World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v7.i17.2119

World J Hepatol 2015 August 18; 7(17): 2119-2126
ISSN 1948-5182 (online)

Model for end-stage liver disease-Na score or Maddrey discrimination function index, which score is best?

Mercedes Amieva-Balmori, Scherezada María Isabel Mejia-Loza, Roberto Ramos-González, Felipe Zamarripa-Dorsey, Eli García-Ruiz, Nuria Pérez y López, Eumir I Juárez-Valdés, Adriana López-Luria, José María Remes-Troche

Mercedes Amieva-Balmori, Scherezada María Isabel Mejia-Loza, Roberto Ramos-González, Felipe Zamarripa-Dorsey, Eli García-Ruiz, Nuria Pérez y López, Eumir I Juárez-Valdés, Adriana López-Luria, Servicio de Gastroenterología, Instituto de Investigaciones Médico-Biológicas de la Universidad Veracruzana, Hospital Juárez de México, Ciudad de México 07760, México

José María Remes-Troche, Laboratorio de Fisiología Digestiva, Instituto de Investigaciones Médico-Biológicas de la Universidad Veracruzana, De La Veracruz 51356, México

Correspondence to: Mercedes Amieva-Balmori, MD, Servicio de Gastroenterología, Instituto de Investigaciones Médico-Biológicas de la Universidad Veracruzana, Hospital Juárez de México, Av. Instituto Politécnico Nacional 5160, Gustavo A. Madero, Magdalena de Las Salinas, Ciudad de México 07760, México. mercedesamieva@hotmail.com
Telephone: +52-55-57477560
Fax: +52-229-2021231

Author contributions: Amieva-Balmori M and Remes-Troche JM contributed to the outlining of the study, generation, collection, assembly, analysis and/or interpretation of data and writing and revision of the manuscript; Mejia-Loza SMI, Ramos-González R, López-Luria A, García-Ruiz E, Pérez y López N, and Juárez-Valdés EI contributed to the generation, collection, analysis and assembly of data; Zamarripa-Dorsey F contributed to the analysis and/or interpretation of data and writing and revision of the manuscript; all authors approved the final version of the manuscript.

Conflict-of-interest statement: Amieva-Balmori M, Mejia-Loza SMI, Ramos-González R, López-Luria A, García-Ruiz E, Pérez y López N, Juárez-Valdés EI and Zamarripa-Dorsey F do not have conflict of interest. José María Remes-Troche is member of the Advisory Board for Takeda Pharmaceuticals, Alfa-Wasserman, Almirall and Janssen. Also, he is Speaker for Nycomed-Takeda, Advance Medical, Endomedica, Astra-Zeneca and Bristol-Myers-Squibb.

Data sharing statement: No additional data are available.

Received: October 10, 2014
Peer-review started: October 13, 2014
First decision: December 17, 2014
Revised: June 24, 2015
Accepted: July 16, 2015
Article in press: July 17, 2015
Published online: August 18, 2015

Abstract

AIM: To compare the ability of model for end-stage liver disease (MELD)-Na and Maddrey discrimination function index (DFI) to predict mortality at 30 and 90 d in patients with alcoholic hepatitis (AH).

METHODS: We prospectively assessed 52 patients with AH. Demographic, clinical and laboratory parameters were obtained. MELD-Na and Maddrey DFI were calculated on admission. Short-term mortality was assessed at 30 and 90 d. Receiver operating characteristic curve analysis was performed.

RESULTS: Thirty-day and 90-d mortality was 44% and 58%, respectively. In the univariate analysis, sodium levels was associated with mortality at 30 and 90 d (P = 0.001 and P = 0.03). Child stage, encephalopathy, ascites, or types of treatment were not associated with mortality. MELD-Na was the only predictive factor for mortality at 90 d. For 30-d mortality area

under the curve (AUC) was 0.763 (95%CI: 0.63-0.89) for Maddrey DFI and 0.784 for MELD-Na (95%CI: 0.65-0.91, P = 0.82). For 90-d mortality AUC was 0.685 (95%CI: 0.54-0.83) for Maddrey DFI and 0.8710 for MELD-Na (95%CI: 0.76-0.97, P = 0.041).

CONCLUSION: AH is associated with high short-term mortality. Our results show that MELD-Na is a more valuable model than DFI to predict short-term mortality.

Key words: Alcoholic hepatitis; Model for end-stage liver disease-Na; Maddrey; Mortality

Core tip: Alcoholic hepatitis (AH) is a severe condition associated with high mortality. The model for end-stage disease (MELD) score is widely used to predict mortality in end-stage liver disease, and the addition of sodium (MELD-Na) increase its utility. However, few studies have evaluated the utility of MELD-Na in AH. In this study, we found that MELD-Na is useful for predicting 90-d mortality in patients with AH and preserve prognostic advantage over Maddrey discrimination function index score. It represents a valuable tool to stratify patients by risk, however further studies are required to validate the prognostic utility of MELD-Na score in patients with AH.

Amieva-Balmori M, Mejia-Loza SMI, Ramos-González R, Zamarripa-Dorsey F, García-Ruiz E, Pérez y López N, Juárez-Valdés EI, López-Luria A, Remes-Troche JM. Model for end-stage liver disease-Na score or Maddrey discrimination function index, which score is best? *World J Hepatol* 2015; 7(17): 2119-2126 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i17/2119.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i17.2119

INTRODUCTION

It is estimated that 6% of the Mexican population is dependent on alcohol which equals to 4.9 million people[1]. Chronic alcohol consumption is the leading cause of liver failure in our country, and alcohol intake > 120 g/d is a factor associated with the development of alcoholic hepatitis (AH)[1-3]. AH was first described by Gordon Beckett in 1961 and clinical description of the syndrome is still valid after 50 years[4]. This entity is an acute form of alcohol induced liver injury that is seen in patients who consume large quantities of alcohol during a prolonged period of time. Its spectrum is wide and ranges from a silent disease to fulminant liver failure with a high mortality rate. Patients with severe AH have been reported to have 30-d mortality up to 50%[5,6].

