1130-0108/2013/105/9/513-520
Revista Española de Enfermedades Digestivas

Rev Esp Enferm Dig (Madrid
Vol. 105, N.º 9, pp. 513-520, 2013

ORIGINAL PAPERS

Prognostic factors associated with mortality in patients with severe alcoholic hepatitis

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ABSTRACT

Severe alcoholic hepatitis is associated with high early mortality. This study aimed at identifying prognostic factors associated with in-hospital, medium- and long-term mortality of severe alcoholic hepatitis and to evaluate the different prognostic scoring systems on a cohort of patients in our hospital. To this end, we conducted a retrospective analysis of 66 episodes admitted between 2000 and 2008. Clinical and laboratory data on admission, at 7 days, 1 month, 6 months, and after one year were collected and analyzed, as were the details on the treatment and complications that occurred during hospitalization; the different prognostic indices used in the literature were calculated. Death event associated with an episode of severe alcoholic hepatitis occurs primarily during the first month, with an average mortality rate of 16.9. Infectious complications were associated with lower in-hospital survival. MELD score, urea and bilirubin values one week after admission were independently associated with both in-hospital survival (OR = 1.14, 1.012 and 1.1, respectively), and survival at 6 months (OR = 1, 15; 1.014 and 1.016, respectively). Only MELD score and urea values at 7 days were independent predictors of survival twelve months after the acute hepatitis episode. MELD score, urea, and bilirubin 7 days after admission were the only independent in-hospital survival and also long-term survival factors 6 months and one year after the episode. In our cohort, the MELD score was the best prognostic index to predict mortality associated with an episode of severe alcoholic hepatitis.

Key words: Severe alcoholic hepatitis. Mortality. MELD. Glasgow index. ABIC. Survival.

INTRODUCTION

Alcoholic liver disease is one of the leading causes of cirrhosis in developed countries and is caused by chronic excessive alcohol consumption (1), in addition to individual susceptibility factors, such as female gender, malnutrition, obesity, genetic factors, chronic hepatitis virus infection and exposure to other hepatotoxic substances (2). Alcoholic liver disease comprises a series of developmental stages that occasionally overlap: Hepatic steatosis, alcoholic hepatitis and chronic hepatitis with liver fibrosis or cirrhosis, which may be differentiated by biopsy. The diagnosis of acute alcoholic hepatitis (AH) is mainly clinical, determined by excessive alcohol consumption and clinical and laboratory abnormalities consistent with the condition. Biopsy confirms the diagnosis in 80 % of cases (3,4) and, although not essential, it enables the diagnosis to be confirmed and other causes of liver disease discarded.

The mortality following an episode of acute hepatitis varies according to its severity, and is around 50 % in cases that require hospital admission and do not receive specific treatment (5). The clinical spectrum is very wide, and the severity and mortality are variable, even in cases in which the acute liver disease is caused by alcohol consumption on underlying liver disease or cirrhosis, with a varied prognosis (6). The therapeutic strategies used to reduce the short-term mortality are alcohol withdrawal, nutritional support and, in severe cases, the administration of steroids or pentoxifylline. Early mortality (< 3 months) of patients hospitalized for AH varies from 15 to 55 % for cases of mild or severe AH, respectively (7). The long-term survival of patients with alcoholic liver disease is 58 % in patients with alcoholic hepatitis, 49 % in patients with

Received: 04-12-2012
Accepted: 16-09-2013

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Bargalló-García A, Serra-Matamala I, Marin-Fernández I, Masnou-Ridaura H, Leal-Valdivieso C, Marcos-Neira P, Sala-Llinars M, Morillas-Cunill R, Planas-Vila R. Prognostic factors associated with mortality in patients with severe alcoholic hepatitis. Rev Esp Enferm Dig 2013;105:513-520.

alcoholic cirrhosis and 35 % in patients with AH superimposed upon cirrhosis (8).

