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IMPACT OF RENAL PROFILE AND SERUM SODIUM ON PATIENTS WITH END STAGE LIVER DISEASE (CTP – C) : A HOSPITAL BASED PROSPECTIVE STUDY FROM SUB-HIMALAYAN RURAL AREA

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ABSTRACT

BACKGROUND : Himachal Pradesh with a population with 68,64,602 is situated in the Northern part of India and is mainly a hilly state. Dr.Rajendra Prasad Government Medical College & Hospital in district Kangra is the only major referral hospital in this part of the state catering to approximately 60% of the population of the state mainly of rural background.. In this study End Stage Liver Disease has been defined by Child Turcot Pugh i.e CTP – C . Creatinine is produced in patients with cirrhosis lower than the the normal rate. Lower serum creatinine values lead to over-estimation of renal function by predictive equations , which can result in higher creatinine clearance calculated from timed urine collection compared with true GFR. Hyponatremia is a frequent complication of advanced cirrhosis. Hyponatremia in cirrhosis is associated with increased morbidity and mortality. There is evidence suggesting that hyponatremia may affect brain function and predispose to hepatic encephalopathy. We have designed the study to evaluate the impact of serum sodium and creatinine on 6 month mortality.

1. Most of the available literature on this topic from studies based on urban population and studies in developed countries. Moreover the inference from studies on western population or urban population may not be uniformly applicable to the rural.
2. Serum creatinine can not be a reliablemarker for mortality in cirrhosis as it may underestimate renal dysfunction.
3. In literature most of the study on hyponatremia was done in cirhhosis (CTP-A to CTP –C) but serum sodium may have a greater implication on patients with end stage renal disease, so we have included only CTP-C cirrhosis here.

METHOD : It is hospital based prospective study . The study has been conducted for a period of 15 months that include 9 months of data collection and 6 months of follow-up in all patient admitted in medicine department of Dr. RPGMC ,Tanda. Sample size is 100. Data have been analysed using computer software MS Excel. Primary end point death has been observed in patients with CTP C ESLD with the impact of serum sodium and renal profile on mortality.

RESULTS : Mean serum sodium level in study population was 130.83 mmol / L . Patient who died in 6 months had mean serum sodium level of 124.24 mmol/L and who survived had a level of 137.42 mmol/L . And this value was significant for 6 month mortality (P value < .05). In our study hyponatremia was associated with significant 6 month mortalilty which corresponds with other studies. Apart from mortality low serum sodium was associated with increased decompensation related hospital admission , HE and SBP. Serum creatinine mean value was 1.885 mg / dL. Patient who died by 6 months had value of 2.03 mg / dL and among survived patients it was 1.74 mg , but it was not stasistically significant. In our study high serum creatinine was not associated with significant mortality in end stage liver disease. Reasons of which may be attributable to low sample size , short follow-up period , prevalence of prerenal AKI and drug induced AKI which was corrected by albumin infusion or withdrawal of offending drugs.

CONCLUSION : Hyponatremia has a negative impact on survival of patients with ESLD. It is associated with hepatic encephalopathy , SBP , decompensation related hospital admission and death. Identifying hyponatremia in patient with ESLD is very important whereas renal dysfunction is ESLD is mostly avoidable and treatable. Judicial use of diuretics , contrast agents and water restriction can prevent hyponatremia in large group of patients. Pre-renal or drug induced azotemia can be treated succesfully by administration of albumin and withdrawal of offending drugs.

KEYWORDS : Cirrhosis , Hyponatremia , Renal Dysfunction , Child Turcot Pugh Score

INTRODUCTION :

Acute renal dysfunction occurs in 15% to 20% of hospitalised patients with cirrhosis [1] . and Hepatorenal Syndrome (HRS) is found in only 10% to 20% of such patients. HRS is found in 10% to 30% of such patients and appears to be an extension of the pathophysiology of prerenal azotemia and therefore potentially reversible [2] . The annual frequency of HRS in cirrhotic patients with ascites is roughly 8% and, in some reports, as high as 40% [3,4] . HRS develops in approximately 30% of cirrhotic patients who are admitted with SBP or other infection, 25% who are hospitalized with severe alcoholic hepatitis , and 10% who require serial large-volume paracentesis [5] . As renal function declines in cirrhosis, tubular secretion of creatinine increases, which can result in higher creatinine clearance calculated from timed urine collection compared with true GFR [6] .

