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Prognostic value of the galactose test in predicting survival of patients with cirrhosis evaluated for liver transplantation

A prospective multicenter Italian study

Francesco Salerno, Gianmario Borroni, Pamela Moser, Angelo Sangiovanni, Piero Almasio[1], Gabriele Budillon[2], Gaetano Capuano[2], Maurizio Muraca[3], Giulio Marchesini[4], Mauro Bernardi[5], Giorgio Marenco[6], Gianpaolo Molino[7], Lorenzo Rossaro[8], Antonio Solinas[9], Antonio Ascione[10] and the AISF Group for the Study of Liver Transplantation*

Istituto di Medicina Interna della Università di Milano, [1]Istituto di Medicina Generale, Ospedale Cervello, Università di Palermo, [2]Cattedra di Gastroenterologia, Università di Napoli, [3]Patologia Medica I, Università di Padova, [4]Istituto di Clinica Medica II, Università di Bologna, [5]Patologia Speciale Medica Università di Bologna, [6]Medicina Generale, Ospedale Santa Corona, Pietra Ligure, [7]Medicina Generale A, Ospedale Molinette, Torino, [8]Cattedra di Gastroenterologia, Università di Padova, [9]Patologia Medica, Università di Sassari, and [10]Fisiopatologia Epatica, Ospedale Cardarelli, Napoli, Italy

Aims/Methods: **The present study aimed to examine whether the galactose elimination capacity can be used to predict the survival of patients with advanced liver disease. We studied 194 patients with cirrhosis, belonging to Child class B and C, for 2 years each.**

Results: **The overall probability of survival was 79% at 6 months, 72% at 1 year and 62% at 2 years. Variables significantly associated with the duration of survival, as assessed by univariate analysis, were the Child-Pugh score, presence of ascites, size of esophageal varices, prothrombin time, albumin, bilirubin, urea, creatinine, glucose and galactose elimination capacity. By a multivariable analysis, only Pugh score (p=0.005), creatinine (p<0.001), varices (p=0.001) and galactose elimination capacity (p<0.001) were independent predictors of mortality. The galactose elimination capacity was even more sensitive when the endpoint was limited to deaths due to liver failure and hepatorenal syndrome. A new score obtained by summing the Pugh score with a score derived from galactose elimination capacity was quite simple and accurate for predicting survival.**

Conclusions: **The quantitative measurement of liver function as the galactose elimination capacity could be of use to identify patients with cirrhosis and probable short survival who might benefit most from urgent transplantation.**

Key words: **Child-Pugh score; Galactose; Liver transplantation; Survival.**

Liver cirrhosis is one of the leading nonmalignant causes of death in the developed world. The survival of patients with advanced cirrhosis is very brief (1) unless orthotopic liver transplantation (OLT) is performed. However, because of shortage of organ donors, only a few patients are successfully transplanted, while many die while on the waiting list. Exact prediction of survival over a short period of time for an individual patient with cirrhosis is not easy. Many studies have investigated factors that predict survival in patients with cirrhosis (2–10); however, most were retrospective or included patients with early cirrhosis (5,9,10). Child classification (11) is still the most widely used tool to estimate the severity of disease in patients with cirrhosis and to predict survival (7–9). In Child class C patients the probability of survival at 1 year is 50–60%, but 20–30% of them will survive for more than 2 years. Some of these patients die before receiving a new liver, while others

* AISF=Associazione Italiana per lo Studio del Fegato. Other participants in the study group: Luca Carpinelli (Milano); Flavia Politi (Palermo); Giovanni Giuseppe di Costanzo, Lucia Boselli (Napoli); Franco Trevisani, Andrea Fabbri, Claudia Sama (Bologna); Antonio Giudici, Irene Ponassi (Pietra Ligure); Angelo di Napoli, Paolo Avagnina, Anna Grazia Niro (Torino); Angelo Deplano (Sassari); Luca Fabris, Rosa Maria Iemmolo, Gerald Eko, Mario Salvagnini (Padova).

