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Evaluation of Hepatic Function in Liver Cirrhosis

Clinical Utility of Galactose Elimination Capacity, Hepatic Clearance of D-Sorbitol, and Laboratory Investigations

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Assessment of hepatic function is based on both liver blood tests and functional tests, the extensive application of which is still controversial. The aim of this study was to evaluate the clinical utility of a few selected tests as discriminatory and prognostic indexes: serum albumin, pseudocholinesterase, prothrombin time, as well as galactose elimination capacity and hepatic sorbitol clearance. Two separate studies were performed: Study I to investigate how well these tests assessed severity, and Study II to evaluate their prognostic value. A total of 128 consecutive cirrhotic patients classified according to the Child-Pugh score were included in Study I; Study II was carried out on 47 of these 128 during a two-year follow-up period. Pairwise correlations between all tests and Child-Pugh score yielded higher significant values for liver blood tests than for the functional ones. In Study I functional tests such as galactose elimination capacity and hepatic sorbitol clearance did not appear to be better than conventional biochemical tests in discriminating clinical severity of cirrhotic patients, as defined by Child-Pugh classification. Results of Study II confirmed that in severe liver cirrhosis Child-Pugh score remains the best method for medium- and long-term prognosis and for planning liver transplantation. Functional tests should be reserved for defining the residual functioning liver mass or for studies about functional liver plasma flow.

KEY WORDS: galactose elimination capacity; hepatic sorbitol clearance; liver cirrhosis; Child-Pugh score.

In cirrhotic patients complications such as ascites, upper gastrointestinal bleeding, and encephalopathy may substantially shorten survival. Assessment of functional severity is therefore very important not only for determining prognosis but also because of the availability of orthotopic liver transplantation (OLT), a life-saving treatment for end-stage cirrhotic patients. Hepatic function is currently evaluated by measuring plasma concentrations of substrates or final products of liver metabolism, such as albumin, fibrinogen, pseudocholinesterase, prothrombin, bilirubin, cholesterol, etc. Such an approach has some negative aspects: (1) parameters are not very specific for a single pathophysiological alteration (eg, albumin plasma level decreases in the presence of renal or intestinal loss; fibrinogen concentration increases in chronic inflammation; bilirubin increases in hemolytic disorders); (2) test sensitivity is sometimes too low to detect mild liver alterations; (3) as a consequence,

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most biochemical parameters do not directly provide reliable quantitative evaluations of the integrity and functional reserve of the hepatic parenchyma. Although some authors have shown that scoring systems based on liver blood tests hold prognostic information, their use may be limited by a number of drawbacks, including inappropriate cutoff points, unequal importance of diverse variables, and exclusion of important prognostic factors (1). To avoid such limitations several functional tests have been proposed in recent decades, based on the analysis of the complex elimination kinetics of substances metabolized by the liver (2, 3). However, uncertainties still exist as to the actual utility of an extensive clinical application of these tests, mainly because of their complexity and cost. The present study was designed with the aim of evaluating the clinical utility of a few selected tests (liver blood tests and functional tests, respectively), regarding their discriminatory capacity with respect to a traditional severity score based on clinical data, as well as their capacity to predict evolution towards survival or death. A few biochemical tests reflecting liver synthetic activity—serum albumin (ALB) (4–6), serum pseudocholinesterase (CHE), and prothrombin time (PT) (7)—were considered in the present work (8). Among functional tests, the galactose elimination capacity (GEC) and the hepatic sorbitol clearance (HSC) tests were selected because they are simple, safe, cheap, and directly measure two typical functional parameters, functioning liver mass (9, 10) and functional hepatic plasma flow (11–16), respectively. The present study was aimed at evaluating in cirrhotic patients the clinical utility of all the above parameters, assuming the Child-Pugh score (CPS) and the Child classification as gold standards for clinical severity (17). Two separate studies were designed: Study I was aimed at evaluating the clinical utility of selected tests in assessing the clinical severity; Study II focused on changes in test results during the natural history of cirrhosis and on the prognostic value of each test in predicting long-term survival.

