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Original Research Article

Serum Sodium Concentration Profile in Cirrhotic Patients and its Effect on the Prognostic Value of the MELD Score

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Abstract: Serum sodium is common in cirrhotic patients and can predicts prognosis in cirrhosis and its addition to the model for end-stage liver disease (MELD) score and may improve the prognostic accuracy. The aim of the present study was to analyze the characteristics of serum sodium in decompensated cirrhosis and to assess the prognostic value of serum sodium in the prediction of mortality at 3 and 6 months and to compare the prognostic ability of the model for end-stage liver disease (MELD) score and other Na-containing MELD scores models for prediction of mortality. This study was conducted on 200 patients with decompansated cirrhosis (child B & C),patients were divided into two groups according to their serum sodium group(1)include patients with Na≤125,group(2) include patients with Na>125, Patients were evaluated, and their medical and laboratory profiles were evaluated and the severity of liver disease was assessed using Modified Child score ,and seven MELD scores models(MELD, MELD-Na, MELDNa, iMELD, uKELD, MESO index, and uMELD, The outcome was assessed at the 3- and 6- month for prediction of mortality. This study found that mortality among hyponatremic patients was more than non hyponatremic at both 3 and 6 month time point, and sodium containing-MELD scores models had better prognostic value for prediction of both 3 and 6 month mortality. The incorporation of Na into the MELD may enhance its prognostic accuracy.
Keywords: Cirrhosis; Model for end-stage liver disease; Serum sodium; Prognosis; mortality.

INTRODUCTION

Hyponatraemia in cirrhosis has been clearly described as an independent risk factor for mortality and is common in patients with end-stage liver disease [9].

Hyponatremia has been well described in associations with hepatorenal syndrome, ascites [3], and liver-related mortality [18]. Recently, the model for end stage liver disease (MELD) was introduced as a tool to predict mortality risk and to assess disease severity in patients with liver cirrhosis so as to determine organ allocation priorities [30]**.** Recent studies have shown that serum sodium concentration correlates with survival in patients with cirrhosis awaiting liver transplantation, and the suggestion has been made that serum sodium could be added to the calculation of model for end-stage liver disease score to improve the accuracy of this scoring system in organ allocation for liver transplantation [27]. 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 a liver score model [8].

AIM OF THE WORK

In this study, we evaluated serum sodium as a predictor of death in patients with cirrhosis and tried to found wheather the addition of serum sodium to MELD yields superior accuracy to MELD alone in predicting three and six month mortality**.**

PATIENTS AND METHODS

This study was conducted on 200 patients with decompansated liver cirrhosis admitted to department of Hepatology, Gastroenterology and Infectious diseases of Mansoura Health Insurance Hospital within the period between January 2014 to January 2015.

The study included All patient with decompansated liver cirrhosis 18 years or older. The exclusion Criteria were all patients with Chronic heart disease, Chronic lung disease, Chronic renal disease, hepatocellular carcinoma, patients with gastroenteritis, endocrinal.

Patients were subjected to the following: thorough history taking Age, Sex ,Residential history, Occupational history , history of Smoking and Alcohol intake and Medical history.

Clinical examination

general examination, cardiovascular, chest and abdominal examination.

Laboratory investigations

Included serum creatinine, markers of liver injury (Serum alanine aminotransferase (ALT), Serum aspartate aminotransferase (AST)and Serum alkaline phosphatase (ALP)). Liver function tests(Serum bilirubin (total, conjugated),Serum albumin and International normalizing ratio (INR)).

Viral markers: HBsAg, and Anti-HCVAb: by using third generation enzyme – linked immunosorbent assay technique (ELISA).

Serum sodium

The severity of liver cirrhosis was assessed using

i. Modified Child score [36]

Evaluation of the severity of liver cirrhosis was obtained in each cirrhotic patient with modified Child-Pugh score. This system relies on clinical and laboratory evaluation including ascites, grade of encephalopathy, serum albumin, bilirubin and prothrombin time.

Table 1: Clinical profiles

Parameter	1	2	3
Ascites	None	Easily controlled	Poorly controlled
Encephalopathy	None	grades 1-2	grades 3-4
Bilirubin (mg/dl)	< 2.0	2-3	> 3.0
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Prothrombin time (seconds increased)	< 4	4-6	> 6
Total numerical score	**Child-Pugh class**		
5-6	A		
7-9	B		
10-15	C		

ii. MELD score ={ 9.6 × log (creatinine mg/dL) + 3.8 × log (bilirubin mg/dL) + 11.2 × log (INR) + 6.4} [25].

iii. MELD-Na = MELD + 1.59 (135-Na) [8].

iV. MELDNa score = MELD-Na− [0.025×MELD× (140−Na)] + 140 [26].

