MELD Score and Clinical Type Predict Prognosis in Hepatorenal Syndrome: Relevance to Liver Transplantation

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Important progress has been made recently regarding the pathogenesis and treatment of hepatorenal syndrome (HRS). However, scant information exists about factors predicting outcome in patients with cirrhosis and HRS. Moreover, the prognostic value of the model of end-stage liver disease (MELD) score has not been validated in the setting of HRS. The current study was designed to assess the prognostic factors and outcome of patients with cirrhosis and HRS. The study included 105 consecutive patients with HRS. Forty-one patients had type 1 HRS, while 64 patients had type 2 HRS. Patients with type 1 HRS not only had more severe liver and renal failure than type 2 patients, they also had greater impairment of circulatory function, as indicated by lower arterial pressure and higher activation of vasoconstrictor factors. In the whole series, the median survival was 3.3 months. In a multivariate analysis of survival, only HRS type and MELD score were associated with an independent prognostic value. All patients with type 1 HRS had a high MELD score (≥20) and showed an extremely poor outcome (median survival: 1 mo). By contrast, the survival of patients with type 2 HRS was longer and dependent on MELD score (≥20, median survival 3 mo; <20, median survival 11 mo; $P < .002$). In conclusion, the outcome of patients with cirrhosis and HRS can be estimated by using two easily available variables, HRS type and MELD score. These data can be useful in the management of patients with HRS, particularly for patients who are candidates for liver transplantation. (HEPATOLOGY 2005;41:1282-1289.)

The knowledge regarding hepatorenal syndrome (HRS) has experienced a great expansion in recent years. There are now a widely accepted definition and consensus-based diagnostic criteria[1]; a pathogenic link between circulatory dysfunction and renal vasoconstriction has been clearly established[2-4]; effective methods for the prevention of HRS in specific settings (*i.e.*, spontaneous bacterial peritonitis or severe alcoholic hepatitis) have been reported[5,6]; and, finally, therapeutic methods effective in improving renal function have been introduced, particularly the administration of vasoconstrictors associated with intravenous albumin.[7-12]

One aspect of HRS that has not been specifically addressed in recent years is how to assess prognosis in patients with HRS. This information is particularly relevant to establish priority for patients who are candidates for liver transplantation. Most of the existing information on outcome and prognostic factors in patients with HRS is derived from studies performed years ago, long before the introduction of the new diagnostic criteria and classification of HRS into two distinct clinical types, type 1 and type 2, in 1996.[13-15] Moreover, no information exists on the usefulness of the recently introduced model of end-stage liver disease (MELD) score in the assessment of prognosis of patients with HRS. Because this score is used now in many countries for organ allocation in liver transplantation for patients with cirrhosis,[16-21] this informa-

Abbreviations: HRS, hepatorenal syndrome; MELD, model for end-stage liver disease; ROC, receiving operating curve.

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tion may be of clinical relevance. Therefore, the aim of the current study was to investigate factors predicting outcome of patients with cirrhosis and HRS.

Patients and Methods

Study Population. Data from all patients with cirrhosis and HRS admitted to the Liver Unit of the Hospital Clínic (Barcelona, Spain) since 1992 were incorporated into a database that included demographic, clinical, biochemical, and neurohormonal parameters as well as outcome. The current study reports on the 105 consecutive patients included in the database between January 1992 and December 2001. All of these patients were included in prospective clinical studies investigating the pathogenesis and/or treatment of HRS.[7,10,12,22-24] The institutional review board approved the studies, and patients gave informed consent to participate. Most patients were followed prospectively in the outpatient clinic after discharge from the hospital, because survival was an end point of most of these investigations. Only 7 patients were lost to follow-up at different time points after discharge from the hospital. HRS was defined according to consensus-based diagnostic criteria proposed by the International Ascites Club in 1996 and was classified as type 1 or type 2. Type 1 involves a rapidly progressive renal failure defined as doubling of serum creatinine reaching a level greater than 2.5 mg/dL in less than 2 weeks; type 2 HRS is defined as a moderate and stable renal failure not meeting the previous criteria.[1]

