

Platelet Count/Spleen Diameter Ratio for the Noninvasive Diagnosis of Esophageal Varices: Results of a Multicenter, Prospective, Validation Study

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BACKGROUND AND AIMS: Noninvasive assessment of esophageal varices (EV) may improve the management of patients with cirrhosis and decrease both the medical and financial burden related to screening. In this multicenter, international study, our aim was to prospectively validate the use of the platelet count/spleen diameter ratio for the noninvasive diagnosis of EV.

METHODS: A total of 218 cirrhotic patients underwent screening endoscopy for EV. Platelet count/spleen diameter ratio ((N/mm³)/mm) was assessed in all patients and its diagnostic accuracy was calculated. On the basis of previous results, a platelet count/spleen diameter ratio cutoff of 909 was applied to this population. The diagnostic accuracy of the platelet count/spleen diameter ratio was further evaluated for both severity and etiology of disease subgroups.

RESULTS: Prevalence of EV was 54.1%. The platelet count/spleen diameter ratio had 86.0% (95% CI, 80.7–90.4%) diagnostic accuracy for EV, which was significantly greater as compared with either accuracy of platelet count alone (83.6%, 95% CI 78.0–88.3%, $P = 0.038$) or spleen diameter alone (80.2%, 95% CI 74.3–85.3%, $P = 0.018$). The 909 cutoff had 91.5% sensitivity (95% CI 85.0–95.9%), 67.0% specificity (95% CI 56.9–76.1%), 76.6% positive predictive value, 87.0% negative predictive value, 2.77 positive likelihood ratio, and 0.13 negative likelihood ratio for the diagnosis of EV. Accuracy of the platelet count/spleen diameter ratio was maintained for both severity and etiology of disease subgroups.

CONCLUSIONS: The platelet count/spleen diameter ratio may be proposed as a safe and reproducible means to improve the management of cirrhotic patients who should undergo screening endoscopy for EV.

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INTRODUCTION

In patients with chronic liver disease, endoscopic screening for esophageal varices (EV) is currently recommended in all patients at the time of diagnosis of cirrhosis (1). As far as patients with no varices at screening endoscopy are concerned, surveillance should be performed every 2 yr on patients with stable liver function and every year on those who show signs of liver function deterioration. Finally, endoscopy should be repeated every year when screening endoscopy reveals small varices (2, 3).

These practices are recommended because if high-risk EV are detected, then either pharmacologic or endoscopic treat-

ment aimed at preventing first bleeding can be started (4). Nevertheless, although criteria for this surveillance practice are part of well-established guidelines (1–3), they stem from the opinions of experts rather than being evidence based (5). Furthermore, such policy eventually places a strong burden on medical resources, and may be hampered by the lack of compliance with both screening and surveillance. Indeed, one recent study compared universal endoscopic screening and treatment of high-risk varices with treating all cirrhotic patients with β -blockers, and the latter approach proved to be more cost-effective (6). In another similar study, screening endoscopy proved to be cost-effective in patients with decompensated disease alone (7). Lastly, although administering

timolol to cirrhotic patients without EV proved to be ineffective at preventing the formation of varices and propranolol seemed to be ineffective in the prevention of the development of large varices (8, 9), a large, placebo-controlled study recently showed that administering nadolol prevented small varices from increasing in size, and decreased the probability of variceal bleeding (10). Taking into account the above-mentioned considerations, the cost-effectiveness of universal empiric β -blocker treatment should be even greater, although in some patients it would be useless. In fact, the average prevalence of EV in cirrhotic patients ranges from 60% to 80%, depending on severity and etiology of liver disease (4), and empiric treatment of all cirrhotic patients would expose a significant proportion of treated patients to unnecessary and potentially harmful side effects. Therefore, the use of accurate and specific means that could noninvasively diagnose EV would likely increase the cost-benefit of empiric treatment by decreasing the number of patients who are administered avoidable treatment and by increasing the number of properly screened and treated patients. Such a noninvasive means should have a confident safety profile (*i.e.*, a negative predictive value approaching 100%) so as to avoid missing the diagnosis in patients at risk, and a relevant cost-benefit profile so as to avoid unnecessary endoscopy and/or treatment of patients who would not benefit from therapy (*i.e.*, high positive predictive value) (11). In this scenario, we previously showed that the use of the platelet count/spleen diameter ratio for the noninvasive assessment of EV seems to fulfill these requirements and is based on pathophysiological criteria as well (12). Furthermore, we validated the diagnostic accuracy of this parameter in the follow-up of patients free from EV at screening endoscopy (13). Lastly, preliminary results obtained by other authors demonstrated that the diagnostic accuracy of the platelet count/spleen diameter ratio is maintained in subsets of patients with different etiologies of liver disease and by applying different methodologies (14), thus suggesting the generalizability of the diagnostic method (15).