V. MESO index = (MELD Score/SNa mEq/L) x 10 [22].

Vi. The United Kingdom MELD (uKELD) score = {(5.395 X ln(INR))+ (1.485) ln(creatinine, mmol/L))b+ (3.13 X ln(bilirubin, mmol/L)) - (81.565 X ln(Na, mmol/L))+ 435} [5].

Vii .The updated MELD (uMELD) = {1.266$\log_e$(1+creatinine) +0.939 $\log_e$ (1+bilirubin) +1.658 $\log_e$ (1+INR)} [25].

Viii.Integrated MELD (iMELD) = {MELD + (age (years) x 0.3) – (0.7xNa (mmol/L)) + 100} [28].

IV-Follow-up (survival)

All cases will be followed-up at three and six month to assess their survival.

STATISTICAL ANALYSIS

Statistical presentation and analysis of the results was done using SPSS computer package (SPSS, version 21) for data management. The normality of data was first tested with one-sample Kolmogorov-Smirnov test. qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test.

Continuous variables were presented as mean ± SD (standard deviation) for parametric data and Median for non-parametric data. Analysis Of Variance (ANOVA test) used for comparison of means of more than two groups (parametric data) and Kruskal Wallis Test for comparison of means of more than two groups (non parametric data). Kaplan- Meier test was used for survival analysis and statistical significance of differences among curves was determined by Log-Rank test. Cox regression analysis of factors potentially related to survival was performed to identify which independent predictors might have significant influence on survival. The area under receiver operating characteristic curve (AUC) curves were plotted to measure the performance of different prognostic scores in predicting the three and six month mortality of the studied patients.

Significance level

For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (p-value)The results was considered Non-significant when the probability of error is more than 5% ($p > 0.05$), Significant when the probability of error is less than 5%

($p \leq 0.05$), and Highly significant when the probability of error is less than 0.1% ($p \leq 0.001$).

RESULTS

This study was designed to include two hundred patients with liver cirrhosis attending Mansoura Health Insurance Hospital from January 2014 to January 2015. Patients were divided into two groups according to serum sodium, Group (I) included eighty seven patients(serum sodium≤125)and Group (II) included one hundred and thirteen patients (serum sodium>125).

Table 1: Overview of the studied groups

	Na≤125 (N=87)	**Na>125 (N=113)**	**P value**
Age			
Mean±SD	59± 9.831	56.460 ± 9.896	0.073
Range	28-86	30- 77	
Gender			
Male	77(88.51%)	92(81.42%)	P= 0.170
Female	10(11.49%)	21(18.58%)	
Occupation			
Non farmer	86 (98.85%)	112 (99.12%)	P = 0.852
Farmer	1(1.15%)	1(0.89%)	
Residency			
Urban	48(55.17%)	68(60.18%)	P= 0.477
Rural	39(44.83%)	45(39.82%)	
Alcohol	0	0	-
Smoking	11(12.64%)	22 (19.47%)	P= 0.197
Diuretic response	22(25.29%)	83(73.45%)	P<0.001*****
Spontaneous bacterial peritonitis	12(13.79%)	12(10.62%)	P=0.494
Hepatic encephalopathy	80(91.95%)	93(82.30%)	P=0.048*
Upper gastrointestinal bleeding	4(4.50%)	24(21.24%)	P=0.001*
Creatinine mg/dL (0.4-1.4)	1.192 ± .452	1.085 ± 0.472	0.105
Albumin gm/dL (3.5-5.1)	2.564 ± 0.440	2.680 ± 0.588	0.127
ALP (1 fold)	167.901 ± 75.663	150.286± 69.466	0.088
ALT (1 fold)	47.793 ± 30.250	51.00 ± 49.845	0.596
AST (1 fold)	58.770 ± 39.932	60.451± 46.783	0.788
Bilirubin mg/dl (0.2-1.1)	5.651 ± 4.402	5.229 ± 4.573	0.511
INR	1.644 ± .445	1.586 ± .4825	0.385
HCV Ab	51(58.62%)	73 (64.60%)	P = 0.388
HBs Ag	1(1.15%)	0	P=0.4
Non HBV non HCV	35(40.23%)	40(35.40%)	P=0.07
Child grade			
B	34(39.08%)	57 (50.44%)	P=0.23
C	53(60.92%)	56 (49.56%)	P=0.38
Child score			
Mean ± SD	10.514± 2.832	9.664± 1.806	P=0.01*

HCV Ab =hepatitis c virus antibody.**, HBV Ag**=hepatitis B virus antigen

Table 2: The severity of liver cirrhosis assessed by MELD scores among the studied patients

	Na≤125 (N=87)	**Na>125 (N=113)**	**P value**
MELD	18.198 ± 5.369	16.178 ± 6.215	0.0166*
uMELD	4.180 ± 0.648	4.001 ± 0.708	0.0534
UKELD	47.898 ± 3.951	40.227 ± 3.729	0.0000*
MELD-Na	44.799 ± 10.201	21.830 ± 8.263	0.0000*
MELDNa	30.109 ± 3.926	21.343 ± 5.250	0.0000*
iMELD	53.105 ± 7.204	41.106 ± 7.512	0.0000*
MESO index	15.402 ± 4.545	12.3 ± 4.685	0.0000*

MELD=model for end stage liver disease, **UMELD**=updated model for End-Stage liver disease, **UKELD**=united kingdom End-Stage liver disease, **MELD-Na**= Model for End-Stage Liver Disease with the incorporation of serum sodium, **IMELD**=integrated model for end stage liver disease, **MESO** index=the Model for End-Stage Liver Disease to sodium.