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Correspondence: Francesco Salerno, MD, Istituto di Medicina Interna, Centro per lo Studio delle Malattie di Fegato, Università degli Studi, Via Pace, 9, 20122 Milan, Italy. Tel. (39)-2-55035327, Fax. (39)-2-59902598.

may remain on a waiting list for a long time in a stable condition and in a stage of low priority for OLT. Therefore, Child's score is not accurate enough in predicting survival for this particular group of patients and factors able to predict survival, independently of the components of the Child classification, would be very useful for optimal selection of transplant recipients. In recent years, there has been growing interest in tests which measure liver function quantitatively, because they should improve the accuracy of estimating the severity of liver failure (12,13). These tests are strong predictors of survival in fulminant liver failure and in alcoholic hepatitis superimposed on cirrhosis (14,15). Thus, it is conceivable that they should have strong short-term prognostic value. Their value in uncomplicated cirrhosis, however, is less sure (16–19). The aim of the present study was to evaluate the ability of the galactose elimination capacity (GEC) to predict short-term survival of patients with cirrhosis who may be referred for OLT. Therefore, we undertook a prospective trial in patients of Child class B and C, who were followed for 2 years.

Materials and Methods

The study began in 1989, when 14 Italian centers involved in the care of patients with liver disease started to recruit up to 20 consecutive patients with cirrhosis each to study their survival. The study was approved by the Ethical Committees of the participating centers. Inclusion criteria were: diagnosis of liver cirrhosis; class B or C according to Child-Pugh score; age <65 years. Exclusion criteria were: bacterial infection; liver cancer (documented by ultrasonography or plasma alpha-fetoprotein levels >500 ng/ml); associated conditions affecting survival (e.g., heart failure, organic renal failure, pulmonary disease, etc.); gastrointestinal bleeding during the previous 30 days; surgical portosystemic shunt; and thrombosis of the portal vein. From January 1989 to February 1990, 194 patients fulfilled these criteria. The sample size was based on the expected number of events (death), taking into consideration that each variable included in the multivariable analysis must be associated to 8–10 events and that the 2-year mortality rate of a mixed group of Child class B and C patients with cirrhosis may vary from 40% to 60%.

One hundred and twenty-two patients were male and 72 female; 104 belonged to Child class B and 90 to class C. The median age was 50 years (range 18–65). The diagnosis of cirrhosis was based on clinical and laboratory data combined with ultrasonographic findings (US). Previous histological diagnoses were available for 34% of the cases. The etiology was defined on the basis of the history obtained from the patients and their relatives and the results of serological tests for viruses. Antibodies to HCV were looked for in 106 cases. The cause of liver disease was alcoholic for 63, viral for 63 (44 HCV+), mixed for 27 (viral+alcohol), PBC for 7, cryptogenic for 33 and Wilson's disease for 1 case. Patients were investigated in stable hemodynamic and clinical conditions, e.g. at least 30 days after infectious episodes or bleeding. For all the patients, the presence and the degree of ascites and encephalopathy (PSE) were assessed clinically. Ascites was also confirmed by US. PSE was graded according to the West Haven criteria (20), and we differentiated patients without overt encephalopathy, patients with encephalopathy grade I–II and patients with encephalopathy grade III–IV. Laboratory tests included blood cell counts, blood sugar, urea, creatinine, AST, ALT, alkaline phosphatase (ALP), bilirubin, total proteins, albumin, alpha-fetoprotein, and prothrombin time (PT). Abdominal US was performed for all the cases and endoscopy of the upper digestive tract for 167 cases. GEC was measured according to Tygstrup et al. (21), with the following modifications: patients were infused intravenously with a 30% solution of galactose (0.5 g per kg b.w.) over a period of 3–5 min. Capillary blood samples (100 µl) were drawn at intervals of 10 min from 20 to 70 min after galactose injection, and rapidly deproteinized with 0.5 ml of 0.33 M perchloric acid. After centrifugation, the galactose concentrations were measured enzymatically (22) and GEC was calculated with the following formula:

$$\frac{450 \cdot \text{body weight}}{(-a/b)+7}$$

in which a/b is the linear slope of blood galactose concentration-time curve, 450 is the amount of galactose administered, corrected for a 10% urinary loss, and 7 is a correcting factor for the non-uniform distribution of galactose within the body (21). Results were expressed as mg/min per kg of body weight.