Due to the need for proper classification of disease severity to enable us to predict its mortality, and to identify those patients who require specific treatment (7), numerous markers have been evaluated to establish the prognosis. Factors that have been associated with a poor prognosis are hepatic encephalopathy, high serum bilirubin (> 12 mg/dl), prothrombin time less than 50 %, ascites, renal failure and bacterial infections (8-12). Several indices currently used to establish the disease prognosis have been developed, such as the modified Maddrey's discriminant function (mDF) (10,13), which is based on the prothrombin time and serum bilirubin levels. In this index, a value greater than 32 is diagnostic of severe AH and an indication for steroid treatment. Recent studies have shown that this classification may be erroneous, as some patients have been found to have mDF < 32 and high early mortality (13,14). The Model of End-stage Liver Disease (MELD) (15,16) includes bilirubin, INR and creatinine, and has been shown to be a good predictor of mortality at different times (13,16,17). Somewhat more recent is the Glasgow scale (18,19), based on analytical variables and which includes age as an independent variable. Finally, the ABIC score has recently been developed (13), which is based on age, bilirubin, INR and creatinine as independent variables, and classifies patients into three 3-month survival levels. This system allows patients to be classified into low risk (candidates for support treatments) (7,20), moderate risk (patients who will benefit from a specific treatment such as steroids or pentoxifylline) and high risk of mortality despite receiving treatment. It has been shown to be a good predictor of mortality and is useful for assessing the response to treatment (13).

The aims of this study were to identify, in our cohort, the independent prognostic factors that influenced the in-hospital, 6-month and long-term mortality after an episode of severe AH, and to evaluate the usefulness of the various prognostic indices in our group.

MATERIALS AND METHODS

Patients

A retrospective, observational analysis was performed of 66 consecutive episodes of severe AH in a total of 61 patients admitted to Hospital Germans Trias i Pujol (Badalona, Spain) during the period 2000-2008. The diagnosis of AH was established by clinical (decompensated liver disease) and laboratory criteria (high transaminases, GGT and bilirubin) and previous alcohol consumption of > 60 g/day. It was considered severe when the modified mDF was greater than 32 (10) or there was hepatic encephalopathy. Histological confirmation was not essential.

Clinical follow-up

Clinical and laboratory data were collected on admission, after one week, one month, 6 months, one year and 5 years of follow-up; data on the treatment and complications during admission were also collected. The quantitative variables included epidemiological data (age, BMI and alcohol use in g/day), Child-Pugh score prior to admission in the case of cirrhosis, length of hospital stay, mDF on admission, laboratory data (hemoglobin, white blood cell count, polymorphonuclear (PMN) leukocytes, prothrombin levels, INR, GOT, GPT, alkaline phosphatase, GGT, bilirubin, urea, creatinine, electrolytes, cholesterol, triglycerides, total protein and albumin), clinical data on hepatic encephalopathy and ascites and the scores in the prognostic indices (Child-Pugh, MELD, Glasgow and ABIC). Treatment data recorded were the doses of steroids and enteral nutrition (EN) received and the duration of treatment, as well as the prophylactic antibiotic regimens. Data of interest was collected from the medical record and included toxic habits, tests related with the severe AH episode (biopsy, ultrasound, fibrogastroscopy and signs of portal hypertension) and details of treatment and complications during admission (ascites, encephalopathy, infections, gastrointestinal bleeding, renal failure and hepatorenal syndrome). In-hospital mortality, its causes and survival one month, 6 months and 1 year after the episode were recorded.

Statistical analysis

Descriptive analysis of the population and clinical variables was performed. Chi-squared and Student's t-tests were used in the bivariate analysis, and when parametric tests were not possible, the Mann-Whitney U test was applied. Survival analysis was carried out using the actuarial and Kaplan-Meier methods, and the survival curves were compared using the Log Rank test. Finally, the independent survival factors were analyzed using a Cox regression model. Logistic regression of ROC curves was performed to establish the prognostic value and best cut-off point in the indices for predicting the mortality of an episode of AH. All analyses were carried out using the SPSS statistical package, version 15.00. The frequency results are given in percentage and the measure of central tendency shown is the mean and standard deviation when the distribution of the variable is normal and median with the range when it is not.