In the majority of patients hyponatremia occurs in close association with renal failure and correlates with a poor prognosis. The mechanisms leading to hyponatremia in these patients are not known and deserve specific investigation. Finally, it is important to note that patients with hyponatremia constitute a unique population with a very high risk of devel oping hepatorenal syndrome [7] . Low serum sodium levels are a very common finding in patients with hepatorenal syndrome. In this situation, hyponatremia may be due not only to increased AVP levels but also to a markedly reduced glomerular filtration rate. Information on the impact of hyponatremia on health-related quality of life in patients both with and without liver disease is very limited. In patients with cirrhosis, hyponatremia impairs quality of life because patients require a restriction of daily fluid intake to prevent further reductions in serum sodium concentration, and this is usually poorly tolerated. In a recent study in a large population of patients with cirrhosis, hyponatremia was an independent predictive factor of the impaired health-related quality of life [8] . The main mechanisms that result in dilutional hyponatremia are renal hypoperfusion, which reduces the kidneys' ability to handle sodium and peripheralarterial vasodilation, which causes reduced effective volemia and increased secretion of arginine- vasopressin . Increased production of nitric oxide (NO) leads to arterial vasodilation and enhances the biological effects of arginine vasopressin (AVP), which plays a pivotal role in renal handling of sodium and water in cirrhosis . The systemic hemodynamic status of cirrhosis unloads the high-pressure baroreceptors, which results in the nonosmotic stimulation of AVP that is mediated by the baroreceptors [9,10] .

Mauro Bernardi , Carmen Serena Ricci and Luca Santi in clinical journal of medicine showed patients with hyponatremia in advanced liver disease has got increased mortality [11] . Hyponatremia in cirrhosis

is currently defined as a reduction in serum sodium below 130 mmol/L [12] .Normal of serum sodium concentration is 135 mmol/L, and a significant proportion of patients with cirrhosis have a serum sodium concentration above 130 mmol/L but below the lower limit of norma l values.These patients are not considered to have hyponatremia with the current definition but show pathogenic and clinical features similar to those of patients with serum sodium below 130 mmol/L. The prevalence of hyponatremia, as defined by serum sodium 130 mmol/L, is 21.6%. If the cutoff level o f 135 mmol/L is used,the prevalence increases upto 49.4% [13].

Patients with cirrhosis may develop two types of hyponatremia. In some patients, hyponatremia is due to important losses of extracellular fluid, most commonly from the kidneys (because of overdiuresis due to treatment with excessive doses of diuretics) or from the gastrointestinal tract. This condition, known as hypovolemic hyponatremia,is characterized by low serum sodium associated with contraction of plasma volume, lack of edema and ascites, signs of dehydration, and prerenal renal failure.

CLINICAL SIGNIFICANCE OF HYPONATREMIA IN CIRRHOSIS

There is limited information on the clinical consequences of hyponatremia in cirrhosis because hyponatremia almost always occurs in the setting of advanced liver failure, which causes a wide array of clinical manifestations.

BRAIN ADAPTATION TO HYPONATREMIA

Sterns RH and Silver SM thoroughly studied the impact of hyponatremia in the brain. Serum sodium decreases below normal values (hyponatremia) water moves into the cells to attain the osmotic balance , causing cell swelling [14,15].

Increases of cell volume may affect all cells but electrolytes are particularly important in the brain, as the brain size enlargement is limited by the skull. For this reason, brain cells have defensive mechanisms to limit cerebral edema [16]. The coordinate losses of both electrolytes and organic osmolytes from the brain cells enable a very effective regulation of brain volume during hyponatremia [17] . A few experimental and clinical studies have shown a reduced cerebral concentration of organic osmolytes, which is consistent with the existence of adaptive osmoregulatory mechanisms [18,19,20]. Evidence for a low-grade cerebral edema derives from experimental and human studies using magnetic resonance [21,22,23] several line of evidences suggest that . First, serum sodium levels and serum ammonia levels are major factors determining electroencephalographic abnormalities in cirrhosis[24] .