In this prospective, multicenter study, our aim was to assess the validity of using the platelet count/spleen diameter ratio for the noninvasive diagnosis of EV. In particular, we deemed it of interest to assess the validity of this diagnostic tool in patients with various degrees of liver function impairment and in patients with various etiologies of liver disease. The international, multicenter setting of this study allowed us to fulfill the prerequisites for the generalizability (*i.e.*, reproducibility and transportability) of our diagnostic model (15).

PATIENTS AND METHODS

Patients

This prospective, multicenter study included a total of 218 consecutive cirrhotic patients who underwent screening endoscopy for EV at four centers (three in Europe [N = 143] and one in the United States [N = 75]). The study population was represented by cirrhotic patients undergoing screening

endoscopy at the time of cirrhosis diagnosis, and patients with a known diagnosis of liver cirrhosis but who had never undergone screening endoscopy for EV. Exclusion criteria from the study included: active bleeding; current alcohol intake, considered as any alcohol intake (patients with alcohol-related liver cirrhosis were included if abstinent for at least 6 months prior to endoscopy); previous endoscopic sclerosis or band ligation of EV; previous surgery for portal hypertension or transjugular intrahepatic porto systemic stent shunt placement. None of the patients was on β -blocker therapy. Hepatocellular carcinoma, spontaneous bacterial peritonitis, or portal vein thrombosis were not exclusion criteria for the study, and their presence was recorded.

Methods

The following information was collected for each patient: age, gender, etiology of cirrhosis, biochemical parameters (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, serum albumin, prothrombin activity (%), serum creatinine, platelet count, presence and degree of ascites and encephalopathy assessed according to Child-Pugh criteria (16), treatment with diuretics, and presence of contraindications to the use of nonselective β -blockers.

The presence and size of EV were determined and recorded for each patient. The size of varices was subdivided into two classes—small to screen and large to treat—according to the criteria proposed at the Baveno I Consensus Conference (17). Small EV were defined as varices that flatten with insufflation or minimally protrude into the esophageal lumen, while large EV were defined as varices that protrude into the esophageal lumen and touch each other (presence of confluence), or that fill at least 50% of the esophageal lumen (18). This semi-quantitative approach was chosen because it provides better interobserver agreement as compared with quantitative grading (19).

All patients underwent ultrasonographic examination of the upper abdomen including spleen bipolar diameter measurement. Ultrasonographic measurement of spleen bipolar diameter was technically feasible in all patients. The intra- and interobserver coefficients of variation for measuring the spleen bipolar diameter were evaluated in 64 patients and were 1.8% and 1.4%, respectively.

Both endoscopy and abdomen ultrasonography operators were blinded to the others' instrumental results and to the patients' biochemical data. The whole evaluation (endoscopy, spleen measurement, determination of platelet count) was carried out within 10 days in 89.6% of the study population, and within 3 months in the remaining patients.

Platelet count/spleen diameter ratio was calculated in all patients as platelet count (N/mm³)/spleen diameter (mm). The diagnostic accuracy of the platelet count/spleen diameter ratio was evaluated in the whole cohort of patients as well as in two subanalyses carried out by considering groups of patients with various degrees of liver function impairment (Child-Pugh classes) and patients with various etiologies of liver disease. For this latter analysis, etiology of liver disease

was classified into viral (hepatitis virus infections, hepatitis virus infections, and alcohol use), alcohol abuse, and primary biliary cirrhosis (PBC).

The study conformed to the ethical guidelines of the Declaration of Helsinki, and was approved by the senior staff of the participating centers.

Statistical Analysis

Mann-Whitney *U*-test was used to compare continuous variables, while qualitative variables were compared using the χ^2 test. Kruskal-Wallis test with internal comparisons was used to compare the platelet count/spleen diameter ratios in patients without EV, and with small and large EV. The receiver operating characteristic curves (ROC curves) were applied to calculate and compare the accuracy of the platelet count, spleen diameter, and platelet count/spleen diameter ratio for the diagnosis of EV (20). The validity of the model was measured by means of the concordance (*c*)-statistic (equivalent to the area under ROC curve). A model with a *c*-index above 0.7 is considered useful, while a *c*-index between 0.8 and 0.9 indicates excellent diagnostic accuracy. The platelet count/spleen diameter ratio cutoff that we had identified in our previous study (*i.e.*, 909 (N/mm³)/mm) (12) was applied to this cohort of patients, and its sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and positive and negative likelihood ratios for the diagnosis of EV were calculated. Efficiency (true positives + true negatives/N) of the platelet count/spleen diameter ratio 909 cutoff for ruling out the presence of EV was also calculated.