RESULTS

There was a predominance of males (65.2 %). Two episodes of severe AH were observed in five patients, with a mean time between the first and second episode of 19.4 months (range: 12-23 months). As 65.6 % of patients

had a history of liver disease prior to admission, they were included in the sample (50.8 % of alcoholic etiology, 6.6 % steatosis, 1.6 % hepatitis C virus (HCV) infection and 4.9 % mixed viral and alcoholic etiology); 20 patients (32.8 %) had already been diagnosed with cirrhosis, mostly moderate liver failure. The diagnosis of severe AH was established by clinical and laboratory criteria; liver biopsy was performed in only 34 episodes (53.1 %). The diagnosis was confirmed in all patients. Of the episodes in which a biopsy was performed, 55.9 % were diagnosed with alcoholic hepatitis superimposed on a cirrhotic liver. Signs of portal hypertension were present in 96.7 % of cases during admission: 86.9 % clinical, 88.5 % ultrasound and 87.9 % endoscopic.

With respect to complications that presented during admission (Table I), the most common was ascites, which was mainly controlled with diuretic treatment. This was followed by infectious complications, the most common causes being: Urinary infection (35.2 %), bacteremia with positive blood culture (20.4 %), respiratory infections (18.5 %) and spontaneous bacterial peritonitis (7.4 %). Patients who presented any infection had a lower in-hospital survival ($p = 0.015$). Hepatic encephalopathy occurred in 39.4 % of episodes; it was mostly secondary to an infection (50 %) and was spontaneous in 39 %. Bleeding complications were described in 12 episodes, mostly secondary to lesions due to portal hypertension (81.8 %). Seven patients experienced a deterioration in renal function during the first week of admission and three patients were diagnosed with type 1 hepatorenal syndrome (HRS-1); all patients with HRS-1 died during admission.

Table I. Summary of epidemiological data and patient history

n = 66 episodes	*No.*	*Median*	*Frequency*	*Range*
Age (years)		52.3		28.4-77.2
Alcohol consumption (g/day; mean ± SD)	123.7 (SD = 39)			
Body mass index (kg/cm^2)		27.9		16.1-14.1
Gender (male)	42		65.2 %	
Known history of liver disease	40		65.6 %	
Previous cirrhosis	20		32.8 %	
Liver biopsy	34		53.1 %	
Complications during the episode				
Ascites	51		77.3 %	
Hepatic encephalopathy	26		39.4 %	
Upper gastrointestinal bleeding	12		18.2 %	
Infections	38		57.6 %	
HRS-I	3		4.6 %	
Treatment				
EN supplements	66		100.0 %	
Steroids	44		72.7 %	
Antibiotic prophylaxis	19		32.2 %	
Steroids + antibiotic prophylaxis	14		21.2 %	
Alcohol abstinence	21		34.4 %	
Follow-up time (months)		16.6		0.13-88.7
Hospital stay (days)		25		(4-49)
Mortality (calculated on patients, n = 61)				
In-hospital	14		23.0 %	
6 months	22		36.1 %	
12 months	24		39.3 %	
5 years	33		54.0 %	
			95 % CI	
Mean survival time (months)	36.3		17.8 - 59.4	
Cumulative probability of survival				
After one month	83.1 %		73.9-92.2	
After 3 months	76.9 %		66.6-87.1	
After 6 months	73.6 %		62.8-4.4	
After 12 months	70.2 %		59.0-1.5	

In relation to treatment, during admission all patients received EN and 72.7 % (44 patients) received corticosteroid treatment, normally with a starting dose of 40 mg/day (oral or i.v. as appropriate), with dose reductions as indicated in the clinical guidelines. The mean steroid treatment time was 31 days (SD = 16.3). Antibiotic prophylaxis was not widely administered, and was used in 19 episodes (32.2 %) (Table I). There were no differences with respect to the onset of infectious complications between the group of patients who received prophylactic antibiotics at the start and the group which did not (63.2 and 65 %, respectively). A description of the laboratory variables and prognostic indices of the patients over time can be seen in tables II and III. The median hospital admission was 25 days (4-49 days).

The mean mortality rate during the first month was 16.9 %. In-hospital mortality occurred mainly due to infectious complications, as can be seen in table IV. Six months and one year after the episode, 36.1 and 39.3 % of patients had died, respectively. Figure 1 shows the survival in-hospital and during follow-up.