Second, in patients treated with transjugular intrahepatic portosystemic shunts, hyponatremia is a major risk factor for hepatic encephalopathy [25] .

Finally, a study by **Baccaro ME , Guevara M, Torre A , Arcos E, Martın-Llahı M , Terra C et al** in patients with cirrhosis using a time-dependent statisticical

analysis indicates serum sodium was an independent predictive factor of hepatic encephalopathy [26].

HYPONATREMIA AND LIVER TRANSPLANTATION

Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. demonstrated patients with cirrhosis and hyponatremia are at increased risk of developing central pontine myelinolysis after transplantation, and this is related to a rapid change in serum sodium in the early postoperative period[27,28.]

Arpan Mohanty, MD, and Guadalupe Garcia-Tsaos in a studiy showed that hyponatremia and HRS is the end stage complication of cirrhosis. And it is due to the most advanced stage of the various pathophysiologic derangements that take place in patients with cirrhosis [29] . Type 2 HRS usually progress slowly with the progression of cirrhosis, whereas type 1 an acute deterioration in kidney function associated with severe renal vasoconstriction and failure of compensatory mechanisms that are responsible for maintenance of renal perfusion [30].

The distinction between hypovolemic and hypervolemic hyponatremia is very important from a therapeutic perspective. Patients with hypovolemic hyponatremia must be treated with saline solutions aimed at increasing plasma volume and normalizing the low total body sodium along with the removal of the precipitating factor (usually diuretics). In contrast, patients with hypervolemic hyponatremia should be managed with interventions aimed at increasing renal solute–free water excretion with the final goal of reducing the excess of water with respect to sodium in the circulation. ***Gines P, Wong F, Watson HR , RuizdelArbolL , Bilic A , Dobry D*** studied Effects of a selective vasopressin V2 receptor antagonist , satavaptan (SR121463B) , in patients with cirrhosis and ascites without hyponatremia s like comparing vaptans to placebo, in which patients from both groups were managed with fluid restriction, the efficacy of this latter intervention in the placebo group in improving serum sodium concentration more than 5 mmol/L ranged from 0% to 26% [31-33.] Finally, albumin has been shown to improve serum sodium concentration in a few studies, but the number of patients included has been low, and the follow-up has been short [34,35]

MATERIALS AND METHODS

Study area : It is a hospital based study. conducted in Dr. Rajendra Prasad Government Medical College, Tanda at Kangra.

Study period : The study has been conducted for a period of 15 months that include 9 months of data collection and 6 months of follow-up. All patients admitted in the indoor ward of the department of medicine within this duration fulfilling the inclusion criteria will be included in the study.

Study design : Prospective / observational

Sample size : 100

Study population : Total number of patients included in the study comprises of patients with end stage cirrhotic ascites (CTP C) with renal diseases and without renal diseases. Patients with renal diseases will be further evaluated for presence of Hepato-renal syndrome and the impact of renal functions and hyponatremia on these both groups have been compared by the mean of primary event of interest i.e 6 month death.

INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA

All patients with chronic End Stage Liver disease (CTP-C) of varying etiology i.e
Alcoholic Liver Disease
Chronic Hepatitis B and C related cirrhosis
Non Alcoholic Fatty Liver Disease NAFLD etc.

EXCLUSION CRITERIA

Patients who did not give consent
Patient below 18 years
Patients with hypovolemia i.e Systolic Blood Pressure (SBP) <90 Diastolic blood pressure (DBP) < 60 mm of Hg
Patient with hepatocellular carcinoma (HCC) or other known malignany

METHODOLOGY

The patients have been included in the study as per the performa and inclusion criteria for 9 months and then follwed up for next 6 months from the date of assignment for the study for each patient.

Clinical examination are to be done for ascites and stigmata of chronic liver disease and apart from that necessary tests were done for free along with upper GI endoscopy. Data were collected after cosent.

