Predicting utility of a model for end stage liver disease in alcoholic liver disease

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AIM: To validate the statistic utility of both the Maddrey Discriminant Function score and the Model for End-Stage Liver Disease as predictors of short term (30 d and 90 d) mortality in patients with alcoholic hepatitis and to assess prognostic factors among clinical characteristics and laboratory variables of patients with alcoholic hepatitis.

METHODS: Thirty-four patients with the diagnosis of alcoholic hepatitis admitted to Hippokration University Hospital of Athens from 2000 to 2005 were assessed in the current retrospective study and a statistical analysis was conducted.

RESULTS: 30- and 90-d mortality rates were reported at 5.9% (2/34) and 14.7% (5/34), respectively. Significant correlation was demonstrated for the Model for End-Stage Liver Disease (P90 = 0.094, P30 = 0.046) and the Maddrey Discriminant Function score (P90 = 0.033, P30 = 0.038) with 30- and 90-d mortality whereas a significant association was also established for alanine aminotransferase (P = 0.057), fibrin degradation products (P = 0.048) and C-reactive protein (P = 0.067) with 90-d mortality. For 30-d mortality the Area Under the Curve was 0.969 (95%CI: 0.902-1.036, P = 0.028) for the Model for End-Stage Liver Disease score and 0.984 (95%CI: 0.942-1.027, P = 0.023) for the Maddrey Discriminant Function score with the optimal cut off point of 30.5 (sensitivity 1, specificity 0.937) and 108.68 (sensitivity 1, specificity 0.969), respectively. Accordingly, for 90-d mortality the Area Under the Curve was 0.762 (95%CI: 0.559-0.965, P = 0.065) for the Model for End-Stage Liver Disease score and 0.752 (95%CI: 0.465-1.038, P = 0.076) for the Maddrey Discriminant Function score with the optimal cut off point of 19 (sensitivity 0.6, specificity 0.6) and 92 (sensitivity 0.6, specificity 0.946), respectively. The observed Kaplan Meier survival rates for different score-categories were compared with log-rank tests and higher score values were correlated with a lower survival.

CONCLUSION: Equivalency of the Model for End-Stage Liver Disease and the Maddrey Discriminant Function score is implied by the current study, verified by the plotted Receiver Operative Curves and the estimated survival rates. A statistically significant utility of C-reactive protein, fibrin degradation products and alanine aminotransferase as independent predictors of 90-d mortality has also been verified.

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Key words: Alcoholic liver disease; Alcoholic hepatitis; Maddrey discriminant function score; Model for end-stage liver disease score

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INTRODUCTION

Alcoholic hepatitis (AH) is an acute or acute-on-chronic inflammatory hepatic syndrome manifesting as a result of severe alcohol consumption and correlating with increased mortality rates[1]. Assessing the severity of the disease is essential for the stratification of patients in need of aggressive therapeutic intervention including corticosteroids and pentoxifylline. A disease severity index for such a purpose should not only have statistical and clinical validity but should preferably rely on a few, readily available, objective parameters and be generalizable to a heterogeneous group of patients[2].

In 1964 Child and Turcotte introduced the first classification index modified to assess prognosis in patients with severe liver disease. In 1972 Pugh improved that first classification in line with the criticisms of Conn[3]. The CTP classification is based on serum albumin, serum bilirubin, prothrombin time, ascites and encephalopathy. Although its statistical accuracy has not been methodically evaluated, CTP classification is used as a disease severity...
index to determine priority in organ allocation.

The Maddrey Discriminant Function (DF = 4.6*PT\textsubscript{control}/PT\textsubscript{w-
control} + serum total bilirubin\textsubscript{mg/dL}] + 11.2*log\textsubscript{[INR]} + 9.6*log\textsubscript{[creatinine, mg/dL}] was derived from a
heterogeneous group of patients from 4 medical centres in the United States and validated in an independent data
set from the Netherlands to assess short term survival in cirrhotic patients undergoing elective Transjugular
Intrahepatic Portosystemic Shunt (TIPS)[6]. In the MELD
score variables are expressed as logarithm values to
avoid extreme values, creatinine is co-evaluated and PT
is expressed as an INR which does not depend on the
sensitivity of the thromboplastin used by the laboratory.

The aim of the current study is to validate the statistic
utility of both DF and MELD scores as predictors of
short term (30-d and 90-d) mortality in patients with
AH and to assess prognostic factors from among clinical
characteristics and laboratory variables of patients with
alcoholic hepatitis.