Only 21 subjects (34.4 %) of those discharged successfully abstained from alcohol during follow-up. These patients had longer survival with respect to those who were unable to do so, although there were no significant differences (55 % compared to 30.2 %, respectively; p = 0.06). Infectious complications and the onset of HRS or encephalopathy were associated with shorter survival, both in-hospital and after one year of follow-up. None of the treatment variables were related with survival.

In the bivariate analysis, the Child-Pugh, ABIC and MELD scores, both at baseline and 7 days after admission, were related with in-hospital mortality, but the Glasgow scores were not. With respect to the analytical variables, the bilirubin and urea values had prognostic value, both at baseline and after 7 days.

In the multivariate analysis, the MELD, urea and bilirubin values 7 days after admission were independently related with both in-hospital (OR = 1.14; 1.012 and 1.1, respectively) and 6-month survival (OR = 1.15; 1.014 and 1.016, respectively). After 12 months, only the 7-day MELD and urea values were independent factors of survival (OR = 1.16 and 1.014, respectively). Comparing the different prognostic scores validated in AH, the best ROC curve for predicting in-hospital mortality at 6 months and

Table II. Description of analytical data and prognostic indices in our cohort over time (according to available data)

	Admission *n = 66*	*1st week* *n = 57*	*One month* *n = 36*	*6 months* *n = 20*	*12 months* *n = 25*	*5 years* *n = 6*
Hemoglobin (g/dL)	10.7 ± 2.1	10.5 ± 1.6	11 ± 2.3	11.9 ± 2	12 ± 1.6	14.1 ± 1.7
White blood cells (× 10^9)	7.65 (1.7-32.7)	10.8 (2.2-30.8)	9.8 (1.4-47)	6.5 ± 3.6	5.75 ± 9.7	4.2 ± 2.3
PMN leukocytes (%)	68 ± 11.3	69.6 ± 13.2	65.6 ± 15.1	54.5 ± 15.4	56.9 ± 16	63.3 ± 11.7
Prothrombin time (%)	41.2 ± 11.7	43.9 ± 16.8	47 ± 15.1	53 ± 18.3	60.4 ± 19	72.7 ± 24
INR	1.7 (1.1-4.1)	1.5 (1-4)	1.5 (1-3.3)	1.4 (1-5.1)	1.3 ± 0.3	1.2 ± 0.2
GOT (U/L)	102 (27-1541)	86 (29-239)	64 (17-737)	50 (30-3016)	71 ± 48	32.2 ± 13.7
GPT (U/L)	38 (13-218)	47 (18-331)	54.5 (14-183)	31 (16-769)	71 ± 24	30.4 ± 16.6
Bilirubin (mg/dl)	10.3 (2-42)	8.2 (1.3-45)	4.8 (0.6-22.1)	2 (0.7-18.6)	2.4 (0.7-14.3)	1.6 (1-11)
Alk. phosphatase (U/L)	116 (16-521)	105 (39-232)	11 (58-461)	116 (56-287)	118.5 (65-371)	87 (71-307)
GGT (U/L)	168 (35-1183)	116 (18-653)	99.5(26-705)	109 (24-1049)	71 (22-2678)	55 (38-72)
Urea (mg/dL)	24 (9-153)	38 (12-281)	33 (7-146)	27.5 (14-52)	29 ± 11	27.3 ± 10
Creatinine (mg/dL)	0.6 (0.4-2)	0.7 (0.3-7.6)	0.7 (0.1-5.2)	0.8 (0.5-1.6)	0.9 (0.5-1.4)	0.7±0.14
Sodium (mmol/L)	134 (114-145)	133 (115-140)	133.6 ± 6.4	137.6 ± 4.5	137 ± 5.1	137.3 ± 2.4
Potassium (mmol/L)	3.7 (2.6-5.3)	4.18 ± 0.7	4.6 ± 0.8	4.2 ± 0.5	4.1 (2.5-5.4)	4.1 ± 0.4
Triglycerides (mg/dL)	105 (44-559)	96 (26-376)	83.4 ± 51.8	94 ± 30.4	96 (53-201)	107.2 ± 49
Cholesterol (mg/dL)	117 (46-348)	104 (31-298)	146.2 ± 83	171 ± 52	165.3 ± 48.5	144.2 ± 44.3
Proteins (mg/dL)	63 (49-80.6)	63.2 (41.8-76)	61.8 ± 8.3	70.5 ± 8.6	69.2 (57-82.3)	74.1 ± 11
Albumin (mg/dL)	25.8 (17.8-39.2)	26 (18.4-38.5)	28.1 (19.5-38)	39 (22.5-46)	34.1 (23-43.5)	37.7 ± 8.1
Prognostic indices						
Child-Pugh	11 (8-13)	11 (6-14)	10 (5-14)	7.5 (5-12)	7 (5-9)	6 (5-10)
MELD	22.1 (15-36)	20.1 (10-40)	17.7 (6-27)	12.9 (6-34)	11.9 (6-24)	8.6 (6-13)
Glasgow	8 (5-11)	8 (5-12)	7 (5-11)	7 (5-10)	6 (5-9)	6 (5-8)
ABIC	7.8 (5-12.3)	7.6 (4.1-13.2)	7 (3.9-11)	7.2 (5.8-11.3)	6.9 (3.9-10.6)	6.2 (6-10.6)