STATISTICAL ANALYSIS

Data have been analysed using computer software MS Excel. Primary end point death has been observed in patients with CTP C ESLD with the impact of serum sodium and renal profile on mortality.

OBSERVATION AND RESULTS:

We have evaluated and follwed up 100 patients with CTP C cirrhosis over the period of 6 months in Dr Rajendra Prasad Govt. Medical college.

TABLE 1 : SEX COMPOSITION OF STUDY GROUP

	FREQUENCY	PERCENTAGE
MALE	83	83%
FEMALE	17	17%
TOTAL	**100**	**100%**

Age distribution were assesed from 18 years to 79 years. Age group from 40 years to 49 years constitute the major proportion among the patients studied (59 %).Most common complaints for hospital admission admission was ascites (98%) followed by hepatic encephalopathy (78%) and upper GI bleed (51%) in the form of hematemesis and malena . only 18 % patients presented with jaundice as a chief complaint. 10 patients had chief complaints of decreased urine output most of them had more than one presenting complaints in form of the combinations of above mentioned complaints. Among them ascites and hepatic encephalopathy and upper GI bleed (31%) was the most common combination followed by ascites and hepatic encephalopathy (21%) and ascites and UGI bleed (18%). Almost all patients had hepatic encephalopathy including minimal HE. Grade 2 hepatic encephalopathy was most common among them 48% , followed by grade 3 HE grade 1 and grade 4. Most common etiology for cirrhosis was alcohol related liver disease (61%) . Hepatitis B and hepatitis C related cirrhosis was present in patient with 6 and 8 patients respectively whereas 9 patients were diagnosed to have NASH related cirrhosis. Only 1 patient was having autoimmune hepatitis related cirrhosis and 1 had methotrexate induced cirrhosis. Exhaustive evaluation for 12 patients revealed nothing and possibility of cryptogenic cirrhosis was kept.

SBP was presnt in 18 patients among them 17 patients died within 6 months. Most common etiology was E.coli followed by klebsiella. All patient underwent upper GI endoscopy . among them 57 % patients had gastroesophageal varices and grade 2 varices were most common among them. 23 patients ahd portal hypertensive gastropathy. Among all patients presented with upper GI bleed 5 patients had peptic ulcer diseases. Rectal varices were present in 3 patients. Mean hemoglobin level , platelets and leukocytes counts were 8.94gm% , 98251 and 7652 per mm^3 respectively and none of them were associated with significant mortality in 6 months. Mean bilirubin level were 3.15 mg / dL higher level more than 5mg /dL were seen in patints with superimposed alcoholic hepetitis and ACLF (18 %). Mean AST , ALT and ALP level were 150 U/L , 71.3 U/L and 186.2 U/L respectively . Mean albumun was 2.65 g/dL. None of them were associated with higher 6 month mortality.

IMPACT OF RENAL PROFILE AND SERUM SODIUM ON CTP C CIRRHOSIS

Serum creatinine mean value was 1.885 mg / dL. Patient who died by 6 months had value of 2.03 mg / dL and among survived patients it was 1.74 mg /dL. 48 % patient had no renal dysfunctions in our study whereas 52% patients had renal dysfunction either in the form of pre-renal azotemia (11%) , drug induced nephrotoxicity (5%) , CKD (11 %) or HRS (24%). Commonly implicated drugs were diuretics and contrast media used for CECT. Though CKD were mostly present in diabetic patients associated with NASH and hepatitis B , hepatits C related CKD. HRS constitutes a majority of patients (46.15%) with renal dysfunction.

