CORRELATION BETWEEN MODEL FOR END STAGE LIVER DISEASE (MELD) SCORE AND URINARY SODIUM - POTASSIUM RATIO IN PREDICTING HEPATORENAL SYNDROME IN CIRRHOTIC PATIENTS, TERTIARY CARE HOSPITAL, EAST GODAVARI.

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INTRODUCTION

Cirrhosis, being a late stage progressive hepatic fibrosis, is characterized by the distortion of architecture and formation of regenerative nodules [1].The natural history of the disease is characterized by an asymptomatic compensated phase followed by a decompensated phase marked by development of overt clinical signs, the most frequent being ascites, bleeding, encephalopathy, and jaundice [2]. Hepatorenal syndrome is a common cause of renal failure in cirrhosis and is characterized by functional renal vasoconstriction leading to severe reduction in GFR with minimal renal histologic abnormalities [3,4,5,6,]. Recently introduced therapies have demonstrated efficacy in the prevention and management of Hepatorenal syndrome. Therefore, it is important to identify the patients who are at risk of developing Hepatorenal syndrome early at the time of admission. This study focuses on identifying Hepatorenal syndrome using limited available resources which includes the MELD score which is objective, reproducible, and readily available in all settings. Random urinary sodium-potassium ratio can replace 24-hour collection for sodium excretion in daily clinical practice.

STUDY DESIGN AND PARTICIPANTS:

A Cross Sectional study was conducted in which all 147 subjects those who satisfied inclusive and exclusive criteria with cirrhosis of liver between 18 and 70 years of age attended to the Department of General Medicine, tertiary care hospital, Rajahmundry, East Godavari, India within the study duration from 1st Oct 2019 to 30th Sep 2021 were included after proper written informed consent being obtained. Patients having evidence of Hepatocellular carcinoma, previous kidney transplantation, liver transplantation, ongoing haemodialysis, diuretic therapy, intrinsic renal diseases, shock and nephrotoxic drug usage were excluded from the study. Protocol approval was obtained from institutional ethical committee.

METHODOLOGY:-

Data regarding demographic variables, clinical features (presenting complaints, ascites, jaundice, encephalopathy, history of alcoholism, etc), and clinical examination findings of liver cell failure were collected using a predesigned study proforma. Also, data regarding symptoms suggestive of renal impairment such as reduced urine output, periorbital edema, and haematuria were collected. Lab investigations including complete blood picture, coagulation profile, liver function tests, renal function tests, and viral markers for hepatitis B and hepatitis C were done and results noted. Complete urine examination, urine sodium, and potassium, 24 hours urine protein were done to rule out renal parenchymal disease, and results were noted. Ultrasound abdomen was done to confirm the diagnosis and to rule out structural abnormalities of the kidneys. Subjects with impaired renal function were identified clinically and by assessing the serum creatinine where values more than 1.5mg/dl were

suggestive of renal disease and less than 1.5mg/dl was considered normal. The major diagnostic criteria of hepatorenal syndrome defined by International Ascites Club(IAC) was applied to the cases with renal dysfunction. Those satisfying all the major criteria were graded as hepatorenal syndrome. The remaining cases were identified as non-HRS cases.

STATISTICAL ANALYSIS:-

All statistical analysis was done by using SPSS software version 20.0 and M.S Excel-2007. Descriptive data was expressed as Mean ± Standard deviation and percentages. Student Unpaired t test was performed to compare the means of two continuous variable groups. Chi-Square Test was done to assess the association among categorical variable. The cut-off value of independent predictors of mortality variables with best sensitivity and specificity was determined using Receiver Operating Characteristic (ROC) Curve. A two-tailed P value of <0.05 was considered statistically significant.

