

# Short-term Survival in Acutely Decompensated Cirrhotic Patients

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## Abstract

**Aim:** The present study was aimed at the early identification of the prognostic factors for 30-day mortality in acutely decompensated cirrhotic patients.

**Methods:** Logistic regression models were used to study the predictors of mortality. Variables significant on univariate testing were included for the multivariate analysis. ROC curves were constructed. The model used retrospective data from 228 patients; and was prospectively validated among 64 patients from the Hospital Clinic: internal validation, and 90 patients from Hospital Gregorio Marañon: external validation.

**Results:** The model identified age at admission, serum concentrations of bilirubin, creatinine and sodium, and INR obtained 2 to 8 days after admission as predictors of death in this population. The resulting risk score was highly accurate (AUROC: 0.9150, 95%CI: 0.8509-0.9790) also in the internal and external validation series, but not better than the most widely used scores in hepatology: MELD (0.8335, 95%CI: 0.7486-0.9184), MELD-Na (0.8565, 95%CI: 0.7774-0.9356), iMELD (0.8972, 95%CI: 0.8297-0.9648) and MESO Index (0.8464, 95%CI: 0.7656-0.9272). The cutoff levels: LR+, LR- of the new score, MELD and MELD-Na that best predicted 30 days mortality were -0.09 (38.6, 0.51), 28 (16.7, 0.42) and 47 (12, 0.7), respectively.

**Conclusions:** MELD, as well as new, more complicated and scanty used scores, obtained 2 to 8 days after admission allows the early and easy identification of patients with an acute decompensation of cirrhosis at high-risk of death on short-term follow-up. These scores may represent a useful tool to select the population suitable for studies to evaluate the efficacy of new therapies and stratify patients in randomized trials.

**Keywords:** Liver cirrhosis; Liver failure; Clinical decision making; Prognostic factors

**Abbreviations:** ADS: Acute Decompensation Score; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; AUROC: Area Under the ROC Curve; GGT: Gamma-Glutamyl Transpeptidase; iMELD: Integrated Model for End-stage Liver Disease Model; INR: International Normalized Ratio for Prothrombin Time; LR: Likelihood Ratio; MARS: Molecular Adsorbent Recirculating System; MELD: Model for End-stage Liver Disease; MELD-Na: Model for End-stage Liver Disease-sodium score; MESO Index: Model for End-stage Liver Disease to Sodium; NPV: Negative Predictive Value; OLT: Orthotopic Liver Transplantation; PPV: Positive Predictive Value; ROC: Receiver Operating Characteristic; S: Sensitivity; SMT: Standard Medical Therapy; SOFA: Sepsis-related Organ Failure Assessment; Sp: Specificity

## Introduction

Patients with previously stable chronic liver disease often develop an acute deterioration in their liver function following a precipitating event, liver-related or not [1]. This clinical pattern is often reported as Acute-on-Chronic Liver Failure (ACLF) [2]. The most frequent and severe consequences of the acute decompensation are: hepatorenal syndrome (HRS), severe hepatic encephalopathy (HE), grade II or more, organ failure, other than the liver and, finally, multiple organ dysfunction; leading to death in 50 to 90% of these population [2-6].

Up to now, orthotopic liver transplantation (OLT) provides the only possible curative therapy for patients achieving this extremely severe liver dysfunction. Unfortunately, the precipitants leading to the acute deterioration: infection, acute bleeding, acute renal failure, surgical procedures, etc. often contraindicate an emergency liver transplantation.

Artificial liver support has been postulated as an effective therapy to bridge patients developing acute deterioration of cirrhosis to OLT in safe conditions [1]. Unfortunately, studies on the efficacy of albumin dialysis failed to demonstrate a beneficial effect of this therapy in the survival of the overall population of cirrhotic patients studied [7,8]. However, it seems plausible that some selected populations of ACLF patients, such as those at high-risk of death, would benefit from these new and expensive liver-support therapies [7,8].