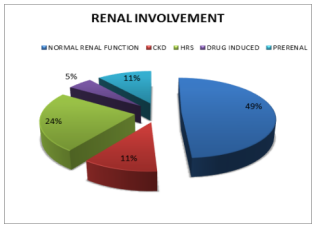


FIGURE 6 : MODE OF RENAL INVOLVEMENT

TABLE 3 : MODE OF RENAL INVOLVEMENT AND THEIR IMPACT ON MORTALITY

Total Patients With Renal Involvement (51%)			
Etiology	Percentage	6 Month Mortality	
		No	Yes
CKD	Count	2	9
	% of renal involvement	18.2%	81.8%
	% with 6 month death	6.1%	13.6%
DRUG INDUCED	Count	2	3
	% of renal involvement	40.0%	60.0%
	% with 6 month death	6.1%	4.5%
HRS	Count	7	17
	% of renal involvement	29.2%	70.8%
	% with 6 month death	21.2%	25.8%
PRERENAL AKI	Count	4	7
	% of renal involvement	36.4%	63.6%
	% with 6 month death	12.1%	10.6%

Comparison between serum creatinine and serum sodium shows that serum creatinine does not affect 6 month moartality (Pvalue < .185) but hyponatremia has significant impact on 6 month mortality (p value <.05) .

Parameter	6 Month Mortality	No of subjects	Mean	P value
Creatinine (mg/dL)	YES	66	2.032 ±1.05	.185
	N0	34	1.745 ±.91	

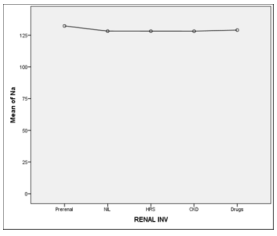


FIGURE 8 : RENAL INVOLVEMENT AND HYPONATREMIA : NO ASSOCIATION IN BETWEEN

SERUM SODIUM AND MORTALITY:

Total 47% patients in our study group had hyponatremia.
72% (34 patients) have hypervolumic hypernatrmia,10

patients had hypovolumic hyponatremia (21%) and 3 had euvolumic hyponatremia.

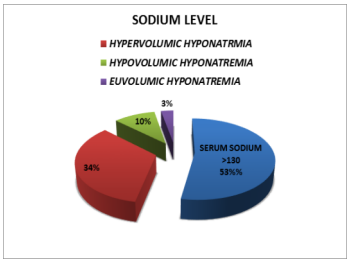


FIGURE 7: CLASSIFICATION AND PREVALENCE OF HYPONATREMIA

Mean serum sodium level in study population was 130.83 mmol / L . Patient who died in 6 months had mean serum sodium level of 124.24 mmol/L and who survived had a level of 137.42 mmol/L . And this value was significant for 6 month mortality (P value < .05).

TABLE 5 : SERUM SODIUM AND MOARTALITY

	6 month mortality	No of subjects	Mean Sodium ± SD	P Value
Na(mmol/L)	YES	66	124.24 ± 10.11	<.001
	NO	34	137.42 ± 6.63	

Not only mortality low mean serum sodium level was associated with number of hospitalisation for decompensation in 6 months , hepatic encephalopathy and SBP.

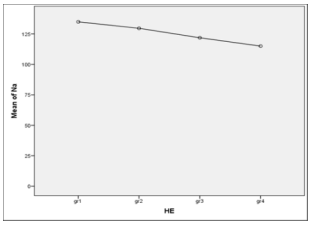


FIGURE 8 : MEAN SODIUM WITH GRADE OF HEPATIC ENCEPHALOPATHY

Among patients with SBP mean sodium level was 116.50 mmol/L with standard deviation of 4.8 but in patients without SBP serum sodium was 131.33mmol/L with SD of 10.15 with a significant p value of <.001 .

TABLE 6 : SERUM SODIUM LEVEL ON SBP

PARAMETER	SBP	NO	Mean ± SD	P value
SODIUM (mmol/L)	YES	18	116.50 ± 4.81	<0.001
	NO	82	131.33 ± 10.15	