Because the current study includes patients diagnosed before the publication of the International Ascites Club criteria, the clinical records of all patients diagnosed with HRS before 1996 were carefully reevaluated, and patients who did not fulfill the criteria were not included in the study. All patients were evaluated following a similar protocol, with the collection of clinical, exploratory, and analytical data, including standard liver and renal function tests. In addition, a large proportion of patients had measurements taken of plasma levels of vasoactive factors involved in the pathogenesis of HRS—including the renin-angiotensin-aldosterone system, the sympathetic nervous system, atrial natriuretic peptide, arginine vasopressin, and endothelin—and assessment of glomerular filtration rate was performed using sensitive methods (insulin or ^{125}I-iothalamate clearances). In all cases, blood samples for analytical and hormonal determinations were obtained after patients underwent diuretic withdrawal and were placed on a low-sodium diet using methods described in detail elsewhere.[25-27] MELD score was calculated using the following formula: $3.8 \times \log_e(\text{bilirubin(mg/dL)}) + 11.2 \times \log_e(\text{INR}) + 9.6 \times \log(\text{creatinine(mg/dL)}) + 6.43$, which is available at www.mayoclinic.org/gi-rst/mayomodel5.html. A direct measurement of international normalized ratio was not available until 1997. In patients included from 1992 until 1997, international normalized ratio was calculated according the following formula: (prothombin time of patient/control prothrombin time)^{ISI}, ISI being the international sensitivity index for thomboplastin.[28]

All patients were managed with a similar treatment protocol including general supportive measures, and treatment of associated complications, such as infections, hepatic encephalopathy, and gastrointestinal bleeding. Since 1995, 47 patients received specific therapies aimed at improving renal function (either vasoconstrictors, ornipressin or terlipressin, with or without intravenous albumin [29 patients] or transjugular intrahepatic portosystemic shunt [18 patients]).

Statistical Analysis. The analysis of survival was calculated using the Kaplan-Meier method. Clinical and analytical variables were analyzed as possible predictors of survival in a univariate analysis, and survival curves were compared using the log-rank test. Although some patients with type 2 HRS developed type 1 HRS at different time intervals (median time: 90 d), only the clinical type of HRS at diagnosis was considered in the statistical analysis. A multivariate analysis of survival was performed using a Cox regression method. Patients treated with liver transplantation ($n = 15$) were included in the calculation of overall survival and were considered censored at time of surgery. However, these same patients were excluded from the analysis of predictive factors of survival, because transplantation modifies the natural history of HRS. Comparisons of variables between patients with type 1 and type 2 HRS were made using the Student t test for categorical data and the χ^2 test for continuous data. Statistical analysis was performed using SPSS version 10 for Windows (SPSS Inc., Chicago, IL). Results are expressed as the mean ± SEM. A P value of less than .05 was considered statistically significant. Comparison between receiving operating curves has been performed using the statistical package available at www.analyse-it.com. A logistic regression model has been used to estimate 3-month survival probability according to MELD score.

Results

Patient Characteristics. One hundred five patients with HRS were included in the study. Forty-five patients (43%) had alcoholic cirrhosis, and the remaining patients had nonalcoholic cirrhosis, mainly due to chronic hepatitis C virus infection. Most patients had severe liver failure as indicated by high serum bilirubin levels (5.4 ± 0.8

