Which Patients With Cirrhosis Should Undergo Endoscopic Screening For Esophageal Varices Detection?

FILIPPO SCHEPIS,[1] CALOGERO CAMMÀ,[2] DOMENICO NICEFORO,[1] ANTONIO MAGNANO,[3] SOCRATE PALLIO,[1] MAURIZIO CINQUEGRANI,[1] GENNARO D'AMICO,[4] LINDA PASTA,[4] ANTONIO CRAXÌ,[5] ANTONINO SAITTA,[1] AND GIOVANNI RAIMONDO[1]

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Our aims were to develop a noninvasive predictive tool to identify cirrhotic patients with esophageal varices and to evaluate whether portal Doppler ultrasonographic parameters may improve the value of other predictors. One hundred forty-three consecutive compensated cirrhotic patients underwent upper gastrointestinal endoscopy. Fourteen clinical, biochemical, ultrasonographic, and Doppler ultrasonographic parameters of each patient were also recorded. Esophageal varices were detected in 63 of the 143 patients examined (44%; 95% confidence interval [CI] 36.2-52.6). Medium and large esophageal varices were observed in 28 subjects (44%; 95% CI 31.4-58.4). Using stepwise logistic regression, presence of esophageal varices was independently predicted by prothrombin activity less than 70% (odds ratio [OR]: 5.83; 95% CI: 2.6-12.8), ultrasonographic portal vein diameter greater than 13 mm (OR: 2.92; 95% CI: 1.3-6.4), and platelet count less than 100 × 10^9/L (OR: 2.83; 95% CI: 1.27-6.28). Variables included in the model were used to generate a simple incremental rule to evaluate each individual patient. The discriminating ability of the prediction rule was relevant (area under the curve: 0.80) and did not change by replacing ultrasonographic portal vein diameter with congestion index of portal vein. We concluded that compensated cirrhotic patients should be screened by upper gastrointestinal endoscopy when prothrombin activity less than 70%, platelet count less than 100 × 10^9/L, and ultrasonographic portal vein diameter greater than13 mm are observed, whereas those without any of these predictors should not undergo endoscopy. The contribution provided by portal Doppler ultrasonographic parameters does not appear of practical utility. (HEPATOLOGY 2001;33:333-338.)

Portal hypertension (PHT) is a common complication of hepatic cirrhosis. Cirrhotic patients with PHT develop esophageal varices (EV) and are at very high risk of variceal bleeding.[1] The available evidence shows that severity of liver dysfunction, size of varices, presence of red signs on varices, and a portal pressure greater than 12 mm Hg are the most reliable predictors for the first episode of variceal bleeding.[2,3] In particular, size of the varices has been identified as the principal endoscopic predictor for the first bleeding occurrence, although variceal hemorrhage is not confined to subjects with large varices.[4]

The incidence of EV development is approximately 5% per year in patients with cirrhosis,[5,6] and the progression from small to large varices occurs in 10% to 20% of cases after 1 year.[7] In the 2 years following the first detection of EV, the risk of variceal bleeding ranges between 20% to 30%[5-7] and results in a mortality of 25% to 50% within a week of the first bleeding episode.[8] Therefore, portal hypertensive bleeding prevention remains at the forefront of long-term management of cirrhotic patients.

In 1996, the AASLD single topic symposium on PHT recommended that Child's class A cirrhotics should be screened endoscopically for the presence of varices if and when there is clinical evidence of portal hypertension, *e.g.*, a low platelet count (<140 × 10^9/L), and/or an enlarged portal vein diameter (>13 mm).[4] However, this strategy has not been evaluated prospectively to date, particularly regarding its cost-effectiveness, and there is concern that it will subject a large number of patients to unnecessary and invasive procedures.

An intensive endoscopic program of screening in cirrhotic patients that have never had ascites or hepatic encephalopathy should be confined to subjects with a high likelihood of EV, given that definitive results of preprimary prophylaxis are not yet available and β-blockers are recommended in patients with high-risk varices.[1] Furthermore, it must be considered that EV presence is a prognostic indicator[9] and a factor affecting the morbidity and mortality of surgical procedures[10] in cirrhotic patients. Consequently, the development of an accurate and reliable method of identifying individual patients with EV while avoiding any invasive procedure would greatly improve the current guidelines.