Data with normal distribution are expressed as mean ± standard deviation. Data that do not follow a normal distribution are expressed as median (range).

Table III. Factors significantly associated with survival at different times

	OR (95 % CI) p value		
Associated with survival:	*After one month*	*After 6 months*	*After 12 months*
MELD after one week	1.14 (1.05-1.25) p = 0.003	1.15 (1.06-1.25) p = 0.001	1.16 (1.07-1.25) p = 0.000
Urea after one week	1.012 (1.004-1.02) p = 0.002	1.014 (1.007-1.021) p = 0.000	1.014 (1.008-1.021) p = 0.000
Bilirubin after one week	1.1 (1.03-1.16) p = 0.004	1.06 (1.007-1.112) p = 0.025	---

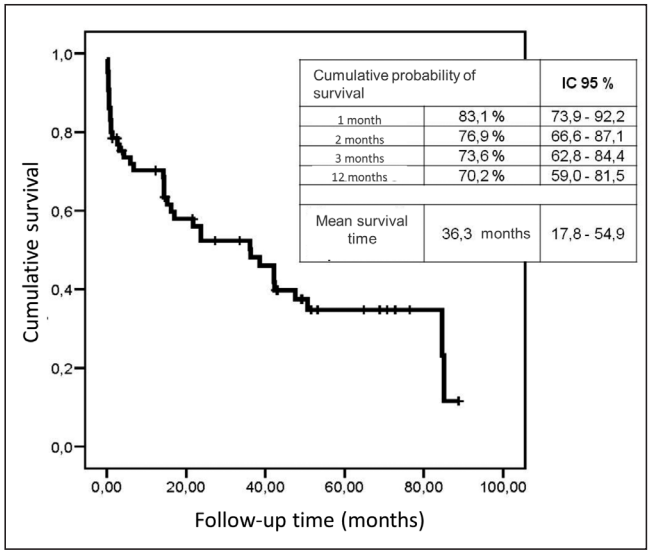

Fig. 1. Survival analysis. The mean follow-up time was 16.6 months (minimum 0.13, maximum 88.7 [7.4 years]). Twenty-four patients (39.3 %) were alive at the end of follow-up. The mean mortality rate during the first month was 16.9 %.

one year was that of the MELD; a score of 22 was found to have the best predictive value (Fig. 2). The analytical variables that best predicted the in-hospital mortality were the urea and bilirubin 7 days after admission, with values of 50 mg/dL and 19 mg/dL, respectively. Furthermore, those that best predicted the mortality 6 months and 1 year after the episode were also the urea and bilirubin 7 days after admission, with values of 53.5 mg/dL and 8.7 mg/dL, respectively (Fig. 2).