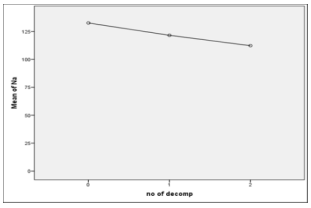


FIGURE 9 : LOW SERUM SODIUM IS ASSOCIATED WITH INCREASED NUMBER OF DECOMPENSATION RELATED HOSPITALISATION

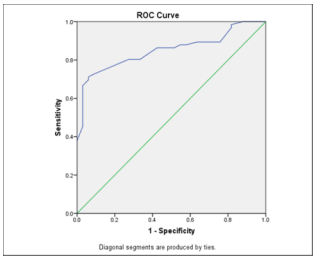


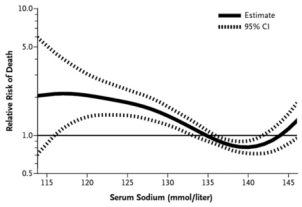
FIGURE 10 : ROC CURVE DEPICTING THE IMPACT OF HYPONATREMIA ON 6- MONTH MORTALITY

DISCUSSION

In the present study we have assesed the impact of renal profile and serum sodium on mortality with patients with CTP C cirrhosis. And we have found that not high creatinine level but low serum sodium was associated with significant mortality in end stage liver disease. Renal impairment, whether acute or chronic, is a highly preva- lent comorbid condition in cirrhotic patients, which is associated with a poor prognosis[36]. The detrimental clinical impact of the existence of either CKD and/or AKI on the outcomes of cirrhotic patients has been highlighted by several studies. In the study by Ojo et al[37] a prevalence of 26.8 % of stage 3-5 CKD was found in patients who subsequently received a liver transplant between 1990 and 2000 in the United States [however, in this study, analysis was based on the eGFR instead of measured GFR (mGFR)].. About the frequency of AKI in cirrhotic patients, some authors found that it could occur in 50% to more than 90% of patients in the perioperative period of LT and in 20% of hospitalized patients with LC[38] . Majority of the studies have found that there are increased odds ratio, which strongly suggests a negative impact of impaired renal function, either acute or chronic, on the survival of cirrhotic patients[39]. Though in our study high serum creatinine was not associated with significant mortality in end stage liver disease. Reasons of which may be attributable to low sample size , short follow-up period , prevalence of prerenal AKI and drug induced AKI which was corrected by albumin infusion or withdrawal of offending drugs .

Evidence of the relationship between hyponatremia and the severity of cirrhosis is clearly demonstrated in its close association with the prevalence of hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, the occurrence of interrelated complications [40,41] . and hepatic hydrothorax. Hyponatraemia is frequently encountered in patients with end-stage liver disease. The incidence and severity are variable, but have been shown to occur in up to 57% of hospitalized patients with cirrhosis[42]. In our study also it was present in 48 patients . Hyponatraemia has been shown to be an independent predictor of poor out- comes in cirrhosis and is often associated with refractory ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy[43,44].

Study in NEJM titled " Hyponatremia and Mortality among Patients on the Liver-Transplant Waiting List " published in 2008 showed that among patient waiting for liver transplantation MELD score and serum sodium are the best predictors for survival [45]. A total of 14,130 adults on the waiting list for liver transplantation met the inclusion criteria in 2005 and 2006. Predictor and outcome variables were complete for 13,940 patients (99%). Overall, 31% of the pa tients had hyponatremia (serum sodium concen- tration <135 mmol per liter), and in 2.5% of the patients, the serum sodium concentration was less than 125 mmol per liter. Both the MELD score and the serum sodium concentration were significantly associ- ated with mortality (hazard ratio for death, 1.21 per MELD point and 1.05 per 1-unit decrease in the serum sodium concentration for values between 125 and 140 mmol per liter; P<0.001.



Serum sodium concentration and and the relative risk of death after adjustment for MELD score

Serum sodium concentration has been recognized as an important prognostic factor in patients with liver cirrhosis. For example, hyponatremia has been associated with the hepatorenal syndrom,46,47,48,49 ascites 50 and death from liver diseas,51,52,53,54 .

In our study instead of MELD score we have evaluated patients with CTP C score and here also hyponatremia was associated with significant 6 month mortalilty which corresponds with other studies. Apart from mortality serum low serum sodium was associated with increased decompensation related hospital admission , HE and SBP.

ABBREVIATION :

CTP : Child Turcot Pugh score , ESLD : End Stage Liver Disease, HE :Hepatic Encephalopathy, SBP: Spontaneous Bacterial Peritonitis, GFR : Glomerular Filtration Rate.

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