Doppler ultrasonography (US) provides noninvasive access to the portal system and allows for the estimation of both

Abbreviations: PHT, portal hypertension; EV, esophageal varices; AASLD, American Association for the Study of Liver Disease; US, ultrasonography; HIV, human immunodeficiency virus; HCC, hepatocellular carcinoma; P, ultrasonographic portal vein diameter; PV_{max}, maximum portal flow velocity; PV_{mean}, mean portal flow velocity; CI_x, congestion index of portal vein; J.R.S.P.H., Japanese Research Society for Portal Hypertension; PLT_c, platelet count; PT_p, prothrombin activity; ROC, receiver-operating characteristic; AUC, area under the curve; HBV, hepatitis B virus; HCV, hepatitis C virus; CI, confidence interval; OR, odds ratio.

From [1]Dipartimento di Medicina Interna e Terapia Medica, Policlinico Universitario, Messina, Italy; [2]Istituto Metodologie Diagnostiche Avanzate, Consiglio Nazionale delle Ricerche, Palermo, Italy; [3]II Divisione di Chirurgia Generale, Policlinico Universitario, Messina, Italy; [4]Divisione di Medicina, Ospedale V. Cervello, Palermo, Italy; [5]Divisione di Medicina Generale e Gastroenterologia, Policlinico Universitario, Palermo, Italy.

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Address reprint requests to: Prof. Giovanni Raimondo, M.D., Dipartimento di Medicina Interna e Terapia Medica, Policlinico Universitario, Via Consolare Valeria, 98100, Messina, Italy. Email: raimondo@unime.it; fax: (39) 90-2935162.

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arterial and venous flow. It has been previously suggested that some Doppler parameters have a prognostic value[11] and can be useful in the assessment of the risk of bleeding.[12] Although in cirrhotic patients a diagnostic gray scale US is widely used in the evaluation of portal hypertension, Doppler is rarely employed, and its actual utility is still debated.[13]

The aims of this cross-sectional study were to develop a predictive model for EV presence in compensated cirrhotic patients and to evaluate whether Doppler US may provide relevant improvement to clinical, biochemical, and ultrasonographic predictive parameters.

PATIENTS AND METHODS

Patients. All newly diagnosed consecutive cirrhotic patients, either self-referred or referred by attending physicians, observed between November 1997 and December 1998 in the Liver Unit of the Policlinico Universitario of Messina, which serves a tertiary referral function, were considered for the study. Subjects were eligible if they had a diagnosis of cirrhosis based on liver biopsy or history, physical examination, and biochemical parameters.[2] Patients with advanced cirrhosis (Child-Pugh class C), antibodies against human immunodeficiency virus (HIV), present or previous history of portal hypertensive bleeding, hepatocellular carcinoma (HCC), portal vein thrombosis, reverse or alternating portal flow, parenteral drug addiction, current alcohol abuse, previous or current treatment with β-blockers, diuretics or other vasoactive drugs were excluded. One hundred and forty-three patients (79.8%) out of the 179 cirrhotic subjects observed during the accrual period met criteria of eligibility and were included in the study. Eighty-two percent of patients not fulfilling inclusion criteria had advanced liver disease, 3% had HCC, 2% had portal vein thrombosis, whereas 13% of them were current alcohol abusers or were under treatment with vasoactive drugs. The study was performed according to the principles of the Declaration of Helsinki, and informed consent was obtained in each case.

At entry into the study, all patients underwent a full clinical evaluation, with biochemical and virological tests, diagnostic gray scale US of the liver, qualitative and quantitative Doppler ultrasonographic evaluation of the portal system, and upper gastrointestinal endoscopy. Cirrhosis was defined histologically in 122 patients (85.3%).

Doppler Ultrasonographic Evaluation. Color-Doppler US was performed by real-time ultrasound equipment (Color Doppler Vingmed CFM 750, Norway) consisting of a 3.5-MHz convex transducer and a pulsed-Doppler device working at 3.5-MHz frequency. All Doppler investigations were performed by the same examiner (M.C.) who was unaware of the patients' clinical and laboratory data. The intraobserver variation of Doppler measurements, as evaluated by k statistic, was 0.80.

