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**Comprehensive approach to esophageal variceal bleeding: From prevention to treatment**

Approach to esophageal variceal bleeding

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## **Abstract**

Esophageal variceal bleeding is a severe complication often associated with portal hypertension, commonly due to liver cirrhosis. Prevention and treatment of this condition are critical for patient outcomes. Preventive strategies focus on reducing portal hypertension to prevent varices from developing or enlarging. Primary prophylaxis involves the use of non-selective beta-blockers, such as propranolol or nadolol, which lower portal pressure by decreasing cardiac output and thereby reducing blood flow to the varices. Endoscopic variceal ligation (EVL) may also be employed as primary prophylaxis to prevent initial bleeding episodes. Once bleeding occurs, immediate treatment is essential. Initial management includes hemodynamic stabilization followed by pharmacological therapy with vasoactive drugs like octreotide or terlipressin to control bleeding. Endoscopic intervention is the cornerstone of treatment, with techniques such as EVL or sclerotherapy applied to directly manage the bleeding varices. In cases where bleeding is refractory to endoscopic treatment, transjugular intrahepatic portosystemic shunt (TIPS) may be considered to reduce portal pressure effectively. Long-term management after an acute bleeding episode involves secondary prophylaxis using beta-blockers and repeated EVL sessions to prevent rebleeding, complemented by monitoring and managing liver function to address the underlying disease. In light of new scientific evidence, including the findings of the study by Peng *et al.* (World J Gastroenterol 2024; In press; ISSN 1007-9327 [print] and 2219-2840 [online]), this editorial aims to review available strategies for the prevention and treatment of esophageal varices.

**Key Words:** Esophageal variceal; Portal hypertension; Cirrhosis; Bleeding; Prevention; Treatment

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**Core Tip:** Despite the advancements in prophylaxis and treatment of esophageal variceal bleeding, the rebleeding rates and mortality remain high. Among the prediction tools assessing the risk of variceal bleeding, imaging modalities such as computed tomography and endoscopy are commonly used, with the upcoming field of radiomics showing promising results.

## **INTRODUCTION**

Esophageal varices represent collaterals between the portal and systemic circulations in patients with portal hypertension[1]. These are present in around 30% of cirrhotic patients at diagnosis, which increases up to 90% in 10 years. Rupture of the varices is one of the most fatal complications in cirrhosis[2]. Management of esophageal varices has been divided into primary prophylaxis, treatment of acute bleeding and secondary prophylaxis, encompassing the various pharmacological, endoscopic and radiological therapies[3-9].

Given the significant mortality risk with the initial and subsequent variceal bleeding episodes, there remains an unmet need for a prediction tool to determine the risk of esophageal varices[10]. Several recent studies have evaluated different diagnostic methods with varying correlation rates, including shear wave elastography, computed tomography, magnetic resonance imaging and machine learning models[11-16]. A major limitation in these imaging modalities is the dependence on observer training and skills[17-20]. To that end, endoscopy is the current standard to assess the variceal bleeding risk in patients with cirrhosis[21]. However, the presence of comorbidities in cirrhotic patients may limit the feasibility of pursuing endoscopic examination, and the findings may vary due to inter-observer heterogeneity. Further, the Baveno VII consensus recommended that patients with compensated cirrhosis on non selective beta blockers may not even need screening endoscopy as it will not change the management[22].

One of the upcoming fields to enhance the diagnostic capabilities of imaging modalities is radiomics[23]. In this field, data is obtained from the medical images using mathematical algorithms, which can supersede the information obtained by human operators. Prior studies using radiomics for prediction of variceal bleeding risk showed promising results with data from a single organ or a portion of multiple organs[24]. In this editorial, we comment on the article by Peng *et al.* published in the recent issue of the World Journal of Gastroenterology 2024 (In press; ISSN 1007-9327 [print] and 2219-2840 [online])[25].

