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ORIGINAL ARTICLE

Aminopyrine breath test compared to the MELD and Child-Pugh scores for predicting mortality among cirrhotic patients awaiting liver transplantation

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Abstract Better tools for predicting the risk of death while awaiting transplantation are urgently needed because organ shortage is increasing the numbers on transplantation waiting lists. The aminopyrine breath test (ABT), model for end-stage liver disease (MELD), and Child-Pugh (C-P) score were compared as predictors of this risk in 137 cirrhotic candidates for liver transplantation. Eighty-three were transplanted within 3 months of registration, 35 others survived, 13 died before transplantation, and 6 were removed from the list. By univariate analysis, the continuous variables significantly associated with death while awaiting transplantation were: history of infected ascites, C-P score, ABT, and international normalized ratio or prothrombin time. Receiver operating characteristic curves for quantitative variables showed that the area under the curve was greatest for ABT (0.858 ± 0.067). By Youden curve analysis, the best cut-off points for identifying cirrhotic patients at high risk of death while on the waiting list were: >10, >16, and $<0.7\%$ for the C-P score, MELD score, and ABT, respectively. These results show that ABT is as good as the MELD and C-P scores, or better, as a predictor of death among cirrhotic patients awaiting liver transplantation.

Keywords Liver cirrhosis prognosis · Liver transplantation · Liver waiting list · Organ allocation

Introduction

Liver transplantation (LT) is an accepted treatment modality for end-stage liver disease, resulting in excellent survival rates. However, it has fallen victim to its own success, as both in Europe and the USA the demand for LT continues to increase dramatically, in contrast to the stagnation of number of donors and liver transplants [1, 2]. This widening gap has given rise to an accumulation of patients on the waiting list [3], longer waiting times, and—while waiting—higher mortality, ranging from 15–28% [1, 4, 5]. Although strategies such as the use of marginal livers, split liver, domino and living donor LT are currently being adopted to overcome the organ shortage, the future is not encouraging, as recent estimates suggest that there will be a 500% increase in the demand for LT by the year 2008, largely due to the burden caused by hepatitis C [6].

Current transplant allocation systems in Europe and the USA based on waiting times, medical urgency categories, and geographical distribution are not satisfactory [7, 8] because they do not solve the problem of high mortality on the waiting list and do not define grades for Child C cirrhosis, which affects 57% of the patients listed for LT [9].

More verifiable and patient-oriented medical urgency criteria such as the model of end-stage liver disease (MELD) score [10] and the medical urgency criteria (MUC) [11] were recently implemented by the United Network for Organ Sharing (UNOS) and the Eurotransplant Liver Advisory Committee (ELAC). The challenge was to create an allocation policy that makes

the most effective use of the few available organs and is based on simple, objective variables applicable to the large heterogeneous group of patients with end-stage liver disease now listed for LT.

The aims of our study were to analyze risk factors for death while on the liver transplant waiting list for patients with cirrhosis and to define accurate, objective, and practical criteria of disease severity in order to establish priorities for these patients.

Patients and methods

Patients

One hundred and thirty seven adult cirrhotic patients, registered consecutively at our center for their first cadaveric liver allograft between October 1992 and May 2000, were included in the study. All of these patients had cirrhosis and either a Child-Pugh (C-P) score of 7 or more or any complication caused by portal hypertension besides gastrointestinal bleeding. Inclusion was stopped in June 2000 because a new, more patient-oriented European Liver Allocation System was implemented at that time [11].

Continuous and categorical variables were recorded at the time of the evaluation work-up preceding registration on the waiting list. Continuous variables were: age, serum bilirubin, serum albumin, alanine (ALAT) and aspartate (ASAT) aminotransferase levels, prothrombin time (PT), international normalized ratio (INR), serum creatinine, and the aminopyrine breath test (ABT), expressed as the percentage [12] of the administered dose recovered after 2 h (25th–75th percentiles in our laboratory: 4.2–9.3%). The INR was not measured in the first 20 consecutive patients of our series. For these patients, PT was converted into INR using a best-fit formula derived from the analysis of 117 patients whose PT and INR were both measured (Fig. 1). An excellent correlation between INR and PT was observed ($r = 0.96$).

Categorical variables were: sex, etiology of cirrhosis (alcoholic, viral, or other origin), degree of ascites and encephalopathy according to the C-P classification [13], history of infected ascites and variceal bleeding, and presence of hepatocarcinoma.

