Esophagus (2020) 17:19–24
https://doi.org/10.1007/s10388-019-00699-4

REVIEW ARTICLE

Remaining challenges for the noninvasive diagnosis of esophageal varices in liver cirrhosis

Tetsuo Takehara[1] · **Ryotaro Sakamori**[1]

Received: 20 August 2019 / Accepted: 1 October 2019 / Published online: 16 October 2019

Abstract

Although endoscopy is the recommended method for detecting esophageal varices, noninvasive methods for diagnosing esophageal varices are needed to avoid unnecessary invasive endoscopic examinations. In recent years, many studies have been performed to predict the presence of high-risk varices in noninvasive ways. The most widely used tools for noninvasive screening for esophageal varices are the Baveno VI and expanded Baveno VI criteria. Even these accepted criteria are not 100% accurate and have some limitations. Here, we summarize the current literature on the noninvasive diagnosis of esophageal varices in liver cirrhosis patients and highlight the remaining issues.

Keywords Varices · Liver cirrhosis · Portal hypertension · Baveno criteria

Abbreviations

HVPG	Hepatic venous pressure gradient
VNT	Varices needing treatment
cACLD	Advanced chronic liver disease
EGD	Esophago-gastro-duodenoscopy
EVL	Endoscopic variceal ligation
TE	Transient elastography
LSM	Liver stiffness measurement
ARFI	Acoustic radiation force impulse
SVR	Sustained virologic response
HCV	Hepatitis C virus

Cirrhosis is a chronic disease with a high mortality rate, and it is the fourth leading cause of death in adults in Western countries [1]. Cirrhosis is a heterogeneous disease that causes numerous clinical contacts due to its complications, and the clinical course of cirrhosis is typically described as a compensated and decompensated state [2]. Esophageal varices are one of the most common and lethal complications in cirrhotic patients. Approximately 50% of patients with cirrhosis have esophageal varices [3]. The prevalence rate of esophageal varices increases with liver disease progression: 42.7% of patients with Child–Pugh class A, 70.7% of patients with class B, and 75.5% of patients with class C have esophageal varices [4]. The development of new varices is linear over time at a rate of approximately 9% per year and new varices increase in size by 10–12% each year [5, 6]. The incidence rate of bleeding from untreated esophageal varices ranges from 20 to 76% [7, 8]. Bleeding from ruptured esophageal varices is directly linked to high mortality in patients with cirrhosis [9]. The mortality rate at 6 weeks is as high as 16–26% for patients with acute variceal bleeding despite the advances in its treatment [10, 11]. Moreover, most deaths occur after early rebleeding, which occurs in 20–50% of patients within 7–10 days of the first bleeding incident [4]. Therefore, the early detection and management of esophageal varices might lead to survival benefits, and identifying the presence of varices needing treatment (VNT) is an essential part of the diagnostic examination for cirrhotic patients [4]. In this review, we focus on the noninvasive detection of VNT in cirrhotic patients.

Cirrhosis is often complicated by the development of portal hypertension. When clinically significant portal hypertension (CSPH), the definition of which is a hepatic venous pressure gradient (HVPG) ≥ 10 mmHg, develops, collaterals such as varices appear. The increase in portal pressure above the threshold of CSPH is a point in the natural course of advanced chronic liver disease (ACLD). Screening for VNT

Tetsuo Takehara and Ryotaro Sakamori contributed equally to this manuscript.

✉ Tetsuo Takehara
takehara@gh.med.osaka-u.ac.jp

[1] Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

in CSPH patients is essential to medical treatment. Although portal hypertension is measured by the HVPG, it is limited by the invasiveness of the procedure.