Therefore, assessment of the disease severity becomes an important and practical issue for clinicians involved in the management of patients with AH[6]. There are several prognostic models to assess severity in patients with AH including the Maddrey's discriminant function index (DFI)[7], the Glasgow AH score (GAHS)[8], the age- bilirubin- international normalized ratio (INR) - creatinine (ABIC) score[9], the Lille score[10] and the model for end-stage liver disease (MELD)[11]. Among the many scoring systems, the DFI is the most used. A score higher than 32 in the DFI is considered as a severe AH and mortality rates are close to 65% at 28 d[8,12]. Also, DFI allows identifying patients who may benefit from treatment with steroids[13]. However, some studies have shown that the cut-point of 32 of DFI could be inaccurate and higher cut-offs have been proposed (from 37 to 44)[12,14].

Although MELD score was designed for evaluation of patients awaiting liver transplantation[15], its use has been expanded and now, is used as a prognostic scale in various liver diseases such as AH[16,17], viral hepatitis[18], hepatocellular carcinoma[19] and autoimmune diseases[20]. As hyponatremia is associated with poor prognosis in cirrhosis, inclusion of serum sodium (Na) into the MELD (MELD-Na) was found to improve its predictive value in chronic liver diseases[21,22]. MELD-Na is more efficient than MELD to identify subjects with poor outcome and significantly increase the efficacy of the score to predict waitlist mortality[22].

Several studies have examined the use of MELD in assessing the severity of AH[12,16,17,23,24] and sensitivity and specificity in predicting 30-d mortality ranges from 75% to 86%. Few studies, have evaluated the usefulness of the MELD-Na in AH[24-26] and results are controversial.

As sodium abnormalities are close related to end stage liver disease conditions such as ascites and hepatorenal syndrome (HRS), we hypothesize that MELD-Na is better to predict short-term mortality in patients with AH compared to the Maddrey DFI (the most used score).

MATERIALS AND METHODS

Patients and procedures

We prospectively identified 52 patients admitted to our Gastroenterology Service (Hospital Juarez de Mexico, Mexico City, Mexico) between March 2011 and March 2013, with a diagnosis of AH and history of long alcohol consumption. The patients were diagnosed with AH based on the following clinical and biochemical characteristics: excessive alcohol consumption (> 100 g/d) at least 2 mo prior to admission, serum total bilirubin level above 5 mg/dL, aspartate/alanine aminotransferase ratio above 2, aspartate aminotransferase level below 300 IU/mL, history of longstanding alcoholism, and finally the absence of a coexistent primary cause of liver disease, such as viral hepatitis, drug induce liver diseases, non-alcoholic hepatitis, autoimmune hepatitis and hepatocellular carcinoma. Only patients with laboratory values available within 24 h of admission were included.

Data collection

The following data were obtained for all patients: age, sex, history of alcohol consumption, clinical complications at admission and during hospitalization [ascites, hepatic encephalopathy, renal failure (as defined as serum creatinine $\geqslant$ 1.5 mg/dL), HRS, bacterial infections and gastrointestinal bleeding]; length of hospital stay, treatment received and cause of death. The analytical parameters at admission or within 48 h of admission included serum glucose, cholesterol, triglycerides, sodium, albumin, aminotransferases, bilirubin and creatinine levels, blood urea nitrogen, INR, leukocyte count, neutrophil count, platelet count, and hematocrit.

Short-term mortality was assessed at 30 and 90 d. The Child-Turcotte-Pugh (CTP) score was calculated for all patients regardless the presence or absence of cirrhosis. Medical treatment was also assessed. Both, Maddrey DFI and MELD-Na scores were based on clinical and laboratory parameters collected at the time of diagnosis of AH. Maddrey DFI was calculated using the formula: DFI = 4.6 × (PTsec-control PTsec) + serum total bilirubin in mg/dL. MELD-Na score was calculated using the formula: 3.8 (log bilirubin mg/dL) + 11.2 (ln INR) + 9.6 (ln creatinine mg/dL) + 6.4 + 1.59 (135 - Na). Maddrey DFI and MELD-Na scores higher than 32 and 21, respectively, were considered as a more severe disease and associated with poor outcomes[6,8]. Patients received oral corticosteroids if they met the following criteria: a modified Maddrey's DFI > 32 or hepatic encephalopathy at admission, recent onset of jaundice, and biochemical changes suggestive of AH. Prednisone was given orally (40 mg/d) for 4 wk followed by a taper of 2-3 wk. Contraindications for corticosteroid treatment were severe bacterial infections, renal dysfunction, diabetes mellitus with poor metabolic control, and the presence of acute gastrointestinal bleeding. For those patients, pentoxifylline was prescribed 400 mg thrice/d.

Statistical analysis

Continuous variables were expressed as means with standard deviation and range. Categorical variables were expressed with percentage. χ^2 analysis was used to compare categorical variables, and continuous variables were analyzed using the Student *t*-test and Mann-Whitney. The primary end point was death from any cause at 30 and 90 d from hospital admission. With the significant prognostic variables obtained from the univariate analysis, multivariate logistic regression was carried out using forward selection model.

