ORIGINAL PAPERS

Assessing the short- and long-term prognosis of patients with cirrhosis and acute variceal bleeding

L. Sempere, J. M. Palazón, J. Sánchez-Payá[1], S. Pascual, E. de Madaria, M. J. Poveda[2], F. Carnicer, P. Zapater[3] and M. Pérez-Mateo

Liver Unit. [1]Epidemiology Service. Hospital General Universitario. Alicante, Spain. [2]Gastroenterology Unit. Hospital General Universitario. Alcoy, Alicante, Spain. [3]Clinical Pharmacology Unit. Hospital General Universitario. Alicante, Spain

ABSTRACT

Objective: to evaluate the efficacy of various indicators in predicting short- and long-term survival in patients with cirrhosis and acute variceal bleeding.

Material and methods: prognostic indicators were calculated for a cohort of 201 cirrhotic patients with acute variceal bleeding hospitalized in our center, a third-level teaching hospital. The studied variables were: age, sex, etiology of cirrhosis, endoscopic findings, previous variceal bleeding episodes, human immunodeficiency virus (HIV) infection, hepatocellular carcinoma (HCC), infection during episode, and Child-Turcotte-Pugh (CTP) and Model for End-stage Liver Disease (MELD) scores within 24 hours of bleeding onset. Patients were followed up for at least 6 months until death, liver transplantation, or end of observation.

Results: median follow-up was 66.85 weeks (range 0-432.4). The 6-week, 3-month, 12-month and 36-month mortality rates were 22.9, 24.9, 34.3, and 39.8%, respectively. Age ≥ 65 years, presence of HCC, CTP score ≥ 10, and MELD score ≥ 18 were the variables associated with mortality in the multivariate analysis. The accuracy of MELD scores as predictors of 6-week, 3-month, 12-month, and 36-month mortality was better than that of CTP scores (c-statistics: 6 week MELD 0.804, CTP 0.762; 3-month MELD 0.794, CTP 0.760; 12-month MELD 0.766, CTP 0.741; 36 month MELD 0.737, CTP 0.717).

Conclusion: MELD and CTP scores together with age and a diagnosis of hepatocellular carcinoma are useful indicators to assess the short- and long-term prognosis of patients with acute variceal bleeding.

Key words: Prognosis. Variceal bleeding. Portal hypertension. Child-Turcotte-Pugh score. MELD score.

INTRODUCTION

Acute variceal bleeding is a frequent complication of cirrhosis with high mortality (1). Advances in pharmacological and endoscopic therapies have led to a decrease in mortality over the past two decades (2,3). Mortality at 6 weeks seems to be more related to stage of liver disease than to bleeding severity (4). Nowadays the adequate management of portal hypertension with the prophylactic treatment of variceal rebleeding has increased survival for patients with a history of variceal bleeding permitting the progression of liver disease (5).

Many prognosis models for liver disease have been developed for patients with cirrhosis. At present the most highly used ones are the Child-Turcotte-Pugh (CTP) and Model for End-stage Liver Disease (MELD) scores (6-8). Recent papers have validated the ability of both models to predict short-term survival in patients with acute variceal bleeding (9-11). It seems interesting to assess the ability of prognosis models to predict survival beyond 12 months since variceal bleeding. On the other hand important changes in the natural history of cirrhosis – increased incidence of hepatocellular carcinoma (HCC) and co-infected hepatitis with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) – have occurred in the last few years (12,13).

Changes in the natural history of cirrhosis made it necessary to review all factors implicated in the survival of patients with acute variceal bleeding. Thus, the main ob-

jective of this study was to assess the prognostic indicators of short- and long-term survival in patients with cirrhosis and acute variceal bleeding in a recent series of patients.

PATIENTS AND METHODS

Study population

We present a retrospective study of patients with cirrhosis and acute variceal bleeding admitted to Hospital General Universitario, Alicante, between January 1996 and December 2003. Cases were identified by prospective database searching and variables were extracted from clinical records. We included only the earliest episode for each patient (one episode per patient). The diagnosis of liver cirrhosis was based on liver histology or a combination of clinical, biochemical, and ultrasonographic findings. The diagnosis of acute variceal bleeding was based on the presence of hematemesis and/or melena at admission, and active variceal bleeding or non-bleeding varices but evidence of blood with no other potential source of gastrointestinal bleeding on endoscopy. Our exclusion criteria included age younger than 18 years, significant cardiopulmonary comorbidity, organic renal disease, neurological disease, malignant tumors (except HCC), previous severe infection (except spontaneous bacterial peritonitis), severe immunodeficiency (except HIV infection), liver transplantation, and inability to obtain scores on the first day of variceal bleeding.

Predictor variables

Laboratory data and scores were determined within 24 hours of bleeding onset, with the first available laboratory test performed before blood derivative transfusions. For the calculation of the CTP score we used the Pugh score modification (6). The MELD score was calculated using the original formula without including the cause of liver disease (7).

MELD score = $0.957 \times \log_e$ (creatinine mg/dL) + $0.378 \times \log_e$ (bilirubin mg/dL) + $1.120 \times \log_e$ (INR) + 6.43.

The additional variables studied were: age, sex, etiology of cirrhosis, endoscopic findings, previous episodes of variceal bleeding, HIV infection, presence of HCC, and infection during episode.