RESULTS:-

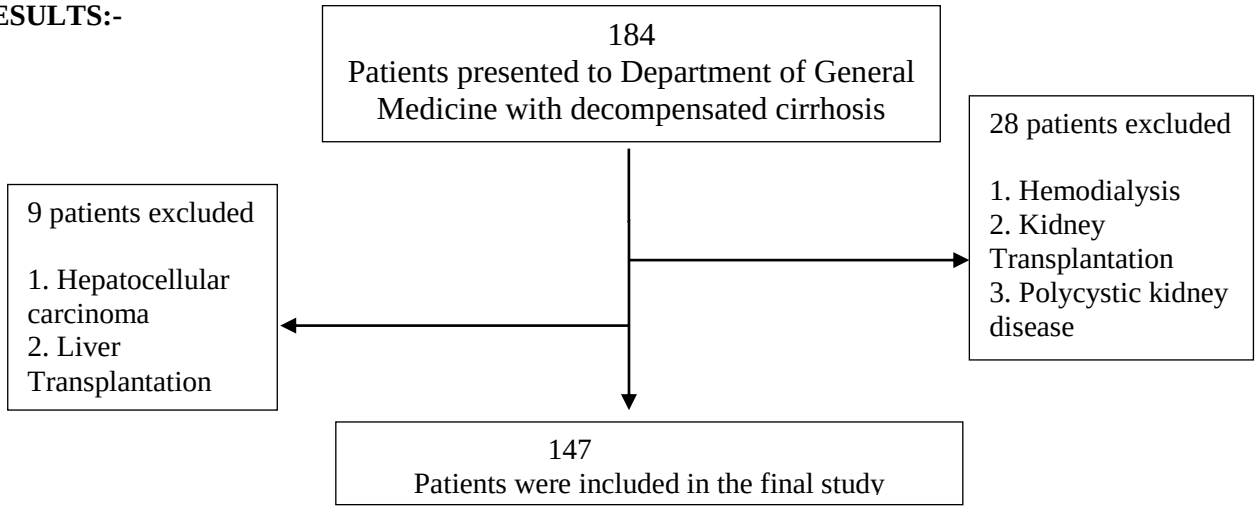

Figure 1: Schematic Diagram showing inclusion criteria of patients in the study.

A total of 184 patients presented to the department of General Medicine, tertiary care hospital, diagnosed as decompensated cirrhosis. Out of 184 patients, 37 were excluded due to various reasons and only 147 patients were finally included after scrutiny of all the criteria of exclusion in our study (Figure 1). The mean age of subjects with cirrhosis was 48.3 ± 11.69 years with majority of them in the age group of 41 to 60 years.124 patients (84%) were males and 23 patients (16%) were females. Alcohol was the most common etiological factor in 81 participants and Hepatitis B and Hepatitis C having 13 and 12 participants respectively.

Table 1: Baseline characteristics of study population

Parameter	**N=147**
Age, y	48.3 ±11.69
Male, n (%)	124 (84.35)
Comorbidities, n (%)	
Diabetes	39 (26.53)
Hypertension	38 (25.85)
Etiology of Cirrhosis, n (%)	
Alcoholic	81 (55.10)
Hepatitis B	13 (8.84)
Hepatitis C	12 (8.16)
Others	41 (27.89)
Presentation, n (%)	
Jaundice	135 (91.83)
Oliguria	76 (51.70)
Abdominal Distention	131 (89.11)
Malena	55 (37.41)
Hematemesis	29 (19.72)
Laboratory Parameters	
Hb (gm%)	9.52 ±1.74

TLC (cells/cumm)	10840 ±5107
Platelets (lakhs/cumm)	1.6 ±0.97
Serum Total Bilirubin (mg/dl)	4.01 ±5.76
Serum Albumin (g/dl)	2.50 ±0.44
Serum Creatinine (mg/dl)	1.93 ±1.48
Serum Sodium (mEq/L)	129.91 ±10.31
Serum Potassium (mEq/L)	4.33 ±0.59
24 hr Urine Protein (mg/day)	250.2 ±152
INR	1.7 ±0.5
Urine Na/K ratio	1.06 ±0.53
MELD score	19.93 ±8.08
With HRS, n (%)	26 (17.68)
All continuous data was expressed as Mean ± Standard Deviation; Hb, Haemoglobin; TC, Total Leucocyte Count; Na/K, Sodium/Potassium; INR, international normalised ratio; MELD, Model for End Stage Liver Disease; HRS, Hepato Renal Syndrome	