Patients were followed closely and seen at least every 6 months up to 2 years after the inclusion date. Alcoholic patients were urged to abstain from alcohol.

Data analysis

Survival analysis, irrespective of the cause of death, was carried out with the Kaplan-Meier method.

Sixteen variables obtained at entry into the study were considered for predicting survival. The Mantel-Cox test was used to compare survival curves. To favor proportional survival patterns, the cut-off levels

chosen for quantitative variables were the median values found in the group of patients who died during the follow-up. For qualitative variables, patients were grouped according to the presence or absence of each variable or to scores of severity for ascites, PSE and to size of esophageal varices.

To identify the independent contribution of each abnormality, all the variables with significant prognostic power ($p<0.05$) were introduced in a multiple regression, using a step-wise forward procedure according to the hazard model proposed by Cox (23). The Cox analysis was performed initially without including the Child-Pugh score, and, in a second step, the Child-Pugh score was substituted for its components. The statistical analysis was performed with a BMDP statistical package (24).

Receiver-operator characteristic (ROC) curves were built to compare the accuracies to predict mortality of some variables. For GEC, ROC curves were built taking into consideration as an end-point both the overall mortality rate and the mortality rate due only to liver failure or hepatorenal syndrome.

Results

Table 1 shows the clinical and biochemical features of the patients. During the 2-year period of study of each, 21 patients were lost to follow-up (drop-out) and 34 patients were given transplants. These patients were censored at the time of drop-out or on the day of OLT. Characteristics of these patients are reported in table 2 and compared with those of patients who survived. Patients with OLT were younger and had higher values of bilirubin and Pugh scores and lower PT than patients who survived without OLT. Sixty-

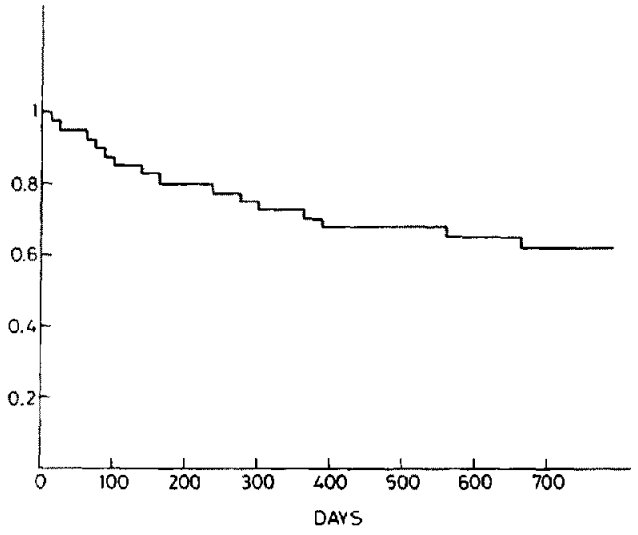

Fig. 1. Actuarial curve for survival of 194 patients with cirrhosis over 2 years.

TABLE 1
Clinical and biochemical characteristics of 194 patients with cirrhosis included in the study

Age (years)	49.7 (18–65)
Sex (male/female)	123/71
Child (B/C)	104/90
Ascites (%)	70
PSE (%)	27
Bilirubin (mg/dl)	3.7 (0.4–32)
Albumin (g/dl)	3.3 (1.5–5.2)
PT (%)	50 (20–90)
Glucose (mg/dl)	95 (60–200)
Urea (mg/ml)	36 (12–103)
Creatinine (mg/ml)	0.9 (0.5–2.1)
GEC (mg min^{-1} kg^{-1})	3.77 (1.68–5.95)

Data are reported as means (range).