Table 3: Three months morality among studied group

	Na≤125 (N=87)	Na>125 (N=113)	P value
Survived	64(73.56%)	95(84.07%)	0.068
Died	23(26.43%)	18(15.93%)	

Table 4: Six months mortality among studied group

	Na≤125 (N=87)		Na>125 (N=113)		P value
Survived	36	41.37	66	58.41	0.017*
Died	51	58.62	47	41.59	

Table 5: Univariate Cox proportional hazards regression model for 3 month mortality.

	Hazad ratio	Standad error	Z value	P value	95% CI
Serum sodium	1.547	0.313	2.15	0.031*	1.040 - 2.300
Hyponatremia (Na≤125)	0.972	0.011	-2.34	0.019*	0.949 - 0.995
Child score	1.090	0.057	1.64	0.101	0.983 - 1.209
MELD	1.063	0.018	3.57	0.000*	1.028 - 1.099
uMELD	1.847	0.260	4.20	0.000*	1.387 - 2.459
UKELD	1.084	0.021	4.20	0.000*	1.043 - 1.124
MELD-Na	1.023	0.001	3.50	0.000 *	1.010 - 1.037
MELDNa	1.023	0.001	3.50	0.000*	1.010 - 1.037
iMELD	1.048	0.012	4.20	0.000*	1.025 - 1.071
MESO index	1.086	.0232	3.86	0.000*	1.041 - 1.132

MELD=model for end stage liver disease, **uMELD**=updated model for End-Stage liver disease, **UKELD**=united kingdom End-Stage liver disease, **MELD-Na**= Model for End-Stage Liver Disease with the incorporation of serum sodium, **iMELD**=integrated model for end stage liver disease, **MESO** index=the Model for End-Stage Liver Disease to sodium.

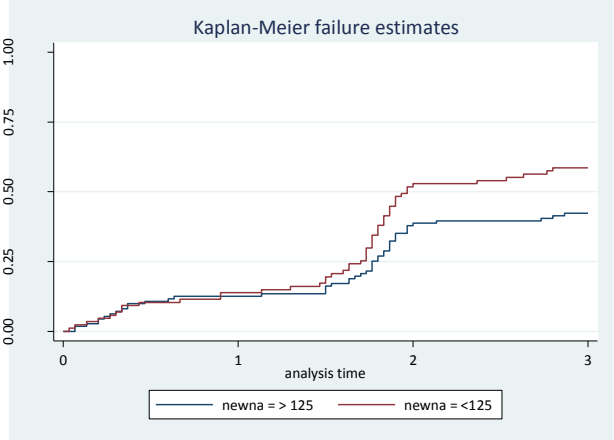

Fig-1: Kaplan-Meier survival graph for 3month mortality by recipient serum sodium concentration [Na] category
As seen in Kaplan Meier curve, patients with hyponatremia had higher mortality rate. Log rank test p value 0.02.

Table 6: Univariate Cox proportional hazards regression model for 6 month mortality

	Hazard ratio	Standad error	Z value	P value	95% CI
Serum sodium	1.792	0.3193	3.27	0.001*	1.264-2.541
Hyponatremia (Na≤125)	0.960	0.0102	-3.73	0.000*	0.941-0.981
Child score	1.081	0.049	1.71	0.086	0.989-1.182
MELD	1.075	0.016	4.70	0.000*	1.043-1.101
uMELD	1.898	0.247	4.93	0.000*	1.471-2.450
UKELD	1.104	0.019	5.75	0.000 *	1.067-1.142
MELD-Na	1.031	0.006	5.19	0.000*	1.019-1.043
MELDNa	1.031	0.006	5.19	0.000*	1.019 - 1.043
iMELD	1.058	0.010	5.59	0.000*	1.037 - 1.078
MESO index	1.105	0.021	5.18	0.000*	1.064 - 1.148

MELD=model for end stage liver disease, **uMELD**=updated model for End-Stage liver disease, **UKELD**=united kingdom End-Stage liver disease, **MELD-Na**= Model for End-Stage Liver Disease with the incorporation of serum sodium, **iMELD**=integrated model for end stage liver disease, **MESO index**=the Model for End-Stage Liver Disease to sodium.