The MELD score has been developed as a predictor of early (3-month) mortality in patients after transjugular intrahepatic portosystemic shunt [9]. Actually, a slightly modified MELD score is used all over the world to allocate patients in liver transplant list since 2002 [10]. Several attempts have been done to improve the prognostic accuracy of the MELD score, including the recently introduced MELD-Na [11], iMELD [12] and MESO index [13] which incorporate serum sodium to the originally described MELD score. Regarding these prognostic scores, two main considerations have to be done: first, we don't know for sure its prognostic accuracy in a period of time shorter than 3 months, and we know that most of our acutely decompensated

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patients will die within this period; and second, these scores were initially developed to assess the survival prognosis in populations significantly different from patients developing severe liver dysfunction following a precipitating event, who hardly ever could be considered for immediate liver transplantation.

A recent study identified a new score, the CLIF-C ADs, as a prognostic score for 28-day survival in ACLF patients [14]. This score resulted more accurate than MELD in this setting. However, whereas hepatologists are very familiar with MELD score, the knowledge and using of this newly introduced score is scarce.

The aim of the present study was to identify an early and easily available prognostic score, new or already used: MELD, MELD-Na, iMELD or MESO index, to identify patients with previously compensated cirrhosis developing an acute deterioration of their liver disease and showing an extremely high risk of death at short-term follow-up.

## Patients and Methods

The study was developed in 3 phases according to the population studied. The sample population in which the initial study was developed consisted in 228 consecutive patients with previously known cirrhosis without hepatocellular carcinoma admitted to the Liver Unit at the Hospital Clinic of Barcelona because of an acute deterioration of liver disease from January 2004 through December 2005. All patients included had been previously followed as outpatients in our and other centers in Barcelona. Acute deterioration was defined as the presence of any of the following: jaundice, ascites and/or peripheral edema, hepatic encephalopathy or renal failure requiring hospital admission. We excluded 5 patients from this initial series, 2 because of concomitant AIDS and 3 who died during the first 48 hours after admission, precluding the obtention of complete baseline data.

Cirrhosis was previously diagnosed following liver biopsy or compatible clinical and imaging findings in all cases. Hepatocellular carcinoma was ruled out by ultrasonography performed within the previous 6 months after admission or during the present hospitalization.

The following data were recorded: date of birth, gender, etiology of liver disease, type of precipitant (any event, liver-related or not, occurring during the last 4 weeks before admission), Child-Pugh score, MELD, MELD-Na, iMELD and MESO index at admission (first 48h), analytical values (including albumin, aspartate aminotransferase or AST, alanine aminotransferase or ALT, gamma-glutamyl transpeptidase or GGT, alkaline phosphatase, bilirubin, creatinine, hemoglobin, leukocyte and platelet count, international normalized ratio or INR and serum sodium at admission and 2 to 8 days) duration of hospitalization and outcome at 30 days after the index admission.

The MELD score was calculated using the standard formula as follows [10]:  $11.2 \times \ln(\text{INR}) + 9.57 \times \ln(\text{creatinine, in mg/dl}) + 3.78 \times \ln(\text{bilirubin, in mg/dl}) + 6.47$ . No patient was on renal-replacement therapy at entry into the study. The MELD-Na score was calculated as described elsewhere [11]:  $\text{MELD} + 1.59 (135 - \text{Na, in mEq/L})$  with maximum and minimum sodium levels of 135 and 120 mEq/L, respectively. The iMELD equation was based on the MELD score, age and sodium [12]:  $\text{original MELD score} + (0.3 \times \text{age, in years}) - (0.7 \times \text{Na, in mEq/L}) + 100$ . The MESO index [13] was defined as  $[\text{MELD}/\text{Na (mEq/L)}] \times 100$ .