The diagnosis of HCC was made according to the Barcelona-2000 conference on the clinical management of hepatocellular carcinoma (14). Bacterial infection at admission and its development during hospitalization were defined as the presence of non-contaminated positive cultures of organic fluids or fever ≥ 38 °C lasting more than 24 hours.

All patients, including the cohort with HCC, were managed for acute bleeding and rebleeding prevention according to Baveno Consensus guidelines (15-17).

Outcome variables

Survival was calculated from the date of variceal bleeding. Patient outcome was obtained from hospital records and phone contacts. Patients were followed until death, liver transplantation, or end of observation (June 30, 2004). Transplanted patients were censored on the day of liver transplantation. Patients lost to follow-up before end of observation were censored at the last date known to be alive.

Mortality due to the episode of variceal bleeding included in the study was defined as death within 6 weeks of episode onset. Late mortality was defined as death after 6 weeks from variceal bleeding onset.

Short-term survival was defined as the interval from the date of bleeding to 3 months later. Long-term survival was defined as survival after 12 months from bleeding onset.

Statistical methods

In order to investigate the efficacy of the parameters to discriminate groups of different survival rates we used survival curves. Univariate survival curves were estimated using the Kaplan-Meier method and compared using the Log-rank test. We selected score cut-offs by means of receiver operating characteristic (ROC) curves with specificity around 90% to avoid a high number of false positive results. The multivariate analysis was performed using the Cox regression test to identify independent predictors of mortality. For all analyses a p value lower than 0.05 was considered statistically significant.

To compare the accuracy of scores as predictors of mortality we employed concordance c-statistics; this index is equivalent to the area under the ROC curve. A score with a c-statistic > 0.7 should be considered useful. C-statistics were applied for 6-week, 3-month, 12-month, and 36-month survival.

An additional statistical analysis was made to validate the UNOS-modified MELD score. The UNOS-modified MELD score was calculated using the formula available at: http://www.mayoclinic.org/gi-rst/mayomodel6.html.

RESULTS

Between January 1996 and December 2003, 270 variceal bleeding episodes were recorded for 215 cirrhotic patients admitted to our Unit. We included only the earliest bleeding episode for each patient. Fourteen patients were excluded from the analysis (6 patients had organic renal

disease, 1 patient had a malignant tumor other than HCC, 1 patient had a previous severe infection, 2 patients had undergone liver transplantation, and 4 patients were impossible to score on the first day of variceal bleeding).

The demographic and clinical characteristics of the 201 patients eligible for the study are summarized in table I. Median follow-up was 66.85 weeks (range 0-432.4) and median survival was 207 weeks (range 0-432.4). The survival rate of the cohort was 77.1% at 6 weeks, 75.1% at 3 months, 65.7% at 12 months, and 60.2% at 36 months (Fig. 1). During follow-up, 96 patients (47.8%) died, 12 patients (6%) underwent liver transplantation, and 7 patients (3.5%) were lost to follow-up after discharge.

Of all 96 deaths, 46 (47.9%) patients died from the episode of variceal bleeding included in the study. The mortality rates of these episodes according to the presence of HCC were: patients without HCC 32/178 (17.2%) and patients with HCC 14/23 (60.8%). The causes of death in patients with late mortality are reported in table II – rebleeding was the main cause of late mortality.

Table I. Demographic and clinical characteristics of the 201 patients included in the study

	Patient population (n = 201)
Age (mean ± SD) (yr)	59.48 ± 11.78
Sex (male/female), n (%)	142 (70.6%) / 59 (29.4%)
Etiology of cirrhosis, n (%)	
Alcoholic	91 (45.3%)
Viral	63 (31.3%)
Alcoholic + viral	27 (13.4%)
Other	20 (10%)
Endoscopic finding, n (%)	
Varices	187 (93%)
Portal hypertensive gastropathy	14 (7%)
Previous episode of variceal bleeding (yes/no), n (%)	56 (27.9%) / 145 (72.1%)
HIV infection (yes/no), n (%)	6 (3%) / 195 (97%)
Hepatocellular carcinoma (yes/no), n (%)	23 (11.4%) / 178 (88.6%)
Ascites (absent/slight/moderate)	111 (55.2%) / 72 (35.8 %) / 18 (9%)
Hepatic encephalopathy (stage 0/1-2/3-4), n (%)	154 (76.6%) / 37 (18.4%) / 10 (5%)
Creatinine (mg/dl), median (range)	0.8 (0.3-3.4)
Bilirubin (mg/dl), median (range)	2.1 (0.5-33.1)
INR, median (range)	1.52 (1.0-3.6)
CTP score, n (%)	
Class A	19 (9.5%)
Class B	113 (56.2%)
Class C	69 (34.3%)
CTP score, median (range)	9.0 (6-15)
MELD score, median (range)	12 (-2-35)
Infection (yes / no), n (%)	48 (23.9%) / 153 (76.1%)

