

Noninvasive Markers of Esophageal Varices: Another Round, Not the Last

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Esophageal varices are a serious consequence of portal hypertension. They appear only after the hepatic venous pressure gradient (HVPG) has increased to at least 10 to 12 mm Hg.^{1,2} In patients with cirrhosis the incidence of esophageal varices increases by nearly 5% per year, and the rate of progression from small to large varices is approximately 5 to 10 % per year.^{3,4} Increasing size of varices is associated with an increase in variceal-wall tension to a critical level at which varices rupture and cause life-threatening bleeding. The mortality rate from variceal bleeding is about 20% when patients are treated optimally in hospital.⁵ However, an appreciable proportion of patients with variceal bleeding die before reaching the hospital.⁶ Thus, the true mortality rate from bleeding varices is considerably higher than relatively optimistic estimates based on hospitalized patients.

Because nonselective β -blockers and banding ligation prevent bleeding in more than half of patients with medium or large varices,^{7,8} practice guidelines for the treatment of portal hypertension in the United States⁹ and Europe¹⁰ have recommended endoscopic screening of patients with cirrhosis for varices, and treatment of patients with medium or large varices to prevent bleeding. It has been suggested that all patients should undergo endoscopic screening for varices at the time that cirrhosis is diagnosed, and every 2 to 3 years thereafter in those with compensated disease and no varices; the recommended time intervals between endoscopies for those with small varices was 1 to 2 years,¹¹ and 1 year for those with decompensated disease, with or without varices.^{9,11} These recommendations imply a considerable burden of endoscopies and related costs; they require that patients repeatedly undergo an unpleasant procedure, even though up to 50% of them may still not have developed esophageal

varices 10 years after the diagnosis of cirrhosis.⁴ Therefore, these guidelines might not be ideal for clinical practice. This inference is supported by recent studies from the United States¹² and Italy⁵ suggesting that the guidelines are not being fully adopted. Moreover, the guidelines were based largely on studies of patients with cirrhosis due to viral hepatitis or alcohol abuse; accordingly, it is unclear to what extent the guidelines may apply to patients with other causes of portal hypertension.

To reduce the number of unnecessary endoscopies in patients with cirrhosis but without varices, several studies have evaluated possible noninvasive markers of esophageal varices in patients with cirrhosis.^{13–21} The conclusion from most of these studies is that by selecting patients for endoscopic screening based on a few laboratory and/or ultrasonographic variables (usually the platelet count and the diameter of the portal vein), an appreciable number of endoscopies may be avoided, while keeping the rate of undiagnosed varices, which are at risk of bleeding, acceptably low (Table 1). However, the predictive accuracy of such noninvasive markers is still considered to be unsatisfactory, and none of them has been recommended for use in clinical practice so far.¹¹

Prevention of bleeding from esophageal varices is further complicated by uncertainty about whether nonselective β -blockers can prevent the development of varices or the progression of small varices to larger varices that may bleed. Multicenter, randomized, controlled trials to address this issue are ongoing in the United States and Europe. However, two recent analyses of cost-effectiveness^{22,23} suggested that the strategy of treating all cirrhotic patients without a history of bleeding with nonselective β -blockers, irrespective of the presence or size of varices (*i.e.*, avoiding endoscopy) is more cost-effective than the strategy of treating only patients with endoscopically proven risk-varices with β -blockers or banding ligation. A third analysis, however, confirmed that this strategy is most cost-effective only for patients who have decompensated disease; for patients who have compensated disease screening and treating only those with large varices is more cost-effective.²⁴

In this issue of HEPATOLOGY, Zein and colleagues at the Mayo Clinic report a study of potential noninvasive markers of esophageal varices in a consecutive series of 183 patients with primary sclerosing cholangitis (PSC).²⁵ The results of the study show that a platelet count of $< 150 \times 10^3/\text{dL}$ is associated with an odds ratio of 6.3 (95%

Abbreviations: HVPG, hepatic venous pressure gradient; PSC, primary sclerosing cholangitis; ROC, receiver operating characteristic.

