downhill" varices are localized in the proximal esophagus and are a complication of dialysis access. These patients are at greater risk of rebleeding within 6 weeks. Angiodysplasias is the most common cause of recurrent lower GIT bleeding in hemodialysis patients. Angiodysplasias is most commonly localized in the cecum and colonic ascens. The incidence of anemia in patients with CKD is twice that of the general population. Associated with underlying disease, decreased erythropoietin synthesis and low serum iron levels. Uremia causes impaired platelet

glycoprotein GPIIb/IIIa function and disturbances in prostaglandin and arachidonic acid metabolism that compromise platelet adhesion and aggregation. Increased platelet dysfunction results in a higher risk of GIT bleeding. There is a high risk in patients on peritoneal dialysis. A study on the relationship between the risk of GIT bleeding and eGFR and ACR (albumin - to - creatinine ratio) levels has been conducted. An eGFR of 30-59 ml/min per 1.73 m2 is associated with a 50% higher risk of bleeding and an eGFR,30 ml/min per 1.73 m2 is associated with a seven times higher risk. (2. Clinical Characteristics and Risk Factors for Rebleeding in Patients with Obscure Gastrointestinal Bleeding: Yuki Baba, Seiji Kawano, Yoshiyasu Kono, Toshihiro Inokuchi, Hiromitsu Kanzaki, Masaya Iwamuro, Keita Harada, Sakiko Hiraoka, Yoshiro Kawahara and Hiroyuki Okada)

In patients with CKD, the positive prognosis is worse. The Rockall risk prognostic score itself uses renal failure as a predictor of mortality. The risk of rebleeding is significantly higher in patients with ESRD compared to patients with CKD and patients with normal renal function.

An observational cohort study conducted in Taiwan: End stage renal disease (ESRD) patients receiving regular hemodialysis, CKD patients without dialysis and controls without renal impairment. As these subjects in the groups were matched for age, sex and comorbidity. As an observed outcome, CKD patients on dialysis had a higher incidence rate of lower GIT bleeding compared to CKD patients not on dialysis. In addition, CKD patients on dialysis also had a higher incidence of angiodysplasia as a source of bleeding compared to CKD patients without dialysis and control subjects.(3. Hemodialysis Increases the Risk of Lower Gastrointestinal Bleeding and Angiodysplasia Bleeding: A Nationwide Population Study)

Diabetes

Diabetes is one of the most common diseases with an ever-increasing prevalence. Diabetic ketoacidosis is an acute-onset complication of uncontrolled diabetes requiring hospitalization. It can present itself with a spectrum of gastrointestinal syndromes such as abdominal pain, nausea and vomiting. It is often a prerequisite for gastrointestinal bleeding.

Oxford published a study (4. Predictors of acute gastrointestinal bleeding in diabetic ketoacidosis: a retrospective observational study in minority population (Gastroenterol Rep (Oxf). which examined the incidence of gastrointestinal bleeding, associated risk factors and prognosis in patients with diabetic ketoacidosis. A retrospective review of all patients admitted from 01.2010 to 12.2015 was performed. The selected patients were divided into two groups based on the presence or absence of gastrointestinal bleeding. The second group of patients was divided into two subgroups: with occult and with acute bleeding. The incidence of those with acute bleeding was 10.2% of the total number of patients with DKA, of whom 9.4% had upper GIT bleeding. Gender and ethnicity were also found to have no significant role in the occurrence of GIT bleeding. From the endoscopic examinations performed on the patients with GIT bleeding, lesions of the esophagus, erosive gastritis and erosive bulbitis were objectified as findings.

Fraigel's study concluded that the risk of GIT bleeding is related to serum glucose and creatinine levels. Also the need for blood transfusion, higher number of hospitalizations and increased mortality were found in patients with DKA and GIT bleeding.

Liver cirrhosis

Cirrhosis of the liver is a diffuse disease characterized by the simultaneous presence of fibrosis, regenerative nodules and a disturbance in the architectonics of the liver. Irreversible liver damage leading to liver failure and circulatory disturbance. Intrahepatic vascular remodelling and formation of intrahepatic shunts occurs, leading to an increase in portal pressure. Portal hypertension is an expression of a violation in the ratio of the pressure in the portal vein and the pressure in the hepatic veins. The gradient of hepatic venous pressure correlates with the risk of bleeding from esophageal varices. With values >12mmHg there is a significant risk of bleeding, with HVPG >16mmHg there is a lethal outcome and with HVPG >20mmHg a high risk of uncontrollable bleeding within five days or of recurrent variceal bleeding and mortality. Variceal bleeding in patients with liver cirrhosis has a high incidence and is at high risk of mortality and morbidity.

