Chapter 3

Alternative Diagnostic Tests of Gastroesophageal Varices in Liver Cirrhosis: Recent Advance

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Abstract

Routine screening for gastroesophageal varices in liver cirrhosis is necessary. At present, upper gastrointestinal endoscopy is the golden diagnostic test of gastroesophageal varices. However, the use of upper gastrointestinal endoscopy is restricted because of its poor compliance and adverse events. In this chapter, we reviewed the recent evidence regarding the value of noninvasive or less invasive tests for the diagnosis of gastroesophageal varices in liver cirrhosis.

Keywords: varices, liver cirrhosis, endoscopy, meta-analysis, noninvasive

1. Introduction

Gastroesophageal varices and their related bleeding are one of the most common and lethal complications of liver cirrhosis [1, 2]. The prevalence of gastroesophageal varices is approximately 50% at the diagnosis of liver cirrhosis [2]. In the absence of any interventions, Groszmann et al. reported that the incidence of confirmed small varices, large varices, and variceal bleeding in patients without any previous history of varices was 28.6, 3.8, and 2.9% during a median duration of follow-up of 54.9 months, respectively [3]. Merli et al. reported that the 1-, 2-, and 3-year incidence of varices in cirrhotic patients without varices was 5, 17, and 28%, respectively [4]. In this chapter, we mainly review the following contents: the practice guideline and consensus recommendations regarding screening for gastroesophageal varices in liver cirrhosis, current understanding regarding alternative diagnostic tests of gastroesophageal varices in liver cirrhosis, and diagnostic accuracy of different alternative diagnostic tests.

2. Screening for gastroesophageal varices in liver cirrhosis

Upper gastrointestinal endoscopy is the golden diagnostic test of gastroesophageal varices. There are some recommendations from practice guideline and consensus regarding endoscopic screening for gastroesophageal varices in liver cirrhosis.

According to the UK practice guideline on the management of variceal hemorrhage in cirrhotic patients, there are high levels of evidence regarding the surveillance of gastroesophageal varices in liver cirrhosis [5]. First, all patients with cirrhosis should undergo endoscopy at the time of diagnosis. Second, in the absence of varices, patients with cirrhosis should undergo endoscopy every 2–3 years. Third, in the cases of grade I varices, patients with cirrhosis should undergo endoscopy every year. Fourth, in the cases of disease progression, the intervals of endoscopy can be modified by the clinicians.

According to the Baveno VI consensus workshop, there are low levels of evidence and weak grade of recommendation regarding the surveillance of esophageal varices in liver cirrhosis [6]. First, compensated cirrhosis without ongoing liver injury or varices should undergo endoscopy every 3 years. Second, compensated cirrhosis with ongoing liver injury without varices should undergo endoscopy every 2 years. Third, compensated patients with small varices without ongoing liver injury should undergo endoscopy every 2 years. Fourth, compensated patients with ongoing liver injury and small varices should undergo endoscopy every year.

The recommendations of the 2016 Practice Guidance by the American Association for the Study of Liver Diseases are similar to those of the Baveno VI consensus [7]. First, in the absence of varices, compensated cirrhosis with and without ongoing liver injury should undergo endoscopy every 2 and 3 years, respectively. Second, in the presence of small varices, compensated cirrhosis with and without ongoing liver injury should undergo endoscopy every 1 and 2 years, respectively. Third, compensated cirrhosis should undergo endoscopy at the time when decompensation events develop.

Although the recommendations regarding the interval of endoscopy and target population are heterogeneous among practice guidelines, repeated endoscopy is necessary for cirrhotic patients. However, endoscopic examinations have several limitations. First, nearly all patients are reluctant for endoscopy. Patients may have poor complaint regarding endoscopy. Second, not all endoscopic examinations are safe. The endoscopy-related adverse events are more frequent and severe in patients with cardiovascular and cerebrovascular diseases.

3. Current knowledge about alternative diagnostic tests of gastroesophageal varices in liver cirrhosis

A questionnaire survey assessed the knowledge about alternative diagnostic tests of gastroesophageal varices in 42 members from the Gastroenterology Branch of the Liaoning Medical Association, China [8]. Indeed, alternative diagnostic tests are rarely or never employed in

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clinical practice. In the following text, several major alternative diagnostic tests, such as serum liver fibrosis parameters, platelet count to spleen diameter ratio (PSR), liver and spleen stiffness, capsule endoscopy, and computed tomography, are reviewed on the basis of major evidence, especially the results of meta-analyses. The data regarding sensitivity and specificity are primarily presented.