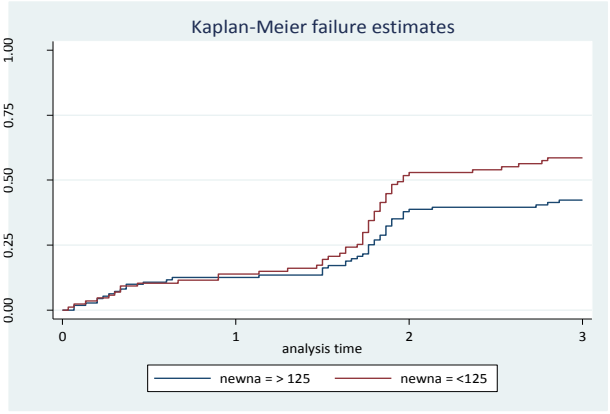

Fig-2: Kaplan-Meier survival graph for 3month mortality by recipient serum sodium concentration [Na] category

As seen in Kaplan Meier curve, patients with hyponatremia had higher mortality rate. Log rank test p value 0.0

Table 7: Death risk difference

Time	Na≤125 (N=87)	Na>125 (N=113)
1 month	13.7%	12.6 %
3 month	58.6%	42.3 %
6 month	78.2%	54.1%

Table 8: Accuracy of MELD scores in prediction of 3month mortality

		Cutoff value	Sensitivity	Specificity	PPV	NPV	AUC
3Months	**MELD-Na**	33.85	90.7	87.8	89.1	0.96	96%
	UKELD	44.05	81.5	75.5	78.6	0.90	90%
	MELDNa	26.5	85.2	71.4	76.7	0.89	89%
	iMELD	48.55	81.5	73.5	77.2	0.87	87%
	MESO index	14.90	66.7	53.1	61.01	0.65	65%
	MELD	20.0	51.9	57.1	57.14	0.55	55%
	uMELD	4.25	50.0	49.0	51.9	0.52	52%

AUC: Area under the curve **CI:** confidence interval **PPV**: Positive predictive value **NPV**: Negative predictive value

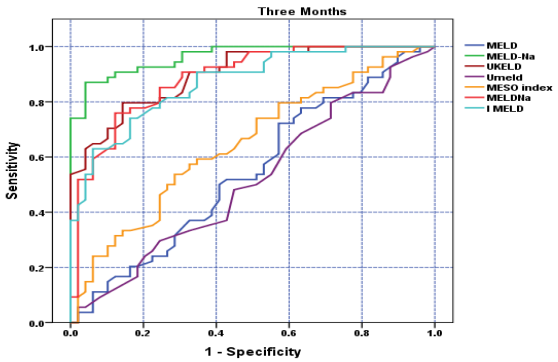

Fig-3: accuracy of MELD scores in prediction of 3 month mortality

ROC curve show that MELD-Na ,uKELD,MELDNa and iMELD had the highest AUC while MELD had the lowest AUC

Table 9: Accuracy of MELD scores in prediction of 6month mortality

		Cutoff value	Sensitivity	Specificity	PPV	NPV	AUC
6Months	**MELD-Na**	29.15	100.0	93.3	94.11	100.0	99%
	UKELD	43.20	100	80.0	84.2	100.0	98%
	MELDNa	26.80	81.3	93.3	92.9	82.4	90%
	iMELD	46.05	75.0	66.7	70.6	71.4	79%
	MESO index	14.75	50.0	46.7	50.0	46.7	49%
	uMELD	4.25	43.8	60.0	53.8	50.0	45%
	MELD	17.70	50.0	40.0	47.05	42.9	43%

AUC: Area under the curve **CI:** confidence interval

PPV: Positive predictive value **NPV:** Negative predictive value

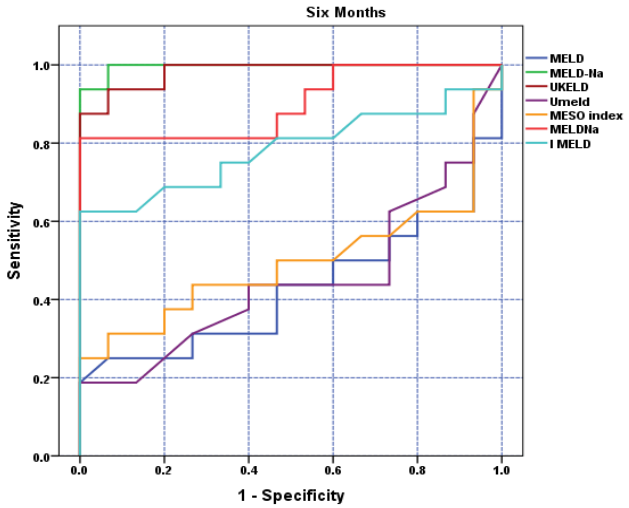

Fig-4: accuracy of MELD scores in prediction of 6 month mortality

ROC curve show that MELD-Na ,UKELD,MELDNa and iMELD had the highest AUC while MELD had the lowest AUC

Our study found that patients with low serum sodium Na≤125were 87(43.5%), patients with serum sodium Na>125 were 113(56.5%).**(table 1).**

There is no statistical significant difference between the groups as regards the age and gender, however patients with hyponatremia tends to be older and of male gender Concerning the residence, either rural or urban 44.83 % of group (I) cases had a rural residence in comparison with group (II) 39.82% which is statistically not significant.In addition, non-farming is found by history in 98.85% of group (I) and 99.12% of group (II) with no statistical significance (table 1).