Upper gastrointestinal bleeding in patients with liver cirrhosis is most commonly associated with gastroesophageal varices and portal hypertensive gastropathy. Other causes are gastric and duodenal ulcer, Mallory - Weiss and GAVE s-m. A study in Washington included 40 patients with liver cirrhosis: 70% had gastroesophageal varices diagnosed on fibrogastroscopy, with 50% having variceal bleeding (28 patients had gastroesophageal varices, 20 of these had variceal bleeding, 12 of the patients without established varices bled from other lesions) (6. Upper gastrointestinal bleeding in patients with liver cirrhosis: Olajide O. Odelowo MD., Duane T. Smoot MD, Kyungsook Kim, PhD. Washington, D.C)

Another source of bleeding in liver cirrhosis is portal hypertensive gastropathy. The incidence and severity of PHG is directly related to the severity of portal hypertension including HVPG, the severity of liver cirrhosis (Child - Pugh), the duration of disease and the presence and size of esophageal varices. PHG is diagnosed by a characteristic endoscopic finding: mosaic-like gastric mucosa with red punctate lesions, red or red-brown spots. In PHG, acute and chronic GIT curdling is observed. The main risk factors for bleeding are the duration, extent and severity of PHG. Over 90% of acute bleeding occurs in severe PHG. Haemodynamic changes in portal hypertension lead to hyperdynamic congestion, which is a prerequisite for the release of anti-inflammatory mediators, growth factors are inhibited, making the gastric mucosa more susceptible to injury. Reduced perfusion is a prerequisite for the formation of erosions and ulcerative defects. The risk of GIT bleeding increases.

From a study in which 222 patients diagnosed with liver cirrhosis and portal hypertension participated, 48 of them with PHG. Acute bleeding from PHG was observed in 9 patients and chronic bleeding in 7 patients (Merli *et al* 2004d). From another study (Primignani *et al*, 2000d) involving 373 patients with ductal cirrhosis, 299 of them with PHG. Acute bleeding from PHG was observed in 8 of them and chronic bleeding in 34 patients. Kimura *et al* in 2014 followed up 297 patients with liver transplantation, with only 2 bleeding from PHG three months after transplantation (Mihajlo Gjeorgjievski and Mitchell S Cappell).

Gastric and duodenal ulcers are another cause of GIT bleeding in patients with liver cirrhosis. With an incidence ranging from 4.3 - 49%. In patients with liver cirrhosis, the incidence of peptic ulcers is higher due to disturbance in microcirculation of gastric mucosa caused by portal gastropathy and impaired defense mechanisms. According to a study in patients with liver cirrhosis conducted eradication against Helicobacter pylori, recurrence of duodenal ulcer was observed in 58% of cases. According to which, it is clear that risk factors for recurrence of peptic ulcer are severity of liver injury and presence of variceal bleeding (7. Management of portal hypertensive gastropathy and other bleeding: Woo Jin Chung Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea).

Cancer

In 2013, an article was published in the United European Gastroenterology Journal which researches the causes of gastrointestinal bleeding in the cancer population and long-term prognosis. 324 patients with suspected bleeding participated, and it was confirmed endoscopically in 147 of them. One hundred and four patients had metastases, 38 had tumor with regional invasion, and five were unstaged. There were no patients with early cancer.

As a result of the study, it was found that the most common cause of GIT bleeding was tumor formation, followed by varices, peptic ulcer, gastroduodenal erosions, angioectasias and metastasis. Patients were divided into two groups, one with primary focus localized in the gastrointestinal tract, the other with neoplasia outside the GIT. In the first group, in 84.5% of cases the source of bleeding was the tumor formation, and in 6.3% it was peptic ulcer. In patients with tumor formation localized outside the GIT, the most common cause was peptic ulcer (23.6%), gastroduodenal erosions (16.4%), varices (14.5%), and metastasis (10%).