MATERIALS AND METHODS

Materials

Thirty four patients with the diagnosis of AH admitted to
Hippokration University hospital of Athens between January
1, 2000 and April 30, 2005 were assessed in the cur-
rent retrospective study. The patients were diagnosed with
AH based on the following clinical characteristics: (1) total
bilirubin > 1.5 mg/dL, (2) aspartate/alanine aminotrans-
ferase ratio above 1.5 with an aspartate aminotransferase
level above 45 U/L, (3) alcohol consumption within 2 mo
exceeding 40 g/d for male and 20 g/d for female patients
and finally (4) absence of a coexistent primary cause of
liver disease[7]. Patients with preexisting viral hepatitis were
not excluded from the study on the basis that regeneration of
the viral infection could not be established nor an acute
viral hepatitis verified as the cause of hospital admission.
Survival at 30 and 90 d following hospital admission was
verified by chart review or telephone follow-up.

Only laboratory values obtained within 24 h of admis-
sion were utilized for calculation purposes. In those pa-
tients presenting several hospital admissions only the initial
episode was included. The probability of 90-d mortality
was calibrated to \( P = e^{(5.3+0.10\text{MELD})/1+e^{(5.3+0.10\text{MELD})}}\) [7].

The epidemiological data included age, gender, history of
alcohol consumption and days of abstinence. Several clinical
characteristics and laboratory variables were evaluated as
independent prognostic variables including fever, corti-
costeroids or diuretic treatment, infection, hemoglobin,
mean corpuscular volume, platelets’ count, white blood
cell count, spurrcells, aminotransferases, alkaline phos-
phatase, gamma-glutamyl transpeptidase, bilirubin, creati-
nine, C-reactive protein, erythrocyte sedimentation rate,
\(\alpha\)-fetoprotein, prothrombin time, international normalized
ratio, fibrinogen, d-dimers, fibrin degradation products,
albumin, ammonia. Clinical features of decompensated he-
patic disease including ascites, encephalopathy and edema
and also the presence of jaundice were reviewed from the
admission history charts. Diagnosis of ascites was based
on ultrasonic findings and diagnosis of a coexist-
ing infection was established by a positive culture. Hepatic
encephalopathy was verified after exclusion of space occu-
yming intracranial lesions, concurrent metabolic, endocrine,
traumatic or epileptiform disorders and alcoholic or drug
intoxication. Regarding diuretics only those patients receiv-
ing diuretics before their hospital admission were evalu-
ated as positive. Non sufficient data was demonstrated
regarding the patients’ history of alcohol consumption or
alcohol abstinence resulting in a request for more detailed
documentation of such information in the future.

We searched the database PubMed (1995-2005) using
the following key-words: “alcoholic hepatitis”, “MELD
score”, “DF score”, “prognosis in alcoholic hepatitis”.
We also included review articles, book chapters, or com-
monly referenced older publications. We reviewed the refe-
rence lists of articles identified by the search strategy and
selected those we judged relevant. The search was restrict-
ed to papers published in English.

Methods

Data were analysed using SPSS 11.0 for Windows. Descrip-
tive statistics including mean, median, ranges and standard.
Deviation values were calculated for all the continuous
baseline demographic, clinical and laboratory characteris-
tics. Univariate logistic regression (backward elimination)
was used to screen the variables for statistically significant
association with respect to 30- and 90-d mortality. Vari-
ables that were statistically significant formed a pool of
potential independent predictors. Multivariable logistic
regression (backward elimination variables selection pro-
cedure) was performed for those variables. The significant
factors were kept in the model if the maximum likelihood
ratio criterion had a \( P\)-value below 0.10. Prognostic utility
of the different scores was determined by generating a
receiver operating characteristic curve (ROC curve).
Concordance (range 0.0-1) is equivalent to the area under
the curve (AUC) and quantifies the prognostic validities
of the variables. Excellent diagnostic accuracy is indicated
by AUC between 0.8-0.9 and a \( c\)-statistic greater than 0.7
is generally considered a useful test. From the ROC curve
coordinates, cut-off points with best sensitivity and speci-
cificity of the different scores were determined and pre-
dictive values, likelihood and odds ratios were calculated.
Overall survival was estimated from the admission data of
the patient to the hospital to the date of last follow up or
until the patient’s death. Kaplan Meier method was used to
calculate median follow up and survival curves while the
log rank test was used to compare time to events distribu-
tions with respect to MELD and DF categories. The death
incidences in correlation with MELD and DF values were
displayed on scatter plot diagrams.

RESULTS

Thirty four patients with a median age of 49 (± 7.74, 9
female and 25 male patients) who met the inclusion cri-
A statistically significant association couldn’t be verified for components that comprise the MELD and DF scores (creatinine, total bilirubin and INR). Variables that exhibited a significant correlation in univariate evaluation were thereafter entered in a multivariate logistic regression process. No additional variables increased the predictive accuracy of either MELD or DF score. In fact all the variables lost significance when they were co-evaluated in a backward variable selection procedure.