Esophago-gastro-duodenoscopy (EGD) is the gold standard for diagnosing the presence of varices [12], and current guidelines recommend that all patients identified as having ACLD should undergo screening for EGD [13]. 'General Rules for Recording Endoscopic Findings of Esophagogastric Varices (2nd Edition)' (Table 1) is used in many countries for the classification of esophageal varices [14]. There are several reports that large varices are a risk factor for bleeding esophageal varices [15–17]. The presence of red color signs was also identified as an independent risk factor for variceal bleeding even in patients with small varices [5]. Red color signs are reddish changes observed beneath the submucosa [12, 15–18]. According to these risk factors, the therapeutic indication for esophageal varices is guided by several guidelines (Table 2) [2, 12, 19, 20]. Esophageal varices can be classified as low-risk and high-risk varices according to the respective risk for variceal bleeding determined by the size of the varices, the presence of red color signs, and Child–Pugh class [12]. Reiberger reported that only 2% of patients without varices on first endoscopy bled within 2 years and that the rate of progression from small esophageal varices at baseline to large esophageal varices was 12% (5.6–18.4%) and 31% (21.2–40.8%) at 1 and 3 years, respectively [21]. Assessment of the presence of varices, red color signs, and the size of varices necessitates EGD examination. Because the risk of variceal bleeding can be reduced with advanced endoscopic treatment and appropriate medical therapy in patients with high-risk esophageal varices, the endoscopic screening of esophageal varices is currently the normal medical countermeasure in patients with liver cirrhosis [19]. The American Association for the

Table 1 General rules for recording endoscopic findings of esophagogastric varices

Category	Code subcategory	
	Esophageal varices	Gastric varices
Location (L)	Ls: Locus superior	Lg-c: Adjacent to the cardiac orifice
	Lm: Locus medialis	Lg-cf: Extension from the cardiac orifice to the fornix
	Li: Locus inferior	Lg-f: Isolated in the fornix
		Lg-b: Located in the gastric body
		Lg-a: Located in the gastric antrum
Form (F)	F0: No varicose appearance	
	F1: Straight, small-caliber varices	
	F2: Moderately enlarged, beady varices	
	F3: Markedly enlarged, nodular or tumor-shaped varices	
Color (C)	Cw: White varices	
	Cb: Blue varices	
	Cw-Th: Thrombosed white varices	
	Cb-Th: Thrombosed blue varices	
Red color sign (RC)	RWM: Red wale marking	RC0: Absent
	CRS: Cherry red spot	RC1: GV with RWM, CRS, and/or HCS
	HCS: Hematocystic spot	
	RC0: Absent	
	RC1: Small in number and localized	
	RC2: Intermediate between RC1 and RC3	
	RC3: Large in number and circumferential	
	TE: Telangiectasia	
Bleeding sign	Gushing bleeding	
	Spouting bleeding	
	Oozing bleeding	
	Red plug	
	White plug	
Mucosal finding	E: Erosion	
	Ul: Ulcer	
	S: Scar	

Table 2 Therapeutic indication for esophageal varices

Guideline	Therapeutic indication
AASLD [19]	Medium/large varices (≥ 5 mm diameter)
	Small varices (< 5 mm) with red wale signs
	Decompensated patients with small varices
Baveno VI Consensus Workshop [2]	Medium/large size (≥ 5 mm diameter)
	Small varices (< 5 mm) with red spot signs
North Italian Endoscopic Club [12]	Medium/large size (≥ 5 mm diameter)
	Small varices (< 5 mm) with red spot signs
	Small varices in patients with Child–Pugh C
Japan [20]	≥ F2 (Moderately enlarged, beady varices)
	RC 2–3

Study of Liver Disease (AASLD) clinical practice guidelines recommend that all patients with liver cirrhosis receive an EGD at the time of liver cirrhosis diagnosis to screen for esophageal varices and describe the presence or absence of VNT. In this way, clinicians can make evidence-based decisions regarding primary prevention against esophageal variceal bleeding [13]. Based on the endoscopic evaluation, esophageal varices are classified by size into small (< 5 mm) and large varices (> 5 mm) [19] for the prediction of the risk variceal bleeding. In liver cirrhosis patients without varices who have ongoing liver injury (e.g., alcohol use and presence of hepatitis virus) and/or other liver-related disease (e.g., obesity), screening endoscopies should be repeated at 2-year intervals. An endoscopy is recommended every 2 years for patients with small varices (< 5 mm) without present continuous liver disease. Annual endoscopic examination is recommended if patients present with continuous liver disease. Patients who have large varices (> 5 mm) should be started on treatment with nonselective beta blockers, which are used in the treatment of portal hypertension to reduce portal pressure, thereby preventing variceal bleeding, and no further surveillance endoscopy is needed. Endoscopic treatment, such as endoscopic variceal ligation (EVL) and endoscopic injection sclerotherapy (EIS), is recommended for patients with large varices. If endoscopic treatment is performed for primary prophylaxis, following endoscopic examination should be performed every 1 week or 2 weeks until the varices disappearance and then repeated every 6 or 12 months. In addition, patients require routine endoscopic examination after EVL or EIS for the surveillance of variceal recurrence. However, screening by endoscopy results in many unnecessary unpleasant procedures, because VNT are not common in patients with liver cirrhosis. Meanwhile, EGD is an invasive technique that is not easily accepted by patients and has some disadvantages, such as higher cost and interobserver variability [2, 19]. Therefore, some approaches to reducing the frequency of unnecessary EGD procedures have been advocated. Recently, several noninvasive techniques for the diagnosis of liver cirrhosis have been developed. Considering the well-established relationship between fibrosis, portal hypertension, and esophageal varices, noninvasive tests for fibrosis in liver cirrhosis should also be useful methods for screening for esophageal varices.

