—Review—

Risk Factors for Bleeding Esophagogastric Varices

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Abstract

Bleeding from gastric varices (GVs) is generally considered more severe than that from esophageal varices (EVs) but occurs less frequently. We review the risk factors for bleeding EVs and GVs. GVs were divided into 2 groups: cardiac varices (CVs, Lg-c) and fundal varices (FVs), i.e., varices involving the fundus alone (Lg-f) or varices involving both the cardia and fundus (Lg-cf). Elevated pressure in the portal vein is a risk factor for bleeding EVs. The portal pressure in patients with GVs and a gastrorenal shunt is lower than that in patients with EVs. The large size of varices is a risk factor for bleeding EVs. Red color signs are elevated red areas that are important for predicting the risk of variceal bleeding, and red wale markings, dilated venules oriented longitudinally on the mucosal surface, have been considered to be the sign with the highest risk. Red color signs are rare in FVs, possibly because of the pronounced thickness of the mucosal layer. Bleeding EVs are not associated with use of antiulcer drugs or nonsteroidal anti-inflammatory drugs (NSAIDs). Although, in patients with bleeding GVs, "occasional" use of an oral NSAID is an important step leading to variceal hemorrhage, especially from FVs, even if the mucosa is protected by antiulcer drugs. Constipation, vomiting, severe coughing, and excessive consumption of alcohol may precipitate rupture of EVs.
(J Nippon Med Sch 2013; 80: 252–259)

Key words: esophageal varices, gastric varices, bleeding, surgery

Introduction

Portal hypertension is a clinical syndrome triggered by a pathological increase in portal vein pressure due to various causes, liver cirrhosis being the most common. Bleeding from esophageal varices (EVs) or gastric varices (GVs) is a consequence of portal hypertension. Bleeding from GVs is generally considered more severe than that from EVs[1] but occurs less frequently[2–5]. In this paper, we review the risk factors for bleeding EVs and GVs.

Abbreviations: esophageal varices (EVs), gastric varices (GVs), cardiac varices (CVs), fundal varices (FVs), nonsteroidal anti-inflammatory drugs (NSAIDs), hepatic venous pressure gradient (HVPG), balloon-occluded retrograde transvenous obliteration (B-RTO), partial splenic embolization (PSE)

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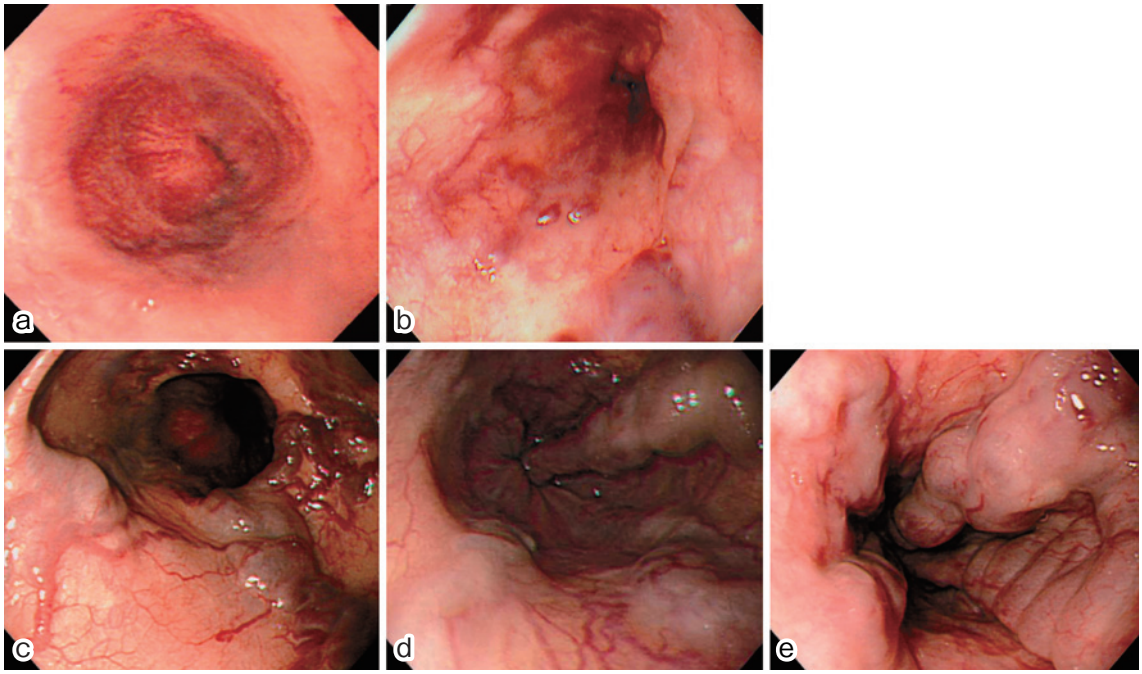