Outof147 patients,135 participants had jaundice at presentation,131had abdominal distension, 76 had oliguria, 55 had melena and 29 had hematemesis. Renal dysfunction was observed in 55 patients with serum creatinine ≥1.5 mg/dl. Among them, 26 were identified as hepatorenal syndrome (HRS) based on diagnostic criteria while the remaining 29 with renal dysfunction were grouped under the 92 cases with normal renal function as Non Hepatorenal syndrome (Non-HRS) (Table 1).

Table 2: Comparison of characteristics between patients with HRS and without HRS in study population.

Variables	**HRS (N=26)**	**NON-HRS (N=121)**	**P value**
Age, years	50±14.74	48.19±11.91	0.549
Male, n (%)	22 (84.61)	102 (84.29)	0.925
Diabetes, n (%)	11 (42.3)	28 (23.14)	0.087
Hypertension, n (%)	9 (34.6)	29 (23.96)	0.350
Alcoholism, n (%)	14 (53.84)	67 (55.37)	0.811
Abdominal Girth, Cm	106.27±12.85	99.66±12.18	0.014
Haemoglobin(gm%)	9.47±1.87	9.53±1.72	0.87
Platelet count (cells/mm^3)	138498±95533	170598±97914	0.12
Total bilirubin(mg/dl)	8.04±9.98	3.16±3.98	0.0001
Serum albumin(g/dl)	2.28±0.34	2.55±0.44	0.003
S. Creatinine(mg/dl)	2.79±1.70	1.75±1.38	0.001
S. Sodium(mEq/L)	123±9.9	131±9.9	0.0003
S. Potassium(mEq/L)	4.15±0.52	4.37±0.60	0.08
24 hours urine protein(mg/day)	259.8±96.6	248±161.4	0.72
INR	2.08±0.95	1.62±0.43	0.0002
Urine sodium(mEq/L)	7.57±1.77	34.8±24.3	<0.0001
Urine potassium(mEq/L)	27.27±23.57	32.09±20.7	0.29
U Na-K ratio	0.73±0.69	1.14±0.46	0.0002
MELD	26.61±10.21	18.52±6.8	<0.0001
All continuous data was expressed as Mean ± Standard Deviation; Hb, Haemoglobin; TC, Total Leucocyte Count; Na/K, Sodium/Potassium; INR, international normalised ratio; MELD, Model for End Stage Liver Disease; HRS, Hepato Renal Syndrome			

PRIMARY OBJECTIVE:-

On univariate analysis, higher total bilirubin (p <0.0001), lower serum albumin (p=0.003), higher serum creatinine (p=0.001), lower serum sodium (p=0.0003), higher INR (p=0.0002), lower urine sodium (p<0.0001), lower urine sodium-potassium ratio (p=0.0002), higher MELD score (p<0.0001) were significantly associated with presence of HRS in cirrhosis patients. (Table 2)

SECONDARY OBJECTIVE:-

In the total study subjects of 147, majority (56%) were with MELD scores in the range of 10 and 19. In the 26 study subjects with HRS, majority (42.4%) were with MELD scores in the range of 30 and 39. On comparing the MELD score among HRS and Non-HRS subjects, a statistically significant difference was observed with MELD scores >9. Of the 26 cases with Hepatorenal syndrome, the ratio of urine sodium-potassium is less than 1 in 16 (61.5%) cases whereas the value is more than or equal to 1 in 10 (38.5%) cases.

Table 3: Receiver operator curve analysis of MELD score and Urine Na/K ratio

Parameter	Cutoff	Sensitivity	Specificity	AUC (95 CI)	P value
MELD	14	96%	49%	0.757 (0.641-0.872)	0.003
Urine Na/K Ratio	0.95	69%	61%	0.695 (0.548-0.842)	0.004

Using ROC curve, cut-off values of clinically relevant selected independent predictors of in hospital mortality with best sensitivity and specificity were derived with MELD > 14, Urine Na/K ratio >0.95. (Table 3).