To verify the generalizability of the prognostic information obtained, we validated the model by applying it to two prospective and independent sets of patients: 64 consecutive patients admitted to the

Hospital Clínic of Barcelona from February 2006 to February 2007: internal validation sample; and 90 patients admitted to the Hospital Gregorio Marañón, Madrid, from December 2007 to August 2008: external validation sample. The latter group was chosen to assess geographic and methodologic transportability of our predictions. The two series consisted of patients with already known cirrhosis that were consecutively admitted due to an acute deterioration in specialized Liver Units. Again, we excluded patients with known hepatocellular or other cancer, patients with advanced HIV infection: C stadium, patients not surviving the first 48h after admission and those who received albumin dialysis to treat the current decompensation: 2 cases. Patients in both samples were also followed until death or 30 days after admission. No patient underwent OLT within 30 days of admission. The demographic data, clinical characteristics, liver and renal tests at admission of the three series of patients included in the study are shown in Table 1.

## Statistical methods

Results are expressed as means and standard deviation: SD, medians and range, odds ratios [95% CI] and frequencies and percentages (%) or as otherwise specified. We used the Fisher's exact test to compare

	All patients (n=382)	Sample population (n=228)	Internal validation (n=64)	External validation (n=90)	p*
<b>Age at admission (years)<sup>a</sup></b>	56 ± 11	57 ± 11	55 ± 11	55 ± 12	NS
<b>Etiology of cirrhosis (%)</b>					NS
Alcoholic	51	53	38	54	
HCV	22	22	28	19	
Alcohol + HCV	15	15	19	14	
Cryptogenic	7	6	8	6	
Others	5	4	4	7	
<b>Cause of acute decompensation (%)</b>					NS
Unknown	24	30	16	10	
Acute bleeding	27	23	25	39	
Infection	33	28	44	34	
Increased alcohol abuse	8	11	5	5	
Others	9	8	11	12	
<b>Biochemistry<sup>a</sup></b>					
Serum bilirubin (mg/dL)	6.2 ± 7.7	5.5 ± 6.1	7.7 ± 9.1	6.9 ± 10	NS
Serum creatinine (mg/dL)	1.5 ± 1.2	1.2 ± 0.7	1.5 ± 1.4	1.8 ± 1.4	0.001
Serum sodium (mEq/L)	133 ± 7	133 ± 6	131 ± 6	134 ± 8	0.031
INR	1.6 ± 0.6	1.5 ± 0.4	1.6 ± 0.4	1.9 ± 1	0.0001
MELD <sup>a</sup>	18.3 ± 7.7	16.6 ± 6.1	19.6 ± 8.1	21.5 ± 9.6	0.0001
MELD-Na <sup>a</sup>	21.3 ± 14.5	19.4 ± 12.4	26.1 ± 14	23 ± 18.4	0.002
iMELD <sup>a</sup>	41.9 ± 10.1	40.3 ± 8.3	44.8 ± 9.6	44.2 ± 13.3	0.0001
MESO index <sup>a</sup>	13.9 ± 6	12.5 ± 4.8	15.4 ± 6.2	16.2 ± 7.6	0.0001
Days for 2nd measurement <sup>b</sup>	4 (2-8)	5 (4-6)	5 (2-8)	4 (3-7)	NS

<sup>a</sup> Results expressed as mean ± SD

<sup>b</sup> Results expressed as median (range)

\* p is the result of the comparison of the 3 series included (ANOVA)

**Table 1:** Demographic, clinical and biochemical characteristics of patients included in the study.

categorical data, t-test for continuous variables and the Mann-Whitney test for ordinal and non-normally distributed variables. The Friedman non-parametric test was used when necessary. The missing values in the initial sample population were calculated using a linear regression model with available variables and were imputed for survival modeling. No values were missing in the two validation samples.

Logistic regression models were used to study the predictors of mortality. Variables significant on univariate testing with a p value less than 0.10 (except composed variables: MELD and MELD-based prognostic models) were included for the multivariate analysis. For the selection of the final model, we constructed Receiver Operating Characteristic (ROC) curves for the multivariate models, and we selected the model with the greater Area Under the ROC (AUROC curve). This model was named Acute Decompensation Score (ADS). The resulting actuarial probability of death was:  $p(\text{death}) = 1 / (1 + \exp(-1 \times \text{ADS}))$ .