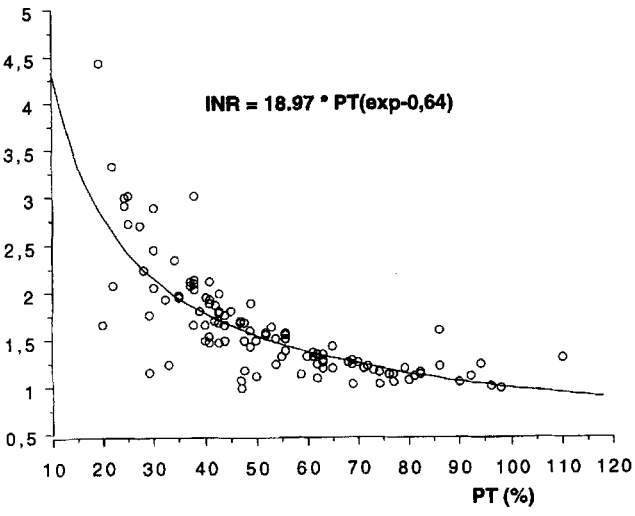

Fig. 1 Relationship between international normalized ratio (*INR*) and prothrombin time (*PT*) in 117 patients

The C-P score was computed from the degree of ascites and encephalopathy and the serum concentrations of bilirubin, albumin, and PT. The MELD score was computed from the $\log_e$-transformed values of bilirubin, INR, and serum creatinine, and 6.4 points were then added to each patient's score to make the results comparable with those of the original published studies [10, 14]. Patient survival within 3 months after surgery was analyzed according to pretransplantation ABT, MELD, and C-P scores.

Statistical methods

All continuous variables that were skewed to the right were $\log_e$-transformed in order to normalize their distribution prior to any computation. Differences between continuous variables were assessed by Student's *t*-test and between categorical variables by Fisher's exact or χ^2-test, whether there were two, or more than two, categories for assessment.

The ability of three prognostic criteria, the C-P score, MELD score, and ABT, to detect patients at risk of death during the 3 months after inclusion on the waiting list was estimated using the area under the curve (AUC) of the receiver operating characteristics (ROC) curve [15] and its standard error (SE). AUCs were calculated by the trapezoidal rule.

Significant differences were tested between the AUCs of several ROC curves, taking into account the correlation existing between these AUCs, calculated from the same set of patients [16]. Youden curves were computed from the true-positive (sensitivity) and false-positive (1-specificity) rates calculated for these two criteria to determine the optimal cut-off thresholds for the prediction of poor prognosis, the peak of the curve indicating the best cut-off point [17].

Six patients were removed from the waiting list during the first 3 months for various reasons: evolutive hepatocellular carcinoma in three, psychiatric disease in one, recurrence of alcoholism in one, and extension of portal thrombosis in one patient. After exclusion of these patients, 131 were therefore available for the ROC studies: 13 died during the first 3 months (8 of sepsis, 2 of variceal hemorrhage, 1 of liver failure, and 2 of unknown cause), and 118 were still alive at the end of that period (83 transplanted and 35 not yet transplanted). For the series of 131 patients, mean (±SEM) waiting time until death on the waiting list or transplantation or May 2000 was 111.5 ± 30.9 and 84 ± 7.4 days respectively ($P = 0.22$).

Survival studies were conducted according to the Kaplan-Meier method [18] on the original total of 137 patients. Death on the waiting list was considered as the event (uncensored data), and all patients who were alive at the time of their last evaluation were censored (that time was defined as the end-point of the study, transplantation, or the last evaluation for patients lost to follow-up). Differences between survival curves were tested using the Breslow-Gehan-Wilcoxon test, which takes into account the number of patients at risk at each point of the survival curve [19]. This test seems more appropriate than the commonly used Mantel-Cox test (in which all points of the survival curve are equally weighted) in case the numbers of patients at risk quickly decline with time (see Results section). Lastly, a validation study was undertaken, using the split sample technique [20], for which the test and control samples were randomly chosen.