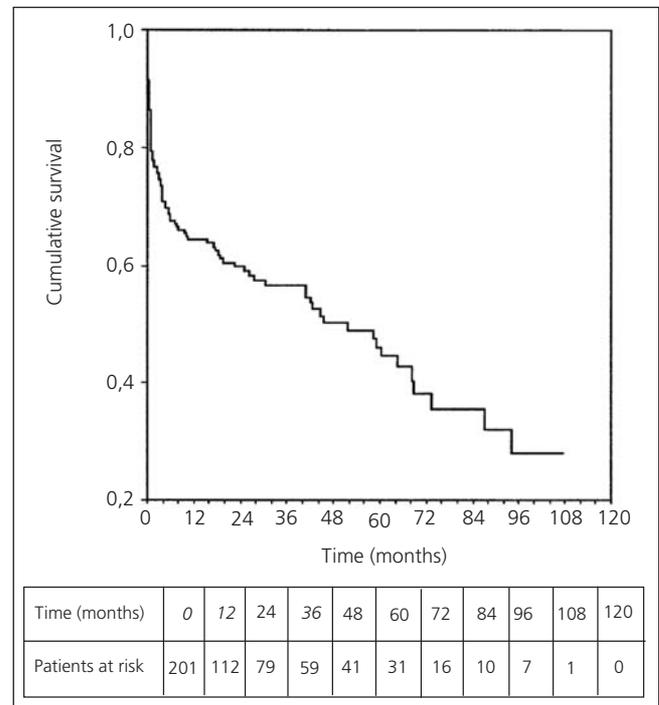| Time (months)	0	12	24	36	48	60	72	84	96	108	120
Patients at risk	201	112	79	59	41	31	16	10	7	1	0

Fig. 1. Cumulative survival of the 201 patients included in the study.
Supervivencia acumulada de los 201 pacientes incluidos en el estudio.

Table II. Causes of death in 50 patients with late mortality

Causes of death	n (%)
Variceal rebleeding	19 (38%)
Hepatocellular carcinoma	2 (4%)
Complications of cirrhosis	13 (26%)
Surgery	5 (10%)
Causes unrelated to cirrhosis	5 (10%)
Unknown causes	6 (12%)

Tables III and IV report the statistical analysis of survival. On the univariate analysis (Table III) age ≥ 65, previous variceal bleeding, presence of HCC, infection during the episode, a CTP score ≥ 10, and a MELD score ≥ 18 were significantly associated with survival. The multivariate analysis (Table IV) confirmed age ≥ 65, presence of HCC, CTP score ≥ 10, and MELD score ≥ 18 as the independent predictors of mortality. Infection did not show significant differences, and previous variceal bleeding showed significant correlations but with confidence intervals (CIs) including the unit. Age ≥ 65 and presence of HCC were the variables with a higher odds ratio, 4.65 (95% CI 2.24-9.65) and 9.0 (95% CI 2.35-34.52), respectively. Figures 2, 3, 4 and 5 show survival curves according to independent predictor variables. Presence of HCC and a MELD score ≥ 18 were highly effective as predictors of short-term survival after bleeding (Figs. 3B and 5B). The four parameters discriminated be-

Table III. Results of the univariate analysis of survival

| | Univariate analysis | | |
| | Log-Rank test | | Chi-squared test |
	Survival (weeks)*	p value	Relative risk (95% CI)
Age (≥ 65/< 65) yr	40.3 (0.14-385.7) / 274.9 (0.0-432.4)	p < 0.001	1.91 (1.45-2.51)
Sex (male/female)	182.4 (0.14-425.4) / 241.7 (0.0-432.4)	p = ns	1.19 (0.8-1.56)
Etiology of cirrhosis			
Alcoholic/viral /alcoholic + viral / other	257.7 (0.14-425.4) / 74.7 (0.29-432.4)/207.1 (0.0-385.7) / NC	p = ns	NC
Endoscopic finding			
Varices/portal hypertensive gastropathy	182.4 (0.0-423.4) / 241.7 (4-254.1)	p = ns	1.36 (0.66-2.79)
Previous episode of variceal bleeding (yes/no)	69.0 (0.29-415.1) / 257.7 (0.0-432.4)	p = 0.009	1.48 (1.12-1.96)
HIV infection (yes/no)	15.6 (1.71-117) / 207.1 (0.0-423.4)	p = ns	1.05 (0.46-2.36)
Hepatocellular carcinoma (yes/no)	3.6 (0.14-111) / 241.7 (0.0-432.4)	p < 0.001	2.03 (1.61-2.56)
Infection (yes/no)	77.7 (0.0-387) / 273.4 (0.14-432.4)	p = 0.019	1.31 (0.97-1.76)
CTP score (≥ 10/< 10)	18.1 (0.0-403.3) / 292.9 (0.14-432.4)	p < 0.001	1.91 (1.45-2.51)
MELD score (≥ 18/< 18)	3.6 (0.0-403.3) / 273.4 (0.14-432.4)	p < 0.001	2.04 (1.59-2.62)

*Value expressed as median (range). CI: confidence interval; ns: not significant ; NC: not calculable.

Table IV. Results of the multivariate analysis of survival

| | Multivariate analysis (Cox regression test) | |
	Odds ratio (95% CI)	P value
Age (≥ 65/< 65) yr	4.65 (2.24-9.65)	p < 0.001
Previous episode of variceal bleeding (yes/no)	2.11 (1.0-4.45)	p = 0.049
Hepatocellular carcinoma (yes/no)	9.0 (2.35-34.52)	p = 0.001
Infection (yes/no)	0.86 (0.37-1.97)	p = ns
CTP score (≥ 10/< 10)	3.23 (1.48-7.08)	p = 0.003
MELD score (≥ 18/< 18)	3.93 (1.47-10.48)	p = 0.006

CI: confidence interval; ns: not significant; NC: not calculable.

tween patients who survived and those who died after 12 months from bleeding, but age was the only variable that increased differences between both groups during the long-term survival study (Fig. 2).