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Table 1. Studies Assessing Noninvasive Predictors of Varices or Large Varices

| Author | Year | No. Pts | No. Pts With Varices | Child-Pugh Class A/B/C (%) | Predictors | Sensitivity | Specificity | False-Negative Rate* | Negative Rate† | Validation |
|---|------|---------|----------------------|----------------------------|---|-------------|-------------|----------------------|----------------|------------|
| Studies Assessing Noninvasive Predictors of Varices | | | | | | | | | | |
| Fook-Hong et al. ¹⁴ | 1999 | 92 | 53 | 41/47/12 | PLT < 150,000 and ascites | 0.75 | 0.62 | 0.35 | 0.40 | No |
| Schepis et al. ¹⁹ | 2001 | 143 | 80 | 59/41/0 | PLT < 100,000 or prothrombin < 70% or PV > 13 mm | 0.96 | 0.44 | 0.10 | 0.22 | External |
| Schepis et al., validation | 2001 | 105 | 57 | 68/32/0 | PLT < 100,000 or prothrombin < 70% or PV > 13 mm | 0.89 | 0.27 | 0.32 | 0.18 | External |
| Giannini et al. ²⁰ | 2003 | 145 | 89 | 37/36/27 | PLT/spleen ratio > 909‡ | 1.00 | 0.93 | 0.00 | 0.36 | No |
| Giannini, compensated patients | 2003 | 145 | 53 | 69/31/0 | PLT/spleen ratio > 909‡ | 1.00 | 0.77 | 0.00 | 0.49 | No |
| Thomopoulos et al. ²¹ | 2003 | 184 | 92 | | PLT < 118,000 or spleen > 135 mm§ or ascites | 0.95 | 0.37 | 0.13 | 0.21 | No |
| Zein et al. ²⁵ | 2004 | 183 | 47 | Nr | PLT < 150,000 | 0.62 | 0.90 | 0.13 | 0.77 | External |
| Zein, validation | 2003 | 70 | 26 | Nr | PLT < 150,000 | 0.62 | 0.86 | 0.21 | 0.69 | External |
| Studies Assessing Noninvasive Predictors of Large Varices | | | | | | | | | | |
| Cottone et al. ¹³ | 1986 | 213 | 43 | Nr | PV > 13 mm and no respiratory variations in SV and MV | 0.95 | 0.55 | 0.02 | 0.45 | No |
| Chalasan et al. ¹⁵ | 1999 | 346 | 70 | 22/48/30 | PLT < 88,000 and/or splenomegaly | 0.90 | 0.36 | 0.07 | 0.30 | Internal |
| Pilette et al. ¹⁶ | 1999 | 124 | 59 | 50/24/26 | PLT < 160,000 | 0.83 | 0.58 | 0.21 | 0.39 | No |
| Zaman et al. ¹⁷ | 1999 | 98 | 20 | 33/50/15 | PLT < 88,000 | 0.80 | 0.59 | 0.08 | 0.51 | No |
| Fook-Hong et al. ¹⁴ | 1999 | 92 | 19 | 41/47/12 | PLT < 150,000 and ascites | 1.00 | 0.51 | 0.00 | 0.40 | No |
| Madhotra et al. ¹⁸ | 2002 | 184 | 24 | 43/34/23 | PLT < 68,000 | 0.71 | 0.73 | 0.06 | 0.67 | No |
| Madhotra | 2002 | 184 | 24 | 43/34/23 | Splenomegaly | 0.75 | 0.57 | 0.06 | 0.53 | No |
| Zein et al. ²⁵ | 2004 | 183 | 19 | Nr | PLT < 150,000 | 0.74 | 0.82 | 0.04 | 0.77 | External |
| Zein, validation | 2003 | 72 | 9 | Nr | PLT < 150,000 | 0.88 | 0.76 | 0.02 | 0.69 | External |

Abbreviations: Pts, patients; Plt, platelet count/dL; PV, portal vein diameter on ultrasound; SV, splenic vein diameter on ultrasound; MV, mesenteric vein diameter on ultrasound.
 *False negative / (false negative + true negative). Indicates the rate of patients who would be erroneously classified as not having varices and thus would not be submitted to endoscopy.
 †(False negative + true negative) / total of patients. Indicates the rate of patients who would be excluded from endoscopy.
 ‡Platelet count per dL/longitudinal spleen diameter in mm on ultrasound.
 §Longitudinal spleen diameter.