The portal vein was visualized longitudinally in B-mode, and the sample volume, with a width of approximately half of the lumen, was positioned in the middle of the portal trunk. All measurements were performed at the cross point between the hepatic artery and the portal vein. An angle of insonation less than 60° was used each time.[13]

The portal vein diameter (P)(mm) and the maximum portal flow velocity (PV_{max})(cm/min) were measured during suspended respiration. The mean portal flow velocity (PV_{mean})(cm/min) was calculated according to the Moriyasu formula.[14] Each result was reported as the mean of at least 3 measurements. Congestion index (CI_x)(cm^2/[cm/sec]) of the portal vein was calculated as follows:

$$CI_x = (\pi\ P^2/4)/PV_{mean}$$

where P represents the portal vein diameter and PV_{mean} the mean portal flow velocity.

For technical reasons (poor echo transmission and/or poor cooperation of the patients in maintaining apnea) quantitative Doppler flowmetric study was performed in 127 (88%) of the 143 patients.

All Doppler examinations were performed in the early morning after an overnight fast and were shortly followed by upper gastrointestinal endoscopy.

Endoscopic Features. All the gastrointestinal endoscopies were performed by 2 endoscopists (A.M. and S.P.) who were unaware of all clinical, laboratory, ultrasonographic, and Doppler ultrasonographic evaluations. The size of the varices was determined according to J.R.S.P.H. endoscopic rules.[15] Discrepancies between examiners were infrequent (the k value of the interobserver agreement for the size of EV was 0.80) and were solved by discussion.

Statistical Analysis and EV Prediction Model. Data were collected with a predefined pro-forma. Clinical, biochemical, ultrasonographic, and portal quantitative Doppler ultrasonographic results were entered into a computerized data-base together with data on endoscopic features for each patient.

On the basis of experience gathered from literature[11,12,14,16-25] and from our preliminary evidence, we selected age, sex, platelet count (PLT_c), serum albumin, bilirubin and cholinesterase levels, prothrombin activity (PT_p), ascites, hepatic encephalopathy, ultrasonographic longitudinal spleen axis, P, PV_{max}, PV_{mean}, and CI_x as candidate predictors of the endoscopic presence of EV. Variables found to be significant in the univariate analysis ($P < .05$) were included in a multivariate stepwise logistic regression model. The significant continuous variables were dichotomized by using their mean values as cut-off points. The values of CI_x were calculated by a formula that required P and PV_{mean}. Therefore, all aforementioned variables could not be included together in the same multivariate model. Statistical significance was tested by means of the maximum-likelihood approach, and two-tailed values are reported. Regression analyses were performed with the PROC LOGISTIC program (SAS Institute, Inc., Cary, NC).[26]

Significant variables in the multivariate analysis were also used to generate a prediction rule. For each case a score was calculated and a probability of response assigned giving a set of values for the variables. In this model, the predictive role of each candidate predictor is evaluated by the following expression:

$$\text{logit}\ P(X_{kn}) = \log \frac{P(X_{kn})}{1-P(X_{kn})} = \alpha + \sum_{k=1}^{k} \beta_k X_{kn}$$

where:

$P(X_{kn})$ = the likelihood of event (in this case, the presence of esophageal varices) in the examined series of n patients characterized by the set of variables Xk; $n = 1, 2, \ldots 143$.

α = log-odds of event likelihood for a patient with a standard set of variable ($Xkn = 0$).

X_{kn} = vector of variables $X0n$, $X1n$, $\ldots X_{kn}$ for the n-th patients. $k = 0, 1, 2$.

β_k = vector of parameters 0, 1, . . . k that weights the contribution of each variable to the likelihood of event.

$\sum_{k=1}^{k} \beta_k X_{kn}$ = sum of the products of parameter k by the variables X_{kn} of the n-th patient.

From the scoring of all significant predictors at multivariate analysis, a simple incremental rule (from 1 to 8) was established to evaluate each individual patient in the database. The sensitivity and specificity of the prediction rule were estimated by means of a receiver-operating characteristic (ROC) curve, determined by the Hanley and McNeil method.[27] The curve shows the capacity of the related model to discriminate between patients with EV and those without EV. The larger the area under the curve (AUC), the better the discriminating ability of the rule (range: from 0.5, chance performance, to 1.0, perfect prediction).