Data are shown as the median and range, and percentages are shown as absolute values and 95% confidence interval (95% CI). A *P* value <0.05 was considered statistically significant for all analyses. Data were analyzed using the MedCalc statistical package (MedCalc, MariaKerke, Belgium).

RESULTS

Among the 218 cirrhotic patients who underwent upper digestive endoscopy, 111 were Child-Pugh class A (50.9%), 75 were class B (34.4%), and 32 were class C (14.7%). Sixty-

seven patients had ascites (30.7%), which was tense in 10 (4.6%), while hepatic encephalopathy was present in 25 patients (11.5%). Ninety-eight patients (44.9%) were on diuretic treatment. Hepatocellular carcinoma was present in 19 patients (8.7%) and portal vein thrombosis was observed in 7 (3.2%). None of the patients had spontaneous bacterial peritonitis. Etiology of liver disease was hepatitis virus infection in 105 patients, alcohol abuse in 41 patients, hepatitis virus infection and previous alcohol use in 27 patients, PBC in 35 patients, cryptogenic in 8 patients, and autoimmune hepatitis in 2 patients.

Overall, 118 patients had endoscopic evidence of EV (54.1%), and among these patients 47 had large EV (21.6%). Twenty patients (9.2%) had contraindications to treatment with nonselective β -adrenergic blockers (5 patients had diabetes mellitus, 4 patients had cardiac arrhythmia, 4 patients had arterial hypotension, 3 patients had severe chronic obstructive pulmonary disease, 2 patients had ischemic heart disease, and 2 patients had more than one condition), and among these patients 9 had EV (3 patients had large EV).

Table 1 shows the clinical, biochemical, and ultrasonographic characteristics of the patients according to the presence of EV. There was no gender prevalence between patients with or without EV, and a trend toward older age among patients without EV was observed. EV patients had significantly higher serum total bilirubin levels as well as lower serum albumin, prothrombin activity, and platelet count as compared to patients without EV. Child-Pugh score was significantly higher in patients with EV, and among these patients 38 were Child-Pugh class A, 55 were class B, and 25 were class C ($\chi^2 = 36.255$, *P* < 0.0005). Spleen diameter was higher, while platelet count/spleen diameter ratio was lower in patients with EV. Figure 1 shows the distribution of the platelet count/spleen diameter ratio according to the presence and size of EV. The platelet count/spleen diameter ratio was significantly different among all three groups of patients (without EV, small EV, large EV; Kruskal-Wallis test, *H* corrected for ties = 93.4, *P* < 0.001).

Table 1. Main Characteristics of the 218 Cirrhotic Patients Included in the Study, Subdivided According to the Presence of Esophageal Varices

Variable	Unit	No Varices	Varices	<i>P</i> Value
Gender	Males	54 (54%)	74 (63%)	0.2506
Age	Years	58 (29–83)	54 (22–88)	0.0532
AST	IU/mL	63 (19–426)	70 (21–519)	0.1939
ALT	IU/mL	61 (13–402)	48 (11–442)	0.1934
Albumin	mg/dL	3.7 (1.7–4.8)	3.3 (1.7–4.8)	<0.0001
Total bilirubin	mg/dL	1.0 (0.3–36.4)	1.8 (0.5–35.2)	<0.0001
Prothrombin activity	%	88 (43–115)	66 (26–113)	<0.0001
Child-Pugh	Score	6 (5–12)	7 (5–14)	<0.0001
Platelet count	N/mm ³	139,000 (30,000–391,000)	85,000 (25,000–231,000)	<0.0001
Spleen diameter	mm	123 (80–196)	153 (100–289)	<0.0001
Platelet count/spleen diameter	(N/mm ³)/mm	1,107 (153–4,888)	558 (135–2,130)	<0.0001

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Data are shown as median and range except for gender, which is shown as an absolute number and as a percent.

Statistical analysis was carried out by means of χ^2 test and Mann-Whitney *U*-test.