The accuracy of the MELD-Na score was compared with the Maddrey DFI score, through the analysis of their area under the receiver operating characteristic (AUROC) curve. Receiver operating characteristic (ROC) curves were generated to assess the prognostic utility of Maddrey DF and MELD score, evaluated by their ability to rank patients according to the risk of mortality at 30 and 90 d. An AUROC value of > 0.70 was considered clinically relevant. Comparison between AUROC curves was performed by the method of Hanley and McNeil[27] using MedCalc version 9.3.0.0. (Medisoftware, Mariakerke, Belgium). From ROC curves coordinates, cut-off points with best sensitivity and specificity of the different scores were determined. A *P* value less than 0.05 was considered statistically significant. Statistical interpretation of data was performed using statistical package for social sciences (SPSS) version 16.0 for Windows (SPSS, Inc., Chicago, Illinois, United States). The Institutional Review Board and the Ethics Committee approved this study.

RESULTS

Fifty two subjects met the inclusion criteria. Forty eight patients (92%) were males, and mean age was 42.8 ± 8.7 years. Mean alcohol consumption per day was 283 g and mean days of continuous alcohol consumption prior to admission was 24 d. Thirty eight patients (73%) developed ascites and 24 (46%) encephalopathy. A concomitant infection process was detected in 16 (31%) of the patients; 7 (44%) had a urinary tract infections and 5 (31%) spontaneous bacterial peritonitis, and 4 (25%) had both urinary tract infection and spontaneous bacterial peritonitis. At admission mean MELD score was 30.8 ± 3.3, MELD-Na was 27.5 ± 7.7 (range, 12 to 48) and Maddrey DFI values was 79.7 ± 54 (range, 13 to 321). Specific treatment for AH was used in 75% (*n* = 39) of patients: pentoxifylline was used in 48% (*n* = 25), prednisone alone was used in 17% (*n* = 9), and 10% (*n* = 5) received prednisone in combination with pentoxyfylline.

Mortality rate at 30 d was 44% (*n* = 23), and the attributable causes were: multiple organ failure in 44% (*n* = 10), renal insufficiency from HRS in 44% (*n* = 10) and gastrointestinal hemorrhage in 13% (*n* = 3). Mortality rate at 90 d was 57.6% (*n* = 30) and multiple organ failure occurred in 47% (*n* = 13), renal insufficiency from HRS in 40% (*n* = 12) and gastrointestinal hemorrhage in 13% (*n* = 5). The variables that were significantly associated with 30-d and 90-d mortality in the univariate analysis are presented in Tables 1 and 2.

Lower sodium levels (*P* = 0.019), higher total bilirubin levels (*P* = 0.018), higher creatinine levels (*P* = 0.001), Child class C (*P* = 0.023), development of HRS (*P* = 0.001) and a higher MELD-Na (*P* = 0.003) were significant factors associated with 30-d mortality. Lower sodium levels (*P* = 0.03), higher total bilirubin levels (*P* = 0.009), higher creatinine levels (*P* = 0.01), higher INR (*P* = 0.002), higher prothrombin time (*P* = 0.0003), lower cholesterol levels (*P* = 0.01), Child class C (*P* = 0.05), development of HRS (*P* = 0.05) and a higher MELD-Na (*P* = 0.01) were significant factors associated with 90-d mortality. Treatment with specific medication, development of infections or gastrointestinal bleeding did not influence survival.

In the multivariate logistic regression, HRS was the strongest and independent predictor of mortality at 30-d (*P* = 0.001). MELD-Na was a predictor of mortality at 90-d (*P* = 0.036) (Table 3). No additional variables

Table 1 Univariate analysis between survived and deceased patients at 30 d

Variables	Survived (n = 29)	Deceased (n = 23)	P
Demographic			
Age (yr)	40 ± 9.6	44 ± 12	0.114
Alcohol consumption per day (g/d)	291 ± 140	302 ± 159	0.809
Male, n (%)	28 (97)	20 (87)	0.222
Laboratory parameters at admission			
White blood cell counts (10^3/μL)	17362 ± 9807	21772 ± 10131	0.11
Glucose (mg/dL)	102 ± 49	102 ± 61	0.987
Sodium (mmol/L)	132 ± 6	128 ± 6	0.019[a]
Total bilirubin (mg/dL)	17.3 ± 8.9	23.6 ± 9.4	0.018[a]
AST (IU/L)	172 ± 111	189 ± 93	0.55
ALT (IU/L)	66.9 ± 40.5	71.5 ± 33	0.66
γGT (IU/L)	369 ± 254	291 ± 183	0.282
Alkaline phosphatase (IU/L)	254 ± 109	222 ± 112	0.344
Creatinine (mg/dL)	1.61 ± 1.5	3.5 ± 2.5	0.001[a]
INR	2.05 ± 0.6	2.49 ± 1.48	0.079
Prothrombin time (s)	23.14 ± 8.1	27.2 ± 11.2	0.142
Albumin (mg/dL)	2.8 ± 0.5	2.5 ± 0.6	0.73
Cholesterol (mg/dL)	150.8 ± 68	116 ± 53	0.081
Triglycerides (mg/dL)	222 ± 122	230 ± 178	0.869
Calcium (mg/dL)	7.9 ± 0.7	7.5 ± 1.1	0.10
Clinical manifestations at admission			
Ascites, n (%)	25 (86)	22 (95)	0.468
Child status			0.023[a]
Grade B, n (%)	6 (20)	0	
Grade C, n (%)	23 (80)	23 (100)	
Encephalophaty, n (%)			0.335
None	13 (45)	7 (30)	
Stage Ⅰ	4 (14)	5 (22)	
Stage Ⅱ	8 (28)	10 (43)	
Stage Ⅲ	4 (14)	1 (4)	
Hepatorenal syndrome, n (%)	5 (17)	14 (61)	0.001[a]
Severity of liver disease at admission			
MELD-Na score	25.5 ± 8	31.9 ± 6	0.003[a]
Maddrey DFI	69.4 ± 42	93 ± 53.8	0.08
MELD	32.1 ± 6.5	25.1 ± 2.9	0.79

[a]P < 0.05 *vs* survived patients at 30 d. MELD: Model for end-stage liver disease; DFI: Discrimination function index; INR: International normalized ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; γGT: Gamma glutamyl transpeptidase.

increased the predictive accuracy of MELD-Na (bilirubin, INR, and creatinine, as factors included in Maddrey DF and/or MELD score, were excluded from the analysis).