4. Serum liver fibrosis parameters for diagnosis of gastroesophageal varices

Hyaluronic acid (HA), laminin (LN), amino-terminal propeptide of type III procollagen (PIIINP), and collagen IV (CIV) are major serum parameters for the assessment of liver fibrosis. A retrospective study evaluated their value of diagnosis of gastroesophageal varices [9]. Unfortunately, all of them could not accurately predict the presence of gastroesophageal varices.

APRI, AAR, FIB-4, FI, King, Lok, Forns, and FibroIndex are the major scores for the assessment of liver fibrosis. Deng et al. systematically reviewed their diagnostic accuracy of gastroesophageal varices [10]. The authors found that APRI, AAR, FIB-4, Lok, Forns, and FibroIndex scores had been evaluated, but not FI or King score. As for the diagnosis of gastroesophageal varices, the sensitivity and specificity of APRI were 0.60 and 0.67, respectively; those of AAR were 0.64 and 0.63, respectively; those of Lok were 0.74 and 0.68, respectively; and the area under the summary receiver operating characteristic curve of these scores ranged from 0.6774 to 0.7885. As for the diagnosis of large varices, the sensitivity and specificity of APRI were 0.65 and 0.66, respectively; those of AAR were 0.68 and 0.58, respectively; those of FIB-4 were 0.62 and 0.64, respectively; those of Lok were 0.78 and 0.63, respectively; those of Forns were 0.65 and 0.61, respectively; and the area under the summary receiver operating characteristic curve of these scores ranged from 0.6530 to 0.7448. More recently, a retrospective study further confirmed these findings [11]. More importantly, their diagnostic accuracy should be improved after the exclusion of previous gastrointestinal bleeding and splenectomy.

5. PSR for diagnosis of gastroesophageal varices

PSR is a ratio of the platelet count (/mm^3) to the spleen diameter (mm). Multiple meta-analyses evaluated the diagnostic accuracy of PSR for varices. Chawla et al. conducted a meta-analysis of eight studies to explore the diagnostic accuracy of PSR with a cut-off value of 909 for the presence of esophageal varices in cirrhosis [12]. They found a sensitivity of 0.89 and a specificity of 0.74, but the evidence was of low quality according to the GRADE rule. Ying et al. performed another meta-analysis of 20 studies to assess the value of PSR with a cut-off value of 909 for esophageal varices in cirrhosis [13]. By comparison, they showed a relatively higher sensitivity of 0.92 and a specificity of 0.87, and the quality of studies was moderate according to the quality assessment of diagnostic accuracy studies (QUADAS) questionnaires. More recently, Chen et al. reported the results from an updated meta-analysis of 49 studies that the

summary sensitivity and specificity of PSR for any varices were 0.84 and 0.78, respectively, and that the summary sensitivity and specificity of PSR for high-risk varices were 0.78 and 0.67, respectively [14]. Similarly, the authors considered that the quality of included studies was moderate. Taken together, the evidence supported the use of PSR for identifying the presence of varices. However, its diagnostic accuracy is not high.