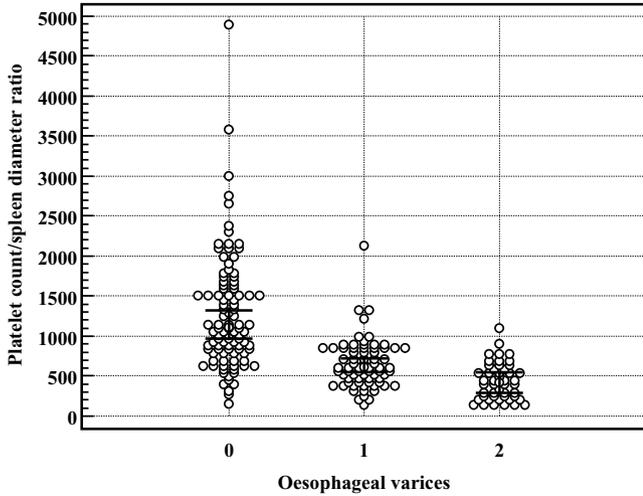


Figure 1. Platelet count/spleen diameter ratio distribution subdivided according to the absence (0) or presence of small (1) and large (2) esophageal varices. Each dot represents a patient, and bars indicate median values and 95% confidence interval.

Considering the entire cohort of patients, the accuracy (area under the ROC curve or *c*-index) of the platelet count/spleen diameter ratio for the diagnosis of EV was 0.860 (standard error 0.026, 95% CI 0.807–0.904). In particular, the diagnostic accuracy of the platelet count/spleen diameter ratio for EV was significantly greater as compared with either accuracy of platelet count alone (*c*-index = 0.836, standard error 0.028, 95% CI 0.780–0.883. Difference between areas = 0.024, standard error 0.012, 95% CI 0.001–0.048, *P* = 0.038; Fig. 2A) or accuracy of spleen diameter alone (*c*-index = 0.802, standard error 0.029, 95% CI 0.743–0.853. Difference between areas = 0.058, standard error 0.025, 95% CI 0.010–0.107, *P* = 0.018; Fig. 2B).

A platelet count/spleen diameter ratio cutoff of 909 (N/mm³)/mm had 91.5% sensitivity (95% CI 85.0–95.9%), 67.0% specificity (95% CI 56.9–76.1%), 76.6% PPV, 87.0% NPV, 2.77 positive likelihood ratio, and 0.13 negative likelihood ratio for the diagnosis of EV. Figure 3 shows a plot of both positive and negative predictive values of the platelet count/spleen diameter ratio 909 cutoff considering various prevalence of disease.

The diagnostic efficiency (true positives + true negatives/N) of the platelet count/spleen diameter ratio 909 cutoff was 80.3% (95% CI 74.4–85.3%). Briefly, by applying the platelet count/spleen diameter ratio 909 cutoff, 10 patients with varices were misclassified as having no varices (8 Child-Pugh class A patients, 2 Child-Pugh class B patients). In this group of patients, which accounted for 8.5% of the patients with EV and 4.6% of the whole study population, varices were small in 9 (7 Child-Pugh class A patients, 2 Child-Pugh class B patients) and large in 1 (Child-Pugh class A). The median platelet count/spleen diameter ratio among these patients was 1,048 (N/mm³)/mm (range 925–2,130), and cause of cirrhosis was hepatitis viruses in 5 patients (4.8% of the