MATERIALS AND METHODS

Subjects

Study I was performed from October 1995 to October 1996 on 128 consecutive patients with biopsy-proven liver cirrhosis followed in the Department of Gastroenterology (San Giovanni Battista Hospital of Turin): there were 76 men (59.8%) and 52 women (40.2%); mean age was 49.2 years, range 17–75 years. Causes of cirrhosis are shown in Table 1. At study entry 37 patients (28.9%) were in Child class A, 52 patients (40.6%) in class B, and 39 (30.5%) in class C. During the study 20 patients (15.6%) died and 32 (25%) needed liver transplantation. The prognostic and prospective two-year follow-up study (Study II) included 47 of the 128 patients (28 men and 19 women; mean age 49 years, range 32–66), whose GEC, HSC, ALB, PT, and CHE were evaluated every four months during the first year, then every six months. Causes of cirrhosis in this subgroup of patients are shown in Table 1. At the beginning of this study 16 patients belonged to Child class A, 17 to class B, and 14 to class C; during this prognostic study 12 patients (25.5%) died and 14 (29.7%) needed liver transplantation. At the end of the follow-up, the 21 survivors (mean age 50.2 years, range 36–67) were classified as follows: 12 in Child class A, 8 in B, and 1 in C, respectively.

Table 1. Clinical Features of Study Population

	Study I (N = *128*)	*Study II* (N = *47*)
Mean age [yr (range)]	49.2 (7–75)	49 (32–66)
Sex (M/F)	76/52	28/19
Etiology [*N* (%)]		
HBV	12 (9.7)	7 (14.9)
HCV	55 (42.8)	23 (48.9)
HDV	7 (5.8)	3 (6.4)
HCV + HBV or HDV	4 (2.9)	
Alcoholic	13 (9.7)	3 (6.4)
Cryptogenetic	15 (11.7)	9 (19.1)
Autoimmune	2 (1.9)	
Hemocromathosis	2 (1.9)	
PBC	8 (5.8)	2 (4.3)
Alcoholic + viral	10 (7.8)	
Child-Pugh at entry [*N* (%)]		
Class A	37 (28.9)	16 (34.0)
Class B	52 (40.6)	17 (36.2)
Class C	39 (50.5)	14 (29.8)

Study Design

Overall, 316 evaluations were performed according to the study design on two subsequent days. At each evaluation on the first day, after clinical examination, blood samples were taken to determine all requested biochemical parameters (ALB, CHE and PT), then the GEC test was immediately performed; HSC was determined on the following day.

Severity Score Calculation. At each evaluation the severity score was computed according to Child-Pugh (18) from clinical parameters and biochemical investigations (appropriate adaptation of the Child-Pugh score was used in patients with primary biliary cirrhosis); patients were then classified according to the Child classification as class A (score 5–6), B (score 7–9), and C (score 10–15).

Biochemical Investigations. Conventional laboratory parameters, including ALB, CHE, and PT, were evaluated by the usual laboratory methods.

Galactose Elimination Capacity. After overnight fasting, a bolus of 500 mg/kg galactose (30% water solution) was infused intravenously in resting patients and plasma samples were drawn every 10 min starting from 20 to 70 min (during this period galactose elimination is saturated and plasma levels decrease linearly). Cumulative galactose urinary elimination was measured on urine collected for 70

Table 2. Biochemical Parameters in Normal Controls and Patients Stratified According to Child-Pugh Classes*

	HSC (ml/min)	*GEC (mg/min)*	*ALB (g/dl)*	*PT (%)*	*CHE (IU/liter)*
Normals	911 ± 137	508 ± 64	4.4 ± 0.8	100 ± 30	9500 ± 5000
Child A	595 ± 258	332 ± 106	4.05 ± 0.42	80 ± 16	5976 ± 2625
Child B	425 ± 225	278 ± 90	3.5 ± 0.49	59 ± 13	3649 ± 1834
Child C	343 ± 217	234 ± 80	2.98 ± 0.5	45 ± 12	2106 ± 1498

* Values are expressed as mean ± SD.

min after the start of the infusion. Plasma and urine samples were immediately deproteinized; galactose concentrations were determined by spectrophotometric–enzymatic assay according to Tygstrup and Winkler (10). The GEC was measured as follows:

$$GEC = \frac{(C_0 - C_t)V_d}{t} - U$$

where C_0 is the galactose plasma concentration extrapolated at time 0 (milligrams per deciliter); C_t is the galactose plasma concentration at time t; V_d is the distribution volume (dose/C_0); and U is the rate of galactose urinary elimination (milligrams per minute).