TABLE 2
Characteristics of patients who had a transplant (A) or who dropped out (B), compared to patients who survived at the end of follow up (C)

	Group A (n=34)	Group B (n=21)	Group C (n=77)
Age (years)	42±8*°	48±10	51±7
Child-Pugh (score)	10±2*°	8.4±1.4	9±2
Ascites (%)	76	71	70
PSE (%)	29	10	30
Bilirubin (mg/dl)	5±4.5*°	2.4±2.3	3±4.5
Albumin (g/dl)	3.3±0.5	3.4±0.7	3.4±0.6
PT (%)	46±15*	57±16	53±13
Glucose (mg/dl)	94±24	97±31	92±21
Urea (mg/dl)	38±19	29±11	33±14
Creatinine (mg/dl)	0.9±0.3	0.8±0.2	0.8±0.2
GEC (mg min^{-1} kg^{-1})	3.9±1	4.3±1.3	4±1

Values are reported as means±SD.
* =significantly different from group B by one-way ANOVA.
° =significantly different from group C by one-way ANOVA.

TABLE 3
Variables considered at the beginning of the study, cut-off levels, and significances of their correlations with survival obtained with univariate analysis

Variable	Cut-off	F	p
Age (years)	53	2.5	0.11
Sex	male/female	3	0.09
Child-Pugh (score)	9.5	8.7	0.003
Etiology	alcohol/other	0.47	0.49
Ascites	0/1/2 ^	11.5	0.003
PSE	0/1/2 ^	2.36	0.30
Varices	0/1/2/3 *	17	0.0007
Gallstones	yes/no	0.03	0.86
Bilirubin (mg/dl)	2.8	5.95	0.02
Albumin (g/dl)	3.2	5.62	0.02
PT (%)	47	4.63	0.03
Glucose (mg/dl)	91	4.25	0.04
Urea (mg/ml)	39	8.8	0.003
Creatinine (mg/ml)	0.9	9	0.003
α-fetoprotein (mg/ml)	7	1.9	0.15
GEC (mg min^{-1} kg^{-1})	3.255	12.86	0.0003

^ 0=absent; 1=moderate; 2=severe.
* 0=absent; 1=small; 2=medium; 3=large.

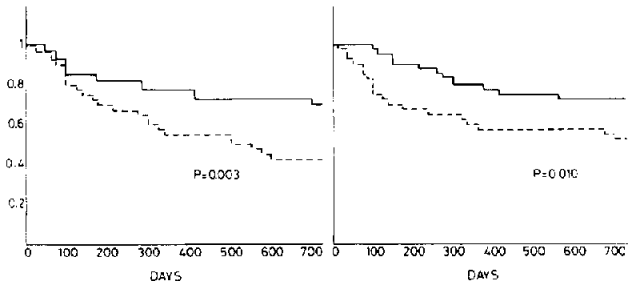

Fig. 2. Left panel: Survival curves according to GEC values higher (——) or lower (----) than 3.255 mg min^{-1} kg^{-1}. Right panel: Survival curves according to Child class B (——) or C (----).

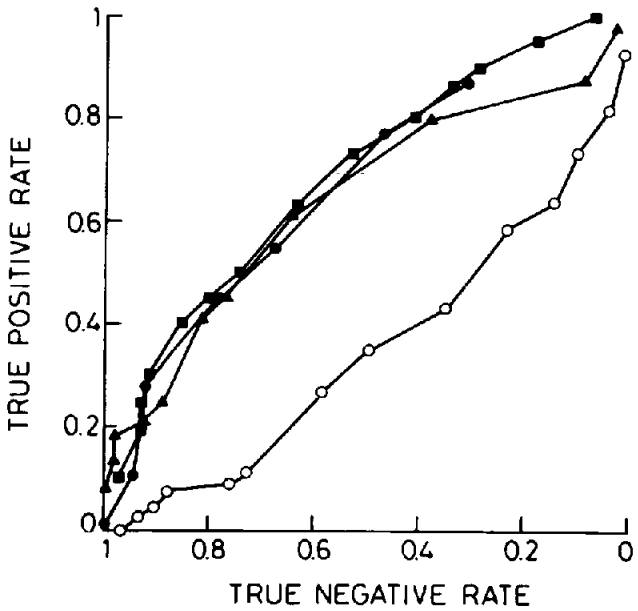

Fig. 3. ROC curves for creatinine (▲), GEC (■), Child-Pugh score (●) and PT (○) for prediction of mortality in patients with cirrhosis.