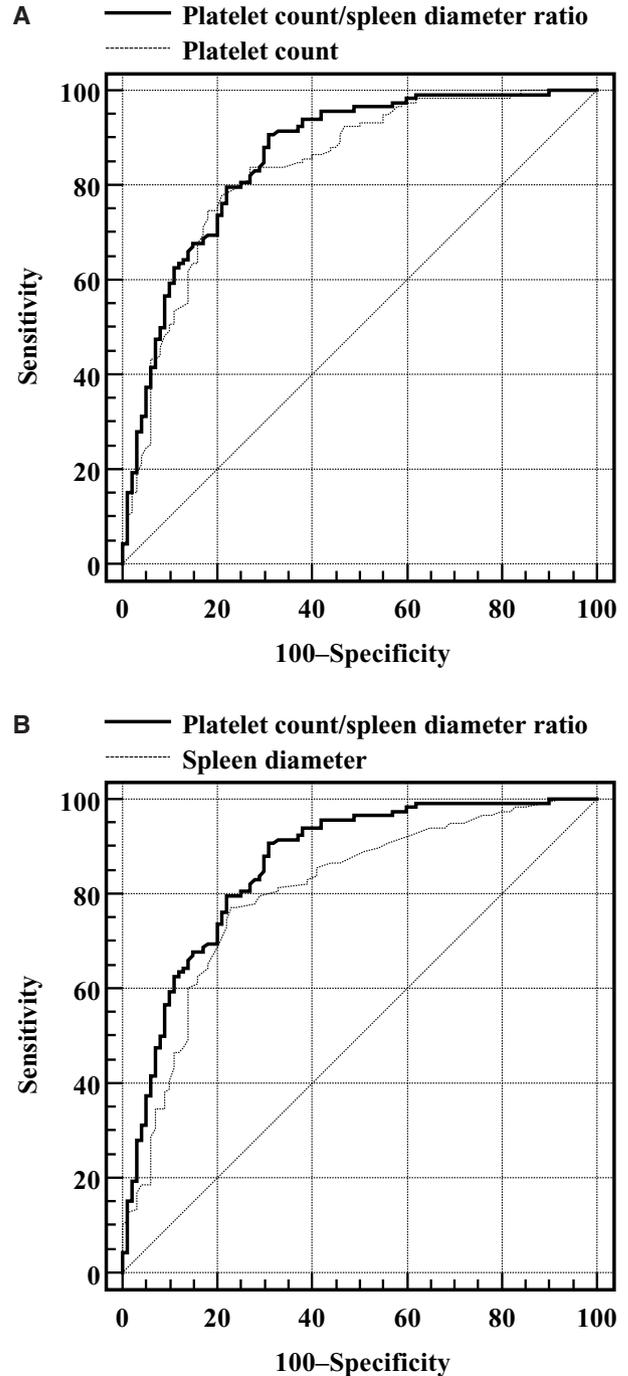


Figure 2. Receiver operating characteristic curves for the diagnosis of esophageal varices of the platelet count/spleen diameter and either platelet alone (A) or spleen diameter alone (B).

population with viral disease), alcohol in 2 (4.9% of alcoholic patients), and PBC in 3 (8.6% of patients with PBC).

Validation in Patients with Various Degrees of Liver Function Impairment

The diagnostic accuracy of the platelet count/spleen diameter ratio was 82.2% in Child-Pugh class A patients (95% CI 73.8–88.8%), 83.0% in class B patients (95% CI

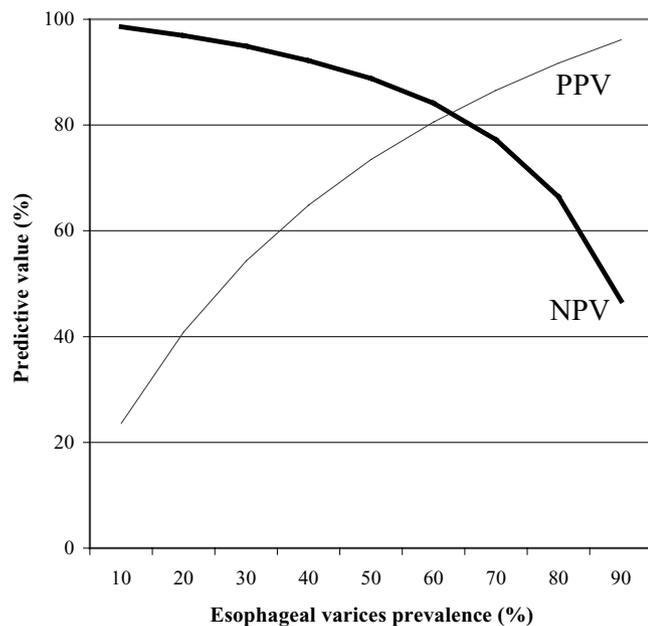


Figure 3. Plot of positive predictive values (PPV, thin line) and negative predictive values (NPV, solid line) of a platelet count/spleen diameter ratio 909 cutoff versus various arbitrary prevalence of esophageal varices.

72.6–90.7%), and 83.4% in class C patients (95% CI 66.1–94.1%). Table 2 shows the diagnostic performance of the platelet count/spleen diameter ratio 909 cutoff in the various Child-Pugh classes. Prevalence of EV ranged from 34.2% in Child-Pugh class A patients to 78.1% in class C patients. Sensitivity of the cutoff showed a progressive increase as the severity of disease increased, and reached 100% (95% CI 86.3–100%) in Child-Pugh class C patients, while specificity decreased in patients with advanced disease. Noteworthy, NPV was well above 80% in all severity subgroups, and negative likelihood ratios confirmed a large decrease in post-test probability.