Table 4: Correlation between low urine sodium-potassium ratio and high MELD score in cases with hepatorenal syndrome.

HRS Status	U-Na/k ratio	MELD<15	MELD≥15	P value
HRS, n	U-Na/k<1	3	13	0.031
	U-Na/k≥1	6	4	
Non HRS, n	U-Na/k<1	27	34	0.151
	U-Na/k≥1	33	27	

A statistically significant correlation was observed between low urine sodium-potassium ratio and high MELD score in cases with hepatorenal syndrome (Table 4).

DISCUSSION:

The diagnosis of HRS is a challenge for clinicians, however early diagnosis and prompt management is vital for better outcome. Prior to confirming the diagnosis of HRS, patients need to receive appropriate volume resuscitation for 48 hours, and withdrawal of diuretics and other causes of AKI must be taken care of. This leads to a delay in the diagnosis of HRS resulting in deferral of appropriate treatment with albumin infusions, terlipressin, or other vasoconstrictors. In our study, we demonstrate that clinical and laboratory features in cirrhotic patients admitted with AKI may assist in predicting progression to HRS-AKI and potentially result in an earlier diagnosis of hepatorenal syndrome. Studies on predictors of the development of HRS are scarce and most studies are limited by difficulties in establishing the diagnosis and changing conceptual understanding of the pathophysiology and definition of HRS-AKI.

In this prospective cross-sectional study among cirrhotic patients admitted to tertiary care hospital during the study period, we evaluated the predictors of HRS. We found that higher total bilirubin, lower serum albumin, higher serum creatinine, lower serum sodium, higher INR, lower urine sodium, lower urine sodium-potassium ratio, and higher MELD score were significantly associated with the presence of HRS in cirrhotic patients. A statistically significant correlation was observed between low urine sodium-potassium ratio and high MELD score in cases with hepatorenal syndrome.

In patients with decompensated cirrhosis and portal hypertension, there will be splanchnic vasodilatation with decreased effective arterial blood volume causing activation of Renin-Angiotensin-Aldosterone-System (RAAS), causing retention of sodium and water leading to ascites and hyponatremia. On the other hand, RAAS activation causes renal vasoconstriction and decreased renal blood flow leading to Hepatorenal syndrome (HRS). [7].HRS occurs with the progression of cirrhosis with many precipitating factors such as large-volume paracentesis, gastrointestinal bleeding, spontaneous bacterial peritonitis, and alcoholism. Gines A et al. showed variables such as nutritional status, serum creatinine, serum sodium, serum potassium, urinary sodium excretion, and oesophageal varices had a predictive value for HRS in patients with cirrhosis and ascites. [8]

With the activation of neurohormonal systems in cirrhotic patients, retention of water and sodium causes hyponatremia and decreased urine sodium excretion, 24-hour urine sodium measurement is done to document the renal dysfunction along with serial elevation in serum creatinine predicting the progression of HRS. da Silva et al., concluded spot urine sodium/potassium ≤ 1 is sensitive and specific, substantially correlating with 24-hour urine sodium[9]enabling the use of this test in evaluation of cirrhotic patients with ascites, progressing to HRS.

MELD score from its time of description in 2000, at mayo clinic being initially adopted by the United Network for Organ Sharing (UNOS) for prioritising patients awaiting liver transplantation in 2002, had evolved as a validated scoring system for 3-month mortality because of its accuracy in prediction of prognosis, involving simpler components which had multifaceted usage and availability. Serum creatinine which is an important component of HRS also one of the components in calculation of MELD score, making its usage in predicting the HRS in cirrhotic patients, the basis for our present study.

We found a statistically significant correlation between MELD score and urinary sodium-potassium ratio in predicting hepatorenal syndrome in cirrhotic patients, similar to that being observed in Iqbal et al., study in Karachi. [10]

Higher bilirubin was shown as a predictor of the development of HRS. Many studies suggested that elevated bilirubin might result in hypotension and decreased response to vasopressors. Patients with elevated bilirubin and cirrhosis were termed cholaemic nephropathy where a decreased expression of aquaporins was suggested in some studies. There is a significant pathophysiological correlation between elevated bilirubin and the development of HRS wherein some studies have suggested less response to terlipressin and albumin among HRS-AKI patients.

