Longitudinal assessment of prognostic factors for patients with hepatorenal syndrome in a tertiary center

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Abstract

Introduction Hepatorenal syndrome (HRS) is one of the serious complications in patients with advanced cirrhosis and ascites. In tertiary centers, most patients were classified as having type 1 HRS for their rapid progressive diseases. However, no significant predictors have been assessed previously for patients with type 1 HRS. In addition to the initial model of end-stage liver disease (MELD) scores and biochemistry parameters, we want to further investigate the prognostic importance of changes in MELD scores and biochemistry parameters over time for patients with type 1 HRS.

Materials and methods Data from type 1 HRS patients were incorporated, including their demographic, clinical progression, all recording biochemical parameters, therapeutic methods, and outcomes.

Results A total of 103 patients were included in our study. According to the definition of the International Ascites Club, 67 patients (or 65%) had type 1 HRS whereas 36 (or 35%) had type 2 HRS. According to the multivariate COX proportional hazards regression model, either initial biochemistry parameters or MELD scores were not significantly associated with prognosis. By time-dependent proportional hazards model, each point elevated in creatinine (CRE) and total bilirubin (TBI) levels during the

admission increased mortality risk by 29 and 4%, respectively. Increasing albumin level during the admission showed its protective value. Changes in MELD score simple during the admission, which were calculated by CRE and TBI [$3.8 \times \log (\text{bilirubin (mg/dl)}) + 9.6 \times \log [\text{Creatinine (mg/dl)} + 6.43]$], were significant predictor for patients with type 1 HRS.

Conclusion In patients with type 1 HRS, changes in TBI, CRE, and albumin level during the admission were associated with prognosis. Changes in MELD score simple is superior to initial and changes in MELD scores to predict prognosis in patients with type 1 HRS.

Keywords Hepatorenal syndrome · Liver transplantation

Introduction

Hepatorenal syndrome (HRS) is a serious complication that occurs in patients with advanced cirrhosis and ascites. It is characterized by circulatory dysfunction and intense renal vasoconstriction and thus leads to very low renal perfusion and glomerular filtration rate [1–3]. HRS is defined according to the diagnostic criteria proposed by the International Ascites Club in 1996. Type 1 HRS is classified as having rapid progressive renal failure, doubling of serum creatinine (CRE) that reaches a level more than 2.5 mg/dL, which occurs in <2 weeks, whereas type 2 HRS has moderate change.

In recent years, many authors have emphasized on assessing the prognosis of patients with HRS. One accepted method was initially termed the model of end-stage liver disease (MELD) score. It was initially created to predict survival following the elective placement of TIPS (transjugular intrahepatic portosystemic shunt) but has now been

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validated as a predictor of survival in patients with a wide variety of liver diseases [4]. Previous studies have pointed out that HRS patients have significantly higher MELD scores and shorter life expectancies. MELD scores also had independent predictive values of prognosis [5, 6]. In these studies, MELD scores were calculated at the time of admission and were just used to reflect initial conditions. After admission, a patient's MELD score may change over time under different conditions and therapeutic methods.

In epidemiology, patients with type 2 HRS were more than those with type 1 HRS. In tertiary centers, patients with diagnosis of conditions that are severe at the time of admission have rapid progressive diseases. Most of them were admitted with higher initial MELD scores and were classified as having type 1 HRS for their disease progression. However, no significant predictors have been assessed previously for patients with type 1 HRS. In addition to the initial biochemistry parameters and traditional MELD score, we want to further investigate the prognostic importance of changes in biochemistry parameters and MELD scores over time for patients with type I HRS in tertiary centers.

Materials and methods

Patients

This is a retrospective study. Data from all patients with HRS who were admitted to the National Taiwan University Hospital from 2004 to 2007 were incorporated, including their demographic, clinical progression, all recording biochemical parameters, therapeutic methods, and outcomes. One hundred three patients were enrolled in our study. MELD scores were calculated using the following formula: $[3.8 \times \log \text{bilirubin (mg/dL)} + 11.2 \times \log \text{INR}] + 9.6 \times \log \text{CRE (mg/dL)} + 6.43$, where INR is international normalized ratio. MELD scores simple were calculated using the following formula: $[3.8 \times \log \text{bilirubin (mg/dL)} + 9.6 \times \log \text{CRE (mg/dL)} + 6.43]$. All patients were treated with a similar protocol through clinical changes, which include volume expansion, vasopressin used, hemodialysis, and plasmapheresis. MELD scores were calculated at the time of patients' admission. MELD scores and MELD scores simple were calculated during the admission with the recorded biochemistry parameters.