A clinical utility analysis was performed using the pre-established cut-off values for Maddrey DFI and MELD-NA (> 32 and > 21, respectively) and considering death at 30 and 90 d as the outcome. Sensitivity, specificity, positive predictive values, negative predictive values and accuracy are shown in Table 4. Receiver operating characteristic curves were created in order to estimate the predictive accuracy of the different scores to evaluate 30-d and 90-d mortality (Figure 1). For 30-d mortality the area under the curve (AUC) was 0.763 (95%CI: 0.63-0.89) for Maddrey DFI and 0.784 for MELD-Na (95%CI: 0.65-0.91, P = 0.82). For 90-d mortality the AUC was 0.685 (95%CI: 0.54-0.83) for Maddrey DFI and 0.8710 for MELD-Na (95%CI: 0.76-0.97, P = 0.041).

DISCUSSION

Excessive alcohol consumption is a social problem in Mexico and it has been estimated that alcohol related liver diseases (ALD) are responsible to approximately 9% of all diseases in Mexico[28]. A subset of patients with ALD will develop severe AH (AH), which has a substantially worse short-term prognosis[29]. The true prevalence is unknown, but histologic studies of patients with ALD suggest that AH may be present in as many as 10%-35% of hospitalized alcoholic patients[30,31].

Although a recent publication reported that the inpatient mortality rate in AH has decreased in the United States (from 10.07% in 2002 to 5.76% in 2010), in this cohort of Mexican patients with AH we found a high mortality rate, 44% at 30 d and 57.6% at 90 d[32]. Our results are similar to that reported in a recent multicentric study in Mexico in 175 patients with AH, where overall and 90-d mortality rate were 36% and 51%, respectively[3]. Similar to other cohorts, we found that most common causes of mortality were portal hypertension and HRS. This increased mortality rate could be explained by socioeconomic factors, quality of health services, higher amount of alcohol consumption in Mexican patients, as well as genetic factors[3,29]. For

Table 2 Univariate analysis between survived and deceased patients at 90 d

Variables	Survived (n = 22)	Deceased (n = 30)	P
Demographic			
Age (yr)	41 ± 9	44 ± 11	0.27
Alcohol consumption per day (g/d)	284 ± 148	303 ± 143	0.584
Male, n (%)	21 (95)	27 (90)	0.94
Laboratory parameters at admission			
White blood cell counts (10^3 /μL)	284 ± 148	303 ± 143	0.584
Glucose (mg/dL)	108 ± 59	99 ± 49	0.55
Sodium (mmol/L)	133 ± 5	129 ± 6	0.03[a]
Total bilirubin (mg/dL)	16 ± 8	22 ± 10	0.009[a]
AST (IU/L)	192 ± 137	177 ± 84	0.61
ALT (IU/L)	103 ± 150	67 ± 39	0.24
γGT (IU/L)	577 ± 656	399 ± 480	0.29
Alkaline phosphatase (IU/L)	281 ± 91	211 ± 105	0.01[a]
Creatinine (mg/dL)	2 ± 1.8	3 ± 2.11	0.01[a]
INR	2 ± 0.4	3 ± 1.3	0.002[a]
Prothrombin time (s)	19 ± 4	28 ± 12	0.0003[a]
Albumin (mg/dL)	3 ± 0.5	3 ± 5	0.54
Cholesterol (mg/dL)	176 ± 90	119 ± 51	0.01[a]
Triglycerides (mg/dL)	240 ± 163	226 ± 162	0.76
Calcium (mg/dL)	7.9 ± 0.8	7.3 ± 1.5	0.28
Clinical manifestations at admission			
Ascites, n (%)	19 (86)	28 (93)	0.71
Child status			0.05[a]
Grade B, n (%)	8 (37)	3 (10)	
Grade C, n (%)	14 (63)	27 (90)	
Encephalophaty, n (%)	0 (0)		
None	10 (45)	0 (30)	0.106
Stage Ⅰ	8 (37)	3 (10)	
Stage Ⅱ	4 (18)	19(63)	
Stage Ⅲ		8 (26)	
Hepatorrenal syndrome, n (%)	5 (22)	16 (53)	0.05[a]
Severity of liver disease at admission			
MELD-Na score	24.95 ± 8	30.9 ± 7.79	0.01[a]
Maddrey DFI	68.5 ± 42	88.3 ± 48.6	0.12
MELD	22.1 ± 7.5	23.1 ± 3.1	0.28

[a]P < 0.05 *vs* survived patients at 90 d. MELD: Model for end-stage liver disease; DFI: Discrimination function index; INR: International normalized ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; γGT: Gamma glutamyl transpeptidase.