two patients died during the follow up, 22 during the first 3 months. Causes of death were liver failure (n=20), gastrointestinal bleeding (n=20), hepatorenal syndrome (n=8), hepatocellular carcinoma (n=3), bacterial peritonitis (n=2), non-liver-related (n=4) and unknown (n=5). The mean survival time was 520 days and Fig. 1 shows the actuarial curve for survival. The overall probability of survival was 79% at 6 months, 72% at 1 year and 62% at 2 years.

Univariate analysis showed that Child-Pugh score, ascites, albumin, bilirubin, PT, glucose, creatinine, urea, GEC and the size of varices were all significantly correlated with survival (Table 3). The actuarial curves of the different populations identified by GEC and by Child-Pugh scores are reported in Fig. 2.

Multivariable examination demonstrated that

TABLE 4
Variables with independent prognostic value, as indicated by two Cox's models

Variable	Coefficient	Standard error	Improvement χ^2	p
1.				
PT	−0.0263	0.0118	4.97	0.026
Creatinine	0.2069	0.0447	14.30	0.000
GEC	−0.0040	0.0017	14.40	0.000
Varices	0.5092	0.1564	10.21	0.001
2.				
Child-Pugh	0.2282	0.0807	7.94	0.005
Creatinine	0.1803	0.0428	14.30	0.000
GEC	−0.0041	0.0017	14.40	0.000
Varices	0.5058	0.1541	10.21	0.001

Note: The first Cox's model included all variables significant in the univariate analysis except the Child-Pugh score; the second Cox's model included the Child-Pugh score.

TABLE 5
Distribution of patients with cirrhosis in five categories of progressive severity as indicated by GEC values

Cut-off values (mg min^{-1}kg^{-1})	Number and % of patients		Median (mg min^{-1} kg^{-1})	Mean (mg min^{-1} kg^{-1})	Standard error
>4.5	37	20	4.94	5.41	0.77
4.0–4.5	25	13	4.21	4.24	0.17
3.5–4.0	39	21	3.69	3.71	0.16
3.0–3.5	38	20	3.34	3.32	0.14
<3.0	47	25	2.72	2.59	0.36

GEC, creatinine and varices were independent predictors of survival, while PT was replaced by the Child-Pugh score when this was introduced into the analysis (Table 4). ROC curves showed that creatinine, GEC and Child-Pugh score have similar accuracy for prediction of survival, while PT was a less accurate prognostic factor (Fig. 3). The maximum discrimination point (sensitivity+specificity/2) for GEC was 64.5%. When only deaths because of liver failure or hepatorenal syndrome were considered in the end point, GEC predicted survival with a discrimination point of 69%.

To maximally improve the accuracy of predicting survival, we calculated three different scores: two scores derived from the correlation coefficients of the two Cox analyses, and a simpler one adding the Child-Pugh score to a score derived from the GEC values (Table 5). This last score was quite accurate, similar to the score derived from the Cox model including the Child-Pugh (0.228×Pugh+0.18×creatinine+0.506×varices −0.004×GEC) and better than the score derived from the Cox model including PT (Fig. 4). Fig. 5 shows the survival curves for three groups of patients identified according to the new score.