Low serum albumin levels indicate impaired liver function, and hypoalbuminemia which eventually results in ascites, increased fluid third spacing, and intravascular volume loss, all of which are consistent with the pathophysiology of HRS. These events activate the renin-angiotensin system and cause kidney vasoconstriction. Ascites must be present in order to diagnose HRS, which is further supported by the over activation of neuro-hormonal responses that have been previously observed.

One independent predictor of HRS was found to be serum creatinine >2.5 mg/dl, but this was only statistically significant in participants without CKD at baseline. This may indicate the extent of renal dysfunction in patients with HRS, but it could also be a result of the previously specified criteria for diagnosing HRS, which call for a creatinine level greater than 2.5 mg/dL. Furthermore, because cirrhotic individuals typically have decreased muscle mass and hepatic creatine synthesis, blood creatinine may not be a constant and accurate indicator of the degree of renal failure in these patients. [11]

A serum sodium level of less than 130 meq/L is currently considered as hyponatremia in cirrhosis. In patients with cirrhosis and ascites, it has been estimated that the prevalence of blood sodium concentrations below 135, 130, and 120 meq/L is 49.4%, 21.6%, and 1.2%, respectively. Additionally, it has been asserted that serum sodium is a more rapid and precise test than serum creatinine for identifying circulatory dysfunction that results in renal failure and/or mortality [12]. Although those who have hyponatremia are at a very high risk of developing hepatorenal syndrome, the condition is also characterized by low serum sodium due to high levels of ADH, reduced GFR, and proximal salt reabsorption.[12]

INR was observed to play a pivotal role in early diagnosis of HRS wherein the levels were seen to be consistently low in patients with cirrhosis suggesting a pattern similar to those observed in other studies.[13,14]

It is well known that the most consistent urine finding in HRS patients is a startlingly low sodium concentration along with a high urinary osmolarity as a result of intact tubular function and activated tubular reabsorption of sodium. Our findings point to urine sodium as a predictive indicator for survival in HRS. This observation is new and possibly significant because it makes use of a readily available clinical parameter and integrates well-known urine traits of HRS patients. As a result, its predictive ability might be easily evaluated in future research using bigger patient populations. A high pre-treatment urinary sodium level may counteract the sodium depletion caused by arterial vasodilation because it causes the effective arterial blood volume to decrease, especially in the splanchnic bed, which in turn causes the activation of renal sodium-retentive mechanisms and intrarenal arterial vasoconstriction. Alternately, increased levels of sodium in the urine may indicate a less advanced destructive HRS cascade.[15]

Advanced cirrhosis, as evidenced by considerably worse ascites, lower systolic arterial pressure, and lower serum sodium levels, is characterised by splanchnic arterial vasodilatation and activation of vasoconstrictive mechanisms. Therefore, in individuals with decompensated cirrhosis, a random UNa/K value of less than 1 tends to indicate the degree of liver disease. Even when the random UNa/K ratio was not a cause of mortality on its own, it exhibited equal discriminative power to the MELD score, suggesting that UNa/K ratio alone might be an individual predictive marker of mortality.[16]

Our study being a pioneer and pilot study, had certain limitations such as a small sample size, done at a single centre, needing further validation by performing a large multicentre trial. This study could become a basis for a simpler way of predicting the hepatorenal syndrome in decompensated cirrhosis, initially at presentation to the hospital.

CONCLUSION:

Hepatorenal Syndrome being a grave complication of cirrhosis of liver requires emergent measures to be diagnosed and treated early. Simpler measures such as MELD score and Urinary Na/K ratio which were easily accessible at a preliminary set-up makes the diagnosis easier thereby warranting earlier management and better prognosis of the disease.

Further research is required to see whether this would make it simpler to diagnose or predict HRS in cirrhotic patients.

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