Chapter

Non-Invasive Prediction of Gastroesophageal Varices in Patients with Portal Hypertension

Ran Wang, Xiaozhong Guo and Xingshun Qi

Abstract

Gastroesophageal varices are the most common complication of portal hypertension and associated with a worse prognosis. Endoscopy is the gold standard method to diagnose gastroesophageal varices. However, endoscopy is an invasive method with potential complications and is not well adhered by patients. Non-invasive methods, including serum markers or scores, computed tomography, ultrasonographic, and elastography-based methods, have been explored for the diagnosis of gastroesophageal varices. In the current chapter, we will briefly review non-invasive methods for the prediction of gastroesophageal varices.

Keywords: portal hypertension, gastroesophageal varices, non-invasive, diagnosis, prediction

1. Introduction

Portal hypertension is defined as the pressure of portal vein is 5 mmHg higher than that of inferior vena cava. It is the most important complication of liver cirrhosis. Clinically significant portal hypertension is associated with an increased risk of developing varices, which is defined as hepatic venous pressure gradient over 10 mmHg [1]. Gastroesophageal varices (GEVs) is appeared in approximately 50% of patients with cirrhosis, which is associated with a worse outcome. Despite an improvement of treatment strategy, variceal bleeding is still associated with a 6-week mortality rate of 12–26% [2, 3].

Endoscopy, the gold standard method to diagnose GEVs, is recommended for all patients at the time of diagnosis of cirrhosis. Endoscopy should be periodic for screening GEVs. It is reported that nearly 30% of cirrhotic patients screened by endoscopy found to have moderate-to-large varices [4, 5]. Endoscopy is not only a diagnostic method but also serves as a therapeutic option in the form of sclerotherapy and band ligation. However, endoscopy is an invasive method, which is not well perceived by patients. Complications following diagnostic endoscopy mainly include infection, bleeding, duodenal hematoma, bowel perforation, airway obstruction, arrhythmias, and aspiration. Additionally, in some less developed regions or countries, advanced endoscopy and experienced endoscopists are still in shortage. It is thus important to identify patients who can avoid unnecessary endoscopy or patients with high-risk GEVs that need further treatment should be considered.

Non-invasive prediction of GEVs could relieve medical, social, and economic costs. Numerous efforts have been made to predict GEVs non-invasively, and some progress has been achieved. In the Baveno VI consensus conference, it was underlined that non-invasive methods should be used to rule out patients with varices or high-risk varices [6]. In this chapter, we focus on non-invasive methods in the prediction of GEVs.

2. Serum markers or scores

2.1 Serum ammonia

Serum ammonia is well recognized as a serum marker for hepatic encephalopathy in cirrhotic patients. Studies have demonstrated serum ammonia has a positive correlation with the presence of portosystemic collateral veins including GEVs [7]. In a newly published study by **Darweesh et al.** serum ammonia was found significantly higher in patients with esophageal varices (EVs) than those without [8]. A total of 204 hepatitis C virus (HCV) relate cirrhotic patients were enrolled. Serum ammonia with a cutoff value of 82 μmol/L had a sensitivity of 92.3% and specificity of 92% in detecting EVs and that with a cutoff value of 95.5 μmol/L had a sensitivity of 92.7% and specificity of 92.3% in detecting large EVs. Conversely, a study by **Hafez et al.** found that serum ammonia alone cannot predict the presence or grade of EVs [9]. The predictive value of serum ammonia for GEVs still needs further evaluation.

2.2 Platelet count/spleen diameter ratio

Platelet count/spleen diameter ratio (PSR) was first proposed by **Giannini et al.** [10] to explore the non-invasive method for predicting GEVs. In the first part of Giannini's study, 145 patients were included. The results found that PSR was the only parameter independently associated with the EVs with a cutoff value of 909. The PSR with cutoff value of 909 had a sensitivity of 100%, a specificity of 93%, a positive predictive value (PPV) of 96%, and an negative predictive value (NPV) of 100%. In the second part of this study, 103 patients were included, the results validated that the reproducibility of the predictive value of PSR for EVs. Additionally, in all 266 patients, PSR was the only parameter significantly different between patients with and without EVs at baseline.

