Research Article

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Serum sodium, renal function, and survival of patients with end-stage liver disease

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Background & Aims: Serum creatinine, a component of the model for end-stage liver disease (MELD), is an important prognostic indicator in patients with end-stage liver disease (ESLD). In addition, serum sodium has recently been recognized as an important predictor of mortality in patients with ESLD. We investigate the role of serum creatinine and sodium, and glomerular filtration rate (GFR) as determinants of survival in patients with ESLD.

Methods: A prospective database was utilized to identify all adults listed for primary liver transplantation (LTx) at the Mayo Clinic, Rochester, between 1990 and 1999. GFR was measured by iothalamate clearance.

Results: Among 837 patients listed for LTx, 660 had complete data including measured GFR. There was a significant association between GFR and survival after adjustment for MELD, with a linear rise in the risk of death as GFR decreased between 60 and 20 ml/min/1.73 m^2. Multivariable models showed that GFR is superior to creatinine in predicting mortality – a model consisting of total bilirubin (hazard ratio (HR) = 2.17, $p < 0.01$), INR (HR = 3.26, $p < 0.01$) and GFR (HR = 0.42, $p < 0.01$) was superior to MELD (chi-square 65.6 vs. 59.4, c-statistic 0.792 vs. 0.780). Serum sodium did not contribute to survival prediction when accurately measured GFR data were available.

Conclusions: Serum concentrations of creatinine and sodium in patients with end-stage liver disease reflect a reduction in renal function, the underlying event that decreases survival.

Introduction

The model for end-stage liver disease (MELD) score has been shown to correlate well with mortality risk in patients with cirrhosis [1–4]. The results of MELD-based organ allocation since 2002 in the United States suggest that improvement in survival prediction in waitlist registrants has contributed to reductions in waitlist mortality [4,5]. MELD is based on three common objective and reproducible laboratory tests: serum total bilirubin, the international normalized ratio (INR), and serum creatinine. In addition, recent studies have shown that incorporation of serum sodium can improve the predictive accuracy of MELD [6–10].

One of the strengths of MELD is its inclusion of serum creatinine as an estimate of renal function. Prior to MELD, serum creatinine was shown to be associated with survival in end-stage liver disease (ESLD) patients [11–13]. For example, moderate elevations of creatinine up to 2 mg/dl and more severe renal insufficiency of creatinine >2 mg/dl were associated with 1.7- and 2.7-fold increases, respectively, in the risk of death [14]. Likewise, MELD estimates that a one-unit increase in $\log_e$(creatinine) is associated with a 2.6-fold increase in the risk of death.

Despite the clear statistical significance of serum creatinine as a predictor of survival, its physiologic significance is incompletely understood. Obviously, serum creatinine is considered to reflect renal function; however, it is not a very accurate gauge, especially in detecting early loss of renal function [15,16]. Moreover, in patients with cirrhosis, serum creatinine concentrations may remain within normal limits even in the presence of moderate to severe renal impairment, thus leading to overestimation of the true glomerular filtration rate (GFR) [11,15,17–19]. Similarly, estimation of GFR based on mathematical equations or timed urine collections has been shown to be inaccurate, regardless of the severity of liver disease or renal dysfunction [16,19,20]. To date, direct measurement of GFR using exogenous substances, such as inulin or iothalamate, remains the most accurate means to assess renal function [19]. To the degree that renal excretion of sodium is an important determinant of serum sodium, it is thought that serum sodium also reflects renal function.

In this study, we seek to understand the relationship between renal function and serum concentrations of creatinine and sodium as a predictor of mortality in patients with ESLD. We hypothesize that decreased GFR is the underlying condition that increases the risk of death among patients with ESLD and therefore, a direct measure of GFR in comparison to serum creatinine or sodium, would contribute most in survival prediction in these patients.

Keywords: Glomerular filtration rate; Liver cirrhosis; MELD; Prognosis.
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Abbreviations: MELD, model for end-stage liver disease; INR, international normalized ratio; ESLD, end-stage liver disease; GFR, glomerular filtration rate; LTx, liver transplantation; MDRD, modification of diet in renal disease; SD, standard deviation.

Patient and methods

Study subjects

This is a cohort study which analyzed a prospective database of all adults listed for liver transplantation (LTx) at the Mayo Clinic, Rochester, Minnesota, over a 10-year span between February 1990 and August 1999. The study time frame was chosen to avoid any potential effects of the changes in the organ allocation that occurred with the introduction of MELD (February 2002), while ensuring a reasonable duration of follow-up [21].

To the extent that MELD was developed and validated in patients with ESLD, this study is focused on adult waitlist registrants with ESLD. Thus, pediatric LTx candidates (age < 17 years) and patients with diseases other than cirrhosis, such as acute liver failure, were excluded, as were patients with hepatic malignancies and re-transplantation candidates. The study was approved by the Institutional Review Board of the Mayo Foundation.