Hepatic Sorbitol Clearance. This test was performed in resting patients and after overnight fasting after 180 min of constant intravenous infusion of a 3% D-sorbitol solution at a rate of 30 mg/min. Renal elimination was measured on urine collected between 60 and 180 min during the infusion. Plasma and urinary samples were immediately deproteinized, then plasma and urine sorbitol concentrations were determined by the spectrophotometric–enzymatic method described in Bergmeyer et al (19). The HSC was computed as the extrarenal clearance, as follows:

$$HSC = \frac{I - U}{SC_s}$$

where I is the sorbitol infusion rate (milligrams per minute); U is the mean urinary sorbitol excretion (milligrams per minute); and SC_s is the sorbitol plasma concentration at steady state (milligrams per deciliter).

All patients gave their informed consent and the study was performed according to the 1975 Declaration of Helsinki ethical guidelines.

Statistical Analysis

In order to evaluate the degree of association of each parameter with the reference classification (CPS), Pearson correlation coefficients were calculated in two ways: (1) considering each clinically significant value (5–15) of CPS, and (2) grouping patients into the three Child classes: A–C. In addition, to assess the discriminatory power of the five parameters considered (ALB, CHE, PT, GEC, and HSC) with respect to the three Child classes, we performed one-way analysis of variance with the Bonferroni correction for pairwise comparisons: A vs B, A vs C, B vs C. Survival curves were estimated by the Kaplan-Meier product-limit method. The equality of the curves between the patient groups was tested using the Wilcoxon-Breslow method.

For longitudinal studies, statistical analysis was performed by comparing the relative variation of each measured value with respect to the corresponding initial value. Finally, threshold values of all parameters for prognostic prediction (end point: death or transplantation) were determined on the basis of the median values of the parameter distributions (observed in class C patients). Multiple regression analysis was performed according to the Cox model (20).

All statistical evaluations were performed with the BMDP statistical package (BMDP Statistical Software 1988, Berkeley, California).

RESULTS

Study I

Experimental results are shown in Table 2, where reference values provided by local laboratories for healthy subjects are also given. All five parameters decreased progressively from Child class A to C. Differences between classes A and B and between classes A and C were always highly significant ($P < 0.001$), while comparisons between classes B and C were highly significant for biochemical tests ($P <$

Table 3. Sensitivity, Specificity, and Predictive Values of Each Parameter Evaluated in Study I Patients Grouped by Child-Pugh Class*

Child-Pugh score	*Percent*				
	HSC	*GEC*	*ALB*	*PT*	*CHE*
A vs B + C					
Sensitivity	31	20	59	40	36
Specificity	82	84	84	78	87
PPV	39	32	59	42	53
NPV	76	73	84	77	77
B vs A + C					
Sensitivity	14	15	52	43	53
Specificity	92	79	71	82	84
PPV	54	33	56	64	71
NPV	62	58	67	66	70
C vs A + B					
Sensitivity	83	63	60	70	86
Specificity	68	59	85	85	76
PPV	54	42	64	68	58
NPV	89	77	83	86	93

* PPV: positive predictive value; NPV: negative predictive value.