All patients had no history of alcohol intake , and smoking history that reported by the two groups showed no statistical significant difference (table 1).

Diuretic response in non hyponatremic patients was significantly higher than hyponatremic patients (table 1). Hepatic encephalopathy was more predominant in Group(I) patients than Group(II) with high statistically significant difference. while upper gastrointestinal bleeding was higher in Group(II) than Group(I) with high statistically significant difference, there is no statistical significant difference between both groups as regard spontaneous bacterial peritonitis but it tends to be higher in hyponatremic patients (table 1).

There is no statistical significant difference between the two groups as regards creatinine, ALT, AST, alkaline phosphatase, total bilirubin, INR and albumin. however, serum creatinine, ALP, bilirubin and INR tend to be higher in group (I) (table 1).

Anti HCV Ab was positive in 58.62% of Group(I)cases, 64.60% of Group(II) cases ,with no statistical significance between the two groups. HBsAg was positive in one patient. Non HBV non HCV infection was 40.23% in Group(I) being higher than Group(II) 35.40%. Child score was significantly higher in group(I) patients and tends to be more towards Child grade C (table 1).

All MELD based scores were significantly higher in group (I) patients except uMELD was not significant (table 2).

There was no statistically significant difference between 2 groups as regards 3 months mortality however , it tends to be higher in Group(I) 26.43% than group Group(II) 15.93% (table 3).

There was statistically significant difference between 2 groups as regards 6 months mortality, mortality was higher in Group(I) 58.62% than group Group(II) 41.59% (table 4).

In unadjusted univariate Cox proportional hazards regression model for 3 month mortality, serum Na as a continues variable as well as Hyponatremia as binary one were significant predictors of mortality at 3 month time point. MELD, MELD-Na, MELDNa, uMELD, UKELD, MESO index, and iMELD were highly significant predictor of 3 month mortality Child score was not significant predictor of mortality at 3 month (table 5).

In unadjusted univariate Cox proportional hazards regression model for 6 month mortality, serum Na as a continues variable as well as Hyponatremia as binary one were significant predictors of mortality at 6 month time point MELD, MELDNa, MELDNa, uMELD, UKELD, MESO index, and iMELD were highly significant predictor of 6 month mortality Child score was not significant predictor of mortality at 6 month time point (table 6).

The risk difference between patients in Group(I)Na≤125 compared to those in Group(II)Na>125 is markedly increased over time with higher risk in Group(I) (table 7). **(**It is estimated at 1,3, and 6 month to be 2%, 16%, and 25% respectively.

For the study of different MELD scores and their accuracy for detection of 3 month mortality, MELD-Na gave the highest AUC 96% followed by UKELD, MELDNa, iMELD and MESO index their AUC were 90%, 89%, 87% and 65% respectively.

MELD and uMELD gave the least AUC 55% and 52% respectively. Positive predictive value was ranging from (89.1) to (51.9), and Negative predictive value was ranging from (89.6) to (47.1) (table 8).

For the study of different MELD scores and their accuracy for detection of 6 month mortality, MELD-Na gave the highest AUC 99% followed by UKELD, and MELDNa and iMELD, their AUC was 98%, 90% and 79% respectively. MELD had the least AUC 43% proceeded by uMELD 45%. Positive predictive value was ranging from (94.11) to (47.5), and Negative predictive value was ranging from (100) to (42.9) (table 9)**.**

DISCUSSION

Hyponatremia and impaired solute-free water excretion are well-recognized events in the cascade leading to hepatorenal syndrome [35] and ascites [3] and have been associated with increased liver-related mortality [18] . Serum sodium, like the components of the MELD score, is a readily available, reproducible, and objective laboratory test [35].

Therefore, serum sodium may be useful as a predictor of mortality in patients with advanced liver disease, and that the addition of serum sodium to MELD may be useful indicator of mortality [33].The utilization of the MELD has been demonstrated to have an equal or better ability in short-term or intermediate-term outcome prediction in comparison with the CTP system [34, 23]. In addition, the application of the MELD system has been shown to be a useful model in predicting the outcome of patients with cirrhosis undergoing surgical procedures for hepatocellular carcinoma or non–hepatocellular carcinoma conditions [6, 16].

