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Prognostic Value of Galactose Elimination Capacity, Aminopyrine Breath Test, and ICG Clearance in Patients with Cirrhosis

Comparison with the Pugh Score

CARLO MERKEL, MD, ANGELO GATTA, MD, MARCO ZOLI, MD, MASSIMO BOLOGNESI, MD, PAOLO ANGELI, MD, TIZIANA IERVESE, MD, GIULIO MARCHESINI, MD, and ARTURO RUOL, MD

Seventy-eight patients with cirrhosis were prospectively followed for up to 20 months, on the average. At entry into the study, galactose elimination capacity, aminopyrine breath test, and ICG clearance were measured. At the end of the study, 27 patients had died. Univariate analysis using the Kaplan-Meier method showed that both quantitative liver function tests (galactose elimination capacity: P < 0.025; aminopyrine breath test: P < 0.001; ICG clearance: P < 0.005) and common clinical and biochemical data (encephalopathy: P < 0.001; ascites: P < 0.001; serum bilirubin: P < 0.005; serum albumin: P < 0.001; prothrombin index: P < 0.05) were significant predictors of survival. To investigate whether quantitative liver function tests could contribute to a better definition of the prognosis, once Pugh score had already been taken into account, a multiple regression analysis according to the Cox model was performed. Pugh score and galactose elimination capacity resulted in the only independent prognostic covariates. From them a prognostic index was calculated, and the model was validated in an additional sample of 70 patients investigated according to the same protocol. The contribution GEC gave to the assessment of overall prognosis over that obtained using the Pugh score was slight, as estimated by the statistical parameters of the Cox's model, but was significant as assessed by a ROC curve analysis (P = 0.05). These data show that all quantitative liver function tests were predictors of survival in cirrhosis, and that the galactose elimination capacity added some new prognostic information to those already available using the Child-Turcotte-Pugh classification.

KEY WORDS: liver function; liver cirrhosis; prognosis; liver failure; galactose; aminopyrine; indocyanine green.

Several factors can influence the prognosis in patients with cirrhosis. Therefore clinical, biochemical, and histological data have been employed (1–5) to attempt an accurate prognostic definition.

Some quantitative liver function tests [eg, galactose elimination capacity (GEC), aminopyrine breath test (ABT), ICG clearance (ICG-Cl)] were demonstrated to be of prognostic value in conditions of acute liver damage, such as paracetamol-

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From the Istituto di Medicina Clinica, Università di Padova, and Istituto di Clinica Medica Generale, Università di Bologna, Italy.

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Address for reprint requests: Dr. Carlo Merkel, Istituto di Medicina Clinica, Cattedra di Clinica Medica II, Policlinico Universitario, via Giustiniani, 2, I-35100 Padova, Italy.

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TABLE 1. CLINICAL AND BIOCHEMICAL DATA OF EXCLUDED PATIENTS*

Age	56 (22–79)
Sex (M/F)	26/5
Etiology (alcoholic/nonalcoholic)	25/6
Ascites	15
Encephalopathy	7
Serum albumin (g/dl)	3.3 (1.9–4.0)
Serum bilirubin (mg/dl)	1.35 (0.60–11.75)
Prothrombin index (%)	47 (22–90)

*Data expressed as median and range, when applicable. No significant difference from the group of 78 included patients in any parameter (Mann-Whitney test or Fisher exact test, when applicable).

induced liver injury (6), alcoholic hepatitis (7), or fulminant hepatic failure (8). Recently, they were also shown to provide valuable prognostic information in cirrhosis (9–12). However, in two further studies, ABT and GEC failed to improve the accuracy of prognosis, once the common clinical and biochemical data included in the Child-Turcotte-Pugh (CTP) classification of severity of liver disease (13) had been taken into account (14, 15). A comparison of CTP classification with other quantitative liver function tests has not been reported yet.

Therefore we undertook the present study to investigate whether quantitative liver function tests could improve the prognostic value of the common parameters included in the CTP classification in patients with cirrhosis.