Results

The demographic characteristics at inclusion on the waiting list are reported for two groups of patients: the first comprised 118 patients who were still alive at the end of the first 3 months, and the second consisted of 13 patients who died during that time (Table 1). Significant

Table 1 Demographic characteristics of cirrhotic patients at inclusion on the liver transplantation waiting list (*ABT* aminopyrine breath test, *ALAT* alanine aminotransferase, *ASAT* aspartate aminotransferase, *C-P* Child-Pugh, *INR*international normalized ratio, *MELD* model for end-stage liver disease, *PT* prothrombin time)

	Alive ($n=118$)	Dead ($n=13$)	*P*-value
Categorical variables			
Gender: female/male	22/96	1/12	0.46
Alcoholic etiology: yes/no	46/72	5/8	0.78
Ascites: none/moderate/severe	42/50/26	1/7/5	0.11
Ascites: absent/present	42/76	1/12	0.059
Previous infected ascites: yes/no	20/98	6/7	0.023
Encephalopathy: none/moderate/severe	66/46/6	8/4/1	0.81
Previous variceal bleeding: yes/no	30/88	2/11	0.73
Thrombosis of portal vein: yes/no	16/102	4/9	0.12
Hepatocarcinoma: yes/no	23/95	2/11	0.99
Continuous variables: mean (SEM)			
Age (years)	51.3 (0.8)	53.7 (2.9)	0.38
C-P score	9.1 (0.2)	10.6 (0.4)	0.011
MELD score	15.6 (0.5)	19.1 (1.3)	0.027
ABT (%)[a]	1.3 (0.11)	0.3 (0.05)	0.0001
ALAT (IU)[a]	77 (6)	93 (19)	0.32
ASAT (IU)[a]	54 (5)	51 (10)	0.78
Bilirubin (mg/dl)[a]	3.9 (0.3)	5.5 (1.2)	0.13
Albumin (g/dl)	3.5 (0.7)	3.2 (1.9)	0.15
Serum Na (mEq/l)	135 (0.5)	132 (1.4)	0.075
PT (%)	52 (1.7)	41 (4.7)	0.029
INR[a]	1.6 (0.03)	1.9 (0.12)	0.014
Serum creatinine (mg/dl)[a]	1.1 (0.04)	1.1 (0.15)	0.78

[a]Significance tests were conducted on log-transformed variables when their distribution was not Gaussian

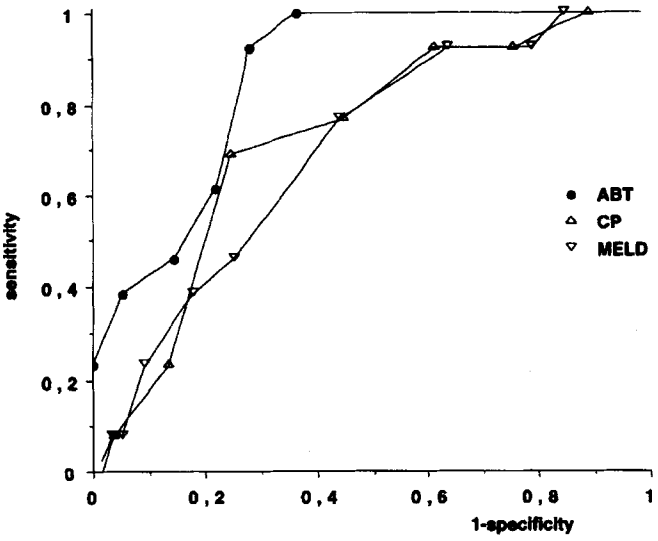

Fig. 2 Receiver operating characteristic (*ROC*) curves of the prediction of death on the liver transplant waiting list within 3 months of registration for aminopyrine breath test (*ABT*), Child-Pugh (*C-P*), and model for end-stage liver disease (*MELD*) scores

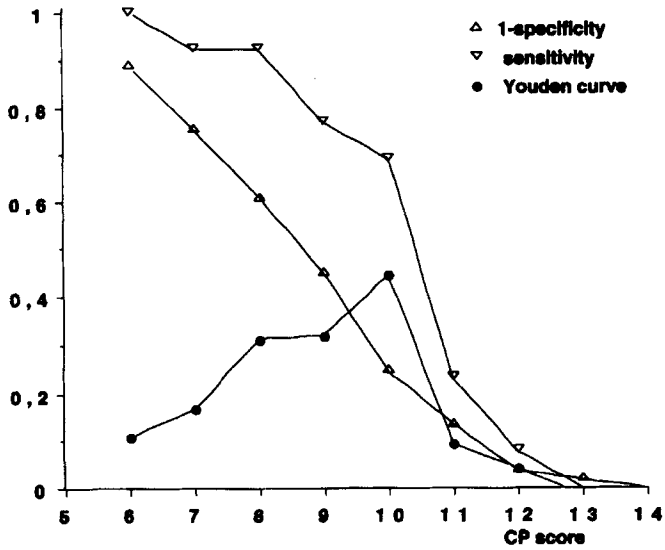

Fig. 3 Sensitivity, 1-specificity, and Youden curves for the Child-Pugh (*C-P*) score