The cutoff level of 125mmol/L was chosen because it is widely accepted to define hyponatremia in patients with cirrhosis, and it remained an independent predictor of mortality after controlling for the contribution of the most recent MELD score [9]. Furthermore, the addition of serum sodium to MELD at the time of listing for liver transplantation was associated with an increase in the accuracy in predicting both three and six month wait-list mortality with cirrhosis,while the level of 135 mmol/L is the lower normal value [9]**.**

In this study, Hyponatremia(serum Na≤125) was found in eighty seven patient(43.5%) ,this result was near to results of an Egyptian study Barakat *et al.,* [4] who reported that Hyponatremia was found in 59.46% of the patients.This result was larger than kim *et al.,* [26] who reported that (31%) of the patients had hyponatremia and also Angeli *et al* ., [1] who reported that The prevalence of hyponatremic patients presented with decompensated cirrhosis was (28%) .

In this study hyponatremia was predominant in male gender(88.51%) more than female(11.49%) also in older age (59± 9.8)this was in agreement with Angeli *et al* ., [1] who reported that male predominancy was more obvious (72.1%) than female (27%) ,and those with old age (58.9 ± 11.3)tends to be hyponatremic .

This study showed that (25.29%)of patients with hyponatremia respond to diuretics this result was near to Angeli *et al*., [1] .who reported that (17.1%) who responded to diuretics. Few studies have been specifically analyzed the relationship between serum sodium levels and responsiveness of ascites to diuretic therapy . Bernardi *et al.,* [7] and Angeli *et al*.,[2] showed that patients who do not respond to diuretics have lower serum sodium concentration compared with patients who respond to diuretics. Biggins *et al*.,[9] reported that the presence of serum sodium 130≤mmol/L was associated with lower glomerular filtration rate and solute-free clearance and a poorer response to diuretics compared with patients with serum sodium>130 mmol/L.

This study suggest a relationship between hyponatremic patients and patients presented with spontaneous bacterial peritonitis(13.79 %) being slightly higher than non hyponatremic (10.62%) these result was in agreement with Angeli *et al.,* [2] who stated that There was a clear inverse relationship between serum sodium levels and frequency of spontaneous bacterial peritonitis, Patients with hyponatremia had a much greater frequency complications compared with that of patients with normal serum sodium concentration. This association probably reflects the impairment in effective circulating blood volume that occurs in patients with cirrhosis in the setting of spontaneous bacterial peritonitis and may lead to hepatorenal syndrome in some patients, while others may develop only hyponatremia [39]**.** Hyponatremia has also been reported in the setting of sepsis unrelated to spontaneous bacterial peritonitis [42]**.**

This study showed significantly strong association between hyponatremia and incidence of hepatic encephalopathy(91.95%), compared to patients

with no hyponatremia(82.30%), this result was in agreement with Angeli *et al*., [2] who reported that More than one third (38%) of the patients with low serum sodium had an episode of hepatic encephalopathy within the previous month, compared with one fourth (24%) of patients with normal serum sodium. Although this association between hepatic encephalopathy and low serum sodium levels may be explained only on the basis of more severe liver failure among patients with hyponatremia, there is also the possibility that the two events may be pathophysiologically linked [2]. In fact, it has been demonstrated that low serum sodium levels in patients with cirrhosis are associated with a remarkable reduction in the cerebral concentration of organic osmolytes that probably reflect compensatory osmoregulatory mechanisms against cell swelling triggered by a combination of high intracellular glutamine, as a consequence of hyperammonemia, and low extracellular sodium [20, 37]. In experimental models of acute liver failure, the presence of hyponatremia is associated with larger brain swelling compared with normal serum sodium concentration [15].

Finally, in patients with acute liver failure and grade IV hepatic encephalopathy, the administration of hypertonic saline to increase serum sodium concentration reduces the incidence and severity of intracranial hypertension compared with a control group of patients receiving the standard of care [32].

This study reported that (4.5%) of patients with hyponatremia presented with gastrointestinal bleeding while patients with no hyponatremia showed higher percentage of gastrointestinal bleeding (21.24%) this result was highly significant and supported by Angeli *et al.,* [2] who reported that the frequency of gastrointestinal bleeding was similar among groups, indicating a lack of association between serum sodium values and this major complication of portal hypertension.

Angeli *et al.,* [2] finding was supported by Borroni *et al*., [11] who reported that Gastrointestinal bleeding is a clinical event present in some hyponatraemic patients, but their prevalence was not different from that found in patients with normal sodium levels. Barakat *et al.,* [4] disagree with this result and reported that there was a significant increase in Gastrointestinal bleeding in patients with hyponatremia compared to patients with no hyponatremia.

