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

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Abstract

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/1.73m². 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.

Keywords

Glomerular filtration rate; Liver cirrhosis; MELD; Prognosis

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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, 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 $\log_e(\text{creatinine})$ 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 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.

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%) has 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 to 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 by either 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 phase to more focused, specialized evaluation in the later phase. GFR measurement has been included in the second phase of evaluation. Therefore, for patients who are determined in the initial phase 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

$$MELD = 11.2 \ln(INR) + 3.78 \ln(Bilirubin) + 9.57 \ln(Creatinine) + 6.43 \quad [1]$$

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:

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

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/min/1.73 m², between 30 and 60 ml/min/1.73 m², and < 30 ml/min/1.73 m² were 91%, 71% and 50%, respectively ($p < 0.001$).

In Fig. 4, adjusting for MELD, decreasing GFR between 60 and 20 ml/min/1.73 m² was associated with a near-linear increase in the risk of death. GFR higher than 60 ml/min/1.73 m² was not associated with further decrease and the risk of death was attenuated. The confidence interval widened markedly in the low range of GFR, due to the small number of observations.

To formally examine the relationship among GFR, serum concentrations of sodium and creatinine, and MELD as predictors of waitlist mortality, several multivariable models were constructed (Table 2). Model 1 contained only MELD, which as expected, was a significant predictor of mortality (HR = 1.18, $p < 0.01$). Model 2, which included GFR as well as the three individual MELD components, showed that once GFR is included, serum creatinine was no longer significant ($p = 0.22$). Model 3 excluded serum creatinine, with the model coefficients refit among the remaining three variables, i.e. bilirubin, INR and GFR. This model represented an improvement over MELD alone (Model 1), as suggested by increases in chi-square (59.4 vs. 65.6) and c-statistic (0.780 vs. 0.792) values. Finally, in Model 4, we tested whether serum sodium adds to Model 3. Although the model fit improved slightly (chi-square 67.1, c-statistic 0.805), serum sodium did not reach statistical significance ($p = 0.20$).

Sensitivity analysis: estimated GFR as a predictor of mortality

Fig. 5 shows the correlation between measured and estimated GFR by the MDRD equation in 660 subjects with available iothalamate data. There was a significant, albeit moderate association between measured and estimated GFR ($R^2 = 0.63$, $p < 0.01$).

Table 3 repeats the analyses presented in Table 2, except that it is based on estimated GFR data of the entire cohort ($n = 837$). Model 1 shows that MELD remained as a significant predictor of mortality in this larger group of patients. In Model 2, when both serum

creatinine and estimated GFR were considered, neither was statistically significant. In Model 3, which excluded serum creatinine, estimated GFR regained significance (HR = 0.39, $p < 0.01$). When compared to Model 1, the model fit as gauged by the c-statistic (0.792 vs. 0.800) was not better. The results of Model 4 were different from those in Table 2 in that the serum sodium adds to the model significantly ($p = 0.01$), which already included total bilirubin, INR and estimated GFR (chi-square 107.9, c-statistic 0.815).

Renal function at transplantation

Laboratory data to assess renal function at the time of LTx were available in 645 patients (98% of 657 that received LTx). The mean serum creatinine at LTx was 1.37 [standard deviation (SD) = 1.13] mg/dl, compared to a mean serum creatinine of 1.17 (SD = 0.87) at the initial assessment. The mean change in serum creatinine was 0.2 (SD = 0.78) mg/dl. Estimated GFR declined from a mean of 76.7 (SD = 29.2) ml/min to 70.8 (SD = 31.7) with a mean reduction of 5.8 (SD = 23.4). These changes in renal function were associated with an increase in the MELD score from 15.9 (SD = 7.4) at initial assessment to 18.5 (SD = 8.5) at the time of LTx.

Discussion

The main results presented in this study are: (1) in patients with ESLD awaiting liver transplantation, directly measured GFR supersedes serum creatinine in assessing mortality risk and (2) serum sodium, which has been shown to be a predictor of mortality in this population independent of MELD, loses its significance once an accurate measure of GFR is taken into account. The goal of this analysis is not to advocate incorporating GFR as a component of MELD. Rather, it is to help understand the relationship between serum creatinine and sodium and renal function as a predictor of survival in patients with ESLD.