6. Liver and spleen stiffness measurement for diagnosis of gastroesophageal varices

Major evidence can be obtained from the results of several large meta-analyses. Pu et al. identified a total of 15 papers regarding liver stiffness measurement by FibroScan transient elastography for esophageal varices [15]. The pooled sensitivity and specificity of liver stiffness for any varices were 0.84 and 0.62, respectively; the pooled sensitivity and specificity of liver stiffness for large varices were 0.78 and 0.76, respectively. Similarly, Qu et al. also performed a meta-analysis of 20 studies to evaluate the performance of liver stiffness by transient elastography for esophageal varices [16]. As for any varices, the pooled sensitivity and specificity were 0.84 and 0.68, respectively. As for large varices, the pooled sensitivity and specificity were 0.84 and 0.72, respectively. Singh et al. synthesized the data from 12 studies regarding spleen stiffness for the diagnosis of esophageal varices [17]. As for any varices, the pooled sensitivity and specificity were 0.78 and 0.67, respectively. As for clinically significant esophageal varices, the pooled sensitivity and specificity were 0.81 and 0.66, respectively. More recently, Ma et al. conducted a meta-analysis of 16 studies to compare the diagnostic accuracy of liver vs. spleen stiffness for the diagnosis of gastroesophageal varices [18]. The authors found that the sensitivity and specificity of liver stiffness for the diagnosis of gastroesophageal varices were 0.83 (95% confidence interval: 0.78–0.87) and 0.66 (95% confidence interval: 0.60–0.72), respectively; those of spleen stiffness were 0.88 (95% confidence interval: 0.83–0.92) and 0.78 (95% confidence interval: 0.73–0.83), respectively. Importantly, the spleen stiffness had a significantly higher diagnostic accuracy than the liver stiffness (summary receiver operating characteristic curve value: 0.88 vs. 0.81, $p < 0.01$; diagnostic odds ratio: 25.73 vs. 9.54, $p < 0.01$).

7. Capsule endoscopy for diagnosis of gastroesophageal varices

Until now, two meta-analyses were published regarding this topic. In 2014, a Cochrane review of 15 studies including 936 patients with liver cirrhosis analyzed the diagnostic performance of capsule endoscopy for the diagnosis of esophageal varices [19]. As for any varices, the pooled sensitivity and specificity were 0.848 and 0.843, respectively. As for large varices, the pooled sensitivity and specificity were 0.737 and 0.905, respectively. More recently, McCarty et al. systematically reviewed the data from 17 studies regarding wireless capsule endoscopy

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for the diagnosis of esophageal varices [20]. As for any varices, the pooled sensitivity and specificity were 0.83 and 0.85, respectively. As for medium to large varices, the pooled sensitivity and specificity were 0.72 and 0.91, respectively.

8. Computed tomography scans for diagnosis of gastroesophageal varices

There are at least two meta-analyses regarding the value of computed tomography scans for the diagnosis of gastroesophageal varices. The first meta-analysis included 11 studies [21]. As for esophageal varices, the sensitivity and specificity were 0.896 and 0.723, respectively; as for gastric varices, the sensitivity and specificity were 0.955 and 0.658, respectively. The second meta-analysis included 17 studies [22]. As for any varices, the sensitivity and specificity were 0.87 and 0.80, respectively; as for any esophageal varices, the sensitivity and specificity were 0.87 and 0.81, respectively; as for any gastric varices, the sensitivity and specificity were 0.86 and 0.79, respectively. As for high-risk varices, the sensitivity and specificity were 0.87 and 0.88, respectively; as for high-risk esophageal varices, the sensitivity and specificity were 0.87 and 0.88, respectively; as for high-risk gastric varices, the sensitivity and specificity were 0.83 and 0.97, respectively. More recently, a retrospective study found that a diameter of esophageal varices of 3.9 mm on computed tomography scans might be the optimal cut-off value for the diagnosis of high-risk varices [23].

9. Endoscopic ultrasound

Researchers also explored the value of endoscopic ultrasound in the diagnostic evaluation of gastroesophageal varices [24]. Endoscopic ultrasound was inferior to conventional endoscopy in the diagnosis and grading of esophageal varices, but superior in the evaluation of para- or peri-esophageal veins and gastric varices. More importantly, the detection of para- or peri-esophageal veins by endoscopic ultrasound predicted the risk of bleeding and outcomes.

10. Conclusions

Alternative diagnostic tests of varices in liver cirrhosis have been widely explored in numerous studies. Several scores for the assessment of liver fibrosis are readily available, but have relatively low diagnostic accuracy. PSR and liver and spleen stiffness are noninvasive and have moderate diagnostic accuracy. By comparison, contrast-enhanced computed tomography and capsule endoscopy have relatively high diagnostic accuracy, but are expensive and potentially invasive (exposure to radiation). Thus, a diagnostic algorithm according to the cost and diagnostic performance of various diagnostic tests and clinical necessity should be

considered. In detail, PSR and liver and spleen stiffness should be the first step for the non-invasive diagnosis of varices; if a thorough evaluation of severity of liver diseases is simultaneously needed, contrast-enhanced computed tomography scans should be preferred and arranged earlier; if available, an endoscopic ultrasound can be performed to more accurately detect the para- or peri-esophageal veins.

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