Table 3 Variables with significance in the multivariate logistic regression analysis

	Significance	Odds ratio	95%CI
30-d mortality			
MELD-Na	0.11	1.25	0.78-1.7
Maddrey DFI	0.14	1.14	0.82-3.04
Bilirubin	0.45	0.7	0.47-3.6
Creatinine	0.38	0.31	0.74-1.98
INR	0.41	0.78	0.68-1.52
Hepatorenal syndrome	0.001	11.5	2.7-48.11
90-d mortality			
MELD-Na	0.036	1.19	1.06-1.232
Maddrey DFI	0.09	1.03	0.87-1.86
Bilirubin	0.23	0.67	0.65-3.56
Creatinine	0.35	0.37	0.8-4.2
INR	0.17	0.272	0.78-2.6

MELD: Model for end-stage liver disease; DFI: Discrimination function index; INR: International normalized ratio.

example, several studiesin Mexican-American and Mestizo populations have identified a virtual absence of some of the alcohol "protective" genes variations (*ADH1B* and *ALDH2*) and a high frequency of CPY2E c2polymorphic allele, which result in increased enzymatic activity,augmented acetaldehyde production, and more severe liver damage[33,34].

Many strategies have been used to predict morbidity and mortality in AH allowing a better medical support for those very ill patients. Such strategies include the search for single parameters (*i.e.,* alkaline phosphatase) or the development of scoring systems like the Maddrey DFI, the GAHS, the ABIC, the Lille score and MELD[20-24]. According to our results we propose that MELD-Na is also a useful scoring system to predict severity in AH.

Although several studies have explored the clinical utility of severity scores in AH, results are variable. For example, Lafferty *et al*[35] in a cohort of 182 patients prospectively evaluated GAHS, MELD, ABIC and DFI scores anddid not found differences in the outcome among them. Other studies have focused in the specific use of MELD in evaluating the severity of AH. Dunn *et al*[11] in a study with 73 patients with AH found that a MELD score of 21 had the highest sensitivity and specificity to predict mortality at 30 and 90 d. In

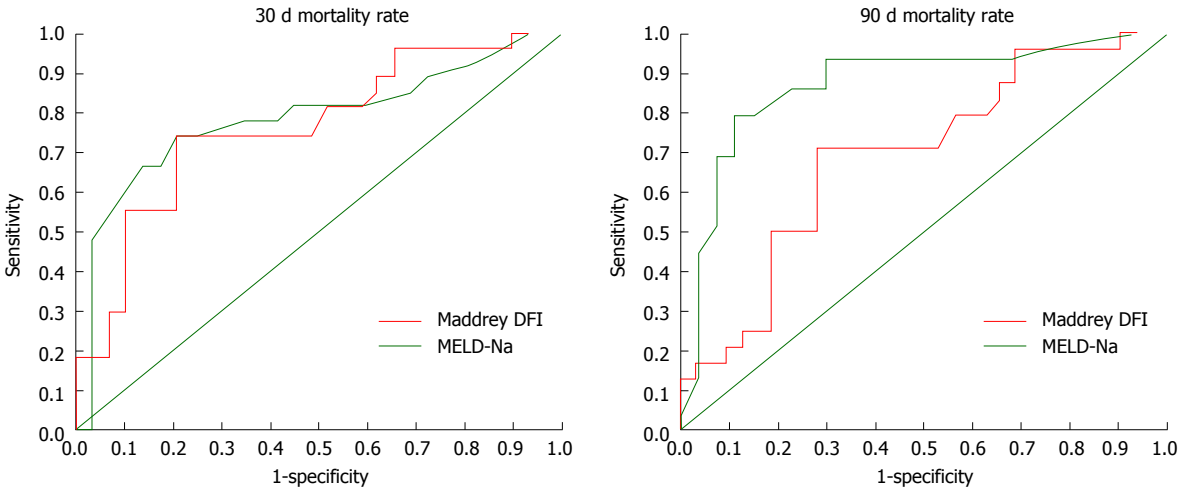

Figure 1 Comparison of Maddrey discrimination function index and model for end-stage liver disease-Na in predicting mortality at 30 and 90 d in alcoholic hepatitis. For 30-d mortality the area under the curve (AUC) was 0.763 for Maddrey DFI and 0.784 for MELD-Na (P = 0.82). For 90-d mortality the AUC was 0.685 for Maddrey DFI and 0.8710 for MELD-Na (P = 0.041). MELD: Model for end-stage liver disease; DFI: Discrimination function index.

Table 4 Clinical utility analysis at 30 and 90 d to predict mortality %

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Maddrey DFI > 32					
Mortality at day 30	96	21	53	86	57
Mortality at day 90	93	22.7	62.2	71.4	63.5
MELD-Na > 21					
Mortality at day 30	85	31	53	69	57.1
Mortality at day 90	87	40	66	69	67.3

MELD: Model for end-stage liver disease; DFI: Discrimination function index.

contrast, Monsanto *et al*[17] in a small sample size (n = 45) and retrospective study found that Maddrey DFI was a more valuable model to predict short-term mortality in patients with AH. Recently, a prospective study in 47 subjects with AH, found that both the MELD score and the Maddrey DFI score at admission were strong and equally good predictors of 28-d mortality in patients with AH[16]. However, in this study the optimal Maddrey DFI cut off point corresponding to the optimal MELD score was higher than the conventional one and the authors propose that MELD score may be used as an alternative to DFI score for predicting short-term mortality in AH[17].