Several laboratory/imaging-derived markers associated with the presence of esophageal varices in liver cirrhosis patients, such as low platelet count [22], splenomegaly [23], increased Child–Pugh score [22], magnetic resonance elastography, and splenic stiffness, have been reported; however, none of them are adequately accurate for the prediction of the presence of high-risk varices when tested in independent validation cohorts [23].

Liver stiffness as measured by transient elastography (TE) can be considered a useful tool for the noninvasive diagnosis of liver fibrosis and has been shown to be very accurate for the evaluation of portal hypertension [24]. Marked progress in noninvasive diagnostic modalities for the estimation of chronic liver disease has enabled the identification of severe fibrosis and cirrhosis in patients. Among the several noninvasive medical tools, the determination of liver stiffness by TE using Fibroscan has gradually replaced liver biopsy for the estimation of liver fibrosis. In addition to the diagnosis of liver cirrhosis, TE has been shown to have good ability to diagnose the presence of high-risk varices [25] and has now been adopted as a valuable noninvasive technique. Because the combination of liver stiffness measured by Fibroscan and platelet count can identify the presence of VNT, the Baveno VI guidelines proposed that patients with liver cirrhosis with a lower liver stiffness measurement (LSM) (< 20 kPa) and a higher platelet count (> 150,000/μl) can avoid unnecessary endoscopy for the surveillance of VNT [2], and the utility of this criteria for excluding the patients without VNT has been validated in different studies [26]. Since even the Baveno VI criteria included many patients who did not have VNT, the expanded Baveno VI criteria, obtained by optimizing the LSM (< 25 kPa) and platelet count value (> 110,000/μl), have been proposed. The expanded Baveno VI criteria resulted in sparing more patients from unnecessary endoscopy procedures than the original Baveno VI criteria [27],

but also resulted in an increased risk of missing high-risk varices. Several researchers have provided validation studies of these criteria [28–32], confirming that the Baveno VI criteria and expanded Baveno VI criteria correctly identify more than 98% of patients who could avoid unnecessary EGD. These two sets of criteria have been adopted in the practice guidelines of the American Association for the Study of the Liver [19], which suggests using noninvasive liver stiffness stratification according to the Baveno VI criteria in all patients with a new diagnosis of cirrhosis. However, the Baveno VI recommendations are not 100% matched to the endoscopic diagnosis of VNT and have some problems that need to be solved. Many researchers have proposed various models and diverse cutoffs to increase the number of EGDs that could be avoided. Although several authors have tried to modify the cutoff values of the LSM (25–30 kPa) and platelet count (100,000–120,000/μl) [31, 33], the best cutoff values have not been definitely identified. Moreover, there are some problems associated with the etiology of liver disease and medical equipment. Because the Baveno VI and expanded Baveno VI criteria were extensively evaluated in patients with cirrhosis mostly due to hepatitis C viral infection or excessive alcohol consumption, they should be validated in patients with other liver diseases. In addition, TE is not available in underdeveloped countries, and new attempts to define other noninvasive criteria that do not require TE by Fibroscan are needed. In those countries, most patients who do not present with high-risk varices according to the Baveno or expanded Baveno VI criteria still have to undergo EGD, and it is becoming evident that the validation of models that do not include LSM by TE are needed to improve risk stratification [34].