We also calculated the AUROC for MELD, MELD-Na, iMELD and MESO index in the sample population to assess the accuracy of the four scores in predicting short-term mortality.

The optimal cutoff point for the ADS, MELD and MELD-Na, the most commonly used scores in Liver Units, were derived from the AUROC of these scores in the overall population studied and selected on the basis of sensitivity: S, specificity: Sp, positive predictive value: PPV, and negative predictive value: NPV to identify death at follow-up. The efficiency of the optimal cutoff point was assessed with the likelihood ratio: LR+ and LR-.

The analysis was performed using SAS version 9.1.3 software: SAS Institute Inc., Cary, NC, USA and the level of significance was established at 0.05: two-sided.

## Results

The precipitating event could not be identified in 68 out of 228 cases. In the remaining 160 cases, the precipitants were as follows: acute infection in 64 cases, acute gastrointestinal bleeding in 53 and high alcohol abuse in the previous days in 25 (Table 1). The remaining 18 patients presented different events responsible for the acute decompensation: abuse of drugs other than alcohol, acute renal failure due to diuretic therapy, traumatic lesions, elective orthopedic surgery, and severe epistaxis. More than one precipitating event was identified in few cases. The 228 patients were followed from their admission until death, liver transplantation, or 30 days after the index admission.

## Survival

From the sample population, 228 patients, 30 patients died (13.2%) during the 30-day follow-up and none were transplanted. Deaths in these 30 patients were related to multiorgan failure in 26 cases, refractory septic shock in 3 cases and cerebral death due to a brain abscess in the remaining patient. Sixteen (25%) and 25 (27.8%) patients from the internal and external validation samples, respectively, died during follow-up. This high mortality, greater than the initial series, was related to the severity of the liver disease in these two groups of patients, whose mean MELD, MELD-Na, iMELD and MESO index scores at admission were significantly higher than in the original sample population (Table 1). The causes of death in the internal and external validation samples were similar to those in the sample population: septic shock in 1 and 3 cases, respectively; esophageal rupture due to a misplaced balloon tamponade and invasive aspergillosis, one each; and multiorgan failure in the remaining cases.

## Development of the prognostic model

Table 2 shows the results of the univariate analysis in the sample population. In the multivariate analysis the following variables were identified as independent predictors of 30-day mortality: age at admission, bilirubin, creatinine, INR and serum sodium; all the analytical values obtained at 2 to 8 days from admission (median: 5 days; ranges: 4-6 days) (Table 3). These variables were used to calculate a specific risk score for death in this population.

**Acute decompensation score:**  $\text{ADS} = -3.87 + 0.114 (\text{Age at admission, years}) + 0.16 (\text{Bilirubin, mg/dL}) + 0.79 (\text{INR}) + 1.01 (\text{Creatinine, mg/dL}) - 0.07 (\text{Serum sodium, mEq/L})$ .

Afterward, we compared the AUROC for the new developed risk score as well as for MELD, MELD-Na, iMELD and MESO index scores, at the two time-frames previously defined in order to ascertain if it was necessary to wait for the subsequent analysis or if data obtained immediately after admission were efficient enough to identify patients at high risk of death.

Table 4 shows the prognostic accuracy of the ADS, MELD and its derivatives calculated as previously described in the sample population. As shown, almost all the scores showed a “satisfactory” value (AUROC = 0.7-0.8), although those using data from 2 to 8 days after admission