Table 4. GEC and HSC Changes During Two-Year Follow-up in 47 Patients Grouped by Child Classification at Entry*

		Months				
Child-Pugh at entry	*Basal*	*4*	*8*	*12*	*18*	*24*
GEC (mg/min)						
Class A	296 ± 61 ($N = 16$)	301 ± 86 ($N = 13$)	291 ± 67 ($N = 13$)	282 ± 76 ($N = 13$)	320 ± 77 ($N = 12$)	317 ± 81 ($N = 11$)
Class B	272 ± 64 ($N = 17$)	255 ± 78 ($N = 15$)	292 ± 47 ($N = 11$)	316 ± 69 ($N = 10$)	319 ± 68 ($N = 8$)	317 ± 100 ($N = 8$)
Class C	221 ± 78 ($N = 13$)	274 ± 61 ($N = 5$)	265, 157 ($N = 2$)	388, 285 ($N = 2$)	278, 365 ($N = 2$)	274, 313 ($N = 2$)
HSC (mL/min)						
Class A	661 ± 197 ($N = 16$)	595 ± 187 ($N = 13$)	530 ± 234 ($N = 13$)	468 ± 173 ($N = 13$)	486 ± 220 ($N = 12$)	517 ± 164 ($N = 11$)
Class B	486 ± 146 ($N = 17$)	398 ± 121 ($N = 15$)	495 ± 272 ($N = 11$)	408 ± 203 ($N = 10$)	492 ± 280 ($N = 8$)	405 ± 169 ($N = 8$)
Class C	350 ± 128 ($N = 14$)	446 ± 104 ($N = 5$)	407, 368 ($N = 2$)	343 ($N = 1$)	237 ($N = 1$)	291 ($N = 1$)

* Mean values ± SD are given whenever more than five patients were observed, otherwise individual values are provided.

0.001), less significant ($P < 0.01$) for GEC and not significant for HSC.

Pairwise correlations between all tests and CPS values were all statistically significant ($P < 0.001$). However, by Pearson's correlation test, higher index values were found for biochemical tests (−0.68, −0.65 and −0.56 for PT, ALB, and CHE, respectively), than for GEC and HSC (−0.36 and −0.38, respectively).

The values for sensitivity, specificity, and positive and negative predictive values are reported in Table 3. All evaluated tests demonstrated a high negative predictive value in each Child-Pugh class.

Study II

During the two-year follow-up period (Table 4), GEC values did not change significantly in any class of patients. On the other hand, HSC values decreased significantly during the first 12 months in patients classified as Child A at entry (661 ± 197 vs 468 ± 173 ml/min; $P < 0.01$), while changes were not significant thereafter or in Child classes B and C. As regards biochemical parameters, in Child classes A and B, no significant changes were detected over time during the follow-up period, while the low number of surviving patients makes such an observation impossible in class C patients.

Another aim of the study was to evaluate the prognostic value of a single determination (basal value) of each parameter (liver blood tests and functional tests as well as CPS) to predict long-term survival in cirrhotic patients. The end point for such an evaluation was death or liver transplantation. To this extent the 47 patients studied were divided with respect to each parameter into two classes (three for Child classes) using the above-defined threshold values (Table 5). Child classes and CPS basal values discriminated very well between survivors and nonsurvivors after a two-year follow up ($P = 0.0005$) (Figure 1); the same results were observed with liver blood tests ($P = 0.001$, $P = 0.006$, and $P = 0.002$ for CHE, PT, and ALB, respectively). GEC and HSC discriminatory capacity was good but lower than that of other tests ($P = 0.01$ and $P = 0.05$, respectively; Figures 2 and 3).

Multiple regression analysis showed that CHE is the only parameter having predictive value for medium- and long-term prognosis in the patients studied ($P < 0.01$).

Table 5. Differences in Two-Year Survival Rates According to Clinical and Biochemical Parameters

Group	*Cases* (N)	*Two-year survival rate (%)*	P
Child A (CPS = 5–6)	16	75	
Child B (CPS = 7–9)	17	47	0.0005
Child C (CPS = 10–15)	14	7.1	
pCHE > 2100 IU/liter	24	75.0	
pCHE < 2100 IU/liter	12	16.6	0.001
PT > 45%	34	58.8	
PT < 45%	10	30.0	0.006
ALB > 3.0 g/dl	34	64.7	
ALB < 3.0 g/dl	9	11.1	0.0029
GEC > 234 mg/min	30	56.6	
GEC < 234 mg/min	17	23.5	0.013
HSC > 343 ml/min	37	51.3	
HSC < 343 ml/min	10	20.0	0.05