MATERIALS AND METHODS

Study Population. During a period of 28 months all patients admitted to the Istituto di Medicina Clinica of the University of Padua, who fulfilled the entry criteria, were included in the present study, which was carried out in accordance with the Declaration of Helsinki. Inclusion criteria were: presence of biopsy-proven cirrhosis, absence of other diseases having a short prognosis by themselves, age lower than 75 years, informed consent to the study, and willingness to collaborate in it. According to these criteria 83 patients were selected from a group of 114 patients with chronic liver disease. Exclusion criteria were absence of histological diagnosis in 12 patients, extrahepatic malignancies in seven, hepatocellular carcinoma demonstrated in previous admissions in five, inability to collaborate in four, age over 75 in three. Among the 12 patients without histological diagnosis, five had severe clotting abnormalities in the presence of unequivocal signs of severe liver disease, and seven refused liver biopsy. Patients were considered unable to collaborate if they lived too far from the hospital to allow them to following the control schedule, or if they lacked a fixed domicile. Main clinical and biochemical data of excluded patients are given in Table 1.

In the 83 selected patients, the reasons for the admission were ascites and/or peripheral edema in 42, presence of esophageal varices without previous hemorrhage in 16, previous digestive hemorrhage for which patients were referred for possible treatment in eight, and acute gastrointestinal bleeding in 17. In this latter group only patients surviving at least 15 days after the end of hemorrhage were included, and data collected 15 days after hemorrhage were considered for the prognostic study. Therefore five patients who died within 15 days from hemorrhage were excluded. The final set was made up of 78 patients.

Mean age was 53 years (range 24–75 years), etiology was alcoholic in 64 (82%), posthepatitic in eight (10%), cryptogenic in six (8%). No patient had primary biliary cirrhosis, or hemochromatosis, or Wilson's disease.

Medication at the time of the study included cimetidine in 5 patients, ranitidine in 23 other patients, spironolactone in 19 patients, furosemide in 11 patients, antibiotics in 5 patients, digoxin in 4 patients. A history of recent alcohol abuse was present in most patients with alcoholic cirrhosis (49/64).

At the time of inclusion in the study, the common clinical and biochemical data included in the CTP classification were recorded, and in 76 patients ABT was performed according to Hepner and Vesell (16), following an oral dose of 2 μCi of [^{14}C]aminopyrine (New England Nuclear, Boston, Massachusetts). In 69 patients, GEC after intravenous load of galactose 0.5 g/kg body weight (Galatest, Boeringher Biochemia Robin, Milan, Italy) was performed according to Tygstrup (17). In 64 patients, ICG plasma clearance at steady state (18) was measured using a primed-continuous infusion of ICG 0.25 mg/m^2 body surface (Cardio-Green, Hynson, Westcott and Dunning, Baltimore, Maryland) and sampling arterial blood at 60, 65, 70 min. Technical details of the procedures have been described previously (19).

Patients were seen as outpatients every three months and as inpatients when necessary and were followed for up to 38 months, with a mean value of 20 months (25 in censored patients). Range of time for death was 1–38 months, for censoring 10–38 months. Two patients were lost to follow-up after three and six months, respectively. Pharmacological treatment included diuretics (spironolactone alone or associated to furosemide) in the presence of fluid retention, lactulose if encephalopathy was present, and blood transfusions, H_2 blockers, and Blakemore tubing in cases of acute gastrointestinal bleeding. As prevention of rebleeding 17 patients received beta-blockers, 12 sclerotherapy, five portal–systemic shunt.

Data Analysis. To evaluate the prognostic value of clinical data, of the common and quantitative liver function tests, and of the CTP classification, Kaplan-Meier survival plots (20) were constructed clustering continuous variables as given in Table 2. In particular serum albumin, serum bilirubin, and prothrombin index were clustered according to the CTP class and ABT, GEC and ICG-Cl into three classes in which one had a cut-off point at the 95% confidence limit in a series of control subjects investigated in our laboratory. The other cut-off point was chosen in order to obtain approximately equal sample sizes in each category. Pugh score was calculated as the