Parameter	Dead at 30 days, n=30	Alive at 30 days, n=198	p
Gender (Male / Female) (n)	17/13	136/62	0.19
Age at admission (years) <sup>a</sup>	63.2 ± 14.4	55.7 ± 10.4	0.002
Etiology of cirrhosis (n)			
(HCV/Alcohol/HCV+alcohol/Others)	7/7/12/4	22/60/90/26	0.3
Precipitating event			
(Absent / Present) (n)	10-Aug	63/134	0.91
Cause of acute impairment			
(Sepsis / Others) (n)	13/17	51/147	0.046
MELD at admission <sup>a</sup>	20.4 ± 7.3	16 ± 5.7	0.004
MELD-Na at admission <sup>a</sup>	27.2 ± 11.8	18.2 ± 12.1	0.001
iMELD at admission <sup>a</sup>	47.9 ± 7.6	30.1 ± 7.8	1
MESO index at admission <sup>a</sup>	15.6 ± 5.6	12.1 ± 4.5	0.002
Analytical values at admission <sup>a</sup>			
Serum sodium (mEq/L)	131 ± 6.2	133 ± 5.8	0.02
Serum creatinine (mg/dL)	1.5 ± 1.1	1.2 ± 0.7	0.35
INR	1.7 ± 0.5	1.5 ± 0.4	0.04
Bilirubin (mg/dL)	10.6 ± 11.4	4.8 ± 4.4	0.001
GOT (U/L)	167 ± 259	108 ± 94	0.001
GPT (U/L)	69 ± 49	68 ± 59	0.9
GGT (U/L)	103 ± 182	139 ± 205	0.2
Platelets (x10 <sup>9</sup> )	93 ± 43	100 ± 55	0.36
MELD 2nd measurement <sup>a</sup>	28.3 ± 9.1	17.2 ± 5.9	0.001
MELD-Na 2nd measurement <sup>a</sup>	41.2 ± 13.1	22 ± 10.4	0.035
iMELD 2nd measurement <sup>a</sup>	58.3 ± 11.5	40.6 ± 8.5	0.001
MESO index 2nd measurement <sup>a</sup>	22.4 ± 7.6	13.0 ± 4.8	0.001
Analytical values 2nd measurement <sup>a</sup>			
Serum sodium (mEq/L)	127 ± 7.7	133 ± 5.9	0.001
Serum creatinine (mg/dL)	2.4 ± 2.0	1.1 ± 0.6	0.001
INR	2.2 ± 1.2	1.6 ± 0.4	0.001
Bilirubin (mg/dL)	14.2 ± 13.4	4.8 ± 5.2	0.001

<sup>a</sup> Results expressed as mean ± SD

**Table 2:** Results of the univariate analysis in the initial series of 228 patients in which the prognostic model was developed (sample population) comparing survivors and not survivors 30 days after admission.

Parameter	Coefficient	Standard error	p value
Age at admission	0.114	0.03	0.0001
Serum sodium (2nd measurement)	-0.07	0.044	0.109
Serum creatinine (2nd measurement)	1.014	0.293	0.001
INR (2nd measurement)	0.79	0.446	0.076
Serum bilirubin (2nd measurement)	0.161	0.04	0.0001

**Table 3:** Variables showing prognostic significance of 30-day mortality in the multivariate analysis (sample population).

At Admission	ADS	MELD	MELD-N <sup>a</sup>	iMELD	MESO index
<b>Sample population</b>					
AUC	0.7636	0.6652	0.7107	0.7865	0.6739
(95% CI)	(0.6420-0.8853)	(0.5533-0.7772)	(0.6155-0.8060)	(0.7028-0.8701)	(0.5665-0.7813)
<b>Internal validation</b>					
AUC	0.8942	0.7845	0.8616	0.9007	0.8457
(95% CI)	(0.7827-1.0057)	(0.6316-0.9374)	(0.7662-0.9570)	(0.8032-0.9983)	(0.7250-0.9663)
<b>External validation</b>					
AUC	0.8492	0.8563	0.7305	0.8086	0.844
(95% CI)	(0.7543-0.9441)	(0.7733-0.9393)	(0.6172-0.8438)	(0.7106-0.9066)	(0.7578-0.9302)
2nd Determination	ADS	MELD	MELD-Na	iMELD	MESO index
<b>Sample population</b>					
AUC	0.915	0.8335	0.8565	0.8972	0.8464
(95% CI)	(0.8509-0.979)	(0.7486-0.9184)	(0.7774-0.9356)	(0.8297-0.9648)	(0.7656-0.9272)
<b>Internal validation</b>					
AUC	0.9275	0.9219	0.913	0.9609	0.9391
(95% CI)	(0.8423-1.0127)	(0.834-1.0098)	(0.8205-1.0056)	(0.9003-1.0214)	(0.8659-1.0123)
<b>External validation</b>					
AUC	0.8234	0.8809	0.7618	0.8394	0.8745
(95% CI)	(0.7238-0.923)	(0.7979-0.9639)	(0.6406-0.8831)	(0.7443-0.9345)	(0.7894-0.9595)