TABLE 1. Baseline Characteristics of the Study Population (143 Cirrhotic Patients)

Sex (M/F)	94 (65.7%)/49 (34.3%)
Mean age (years)*	62.31 ± 8.84
Etiology	
HCV	91 (63.6%)
HBV	10 (6.9%)
HBV/HCV	10 (6.9%)
Alcohol	15 (10.3%)
Autoimmune	2 (1.4%)
Cryptogenic	15 (10.3%)
Known disease duration (months)	22.50 ± 9.30
Child-Pugh class	
A	85 (59%)
B	58 (41%)
Albumin (g/dL)*	3.74 ± 0.57
Bilirubin (mg/dL)*	1.77 ± 1.06
PT_p*	70.51 ± 17.92
Cholinesterase (U/L)*	4109.44 ± 2067.70
PLT_c ($\times 10^9$/L)*	102.31 ± 36.91
Ascites	
Absent	120 (83.9%)
Present	23 (16.1%)
Hepatic encephalopathy	
Absent	128 (89.5%)
Present	15 (10.5%)
Esophageal varices	
Absent	80 (55.9%)
Present	63 (44.1%)
Small (F1)	35 (55.5%)
Medium (F2)	18 (28.5%)
Large (F3)	10 (16%)
P (mm)*	12.99 ± 0.21
PV_{max} (cm/sec)	21.52 ± 6.38
PV_{mean} (cm/sec)*	12.27 ± 3.64
CI_x (cm^2/[cm/sec])*	0.12 ± 0.05
Spleen axis (cm)*	15.12 ± 2.81

* Data expressed as mean ± S.D.

RESULTS

Characteristics of the Patients. The baseline features of the 143 patients included are shown in Table 1. Most of the cases showed HCV infection (63%) as the only cause of cirrhosis. A history of alcohol abuse was present in only 15 subjects (10.4%). Cirrhotics with HBV or HBV + HCV infection were 13.9% of the total cases. The majority of patients were in Child-Pugh class A (58%). Ascites detected by US was present in 16% of the patients. The proportion of patients with minimal encephalopathy was 10.4%. The mean values of P, PV_{max}, PV_{mean}, and CI_x are shown in Table 1.

Variables Associated With the Presence of EV. Using endoscopy, EV were detected in 63 of the 143 patients examined (44%; 95% confidence interval [CI]: 36.2-52.6). Medium and large EV (F2-F3) were observed in 28 of the 63 subjects (44%; 95% CI: 31.4-58.4) with EV and in 16 of them (25%) red markings were detected.

To identify predictors of the presence of EV, univariate and multivariate analyses were performed. Univariate comparison of variables between patients with EV and patients without EV is reported in Table 2. PT_p, serum albumin, bilirubin, and cholinesterase levels, PLT_c, P and ultrasonographic longitudinal spleen axis, and CI_x were significantly associated with the presence of EV. Multivariate analysis showed the following as independent predictors of EV presence, in decreasing order of significance: $PT_p < 70\%$ (odds ratio [OR]: 5.83; 95% CI: 2.6-12.8), $P > 13$ mm (OR: 2.92; 95% CI: 1.3-6.4), and $PLT_c < 100 \times 10^9$/L (OR: 2.83; 95% CI: 1.27-6.28) (Table 3). Albumin, bilirubin and cholinesterase levels, ascites, hepatic encephalopaty, and ultrasonographic longitudinal spleen axis were not significant by multivariate analysis. The prevalence of EV gradually decreased from the "worst" to the "best" class for each variable (Fig. 1). It is noteworthy that only 3 out of 31 patients (9.6%) in the best class ($PT_p \geq 70\%$, $P \leq 13$ mm, and $PLT_c \geq 100 \times 10^9$/L) had EV. Moreover, all 3 of these patients had small sized varices without red markings.

Multivariate analysis performed on the subset of patients without complications related to PHT (ascites and hepatic encephalopathy in our series), again confirmed PT_p less than 70% (OR: 9.38; 95% CI: 3.13-28.13), $P > 13$ mm (OR: 6.58; 95% CI: 2.14-20.24), and $PLT_c < 100 \times 10^9$/L (OR: 3.57; 95% CI: 1.18-10.75) (Table 4) as the only significant predictors of EV presence.