TABLE 2. SCORING OF CONTINUOUS VARIABLES

Variable	*Cut-off points*	*Scoring*
Serum creatinine (mg/dl)	≤1.50	1
	>1.50	2
Serum albumin (g/dl)	≤2.80	1
	2.81–3.50	2
	≥3.51	3
Serum bilirubin (mg/dl)	≤2.00	1
	2.01–3.00	2
	≥3.01	3
Prothrombin time (%)	≤40	1
	41–70	2
	≥71	3
Galactose elimination capacity (mg/min)	≤200	1
	201–315	2
	≥316	3
Aminopyrine breath test (%)	≤2.50	1
	2.51–5.50	2
	≥5.51	3
ICG clearance (ml/min)	≤220	1
	221–340	2
	≥341	3
Pugh score	5–6	1
	7–9	2
	10–15	3

sum of the scores of serum albumin, serum bilirubin, and prothrombin index, and adding 1 point if ascites was absent, 2 point if ascites was mild and easy to control, 3 points if it was tense or resistant to common treatment, 1 point if encephalopathy was absent, 2 points if grade I or II encephalopathy was present, and 3 points in the presence of more severe hepatic encephalopathy. Ascites and encephalopathy were assessed clinically, regardless of the treatment that the patients were receiving.

To investigate whether the individual variables were univariately related to survival, curves were compared by the Mantel-Haenzel test (21) when two curves had to be compared, and with the *t* test for trend (22) when comparing three curves.

To establish if quantitative liver function tests contributed to a better definition of the prognosis in our patients, once the CTP classification had been taken into account, the multiple regression analysis proposed by Cox (23) was employed. Since the procedure requires a complete set of data, the few missing data were replaced by neutral estimates using the maximum likelihood estimate according to Beale and Little (24). The number of missing data was acceptable according to standard statistical practice (25). In a first stage, covariates analyzed for inclusion in the model were sex, etiology, ascites, encephalopathy, previous hemorrhage, previous treatment for portal hypertension, serum creatinine, serum bilirubin, serum albumin, prothrombin index, ABT, GEC, ICG-Cl. Variables were first subjected to univariate analysis, then a predictor covariate was added if its chi-square statistics was the largest and its *P* value was less than 0.10. Then each chosen covariate was reconsidered and eliminated if its chi-square value was the smallest and *P* value was higher than 0.15. The procedure was performed stepwise

TABLE 3. CLINICAL AND BIOCHEMICAL DATA OF THE 70 FURTHER PATIENTS INVESTIGATED FOR VALIDATION OF COX MODEL*

Age	55 (19–74)
Sex (M/F)	51/19
Etiology (alcoholic/nonalcoholic)	41/29
Ascites	28
Encephalopathy	5
Serum albumin	3.4 (1.8)
Serum bilirubin	1.10 (20–8.19)
Prothrombin index	70 (33–100)
Pugh score	7 (5–13)
Galactose elimination capacity (mg/min)	301 (128–496)
Time of follow-up (months)	19 (0.5–38)

*Data expressed as median and range. No significant difference from the group of 78 included patients in any parameter, (Mann-Whitney test or Fisher exact test, when applicable).

until no further covariate could be added or removed according to the above-mentioned criteria. In a second step, the same Cox model analysis was performed substituting Pugh score to the five variables that define the score. Pugh score was used instead of CTP class since it was shown that the former has a better prognostic accuracy than the latter (26). To check proportionality of risk with time in the various classes, log of cumulative hazard was plotted against time, demonstrating a parallel behavior in patients with low and high values of selected predictor covariates. A prognostic index (PI) predicting death was computed using the regression coefficients of the Cox's model (23).

To assess the validity of the model proposed, individual PI's were calculated in a further sample of 70 patients, 15 admitted to the Istituto di Medicina Clinica, University of Padova, Italy, after the end of the study, and 55 admitted to the Istituto di Clinica Medica Generale, University of Bologna, Italy. All patients were selected according to the same inclusion and exclusion criteria. Main clinical and biochemical data in this group of patients are given in Table 3. Patients were divided into two groups by the median value of PI, and median values of PI in the higher and lower groups were computed. Validation was performed comparing the observed outcome of the groups with the survival function of patients with a PI equal to the median values in the groups, calculated according to the Cox model.

The clinical usefulness of the addition of quantitative liver function tests to the Pugh score was assessed constructing a ROC curve of sensitivity and specificity of predicting death within 18 months derived from the PI and a ROC curve derived only from Pugh score. To perform this analysis all patients investigated in Padova and Bologna were considered. PI values were divided into eight equally spaced intervals, and sensitivity and specificity in predicting death within 18 months were computed. The same was performed for Pugh score. Areas under the ROC curve (AUC) and standard errors of AUC were computed and compared according to Hanley and McNeil (27, 28). Since the null hypothesis predicts that no improvement in AUC exists after adding GEC to Pugh score, a one-sided significance test was employed.