CI: 2.6–15.8) for the presence of varices. This figure corresponds to a sensitivity and specificity of 62% and 90%, respectively, for the detection of esophageal varices, and a negative predictive value of 87%. Corresponding figures for large varices are 74%, 82%, and 96%, respectively. These predictive characteristics of the platelet count were validated in a subsequent group of 72 patients with PSC. The authors suggest that a platelet count of $< 150 \times 10^3/\text{dL}$ may be a satisfactory marker for identifying patients with PSC who are likely to benefit from endoscopic screening for esophageal varices.

This study is interesting for several reasons: 1) it provides information on the prevalence of varices (36%), and the prevalence of medium or large varices (20%) in PSC; 2) it is the first study to assess noninvasive markers of varices in this disease; 3) the number of patients included is substantial for such a rare disease; and 4) an external validation of the results is provided. One important finding in this study is that only 53% of patients with esophageal varices had cirrhosis on liver biopsy. This finding may have been influenced by sampling error of liver biopsies which may lead to histological understaging of a considerable proportion of patients, particularly in PSC.²⁶ Thus, noninvasive markers of esophageal varices may be more useful in patients with this disease than in those with portal hypertension due to other causes. However, the inclusion of patients with and without cirrhosis in this study makes the results difficult to interpret with respect to predicting the presence of esophageal varices. Indeed, in the reported multivariable logistic analysis, the presence of cirrhosis on liver biopsy was a significant predictor of esophageal varices, as was a platelet count of $< 150 \times 10^3/\text{dL}$ and a serum albumin concentration of $< 3.3 \text{ g/dL}$. These findings indicate that the probability of esophageal varices being present for a given platelet count and albumin concentration may depend on whether or not cirrhosis is found on liver biopsy. In other words, the predictive value of the platelet count and the albumin concentration would be different in patients with and without cirrhosis on liver biopsy. A separate analysis of patients with and without cirrhosis might have clarified this point, but unfortunately, such an analysis was not included in the report. However, the lack of such an analysis is a minor issue, because a liver biopsy is often not necessary to diagnose PSC.²⁷

There is another uncertainty in interpreting the results of this study. While the reported multivariable logistic analyses reveal three significant predictors of varices (platelets $< 150 \times 10^3/\text{dL}$; serum albumin $< 3.3 \text{ g/dL}$; and cirrhosis on liver biopsy) and two significant predictors of large varices (platelet count and albumin concentration), the authors' interpretation of their results does

not take into account the whole predictive models; the interpretation is mainly based on the predictive value of the platelet count.

Different cutoff values for the platelet count have previously been reported to define significant markers for the presence of varices or large varices (Table 1).^{14–19,21,25} The lower the proportion of patients in Child-Pugh class A is, the lower the level of the cutoff values tends to be. In six studies that suggested a cutoff value of 100,000/dL, the proportion of patients who were in Child-Pugh class A was 41% in one, $\geq 50\%$ in three, and was not reported in two; one of these last two studies was the one by Zein and colleagues, which included more than 50% of patients without cirrhosis (Table 1). In contrast, in all three studies that suggested a cutoff value of $< 100,000/\text{dL}$, the proportion of patients in Child-Pugh class A was $< 50\%$ (Table 1). Moreover, each of these three studies aimed at predicting large varices, whereas those that suggested higher cutoff values aimed at predicting varices irrespective of their size. It seems plausible, therefore, that the different cutoff values for the platelet count in predicting the presence of varices are influenced by the distribution of patients according to the degree of liver dysfunction. This type of influence in the evaluation of diagnostic procedures, known as the *spectrum bias*, may occur when the study population has a different clinical spectrum (either earlier or more advanced stages of disease) than the population in which the test is to be applied.²⁸ Although the number of studies that have assessed the value of the platelet count in the prediction of varices is substantial, we are still not able to determine a reliable cutoff for application in clinical practice. Nevertheless, we have learned that a low platelet count is associated with the presence of esophageal varices, and, consequently, that it has potential for predicting their presence. However, we still lack adequate information on the true dimension of the association, probably because of inadvertent spectrum bias in several of the available studies.