Since then, extensive studies have focused on the PSR for the non-invasive prediction of GEVs. However, a study by **Schwarzenberger et al.** found PSR maybe not sufficient for the diagnosis of GEVs [11]. In this study, a total of 137 patients were enrolled. The diameter of spleen was measured using computed tomography (CT), magnetic resonance imaging, and ultrasonography. Ascites, splenomegaly, Child-Pugh score were found to have a positive correlation with EVs. The PSR with a cutoff of 909 had a sensitivity of 80%, specificity of 66%, and PPV of 74%.

In a recent meta-analysis by **Chen et al.** where 49 studies were enrolled, found that the area under curves (AUC) of PSR for GEVs was 0.8719, the summary sensitivity and specificity were 0.84 and 0.78, respectively [12]. The results suggest that PSR can be used for predicting EVs, especially in patients with viral hepatitis.

2.3 Liaoning score

The Liaoning score was proposed by **Qi et al.** from a prospective cohort of cirrhotic patients who underwent the first-time endoscopy at 11 hospitals in Liaoning

Province, China [13]. In this study, a total of 363 cirrhotic patients were enrolled. The incidence of EVs was 71.63% (260/363). The results suggest that acute upper gastrointestinal bleeding (AUGIB), platelet count, and ascites were independently associated with the presence of EVs. In the whole cirrhotic patients, the Liaoning score, whose equation was 0.466 + 1.088 × AUGIB (1 = yes; 0 = no) + 1.147 × ascites (1 = yes; 0 = no) - 0.012 × platelet count, had an AUC of 0.807 ($p < 0.0001$). The cutoff value was 0.474 with a sensitivity of 70%, a specificity of 77.67%, a PPV of 88.8%, and an NPV of 50.6%. In patients with AUGIB, the equation was 1.205 + 1.557 × ascites (1 = yes; 0 = no) - 0.008 × platelet count, with an AUC of 0.782 ($p < 0.0001$). The results of this study suggested that Liaoning score was a newly developed scoring system which can be employed to predict EVs in cirrhotic patients.

For external validation of Liaoning score, **Li et al.** performed a nationwide multicenter cross-sectional study to evaluate the predictive ability of Liaoning score for EVs and high-risk EVs [14]. In this study, 612 cirrhotic patients with AUGIB were enrolled. The incidence of EVs and high-risk EVs was 96.2% and 95.6%, respectively. The results showed that the AUC of Liaoning score for predicting EVs was 0.708 ($p = 0.0016$), and that of high-risk EVs was 0.702 ($p = 0.0147$).

2.4 Other scores

Other than the non-invasive methods we have discussed above, many scores have been developed for the evaluation of liver fibrosis, including aspartate aminotransferase-to-platelet ratio index (APRI), aspartate aminotransferase-to-alanine aminotransferase ratio (AAR), FIB-4, and Lok scores. Some studies explore the predictive ability of these non-invasive scores for GEVs. In a meta-analysis by **Deng et al.** several non-invasive scores had been systematically reviewed for the predictive ability of EVs [15]. In the overall analysis, a total of 650 patients were included, 81.4% of them had moderate–severe EVs. Only Child-Pugh and FI scores were significantly higher in patients with EVs than those without. The AUC of FI was 0.612, FIB-4 was 0.567, AAR was 0.56, and APRI was 0.539. However, the AUC among these scores was not significantly different. For further validation, **Deng et al**. also performed a retrospective study, the results were in agreement with their previous meta-analysis [16]. A total of 650 cirrhotic patients were included, and 81.4% of them had high-risk EVs. The results of this study concluded that APRI, AAR, and FIB-4 scores had only modest diagnostic accuracy of EVs in cirrhotic patients.

