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RESEARCH ARTICLE

A STUDY OF RENAL FUNCTION, SERUM SODIUM AND THEIR IMPACT ON SURVIVAL OF PATIENTS WITH END STAGE LIVER DISEASE

***Girinadh Lekkala, R.S., Ravi Kumar Allu, Sravan Kumar Korrapati**

Andhra Medical College

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ABSTRACT

Background: Serum creatinine is considered to reflect renal function; however, it is not a very accurate gauge, especially in detecting early loss of renal function. To estimate the role of serum creatinine, sodium, and estimated glomerular filtration rate (eGFR) as determinants of survival in patients with End stage liver disease (CTP-C).

Methods: Patients with decompensated cirrhosis (CTP-C) and serum creatinine ≤ 1.5 mg/dl were included in the study. Patients with Diabetes, Hypertension, Post-transplant candidates were excluded. MELD was calculated by MELD Score. MELD Na was calculated by MELD-Na = MELD +1.59 (135 - Na).eGFR was calculated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. The primary event of interest in this study was death within 6 months.

Results: Total 64 patients were included in the study. 30(46.8%) were having alcohol, 19 (29.6%) patients had viral etiology as the cause of cirrhosis. Out of 64 patients, 18 patients (28.12%) died during 6 months follow up. Hyponatremia was present in 61.1% of dead patients and 21.7% of survived patients. eGFR was ≥90ml/min/1.73m2 in 12 patients, 16% died. eGFR was 60-89 ml/min/1.73m2in 32 patients,25% died and eGFR was <60 ml/min/1.73m2in 20 patients, 40% died. Univariate Analysis of Baseline Variables showed serum creatinine had no significance in the survival of patients with end stage liver disease (CTP-C). MELD score, eGFR, serum sodium and MELD-Na had significance in the survival. Multivariate Cox Regression Summaries for MELD, Hyponatremia, and MELD plus Serum Sodium in Predicting Death Considering 6-Month Follow-Up Data showed c-Static for MELD is 0.75 where as c-Static for MELD-Na is 0.805 and for a model comprising bilirubin, INR, eGFR and sodium is 0.816.

Conclusions: When compared to serum creatinine, eGFR is a better tool for estimating survival of patients with ESLD. As eGFR decreases the percentage of mortality increases.

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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 (Wiesner, 2003 and Kamath, 2007). The MELD score, which estimates the survival probability of a patient with an end-stage liver disease, is based on three commonly obtained laboratory parameters: serum bilirubin, serum creatinine, and international normalized ratio (INR). One of the strengths of MELD is its inclusion of serum creatinine as an estimate of renal function. Despite the clear statistical significance of serum creatinine as a predictor of survival, its physiologic significance is incompletely understood. 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) (Gonwa, 2004 and Sansoe, 2004; and Sherman, 2003). Renal excretion of sodium is an important determinant of serum sodium, it is thought that serum sodium also reflects renal function. Hyponatremia has been well described in associations with hepatorenal syndrome, ascites, and liver-related mortality. Like the components of the MELD score, serum Na is a readily available, reproducible, and objective laboratory test that predicts liver related mortality and is, therefore, a reasonable candidate for inclusion in MELD.

Corresponding author:* **Girinadh Lekkala
Andhra Medical College

Aim

The role of serum creatinine, sodium, and estimated glomerular filtration rate (eGFR) as determinants of survival in patients with ESLD (CTP-C).

MATERIALS AND METHODS

Study population: After obtaining the approval of the university ethical committee as well as written informed

consent from the patients, all decompensated cirrhosis patients (Child Pugh-C) attending King George Hospital ,Vizag ;a major referral center for gastrointestinal diseases in North Andhra, were recruited into the study between May 2015 and November 2016.

Inclusion Criteria

- Patients with decompensated cirrhosis CTP-C
- Age of the patients ≥ 18 years With serum creatinine ≤ 1.5 mg/dl
- Those who were willing to participate in the study

Exclusion Criteria

- Patients with compensated cirrhosis and CTP-B
- Patients with Diabetes, Hypertension ,using nephrotoxic agents
- Patients who are on dialysis
- Post-transplant candidates
- Those who continue to take alcohol
- Who stopped antivirals in case of viral related cirrhosis
- Patients with less than 18 years of age
- Pregnantand lactating mothers.

MELD was calculated by the following formula
MELD Score = 9.57 × loge(Serum Cr) + 3.78 loge(Serum Bilirubin) + 11.2 ×loge(INR) + 6.43

MELD Na was calculated by the following formula.

MELD-Na =MELD +1.59 (135 - Na)

eGFR was calculated by the CKD-EPI formula

$eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]

where SCr is serum creatinine (mg/dL), k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1.

CTP score

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

Measure	1 point	2 points	3 points
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
PT INR	<1.7	1.71-2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above. A total of 5 & 6 points is CTP-A class, 7 to 9 points is CTP-B class and 10 to 15 points is CTP-C class.