The accuracy of the CTP and MELD scores in predicting mortality after variceal bleeding is shown in figure 6. MELD scores had a better discriminatory power than CTP scores at 6 weeks, 3 months, 12 months, and 36 months. The difference in accuracy between both models decreased in the prediction of long-term survival.

Similar results were obtained when all the statistical analyses for the UNOS-modified MELD score were repeated. The only difference was a cut-off value for the UNOS-modified MELD score of 19 points.

DISCUSSION

Variceal bleeding represents a major complication in the natural history of cirrhosis, impairing the balance be-tween portal pressure, and renal and liver function. Patients who suffer from liver and/or renal dysfunction during a bleeding episode can be divided into two groups. The first group comprises those who develop serious irreversible liver and/or renal dysfunction leading to death within a very short period of time. The second group of patients comprises those who suffer from temporary liver and /or renal dysfunction, the recovery of which allows them to get over the episode. In this group of patients this temporary dysfunction is likely indicative of advanced liver disease that remains unrecognized in non-stressful situations. It is not known whether this temporarily dysfunction can help us to stratify survival rates for this group. The introduction of the MELD score as a prognostic indicator in variceal bleeding, as opposed to the CTP score, allows an assessment of renal dysfunction. Impaired renal function has an important prognostic value in patients with advanced liver disease (18,19), even though the use of creatinine as marker in the presence of volume depletion is controversial given that its alteration may represent acute tubular necrosis. Probably early creatinine measurement demonstrates renal dysfunction as a reflection of previous functional renal impairment, not renal tubular necrosis. The current study supports the idea that patients with a poor clinical balance in the first day of variceal bleeding had damaged renal and liver function with prognostic value. The MELD score is a continuous system which takes into consideration objective parameters for liver and renal function. The use of these objective parameters and an accurate assessment of renal function may condition a higher predictive power as compared to the CTP score. In the CTP score the assessment of renal function by means of the presence of ascites is inadequate because it is well known that patients with ascites do not constitute a homogeneous group with similar prognoses (20,21). Albumin is another inap-
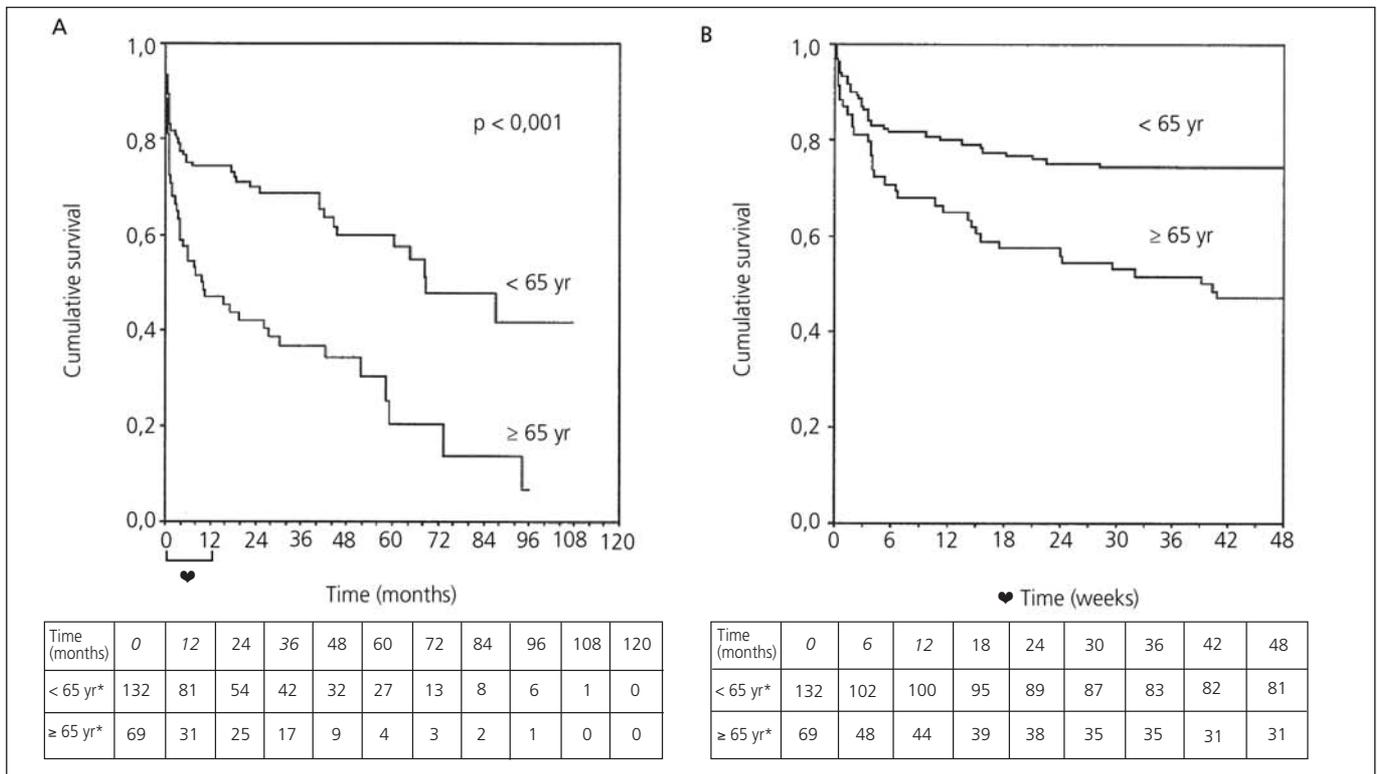
Fig. 2. Survival analysis stratified according to age during: A. all follow-up; and B. during 12 months of follow-up (*patients at risk).
*Análisis de supervivencia estratificado de acuerdo con la edad: A. durante todo el seguimiento; B. durante los 12 primeros meses del seguimiento (*pacientes en riesgo).*
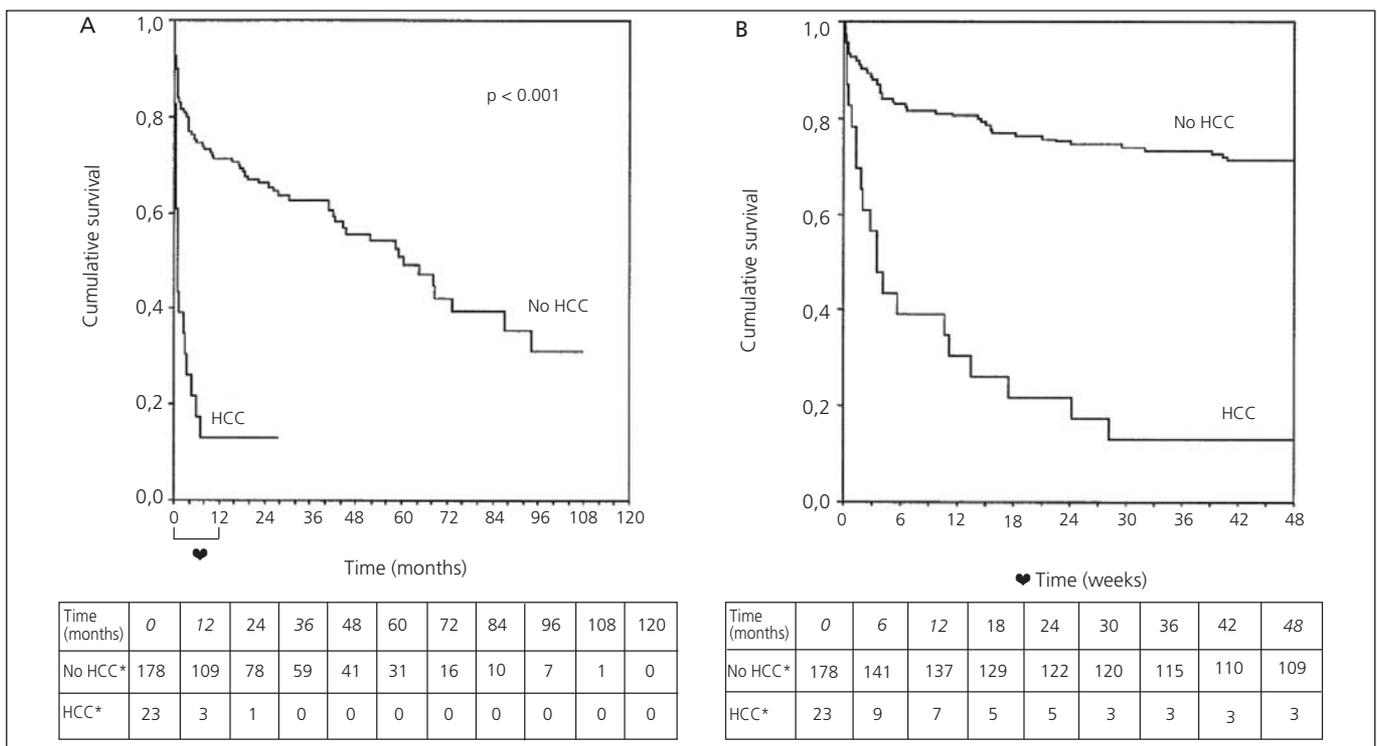