**Table 4:** Comparison of the prognostic value of the ADS, MELD, MELD-Na, iMELD and MESO index at admission and at 2<sup>nd</sup> measurement (2<sup>nd</sup>) in the sample population.

achieved “excellent” results (AUROC = 0.8-0.9). Among the latter, the most “precise”, with AUROC>0.9 was ADS [15].

We validated the model by applying it to the two prospective and independent sets of patients. Again, the prognostic accuracy of the ADS obtained shortly after admission was excellent for both internal and external validation series (Table 4).

It should be emphasized that the prognostic value of MELD and MELD-Na in the validation samples, with patients more severely impaired than the initial series, was excellent or precise. Moreover, there were no significant differences in the predictive value for early death between the scores analyzed. That is why we decided to focus on the prognostic value of MELD, the most simple and widely used score to stratify patients with cirrhosis. In this sense, we calculated the 30-day risk of death according to the MELD value measured at 2 to 8 days from admission (Table 5).

**Identification and characteristics of the population at high risk for death:** Table 6 shows the optimal cutoff point for the ADS according to its AUROC to identify patients at high risk of death at follow-up in the overall population studied. We also calculated the optimal cutoff for the most commonly used prognostic scores in this population, MELD and MELD-Na. As shown, patients with an ADS

≥ 0.09 (corresponding to a probability of 30-day mortality of 48%), a MELD score ≥ 28 or a MELD-Na score ≥ 47, were those at highest risk of death on follow-up.

Thus, we decided to analyze the characteristics of the patients in the “high-risk” group by using the MELD score. Table 7 shows the characteristics of high-risk patients in comparison to low-risk patients. High-risk patients represent 14% (53/382) of the overall series of patients. As expected, patients in the high-risk group had a worse liver and renal function than those in the low-risk group. Interestingly, sepsis was more frequently identified as the acute precipitant of liver decompensation in patients at high-risk of death than in the low-risk population (41 Vs 31%; p=0.01).

The mortality rate in patients having a MELD score ≥ 28 was extremely high, 79% (42/53). Figure 1 shows the actuarial probability of survival of patients at high risk of death as compared to those with low-risk (MELD score<28).

## Discussion

Patients developing an acute and severe decompensation of a previously compensated cirrhosis have an extremely bad prognosis

MELD score	Expected mortality (%)
8	0.7
9	0.9
10	1.2
11	1.6
12	2
13	2.6
14	3.4
15	4.3
16	5.5
17	7
18	8.9
19	11.3
20	14.2
21	17.6
22	21.7
23	26.4
24	31.8
25	37.6
26	43.9
27	50.3
28	56.8
29	63
≥30	68.8

**Table 5:** Expected mortality according to the MELD score obtained 2 to 8 days after admission in the whole series of patients.