Replacing P with CI_x in the multivariate analysis, we obtained a model including $PT_p < 70\%$ (OR: 5.85; 95% CI: 2.5-13.5), $CI_x > 0.12$ (OR: 2.95; 95% CI: 1.2-6.8), and $PLT_c < 100 \times 10^9$/L (OR: 2.86; 95% CI: 1.2-6.6) as the only significant predictors of EV.

We performed the same analysis in the group of 63 patients with EV to identify predictors of the presence of medium and large EV. None of the variables listed in Table 2 allowed for the prediction of EV size (data available from F.S.).

Internal and External Validation Procedures. To assess the internal validity of the model, the jackknife cross-validation method was performed. Figure 2 shows the ROC curve for the rule predicting EV presence in the 143 cirrhotic patients (dashed line). The discriminating ability of the rule generated by the model was high, as shown by the AUC value (0.80; SEM 0.038). As an example, at the cut-off point of 4 ($PT_p < 70\%$, $P \leq 13$ mm, $PLT_c \geq 100 \times 10^9$/L) the model correctly identified 64% of subjects with EV, inappropriately diagnosing 30% of patients without EV.

In addition, a validation of the prediction rule was carried out with data from an external, independent set of 105 con-

TABLE 2. Clinical, Biochemical, and Doppler Ultrasonographic Parameters: Statistical Significance of the Differences Between Patients With and Without Varices

Variables	Patients With Varices (n = 63)	Patients Without Varices (n = 80)	*P*
Sex (M/F)	47 (74.6%)/16 (25.4%)	47 (58.7%)/33 (41.3%)	ns
Age (years)	63.74 ± 8.46	61.17 ± 9.14	ns
Albumin (g/dL)*	3.59 ± 0.57	3.86 ± 0.53	0.008
Bilirubin (mg/dL)*	2.02 ± 1.09	1.57 ± 1.01	0.017
PT_p*	62.17 ± 15.28	77.43 ± 17.19	0.0001
Cholinesterase (U/L)*	3,318.40 ± 1,487.92	4,697.87 ± 2,239.10	0.0003
PLT_c ($\times 10^9$/L)*	85.31 ± 28.38	115.14 ± 37.80	0.0001
Ascites	14 (22.3%)	8 (10%)	ns
Hepatic encephalopathy	9 (14.3%)	5 (6.3%)	ns
P (mm)*	13.82 ± 2.11	12.33 ± 2.04	0.0002
PV_{max} (cm/sec)	21.7 ± 7.71	21.3 ± 50	ns
PV_{mean} (cm/sec)*	12.3 ± 4.39	12.1 ± 2.85	ns
CI_x (cm^2/[cm/sec])*	0.13 ± 0.06	0.10 ± 0.03	0.0015
Spleen axis (cm)*	16.30 ± 2.71	13.91 ± 2.52	0.0001

* Data expressed as mean ± S.D.

TABLE 3. Logistic Regression Model to Predict the Presence of Esophageal Varices at the First Upper Endoscopy in 143 Cirrhotic Patients in Child's Class A and B

Variable	Score	β	S.E.	*P*	Odds Ratio	95% CI
PT_p (%)	0: ≥ 70 1: < 70	1.76	0.40	0.0001	5.83	2.61-12.80
P (mm)	0: ≤ 13 1: > 13	1.07	0.40	0.01	2.92	1.30-6.40
PLT_c ($\times 10^9$/L)	0: ≥ 100 1: < 100	1.04	0.40	0.01	2.83	1.27-6.28

NOTE. Adjusted for albumin, bilirubin, cholinesterase, and ultrasonographic longitudinal spleen axis.

secutive cirrhotic patients who underwent first gastrointestinal endoscopy. This test set belonged to a cohort of patients enrolled at the Cervello Hospital Center, already included in a previous long-term prospective study.[21] The baseline features of this set of patients are shown in Table 5. The ROC curve for the rule predicting EV presence in the test set (AUC 0.70; SEM 0.051) is shown in Figure 2 (solid line). Area under the curves of the 2 sets of patients were not statistically different (Z, 1.55; two-sided *P* value = .21).