MELD and DF scores were plotted in correlation with 30- and 90-d mortality (Figures 1 and 2). Visual inspection of these plots demonstrates that higher MELD and DF values are correlated with an increased death incidence.

Receiver operating characteristics curves were generated in order to validate the predictive accuracy of different scores in assessing 30- and 90-d mortality (Figures 3 and 4). For 30-d mortality the AUC was 0.970 (95%CI: 0.929-1.000, P = 0.017) for the DF score and 0.951 (95%CI: 0.921-0.976, P = 0.028) for the MELD score. This indicates that both scores are useful in predicting 30-d mortality. For 90-d mortality the AUC was 0.976 (95%CI: 0.945-1.000, P = 0.023) for the DF score and 0.942 (95%CI: 0.902-0.982, P = 0.029) for the MELD score. This indicates that both scores are useful in predicting 90-d mortality.

Table 2 Univariate and multivariate logistic regression assessing 30 d and 90 d mortality

| Variable            | P value | Odds ratio 95%CI |
|---------------------|---------|-----------------|
| 30-d mortality      |         |                 |
| DF                  | 0.028   | 1.026           |
| MELD                | 0.046   | 1.101           |
| FS                  | 0.024   | 1.095           |
| SGPT                | 0.023   | 1.090           |
| CRP (<100)          | 0.011   | 0.990-1.000     |
| CRP (>100)          | 0.007   | 0.990-1.000     |
| Multivariate logistic regression |         |                 |
| 30-d mortality      |         |                 |
| DF                  | 0.484   | 1.034           |
| MELD                | 0.707   | 1.120           |
| FS                  | 0.033   | 1.001           |
| CRP (<100)          | 0.016   | 0.990-1.000     |
| CRP (>100)          | 0.067   | 0.990-1.000     |
| 90-d mortality      |         |                 |
| DF                  | 0.997   | 1.000           |
| MELD                | 0.997   | 1.000           |

30-d mortality: Variable(s) entered on step 1: DF, MELD, variable(s) entered on step 2: DF, 90-d mortality: Variable(s) entered on step 1: DF, MELD, FS, SGPT, variable(s) entered on step 5: MELD. Only the statistically significant variables are documented.

Table 1 Demographics and laboratory values

| Variable            | N | Range | Mean | Median | Std. deviation |
|---------------------|---|-------|------|--------|----------------|
| Age                 | 33| 36.00-62.00| 48.939| 49     | 7.7498         |
| Yrs of drink        | 23| 3.00-45.00 | 17.000| 15     | 10.3177        |
| Alc g/d             | 22| 50.00-360.00| 157.727| 150    | 84.3565        |
| DF                  | 34| 15.30-180.72| 55.560| 42.25  | 38.0920        |
| MELD                | 34| 3.00-46.00 | 20.918| 19     | 8.5293         |
| Hb                  | 33| 5.30-14.80 | 10.708| 10.85  | 2.3296         |
| MCV                 | 33| 69.10-121.20| 100.860| 102.3  | 11.6788        |
| WBC                 | 34| 3000-27000| 11300.000| 9340   | 6039.8068      |
| PLT                 | 34| 31000-446000| 171970.588| 150000| 103840.6370    |
| PT                  | 34| 13.10-40.00| 20.004| 18.25  | 6.1619         |
| INR                 | 34| 1.10-3.88 | 1.7415| 1.6    | 0.5922         |
| FIBR/GEN            | 30| 50.00-150.00| 312.670| 289    | 237.3453       |
| ALBUMIN             | 32| 1.50-4.00 | 3.0500| 3.05   | 0.4819         |
| SGOT                | 33| 33.00-970.00| 164.441| 127.5  | 156.1268       |
| SGPT                | 33| 19.00-787.00| 84.9706| 46.5   | 132.8972       |
| γGT                 | 32| 23.00-1967.00| 534.7813| 353.5  | 532.8706       |
| ALP                 | 32| 65.00-561.00| 196.4375| 152.9  | 129.0354       |
| TOTAL BIL           | 34| 1.50-51.00| 17.7841| 14.73  | 13.5573        |
| CREAT.              | 34| 0.28-2.80 | 1.0335| 0.95   | 0.5098         |
| NFS                 | 28| 4.85-225.00| 127.3936| 1.5    | 60.3252        |
| ESR                 | 28| 6.00-141.00| 69.0357| 72.25  | 41.7253        |
| CRP                 | 27| 1.40-126.00| 48.1644| 38     | 40.0220        |

1N = number of patients with known laboratory values, yrs: years, alc: alcohol consumption, Hb: hemoglobin, WBC: white blood count, PLT: platelets, PT: prothrombin time, INR: international normalized ratio, SGOT: aspartate amiotransferase, SGPT: alanine amiotransferase, γGT: γ glutamyl transpeptidase, ALP: alkaline phosphatase, BIL: bilirubin, CREAT: creatinine, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, FIBR/GEN: fibrinogen.
DISCUSSION

Alcoholic liver disease (ALD) encompasses a clinicohistological spectrum of abnormalities ranging from fatty liver, to AH and irreversible liver cirrhosis (Laennec’s cirrhosis). The potentially fatal clinicopathological syndrome of AH develops in a minority of patients \([9,10]\).