differences between the two groups were observed for the C-P and MELD scores, the ABT, INR or PT, and a history of infected ascites. Borderline differences were noted for the presence of ascites and serum Na concentration.

ROC curves were computed for the quantitative prognostic criteria. The AUC was larger for ABT than for the C-P score (0.858 ± 0.067, mean ± SEM vs 0.726 ± 0.084, $P=0.07$) or for the MELD score (0.704 ± 0.084, $P=0.021$). The two scores were obviously not different (Fig. 2). The AUC for INR was 0.702 ± 0.084, i.e., equivalent to the AUC for MELD.

Youden curves were computed for each prognostic criterion. The best cut-off points were >10 for the C-P score (Fig. 3), >16 for the MELD score (Fig. 4), and $<0.7\%$ for the ABT (Fig. 5). These points were used in the survival studies to determine two categories of patients, with a good and poor prognosis, respectively.

Significant differences between these two categories regarding survival were observed for the C-P score (Fig. 6, $P=0.017$), the MELD score (Fig. 7, $P=0.005$),

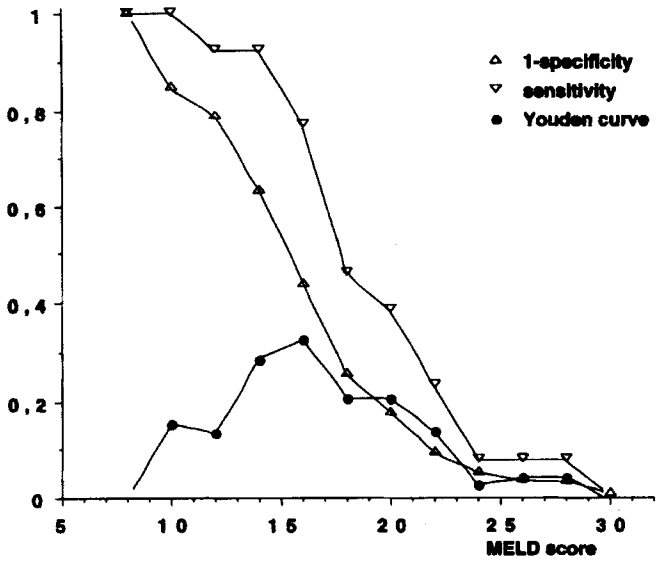

Fig. 4 Sensitivity, 1-specificity, and Youden curves for the model for end-stage liver disease (*MELD*) score

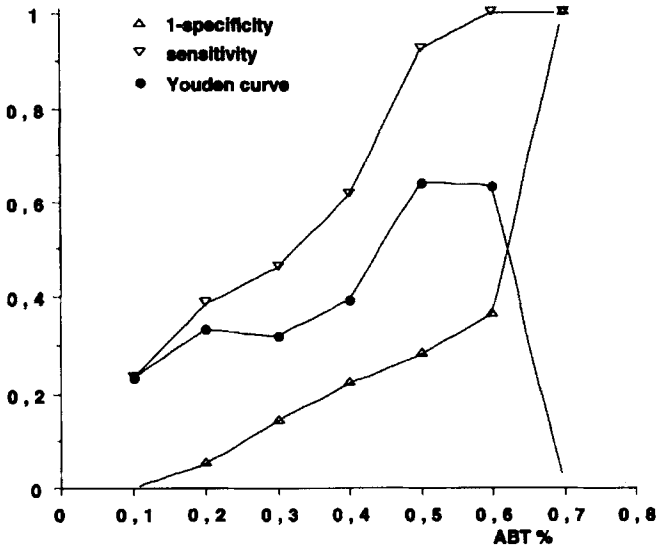

Fig. 5 Sensitivity, 1-specificity, and Youden curves for aminopyrine breath test (*ABT*)

and the ABT (Fig. 8, $P < 0.0001$). For each criterion, the decline in survival rates in the category with a poor prognosis was mainly observed during the first 3 months.