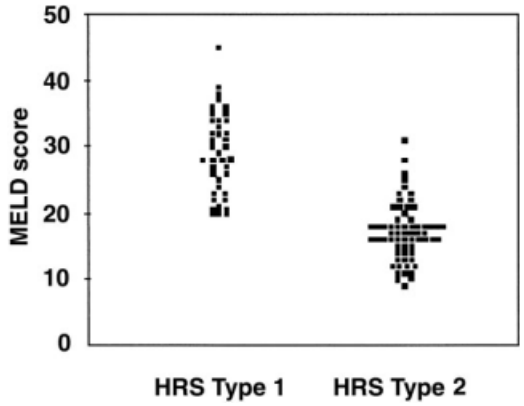

Fig. 1. Individual values of MELD score in all patients included according to the type of HRS (median: 28 and 17 for type 1 and type 2, respectively). MELD, model for end-stage liver disease; HRS, hepatorenal syndrome.

mg/dL), low serum albumin levels (28 ± 1 g/L), low prothrombin time (59% ± 1%), and high MELD (22 ± 2) and Child-Turcotte-Pugh scores (10 ± 0.1) scores. As expected, due to the definition of HRS, renal function was severely impaired, with very low glomerular filtration rates (19 ± 1 mL/min), high serum creatinine levels (2.6 ± 0.1 mg/dL), and low urine sodium levels (7 ± 1 mEq/L). Serum sodium levels were low, and a high proportion of patients (63%) had dilutional hyponatremia (serum sodium ≤130 mEq/L).[29] According to the definition of the International Ascites Club,[1] 41 patients had type 1 HRS and 64 had type 2 HRS. The relationship between HRS type and MELD score is shown in Fig. 1. All patients with type 1 HRS had a MELD score equal to or greater than 20. By contrast, patients with type 2 HRS showed a wide range of MELD scores (9-31), with 15 patients having a MELD score of 20 or more and 49 patients having a score lower than 20.

Survival and Prognostic Factors. During a median follow-up of 2.7 months (range: 0.1-68 mo), 78 patients (74%) died, 15 (14%) underwent liver transplantation, 7 (7%) were lost to follow-up, and only 5 were alive at the end of follow-up. The main causes of death were liver and renal failure in 49 patients, bacterial infections in 16, gastrointestinal bleeding in 7, and other causes in the remaining 6 patients (myocardial infarction in 1 patient, esophageal perforation in another, and unknown in the remaining 4 patients). In the whole population, the probability of survival 1, 3, and 6 months after diagnosis of HRS was 80%, 53%, and 41%, respectively, with a median survival of only 3.3 months. A total of 15 variables selected from the baseline characteristics were analyzed for their prognostic value. Variables associated with prognostic value were serum bilirubin, prothrombin time, MELD score, Child-Turcotte-Pugh score, serum creatinine, blood urea nitrogen, serum sodium, and HRS type (Table 1). Neither age, sex, cause of cirrhosis, treatment for HRS (either vasoconstrictors or transjugular intrahepatic portosystemic shunt), serum albumin, or urine electrolytes were associated with prognosis. In multivariate analysis, only HRS type and MELD score were associated with an independent prognostic value. The survival curves of patients included were classified according to HRS type and median MELD score and are shown in Fig. 2. The median survival in patients with type 1 HRS was 1 month, compared with 6.7 months in patients with type 2 HRS. The median survival in patients with a MELD score of 20 or more was 1 month, compared with 8 months in patients with a MELD score lower than 20. Figure 3 shows the long-term probability of survival of patients with type 2 HRS divided according to MELD score.

To further investigate the role of MELD score in predicting prognosis in patients with HRS, the relationship between MELD score and 3-month probability of survival for patients with type 1 and type 2 HRS was plotted and compared with that reported in a large population of patients with chronic liver disease who were on a waiting list for liver transplantation.[17] As shown in Fig. 4, the curves of patients with both type 1 and type 2 HRS were markedly shifted to the left, indicating that for a given MELD score, patients with HRS have a markedly lower 3-month probability of survival compared with that of the general population of patients awaiting liver transplantation. Besides, there were obvious differences between the curves of patients with type 2 versus those of patients with type 1 HRS. While in patients with type 2 HRS there was a progressive decline in survival with increasing MELD