Fig. 3. Survival analysis stratified according to the diagnosis of hepatocellular carcinoma during: A. all follow-up; and B. during 12 months of follow-up (*patients at risk).
*Análisis de supervivencia estratificado de acuerdo con la presencia de hepatocarcinoma. A. Durante todo el seguimiento. B. Durante los 12 primeros meses del seguimiento (*pacientes en riesgo).*

Time (months)	0	12	24	36	48	60	72	84	96	108	120
CTP < 10*	132	91	64	47	32	27	14	9	6	1	0
CTP ≥ 10*	69	21	15	12	9	4	2	1	1	0	0

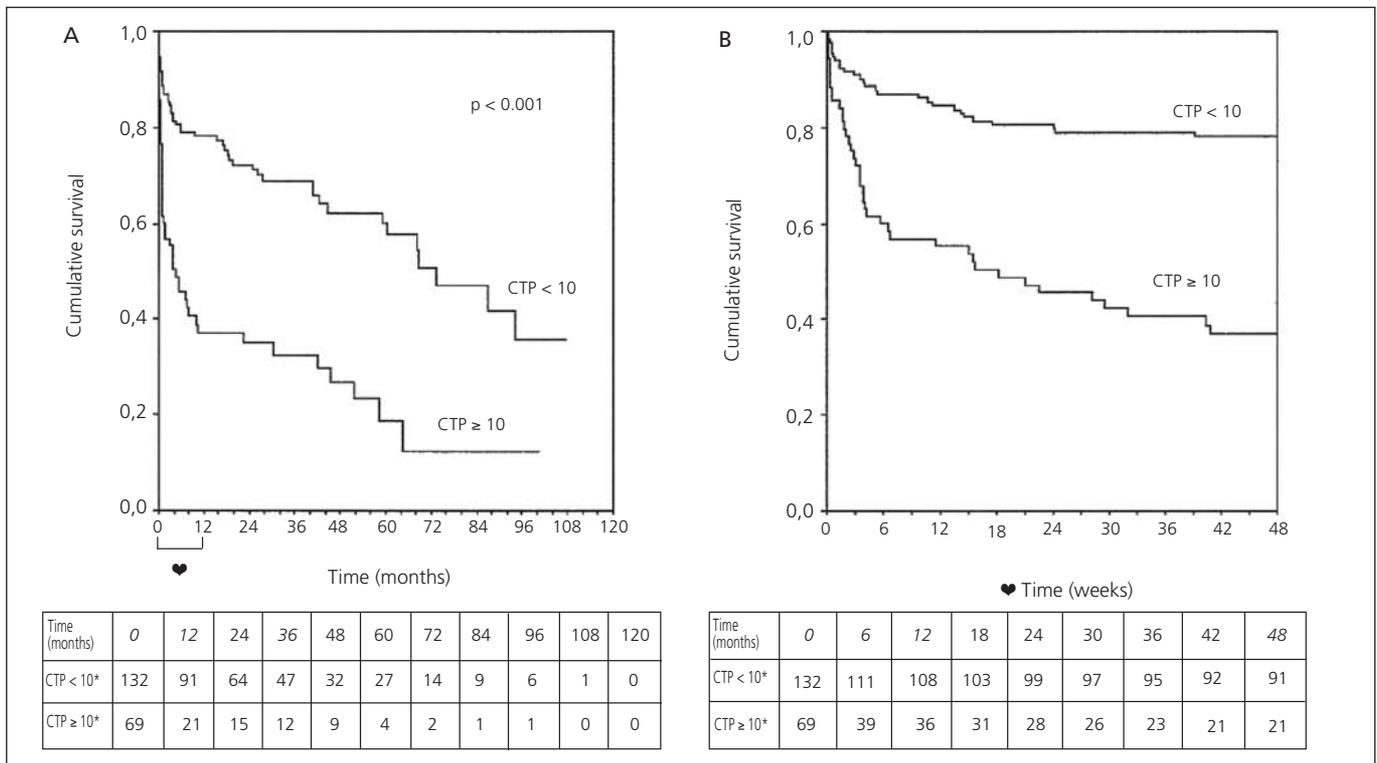| Time (months)	0	6	12	18	24	30	36	42	48
CTP < 10*	132	111	108	103	99	97	95	92	91
CTP ≥ 10*	69	39	36	31	28	26	23	21	21

Fig. 4. Survival analysis stratified according to the Child-Turcotte-Pugh score during: A. all follow-up; and B. during 12 months of follow-up (*patients at risk).
*Análisis de supervivencia estratificado de acuerdo con la clasificación de Child-Turcotte-Pugh: A. durante todo el seguimiento; B. durante los 12 prime-ros meses del seguimiento (*pacientes en riesgo).*

Time (months)	0	12	24	36	48	60	72	84	96	108	120
MELD < 18*	157	105	75	56	38	28	15	9	6	1	0
MELD ≥ 18*	44	7	4	3	3	3	1	1	1	0	0

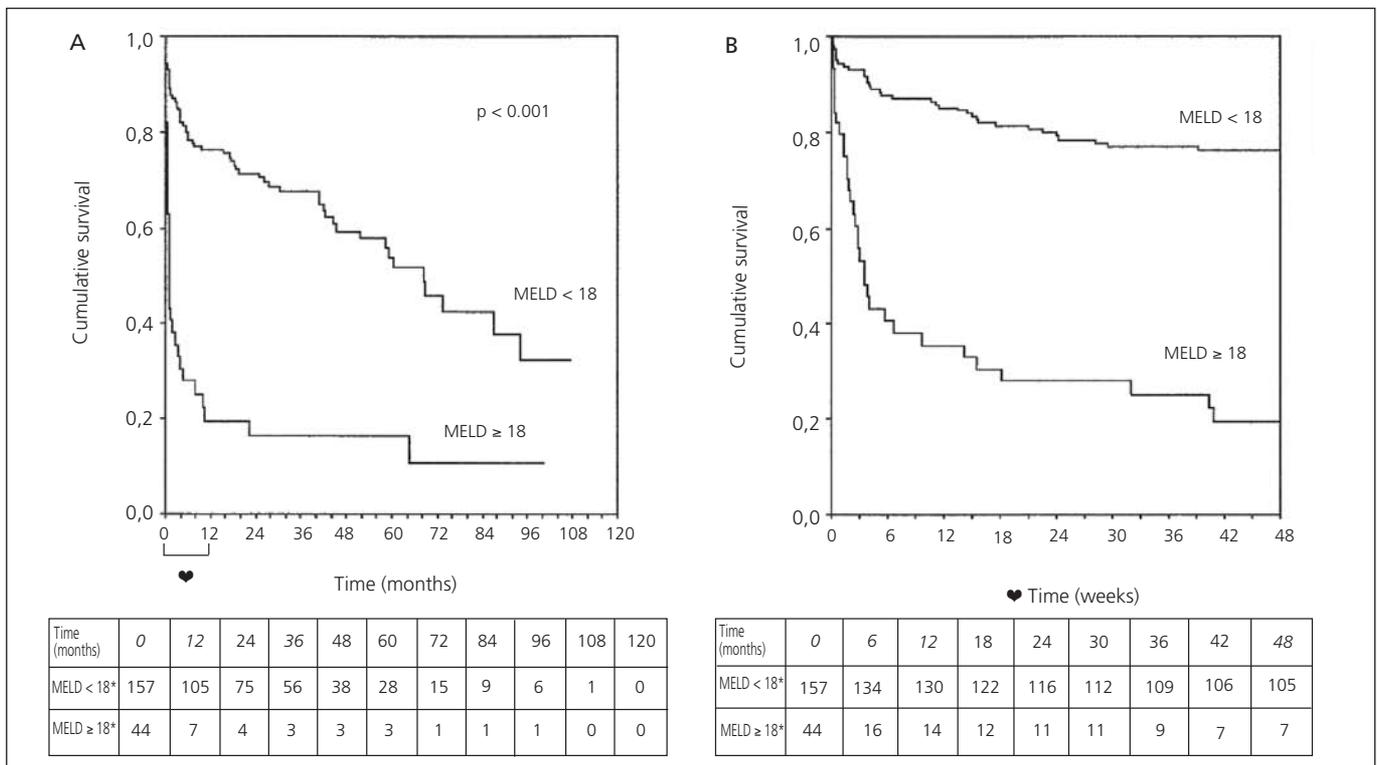| Time (months)	0	6	12	18	24	30	36	42	48
MELD < 18*	157	134	130	122	116	112	109	106	105
MELD ≥ 18*	44	16	14	12	11	11	9	7	7