Validation in Patients with Different Etiologies of Liver Disease

With regards to patients with viral etiology of cirrhosis, a platelet count-spleen diameter ratio cutoff of 909 had 83.9% accuracy for the diagnosis of EV (95% CI 76.5–89.7%), while accuracy was 95.9% in patients with alcohol-induced cirrhosis (95% CI 84.6–99.5%) and 89.5% in patients with PBC (95% CI 74.4–97.2%). Table 3 shows that the sensitivity of the platelet count/spleen diameter ratio 909 cutoff in patients

with various etiologies of liver disease was above 80% in all subgroups, while specificity was lower in patients with virus-induced cirrhosis as compared with both alcoholic and PBC patients. Noteworthy, both PPV and NPV were very high in all the subgroups of patients.

DISCUSSION

In this prospective, multicenter study, we have shown that applying the platelet count/spleen diameter ratio for the non-invasive diagnosis of EV in patients with cirrhosis is both reproducible and transportable. We also observed that this screening method has excellent diagnostic accuracy across the whole spectrum of severity of cirrhosis as well as in patients with various etiologies of liver disease. Noteworthy, diagnostic accuracy for EV of the platelet count/spleen diameter ratio was significantly better than accuracy of either platelet count alone or spleen diameter alone. On the one hand, from a safety point of view, we confirmed that the platelet count/spleen diameter ratio has a very high NPV, and therefore can be confidently applied without significant risk of missing important diagnoses. On the other hand, applying the platelet count/spleen diameter ratio to screen patients who may benefit from endoscopy and prophylactic treatment is likely more cost-effective than universal screening or universal prophylaxis.

This study allowed us to proceed through the validation of our model and to fulfill the criteria that need to be satisfied for generalizability of clinical prediction rules (15, 21). Indeed, we previously observed that the diagnostic accuracy of the platelet count/spleen diameter ratio was maintained in patients who were from an identical population (12, 13), while in this study we found that the platelet count/spleen diameter ratio is accurate in patients drawn from different but related populations (*i.e.*, transportability). Furthermore, the accuracy of the diagnostic model was confirmed when tested on data from different time periods (*i.e.*, historical transportability) and locations (*i.e.*, geographical transportability), and when data were collected by using different methods (*i.e.*, methodological transportability) (15). Finally, the multicenter, international setting of the study allowed for external validation of the model, thus confirming preliminary reports (14, 21). We observed that applying the platelet count/spleen diameter ratio to a large and heterogeneous group of prospectively evaluated cirrhotic patients showed excellent diagnostic accuracy, and the 909 cutoff that we had identified in our previous study (12) showed high sensitivity and NPV, and very low

Table 2. Diagnostic Features of the Platelet Count/Spleen Diameter Ratio 909 Cutoff in Patients with Various Degrees of Liver Function Impairment

Child-Pugh	EV Prevalence	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	+LR	–LR
Class A	34.2%	78.9% (62.7–90.4)	72.6% (60.9–82.4)	60.0%	86.9%	2.88	0.29
Class B	73.3%	96.4% (87.4–99.5)	50.0% (27.2–72.8)	84.1%	83.3%	1.93	0.07
Class C	78.1%	100% (86.3–100)	37.1% (18.8–89.6)	89.3%	100%	2.33	0.01

95% CI = 95% confidence interval; PPV = positive predictive value; NPV = negative predictive value; +LR = positive likelihood ratio; –LR = negative likelihood ratio.

Table 3. Diagnostic Features of the Platelet Count/Spleen Diameter Ratio 909 Cutoff in Patients with Various Degrees of Liver Function Impairment

Etiology	EV Prevalence	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	+LR	-LR
Viral	55.3%	93.2% (84.7–97.7)	54.2% (40.8–67.3)	71.6%	86.5%	2.04	0.13
Alcohol	63.4%	92.3% (74.8–98.8)	86.7% (59.5–98.0)	92.3%	86.7%	6.92	0.09
PBC	42.9%	80.0% (51.9–95.4)	90.0% (68.3–98.5)	85.7%	85.7%	8.00	0.22

95% CI = 95% confidence interval; PBC = primary biliary cirrhosis; PPV = positive predictive value; NPV = negative predictive value; +LR = positive likelihood ratio; -LR = negative likelihood ratio.

negative likelihood ratio for the diagnosis of EV. Overall, we were able to reproduce the results obtained in our development study (12), although the sensitivity and PPV of the test cutoff slightly decreased. As compared with our previous development study, this study had a slightly lower prevalence of EV (54% vs 60%), as well as a more marked, different composition in terms of both severity and etiology of disease. In particular, this study included a greater proportion of Child-Pugh class A patients (51% vs 38%) and of patients with PBC (16% vs 1%), as well as a lower proportion of patients with virus-induced cirrhosis (61% vs 75%). These features may well account for the small differences observed in diagnostic accuracy between the original study and this validation study (22), and, in our opinion, they further strengthen the study results since they avoided both spectrum and selection biases (23).