DISCUSSION

This study has the usual limitations of a retrospective study, among which are the lack of some data that might have been useful for evaluating the prognostic values of other aspects mentioned below. However, it analyses the predictive ability of variables that can be calculated with data obtained in routine clinical practice, so its results are directly applicable. The diagnosis of severe alcoholic hepatitis in our department was established by clinical and laboratory criteria that have already demonstrated their diagnostic reliability in previous series (1,21,22), and it was confirmed in all the cases biopsied. In those patients in whom it was performed, biopsy enabled the evolutionary stage of the disease to be established, other additional causes of liver disease to be discarded, and the subgroup of patients who could have a poorer prognosis to be diagnosed. These were patients in whom the AH was combined with previously established cirrhosis (8,11,20,22,23), which is important, because most patients admitted for an episode of severe AH

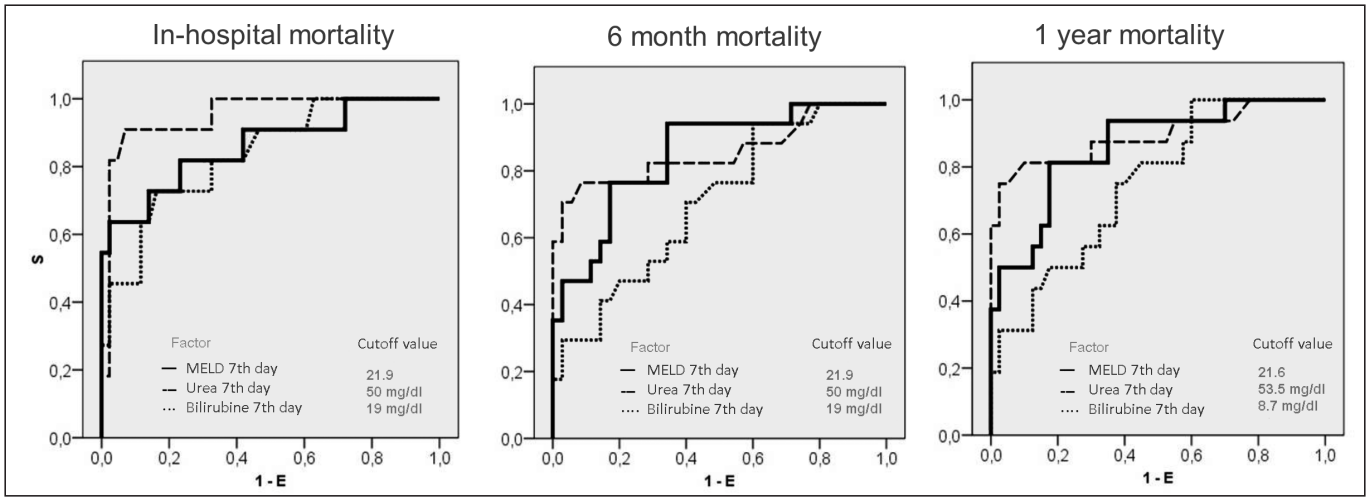

Fig. 2. ROC curves: Prognostic factors of mortality. The best ROC curve for predicting in-hospital, 6 month and one year mortality was the MELD and the analytical variables that best predicted the in-hospital, 6 month and one year mortality were the urea and bilirubin 7 days after admission.

Table IV. Mortality and causes

	In-hospital mortality (n = 14)	*Out-of-hospital mortality (n = 22)***
Alcoholic hepatitis	2 (35.7 %)	---
Gastrointestinal bleeding	2 (14.3 %)	5 (22.7 %)
Infections	6 (42.9 %)	5 (22.7 %)
HRS-1	3 (21.4 %)	---
Others	1 (7.1 %)*	6 (27.3 %)

*Basilar artery thrombosis. **Unknown cause in 6 patients lost to follow-up

have signs of portal hypertension. This retrospective study focused on analyzing the predictive ability of indices that can be calculated with data usually available in the medical record, although recent studies have also examined the role of liver biopsy (24) (not available in our patients when the diagnosis was clear using clinical and laboratory criteria) and portal hypertension (25). This interesting question could not be explored in our sample as we do not have a liver hemodynamic unit in our hospital.

In this study, we stratified the mortality associated with an episode of severe AH into early (in the first 3 months, including in-hospital mortality) and late mortality (13,14,16,18,26,27). The mean hospital stay in our series was 25 days, so the in-hospital and one-month mortality were similar. Approximately one quarter of patients who died did so within 15 days of admission, representing 64 % of the in-hospital mortality. This reflects the need for early prognostic stratification and early initiation of the appropriate treatments in patients with a poor prognosis (1,5,9,20,28,29). Twenty-five percent of patients who died in our series did so during the first year, but 91 % died in the first 6 months, which limits the possibility of liver transplant, even if they manage to abstain from alcohol. The overall survival in our series was similar to that described in other previous studies (10,11,13,17,26,27), with a mean time of 3 years and a one-month survival similar to other series of patients treated with steroids. Gender and age were not independent prognostic factors of mortality.