The major focus of management in AH is abstinence from alcohol, supportive care, treatment of clinical features of decompensated hepatic disease and maintenance of positive nitrogen balance through nutritional support. Although controversy is documented regarding therapeutic issues it is generally agreed that patients with mild disease need not be treated beyond general supportive and symptomatic care and patients with severe disease in extremis may be too ill to correspond in any form of therapy. Identification of those patients who might benefit from aggressive intervention, including corticosteroids or controversial treatment approaches (antioxidant therapy, stimulation of liver regeneration, supplemental amino-acids, inhibition of tumour necrosis factor \(\alpha\) and stimulation of collagen degradation\([1]\)) as well as patients in whom the therapeutic benefit/risk ratio is unfavourable, is currently an issue of great clinical interest.

On that ground the utility of prognostic models in predicting the short-term mortality in AH has been recently assessed by three series in the literature. In 2002 Sheth et al verified the fact that the MELD score performs as well as the DF score in predicting 30-d mortality in AH. A MELD score of greater than 11 or the presence of both ascites and an elevated bilirubin greater than 8 mg/dL should prompt consideration of aggressive therapeutic interventions such as corticosteroids or pentoxifylline according to the authors\([11]\). Three years later a retrospective cohort study assessing 73 patients was conducted by Dunn et al\([7]\), which identified a MELD score of 21 as having the highest sensitivity and specificity for predicting mortality with an estimated 90-d mortality of 20% for patients with this score also manifesting in ascites and encephalopathy. Recommendations were made for such patients to receive aggressive therapeutic agents. According to the authors MELD score maintained some practical and statistical advantages over DF in predicting mortality rates in these patients. Finally in the latest clinical trial conducted in a large cohort of 202 patients with AH, admission, first week and first week change in the MELD score were justified.

Figure 1 Scatter plot graphed for patient death events within 90 d in correlation with corresponding MELD and DF values.

Figure 2 Scatter plot graphed for patient death events within 30 d in correlation with corresponding MELD and DF values.

Figure 3 Predicting utility of MELD score in assessing 30- and 90-d mortality rates in alcoholic hepatitis. Receiver operating characteristic curves were generated and the area under the curve and confidence intervals are indicated.

Figure 4 Predicting utility of DF score in assessing 30- and 90-d mortality rates in alcoholic hepatitis. Receiver operating characteristic curves were generated and the area under the curve and confidence intervals are indicated.
as independent predictors for in-hospital mortality. Also the MELD score outranged the DF and CTP scores when considering prognostic accuracy and cut off points of \( \geq 18 \) for admission MELD score, \( \geq 20 \) for the first week MELD score and \( \geq 2 \) for the first week change in MELD score which were significantly correlated with mortality[8].

In our study a prognostic equivalency of MELD and DF scores was verified whereas the predictive utility of ascites or encephalopathy could not be established. On the other hand, a statistically significant utility of CRP, FS and SGPT as independent predictors of 90-d mortality has been demonstrated. No additional variables significantly changed the prognostic utility of the MELD or DF scores when they were entered in a multivariable analysis. The cut off points were 19 and 30.5 for MELD score and 92 and 108.68 for DF score for 90- and 30-d mortality, respectively.

Despite statistical analysis some practical points favouring the use of the MELD score in this setting should be considered. When compared with the Child-Pugh score the MELD score surpasses in the setting in that: (1) it uses objective parameters which are not subject to center-to-center variability, (2) it increases as the three constituent parameters deteriorate, whereas the individual scoring elements in the Child score remain fixed once a defined threshold has been reached[12].

Presumably CTP classification is an instrument of its time and implementation of the newest therapeutic strategies will require a more refined scale that accurately represents disease severity. Disadvantages were also demonstrated regarding the utility of the DF classification.
for AH including: the use of PT, a variable that is poorly standardized across different laboratories, an established risk of death of up to 17% in patients with a DF score greater than 32\textsuperscript{[13,14]}, and the fact that initial validation of DF correlation to mortality rates is based on series from several decades ago\textsuperscript{[7]}.

In summary, physicians should keep in mind that ALD when complicated by AH should be considered with skepticism and aggressive therapeutic options should be regarded. On that basis prognostic scores should be assessed with a MELD score dominating and presenting sufficient prognostic accuracy.

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