3. Image tools

3.1 CT

CT scanning is one of the most important image tools in clinical practice, is recommended for the surveillance of hepatocellular carcinoma in all cirrhotic patients. GEVs characteristics as round, tubular, or serpentine structures in the esophagus and/or gastric lumen in CT images. It provides a possibility that an experienced physician can diagnosis GEVs using CT images, especially in contrast-enhanced CT images.

Perri et al. designed a prospective study that explores the ability of CT for the prediction of GEVs [5]. A total of 102 patients who had a CT and endoscopy within 5 days were enrolled. Two radiologists read the CT independently. The sensitivity of EVs was 93% in both radiologists, the specificity was 55% and 45%, respectively. The sensitivity of gastric varices was 87% in both radiologists. The results suggest that CT should be used as initial surveillance for GEVs.

In a study by **Li et al.** contrast-enhanced CT was used for the non-invasive prediction of GEVs [17]. In this retrospectively study, a total of 279 patients were included. High-risk varices including EVs and gastric varices was defined as varices that need treatment. All patients were divided into four groups according to the history of bleeding events, endoscopic surveillance, and drug prophylaxis (primary or secondary prophylaxis). In the overall population, only contrast-enhanced CT was significantly associated with EVs, high-risk EVs, and gastric varices. In primary prophylaxis, acute bleeding, previous bleeding, and secondary prophylaxis population, a diameter < 0.5 cm, <0.38 cm <0.46 cm and < 0.33 cm was considered as the cut-off value of high-risk EVs, respectively. Which can spare 47.8%, 10.5%, 12.1%, and 7.8% of endoscopic surveillance with no high-risk EVs was missed, respectively. This study showed a good diagnostic performance for contrast-enhanced CT for patients with GEVs.

3.2 Ultrasonography

Ultrasonography is the most common, cost-effective, and convenient imaging tool in clinical practice, which can be used for screening of hepatocellular carcinoma, measure the width of the portal vein, inferior vena cava, and diameter of the spleen.

Splenoportal index was calculated as the splenic index divided by mean portal vein velocity. In a study by **Mansoor et al.** 200 HCV-induced cirrhotic patients were included [18]. All patients underwent ultrasonography first to calculate splenoportal index and then underwent endoscopy. The incidence of EVs was 60.5% (121/200) in ultrasonography and 63.5% (127/200) in endoscopy. The sensitivity, specificity, PPV, NPV of ultrasonography for predicting EVs was 88.98%, 89.04%, 93.00%, 82.28%, and 89.00%, respectively. This study showed a good diagnostic performance for splenoportal index by ultrasonography for patients with EVs.

3.3 Elastography-based methods

Elastography-based methods, Including transient elastography (TE), point shear wave elastography, two-dimensional shear wave elastography, and magnetic resonance elastography have been used to non-invasively detected liver fibrosis and GEVs. There is substantial evidence suggesting that TE had a good correlation with portal hypertension and varices in cirrhotic patients [19, 20]. In 2015, TE was recommended for the surveillance of GEVs by Baveno VI consensus [6]. According to the Baveno VI consensus, in patients with compensated advanced chronic liver disease, who had a liver stiffness <20 kPa measured by TE and platelet count >150,000/mm^3, had a low risk of developed GEVs that may spear endoscopy. **Augustin et al.** performed a prospective study that taking the Baveno VI recommendation a step forward [21]. This study suggests that platelet count >110,000/mm^3 and liver stiffness <25 kPa can spare more endoscopies than the Baveno VI consensus recommendation (41% vs. 21%). Only minority (0.6%) of overall patients were missed varices needing treatment. The negative predictive value for varices of the Baveno VI consensus and expanded Baveno VI consensus criteria is confirmed by further studies [22, 23].