Table 1. Variables Associated With Prognostic Value in the Univariate Analysis

Variable	Value*	Probability of Survival at 3 Months (%)	*P* Value
Bilirubin (mg/dL)	<3	74	<.001
	≥3	22	
Prothrombin time (%)	<60	29	<.001
	≥60	61	
Child-Turcotte-Pugh score	≤10	70	<.001
	>10	12	
Serum creatinine (mg/dL)	≤2	65	.003
	>2	29	
Blood urea nitrogen (mg/dL)	<60	60	<.001
	≥60	29	
Serum sodium (mEq/L)	≤130	38	.001
	>130	80	
MELD score	<20	77	<.001
	≥20	18	
Type of HRS	Type 1	10	<.001
	Type 2	70	

*The value used as the cutoff was the median value of each variable in the whole series of patients.

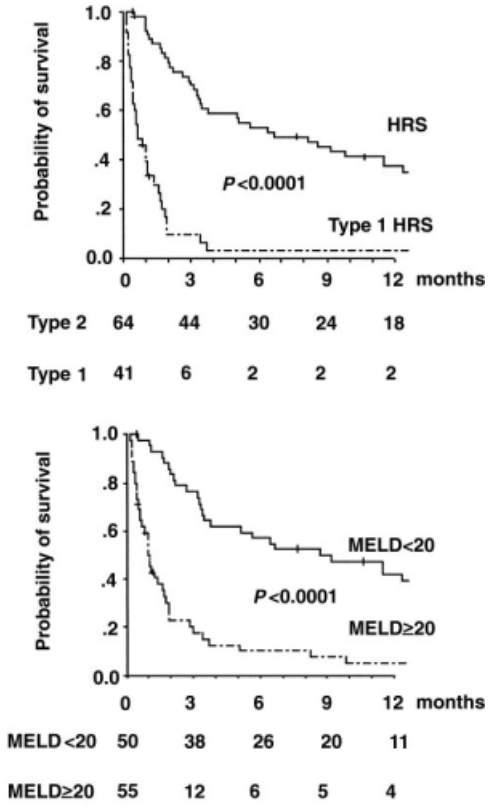

Fig. 2. Probability of survival of patients with HRS according to (A) HRS type and (B) MELD score (≥20 or <20). Values under the curve represent patients at risk at any given time point. HRS, hepatorenal syndrome; MELD, model for end-stage liver disease.

score, in patients with type 1 HRS the curve was almost flat, with only a small reduction in survival despite an increase in MELD score from 20 to 45.

Finally, to assess the extent to which the prognostic value of the MELD score was dependent on serum creatinine, the predictive accuracy of both the MELD score and serum creatinine were compared using ROCs for both parameters, with 3-month mortality as the end point. The ROC for the MELD score had a higher area under the curve (0.80, 95% CI: 0.72-0.88) with respect to the ROC for serum creatinine (0.71, 95% CI: 0.61-0.82) ($P = .05$) (Fig. 5). The optimal cutoff point of the MELD score to predict 3-month mortality was 20.

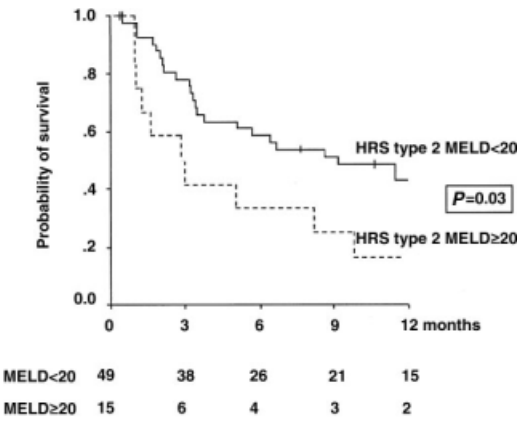

Fig. 3. Probability of survival of patients with HRS type 2 classified according to MELD score (≥20 or <20). Values under the curve represent patients at risk at any given time point. HRS, hepatorenal syndrome; MELD, model for end-stage liver disease.