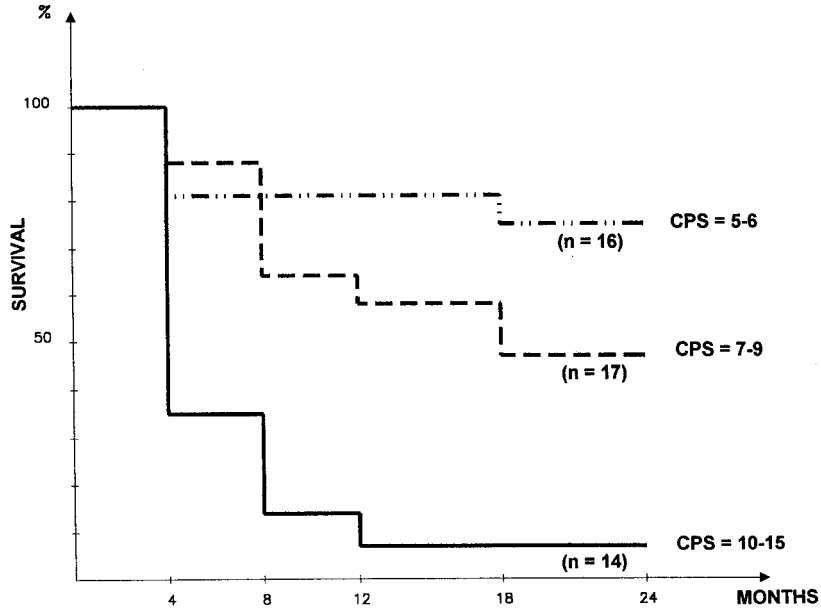

Fig 1. Kaplan-Meier two-year survival analysis for patients classified according to Child-Pugh score ($P = 0.0005$ by the Wilcoxon-Breslow method).

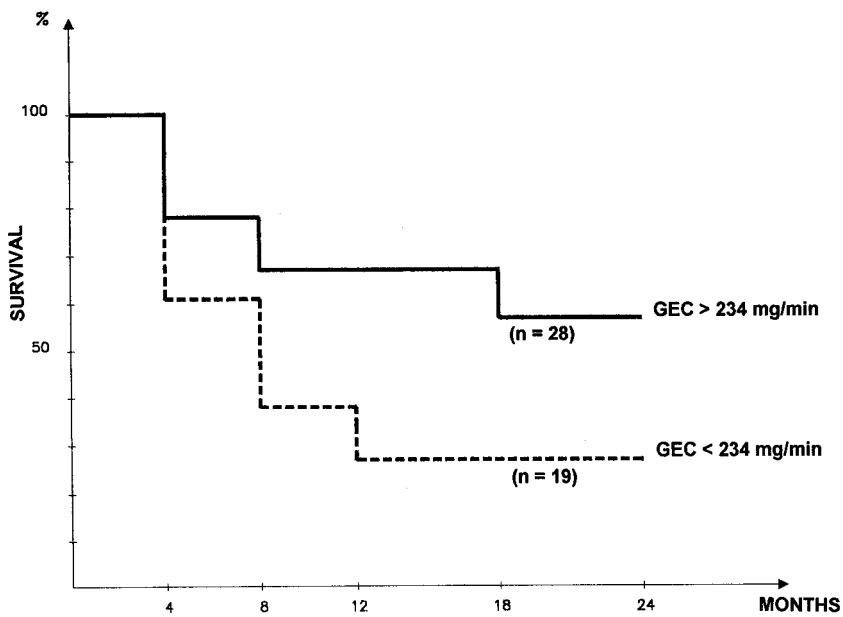

Fig 2. Kaplan-Meier two-year survival analysis when two groups of patients are considered assuming 234 mg/min as threshold value for GEC ($P = 0.01$ by the Wilcoxon-Breslow method).