Statistical analysis

Statistical analysis was performed using the SPSS software, version 12.0 (SPSS Inc., Chicago, IL, USA) and the SAS software, version 9.1.3 (SAS Institute Inc., Cary, NC, USA). Two-sided $P \leq 0.05$ was considered statistically significant. Student's two-sample t test was used to compare the initial,

median, and mean MELD scores between patients with type 1 HRS and patients with type 2 HRS. Kaplan–Meier estimates of survival curves were calculated for patients with type 1 and type 2 HRS. Multivariate analyses were performed by fitting the multiple Cox proportional hazards model to predict patients' prognosis. Time-dependent proportional hazards model was used for predictor analysis of longitudinal biochemistry parameters.

The goal of regression analysis was to find parsimonious regression models that fit the observed survival data well. To ensure the quality of analysis results, basic model-fitting techniques for variable selection, goodness-of-fit (GOF) assessment, and regression diagnostics were used in our regression analyses. Specifically, the stepwise variable selection procedure was applied to obtain the candidate final regression model. Both the adjusted generalized R^2 and the Grønnesby–Borgan GOF test were examined to assess the GOF of the fitted Cox proportional hazards model. Yet, the value of the adjusted generalized R^2 for the Cox proportional hazards model is usually low. Larger P values of Grønnesby–Borgan GOF test indicate better fits. Also, the statistical tools for regression diagnostics such as verification of proportional hazards assumption, residual analysis, detection of influential cases, and check for multicollinearity were used to discover model or data problems.

Results

A total of 103 patients were included in our study. Eighty-three of them were male and 20 were female. During follow-up period, 83 patients (or 81%) died, 6 were lost to follow-up, 7 underwent liver transplantation, and 14 were alive. A median follow-up was 48 days (range 1–476 days). According to the definition of the International Ascites Club, 67 patients (or 65%) had type 1 HRS whereas 36 (or 35%) had type 2 HRS. Initial, median, and mean MELD scores were higher in patients with type 1 HRS than in those with type 2 HRS. The difference in median and mean MELD scores was statistically significant (Fig. 1). The estimated survival period according to the Kaplan–Meier analysis in patients with type 1 HRS was significantly shorter than in those with type 2 HRS (Fig. 2).

Six of seven patients who received liver transplantation were classified as having type 2 HRS. In patients with type 1 HRS, a set of 11 variables selected from the baseline biochemistry parameters was analyzed for their prognostic value by the multivariate Cox proportional hazards regression model. Aspartate aminotransferase, alanine aminotransferase, serum urea nitrogen, CRE, INR, sodium, potassium, total bilirubin (TBI), direct bilirubin, and alkaline phosphatase, or albumin levels were not associated with the prognosis. Initial MELD scores were higher

Fig. 1 The initial, median and mean MELD scores in type 1 and type 2 HRS patients. * $P < 0.05$ versus type 1 HRS patients

Fig. 2 The estimated survival according to the Kaplan–Meier analysis was in type 1 and type 2 HRS patients

(27.7 ± 8) in patients with type 1 HRS and were not associated with the prognosis.

All biochemistry parameters during the admission were recorded and analyzed in a time-dependent proportional hazards model in patients with type 1 HRS. Elevated CRE and TBI levels were associated with poor prognosis. Increasing albumin level showed its protective value in patients with type 1 HRS. During the admission, each point

elevated in CRE and TBI levels increased mortality risk by 29 and 4%, respectively (Table 1). Changes in MELD scores were not associated with the prognosis. INR, which plays a role in the calculation of the MELD score, was not associated with prognosis in patients with type 1 HRS. We further calculated MELD score simple by CRE and TBI [$33.8 \times \log \text{ bilirubin (mg/dL)} + 9.6 \times \log \text{ CRE (mg/dL)} + 6.43$] and analyzed in time-dependent proportional hazards model. Elevated MELD scores simple was a significant predictor in patients with type 1 HRS. Every point elevated in MELD score simple during the admission increases mortality risk by 24% in patients with type 1 HRS (Table 1).