Three previous studies have compared the ability of MELD-NA to predict mortality compared to other scores[24-26]. The first study, a small sample size study from the Mayo Clinic, showed that MELD-Na was a better predictor of 180-d mortality than MELD in patients with ascites[26]. In another study, Kasztelan-Szczerbinska *et al*[25] compared Maddrey DFI, CPT, GAHS, ABIC MELD and MELD-Na in 116 subjects with AH and no statistically significant differences in the models' performances were found. Specifically for MELD-Na, the AUC was 0.83 to predict mortality at 90 d, similar to our findings. In a more recent study, nine scoring models were compared in 71 biopsy-proven patients with AH and all models showed excellent negative predictive values and MELD modifications incorporating sodium did not confer any prognostic advantage over classical MELD[24]. Interestingly, in this cohort the 30-d mortality and 90-d mortality rates were lower compared to other studies (14.1% and 19.7%, respectively). Also the authors did not report the incidence of ascites and HRS.

Hyponatremia is a common clinical problem in patients with end stage liver disease, and has a close relationship with portal hypertension, ascites and HRS. Low sodium levels are related to the impairment of renal solute-free water excretion most likely due to an increased vasopressin secretion, which results in increased sodium retention and reduced renal free water clearance, which predispose to life threatening conditions in the cirrhotic such as HRS and refractory ascites[36]. Also, hyponatremia represents an independent risk factor for brain edema, a fatal complication of acute liver failure[37,38]. Interestingly, we found that low sodium levels were associated with mortality at 30 and 90 d. Also, HRS was associated to mortality in the univariate and multivariate analysis. Thus, for us, was not surprisingly that MELD-Na had better clinical utility performance and ability to predict mortality at 90 d compared to Maddrey DFI.

We need to acknowledge that although we showed that MELD-Na is a useful tool to predict mortality, the treatment provided to our patients did not influence in their survival. Currently, corticosteroids or pentoxifylline

are the main pharmacological treatment options; though the outcomes from the therapies are poor. Because of the limitations in the therapeutic options, it is no doubt that there is a critical need for the newer and more effective.

Other limitations that should be acknowledge include: a small sample size, some patients with suspected AH could not be included in the final analysis because they had incomplete laboratory parameters at admission, lack of comparison with other models that have been shown utility in Mexican population such as ABIC[3] and histological diagnosis of AH was not confirmed. However, several studies have shown that diagnosis of AH is confirmed in almost 80% of the suspected cases when high levels of recent alcohol consumption is confirmed and histological confirmation is not required[39,40]. Intriguingly, we did not find that encephalopathy, ascites and CPT were associated with mortality. However this finding is probably related with the power in our small sample size. Finally, although we found a better performance for MELD-Na to predict 90 d mortality, the clinical relevance of our findings should be assessed in future prospective, multicentric and larger sample size studies.

In conclusion, AH, is associated with high short-term mortality. We found that MELD-Na is useful for predicting 90-d mortality in patients with AH and preserve prognostic advantage over Maddrey DFI score. It represents a valuable tool to stratify patients by risk, however further studies are required to validate the prognostic utility of admission MELD-Na score in patients with AH.

COMMENTS

Background

Alcoholic hepatitis (AH) is a severe condition associated with high mortality. The model for end-stage disease (MELD) score is widely used to predict mortality in end-stage liver disease, and the addition of sodium (MELD-Na) increase its utility. However, few studies have evaluated the utility of MELD-Na in AH.

Research frontiers

Few studies have compared the ability of MELD-NA to predict mortality compared to other scores.

Innovations and breakthroughs

In this study, the authors found that MELD-Na is useful for predicting 90-d mortality in patients with AH and preserve prognostic advantage over Maddrey discrimination function index (DFI) score.

Applications

MELD-Na may represent a valuable tool to stratify patients by risk and to predict in patients with AH.

Terminology

AH: Alcoholic hepatitis; MELD: Model for end-stage disease; MELD-Na: MELD plus sodium; DFI: Discriminant function index; ALD: Alcoholic liver diseases.

Peer-review

This is a well written small study that recommends the use of MELD-Na in the prognostic scoring of patients with acute hepatitis. It warrants publication in its current form.

REFERENCES

1 **Bellentani S**, Saccoccio G, Costa G, Tiribelli C, Manenti F, Sodde M, Saveria Crocè L, Sasso F, Pozzato G, Cristianini G, Brandi G. Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. *Gut* 1997; **41**: 845-850 [PMID: 9462221]

2 **Becker U**, Deis A, Sørensen TI, Grønbaek M, Borch-Johnsen K, Müller CF, Schnohr P, Jensen G. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. *Hepatology* 1996; **23**: 1025-1029 [PMID: 8621128 DOI: 10.1002/hep.510230513]

3 **Altamirano J**, Higuera-de laTijera F, Duarte-Rojo A, Martínez-Vázquez MA, Abraldes JG, Herrera-Jiménez LE, Michelena J, Zapata L, Perez-Hernández J, Torre A, Gonzáles-González JA, Cardenas A, Dominguez M, Arroyo V, Ginès P, Caballería J, Bataller R. The amount of alcohol consumption negatively impacts short-term mortality in Mexican patients with alcoholic hepatitis. *Am J Gastroenterol* 2011; **106**: 1472-1480 [PMID: 21556041 DOI: 10.1038/ajg.2011.141]

4 **Choi G**, Runyon BA. Alcoholic hepatitis: a clinician's guide. *Clin Liver Dis* 2012; **16**: 371-385 [PMID: 22541704 DOI: 10.1016/j.cld.2012.03.015]

5 **Singal AK**, Shah VH. Alcoholic hepatitis: prognostic models and treatment. *Gastroenterol Clin North Am* 2011; **40**: 611-639 [PMID: 21893277 DOI: 10.1016/j.gtc.2011.06.008]

6 **Lucey MR**, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med* 2009; **360**: 2758-2769 [PMID: 19553649 DOI: 10.1056/nejmra0805786]