In a study by **Kim et al.** a new model was generate based on the liver elasticity and the spleen diameter/platelet count (LSPS) [24]. A total of 280 hepatitis B virus relate cirrhotic patients were enrolled into the training cohort, and 121 patients were enrolled into the validation cohort. Liver stiffness was measured by TE. LSPS was calculated by the equation: Liver Stiffness Measurement × spleen diameter/platelet count. In the training cohort, the cutoff value of LSPS was 3.5. In patients

with LSPS <3.5, the absence of high-risk EVs had a sensitivity of 87.7%, a specificity of 91.1%, an NPV of 94%, and a PPV of 82.3%. When applying the cutoff value of LSPS <3.5, the AUC in the validation cohorts was 0.953. The results of this study showed that in patients with LSPS <3.5, endoscopy may avoid safely in cirrhotic patients.

In a study by **Sharma et al.** spleen stiffness was used for the non-invasive prediction of GEVs [25]. A total of 174 cirrhotic patients were prospectively enrolled. Liver stiffness and spleen stiffness were measured by the TE. Median liver stiffness, median spleen stiffness, LSPS, and PSR were significantly different between patients with and without EVs. On multivariate analysis, only liver stiffness and spleen stiffness showed predictive ability of EVs. Liver stiffness with a cutoff value of 27.3 kPa had a higher AUC than spleen stiffness with a cutoff value of 40.8 kPa (0.908 vs. 0.898). The liver stiffness with a cutoff value of ≥27.3 kPa had a sensitivity of 91%, a specificity of 72%, a PPV of 89%, an NPV of 76%, and a diagnostic accuracy of 86% in predicting EVs; the spleen stiffness with a cutoff of ≥40.8 kPa had a sensitivity of 94%, a specificity of 76%, a PPV of 91%, an NPV of 84%, and a diagnostic accuracy of 86% in predicting EVs. In patients who had performed hepatic venous pressure gradient, spleen stiffness showed a correlation with hepatic venous pressure gradient ($r = 0.335$, $P = 0.01$). The results of this study suggest that spleen stiffness can be used for the non-invasive assessment of EVs.

4. Discussion

GEVs exists in almost 30–60% of cirrhotic patients, depending on the severity of portal hypertension [24]. The occurrence of GEVs and varices-related AUGIB significantly worsened the prognosis of patients with portal hypertension, emphasizes the importance of diagnosis and management of GEVs. There are numerous studies have focused on developing non-invasive methods to predict the presence of GEVs, including serum markers, CT scanning, and ultrasonographic parameters. However, endoscopy is still difficult to replace, especially considering cost-effectiveness and diagnostic accuracy [26]. From other perspectives, in regular physical examination or surveillance of hepatocellular carcinoma, non-invasive methods can be employed to predict the severity of portal hypertension and GEVs. In this situation, if the patients have a high-risk of variceal bleeding in a short time, then the patient must perform endoscopy; if the patient has a low-risk of bleeding in a certain period, then the patient can waive an unnecessary endoscopy.

Liver stiffness and spleen stiffness measured by the TE were the most promising non-invasive methods available, as they have proven having a good correlation with liver fibrosis, portal hypertension, and the presence with varices [27, 28]. The limitations of TE is that the results of TE should interpreted by a specialist in liver disease which may not available in less development hospital and TE should inappropriate be performed in patients with ascites and/or obesity [26].

Approximately 10% of the whole portal hypertension patients were non-cirrhotic portal hypertension [29]. In general, patients with non-cirrhotic portal hypertension have higher prevalence and larger size of varices than those in cirrhotic patients [30, 31]. Until now, few studies focus on the non-invasive prediction of GEVs in patients with non-cirrhotic portal hypertension. In a retrospective observational study by **Cunningham et al.** [32] a total of 44 non-cirrhotic portal hypertension patients were enrolled, and 15 of them had high-risk varices. The results of this study found that spleen diameter > 17.2 cm had a sensitivity of 78.6% and specificity of 64.3% for prediction of high-risk varices. In patients with non-cirrhotic portal hypertension, the LSM and PSR may not as useful as cirrhotic patients.