GFR measurement

GFR was measured by renal clearance of iothalamate. The initial technique employed the use of radiolabeled ^{125}I-iothalamate. Subsequently, limitations of the method, including radiation exposure, restriction in handling and disposal of the radioactive material, and cost of isotopes led to modification of the technique using non-radiolabeled iothalamate [22,23]. Excellent correlation (r = 0.998) and reproducibility (inter-assay coefficient of variation = 5%) have been demonstrated between the radiolabeled and non-radiolabeled methods [23–25]. In this study, GFR was measured by radiolabeled iothalamate clearance between 1990 and 1996, and then by non-radiolabeled iothalamate clearance. Briefly, iothalamate was injected subcutaneously after oral hydration with 4–6 glasses of water. Approximately one hour after the injection of iothalamate, GFR was determined by the clearance equation, UV/P, where U = urine iothalamate concentration; V = urine flow during the collection period, and P = serum concentration of iothalamate. Plasma and urine iothalamate was measured either by gamma counter or by capillary electrophoresis (MDQ system®, Beckman Coulter, Fullerton, CA) for the radiolabeled and non-labeled method, respectively. The resulting iothalamate clearance data were normalized to 1.73 m^2 of body surface area.

At the Mayo Clinic Rochester, pre-LTx patient evaluation consists of three phases, advancing from an overall physiologic assessment in the early phases, to more focused, specialized evaluation in the later phase. GFR measurement has been included in the second phases of evaluation. Therefore, for patients who are determined in the initial phases of the evaluation to be 'early' and not requiring imminent LTx, GFR measurement may not be conducted until several months after waitlist registration. In the opposite extreme, pre-LTx evaluation may be expedited in profoundly ill patients, for whom GFR measurement is omitted altogether.

Other data elements

Data elements were selected from a comprehensive, electronic database which has been described previously [26]. These included baseline characteristics, such as demographics and etiology of liver disease, as well as laboratory data including components of the MELD score and serum sodium. MELD was calculated according to the original description, where

$$\text{MELD} = 11.2\text{LN (INR)} + 3.78\text{LN (Bilirubin)} + 9.57\text{LN (Creatinine)} + 6.43 \text{ [1]}.$$

If multiple GFR measurements were available, we used the one nearest to the waitlist registration. Then, other laboratory data (bilirubin, INR, creatinine, and sodium) were selected closest to the date of GFR measurement, but not more than 30 days apart. For patients who did not have measured GFR data, data elements at registration were used for analysis. Finally, laboratory data at the time of LTx were extracted to calculate the MELD score and to describe the changes in renal function while on waitlist.

Statistical methods

The primary analysis for predictors of waiting list mortality was conducted in subjects with measured GFR data. As not all patients underwent GFR measurement, a sensitivity analysis was performed to evaluate whether the conclusion of the primary analysis remained robust when the entire study cohort was included. The sensitivity analysis was conducted using GFR estimated according to the Modification of Diet in Renal Disease (MDRD) equation [27]. The MDRD equation has been shown to have reasonable correlation with renal function in patients with cirrhosis [17]. Of the several versions of the MDRD equation, we used the following, based on data availability:

$$\text{GFR (ml/min/1.73 m}^2) = 175 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}$$

The starting point of our survival analysis was when GFR was measured or estimated, as opposed to waitlist registration, which is an arbitrary point in time that is devoid of biological significance. Patients were followed until death, LTx, withdrawal from the list or the end of the study period. The data on these outcomes in the database were verified with information from the medical records and patient registration data. Follow-up was complete as of the end of December 2002.

The primary event of interest in this study was death on the waitlist. Patients were censored at transplantation or at removal from the list for any other reason. Patients still awaiting transplantation at the last follow-up were censored at that follow-up date.

The Kaplan–Meier method was used to estimate the overall survival rates. The log-rank test was used to compare death rates between groups. The multivariable proportional hazards analysis was used to estimate hazard ratios associated with variables in predicting waiting list mortality. A p value <0.05 was used for statistical significance in all analyses.

Results

Study subjects

A total of 837 patients met our inclusion criteria, of whom 660 had complete data including measured GFR and were included in our primary analysis (Fig. 1). A subsequent sensitivity analysis also included data from the remaining patients (n = 177) such that estimated GFR data of all study patients were used. In Table 1, the overall study cohort consisted of 55% male with a median age of 51 (range, 17–73) years. The etiology of cirrhosis was cholestatic in 35%, hepatitis C in 20%, alcoholic liver disease in 14%, hepatitis B in 4%, and other etiologies in 28% of patients. The median (range) baseline MELD score was 14.8 (0.6–53.7) and serum sodium 137 (117–162) mEq/L. There was no difference between patients with GFR data and those without in most baseline demographic features, including age, gender, race and the etiology of liver disease. However, MELD, INR and serum creatinine were significantly higher, and serum sodium was significantly lower in patients without GFR data.

Waiting list survival

At the end of follow-up, 77 of 837 patients (9.2%) died, 657 (78%) underwent LTx, 37 (4%) were withdrawn, and 66 (8%) were still on the waiting list. Survival was shorter in patients who did not have their GFR measured than in those who did (p < 0.001, Fig. 2), with a 6-month survival probability of 77% and 94%, respectively. These findings, together with the differences in baseline laboratory results, indicate that patients who lacked measured GFR data had more advanced disease than those with GFR data.

Primary analysis: measured GFR, serum sodium and mortality

By the end of follow-up, 48 of the 660 patients with measured GFR data died on the waitlist. Fig. 3 shows that there was a significant association between baseline GFR and survival: The one-year survival probability for patients with GFR ⩾ 60 ml/