Score	OCP	LR+/LR-	S (% , 95%CI)	Sp (% , 95%CI)	PPV (%)	NPV (%)
ADS score	-0.09	38.6/0.51	50 (37.8 to 62.2)	98.7 (96.7 to 99.7)	89.7	89.7
MELD	28	16.7/0.42	59.2 (46.8 to 70.7)	96.5 (93.8 to 98.2)	79.3	91.2
MELD-Na	47.3	16.2/0.67	31.4 (20.3 to 43.7)	98.1 (78.6 to 99.3)	78.6	86.3

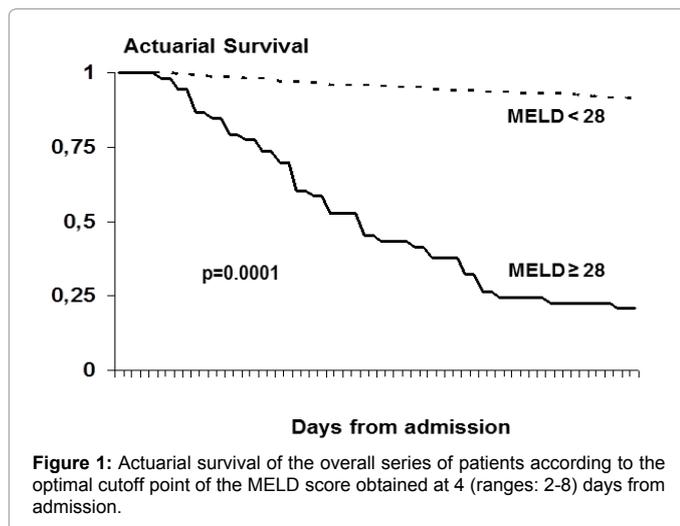
LR: Likelihood Ratio

**Table 6:** Optimal cutoff points (OCP) for ADS, MELD and MELD-Na obtained 2 to 8 days after admission derived from their AUROC in the overall population studied and selected on the basis of sensitivity (S), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) to identify death at follow-up.

Parameter	High-risk (n=53)	Low-risk (n=329)	p
Gender (Male / Female) (n)	32/21	196/133	0.91
Age at admission (years) <sup>a</sup>	55 ± 12	56 ± 11	0.62
Cause of acute impairment (Sepsis / Others) (n)	32/21	95/234	0.0001
Death at 30 days (yes/no) (n)	42/11	29/300	0.0001
Days from admission to death (in patients dying on follow-up) <sup>a</sup>	26 ± 39	55 ± 87	0.018
ADS at admission <sup>a</sup>	0.3 ± 1.8	-2.4 ± 1.1	0.0001
MELD at admission <sup>a</sup>	28.8 ± 8	16.6 ± 6	0.0001
MELD-Na at admission <sup>a</sup>	36.7 ± 13.6	18.9 ± 13.1	0.0001
iMELD at admission <sup>a</sup>	54.6 ± 8.9	39.9 ± 8.7	0.0001
MESO index at admission <sup>a</sup>	22.5 ± 6	12.5 ± 4.8	0.0001
ADS at 2 <sup>nd</sup> determination <sup>a</sup>	1 ± 2.6	-3.8 ± 1.8	0.0001
MELD at 2 <sup>nd</sup> determination <sup>a</sup>	34.4 ± 4.5	16 ± 5.1	0.0001
MELD-Na at 2 <sup>nd</sup> determination <sup>a</sup>	44.9 ± 13.9	18.8 ± 12.7	0.0001
iMELD at 2 <sup>nd</sup> determination <sup>a</sup>	59.8 ± 8.4	39.5 ± 8.5	0.0001
MESO index at 2 <sup>nd</sup> determination <sup>a</sup>	26.5 ± 4.1	12.3 ± 4.1	0.0001

<sup>a</sup> Results expressed as mean ± SD

**Table 7:** Characteristics of the patients according to the risk of death at follow-up. High-risk patients were defined as those having a MELD score ≥ 28 at 4 (range: 2-8) days from admission.



**Figure 1:** Actuarial survival of the overall series of patients according to the optimal cutoff point of the MELD score obtained at 4 (ranges: 2-8) days from admission.

mainly because the scarcity of therapeutic options. In fact, liver transplantation was the only possible curative therapy in this population. Unfortunately, the precipitants leading to the acute decompensation: infection, acute bleeding, acute kidney injury, etc often preclude and/or postpone an emergency liver transplantation.