### KEY FINDINGS

Peng *et al.* conducted a retrospective study to develop a prediction model for esophageal variceal bleeding in cirrhotic patients[25]. Of the total 208 patients in the study, 145 were assigned to the training cohort and 63 to the validation cohort. Multi-organ radiomic features were extracted from the spleen, liver, and lower esophagus/gastric fundus region. A radiomic score (Rad-score) was generated in the training cohort using the observer correlation coefficients. The Rad-score was combined with the clinical risk variables to form the radiomics-clinical model (RC model). Subsequently, the models were tested using the validation cohort. Among the different model combinations, the RC model demonstrated the best performance for prediction of esophageal variceal bleeding (area under the receiver operating characteristic curve [AUC] - 0.951 [0.919-0.983] training and 0.930 [0.872-0.987] validation).

The respective AUC values for the other models in the training and validation cohorts were: Rad-score (liver + spleen + esophagus) 0.930 [0.891-0.970] and 0.886 [0.808-0.964]; Rad-score (liver) 0.801 [0.727-0.875] and 0.763 [0.646-0.880]; Rad-score (spleen) 0.831 [0.766-0.897] and 0.792 [0.677-0.906]; Rad-score (esophagus) 0.864 [0.807-0.922] and 0.857 [0.762-0.952]; clinical model 0.727 [0.644-0.811] and 0.692 [0.556-0.828]. Multivariate analysis revealed ascites ( $P = 0.004$ ), portal vein thrombosis ( $P = 0.003$ ), and plasma prothrombin time ( $P = 0.017$ ) to be independent clinical risk factors. Apart from the limitations of small sample size from a single institution, the study showed promising

results for noninvasive prediction of esophageal variceal bleeding risk in patients with cirrhosis.

Among the other newer diagnostic methods that have shown promise in diagnosing esophageal varices non-invasively, splenic elastography has had good diagnostic performance. In the meta-analysis of 13 studies (1970 patients) by Karagiannakis *et al.*, 2D-Shear Wave Elastography demonstrated pooled sensitivity of 90% and pooled specificity of 68% for detecting varices with high bleeding risk[13].

### CURRENT GUIDELINES

Building upon the previous advisories by the American Gastroenterological Association (AGA), European Society of Gastrointestinal Endoscopy (ESGE) and the Baveno VII consensus, the 2024 <sup>3</sup> American Association for the Study of Liver Diseases (AASLD) guidelines for the management of varices in cirrhotic patients were recently published[22,26,27]. These included: 1) Primary prophylaxis for prevention of variceal bleed using non selective beta blockers (preferred) or endoscopic band ligation; 2) Treatment of active bleeding - vasoactive therapy (such as somatostatin or octreotide), antibiotics, blood transfusion for target hemoglobin ~7 g/dL, upper endoscopy within 12 hours, bleeding control *via* endoscopic variceal ligation (EVL), preemptive transjugular intrahepatic portosystemic shunt (TIPS) in select patients with high Child-Turcotte-Pugh score (> 7 and active bleeding on endoscopy or score 10-13), and expandable esophageal stents or balloon tamponade in patients with uncontrolled hemorrhage; 3) Secondary prophylaxis using non selective beta blockers, endoscopic band ligation or TIPS (in patients with other indications such as refractory ascites)[28]. For gastric and ectopic varices, AASLD recommended: 1) Primary prophylaxis with non-selective beta blockers or endoscopic cyanoacrylate injection (for high-risk cardiofundal varices); 2) Patients with active bleeding to undergo - contrast-enhanced cross-sectional imaging (to define anatomy), endoscopic therapy (via cyanoacrylate injection, TIPS or retrograde transvenous variceal obliteration), and additional directed therapy in form of splenic vein stenting/artery embolization in patients with isolated

splenic vein thrombosis[29]. Specific guidance regarding TIPS in these patients was similar in the French guidelines as well[30].

The AGA released a clinical practice update pertaining to the vasoactive drugs in cirrhotic patients recently[31]. The following were advised: 1) In patients with suspected or confirmed variceal bleeding, vasoactive drugs are to be started immediately, ideally before endoscopy is performed; 2) Vasoactive drugs should be continued for an additional 2–5 days after initial endoscopic treatment to prevent early rebleeding; 3) Among the different agents available (octreotide [somatostatin analogue], somatostatin, and terlipressin [vasopressin analogue]), octreotide is preferable due to lower risk of adverse events.