Fig. 1 1) F_0 lesions lack a varicose appearance. F_0, RC_0, S (a), F_0, RC_1 (b). F_1 lesions are straight, small-caliber varices (c). F_2 lesions are moderately enlarged (d). F_3 lesions are markedly enlarged, nodular, or tumor-shaped varices (e). (Tajiri et al. Dig Endosc 2010; 22: 1-9).

Diagnosis of EVs and GVs

In the grading system for esophagogastric varices proposed by the Japan Society for Portal Hypertension[6], EVs and GVs are evaluated on the basis of form (lack of a varicose appearance [F0], small and straight [F1], nodular [F2], and large or coiled [F3]) **(Fig. 1)**, color (white [Cw], and blue [Cb]) **(Fig. 2)**, and red color signs (RC0-3). Red color signs are classified into the following 3 categories: 1) red wale markings are dilated venules oriented longitudinally on the mucosal surface, somewhat like wale or whip marks; 2) cherry-red spots are small red spots on the mucosal surface; and 3) hematocytic spots are large, round, crimson-red projections that look like blood blisters **(Fig. 3)**.

GVs are divided into cardiac varices (Lg-c), fundal varices (Lg-f), and varices involving both the cardia and fundus (Lg-cf). In this review, we divided GVs into 2 categories: Lg-c (cardiac varices [CVs]) and Lg-cf or Lg-f (fundal varices [FVs]).

Bleeding signs are divided into signs found during bleeding and signs found after hemostasis. Bleeding is classified as gushing, spurting, or oozing. Findings after hemostasis are classified as red plugs or white plugs[6].

Risk Factors for Bleeding from EVs or GVs

EVs are present in about 50% of patients with cirrhosis, whereas GVs are present in 20% of patients with cirrhosis, either in isolation or in combination with EVs. The incidence of variceal bleeding in patients who have not previously received treatment for EVs ranges from 16% to 75.6%[7,8]. The incidence of bleeding from GVs is 25%[2], whereas cumulative rates of bleeding from FVs at 1, 3, and 5 years have been estimated to be 16%, 36%, and 44%, respectively[9]. Bleeding from FVs is more severe and is associated with a higher mortality rate than is bleeding from EVs or GVs[10]. We examined the natural course of GVs in 52 patients, and 4 had bleeding from GVs during a mean follow-up period of 41 months. Hemostasis was successfully achieved in all 4 patients. Cumulative bleeding rates at 1, 3, and 5 years were 3.8%, 9.4%, and 9.4%, respectively[4]. These findings indicate that the overall incidence of bleeding from GVs is lower than that from EVs[2].