Seventeen of the patients experienced rebleeding within 30 days. Comparisons were made by sex, bleeding activity, bleeding source, and chemotherapy administered for the risk of rebleeding within 30 days and the risk of lethality. A trend of increasing risk of rebleeding was observed. Etiology, endoscopic management and mortality of upper gastrointestinal bleeding in patients with cancer: Fauze Maluf-Filho, Bruno da Costa Martins, Marcelo Simas de Lima, Daniel Valdivia Leonardo, Felipe Alves Retes, Fa´bio Shiguehissa Kawaguti, Cezar Fabiano Manabu Sato, Fa´bio Yuji Hondo, Adriana Vaz Safatle-Ribeiro and Ulysses Ribeiro Jr.

Upper GIT bleeding in cancer patients is associated with high mortality despite timely endoscopic treatment. The role of endoscopic examination is limited in patients with advanced disease. It helps to identify the source of bleeding, but in patients with bleeding from the tumor formation, endoscopic treatment does not have a good therapeutic response and does not improve long-term prognosis.

According to a study that aimed to determine risk predictors for uncontrolled bleeding, conversion to surgery, and lethality in the setting of a properly conducted diagnostic and therapeutic process for gastrointestinal hemorrhage. To determine the role of comorbidities using the Charlson comorbidity index. Patients participating in the study were divided into three groups according to their CCI score: Group below 2 points - 52 patients (13.26%), group between 2 and 4 points - 101 patients (25.76%) and group above 4 points - 239 patients (60.97%). (Dissertation of Dr. N. Tsonev. "Gastrointestinal bleeding.) Table 6

Conclusion

As a result, a higher number of patients with conversion to surgery and uncontrolled bleeding, lethality, and need for hemotransfusion were reported in the group of patients with CCI greater than 2 points. Which makes comorbidity in elderly patients a significant predictive factor for a complicated course of CCI bleeding.

After a statistical test of the Charlson index, it was concluded to be unreliable for surviving conversion to surgery, persistent bleeding and haemotransfusion.

The Charlson Comorbidity Index uses age and comorbidity as predictors of long-term prognosis. It is clear from the review that comorbidities influence bleeding risk and long-term prognosis. But CCI cannot be used alone as a predictor of bleeding or to predict bleeding-related risks.

Table 1

Scoring systems	Clinical Factor	result
Modified Glasgow Blatchford	Pulse, beats per minute	
	>100	1
	Systolic blood pressure, mm Hg	
	100-109	1
	90-99	2
	<90	3
	Urea mmol/l	
	>6.5 to <8	2
	≥8 и <10	3
	≥10 и <25	4
	≥25	6
	Haemoglobin (men), g/l	
	120≤ <130	1
	100≤ <120	3
	<100	6
	Haemoglobin (women), g/l	
	100≤ <120	1
	<100	6
Full Glasgow score (includes comorbid factors)	Chronic disease/Severe comorbidities	
	Liver disease	2
	Heart failure	2
	Melena on admission	1
	Syncope on admission	2

Table 2

Risk Factor	Evaluation
Albumin < 30 ml/l	1
INR>1.5	1
Mental status	1
Systolic pressure <90mmHG	1
Age 65+.	1
Maximum Rating	5

Table 3

Age	points
Under 50 years	0 points
Between 50 -59 years	1 point
Between 60-69 years	2 points
Between 70-79 years	3 points
Over 80 years	4 points

Table 4

Comorbidity	Points
Myocardial infarction	1p.
Chronic congestive heart failure	1p.
Peripheral vascular disease	1p.
Cerebrovascular disease	1p.
Dementia	1p.
Chronic obstructive pulmonary disease	1p.
Ulcerative history	1p.
Liver disease - two-factor criterion without complication mild liver disease moderate to severe (cirrhosis)	 1p. 1p. 3p.
Diabetes - a two-factor criterion without complication with complications	 1p. 2p.
Hemiplegia	2p.
Chronic renal failure	2p.
Tumor - two-factor criteria: Located at metastasized	 2p. 6p.
Leukaemia	2p.
Lymphoma	2p.
Spin	6p.

Table 5

1 point	96%
2 points	90%
3 points	77%
4 points	53%
5 points	21%
6 points	2%

Table 6

CCI	Total	Recurrent bleeding	Persistent bleeding	Conversion to surgery	Letalite	Hemotransfusions
Group <2	52	3	3	5	0	5
Group 2-4	101	6	4	6	2	11
Group over 4	239	30	6	25	7	43
Total	392	39	13	36	9	59

References

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