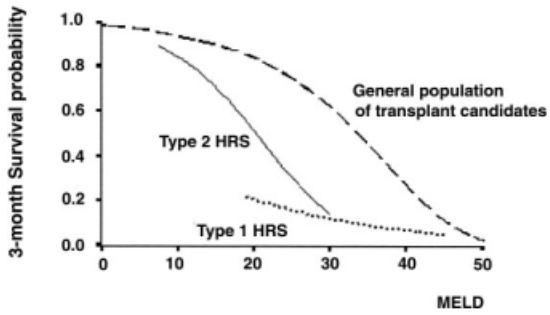

Fig. 4. Relationship between MELD score and estimated 3-month probability of survival in the current series of patients with HRS divided according to type of HRS: type 1 (dotted line) or type 2 (continuous line), and a series of 3,437 adult liver transplant candidates (dashed line). HRS, hepatorenal syndrome; MELD, model for end-stage liver disease. (Reprinted from Wiesner et al.,[17] with permission from the American Gastrointestinal Association.)

Comparison Between Patients With Type 1 and Type 2 HRS. To investigate differences between type 1 and type 2 HRS, variables obtained at diagnosis in both groups were compared (Table 2). As expected, due to the definition of type 1 and type 2 HRS, renal function tests were more severely impaired in patients with type 1 com-

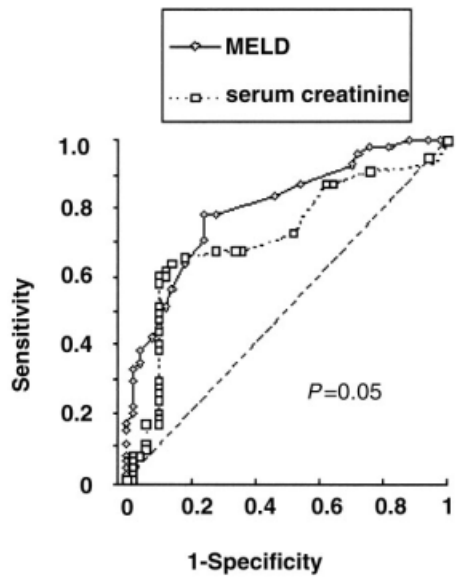

Fig. 5. The area under the ROC for the MELD score (continuous line) and serum creatinine (dotted line) with 3-month mortality as the end point ($P = .05$). The dashed line represents the ROC based on chance alone and has a c-statistic of 0.5.

Table 2. Demographic Data, Renal and Liver Function Tests, Arterial Pressure, and Vasoactive Factors in Patients With Type 1 and Type 2 HRS

Variables	HRS Type 1 (n = 41)	HRS Type 2 (n = 64)	*P* Value
Age	56 ± 2	61 ± 1	.02
Sex (M/F)	36/5	40/24	<.01
Alcoholic cirrhosis (yes/no)	19/22	26/38	NS
Serum albumin (g/L)	28 ± 0.1	30 ± 0.1	.03
Serum bilirubin (mg/dL)	9 ± 2	3 ± 0.6	<.01
Prothrombin time (%)	48 ± 3	66 ± 2	<.001
Child-Turcotte-Pugh score	11 ± 0.2	9 ± 0.1	<.001
MELD score	28 ± 1	17 ± 1	<.001
Blood urea nitrogen (mg/dL)	92 ± 4	52 ± 2	<.001
Serum creatinine (mg/dL)	3.9 ± 0.2	1.8 ± 0.1	<.001
Serum sodium (mg/dL)	122 ± 1	130 ± 1	<.001
Urine sodium (mEq/L)	3 ± 0.1	10 ± 2	.001
Glomerular filtration rate (mL/min)*	8 ± 2	27 ± 2	<.001
Serum potassium (mEq/L)	4.6 ± 0.2	4.8 ± 0.1	NS
Mean arterial pressure (mmHg)	71 ± 2	78 ± 2	<.01
Plasma renin activity (ng/mL × h)†	19 ± 3	13 ± 2	NS
Aldosterone (ng/dL)†	238 ± 27	179 ± 23	NS
Norepinephrine (pg/mL)‡	1166 ± 125	699 ± 73	<.01
Vasopressin (ng/L)‡	4 ± 0.4	3 ± 0.3	.01
Atrial natriuretic peptide (fmol/mL)‡	119 ± 16	57 ± 7	<.01
Endothelin (pmol/L)§	29 ± 4	21 ± 3	.06