Although the importance of renal function in survival of patients with ESLD has been well recognized [12,28-33], this study is unique in being able to make a direct comparison between GFR and serum creatinine in a large cohort of patients with ESLD. Serum creatinine level has been shown to be a relatively inaccurate measure of renal function in ESLD patients for several reasons [15,17,19,34]. First, creatinine production in patients with ESLD is reduced secondary to decreased hepatic creatine synthesis. Creatinine is produced solely by the non-enzymatic conversion of creatine. Cirrhotic patients have been shown to produce creatinine at approximately one half the rate of subjects with normal hepatic function [35]. Second, cirrhotic patients often have decreased skeletal muscle mass and may receive a protein-poor diet for treatment of hepatic encephalopathy. Moreover, tubular creatinine secretion may be increased in patients with ESLD [15,36,37]. All of these factors contribute to a falsely low serum creatinine level.

Our sensitivity analysis is instructive in understanding the significance of various measures of renal function in the context of prediction of survival. First, the MDRD equation, a popular estimator of GFR, was only modestly correlated with measured GFR in our patients. In the sensitivity analysis, when estimated GFR and creatinine were simultaneously put into the model (Model 2, Table 3), neither was significant. This observation likely stems from multi-collinearity – the two variables out competing each other. As serum creatinine is a

component of the MDRD equation, the two are closely correlated, conveying the same information. More importantly, comparison of the last models in Tables 2 and 3 suggests that as the accuracy of GFR estimation decreases, the importance of serum sodium increases. We construe this to indicate that serum sodium may reflect an aspect of renal function that is not captured by other measures such as serum creatinine [6,7,9,38]. In contrast, accurately measured GFR negates the need for the additional information contained in serum sodium. These data indicate that while better markers of renal function help to predict survival more reliably, non-invasive estimation of renal function remains a significant challenge.

Hyponatremia has been clearly demonstrated as an indicator of poor prognosis in patients with ESLD [6-10]. Recently, selective V2 receptor antagonists, so-called the “vaptans,” have been shown to correct hyponatremia effectively in patients with cirrhosis [39,40]. An important clinical question in this context is whether correction of hyponatremia by the use of these agents might improve survival of patients with ESLD. While such data are being gathered and anticipated in the future, the results of this study suggest that hyponatremia is an epiphenomenon of decreased renal function, rather than an independent cause of mortality. The underlying event that drives changes in serum creatinine and sodium concentrations is reduction in renal function or decreased GFR. To the degree that the vaptans do not improve renal function, it is unlikely that they will improve survival of patients with ESLD [39].

This work has some limitations. As was discussed repeatedly, GFR measurement was not undertaken in all waitlist registrants and there were some systematic differences according to the availability of GFR data. We addressed this issue by the sensitivity analysis. Second, although the data were collected in a prospective fashion, not all data elements necessary for this analysis were available at a designated time. For example, GFR was not always coincident with waitlist registration. About 24% of the time intervals from GFR to MELD and sodium measurements were more than 7 days long. For patients with ESLD, in who renal function fluctuate frequently, the correlation between serum creatinine and GFR measured more than seven days apart may be questionable. However, this ‘noise’ in the data is more likely to have led us to underestimate the importance of renal function, rather than to come to a spurious conclusion.

In summary, this analysis reiterates that renal function is a consistently important predictor of mortality among patients with end stage liver disease. Limitations in the ability to accurately measure renal function remain a practical obstacle in implementing this knowledge in daily patient care as well as organ allocation. Thus, our data call for investigation for biomarkers in the serum or urine that accurately represent renal function in patients with end stage liver disease. In the mean time, serum sodium, in conjunction with serum creatinine, remains a useful addition to measures of mortality risk such as MELD.

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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

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Figure 1.
Flow diagram of analyses.

Figure 2. Comparison of survival on the waitlist of patients with (n = 660) and without (n = 177) measured GFR data

Early death occurred more frequently in the latter.

Figure 3. Probability of survival on the waitlist of the patients in relation to baseline GFR
Patients with lower GFR had a progressively higher mortality rates than patients with normal GFR.