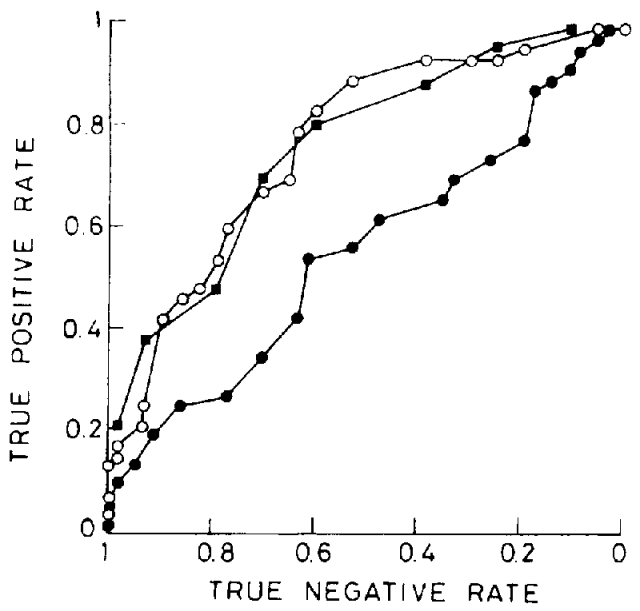

Fig. 4. ROC curves for prognostic indices obtained by variables with independent prognostic value in multivariable analyses. Open circles indicate the score including creatinine, varices, GEC and Child-Pugh; closed circles indicate the score including creatinine, varices, GEC and PT; closed squares indicate Child-Pugh+GEC score.

With 14 chosen as the cut-off, the combination of Child-Pugh and GEC scores had a sensitivity of 38%, a specificity of 92.5% and a positive predictive value of 81.5%, which means that patients with a score >14 have a chance of early death as high as 81.5% but a chance to survive more than 2 years as low as 7.5%. The Child-Pugh score alone, with similar specificity, had a sensitivity of 29% and a positive predictive value of 75%.

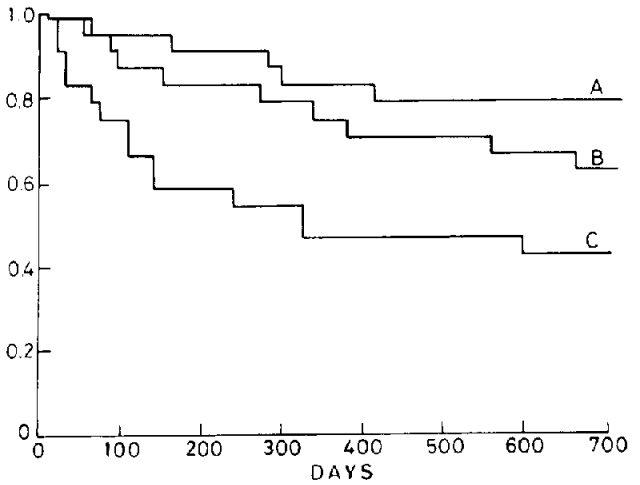

Fig. 5. Survival curves for patients with cirrhosis classified as low (A), moderate (B) and high risk (C) according to the Child-Pugh+GEC scores. p=A vs B<0.09; A vs C <0.0001; B vs C <0.0005.

Discussion

Interest in the search for accurate prognostic tests for patients with chronic liver disease has become more intense since liver transplantation has become a reality. These tests must be safe for the patient and easy to perform. GEC is a simple tool for measurement of residual hepatic function in patients with liver disease. Many investigators have used GEC to predict survival of hepatopathic patients, especially of those with severe liver disease (13,25–27) or primary biliary cirrhosis (28). GEC has also been proposed for patients with cryptogenic or posthepatic cirrhosis being evaluated for OLT (29). However, like other elimination tests or drug metabolism assays, the true utility of GEC in improving prediction of survival in patients with alcoholic or viral cirrhosis has not been demonstrated or validated in different cohorts of patients (26,30). The cirrhosis studies included patients with disease with a wide range of severity with several patients belonging to the Child class A who did not need urgent transplantation.