TABLE 4. CLINICAL AND BIOCHEMICAL DATA OF 78 INVESTIGATED PATIENTS*

Age	53 (24–75)
Sex (M/F)	62/16
Etiology (alcoholic/nonalcoholic)	64/14
Ascites	47
Encephalopathy	9
Gastrointestinal bleeding in index or previous admission	25
Source of bleeding†	13, 10, 3
Previous therapy for portal hypertension‡	8, 2
Serum albumin (g/dl)	3.59 (2.10–4.80)
Serum bilirubin (mg/dl)	1.60 (0.40–14.20)
Prothrombin index (%)	57 (30–95)
Pugh score	8 (5–13)
Galactose elimination capacity (mg/min)	285 (154–518)
Aminopyrine breath test (%)	4.12 (0.93–9.85)
ICG clearance (ml/min)	301 (105–986)

*Data expressed as median and range, when applicable.
†Varices, acute gastric erosions, peptic ulcer.
‡Beta-blockers, sclerotherapy.

All statistical analysis was performed using the BMDP statistical package (29).

RESULTS

The values of the clinical and biochemical data included in the Pugh score, and those of GEC, ABT, and ICG-Cl at the entry into the study in the 78 patients with cirrhosis are illustrated in Table 4.

During the follow-up 27 patients died (14 of liver failure, nine of gastrointestinal bleeding, two of spontaneous bacterial peritonitis, two of hepatorenal syndrome).

The probability of survival was significantly higher in patients with higher levels of serum albumin ($P < 0.001$), prothrombin index ($P < 0.05$), GEC ($P < 0.025$), ABT ($P < 0.001$), ICG-Cl ($P < 0.005$) (Figure 1), with lower levels of serum bilirubin ($P < 0.005$), without ascites ($P < 0.001$) or encephalopathy ($P < 0.001$). Survival was not related to sex, etiology, serum creatinine, previous experience of gastrointestinal hemorrhage, or treatment received for portal hypertension.

From the Cox's model a final configuration including serum albumin, serum bilirubin, encephalopathy, and GEC was obtained. Statistical parameters of the model are given in Table 5. Applying the Cox model after inclusion of Pugh score among the covariates, the final configuration included only Pugh score and GEC. Chi-square to enter the regression was 1.98 for ABT ($P = 0.16$), and 0.90 for ICG-Cl ($P = 0.34$). Statistical data pertinent to the final configuration are given in Table 6. From them a prognostic index (PI) was calculated as

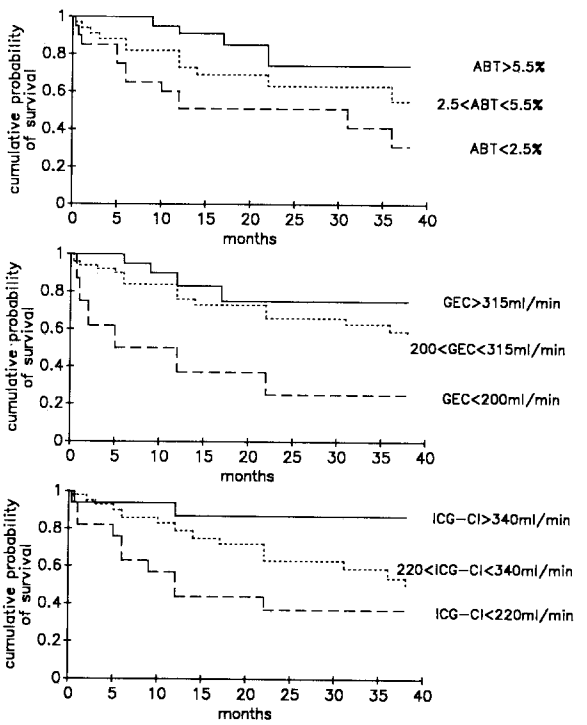

Fig 1. Kaplan-Meier survival curves in patients stratified according to ABT, GEC, and ICG-Cl.

$$PI = (0.53 \times \text{Pugh score}) - [0.006 \times \text{GEC (mg/min)}]$$

Validation of the proposed model is illustrated in Figure 2. The test set of 70 patients was divided into two groups with PI higher or lower than the median value (1.59); the mean estimated survival functions for the patients in the two classes were computed according to the Cox's model. These were compared with observed survival in the same patients calculated according to Kaplan-Meier. No significant difference between observed and expected mortality was found in patients with different levels of PI (Figure 2).