Abbreviations: M, male; F, female; NS, not significant.
*Available in 20 patients with type 1 HRS and 25 patients with type 2 HRS.
†Available in 37 patients with type 1 HRS and 50 patients with type 2 HRS.
‡Available in 26 patients with type 1 HRS and 36 with type 2 HRS.
§Available in 20 patients with type 1 HRS and 25 with type 2 HRS.

pared with those with type 2. The impairment in liver function tests was also more marked in patients with type 1 compared with those of patients with type 2, as were MELD score and Child-Turcotte-Pugh score. Mean arterial pressure was markedly lower, and the plasma levels of norepinephrine, vasopressin, atrial natriuretic peptide, and endothelin were higher in patients with type 1 compared with values in patients with type 2. The activity of the renin-aldosterone system was also higher in patients with type 1 HRS versus type 2, although differences in plasma renin activity and plasma aldosterone levels did not reach statistical significance. Finally, patients with type 1 HRS were younger, and there was a predominance of males compared with patients with type 2 HRS.

Discussion

Since its description in 2000, the MELD score has rapidly gained popularity in the assessment of prognosis of patients with advanced cirrhosis and is now used in the United States as well as many other countries for organ allocation in liver transplantation in patients with cirrhosis.[16-19,30-34] The success of the MELD score is based not only on its accuracy in predicting prognosis, but also on the fact that it is objective, reproducible, and readily available in all settings. Its superiority over other existing prognostic indexes is likely due to the fact that it includes a variable that estimates the degree of renal dysfunction (serum creatinine), because renal function is known to accurately predict prognosis in patients with cirrhosis.[13,35-40]

So far, the value of the MELD score in predicting prognosis in patients with cirrhosis and HRS has not been assessed specifically. The results of the current study extend the observations of previous studies in patients without HRS by showing that the MELD score predicts prognosis in patients with HRS. In the current series of 105 consecutive patients with cirrhosis and HRS, the MELD score showed independent prognostic value among a large number of variables assessed. Patients with HRS and a MELD score lower than 20 had a median survival of 34 weeks, compared with only 4 weeks in patients with a MELD score of 20 or more. Nevertheless, despite this predictive value of MELD scores, it should be pointed out that patients with HRS had a survival expectancy much worse than would be predicted by a MELD score in other populations of patients with cirrhosis. In fact, as shown in Fig. 4, patients with HRS had a shorter survival expectancy for any given value of a MELD score than that of patients with chronic liver disease who were candidates for liver transplantation.[17] This would have to be taken into account when patients with HRS are listed for liver transplantation.