DISCUSSION

The collection of firm data on the natural history of PHT in cirrhosis is necessary for planning a rational and cost-effective screening program for bleeding prevention. Unfortunately, the current available clinical evidence is still insufficient to identify the best timing to perform the first upper endoscopy in compensated cirrhotic patients.

In the present study we address 2 significant issues. First, we have evaluated whether nonendoscopic factors may be reliable predictors of EV and thus may be used to select cirrhotic patients that must undergo a primary endoscopic examination. Secondly, we have investigated the contribution of portal Doppler ultrasonographic parameters in the assessment of noninvasive diagnosis of EV.

The 1996 AASLD consensus conference on PHT suggested that the prevalence of EV in cirrhotics is proportional to the severity of liver disease as evaluated by Child's score, indicating that patients in Child's class A should be screened when a low platelet count (<140 × 10^9/L) and/or an enlarged (>13 mm) portal vein diameter are diagnosed.[4] Our cross-sectional study, showing that PT_p < 70%, P > 13 mm, and PLT_c < 100 × 10^9/L were, independently and in decreasing order of significance, the most reliable markers of EV presence, confirms the AASLD guidelines and provides further relevant information. In particular, we showed that, among the parameters used to determine the Child's class, PT_p was the only independent predictor of EV presence. Furthermore, in terms of both amount of money saved and number of endoscopy spared patients, our prescreening strategy was 25% more cost-effective than the AASLD one (Table 6). Therefore, as a consequence of avoiding useless endoscopies, our prediction rule strategy improves patients' compliance with long-term invasive procedures of screening.

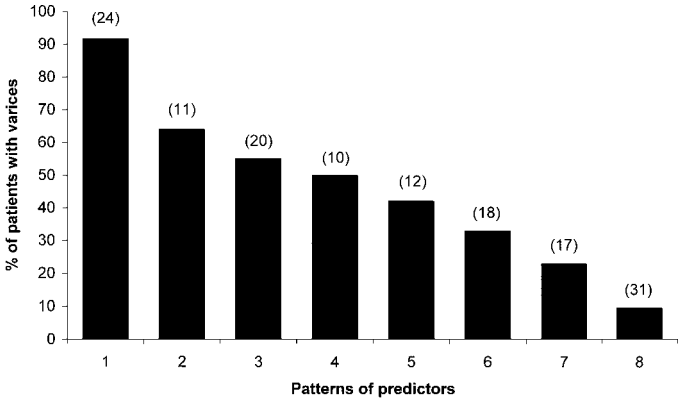

FIG. 1. Prevalence of esophageal varices at the first upper endoscopy according to specific patterns of predictors. In parentheses the number of patients in each class. 1 = PT_p < 70%, P > 13 mm, PLT_c < 100 × 10^9/L; 2 = PT_p < 70%, P > 13 mm, PLT_c ≥ 100 × 10^9/L; 3 = PT_p < 70%, P ≤ 13 mm, PLT_c < 100 × 10^9/L; 4 = PT_p < 70%, P ≤ 13 mm, PLT_c ≥ 100 × 10^9/L; 5 = PT_p ≥ 70%, P > 13 mm, PLT_c < 100 × 10^9/L; 6 = PT_p ≥ 70%, P ≤ 13 mm, PLT_c < 100 × 10^9/L; 7 = PT_p ≥ 70%, P > 13 mm, PLT_c ≥ 100 × 10^9/L; 8 = PT_p ≥ 70%, P ≤ 13 mm, PLT_c ≥ 100 × 10^9/L.

It was previously suggested that ascites,[16,17] splenomegaly,[16,18] spleen thickness,[19] spider nevi,[20] low albumin[20] or cholinesterase levels,[19] and thrombocytopenia[16,20,21-24] could serve as predictors of EV presence. However, these conclusions derive from studies published as abstracts or preliminary reports, either analyzing retrospective data, or performing only univariate comparison, or including end-stage patients. In the present cross-sectional study, by using multivariate analysis, we showed that PT_p, PLT_c, and P were the only independent predictors of EV presence in compensated cirrhotic patients.