To evaluate the clinical usefulness of the addition of GEC to the Pugh score, PI and Pugh score were compared by means of a ROC curve considering sensitivity and specificity in predicting death within 18 months (Figure 3). AUC was significantly larger according to PI than to Pugh score (0.86 ± 0.03 vs. 0.82 ± 0.03; $z = 1.68$; $P = 0.05$; one-sided test), indicating a better prognostic efficiency. Best cutoff points were 2.5 for PI, and 8 for Pugh score. In particular, 78% of patients who died within 18 months had PI higher than 2.5 (ie, sensitivity was

TABLE 5. PROGNOSTIC VARIABLES IN FINAL COX REGRESSION MODEL WHEN PUGH SCORE WAS NOT INCLUDED

Variable	Regression coefficient	Normal deviate	Log likelihood	R^2	Improvement	
					Chi-square	P
Serum albumin	−0.79	−2.14	−96.75	0.08	18.49	0.000
Serum bilirubin	0.24	3.01	−92.33	0.17	8.83	0.003
Encephalopathy	1.36	2.70	−89.44	0.22	5.78	0.016
GEC	−0.006	−1.77	−87.70	0.22	3.49	0.062

78%), and 79% of patients who survived had PI lower than 2.5 (ie, specificity was 79%). Conversely, 78% of patients with Pugh score of 9 or more died within 18 months, but only 70% of patients with Pugh score of 8 or less survived the same time.

DISCUSSION

The results of this study show that (1) both the clinical data and biochemical tests included in the CTP classification, and the quantitative liver function tests, such as GEC, ABT, and ICG-Cl, were predictors of survival in cirrhosis; and (2) GEC added some further prognostic information not included in the CTP classification.

CTP classification, first proposed to assess the risk of surgery for portal hypertension (13), has progressively gained applicability in the general population of conservatively treated cirrhotics (5, 26, 30). In the recent years, further determinants of prognosis have been investigated, and it was shown that histological data such as inflammation in liver connective tissue, liver cell necrosis, eosinophil infiltrate, and the presence of efferent veins in parenchymal nodules are ominous prognostic indicators (1, 2). A different approach to prediction of survival in cirrhosis has originated from the use of quantitative liver function tests, which can be important predictors of survival in patients with acute impairment in liver function, eg, paracetamol-induced liver damage (6), alcoholic hepatitis (7), or fulminant hepatic failure (8). In cirrhosis, quantitative liver function tests were found to be able to discriminate groups of patients with different prognoses (9–12, 14). However, only three studies involving ABT investigated the role of this test in the definition of prognosis, once CTP classification has been taken into account (12, 14, 15). In two studies the quantitative function tests failed to improve prognostic accuracy over that obtained using ABT classification (14, 15), in one ABT and presence of ascites represented the best set of covariates predicting one-year survival (12). In another study GEC and ICG-Cl were compared in males undergoing a testosterone therapeutic trial (31), and both were unable to improve prognostic ability over that arising from common clinical and biochemical variables. No data are available on comparisons among three different quantitative liver function tests. The lack of significance of GEC in the two studies in which it was evaluated (15, 31) is probably dependent, at least in part, on the small number of end points observed in those series. It is clearly established that the number of end points heavily influences the ability to detect significant effects (25).