With regard to other noninvasive methodologies, liver stiffness can also be evaluated by magnetic resonance elastography, shear wave electrography (SWE, Supersonic Imaging), real-time tissue elastography (Hitachi), and acoustic radiation force impulse (ARFI, Siemens). ARFI imaging, which has been proposed as another promising ultrasound-based shear wave elastography with a high level of accuracy for predicting liver fibrosis, can be used even in patients with ascites and obese patients [35]. Several studies have evaluated the usefulness of ARFI elastography for predicting esophageal varices [36–38]. The accuracy of ARFI measurement is greater than that of transient elastography (TE) [39]; however, data in American and European patients are lacking. The spleen and liver react to portal hypertension by changing their stiffness and density. Spleen stiffness and the combination of platelet count, spleen size, and liver stiffness have provided greater accuracy in comparison to other noninvasive parameters with regard to the identification of patients with VNT [37, 40]. In addition, spleen stiffness is superior to liver stiffness for the prediction of portal hypertension [41]. However, spleen stiffness is not yet ready for use in routine clinical practice.

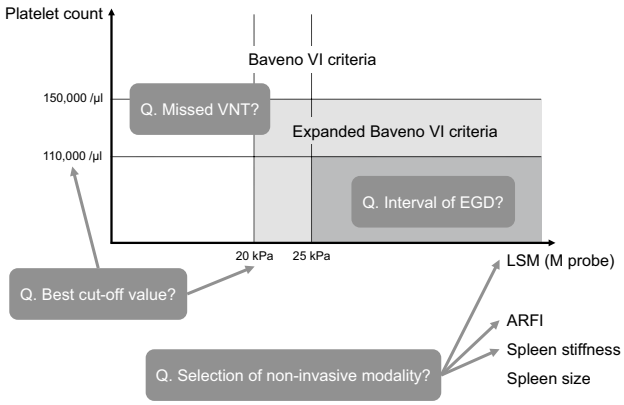

Fig. 1 Remaining challenges of noninvasive diagnosis of esophageal varices. The schematic plot of LSM (*X* axis) vs. the platelet count (*Y* axis) shows the zones needing EGD surveillance. This schematic plot summarizes the three zones needing EGD surveillance: unnecessary endoscopy for the surveillance of VNT according to the Baveno VI criteria (white), additional unnecessary endoscopy for the surveillance of VNT according to the Expanded Baveno VI criteria (light gray), and the presence of high-risk varices according to the Expanded Baveno VI criteria (dark gray). Four rectangles illustrate the limitations and problems to be solved by further investigation. *EGD* esophago-gastro-duodenoscopy, *LSM* liver stiffness measurement, *VNT* varices needing treatment

The cutoff values for liver stiffness for predicting cirrhosis vary according to the underlying cause of liver disease [42]. The etiology of cirrhosis has a strong impact on the liver stiffness cutoff for the diagnosis of large varices [43]. Therefore, there is no consensus regarding the best cutoff value for predicting high-risk esophageal varices, but it is influenced by the etiology of cirrhosis [44]. Sustained virologic response (SVR) after any anti-hepatitis C virus (HCV) therapy with direct-acting antivirals (DAAs) can be obtained in many HCV patients even if they have decompensated cirrhosis. SVR is associated with beneficial effects, such as the improvement of fibrosis [44] and a decline in portal pressure [45], eventually resulting in a marked decrease in death, liver transplantation, hepatocellular carcinoma, and liver-related complications [46, 47]. However, in cirrhotic patients, the elimination of HCV does not lead to a significant reduction in portal hypertension. That is, once chronic liver disease progresses to cirrhosis, it may become worse even after the elimination of HCV infection [48]. If esophageal varices were not present at the start of antiviral therapy, patients who achieve SVR may extend the surveillance interval for EGD. On the other hand, EGD surveillance must be regularly planned in non-SVR patients and in all patients who

have esophageal varices before antiviral therapy. Data in cirrhosis patients who achieve SVR are lacking.

In the future, noninvasive methods may replace the measurement of HVPG or EGD in the follow-up of patients with portal hypertension [49] and in predicting liver disease outcomes [50], including varices bleeding. However, there are several limitations and problems to be solved by further investigation (Fig. 1). First, the best cutoff value for liver stiffness has not been identified. Second, there are no recommendations regarding noninvasive modalities, TE, ARFI, or other tools. The third problem is whether the number of missed VNT is acceptable. Fourth, there is no consensus on the interval at which EGD needs to be performed after treatment. Fifth, in clinical practice, the best performing test to rule out VNT in cirrhotic patients should be explored. Further studies are needed to solve these remaining issues.