In this study Patients with hyponatraemia had higher values of serum bilirubin, INR, and lower values of serum albumin this result was in agreement with Borroni *et al.,* [11] who stated that higher values of serum bilirubin, INR, white blood cell counts patients and lower values of, serum albumin and haemoglobin were observed in hyponatremic patients.The same laboratory results were supported by Barakat *et al* ., [4] who reported that There was a significant increase in direct bilirubin and decreases in serum albumin and haemoglobin in the patients with hyponatremia and significant increases in white blood cell counts,serum bilirubin and INR.This could be explained by Salerno *et al*., [40] who stated that the impairment of liver function which is associated with impairment of free water excretion and which is probably a cause of the sporadic cases of "spontaneous" hyponatraemia.

In this study hyponatremia was associated with severe liver disease as seen in Child-Pugh classification, (60.9%)of patients were class C,this result was nearly in agreement with Angeli *et al.,* [1] who reported that Low serum sodium were more frequent in patients with severe liver failure (55% of patients belonged to Child-Pugh class C). Nevertheless, it should be pointed out that low serum sodium levels were also found in patients with moderate liver failure ,Child-Pugh B (39.08%) ,in this study which is in agreement with Angeli *et al.,* [1]who reported that low serum sodium levels were also found in patients with Child-Pugh B or even Child-Pugh A.

This result show that 3month mortality among hyponatremic patients (26.43%) it was more than patients who are not hyponatremic (15.93%) this result was near to Kim *et al.,* [26] who repoted that 3month mortality amony hyponatremic (39.15%) patients was more than those who are not hyponatremic (15%). Kim *et al.,* [26] stated that decrease in the serum sodium concentration was associated with an increase in the risk of death even after adjustment for the MELD score, The most meaningful differential effect of hyponatremia on mortality appeared to occur at a serum sodium concentration between 125 and 140 mmol per liter.

As regard 6 month mortality the results showed significantly higher mortality among hyponatremic patients (58.62%) in comparison to non hyponatremic (41.59%), Borroni *et al.,* [11] was in agreement with our results, he stated that 6month mortality among hyponatremic patients was significantly higher than non hyponatremic Borroni *et al*.,[11] may explain this result as he stated that hyponatremia is related to mortality because it reflects the severity of the disease and is associated with severe complications, such as bleeding or infection, bearing per se a strong negative prognosis but couldn't be used alone as a predictor of mortality.

This study show that the presence of hyponatremia is associated with increased risk of death in patients with decompensated cirrhosis , the observed mortality rate is greater for patients with hyponatremia than for patients without hyponatremia for all MELD score categories, Increased risk of death associated with hyponatremia is further indicated by the statistical

significance univariately in Cox regression models in conjunction with the MELD scores.This result was in agreement Ruf *et al.,* [38] who stated that patients with hyponatremia were associated with increased risk of death than in patients without hyponatremia with high statistical significance both univariatly and multivariatly in Cox regression models for all MELD score categories.

This study showed that In unadjusted univariate Cox proportional hazards regression model for mortality, serum sodium as a continuous variable as well as Hyponatremia as binary one were significant predictors of mortality at three and six month time point . This result was in agreement with Biggins *et al*.,[9] who stated that hyponatremia was strongly associated with an increased risk of mortality serum sodium as a continous variable and hyponatremia at any point while listed was associated with a 6.3- to 7.8-fold increase in risk of death.

In this study univariate cox regression showed that all MELD based scores were highly significant in prediction of three and six month mortality this result was in agreement with Marroni *et al*.,[31] who reported that the Cox regression analysis including MELD and MELD based scores in the model showed that all scores were significantly associated with mortality within three and six months of LT listing .

All MELD based scores included in this study were highly significant predictors of three and six month mortality however child score was not significant .This result was in agreement with Hassan and Abd El-Rehim., [19] who stated that the prognostic accuracy of the MELD systems is better than child pugh score sytem in predicting mortality in patients with liver cirrhosis, and Biselli et al., [10]who stated that in their study population, child pugh score system was not significant predictor of both three and six month mortality .Inspite of the widespread use of the Child pugh system for several decades in scoring the severity of cirrhosis due to its simplicity and good correlation with long-term outcome, its shortcomings, subjectivity and limited discriminatory ability decrease its validity as a predictor of mortality [17].These results could be explained by Biggins et al., [9] who stated that the Child-Turcotte- Pugh score was limited by a narrow range of disease severity (score range, 7-15) and the inclusion of subjective clinical criteria (hepatic encephalopathy and ascites).In contrast, the MELD score as used by the United Network for Organ Sharing stratifies patients into 35 categories (score range, 6-40) and is based solely on three readily available, reproducible, and objective laboratory tests: serum total bilirubin, the international normalized ratio of the prothrombin time, and serum creatinine [9].