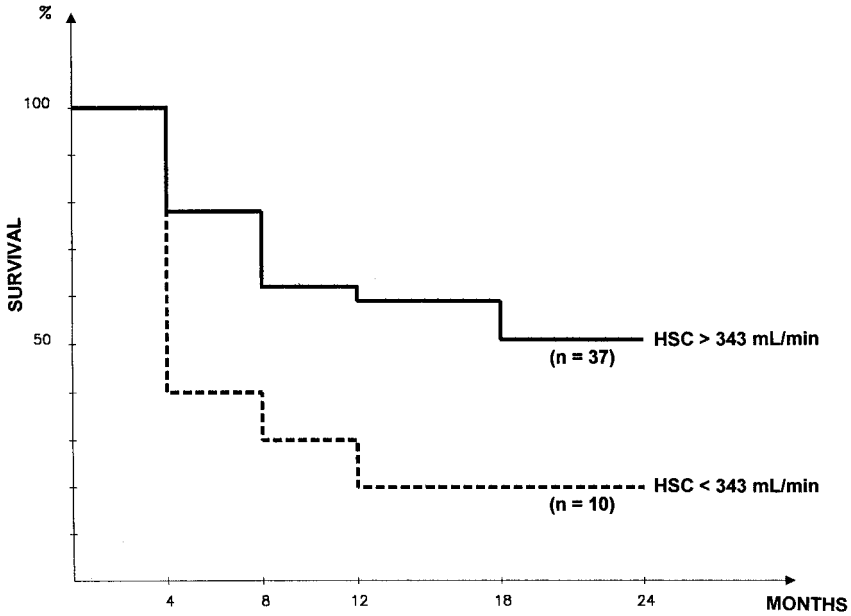

Fig 3. Kaplan-Meier two-year survival analysis when patients are subgrouped into two main classes according to a HSC threshold value of 343 ml/min ($P = 0.05$ by the Wilcoxon-Breslow method).

DISCUSSION

First, it is important to stress that the number of patients studied is too small to give definitive conclusions, and the authors' conclusions may be affected by this. In Study I, all parameters discriminated significantly between Child A and B cirrhotic patients. In contrast, the discrimination between classes B and C was highly significant only for biochemical investigations, while significance was lower for GEC and not significant at all for HSC. Thus, functional tests such as GEC and HSC do not appear to work better than conventional biochemical tests in discriminating clinical severity of cirrhotic patients, as defined by the Child-Pugh classification. Similar conclusions derive from the evaluation of Pearson's correlations. However, it must be considered that our results might be biased by the fact that biochemical parameters reflecting liver biosynthetic activity (namely ALB and PT) are included in the set of data contributing to the calculation of the Child-Pugh score. The lower discriminatory capacity of GEC and HSC might be also tentatively explained by the fact that functioning liver mass (GEC) and functional hepatic plasma flow (HSC) are more focused parameters than laboratory tests; indeed the latter reflect not only hepatic biosynthesis, but also substrate elimination and distribution. Alternatively, one might argue that during the natural history of liver cirrhosis, the functioning liver mass and the functional hepatic blood flow are impaired in a nonlinear way.

Results obtained from Study II indicate that the only significant modification of studied parameters is that observed early in Child class A patients for HSC. This might reflect the primary importance of circulatory changes in the pathogenesis of functional impairment in liver cirrhosis. In this study the end point of the evaluation was the patient's death or liver transplantation within two years. As regards prognostic relevance, basal test values and CPS were evaluated as predictors of either survival or death/transplantation. The discriminatory thresholds identified in an arbitrary way provide very similar results in partitioning the studied group of patients between survivors and nonsurvivors or transplant recipients. The findings of Study II confirm that in severe liver cirrhosis CPS remains a valid method for medium- and long-term prognosis or for planning liver transplantation and show that similar results can be obtained using a single determination of HSC or GEC. However, the CPS also does not appear to be completely satisfactory and other better prognostic variables should be considered (1). The use of functional tests should be

preferable as tools when an evaluation of functional hepatic plasma flow and/or residual functioning liver mass is needed (21, 22).

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