Bleeding from an EV most commonly occurs in

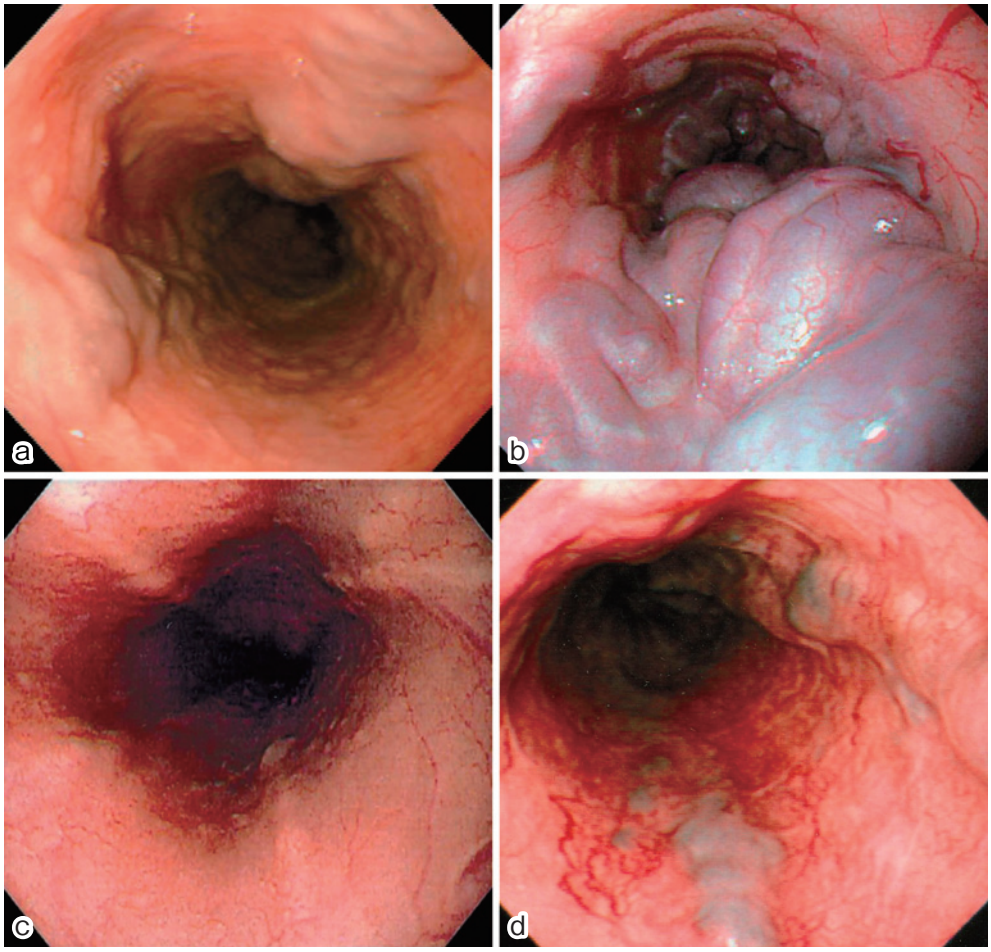

Fig. 2 White varices (Cw) (a), blue varices (Cb) (b), thrombosed white varices (Cw-Th) (c), and thrombosed blue varices (Cb-Th) (d). (Tajiri et al. Dig Endosc 2010; 22: 1-9)

the critical area 3 cm proximal to the esophagocardiac junction. Fine longitudinal veins in the lamina propria originate at the esophagocardiac junction and traverse the lamina propria towards this critical area. EVs consist of multiple dilated veins. Most veins that rupture are located in the lamina propria[11].

In the stomach, unlike in the esophagus, a large winding vein runs through the submucosa without causing varicose veins to pile up. Ruptures in GVs occur in the submucosa, where they disrupt the muscularis mucosae and lamina propria mucosae.

Portal Pressure

EVs and GVs are a direct consequence of portal hypertension. The basic pathophysiologic characteristic of portal hypertension is resistance to portal vein flow or an increase in portal vein flow, which increases pressure in the portal vein and its tributaries and promotes the formation of collateral circulation. In cirrhosis, both resistance to portal vein flow and increased portal vein inflow are detected. Structural distortion of the liver vascular architecture by fibrosis and regenerative nodules increases resistance. Increased hepatic vascular tone due to endothelial dysfunction and decreased nitric oxide bioavailability further increase resistance[12]. The severity of liver dysfunction (Child-Pugh classification) predicts bleeding EVs[13–15]. However, Kleber et al. have reported that the Child classification (encephalopathy and ascites) correlates positively with the mortality rate but not with the incidence of bleeding in patients with cirrhosis and EVs without previous bleeding[14].