Fig. 5. Survival analysis stratified according to MELD score during: A. all follow-up; and B. during 12 months of follow-up (*patients at risk).
*Análisis de supervivencia estratificado de acuerdo con el MELD score. A. Durante todo el seguimiento. B: Durante los 12 primeros meses del segui-miento (*pacientes en riesgo).*

A

AUC
CTP = 0.762
MELD = 0.804

(%)	Sen	Spe	PPV	NPV
MELD 18	56.5	88.4	59.1	87.3
CTP 10	63	74.2	42	87.1

B

AUC
CTP = 0.760
MELD = 0.794

(%)	Sen	Spe	PPV	NPV
MELD 18	54	88.7	61.3	85.3
CTP 10	60	74.2	43.5	84.8

C

AUC
CTP = 0.741
MELD = 0.766

(%)	Sen	Spe	PPV	NPV
MELD 18	47.8	91.6	75	77.1
CTP 10	59.4	78.8	59.4	78.8

D

AUC
CTP = 0.717
MELD = 0.737

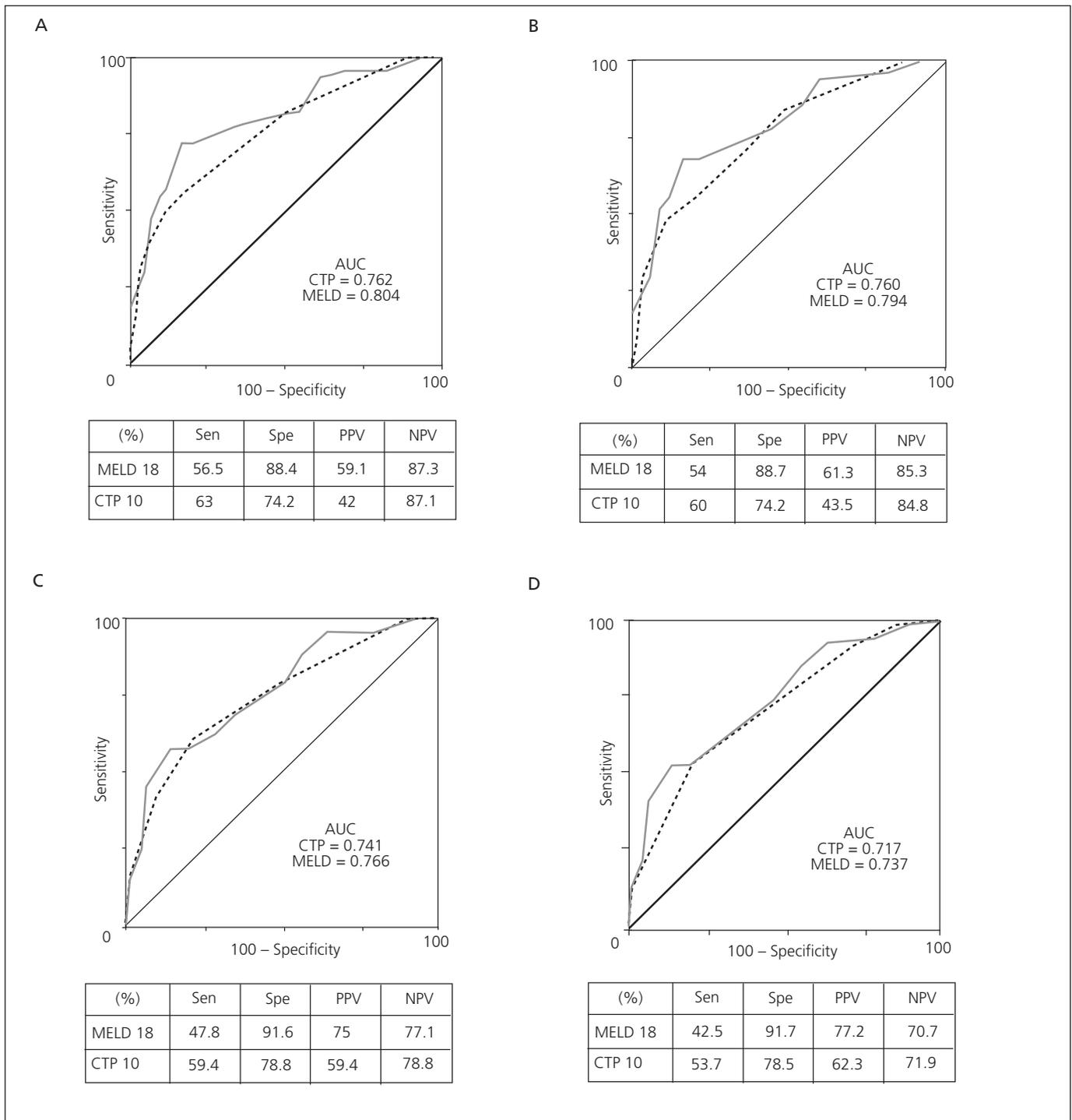| (%)	Sen	Spe	PPV	NPV
MELD 18	42.5	91.7	77.2	70.7
CTP 10	53.7	78.5	62.3	71.9