Patients with HRS are currently classified into two distinct clinical types (type 1 and type 2) according to the classification of the International Ascites Club.[1] This classification takes into consideration the intensity and quickness of the progression of renal failure and was proposed on the basis of findings from previous clinical studies describing the existence of a rapidly progressive form of functional renal failure as opposed to a steady or slowly progressive functional renal failure.[41] However, neither the prognostic value nor the pathogenic significance of this classification have been assessed. The results of the current study indicate that this classification is of major prognostic significance, because it reached prognostic value in a multivariate analysis of survival independently of MELD score. The reason for the prognostic value of HRS type may be related to the greater impairment of renal function of type 1 versus type 2 HRS, greater severity of circulatory failure, and/or other unknown factors. When the relationship between 3-month probability of survival and MELD score was calculated according to type of HRS (Fig. 4), it was found that patients with type 1 HRS had a very poor prognosis, which was almost independent of MELD score. By contrast, in patients with type 2 HRS, the outcome was dependent on MELD score, because 3-month probability of survival decreased exponentially with increasing MELD score values.

Considering the importance of the clinical type of HRS in predicting patient outcome, we also investigated differences between patients with type 1 and type 2 HRS. As shown in Table 2, patients with type 1 HRS had more severe liver failure compared with patients with type 2 HRS. Differences observed in renal function tests are obvious and derive from the criteria used to define the two different types of HRS. Both groups of patients had findings indicative of severe arterial underfilling, as assessed either directly by measuring arterial pressure, or indirectly measuring factors that are activated in response to arterial underfilling.[42] The main conclusions of the comparison of hemodynamic parameters are as follows. (1) Patients with type 1 HRS had lower mean arterial pressure, markedly higher levels of norepinephrine and vasopressin, and slightly higher—yet not statistically significant—plasma renin activity and plasma aldosterone levels compared with values in patients with type 2 HRS. Because the sympathetic nervous system, the renin-angiotensin system, and the release of vasopressin are activated in cirrhosis in response to arterial underfilling,[7,8,43-45] these data suggest a greater degree of arterial underfilling in type 1 HRS versus type 2 HRS. The greater activation of these factors would explain the increased severity of renal dysfunction in type 1 HRS, with lower glomerular filtration rate and more marked impairment of sodium and solute-free water excretion, the latter responsible for lower serum sodium levels. (2) Patients with type 1 HRS had higher circulating levels of endothelin compared with patients with type 2 HRS. Because endothelin is a potent renal vasoconstrictor and has been implicated in the pathogenesis of HRS,[46,47] these findings suggest a possible role of increased endothelin production in the extreme renal vasoconstriction characteristic of type 1 HRS. (3) The plasma levels of atrial natriuretic peptide, a peptide released from the heart with potent vasodilator properties, are markedly higher in patients with type 1 compared with those in patients with type 2 HRS. The actual pathogenic significance of increased atrial natriuretic peptide levels in cirrhosis is unknown, but a role as mediator of splanchnic arterial vasodilation or antagonist of the effects of vasoconstrictor systems in the kidney has been proposed.[48,49] Taken together, these findings indicate that changes in the systemic arterial circulation of patients with type 1 and type 2 HRS are qualitatively similar but of different intensity. In both settings, changes are indicative of the existence of an important arterial underfilling, which is extreme in patients with type 1 HRS. This is in keeping with recent findings indicating that patients with type 1 HRS, besides an important arterial vasodilatation, have an impairment in cardiac function.[50-52] Because cardiac output and systemic vascular resistance are the major determinants of effective arterial blood volume,[53,54] arterial underfilling in type 1 HRS could be the consequence of not only splanchnic arterial vasodilatation causing a reduction in systemic vascular resistance but also of an impaired cardiac output relative to the extremely dilated vascular bed.[55] This attractive hypothesis would require investigation in prospective studies that carefully evaluate circulatory and cardiac function in patients with HRS.

In conclusion, the results of this study show that MELD score and HRS type, which can be easily obtained in all patients and settings, are useful in estimating the prognosis of patients with cirrhosis and HRS. Interestingly, it was found that patients with HRS had a much worse outcome for any given MELD score than other cohorts of patients with cirrhosis who were awaiting liver transplantation. The information obtained can be useful in the management of patients with HRS, especially with respect to determining urgency of candidates for liver transplantation and design and analysis of clinical studies evaluating new therapies for HRS.

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