When the hepatic venous pressure gradient (HVPG) increases above a certain threshold, collaterals develop at sites of communication between the portal and systemic circulations[16]. This

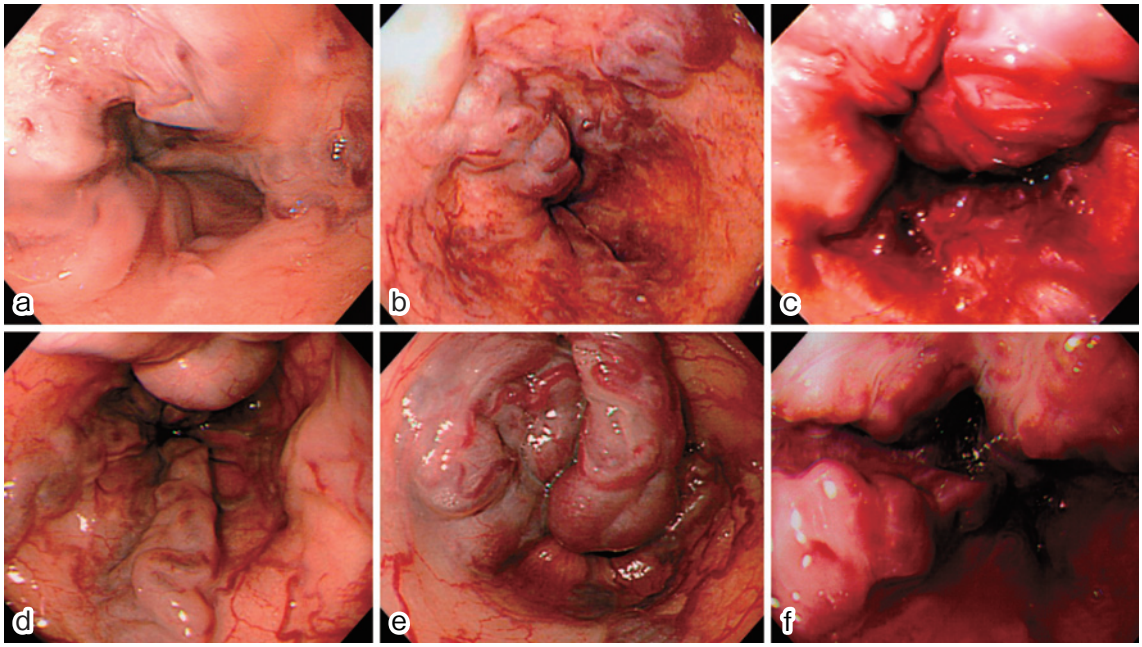

Fig. 3 Red color signs: red wale markings (a), cherry-red spots (b), hematocytic spots (c), RC_1 (d), RC_2 (e), and RC_3 (f). (Tajiri et al. Dig Endosc 2010; 22: 1-9)

process is modulated by angiogenic factors[17,18]. Along with the formation of portosystemic collaterals, portal venous blood inflow increases as a result of splanchnic vasodilatation and increased cardiac output[19]. Increased portal flow maintains and exacerbates portal hypertension. EVs and GVs are the most important collaterals, because as pressure and flow increase through them, these varices grow and eventually rupture[15,20]. However, the portal pressure in patients with GVs and a gastrorenal shunt is lower than that in patients with EVs[21–23].

In patients who are receiving medical treatment to prevent EVs from bleeding, decreased portal pressure (i.e., a decrease in HVPG) is a good predictor of clinical efficacy. A decrease in HVPG to 12 mm Hg or less or a decrease of at least 20% from the baseline value is associated with a low risk of bleeding EVs[24–28]. On the other hand, Mishra et al. have reported that of 55 patients with bleeding GVs, 16% had a baseline HVPG of less than 12 mm Hg[29]. Poor hemodynamic response was found to be the main factor related to bleeding. The response of HVPG to drugs is the best predictor of prophylactic efficacy against variceal bleeding in patients treated with β-blockers alone or with both β-blockers and nitrates[24,30–34].