Statistical Analysis

The primary event of interest in this study was death. A p value <0.05 was used for statistical significance in all analyses. Logistic regression was used to assess the accuracy of serumsodium, hyponatremia and MELD as predictors of deathwithin 6 months of listing; patients transplanted within 6 months were dropped from the analysis. The concordance statistic(c-statistic), which is equivalent to the area under thereceiver operating characteristic curve, was also calculated.

RESULTS

Total of 64 Patients with a diagnosis of decompensated cirrhosis (CTP-C) who were attended to Gastroenterology OPD during the period from May 2015 to November 2016, were included in the study.All patients were enquired regarding the symptoms, drug usage, H/O alcoholism and other co-morbidities as per the proforma. The mean age of the study population is 51.4±8 years and 50 (78%) patients were male and 14 (28%) were female patients. Among the 64 patients, 30 (46.8%) were having H/O consuming significant quantities of alcohol. i.e., >60 gm/day for at least 10 years. 19(29.6%) patients had viral etiology as the cause of cirrhosis and 7 (10.9%) had both alcohol and viral etiology. In 8 (12.5%) patients there were other etiologies.

Serum sodium levels

Among 64 patients 35 patients (54.7%) were having serum sodium of >135mEq/L and 29 (45.3%) of them having serum sodium of ≤ 135mEq/L(table:1). Among 29 patients 8(12.5%) of them had sodium in the range of 130-134mEq/L, 12(18.75%) of them had sodium in the range of 125-129meq/L, 7patients (10.93%) had sodium in the range of 120-124mEq/L and 2 patients(3.125%) had sodium ≤120mEq/L.

Table 1. Serum Sodium levels in the study population

Sodium(mEq/L)	Number of patients	percentage
≥135	35	54.7
130-134	8	12.5
125-129	12	18.75
120-124	7	10.9
<120	2	3.125

Serum Creatinine levels

Out of 64 patients 26 (40.625%) had serum creatinine <1mg/dl and 38 (59.375%) had creatinine 1-1.5mg/dl (Table 2).

Table 2. Serum creatinine levels in the study population

Sr.Creatinine(mg/dl)	Number of patients	percentage
≤ 1	26	40.625
1.1-1.5	38	59.375

eGFR Values

Among the study population 10(15.625%) patients had eGFR of ≥ 90 ml/min/1.73m^2, 32(50%) patients had eGFR(table:3) had 60-89 ml/min/1.73m^2 and 22 (34.375%) of them had eGFR of <60 ml/min/1.73m.^{2}

Table 3. eGFR value in the study population

eGFR(ml/min/1.73m^2)	No of pts	%
≥90	10	15.625
60-89	32	50
<60	22	34.375

MELD Score

Among 64 patients 24(37.5%) of them had MELD of <20, 34(53.125%) patients had MELD in between 21-30 and 6(9.375%) patients had MELD > 30 (Table 4).

Table 4. MELD scores in the study population

MELD score	<20	21-30	>30
No of pts	24	34	6

MELD-Na score

Among 64 patients 18(28.125%) of them had MELD-Na of <20, 37(57.8%) patients had MELD-Na in between 21-30 and 9(14%) patients had MELD-Na > 30 (Table 5).

Table 5. MELD-Na scores in the study population

MELD-Na	<20	21-30	>30
No of pts	18	37	9

Survival Analysis

In the study out of 64 patients 18 patients (28.125%) died during 6 month follow up.

Table 6. Prevalence of hyponatremia in dead and alive

	Dead (%)	Alive (%)
Hyponatremia	11(61.1)	10(21.7)

Serum Sodium of <130meq/mL was taken as hyponatremia. Total 21 patients were having Sodium of <130meq/mL. Hyponatremia was present in 11(61.1%) of 18 dead patients and in 10(21.7%) of 46 survived patients.

Table 7. Mortality in different Sodium level groups

Sodium(mEq/mL)	No of patients	Dead
125-129	12	5(41.6%)
120-124	7	4(57%)
<120	2	2(100%)

As serum sodium decreases the mortality increases.

Table 8. eGFR in dead and alive

eGFR(ml/min/1.73m$^{2)}$	Total	Dead(%)	Alive(%)
≥90	12	2(16.6)	10(83.4)
60-89	32	8(25)	24(75)
<60	20	8(40)	12(60)

eGFR was ≥90ml/min/1.73m^2 in 10 patients. In those patients 2 died and 10 survived during 6 month follow up. eGFR was 60-89 ml/min/1.73m^2 in 32 patients. In those 8 died and 24 survived and eGFR was <60 ml/min/1.73m^{2}in 20 patients. In those patients 8 died and 12 survived during 6 month follow up.