Using the same threshold, mortality within 3 months after transplantation was 9.3% (4/43) for patients with a MELD score > 16 (one patient was lost to follow-up), 8.9% (7/79) for those with a MELD score < 17, 16.6% (4/24) for those with a C-P score > 10 (one patient was lost for follow-up), 6.8% (6/88) for those with a C-P score < 11, 8.8% (3/34) for those with an ABT < 0.7 (one patient was lost for follow-up), and 8.4% (6/71) for those with an ABT > 0.6 ($P = 0.1$).

Internal validation of the results for ABT, using the split sample technique, showed significant differences between the survival of the categories with a good and a poor prognosis, both in the control sample of 67 patients ($P = 0.008$) and in the test sample of 64 patients ($P = 0.005$, Fig. 9).

In the category with a poor prognosis (ABT < 0.7%), survival in the subgroup of 34 patients with an ABT of 0.4–0.6% seemed greater than in the subgroup of 23 patients with an ABT < 0.4%, but the difference was not significant because of the small number of patients in these two subgroups (data not shown).

Discussion

The results of this study demonstrate that the mortality of cirrhotic patients on the liver transplant waiting list is still a major risk, particularly when they have advanced liver disease, and that this risk correlated with five parameters determined at the time of listing: history of infected ascites, ABT, MELD, and C-P scores, and PT or INR.

Among the prognostic scoring systems analyzed, we provide evidence that ABT is a strong predictor of death while awaiting transplantation and constitutes a new non-invasive quantitative tool for the assessment of priority on the liver transplant waiting list. Its accuracy is equal to, or even better than, that of the C-P and MELD scores. A history of infected ascites was the only categorical variable associated with the risk of death while waiting for LT.

Spontaneous bacterial peritonitis is a well-known complication of cirrhosis, particularly when it is decompensated, and carries a high risk of short-term mortality, which ranges from 60–70% [21]. There is, however, no consensus of opinion regarding the criterion for the diagnosis of infected ascites, an entity which encompasses various conditions such as bacteriascites, neutrophilic ascites, and culture-positive ascites.

For the three prognostic criteria (ABT, MELD, and C-P scores), we determined cut-off points of < 0.7, > 16, and > 10, respectively. These were the criteria that best identified the category of cirrhotic patients, listed for LT, at high risk of dying within 3 months. By comparing the AUC of the ROC curves, ABT was demonstrated to be as good as, or even better than, the C-P and MELD scores (0.86 vs 0.72 and 0.70). The 3-month time frame was chosen for three reasons: it is concordant with the results of MELD score studies [10], our mean waiting time between listing and death is 111 days, and our survival curves (Figs. 6, 7, 8) clearly show that most deaths while on the waiting list occur within the first 3 months.

The C-P score is a well-accepted parameter for assessing the prognosis of cirrhotic patients [22], especially before transplantation [23, 24], and constitutes the

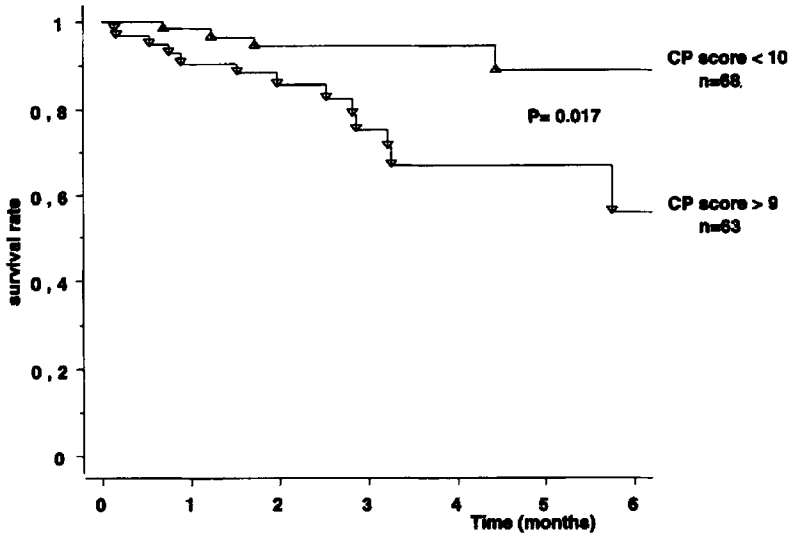

Fig. 6 Kaplan-Meier survival curves according to the best cut-off point (< 10 and > 9) for the Child-Pugh (*C-P*) score