#### RECENT STUDIES

Several new trials and meta-analyses have been published recently evaluating the different management techniques in patients with varices[32-45]. Wang *et al.* randomized patients with Child-Pugh class B or C cirrhosis to TIPS or EVL + propranolol groups, and found the former group to have reduced variceal rebleeding risk ( $P = 0.008$ ), higher incidence of overt hepatic encephalopathy ( $P = 0.03$ ), without any difference in survival ( $P = 0.22$ )[46]. In another randomized trial of patients with gastric fundal varices by Escorsell *et al.*, preemptive TIPS had better rebleeding-free survival as compared with combined endoscopic and pharmacological therapy group ( $P = 0.017$ ), with comparable rates of adverse events and hepatic encephalopathy[47].

Abuelazm *et al.* conducted a meta-analysis of 11 studies in which TIPS combined with variceal embolization was found to be better in preventing variceal rebleeding compared to TIPS alone (risk ratio [RR] 0.58), without any significant differences in terms of shunt dysfunction, encephalopathy and mortality[48]. In the network meta-analysis of 24 randomized studies assessing cirrhotic patients with acute variceal bleeding by Huang *et al.*, early TIPS reduced all cause mortality compared to standard treatment (odds ratio [OR] 0.53), with both the early TIPS group (OR 0.19) and non-early TIPS group (OR 0.30) having lower rebleeding risk[49]. Zhu *et al.* compared

endoscopic therapy plus nonselective beta-blockers *vs* TIPS for preventing variceal rebleeding in a meta-analysis of 5 studies, with the TIPS group showing lower rebleeding rate (OR 0.19,  $P < 0.05$ ), higher portal vein recanalization rate (OR 7.92,  $P < 0.05$ ), and similar rates of hepatic encephalopathy and mortality[50].

Endoscopic ultrasound (EUS)-guided treatments have been widely studied for gastroesophageal varices. Wang *et al.* performed a randomized study of patients with gastroesophageal varices type 1, and reported the EUS-guided cyanoacrylate injection group to have higher eradication success rate, lower late rebleeding rate ( $P = 0.032$ ) and lower incidence of postinjection ulcers ( $P = 0.023$ ) when compared with direct endoscopic injection of cyanoacrylate[51]. In the meta-analysis of 18 studies by Chandan *et al.*, EUS-glue plus coil therapy resulted in 95.4% pooled variceal obliteration rate as the primary prophylaxis[52]. Bleeding rate after the initial treatment was 4.9%. For secondary prophylaxis, the pooled treatment efficacy was 94.3% (EUS-glue), 95.5% (EUS-coil) and 88.7% (EUS-glue plus coil). The rates of variceal obliteration were 84.6% (EUS-glue), 92.3% (EUS-coil) and 84.5% (EUS-glue plus coil). Pooled rebleeding and recurrence rates were 18.1% and 20.6%, respectively.

In patients with acute bleeding, Arora *et al.* conducted a randomized trial comparing different techniques of terlipressin infusions: Low-dose continuous infusion *vs* intravenous bolus injections[53]. The continuous infusion group had a higher rate of hepatic venous pressure gradient response at 24 hours (85.4% *vs* 58.2%,  $P = 0.002$ ), with lower dose of terlipressin ( $P < 0.001$ ), adverse events (36.3% *vs* 56.4%,  $P = 0.03$ ) and rebleeding (1.8% *vs* 14.5%,  $P = 0.03$ ). For patients with refractory variceal bleeding, Songtanin *et al.* reported a meta-analysis of 12 studies assessing the efficacy of esophageal stents: Immediate bleeding control 91%, rebleeding 17%, stent ulceration 7%, stent migration 18% and all-cause mortality 38%[54]. With regards to the injection substance for control of bleeding, the randomized study by Jhajharia *et al.* showed endoscopic thrombin injection to have lower risk of post-treatment ulcers as compared with endoscopic glue injection (0 *vs* 14.81%,  $P = 0.045$ )[55].

## **CONCLUSION**

Variceal bleeding in cirrhosis remains a diagnostic and therapeutic challenge, with high rates of rebleeding and mortality, despite appropriate prophylaxis and treatment[56-63]. Prediction of the bleeding risk, with modalities such as radiomics, can improve patient outcomes[64-75].

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