The accuracy of the platelet count/spleen diameter ratio was maintained across the whole spectrum of disease severity, with a *c*-index well above 80% in all Child-Pugh classes. In particular, the platelet count/spleen diameter ratio obtained very good results even when the prevalence of EV was low as in Child-Pugh class A patients. This is not a negligible result, because prophylaxis of first bleeding is especially important in these patients. The fairly low specificity of the results observed in patients with Child-Pugh classes B and C means that some of these patients with very low platelet count/spleen diameter ratio may not have EV. One of the possible explanations for this result could be the development of spontaneous intra-abdominal shunts that decrease the blood flow of varices while maintaining congestive splenomegaly. However, this aspect does not affect the most important characteristic of the ratio, *i.e.*, the safety profile. In fact, sensitivity of the 909 cutoff is quite high in these patients (96.4% class B patients, 100% class C patients), and therefore ensures that patients without EV are not missed by applying this noninvasive parameter. Importantly, the very low negative likelihood ratios we observed in all the subgroups of patients with various severities of liver disease represented the most convincing evidence that a platelet count/spleen diameter ratio above 909 indicates a large decrease in the likelihood of having EV.

When the diagnostic accuracy of the platelet count/spleen diameter ratio was evaluated in patients with various etiologies of cirrhosis, we obtained overlapping results across the subgroups. In particular, we observed an excellent accuracy in patients with alcoholic cirrhosis, thus confirming preliminary results obtained by other authors (14). Noteworthy, we

also obtained excellent diagnostic accuracy in patients with PBC. This is especially important because the noninvasive parameters, which indicate the need for screening endoscopy, proved to be invalid in this group of patients due to the peculiar pathophysiology of the disease (24). However, we observed lower specificity in patients with viral cirrhosis. This may be, at least in part, due to the multifactorial etiology of thrombocytopenia in patients with virus-induced liver disease (25), which likely causes a disproportionate decrease in the platelet count of patients with normal or slightly enlarged spleens, thus resulting in a falsely low platelet count/spleen diameter ratio.

Although previous studies attempted to identify noninvasive predictors of the presence of EV in cirrhotic patients, none of them reached a satisfactory level of accuracy so as to be applied in clinical practice (26–31). In particular, a model obtained lower accuracy when retested by both the same or other authors (accuracy, 0.80 vs either 0.70 or 0.63) (32, 33). In this regard, the main advantage of the platelet count/spleen diameter ratio can be found in the pathophysiological basis that supports its conception. In fact, the increase in spleen size in patients with chronic liver disease is almost always the expression of greater portal pressure (34, 35), while thrombocytopenia may be the result of either splenic pooling of platelets due to portal hypertension or immune-mediated mechanisms and lower thrombopoietin synthesis (25, 36–38). Integrating platelet count and spleen size in a ratio allowed us to identify the degree of thrombocytopenia that most likely is the result of hypersplenism. From a practical point of view, the ratio is easy to calculate and can be computed at bedside or in the outpatient clinic. From a financial point of view, biannual assessment of the ratio does not lead to additional costs in the management of cirrhotic patients because platelet count is routinely assessed, and abdominal ultrasonography is usually carried out at least semiannually for hepatocellular carcinoma surveillance. Finally, from a technical point of view, spleen bipolar diameter can easily be assessed. In fact, spleen bipolar measurement consistently showed very low intra- and inter-observed variability (1.8% and 1.4% in this study, respectively), thus confirming previous findings regarding the high reproducibility of the spleen bipolar diameter measurement and its low intra- and interobserver variability (39, 40).

In the light of the results of our previous study (12), of the results obtained in this study, and of the current literature regarding the use of prophylaxis of first EV bleeding in cirrhotic patients (6–9), we may ask, “What are the practical