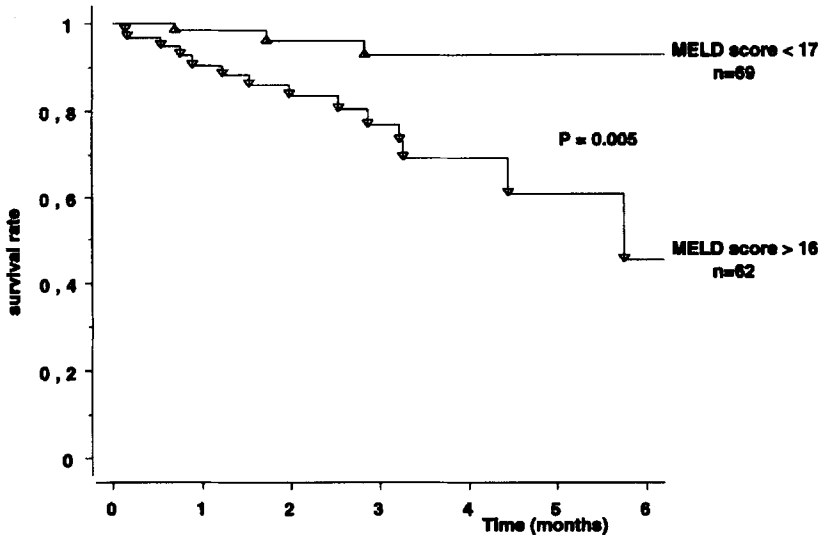

Fig. 7 Kaplan-Meier survival curves according to the best cut-off point (< 17 and > 16) for the model for end-stage liver disease (*MELD*) score

essence of the UNOS score [25] and MUC [11] for the allocation of organs to liver transplant candidates. However, it uses discrete cut-off points and two parameters (degree of ascites and encephalopathy) which lack objectivity and precision, thus explaining its poor reproducibility among different hepatologists [26]. For this reason, the transplant community has sought to develop new scoring systems capable of grading advanced Child C cirrhosis.

UNOS recently proposed the MELD score to establish priorities among transplant candidates for liver graft allocation [27]. This score is based on three well-established, objective biochemical parameters (bilirubin, creatinine, and INR) and has been shown to be a reliable measure of the short-term mortality risk, using a continuous severity scale, in patients with end-stage liver disease [10]. Since February 2002, it has been used to determine organ allocation priority in the United States [28].

Prothrombin time, a component of the MELD score, is a traditional marker of synthetic function of the liver and a well-validated prognostic index [29, 30]. The INR has been proposed to replace PT to avoid disparities between the sensitivity of the thromboplastin reagents of different centers, but it has only been validated for monitoring oral anticoagulation therapy and may provide inadequate standardization in the setting of liver failure [31]. In our study, INR was significantly higher in patients who died while on the liver waiting list, but the AUC of the ROC curve was not greater than that of the other scoring systems for assessing this risk.

Another component of the MELD score is serum creatinine. This is related to renal dysfunction, a well-known frequent complication of advanced cirrhosis [32],