The discriminating ability of our prediction rule, as assessed by a cross-validation protocol, was relevant. More specifically, the area under the curve of the model was 0.80. Furthermore, our prediction rule was validated with data on patients enrolled in a Center different from that where the model was implemented. Similar results were recently reported by Pilette et al.,[25] in a cohort of 116 cirrhotic patients. They showed that EV can be correctly diagnosed in 71% of cirrhotic patients by evaluating PLT_c and PT_p only. It is important to note that patients belonging to all Child's classes and with alcohol-related disease as the main etiologic feature were included in Pilette's study. However, a level of accuracy sufficient to predict the presence of EV in individual patients could not be reached by both models. Furthermore, it must be taken into account that prognostic models, if valuable in predicting the average probability of particular clinical events occurring in a group of patients, are much less accurate in predicting the same probability in individual patients. In the present study we showed that, in patients with the most favorable characteristics (PT_p ≥ 70%, P < 13 mm, PLT_c ≥100 × 10^9/L), the likelihood of EV was very low (9%). Moreover, among the 31 patients with these features, only 3 had small-sized EV, which were without red markings. Therefore, from

TABLE 4. Logistic Regression Model to Predict the Presence of Esophageal Varices at the First Upper Endoscopy in 112 Cirrhotic Patients Without Complication Related to Portal Hypertension

Variable	Score	β	S.E.	P	Odds Ratio	95% CI
PT_p (%)	0: ≥ 70 1: < 70	2.23	0.56	0.0001	9.38	3.13-28.13
P (mm)	0: ≤ 13 1: > 13	1.88	0.57	0.001	6.58	2.14-20.24
PLT_c ($\times 10^9$/L)	0: ≥ 100 1: < 100	1.27	0.56	0.023	3.57	1.18-10.75

NOTE. Adjusted for bilirubin, cholinesterase, ultrasonographic longitudinal spleen axis, and sex.

a practical point of view, we do not recommend endoscopic screening in this subgroup of patients.

When should a cirrhotic patient, who shows no evidence of EV on the first upper endoscopy, undergo a second endoscopy? The AASLD conference indicated that patients in Child's class A who have no varices on screening endoscopy should be rescreened every 2 years if their liver function is stable or every year if there are signs of liver function deterioration.[4] We think that intensive endoscopic screening programs in compensated cirrhotics should be confined to patients with the highest probability of EV presence, and that only future prospective randomized trials comparing 2 different strategies of bleeding prevention (*i.e.*, at fixed interval of rescreening vs. guided by the prediction rule) will provide the answer for planning the best cost-effective screening program.

The second issue we tried to address was the contribution of portal Doppler ultrasonographic flowmetry in the noninvasive diagnosis of EV. The clinical impact of portal flow velocity has already been analyzed by other authors, who, however, failed to identify it as a predictor of EV presence.[28,29] In the present study, PV_{max} and PV_{mean} were not different in patients with or without varices. Although Siringo et al.[30] showed values of PV_{mean} significantly different between subjects with and without varices, they could not find a threshold value discriminating between these 2 categories of patients. Finally, we showed that CI_x was significantly higher in the group of patients with EV than in the other group. Statistically significant differences in the CI_x were also found between patients with small and medium/large EV (data not shown). This confirms CI_x as the most accurate Doppler derived parameter in the evaluation of PHT,[30] although, practically speaking, it does not add any improvement to our model in comparison with the simpler measurement of the portal vein diameter. Furthermore, the discriminating ability of our prediction rule did not change by substituting P with CI_x.

Summarizing, our data lead us to conclude that only patients with a serum prothrombin activity greater than 70%, a portal vein diameter greater than 13 mm, and a platelet count less than 100×10^9/L have a high probability of EV presence. Cirrhotic patients without any of these characteristics should not undergo upper gastrointestinal endoscopy. The contribu-