Figure 4. Effect of baseline GFR on the risk of death on the waitlist, adjusting for MELD
 There was a near-linear rise in the risk of death as GFR decreased between 60 and 20 ml/min/1.73 m². The solid line represents the best fit. Dotted lines represent the 95% confidence band. The confidence interval widened markedly in the low range of GFR, indicating a smaller number of observations.

Figure 5. Correlation between measured GFR and GFR estimated using the Modification of Diet in Renal Disease (MDRD) equation in the primary dataset (n = 660)

There was a significant, but modest linear association between measured and estimated GFR ($p < 0.01$).

Table 1

Comparison of baseline characteristics between patients with and without measured GFR.

Variables	All (n=837)	GFR		<i>p</i> [†]
		measured (n=660)	estimated (n=177)	
Age [*]	51 (17-73)	52 (17-72)	49 (18-73)	0.05
Male (%)	54.7	53.9	57.6	0.38
White (%)	98.7	98.6	99.1	0.71
Etiology (%)				0.08
Cholestatic	34.9	36.8	27.7	
HCV	19.6	20.1	18.1	
Alcoholic	14.0	13.1	17.5	
HBV	3.8	3.3	5.6	
Other [§]	27.7	26.7	31.1	
MELD [*]	14.8 (0.6-53.7)	14.5 (0.6-53.4)	16.7 (0.6-53.7)	<0.01
Bilirubin (mg/dL) [*]	3.4 (0.2-64.2)	3.3 (0.3-56.0)	4.0 (0.2-64.2)	0.06
INR [*]	1.3 (0.9-15.3)	1.3 (0.9-15.3)	1.4 (0.9-10.9)	0.02
Creatinine (mg/dL) [*]	1.0 (0.4-10.5)	1.0 (0.4-72)	1.0 (0.4-10.5)	<0.01
Sodium (mEq/L) [*]	137 (117-162)	137 (118-162)	136 (117-151)	0.04

GFR, glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; MELD, model for end-stage liver disease.

[§] Other diagnosis included non-alcoholic fatty liver disease or cryptogenic cirrhosis (29%), metabolic liver disease (26%), autoimmune (6%), secondary biliary cirrhosis (3%), Budd-Chiari syndrome (3%), other miscellaneous/missing (33%).

^{*} Data are expressed as median (range).

[†] *p*-value for the difference between patients with and without measured GFR data.

Table 2

Primary analysis for predictors of waiting list mortality on patients with measured GFR data.

Model	Variable	Hazard ratio	<i>p</i>	Chi-square	Chi-static
Model 1	MELD	1.18	<0.01	59.4	0.780
Model 2	Bilirubin [*]	2.31	<0.01	67.1	0.791
	INR [*]	3.34	<0.01		
	Creatinine [*]	2.17	0.22		
	GFR [*]	0.56	0.04		
Model 3	Bilirubin [*]	2.21	<0.01	65.6	0.792
	INR [*]	3.26	<0.01		
	GFR [*]	0.42	<0.01		
Model 4	Bilirubin [*]	2.17	<0.01	67.1	0.805
	INR [*]	2.90	0.02		
	GFR [*]	0.45	<0.01		
	Na	0.96	0.20		

Number of patients=660; number of events=48.

* Log_e value.

Table 3

Sensitivity analysis for predictors of waiting list mortality on the entire study patients using estimated GFR data.

Model	Variable	Hazard ratio	<i>p</i>	Chi-square	C-statistic
Model 1	MELD	1.15	<0.01	94.3	0.800
Model 2	Bilirubin *	2.23	<0.01	100.6	0.795
	INR *	3.81	<0.01		
	Creatinine *	2.16	0.37		
	eGFR *	0.73	0.70		
Model 3	Bilirubin *	2.25	<0.01	99.8	0.792
	INR *	3.95	<0.01		
	eGFR *	0.39	<0.01		
Model 4	Bilirubin *	2.15	<0.01	107.9	0.815
	INR *	3.14	<0.01		
	eGFR *	0.44	<0.01		
	Na	0.93	<0.01		

Number of patients=837; number of events=77.

eGFR, estimated GFR by the Modification of Diet in Renal Disease (MDRD) equation.

* Log_e value.