This Study compared MELD score with other MELD scores incorporating sodium ,we found that MELD-Na gave the highest AUC followed by uKELD, MELDNa and iMELD they gave AUC >0.75 while MESO index followed by MELD score gave the least AUC ,the same result was found in both three and six month mortality ,These results were in agreement with Jiang *et al.,* [24] who stated that his study compared MELD with three new MELD based models containing Na. It is discovered that the AUCs of MELD-Na, iMELD, MESO were all larger than MELD in evaluating the short-term and intermediate- term prognosis of decompensated cirrhosis patients. Huo *et al*., [21] was in agreement with our three month results he reported that At three months, the MELD-Na had the highest AUC and was followed by the IMELD , MESO, and MELD. MESO had a significantly higher AUC in comparison with the MELD.but he disagree with our 6 month result ,he stated that At 6 months, the iMELD had the highest AUC and was followed by the MELD-Na , MESO, and MELD. Huo *et al.,*2008(21) also mentioned that the statistical difference between the iMELD and MELD-Na was not significant at both time points, and this suggests that these 2 models may be equally accurate for outcome prediction. Interestingly, in addition to the MELD and Na, the iMELD also takes into account the factor of age [21].

This results showed that sodium-based MELD scores had a better prognostic power than the standard MELD score in prediction of mortality in cirrhotic patient. This was similar to that reported by Luca et al., [28] who showed that iMELD had a better prognostic power than the standard MELD score in cirrhotic patients mortality.

Lv *et al*., [29] stated that MESO index had a better prognostic power than the standard MELD, and Biggins *et al.,* [9]who stated that among the scores proposed for prediction of mortality some of those incorporating sodium, namely MELD-Na and iMELD, are the most accurate , MELD-Na was the best drop-out predictor at 3 months, whereas both MELD-Na and iMELD emerged as highly performing scores in the medium term. Patel et al., [34] was in agreement with this results,he stated that MELD-Na, iMELD and MESO can exactly predict the prognosis of patients with decompensated cirrhosis for short and intermediate periods, and may enhance the prognostic accuracy of MELD.

This study has two important clinical implications. First, the predictive ability of the MELD can be improved by the incorporation of Na into the different forms of the equations. Second, we found that the MELD-Na consistently had the best predictive ability of the models at both three and six months.This result was in agreement with an Egyptian study by Hassan and Abd El-Rehim., [19] who stated that the MELD-Na score had the best accuracy and higher scores among other sodium containing models and were associated with higher mortality.

Ruf *et al.,* [38] confirmed this result and stated that the Risk of death across all MELD scores was higher for patients with advanced cirrhosis and for patients with hyponatremia than those without .Zhang *et al.,* [44] confirmed that hyponatremia was correlated with mortality and complications in decompensated cirrhotic patients and incorporation of Na into the MELD may enhance it's prognostic ability,and Biggins *et al*., [9] who stated that serum sodium < 126 mEq/L is a strong independent predictor of mortality. Addition of serum sodium to MELD increases the ability to predict 3- and 6-month mortality in patients with cirrhosis.

The MELD score had some limitations making it not the ideal system for OLT prioritisation as recently evidenced by increasing the numbers of pre-transplant deaths in individuals with low MELD scores, which suggests that MELD could not apply to all cirrhotics, especially those with ascites [13].

This study also analyzed the performance of two scores that do not include sodium, ie, MELD and uMELD they gave the lowest AUC among MELD scores,this could be explained by Biselli *et al.,* [10] who stated that the mortality risk of patients with renal failure differs from that of patients with normal renal function. Sharma *et al.,* [41] recently tried to improve MELD performance by modifying the three coefficients of the formula (uMELD) using data from the Scientific Registry of Transplant Recipients for all listed adult candidates in the United States. however, uMELD and standard MELD had comparable predictive values at three and six month, Such variant results could likely be explained by differences among enrolled patients [10].

Although the results of serum creatinine were within the normal range with a narrow SD, those enrolled by Sharma *et al*., [41] showed a slightly elevated mean creatinine with a wide SD. Therefore, creatinine may have influenced the score in their study [10].

The applicability of sodium-based MELD scoring systems in organ allocation has some limitations due to interlaboratory variability and the potential variability of serum sodium concentration after simple therapeutic maneuvers such as the administration of diuretics or intravenous hypotonic fluids or plasma volume expansion [12]. The measured serum sodium concentration under these circumstances does not reflect the true status of liver function. Despite these caveats, Na-based MELD scoring systems represent a major advance in the prognostic assessment of patients with cirrhosis [12].

In conclusion, hyponatraemia, which is a common event in liver cirrhosis, was used to assess cirrhosis related complicationsm, It is a useful marker to indicate a status of inadequate liver reserve that is frequently associated with ascites formation and liver-related mortality.

MELD score models combination with serum sodium (MELD-Na, MELDNa, uKELD, iMELD, MESO, uMELD) can all predict the prognosis of patients with decompensated cirrhosis for short and intermediate period, and may enhance the prognostic accuracy of MELD. The MELD-Na and iMELD are better prognostic models for day to day in clinical practice and outcome prediction in patients with decompensated cirrhosis for both mortaity and complications.

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