Table 9. Univariate Analysis of Baseline Variables

Variables	Alive	Dead	p-value
Age (Years)	49±9	52 ± 10	0.430
Sex (M/F)	14/50	4/14	0.308
Ser. Bilirubin (mg/dl)	4.5 ± 2	6.4 ± 3	0.005
Ser. Albumin (g/L)	30 ± 6	28 ± 7	0.367
INR	1.8 ± 0.6	2.3 ± 0.9	0.04
Ser. Creatinine(mg/dl)	0.8 ± 0.3	0.9 ± 0.3	0.26
eGFR	67 ± 11	53 ± 10	0.02
MELD score	20.6 ± 5	24.5 ± 7	0.005
Ser.Sodium(mEq/L)	136 ± 6	129 ± 7	0.001
MELD-Na	22 ± 4.3	26.8 ± 5.2	<0.001

Age, sex and serum creatinine had no significance in survival of patients with end stage liver disease. (CTP-C) MELD score, eGFR,serum sodium and MELD-Na had significance in the survival.

Table 10. Univariate and Multivariate Cox Regression Summaries for MELD, Hyponatremia, and Serum Sodium in Predicting Death Considering 6-Month Follow-Up Data

Variable	C-STATIC
MELD	0.75
Hyponatremia	0.68
MELD score plus serum sodium	0.805
Bilirubin,INR,eGFR,Na	0.816

c-Static for MELD is 0.75 whereas c-Static for MELD-Na is 0.805 and for a model comprising bilirubin,INR,eGFR and sodium is 0.816. This implies MELD-Na and the model is better than MELD alone in estimating the survival of patients with decompensated cirrhosis. Serum creatinine is not a statistically significant tool for estimating the survival but p value of eGFR is <0.001 which denotes its a better tool for evaluating the survival in end stage liver disease. After combining serum sodium to a model that containing eGFR, that gives better prognostication for survival.

DISCUSSION

The aim of this analysisis to understand the relationship between serumcreatinine 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. This study is able to make a direct comparison between eGFR and serum creatinine 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. 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 rateof subjects with normal hepatic function. Second, cirrhotic patients often have decreased skeletal muscle mass and may receive a protein-poor diet for treatment of hepatic encephalopathy. Lastly, renal tubular creatinine secretion may be increased in patients with ESLD. All of these factors contribute to a falsely low serum creatinine level. In a study done by Ruf AE, Kremers WK, Chavez LL *et al*. The reported prevalence of hyponatremia in patients with cirrhosis and ascites ranges from 27 to 44% in agreement with the 32.8% observed in the present study. Borroni et al. showed that in-hospital mortality was significantly higher in patients with hyponatremia compared to those without this complication (26 vs. 9%), with the highest risk of death (48%) in the subgroup with serum sodium<125 mEq/L. In the present study also the prevalence of hyponatremia in dead patients (61%) is more than to that of survived patients. (15%) Based on this serum sodium is an important prognostic marker in survival of patients with end stage liver disease. May be serum sodium reflects the level of portal hypertension or grade of liver injury. Yu-Wei Chen, Chen-Wang Chang studied whether an estimated glomerular filtration rate(eGFR) is better than creatinine to be incorporated into MELD. They constructed three new equations (MELD-MDRD-4, MELD-MDRD-6, MELD-CKD-EPI). OriginalMELD score was a significant

predictor of in-hospitalmortality (odds ratio = 1.25, P < 0.001). MELDMDRD-4 excluded serum creatinine, with the coefficients refit among the remaining 3 variables, i.e., totalbilirubin, INR and 4-variable MDRD eGFR. This modelrepresented an exacerbated outcome over MELD score,as suggested by a decrease in chi-square (2161.45 vs2198.32) and an increase in -2 log (likelihood) (2810.77vs 2773.90). MELD-MDRD-6 included 6-variable MDRDeGFR as one of the variables and showed an improvementover MELD score, as suggested by an increasein chi-square (2293.82 vs 2198.32) and a decrease in-2 log (likelihood) (2810.77 vs 2664.79). Finally, whenserum creatinine was replaced by CKD-EPI eGFR, itshowed a slight improvement compared to the original MELD score (chi-square: 2199.16, -2 log (likelihood): 2773.07).

A study done by Young-Suk Lim *et al*[12], 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) and they are comparable with the present study. In the present study. In the present study eGFR of ≥90 ml/min/1.73m^2 survived better than to that of <60 ml/min/1.73m^2. The risk of mortality in high eGFR (16.6%) is lower than in patients with low eGFR(40%). Hence after this study it is evident that estimation of GFR carries better prognosis than serum creatinine alone. In summary When compared to serum creatinine, eGFR is a better tool in estimating survival of patients with ESLD.As eGFR decreases percentage of mortality increases. Thisstudy shows that hyponatremia is an excellent predictor of outcome in patients with advanced cirrhosis and significantly increases the efficacy of MELD to predict mortality. Serum sodium, in conjunction with eGFR, remains a useful addition to measures of mortality risk such as MELD.

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Authors' Contributions

Study concept and design: Allu Ravi Kumar
Analysis and interpretation of data: Allu Ravi Kumar
Drafting of the manuscript: Sravan Kumar Korrapati
Critical revision of the manuscript for important intellectual content: Girinadh
Statistical analysis: Sravan Kumar Korrapati.
Study supervision: Girinadh

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