Liver-support therapies, mainly albumin dialysis, have been recently introduced as potentially effective therapies to bridge cirrhotic patients developing a severe acute decompensation to OLT, thus raising new hopes for this distressing scenario [1].

There are 2 RCT of albumin dialysis in patients with an acute decompensation of a previously known chronic liver disease [7,8]. Unfortunately, the two studies had negative results in the overall population of patients included. Nevertheless, the results allowed identifying some patients in whom albumin dialysis would be effective [7,8]. It is unknown if albumin dialysis could improve its results in these subgroups of patients by selecting and treating patients at early stages of their diseases.

Several scores had shown accuracy identifying high-risk patients in these conditions. In a previous study from Wehler et al. in 143 patients with cirrhosis admitted in an ICU due to medical reasons, a SOFA (Sepsis-related Organ Failure Assessment) score higher than 8 at 24-hour from admission was associated with a 12% actuarial probability of survival as compared to a 96% survival in patients having a SOFA score lower than 8 [6]. Despite these excellent results, the use of the SOFA score has not become generalized in the non-intensive care environment. Moreover, a new score had been recently introduced in the evaluation of risk of death in ACLF patients, the CLIF-C ADS, however its use is up to now far from being generalized.

The MELD score [9,10] has been specifically designed for patients with liver disease and it's widely used in the liver units to establish the priority for liver transplantation. In this study we investigated the value of newly determined: ADS, and already used: MELD and MELD-Na scores, allowing the clear and early identification of patients at high risk of 30-day mortality after an acute decompensation of previously known liver cirrhosis.

Our results showed that ADS, MELD and MELD-Na represent an easy, reproducible and early way to identify patients at high risk of death after developing an acute liver dysfunction. In addition, it allows quantifying the risk of death and consequently calculating the sample size needed to achieve a determined improvement in survival in a previously characterized population. Considering that the new score, as well as the scanty used MELD-Na, had accuracy close to that of the widely and well known MELD score, we recommend the use of the latter to identify those cirrhotic patients at high-risk of death on short-term follow-up following a precipitating event.

It is important to point out that all the analyzed scores were better at assessing prognosis at subsequent determinations than at admission. We can speculate that it relates to the fact that analytical values at admission not only depend on the degree of liver damage but also on the consequences of the precipitant event, usually reversible by adequate therapy. On the contrary, values at 2 to 8 days: may closely reflect the amount of liver insufficiency after the resolution, or at least initial treatment, of the precipitant.

Following these arguments, we have identified a MELD score ≥ 28 as the optimal cutoff point to discriminate patients actually presenting a high risk of death.

High-risk patients represented the 14% of the overall population and showed an extremely poor survival rate at 30 days: 21%. Interestingly, sepsis was identified as the precipitating event leading to acute decompensation of liver disease in 41% of the high-risk patients Vs 31% of those at low risk of dying. As already known, sepsis may induce multiple organ failure in cirrhosis as a result of a large hyperproduction of pro-inflammatory cytokines and nitric oxide during infection. The imbalance between pro and anti-inflammatory cytokines may trigger the development of liver failure: by hepatocyte death, circulatory failure (worsening an already hyperdynamic circulation), renal failure (by either arterial underfilling leading to hepatorenal syndrome or acute tubular necrosis), respiratory failure (caused by acute respiratory distress syndrome), coagulation failure (by tissue factor activation and further decrease in coagulation factors and platelet count) and neurological failure (by inducing hepatic encephalopathy) [16]. Thus, cirrhotic patients admitted due to sepsis of any origin must be closely monitored to early identify predictors of bad evolution.

In summary, we have proved the prognostic accuracy of a new prognostic score but also of MELD and MELD-Na, obtained early after

patient admission, to assess the short-term survival of cirrhotic patients admitted due to an acute decompensation of their liver disease. These scores may represent a useful tool to select the population suitable for studies to evaluate the efficacy of new therapies and stratify patients in randomized trials.

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