In the present investigation, we selected patients of Child class B and C without evident contraindications for OLT, and we showed that the GEC value has high independent prognostic power. This result agrees with that of Merkel et al. (27), who compared different quantitative liver function tests and found only GEC to be an independent predictor of survival, providing additional prognostic information to the Child classification. In our study, GEC correlated with survival more significantly than any other variable, including the Child-Pugh score, while in Merkel's study, GEC was far less significantly correlated with survival than the Child-Pugh score. It is worth noticing that the predictive value of GEC in our cases became considerably stronger when we considered only the deaths caused by liver failure and hepatorenal syndrome. This suggests that GEC, as a measure of quantitative liver function, is also particularly able to predict the progressive deterioration of the liver function.

The transplants might have affected the correct interpretation of the natural history of cirrhosis. In fact, patients who underwent OLT were younger and had some laboratory differences compared with patients who survived. However, taking into account that our criteria of inclusion/exclusion were similar to the criteria of selection for OLT, it would have been unethical to continue to study these patients without treating some of them by OLT. Moreover, it must be

kept in mind that our study excluded patients with active or recent variceal bleeding. This was done to avoid inaccuracy in determination of the Child-Pugh score and GEC values due to clinical and hemodynamic instability. However, the risk of death for patients with active bleeding depends on factors largely independent of liver function. Our exclusion makes our results invalid for this population of patients with cirrhosis.

The other variables that independently predicted survival were creatinine, the size of varices and Child-Pugh score, confirming the results of some previous investigations (2–9). Creatinine, as a measure of renal function, was shown to have important prognostic power in patients with ascites (6), which most of our patients had. The severity of esophageal varices is also a well known predictor for both bleeding and survival (31). The Child-Pugh score combines functional parameters with signs of portal hypertension, and has repeatedly been validated as a good prognostic indicator (7). Therefore, the combination of some of these four parameters might well be superior to the Child-Pugh score alone in detecting the time for transplantation. Christensen et al. (7) have reported the superiority of combining the Child-Pugh score with other independent prognostic indicators selected by Cox analysis, and Merkel et al. (27) have proposed combining GEC with the Pugh score to improve the prediction of survival of patients with cirrhosis. In our study, also, a score obtained from the correlation coefficients of four variables with independent prognostic value (Pugh score, GEC, creatinine and varices) was quite accurate for prediction of survival, better than that of any single variable. A much simpler new index obtained by combining the Pugh score with a score derived from the GEC values was found to be more sensitive and specific than the Pugh score or the GEC alone. Based on our results, we would recommend urgent transplantation for all patients with scores >14. This could prevent early death in up to 40% of such patients with cirrhosis.

Age and sex were not correlated with survival. This differs from other studies investigating the natural history of cirrhosis (5,9). Ferro et al. (32) also did not find any correlation of age and sex with survival in patients of Child class B and C. It is conceivable that survival is influenced by age and sex only in patients of Child class A.

Other tests measuring the functional reserve of the liver (e.g., aminopyrine breath test and lidocaine disposition) or the functional portal flow (indocyanine green clearance), unlike our results with GEC, were less discriminatory than albumin or ascites, or were not independent in predicting survival (15,33–35). Tests based on drug metabolism may be imprecise because of interference by substances frequently taken by patients with cirrhosis, such as spironolactone and cimetidine, which induce or inhibit the hepatic mixed-function oxidase system. The MEGX test has recently been found to be a good predictor of short-term survival in a group of patients with cirrhosis similar to ours (36), but its use is limited by analytical artifacts in patients with jaundice.

Our study also confirms that patients with advanced cirrhosis are at high risk to die within a very short period of time. Twenty-two patients died during the first 3 months of the study, and another 15 within 3–6 months. In addition, 16 patients were given transplants during the first 6 months. These two groups of patients make up 27% of our cohort. Considering that 37 patients who died had no evident contraindications to OLT (see the criteria of inclusion), it is evident that 70% of patients needing urgent OLT did not get transplants, probably because the number of candidates for OLT exceeds the number of available liver donors. Uncertainty in the prediction of very short survival might be an additional cause.

In conclusion, the present study shows that the determination of GEC is useful for predicting the survival of patients with severe cirrhosis over a short period of time, and suggests that it should be used, alone or combined with Child-Pugh score, in selecting patients who need urgent OLT.

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