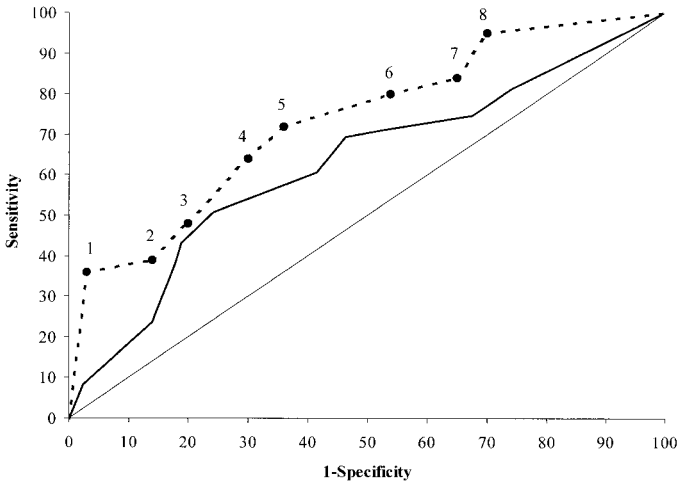

FIG. 2. Evaluation of the rule predicting the presence of esophageal varices at the first upper endoscopy by receiver operating characteristics (ROC) curve in the training set (*dashed line*) and in the test set (*solid line*). The *diagonal line* equals to no discriminating power. Each point indicates a specific pattern of predictors in the training set. 1 = $PT_p < 70$ %, P > 13 mm, $PLT_c < 100 \times 10^9$/L; 2 = $PT_p < 70$%, P > 13 mm, $PLT_c \geq 100 \times 10^9$/L; 3 = $PT_p < 70$%, P ≤ 13 mm, $PLT_c < 100 \times 10^9$/L; 4 = $PT_p < 70$%, P ≤ 13 mm, $PLT_c \geq 100 \times 10^9$/L; 5 = $PT_p \geq 70$%, P > 13 mm, $PLT_c < 100 \times 10^9$/L; 6 = $PT_p \geq 70$ %, P ≤ 13 mm, $PLT_c < 100 \times 10^9$/L; 7 = $PT_p \geq 70$ %, P > 13 mm, $PLT_c \geq 100 \times 10^9$/L; 8 = $PT_p \geq 70$%, P ≤ 13 mm, $PLT_c \geq 100 \times 10^9$/L. *Dashed line*, training set (143 patients; AUC 0.80; SEM 0.038); *solid line*, test set (105 patients; AUC 0.70; SEM 0.051). Areas were not statistically different (Z, 1.55; two-sided *P* value, .21).

TABLE 5. Baseline Characteristics of the Test Population of Cirrhotics (105 Patients)

Sex (M/F)	61 (58.1%)/44 (41.9%)
Mean age (years)*	47.91 ± 11.92
Etiology	
HCV	77 (73.2%)
HBV	6 (5.8%)
HBV/HCV	8 (7.6%)
Cryptogenic	14 (13.4%)
Child-Pugh class	
A	71 (67.6%)
B	34 (32.4%)
Albumin (g/dL)*	3.62 ± 0.61
Bilirubin (mg/dL)*	1.64 ± 0.22
PT_p*	72.23 ± 17.31
PLT_c ($\times 10^9$/L)*	146.34 ± 67.53
Ascites	
Absent	85 (80.9%)
Present	20 (19.1%)
Hepatic encephalopathy	
Absent	89 (84.7%)
Present	16 (15.3%)
Esophageal varices	
Absent	60 (57.1%)
Present	45 (42.9%)
Small (F1)	28 (62.2%)
Medium (F2)	13 (28.8%)
Large (F3)	4 (9%)
P (mm)	13.19 ± 2.03

* Data expressed as mean ± S.D.

TABLE 6. Cost Analysis of Endoscopic Screening for Detection of Esofageal Varices (EV) in 85 Child's Class A Cirrhotic Patients. Twenty-Five of Them Had Varices at Endoscopy

Strategy	Number of Patients That Underwent Endoscopy (%)	Cost of Strategy ($)*	Number of Patients With EV Identified	Cost of EV Detection per Patient ($)#
Scope all strategy	85 (100)	42,500	25	1,700
AASLD 1996 strategy	74 (87)	37,000	25	1,480
Prediction rule strategy	56 (65)	28,000	25	1,120
Ideal strategy	25 (29)	12,500	25	500

* Cost of the endoscopies performed for each strategy. Direct cost of diagnostic endoscopy was 500.[23]

Ratio of the cost of strategy per number of patients with EV identified.

tion provided by Doppler ultrasonographic portal hemodynamic parameters in the noninvasive diagnostic assessment of EV appears too weak to be proposed as a useful clinical tool.

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