Author contributions TT and RS contributed to the study concept and design, interpretation of data, and drafting of the manuscript.

Compliance with ethical standards

Ethical Statement This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385:117–71.
2. de Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI consensus workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63:743–52.
3. Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. Gastroenterology. 2001;120:726–48.
4. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. Hepatology. 1995;22:332–54.
5. Merli M, Nicolini G, Angeloni S, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol. 2003;38:266–72.
6. Groszmann RJ, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med. 2005;353:2254–61.
7. Triger DR, Smart HL, Hosking SW, et al. Prophylactic sclerotherapy for esophageal varices: long-term results of a single-center trial. Hepatology. 1991;13:117–23.
8. Paquet KJ, Kalk JF, Klein CP, et al. Prophylactic sclerotherapy for esophageal varices in high-risk cirrhotic patients selected by endoscopic and hemodynamic criteria: a randomized, single-center controlled trial. Endoscopy. 1994;26:734–40.
9. Kim DJ, Choi MS. Life-sustaining treatment and palliative care in patients with liver cirrhosis - legal, ethical, and practical issues. Clin Mol Hepatol. 2017;23:115–22.
10. Reverter E, Tandon P, Augustin S, et al. A MELD-based model to determine risk of mortality among patients with acute variceal bleeding. Gastroenterology. 2014;146(412–19):e3.
11. Fortune BE, Garcia-Tsao G, Ciarleglio M, 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;51:446–53.
12. North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med. 1988;319:983–9.
13. Tripathi D, Stanley AJ, Hayes PC, et al. UK guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut. 2015;64:1680–704.
14. Tajiri T, Yoshida H, Obara K, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc. 2010;22:1–9.
15. Merkel C, Zoli M, Siringo S, et al. Prognostic indicators of risk for first variceal bleeding in cirrhosis: a multicenter study in 711 patients to validate and improve the North Italian Endoscopic Club (NIEC) index. Am J Gastroenterol. 2000;95:2915–20.
16. Kleber G, Sauerbruch T, Ansari H, et al. Prediction of variceal hemorrhage in cirrhosis: a prospective follow-up study. Gastroenterology. 1991;100:1332–7.
17. Siringo S, Bolondi L, Gaiani S, et al. Timing of the first variceal hemorrhage in cirrhotic patients: prospective evaluation of Doppler flowmetry, endoscopy and clinical parameters. Hepatology. 1994;20:66–73.
18. Jensen DM. Endoscopic screening for varices in cirrhosis: findings, implications, and outcomes. Gastroenterology. 2002;122:1620–30.
19. Garcia-Tsao G, Abraldes JG, Berzigotti A, 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;65:310–35.
20. The Japanese Society of Gastroenterology. Evidence-based clinical practice guidelines for liver cirrhosis. Tokyo: Nankodo Press; 2015.
21. Reiberger T, Bucsics T, Paternostro R, et al. Small esophageal varices in patients with cirrhosis-should we treat them? Curr Hepatol Rep. 2018;17:301–15.
22. Schepis F, Camma C, Niceforo D, et al. Which patients with cirrhosis should undergo endoscopic screening for esophageal varices detection? Hepatology. 2001;33:333–8.
23. de Franchis R. Noninvasive diagnosis of esophageal varices: is it feasible? Am J Gastroenterol. 2006;101:2520–2.
24. Shi KQ, Fan YC, Pan ZZ, et al. Transient elastography: a meta-analysis of diagnostic accuracy in evaluation of portal hypertension in chronic liver disease. Liver Int. 2013;33:62–71.
25. European Association for Study of Liver, Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH clinical practice guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol. 2015;63:237–64.
26. Augustin S, Pons M, Genesca J. Validating the Baveno VI recommendations for screening varices. J Hepatol. 2017;66:459–60.
27. Augustin S, Pons M, Maurice JB, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. Hepatology. 2017;66:1980–8.
28. Abraldes JG, Bureau C, Stefanescu H, et al. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: the "Anticipate" study. Hepatology. 2016;64:2173–84.