There are heterogeneities among these studies and methods. Several reasons for the heterogeneities, including: 1) different target populations were enrolled among studies, including different races, etiology of liver cirrhosis; 2) different severity of underlying liver disease among patients; 3) different definitions for the risk of GEVs: in some studies, such as the study by **Li et al**. the severity of EVs was defined using the shape of varices and the red color sign [17]; in some other studies, the severity of varices was defined using the size of varices [5]. Therefore, the heterogeneities make it difficult to compare different studies or methods systematically.

5. Conclusion

Endoscopy is still the first choice for the diagnosis of GEVs in patients with portal hypertension. Liver stiffness and spleen stiffness measured by TE are the most studied methods. With the development of non-invasive prediction of GEVs, it is promising to exempt some patients from endoscopy.

Author details

Ran Wang*, Xiaozhong Guo and Xingshun Qi
Department of Gastroenterology, General Hospital of Northern Theater Command, Shenyang, China

*Address all correspondence to: wangran891017@163.com

References

[1] Garcia-Tsao, G., et al., *Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases.* Hepatology, 2017. **65**(1): p. 310-335.

[2] Fortune, B.E., et al., *Child-Turcotte-Pugh Class is Best at Stratifying Risk in Variceal Hemorrhage: Analysis of a US Multicenter Prospective Study.* J Clin Gastroenterol, 2017. **51**(5): p. 446-453.

[3] Lee, H.H., et al., *A simplified prognostic model to predict mortality in patients with acute variceal bleeding.* Dig Liver Dis, 2018. **50**(3): p. 247-253.

[4] Zaman, A., et al., *Prevalence of upper and lower gastrointestinal tract findings in liver transplant candidates undergoing screening endoscopic evaluation.* Am J Gastroenterol, 1999. **94**(4): p. 895-899.

[5] Perri, R.E., et al., *A prospective evaluation of computerized tomographic (CT) scanning as a screening modality for esophageal varices.* Hepatology, 2008. **47**(5): p. 1587-1594.

[6] de Franchis, R. and V.I.F. Baveno, *Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension.* J Hepatol, 2015. **63**(3): p. 743-752.

[7] Tarantino, G., et al., *Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins.* BMC Gastroenterol, 2009. **9**: p. 21.

[8] Darweesh, S.K., et al., *Serum ammonia as a non-invasive marker for early prediction of esophageal varices.* Eur J Gastroenterol Hepatol, 2021. **32**(2): p. 230-236.

[9] Hafez, H.A., *Predictive value of non-invasive blood ammonia level for the presence of oesophageal varices in Egyptian patients with liver cirrhosis.* Journal of Gastroenterology, 2015. **4**(5): p. 1613-1617.

[10] Giannini, E., et al., *Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis.* Gut, 2003. **52**(8): p. 1200-1205.

[11] Schwarzenberger, E., et al., *Utilization of platelet count spleen diameter ratio in predicting the presence of esophageal varices in patients with cirrhosis.* J Clin Gastroenterol, 2010. **44**(2): p. 146-150.

[12] Chen, R., et al., *Platelet Count to Spleen Diameter Ratio for the Diagnosis of Gastroesophageal Varices in Liver Cirrhosis: A Systematic Review and Meta-Analysis.* Gastroenterol Res Pract, 2017. **2017**: p. 7407506.

[13] Qi, X., et al., *Liaoning Score for Prediction of Esophageal Varices in Cirrhotic Patients Who Had Never Undergone Endoscopy: A Multicenter Cross-Sectional Study in Liaoning Province, China.* Adv Ther, 2019. **36**(8): p. 2167-2178.

[14] Li, Q., et al., *External validation of Liaoning score for predicting esophageal varices in liver cirrhosis: a Chinese multicenter cross-sectional study.* Ann Transl Med, 2019. **7**(23): p. 755.