Associated complications during admission for severe AH in our series were similar to those published in other studies (17,23,30) and were associated with a poor short and long-term prognosis, with infections the most common cause of in-hospital mortality (Table IV). Furthermore, none of the treatment-associated variables was an independent predictor of mortality, probably due to the relatively small size of the sample studied. Antibiotic prophylaxis was not systematically applied, since its efficacy has not been clearly demonstrated (1,7,20). Approximately one third of the in-hospital mortality was attributed to the AH itself (Table IV).

Abstinence from alcohol, which is a key point in the treatment of patients with alcoholic liver disease (1,7,20), was achieved in one third of our patients and showed a tendency to improve survival (55 % in abstinent patients compared to 30 % in those who continued drinking), although not significantly, probably due to the size of our series.

On admission, all patients had moderate or severe hepatocellular failure and an improvement was observed after the first 6 months of follow-up. In this series, the MELD score in our patients also showed a good correlation with the mDF for classifying the severity of the AH (14,16). The mean ABIC score on admission classified our patients into AH with medium risk and therefore candidates for specific therapeutic measures. However, it must be mentioned that at the time of admission, there was a group of patients with an ABIC score less than 6.71, thus considered low risk despite having an initial mDF greater than 32, which would classify them as severe. This fact has already been described in the series by Domínguez et al. (13). We also found that a small group of patients classified as not severe according to the mDF belonged to the medium and high risk group according to their ABIC score.

Bilirubin and urea were the only analytical variables that were able to predict the in-hospital mortality; only the baseline urea remained as an independent predictor of mortality after one month, 6 months and one year (Fig. 2). In contrast, most of the analytical variables at 7 days (white blood cell count, total protein, bilirubin, urea, creatinine) acquired a prognostic value for mortality. This can probably be explained by the effect of treatment on the evolution of the AH and the predictive ability of the changes in the different variables after 7 days, as has been described in other series (26,30). In the univariate analysis, the laboratory parameters with prognostic value both at baseline and after 7 days were the plasma bilirubin and urea, the latter having better precision and specificity when predicting mortality.

On analyzing the usefulness of the different severity indices (11-17,19,26), we found that, except for the Glasgow index, we obtained results similar to previous studies (10,13,14,16-19,26,30). The precision was better in the indices calculated in the week of admission compared to baseline, with the best AUC obtained for the MELD and ABIC scores. All the prognostic indices, except for the Glasgow score, were shown to be predictors of mortality, both early and after one year, in their baseline score and after one week. Nevertheless, none of them were able to predict the long-term mortality (5 years). The inefficacy of the Glasgow score may be because neither age nor the white blood cell count were independent risk factors in our series. In our cohort, the MELD score was slightly better than the ABIC with respect to its predictive ability, probably because the calculation of both indices is based on the INR, creatinine and bilirubin, while the ABIC also includes the factor age, which in our series was not a prognostic factor. Although most of the analytical variables at 7 days were able to predict the mortality, we chose only bilirubin and urea, as they were equally predictors in the baseline

data and represent liver and renal function, respectively.

In conclusion, the MELD score after 7 days was the only prognostic index in our study that remained as an independent predictor of mortality both in the short and medium-term. With respect to the clinical and laboratory factors, the urea and bilirubin values 7 days after admission were the only ones that remained as predictors of short and medium-term mortality. Severe AH continues to have high early mortality despite currently available therapies, so correct prognostic stratification of patients is necessary. All of the current prognostic indices, with the exception of the Glasgow score, were shown to be effective in our series when assessing the risk of mortality, with the MELD score being the most reliable. Although these indices are good predictors of mortality in severe alcoholic hepatitis, we should take into account that the determination of simple laboratory values, such as urea and bilirubin 7 days after admission allows us to identify patients with a poor prognosis both in the short and medium-term.

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