7 **Maddrey WC**, Boitnott JK, Bedine MS, Weber FL, Mezey E, White RI. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology* 1978; **75**: 193-199 [PMID: 352788]

8 **Forrest EH**, Evans CD, Stewart S, Phillips M, Oo YH, McAvoy NC, Fisher NC, Singhal S, Brind A, Haydon G, O'Grady J, Day CP, Hayes PC, Murray LS, Morris AJ. Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score. *Gut* 2005; **54**: 1174-1179 [PMID: 16009691]

9 **Dominguez M**, Rincón D, Abraldes JG, Miquel R, Colmenero J, Bellot P, García-Pagán JC, Fernández R, Moreno M, Bañares R, Arroyo V, Caballería J, Ginès P, Bataller R. A new scoring system for prognostic stratification of patients with alcoholic hepatitis. *Am J Gastroenterol* 2008; **103**: 2747-2756 [PMID: 18721242 DOI: 10.1111/j.1572-0241.2008.02104.x]

10 **Louvet A**, Naveau S, Abdelnour M, Ramond MJ, Diaz E, Fartoux L, Dharancy S, Texier F, Hollebecque A, Serfaty L, Boleslawski E, Deltenre P, Canva V, Pruvot FR, Mathurin P. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. *Hepatology* 2007; **45**: 1348-1354 [PMID: 17518367 DOI: 10.1002/hep.21607]

11 **Dunn W**, Jamil LH, Brown LS, Wiesner RH, Kim WR, Menon KV, Malinchoc M, Kamath PS, Shah V. MELD accurately predicts mortality in patients with alcoholic hepatitis. *Hepatology* 2005; **41**: 353-358 [PMID: 15660383 DOI: 10.1002/hep.20503]

12 **Kamath PS**, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470 [PMID: 11172350 DOI: 10.1053/jhep.2001.22172]

13 **Mathurin P**, Lucey MR. Management of alcoholic hepatitis. *J Hepatol* 2012; **56** Suppl 1: S39-S45 [PMID: 22300464 DOI: 10.1016/S0168-8278(12)60005-1]

14 **Sheth M**, Riggs M, Patel T. Utility of the Mayo End-Stage Liver Disease (MELD) score in assessing prognosis of patients with alcoholic hepatitis. *BMC Gastroenterol* 2002; **2**: 2 [PMID: 11835693 DOI: 10.1186/1471-230X-2-2]

15 **Said A**, Williams J, Holden J, Remington P, Gangnon R, Musat A, Lucey MR. Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. *J Hepatol* 2004;