Various techniques for embolization, such as transportal obliteration and balloon-occluded retrograde transvenous obliteration (B-RTO), have been used to obliterate feeding veins of EVs or GVs[35,36]. Collateral veins, including feeding veins of EVs or GVs, act to decrease portal hypertension. Obliteration of collateral veins therefore increases portal congestion and portal pressure, especially in patients with cirrhosis. Partial splenic embolization (PSE) has been performed incrementally to reduce portal venous pressure to the level it was before the obliteration of collateral veins[37–45].

We examined divided 25 patients with portal-systemic encephalopathy into 2 groups: 14 patients underwent transportal obliteration or B-RTO or both of portal-systemic shunts, followed by PSE (PSE (+) group), and 11 patients underwent only transportal obliteration or B-RTO or both of portal-systemic shunts but not PSE (PSE (−) group). Portal venous pressures before treatment were similar to those after treatment in the PSE (+) group but were lower than those after treatment in the PSE (−) group. Serum ammonia levels were higher before treatment than 1 week after treatment in both groups, but the levels in the 2 groups were similar before treatment and 1 week, 3 months, 3 years, 4

years, and 5 years after treatment. However, serum ammonia levels were lower in the PSE (+) group than in the PSE (−) group 6 months, 9 months, 1 year, and 2 years after treatment. These findings indicate that PSE reduces portal venous pressure and is highly effective in patients with portal-systemic encephalopathy, EVs, or GVs.

Endoscopic Findings

Form

EV are classified into 4 groups according to their shape and size: F0, F1, F2, and F3. Functional studies have shown decreased function of the lower esophageal sphincter and low amplitude of primary peristalsis and acid clearance in patients with large varices[46,47]. These phenomenon could also be due to a mechanical effect of the presence of varices. There are several reports that large varices are a risk factor for bleeding EVs[13–15,48].

Red color signs

Endoscopic risk factors for bleeding from EVs include the presence of raised red markings, cherry-red spots, blue coloration, and large size[48]. Red color signs are elevated red areas that are important for predicting the risk of variceal bleeding[14,15,48–51], and red wale markings, dilated venules oriented longitudinally on the mucosal surface, have been considered to be the sign with the highest risk[13,52]. Red color signs refer to reddish changes seen immediately beneath the submucosa.

Histologically, red color signs are associated with a thinning epithelial layer. The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices published a report establishing that red color signs on EVs are predictive of bleeding[51]. It remains unclear whether endoscopic red color signs in the stomach have the same clinical significance as red color signs in the esophagus. The latter indicates thinning of the epithelial layer. Varices in the submucosa of the stomach are covered by the muscularis mucosae and propria mucosae. This covering generally confers an appearance differing from that typically associated with the thinning of the epithelial layer of the esophagus[53]. The mucosal layer covering EVs is somewhat thinner than that covering GVs. The lamina muscularis mucosa of the esophagus is loose, and venous pressure in the submucosa is transmitted through communicating branches to veins in the lamina propria. In contrast, the lamina muscularis mucosa of the gastric mucosa is tough and tightly integrated with the lamina propria[54].

We examined red color signs of bleeding EVs and GVs, classified into 3 groups: EVs, CVs, and FVs[55]. Red color signs were more common in EVs than in CVs or FVs ($P<0.0001$). Red color signs, a strong risk factor for ruptures frequently encountered in EVs, were completely absent in FVs. All CVs showing red color signs communicated with EVs that also showed red color signs. The absence of red color signs in FVs might be attributed to the pronounced thickness of the mucosal layer of FVs.

Mucosal injury

The prevalence of gastric ulcer in patients with cirrhosis was 20.8%, which was significantly higher than the 4.0% found in healthy controls[56]. The HVPG was significantly higher in patients with cirrhosis than in patients without gastric ulcer (17.3 ± 4.4 vs 15.5 ± 5.0 mm Hg, $P=0.01$). However, the prevalence of gastric ulcer was unrelated to the degree of portal hypertension[56].