Discussion

In epidemiology, patients with type 2 HRS were more than those with type 1 HRS. In tertiary centers, patients with diagnosis that are always severe at the time of admission have rapid progressive diseases. Most of our patients (67 patients or 65%) were classified as having type 1 HRS. Previous studies demonstrated that initial MELD scores were important predictors of survival in HRS patients. Mean survival was different in HRS patients, with a MELD score of either less than 20 or more than 20 [5, 6]. Still some studies showed change in MELD scores of the past 30 days, whereas the monthly changes were associated with the prognosis in multivariate analysis. In these publications, $\Delta\text{MELD}/\text{month}$ of more than 2.5 was the significant prognostic predictor at 6 and 12 months in multivariate logistic analysis [7–9]. In our study, patients with type 1 HRS were admitted with a higher MELD scores (27.7 ± 8) and initial MELD scores showed no predictive value of prognoses. Most of them died within 30 days (46 patients or 68.7%). $\Delta\text{MELD}/\text{month}$ was calculated in the remaining 21 patients, with a range of -17 to 31 . The mean of $\Delta\text{MELD}/\text{month}$ was 7.3 and more than 2.5 . It may reflect severe disease in patients with type 1 HRS and $\Delta\text{MELD}/\text{month}$ was not a suitable predictor. In the previous studies, patients with type 1 HRS had independent predictive values of poor prognosis [6]. However, no significant predictors have been assessed previously for patients with type 1 HRS. Changes in biochemistry

Table 1 Multivariate analyses of the prognosis using time-dependent proportional hazards model in patients with type 1 HRS

Covariate	Estimate	Standard error	Wald chi-square	<i>P</i> value	Hazard ratio	95% Confidence interval
Creatinine	0.25331	0.05310	22.7540	<0.0001	1.288	1.161–1.43
Total bilirubin	0.04045	0.01228	10.8543	0.0010	1.041	1.017–1.067
Albumin	−1.19986	0.36237	10.9636	0.0009	0.301	0.148–0.613
MELD score simple	0.21434	0.03729	33.0437	<0.0001	1.239	1.152–1.333

parameters and MELD scores reflect dynamic residual liver function changes over time accurately.

In a time-dependent proportional hazards model, changes in CRE, TBI, and albumin levels but not MELD score over time were associated with prognoses in type 1 HRS. Elevated CRE and TBI levels, which reflect disease progression during the admission, were associated with poor prognosis. Increasing albumin level showed its protective value in patients with type 1 HRS. Albumin is the most abundant human plasma protein and is an important transporter of hydrophobic internal and external substances. Liver failure results in decreased albumin-binding capacity because of decreased hepatic synthesis [10]. Albumin level during admission might reflect hepatic synthetic capacity and was a prognostic factor in patients with type 1 HRS.

The MELD score is based on objective laboratory variables [bilirubin, CRE, and the INR for the prothrombin time (PT)] and predicts the prognosis of HRS patients [5, 6]. INR, which plays a role in the calculation of the MELD score, showed no predictive value in patients with type 1 HRS. The pathophysiology underlying coagulopathy in patients with liver failure is more complex than simple synthetic deficiency in assessment of Coumadin therapy for which the PT-INR was originally developed [11]. We calculated MELD scores simple by CRE and TBI [$3.8 \times \log \text{ bilirubin (mg/dL)} + 9.6 \times \log \text{ CRE (mg/dL)} + 6.43$] and analyzed in the time-dependent proportional hazards model. We found that changes in MELD scores simple showed significant predictive value in patients with type 1 HRS.

Although there are many therapeutic methods that have been introduced to improve renal function, HRS is still always associated with a poor prognosis. Some authors believe that liver transplantation is the only effective treatment of HRS. Still some publications showed that only half of patients with type 1 HRS settled for postorthotopic liver transplant [12]. In our study, six of seven patients who received transplantation had type 2 HRS. We need further investigation to evaluate the prognosis of patients with type 1 HRS who receive liver transplantation.

Conclusions

Patients with diagnosis of conditions that are severe at the time of admission have rapid progressive diseases in tertiary centers. Most of them were classified as having type 1 HRS for their rapid progress disease. In addition to initial biochemistry parameters and MELD scores, changes in

TBI, CRE, and albumin levels during the admission were associated with prognosis in patients with type 1 HRS in the time-dependent proportional hazards model. INR, which was used in MELD scores calculation, showed no predictive value of prognosis. Changes in MELD score simple, which was calculated by CRE and TBI values [$3.8 \times \log \text{ bilirubin (mg/dL)} + 9.6 \times \log \text{ CRE (mg/dL)} + 6.43$], is superior to initial and subsequent changes in MELD scores to predict prognosis in patients with type 1 HRS.

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