40: 897-903 [PMID: 15158328 DOI: 10.1016/j.jhep.2004.02.010]
16 **Kadian M**, Kakkar R, Dhar M, Kaushik RM. Model for end-stage liver disease score versus Maddrey discriminant function score in assessing short-term outcome in alcoholic hepatitis. *J Gastroenterol Hepatol* 2014; **29**: 581-588 [PMID: 24117536 DOI: 10.1111/jgh.12400]
17 **Monsanto P**, Almeida N, Lrias C, Pina JE, Sofia C. Evaluation of MELD score and Maddrey discriminant function for mortality prediction in patients with alcoholic hepatitis. *Hepatogastroenterology* 2013; **60**: 1089-1094 [PMID: 23803373 DOI: 10.5754/hge11969]
18 **Yang Y**, Deng L, Li X, Shi Z, Chen D, Chen X, Li M, Ma L. Evaluation of the prognosis of fulminant viral hepatitis in late pregnancy by the MELD scoring system. *Eur J Clin Microbiol Infect Dis* 2012; **31**: 2673-2678 [PMID: 22569645 DOI: 10.1007/s10096-012-1613-y]
19 **Huo TI**, Lin HC, Hsia CY, Huang YH, Wu JC, Chiang JH, Chiou YY, Lui WY, Lee PC, Lee SD. The MELD-Na is an independent short- and long-term prognostic predictor for hepatocellular carcinoma: a prospective survey. *Dig Liver Dis* 2008; **40**: 882-889 [PMID: 18339595 DOI: 10.1016/j.dld.2008.01.015]
20 **Khalaf H**, Mourad W, El-Sheikh Y, Abdo A, Helmy A, Medhat Y, Al-Sofayan M, Al-Sagheir M, Al-Sebayel M. Liver transplantation for autoimmune hepatitis: a single-center experience. *Transplant Proc* 2007; **39**: 1166-1170 [PMID: 17524922 DOI: 10.1016/j.transproceed.2007.02.030]
21 **Biggins SW**, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, Benson J, Therneau T, Kremers W, Wiesner R, Kamath P, Klintmalm G. Evidence-based incorporation of serum sodium concentration into MELD. *Gastroenterology* 2006; **130**: 1652-1660 [PMID: 16697729 DOI: 10.1053/j.gastro.2006.02.010]
22 **Ruf AE**, Kremers WK, Chavez LL, Descalzi VI, Podesta LG, Villamil FG. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. *Liver Transpl* 2005; **11**: 336-343 [PMID: 15719386 DOI: 10.1002/lt.20329]
23 **Srikureja W**, Kyulo NL, Runyon BA, Hu KQ. MELD score is a better prognostic model than Child-Turcotte-Pugh score or Discriminant Function score in patients with alcoholic hepatitis. *J Hepatol* 2005; **42**: 700-706 [PMID: 15826720 DOI: 10.1016/j.jhep.2004.12.022]
24 **Papastergiou V**, Tsochatzis EA, Pieri G, Thalassinos E, Dhar A, Bruno S, Karatapanis S, Luong TV, O'Beirne J, Patch D, Thorburn D, Burroughs AK. Nine scoring models for short-term mortality in alcoholic hepatitis: cross-validation in a biopsy-proven cohort. *Aliment Pharmacol Ther* 2014; **39**: 721-732 [PMID: 24612165 DOI: 10.1111/apt.12654]
25 **Kasztelan-Szczerbinska B**, Slomka M, Celinski K, Szczerbinski M. Alkaline phosphatase: the next independent predictor of the poor 90-day outcome in alcoholic hepatitis. *Biomed Res Int* 2013; **2013**: 614081 [PMID: 24151614 DOI: 10.1155/2013/614081]
26 **Vaa BE**, Asrani SK, Dunn W, Kamath PS, Shah VH. Influence of serum sodium on MELD-based survival prediction in alcoholic hepatitis. *Mayo Clin Proc* 2011; **86**: 37-42 [PMID: 21193654 DOI: 10.4065/mcp.2010.0281]
27 **Hanley JA**, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983; **148**: 839-843 [PMID: 6878708 DOI: 10.1148/radiology.148.3.6878708]
28 **Méndez-Sánchez N**, Aguilar-Ramírez JR, Reyes A, Dehesa M, Juórez A, Castñeda B, Sánchez-Avila F, Poo JL, Guevara González L, Lizardi J, Valdovinos MA, Uribe M, Contreras AM, Tirado P, Aguirre J, Rivera-Benítez C, Santiago-Santiago R, Bosques-Padilla F, Muñoz L, Guerroro A, Ramos M, Rodríguez-Hernández H, Jacobo-Karam J. Etiology of liver cirrhosis in Mexico. *Ann Hepatol* 2004; **3**: 30-33 [PMID: 15118577]
29 **Orrego H**, Blake JE, Blendis LM, Medline A. Prognosis of alcoholic cirrhosis in the presence and absence of alcoholic hepatitis. *Gastroenterology* 1987; **92**: 208-214 [PMID: 3781189]
30 **Christoffersen P**, Nielsen K. Histological changes in human liver biopsies from chronic alcoholics. *Acta Pathol Microbiol Scand A* 1972; **80**: 557-565 [PMID: 5056834 DOI: 10.1111/j.1699-0463.1972.tb00316.x]
31 **Trabut JB**, Plat A, Thepot V, Fontaine H, Vallet-Pichard A, Nalpas B, Pol S. Influence of liver biopsy on abstinence in alcohol-dependent patients. *Alcohol Alcohol* 2008; **43**: 559-563 [PMID: 18621800 DOI: 10.1093/alcalc/agn046]
32 **Jinjuvadia R**, Liangpunsakul S. Trends in Alcoholic Hepatitis-related Hospitalizations, Financial Burden, and Mortality in the United States. *J Clin Gastroenterol* 2015; **49**: 506-511 [PMID: 25198164]
33 **Gordillo-Bastidas E**, Panduro A, Gordillo-Bastidas D, Zepeda-Carrillo EA, García-Bañuelos JJ, Muñoz-Valle JF, Bastidas-Ramírez BE. Polymorphisms of alcohol metabolizing enzymes in indigenous Mexican population: unusual high frequency of CYP2E1*c2 allele. *Alcohol Clin Exp Res* 2010; **34**: 142-149 [PMID: 19860798 DOI: 10.1111/j.1530-0277.2009.01075.x]
34 **Montano Loza AJ**, Ramirez Iglesias MT, Perez Diaz I, Cruz Castellanos S, Garcia Andrade C, Medina Mora ME, Robles Díaz G, Kershenobich D, Gutierrez Reyes G. Association of alcohol-metabolizing genes with alcoholism in a Mexican Indian (Otomi) population. *Alcohol* 2006; **39**: 73-79 [PMID: 17134659 DOI: 10.1016/j.alcohol.2006.07.001]
35 **Lafferty H**, Stanley AJ, Forrest EH. The management of alcoholic hepatitis: a prospective comparison of scoring systems. *Aliment Pharmacol Ther* 2013; **38**: 603-610 [PMID: 23879668 DOI: 10.1111/apt.12414]
36 **Ginès P**, Guevara M. Hyponatremia in cirrhosis: pathogenesis, clinical significance, and management. *Hepatology* 2008; **48**: 1002-1010 [PMID: 18671303 DOI: 10.1002/hep.22418]
37 **Murphy N**, Auzinger G, Bernel W, Wendon J. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. *Hepatology* 2004; **39**: 464-470 [PMID: 14767999 DOI: 10.1002/hep.20056]
38 **Larsen FS**, Wendon J. Prevention and management of brain edema in patients with acute liver failure. *Liver Transpl* 2008; **14** Suppl 2: S90-S96 [PMID: 18825686 DOI: 10.1002/lt.21643]
39 **Ramond MJ**, Poynard T, Rueff B, Mathurin P, Théodore C, Chaput JC, Benhamou JP. A randomized trial of prednisolone in patients with severe alcoholic hepatitis. *N Engl J Med* 1992; **326**: 507-512 [PMID: 1531090 DOI: 10.1056/NEJM199202203260802]
40 **Spahr L**, Rubbia-Brandt L, Pugin J, Giostra E, Frossard JL, Borisch B, Hadengue A. Rapid changes in alcoholic hepatitis histology under steroids: correlation with soluble intercellular adhesion molecule-1 in hepatic venous blood. *J Hepatol* 2001; **35**: 582-589 [PMID: 11690703 DOI: 10.1016/S0168-8278(01)00190-8]

P- Reviewer: Bramhall S, Jin B **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com