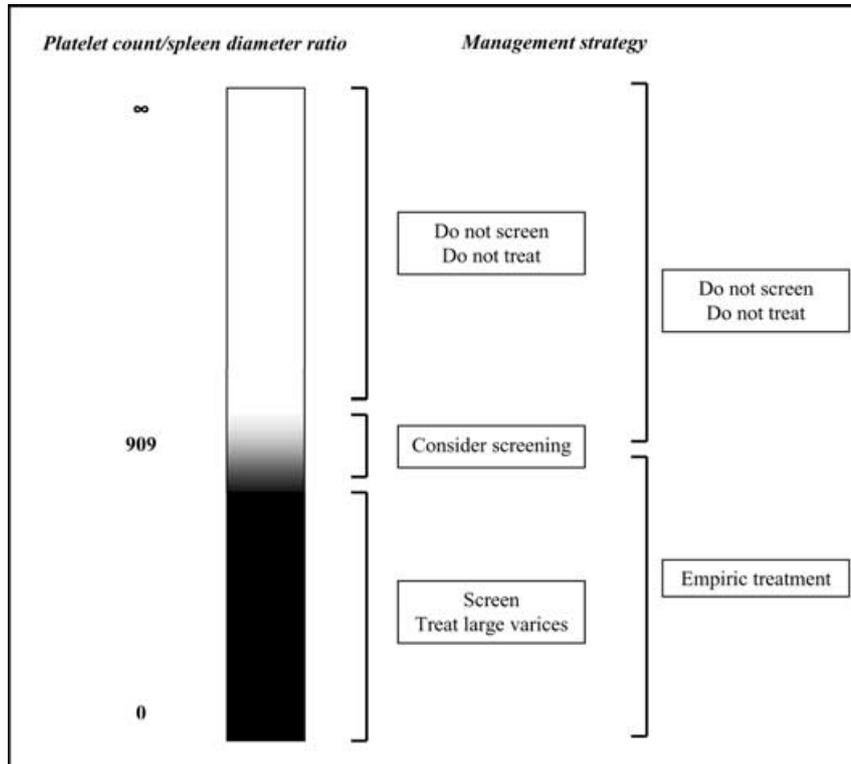


Figure 4. Proposed management algorithm for esophageal varices screening and surveillance.

implications of using the platelet count/spleen diameter ratio?” The most compelling evidence is that applying the ratio would safely avoid endoscopy in patients who are most likely to be free from EV (*i.e.*, those whose ratio is >909). In patients with a ratio ≤ 909 , two strategies may be devised: either perform endoscopy on all patients and treat those with large varices alone, or treat all patients without performing endoscopy. While applying the former strategy would correctly identify all patients for whom treatment is currently indicated (1–4), applying the latter strategy would treat patients for whom there is initial evidence of some benefit (*i.e.*, patients with small varices) (10), and 33% of the patients without varices, who, on the basis of the evidence provided by the literature, do not seem to benefit from β -blocker administration (8, 9). Nevertheless, because patients without varices who show a decrease in the platelet count/spleen diameter ratio are more likely to develop EV (13), dynamic (*e.g.*, annually, semiannually) monitoring of this parameter would help identify which patients should undergo surveillance endoscopy. Because we are well aware that the 909 cutoff cannot be considered a “Holy Grail,” and that a “gray area” likely exists around this cutoff, we tried to depict a possible diagnostic algorithm for EV screening and surveillance based on the use of the platelet count/spleen diameter ratio and on the above-mentioned considerations (Fig. 4).

In summary, the results of this prospective, multicenter study allowed us to further validate the diagnostic accuracy of the platelet count/spleen diameter ratio for the

noninvasive diagnosis of EV. Noteworthy, the use of the platelet count/spleen diameter ratio safely identified patients without EV and allowed us to identify a large number of patients with EV. Applying the platelet count/spleen diameter ratio could be proposed in clinical practice as part of the diagnostic workup of cirrhotic patients in order to decrease the financial and sanitary burden of the endoscopy unit as well medical costs related to EV screening.

STUDY HIGHLIGHTS

What Is Current Knowledge

- In cirrhotic patients, endoscopic screening for esophageal varices is currently recommended at the time of diagnosis of cirrhosis.
- There is no reliable noninvasive indicator for the presence/absence of esophageal varices that can be adopted in clinical practice in order to reduce the financial and sanitary burden of esophageal varices screening.
- We have previously shown that the use of the platelet count/spleen diameter ratio for the noninvasive assessment of esophageal varices in cirrhotic patients has an excellent accuracy and is cost-effective as well.

What Is New Here

- In this study, we have shown that the use of the platelet count/spleen diameter ratio for the noninvasive diagnosis of esophageal varices in cirrhotic patients is reproducible in different populations of cirrhotic patients.
- The diagnostic accuracy of the platelet count/spleen diameter ratio was independent of both etiology and severity of disease.
- On these bases, the use of the platelet count/spleen diameter ratio can be proposed as a screening tool for esophageal varices in cirrhotic patients and may help to reduce the financial and sanitary burden of endoscopy units.

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CONFLICT OF INTEREST

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