Overall, the available studies (Table 1) do provide useful information on noninvasive markers of esophageal varices. In addition to the platelet count, other markers identified are the prothrombin time, albumin concentration, splenic size, and portal vein diameter (on ultrasound). The various predictive rules suggested are associated with sensitivities that range from 0.62 to 1.0 (median, 0.86); values are higher in studies of markers of varices (median, 0.92; range, 0.62–1.0) than in studies of markers of large varices (median, 0.83; range 0.71–1.0). Median (and range) for false-negative rate (the proportion of patients with varices who would be erroneously excluded from endoscopy) in the whole set of studies is 0.07 (0.00–0.35); the corresponding figure in studies of mark-

ers of varices irrespective of their size is 0.12 (0.00–0.35); in studies of markers of large varices, the corresponding figure is 0.07 (0.00–0.21). The whole spectrum of these results is represented in Fig. 1 and Fig. 2 by summary weighted receiver operating characteristic (ROC) curves,²⁹ which clearly show that the dispersion of the discriminating ability of the prediction rules proposed is wider for all varices (Fig. 1) than for only large varices (Fig. 2). This finding probably reflects differences in the characteristics of patients (the *disease spectrum*) in the different studies rather than differences in the markers, which are similar in most of the studies. The summary ROC curves, however, also show that we still cannot identify reliable noninvasive markers of varices that would be acceptable for use in clinical practice. The acceptability of such markers will depend mainly on their false-negative rate, *i.e.* the number of patients with varices and an increased risk of bleeding who will be misdiagnosed because of exclusion from endoscopic screening. It will be difficult to identify the ideal predictor associated with a zero-false-negative rate; the two reported so far^{14,20} have not been validated. Also, it will be difficult to determine an acceptable false-negative rate, which leads to some patients with large varices and an increased risk of bleeding and death being falsely classified as not at risk.

Analyses of cost-effectiveness favor a strategy of treating all patients with cirrhosis who have never bled with β -blockers but without endoscopic screening.^{22–24} However, analyses of cost-effectiveness depend on assumptions, which may be affected by several factors, including biases in the studies on which they are based. Therefore, their conclusions might be inadvertently, but significantly, at variance with reality. Such conclusions, therefore, should be tested in randomised, controlled trials before being incorporated into recommendations for clinical practice.

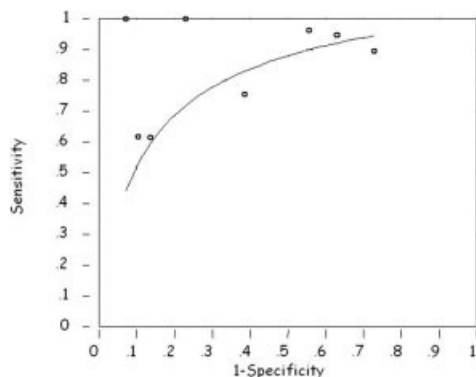


Fig. 1. Summary weighted ROC (receiver operating characteristic) curves of noninvasive predictors of esophageal varices, independent of variceal size. Open circles in the graph represent the studies reported in Table 1. Each study is identified by the sensitivity and specificity values reported in the table.

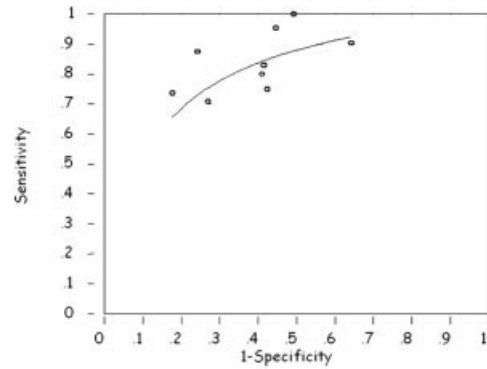


Fig. 2. Summary weighted ROC (receiver operating characteristic) curves of noninvasive predictors of large esophageal varices. Open circles in the graph represent the studies reported in Table 1. Each study is identified by the sensitivity and specificity values reported in the table.

ical practice. The results of the ongoing trials of nonselective β -blockers for the prevention of varices or their progression might modify current guidelines. However, for the time being, it will still be necessary to submit patients with cirrhosis to endoscopic screening, while encouraging further large, multicenter, well-designed studies of noninvasive markers of esophageal varices.²⁸

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