29. Maurice JB, Brodkin E, Arnold F, et al. Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices. J Hepatol. 2016;65:899–905.
30. Jangouk P, Turco L, de Oliveira A, et al. Validating, deconstructing and refining Baveno criteria for ruling out high-risk varices in patients with compensated cirrhosis. Liver Int. 2017;37:1177–83.
31. Llop E, Lopez M, de la Revilla J, et al. Validation of noninvasive methods to predict the presence of gastroesophageal varices in a cohort of patients with compensated advanced chronic liver disease. J Gastroenterol Hepatol. 2017;32:1867–72.
32. Cales P, Sacher-Huvelin S, Valla D, et al. Large oesophageal varice screening by a sequential algorithm using a cirrhosis blood test and optionally capsule endoscopy. Liver Int. 2018;38:84–93.
33. Marot A, Trepo E, Doerig C, et al. Liver stiffness and platelet count for identifying patients with compensated liver disease at low risk of variceal bleeding. Liver Int. 2017;37:707–16.
34. Castera L, Pinzani M, Bosch J. Non invasive evaluation of portal hypertension using transient elastography. J Hepatol. 2012;56:696–703.
35. Bota S, Sporea I, Sirli R, et al. Factors associated with the impossibility to obtain reliable liver stiffness measurements by means of Acoustic Radiation Force Impulse (ARFI) elastography-analysis of a cohort of 1,031 subjects. Eur J Radiol. 2014;83:268–72.
36. Vermehren J, Polta A, Zimmermann O, et al. Comparison of acoustic radiation force impulse imaging with transient elastography for the detection of complications in patients with cirrhosis. Liver Int. 2012;32:852–8.
37. Takuma Y, Nouso K, Morimoto Y, et al. Measurement of spleen stiffness by acoustic radiation force impulse imaging identifies cirrhotic patients with esophageal varices. Gastroenterology. 2013;144(92–101):e2.
38. Morishita N, Hiramatsu N, Oze T, et al. Liver stiffness measurement by acoustic radiation force impulse is useful in predicting the presence of esophageal varices or high-risk esophageal varices among patients with HCV-related cirrhosis. J Gastroenterol. 2014;49:1175–82.
39. Rizzo L, Calvaruso V, Cacopardo B, et al. Comparison of transient elastography and acoustic radiation force impulse for non-invasive staging of liver fibrosis in patients with chronic hepatitis C. Am J Gastroenterol. 2011;106:2112–20.
40. Berzigotti A, Seijo S, Arena U, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterology. 2013;144(102–11):e1.
41. Tseng Y, Li F, Wang J, et al. Spleen and liver stiffness for noninvasive assessment of portal hypertension in cirrhotic patients with large esophageal varices. J Clin Ultrasound. 2018;46:442–9.
42. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology. 2008;134:960–74.
43. Nguyen-Khac E, Saint-Leger P, Tramier B, et al. Noninvasive diagnosis of large esophageal varices by Fibroscan: strong influence of the cirrhosis etiology. Alcohol Clin Exp Res. 2010;34:1146–53.
44. D'Ambrosio R, Aghemo A, Rumi MG, et al. A morphometric and immunohistochemical study to assess the benefit of a sustained virological response in hepatitis C virus patients with cirrhosis. Hepatology. 2012;56:532–43.
45. Rincon D, Ripoll C, Lo Iacono O, et al. Antiviral therapy decreases hepatic venous pressure gradient in patients with chronic hepatitis C and advanced fibrosis. Am J Gastroenterol. 2006;101:2269–74.
46. Morgan TR, Ghany MG, Kim HY, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology. 2010;52:833–44.
47. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;308:2584–93.
48. di Marco V, Calvaruso V, Ferraro D, et al. Effects of eradicating hepatitis C virus infection in patients with cirrhosis differ with stage of portal hypertension. Gastroenterology. 2016;151(130–9):e2.
49. Colecchia A, Montrone L, Scaioli E, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. Gastroenterology. 2012;143:646–54.
50. Colecchia A, Colli A, Casazza G, et al. Spleen stiffness measurement can predict clinical complications in compensated HCV-related cirrhosis: a prospective study. J Hepatol. 2014;60:1158–64.