We examined endoscopic signs of bleeding EVs and GVs, classified into 3 groups: EVs, CVs, and FVs[55]. Mucosal erosion over varices at the site of bleeding, ulcers at the bleeding point, and gastric ulcers were more common in CVs and FVs than in EVs.

FVs are usually 2 to 3 times as large as EVs and drain directly into an extremely dilated left gastric vein or posterior gastric vein[57]. Therefore, blood flow volume is usually greater in FVs than in EVs. Gastric ulcers that develop over GVs represent a break in the protective layer of the gastric mucosa. A break in the mucosal barrier overlying GVs places patients at risk for massive bleeding, especially when FVs are involved. Breaks of this type could be an important precondition leading to variceal hemorrhage.

Drugs

Intragastric effects of nonsteroidal anti-inflammatory drugs (NSAIDs) have been studied to

elucidate the mechanisms underlying acute gastric mucosal injury and defense[58–64]. The prevalence of gastric ulcers in patients with cirrhosis is significantly higher than that in age- and sex-matched healthy subjects[56].

Antiulcer drugs (mucosal protective drugs, H_2-blockers, and proton pump inhibitors [PPIs]) can increase the pH of the stomach, stimulate the aggregation of platelets and the formation of fibrin clots, and prevent or dissolve early blood clots. These kinds of medication are thus beneficial for stopping bleeding and preventing rebleeding.

There are several reports of interactions between antiulcer drugs and NSAIDs as related to bleeding EVs.

Okamoto et al. have evaluated the relationship between gastroesophageal reflux and bleeding EVs. They found that PPIs were more frequently administered to patients with nonbleeding EVs. However, there is a report that bleeding EVs are not associated with PPI use. Patients with cirrhosis were divided in 2 groups: patients who underwent PPI therapy (n=48) and patients who did not (n=57). Seventeen patients (16.1%) presented with upper gastrointestinal bleeding; bleeding was due to EVs in 14 of these 17 patients (82.3%) and was attributed to portal hypertensive gastropathy in 3 of 17 patients. Bleeding related to portal hypertension according to PPI therapy occurred in 18.7% (n=9) of patients receiving PPIs and in 14% (n=8) of patients not receiving PPIs[65]. It is unclear whether the presence of cirrhosis itself could predispose to the onset of gastroesophageal reflux. It seems that the presence of EVs is related to reflux episodes, although it is not clear whether reflux episodes contribute to bleeding from EVs.

Liao et al.[66] have reported no signficant difference in the rate of NSAID/aspirin use in the preceding week between patients with acute bleeding from EVs (n=16, 6.7%) and control subjects (n=12, 5%).

On the other hand, bleeding GVs are associated with antiulcer drugs and NSAID use. The authors examined interactions between antiulcer drugs (mucosal protective drugs, H_2-blockers, and PPIs) and NSAIDs as related to bleeding EVs and GVs, classified into 3 groups: EVs, CVs, and FVs[67]. The use of "standard" NSAIDs on 4 or more of the last 7 days before an initial episode of bleeding was defined as "regular" use; all other use was considered "occasional." The percentage of NSAID users was significantly higher in patients with FVs than in patients with EVs ($p<0.0001$). All users of antiulcer drugs who were nonusers of NSAIDs had varices with red color signs. All NSAID users had used NSAIDs orally within a day before the initial episode of bleeding. All "regular" NSAID users were nonusers of antiulcer drugs. All antiulcer drug users without red color signs were "occasional" NSAID users.

Bleeding EVs are not associated with the use of antiulcer drugs or NSAIDs. However, in patients with bleeding GVs, "occasional" oral NSAID use is an important step leading to variceal hemorrhage, especially from FVs, even if the mucosa is protected by antiulcer drugs. The ability to use NSAIDs for several days without variceal bleeding in some patients with GVs who are concurrently receiving antiulcer drugs suggests that such drugs protect the esophagogastric mucosa[67].

Others

Liao et al. have reported that constipation, vomiting, severe coughing, and excessive consumption of alcohol may precipitate rupture of EVs[66].

Conflict of Interest: None.

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(Received, December 3, 2012)
(Accepted, April 9, 2013)