Fig. 6. Receiver operating characteristic (ROC) curves showing the accuracy of the CTP score (dotted line) and MELD score (solid line) *in predicting:* A. *6-week mortality,* c-statistics for CTP and MELD scores are 0.762 (95% CI: 0.682-0.842) and 0.804 (95% CI: 0.728-0.881), respectively. B. *3-month mortality,* c-statistics for CTP and MELD scores are 0.760 (95% CI: 0.684-0.836) and 0.794 (95% CI: 0.720-0.868), respectively. C. *12-month mortality,* c-statistics for CTP and MELD scores are 0.741 (95% CI: 0.668-0.814) and 0.766 (95% CI: 0.697-0.835), respectively. D. *36-week mortality,* c-statistics for CTP and MELD scores are 0.717 (95% CI: 0.645-0.788) and 0.737 (95% CI: 0.667-0.808), respectively.
Precisión pronóstica de la clasificación de Child-Turcotte-Pugh (CTP) en [línea punteada] y del MELD *score* en [línea continua] *en la predicción de:* A. Mortalidad a las 6 semanas, *valor c-estadístico para la clasificación de CTP y el MELD* score *0,762 (95% IC: 0,682-0,842) y 0,804 (95% IC: 0,728-0,881), respectivamente. B. Mortalidad a los 3 meses, *valor c-estadístico para la clasificación de CTP y el MELD* score *0,760 (95% IC: 0,684-0,836) y 0,794 (95% IC: 0,720-0,868), respectivamente. C. Mortalidad a los 12 meses, *valor c-estadístico para la clasificación de CTP y el MELD* score *0,741 (95% IC: 0,668-0,814) y 0,766 (95% IC: 0,697-0,835), respectivamente. D. Mortalidad a las 36 meses, *valor c-estadístico para la clasificación de CTP y el MELD* score *0,717 (95% IC: 0,645-0,788) y 0,737 (95% IC: 0,667-0,808), respectivamente.*

propriate parameter in the CTP score since protein loss during bleeding leads to early hypoalbuminemia even in non-cirrhotic patients.

The identification of patients with poor prognosis may be essential for the optimal short-term management of variceal bleeding. In the analysis of short-term survival the variables with higher discriminative power in predicting survival were the presence of HCC and the MELD score. Some authors assert that the development of HCC may accelerate the course of liver disease (22). Patients with HCC frequently have portal vein thrombosis, recurrent bleeding after endoscopic treatment, and a high mortality rate within 6 weeks of admission (4,23,24). Thus, short-term survival in patients with variceal bleeding and HCC is probably decreased as a consequence of advanced cirrhosis and difficult portal hypertension management.

In the analysis of long-term survival the discriminative power of MELD scores decreases and becomes similar to that of CTP scores (Fig. 6). We want to emphasize that this paper is the first study to evaluate the MELD score in the prediction of 36-month survival. Maybe for long-term prognosis liver disease staging could be better performed using changes in both models over time. It is well known that in patients with advanced cirrhosis an increasing MELD score is superior to initial CTP and MELD scores for the prediction of mid-term outcomes (25,26). According to the survival study (Fig. 2), the only parameter that increases differences in long-term survival is age. This fact is probably related to the presence of three factors in the older population: a longer duration of liver disease, a greater difficulty to overcome recurrent cirrhotic decompensations, and the absence of liver transplantation indications for the elderly in our country (27).

CTP and MELD scores are important indices in the evaluation of liver transplantation and other procedures, including portosystemic shunt. Our results support that both scores maintain their capacity on the first day of acute variceal bleeding. This study has the limitations of retrospective studies, but the high differences found in the statistical analysis could make these results useful for the management of patients with a recent episode of variceal bleeding.

In summary, assessing liver disease stage within 24 hours of bleeding onset, together with age and a diagnosis of HCC, is useful to assess the short- and long-term prognosis of cirrhotic patients with acute variceal bleeding. In addition, the prognostic variables obtained may be useful to define strategies for management improvement in these patients.

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