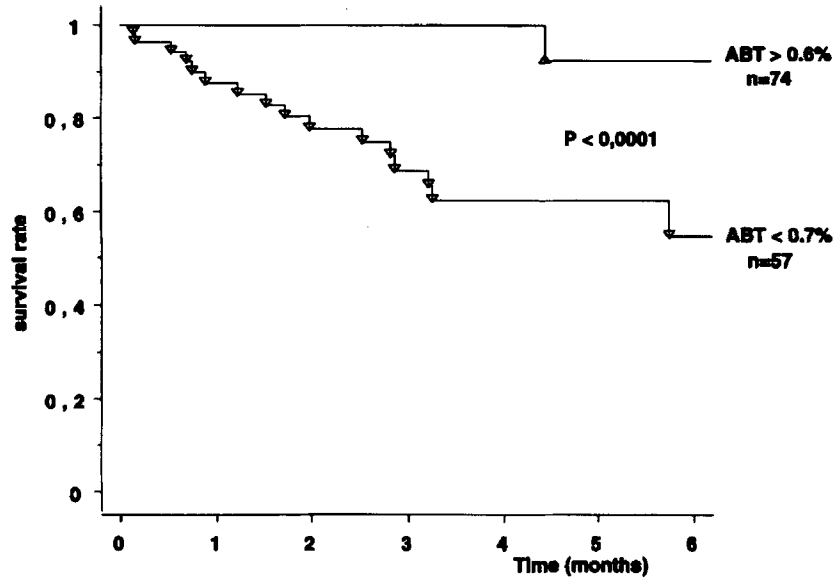

Fig. 8 Kaplan-Meier survival curves according to the best cut-off point (>0.6% and <0.7%) for aminopyrine breath test (*ABT*)

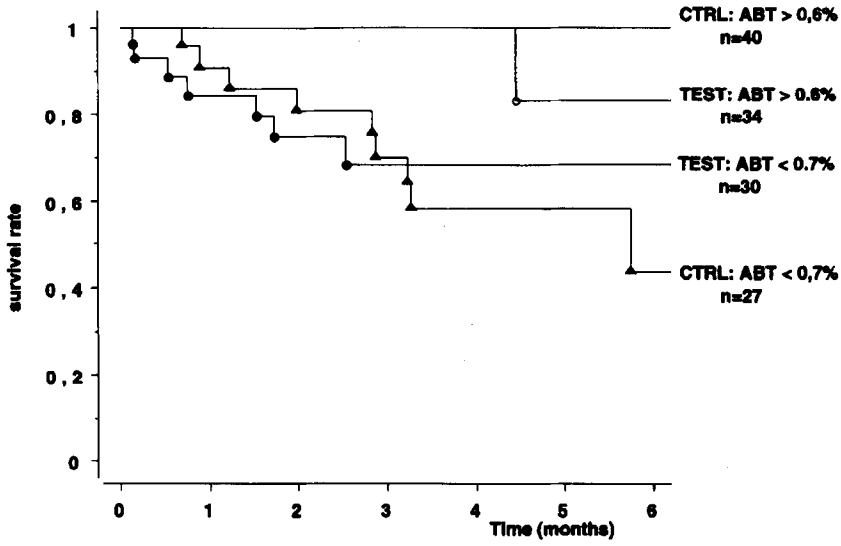

Fig. 9 Validation study of the results for aminopyrine breath test (*ABT*). Kaplan-Meier survival curves according to the best cut-off point (>0.6% and <0.7%) in the control (*CTRL*) series ($n=67$) and the test series ($n=64$)

but it is affected by the malnutrition which often accompanies advanced cirrhosis [33], age, dehydration, and use of diuretics. Serum creatinine therefore does not appear to be a specific parameter of liver dysfunction in itself. Furthermore, our study shows that the AUC is no better for the MELD score than for C-P and ABT. Lastly, the value of the MELD model for predicting mortality while on the liver transplant waiting list has been questioned [34] and, as emphasized by Everson et al. [35], the MELD score might only be an average predictor of the likelihood of survival and may lack accuracy for the individual patient. Therefore, other risk models aside from the MELD score should be developed, especially quantitative methods, in order to improve the selection of candidates for liver transplant allocation.

ABT measures metabolic liver function independently of hepatic blood flow and has been validated by several groups [36, 37, 38] including ours [39] as a non-invasive and objective prognostic indicator. ABT can be labeled with ^{14}C or ^{13}C, and in our unit, correlation between the individual values for both ^{13}C and ^{14}C tests is 0.9.

Furthermore, it is clear from the present results that ABT—with one non-invasive measurement—constitutes a promising disease severity scoring system and performs as well as, or even better, than the MELD score (three measurements) and Child-Pugh score (five measurements) which, moreover, have drawbacks. Lastly, our experience demonstrates that for the most severely ill patients (i.e., those with an ABT < 0.7%) transplantation is not accompanied by a decrease in survival.

In conclusion, our study supports the ability of ABT, a simple, quantitative, accurate, and objective parameter that concentrates all the other predictive factors, to grade cirrhotic patients on the waiting list according to the severity of their disease. ABT should be evaluated and validated externally by independent groups in the setting of a prospective study comparing the ABT and MELD scores. If our results are confirmed, this will improve the allocation policy designed to make the most effective use of organs and ensure that they are available to the most urgent medical cases on the liver transplant waiting list.

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