In the present study all quantitative liver function tests were significant predictors of survival, although not as valuable as albumin, bilirubin, encephalopathy, or the Pugh sore, which contains all these variables. Also in this study, CTP classification showed a remarkably good prognostic efficiency, as reported by others (5, 14, 26, 30). However, GEC had a prognostic value of its own that was not included in that obtained from other prognostic variables, since GEC remained in the final configuration of Cox's model together with serum albumin, serum bilirubin, and encephalopathy, when Pugh score was not considered, and together with Pugh score, when this latter was included among the possible prognostic covariates. The con-

TABLE 6. PROGNOSTIC VARIABLES IN FINAL COX REGRESSION MODEL WHEN PUGH SCORE WAS INCLUDED

Variable	Regression coefficient	Normal deviate	Log likelihood	R^2	Improvement	
					Chi-square	P
Pugh score	0.53	4.55	−94.29	0.11	23.42	0.000
GEC	−0.006	−1.77	−92.55	0.11	3.48	0.062

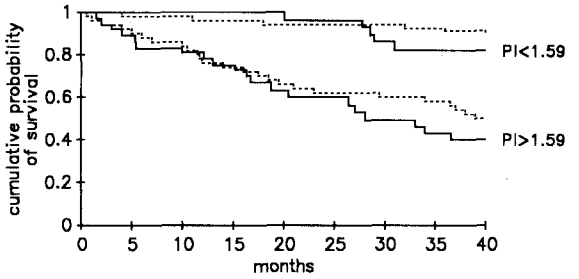

Fig 2. Validation of the final model including Pugh score and GEC. Solid line: observed survival according to Kaplan-Meier in the 70 patients of the test set; dotted line: estimated survival according to the Cox model derived from the data of the 78 original subjects. PI < 1.59: observed = 5; expected = 4. PI > 1.59: observed = 20; expected = 18.

tribution GEC gave to a better definition of prognosis may be derived from the statistical parameters given in Tables 5 and 6 (particularly from the normal deviate, which was approximately 2.5 times higher for Pugh score than for GEC), and from the ROC curve drawn in Figure 3. From the ROC curve analysis, a significant increase in AUC resulted, which means a better efficiency in predicting death. It should be considered, however, that this improvement was not striking, because of the excellent discriminant ability of the Pugh score. Nevertheless, the use of a ROC curve lessens the real significance of PI, since the different times until deaths cannot be taken into account.

GEC appeared to be a better prognostic indicator of survival compared to ABT and ICG-Cl, although correlated to them in the present as well as in other studies (32, 33). Possible explanations for this discrepancy can be as follows: (1) GEC is less prone to enzyme induction from alcohol and/or drugs than ABT (34); (2) GEC determination is not influenced by alterations in the metabolic rate of formate oxidation as a consequence of folate deficiency, at variance with ABT (35); (3) GEC gives an estimate of liver function independent of liver blood flow, while ICG-Cl in cirrhosis depends also on hepatic perfusion (36). In addition, in an experimental model of liver cirrhosis, GEC was also found to be a better prognostic indicator of survival than ABT (37). It should be stressed, however, that the analysis of a larger series of patients might disclose significant effects also using other liver function tests; some preliminary data from our laboratory (38) seems to support this statement.

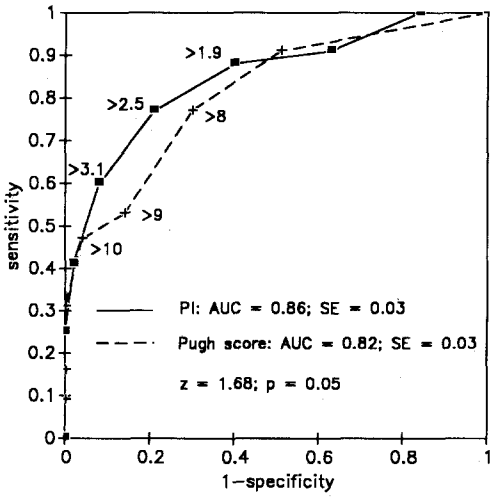

Fig 3. ROC curve of predicting death within 18 months according to Pugh score or to the prognostic index calculated from the Cox model.

In conclusion our data show that in our series of patients with cirrhosis GEC, ABT and ICG-Cl were strong predictors of survival, and that GEC added prognostic information to those obtained from CTP classification. The addition of GEC to Pugh score allowed the computation of PI. The clinical relevance of PI in establishing the overall prognosis however, is slight, since CTP classification has a remarkably good efficiency by itself. Larger cooperative studies will be needed to assess conclusively the usefulness of PI in such patients. If the prognostic value of PI is confirmed in further series, it could be considered a clinically useful tool for the evaluation of patients with liver cirrhosis.

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