[15] Deng, H., X. Qi, and X. Guo, *Diagnostic Accuracy of APRI, AAR, FIB-4, FI, King, Lok, Forns, and FibroIndex Scores in Predicting the Presence of Esophageal Varices in Liver Cirrhosis: A Systematic Review and Meta-Analysis.* Medicine (Baltimore), 2015. **94**(42): p. e1795.

[16] Deng, H., et al., *Diagnostic Accuracy of APRI, AAR, FIB-4, FI, and King Scores*

for Diagnosis of Esophageal Varices in Liver Cirrhosis: A Retrospective Study. Med Sci Monit, 2015. **21**: p. 3961-3977.

[17] Li, Q., et al., *Contrast-Enhanced CT May Be a Diagnostic Alternative for Gastroesophageal Varices in Cirrhosis with and without Previous Endoscopic Variceal Therapy.* Gastroenterol Res Pract, 2019. **2019**: p. 6704673.

[18] Mansoor, A., et al., *Diagnostic Accuracy of Doppler Ultrasonography in Predicting Presence of Esophageal Varices in Patients with Hepatitis-C Induced Cirrhosis.* J Coll Physicians Surg Pak, 2019. **29**(7): p. 612-615.

[19] Jangouk, P., et al., *Validating, deconstructing and refining Baveno criteria for ruling out high-risk varices in patients with compensated cirrhosis.* Liver Int, 2017. **37**(8): p. 1177-1183.

[20] Maurice, J.B., et al., *Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices.* J Hepatol, 2016. **65**(5): p. 899-905.

[21] Augustin, S., et al., *Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease.* Hepatology, 2017. **66**(6): p. 1980-1988.

[22] Giannini, E.G., et al., *Course of oesophageal varices and performance of noninvasive predictors following Hepatitis C Virus clearance in compensated advanced chronic liver disease.* Eur J Clin Invest, 2020. **50**(5): p. e13231.

[23] Gaete, M.I., et al., *Baveno VI and Expanded Baveno VI criteria successfully predicts the absence of high-risk gastro-oesophageal varices in a Chilean cohort.* Liver Int, 2020. **40**(6): p. 1427-1434.

[24] Kim, B.K., et al., *A liver stiffness measurement-based, noninvasive prediction model for high-risk esophageal varices in B-viral liver cirrhosis.* Am J Gastroenterol, 2010. **105**(6): p. 1382-1390.

[25] Sharma, P., et al., *Spleen stiffness in patients with cirrhosis in predicting esophageal varices.* Am J Gastroenterol, 2013. **108**(7): p. 1101-7.

[26] European Association for Study of, L. and H. Asociacion Latinoamericana para el Estudio del, *EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis.* J Hepatol, 2015. **63**(1): p. 237-264.

[27] Carrion, J.A., et al., *Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation.* Liver Transpl, 2006. **12**(12): p. 1791-1798.

[28] Lemoine, M., et al., *Liver stiffness measurement as a predictive tool of clinically significant portal hypertension in patients with compensated hepatitis C virus or alcohol-related cirrhosis.* Aliment Pharmacol Ther, 2008. **28**(9): p. 1102-1110.

[29] Simonetto, D.A., M. Liu, and P.S. Kamath, *Portal Hypertension and Related Complications: Diagnosis and Management.* Mayo Clin Proc, 2019. **94**(4): p. 714-726.

[30] Madhu, K., et al., *Idiopathic non-cirrhotic intrahepatic portal hypertension: common cause of cryptogenic intrahepatic portal hypertension in a Southern Indian tertiary hospital.* Indian J Gastroenterol, 2009. **28**(3): p. 83-87.

[31] Dhiman, R.K., et al., *Non-cirrhotic portal fibrosis (idiopathic portal hypertension): experience with 151 patients and a review of the literature.* J Gastroenterol Hepatol, 2002. **17**(1): p. 6-16.

[32] Cunningham, M.E., et al., *Noninvasive Predictors of High-Risk Varices in Patients with Non-Cirrhotic Portal Hypertension.* Can J Gastroenterol Hepatol, 2019. **2019**: p. 1808797.