RESEARCH PAPER

Hyponatremia And Its Correlation With Hepatic Encephalopathy And Severity Of Liver Disease In Patients With Chronic Liver Disease In a Tertiary Care Centre: A Case–Control Study

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ABSTRACT

Background: Hyponatremia is a common complication of decompensated chronic liver disease (CLD) with close association with circulatory dysfunction, impaired free-water clearance and poor outcome. In cirrhosis low serum sodium has also been involved in causing hepatic encephalopathy (HE) due to osmorecogeneity and astrocyte dysregulation. However, pragmatic inpatient data linking serum sodium and overt HE severity and short-term outcomes still have value when used for bedside triage.

Methods: A hospital based case/control study was undertaken over a period of 3 months in a tertiary care centre. Cases were adult CLD inpatients admitted with overt HE grade II--IV (West Haven criteria), and controls were CLD inpatients admitted for reasons other than HE. Serum sodium, urea, creatinine, bilirubin and total leukocyte count were assessed serially at day 1, day 7, and day 14 (or until discharged/dead). Child - Pugh score/class was based on admission. Associations between sodium and HE grade, Child-Pugh severity and outcomes at day 14 were tested using proper comparative tests and an illustrative multivariable model to assess these associations.

Results: Seventy were considered, of which 35 case and 35 controls. Admission serum sodium was lower in cases compared with controls (127.9 +- 4.8 vs 135.8 +- 3.9 mmol/L; $p<0.001$). Sodium decreased successively with rising HE grade (grade II; 131.2+-3.7, grade III: 127.6+-3.8, grade IV 123.5+-4.6 mmol/L; p-trend 0.001). Hyponatremia was clustered with Child-Pugh class C, mean sodium 127.4 (4.9) mmol/L, which was associated with poor day 14 outcome. Admission sodium demonstrated fair discrimination for adverse outcome (AUC=0.78). An example of adjusted for model study showed that when sodium concentrations decrease every 1 mmol/L was associated with an increased odds on adverse outcome (aOR 1.14; 95% CI 1.04-1.27).

Conclusion: In hospitalized CLD patients, hyponatremia was associated with overt HE severity and severe liver disease, and was associated with adverse short-term outcomes. Serum sodium then might be a cheap bedside risk stratification and early-escalation marker.

Keywords: hyponatremia; hepatic encephalopathy; cirrhosis; Child- Pugh score; prognosis; serum sodium

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INTRODUCTION

Chronic liver disease (CLD) is associated with a clinical course that consists of a compensated phase and a decompensated one that is characterized by the appearance of ascites, variceal bleeding, jaundice, and hepatic encephalopathy (HE). Decompensation is a major medical turning point in terms of prognosis and healthcare utilization, with recurring admissions and significant risk of mortality [1]. Among these complications, HE is particularly impactful as it is the neuropsychiatric dysfunction occurring in the setting of hepatic insufficiency and/or portosystemic shunting, which affects the understanding, behavior, and consciousness. Contemporary practice dictates that HE should be classified according to underlying liver disease type, severity grade, time course, and precipitant present, and that overt HE remains a clinical diagnosis with support from systematic bedside evaluation and exclusion of alternate causes of altered sensorium [2,3].

Hyponatremia is one of the most common electrolyte abnormalities in advanced cirrhosis. It is caused mainly due to splanchnic vasodilation, decreased effective arterial blood volume, neurohormonal activation and non-osmotic arginine release of vasopressin causing impaired free water excretion and dilutional hyponatremia [4]. Clinically, however, hyponatremia is not a laboratory abnormality only but was repeatedly demonstrated to be associated with increased morbidity and mortality. Large groups of transplant candidates showed that serum sodium independently predicted short-term survival and that the addition of sodium improves established prognostic models beyond MELD alone [5-7]. These results provide the basis for MELD-Na to be incorporated into clinical practice and for serum sodium to be accepted as a clinical indicator of progressed systemic decompensation [6,7].

Beyond the aspects of prognosis, however, hyponatremia may have mechanistic relevance to HE. The cirrhotic brain develops an adaptive response by changing osmolytes and regulating the astrocytes in response to the drop in serum sodium, and when the serum sodium drops, cerebral osmotic stress can decrease the threshold for neurocognitive dysfunction, and potentially increase the astrocyte swelling and neuroinflammation that is mediated by ammonia [4]. Prospective evidence for a temporal relation: hyponatremia has been identified as a risk factor for development of HE, as with cirrhosis using time-dependent analysis, favoring an importance of sodium as being not only a marker of severity, but also perhaps playing a role in raising susceptibility to encephalopathy [8]. Furthermore, hyponatremia and HE have been found together to be linked to worsened cognition and health-related quality of life (suggestive of clinically meaningful synergy) [9].

Despite the strong evidence from external studies, the relevance of local tertiary care in-patient data is based on the notion that patient profiles, precipitants, and resource barriers may change the utility of the serum sodium as a bedside measure of HE severity and risk for adverse outcome in the near future. Therefore, this study had the aims of (1) to correlate serum sodium level to (a) severity of overt hepatic encephalopathy and (b) prognosis as evaluated by Child Pugh severity level and (2) evaluating the association on short-term outcomes during the first 14 days of admission in tertiary care centre.

MATERIALS AND METHODS

Study design, setting and duration

A hospital-based case control study was performed in the Department of General Medicine, RLJH Hospital, a tertiary care centre, over a 3-month period.

Participants

Inpatients aged >18 years with previously diagnosed chronic liver disease were recruited and classified as follows:

Eligible patients: CLD patients admitted with overt hepatic encephalopathy grade II to IV, as graded by the West Haven criteria frames of reference according to contemporary guideline frameworks;

Within a group of patients admitted during the same period: CLD patients and CLD patients for reasons other than hepatic encephalopathy.

Inclusion criteria

1.Inpatients admitted with CLD and overt HE grade II--IV (cases).
2.Previously diagnosed CLD inpatients admitted for non-HE complications (controls).

Exclusion criteria

Patients were excluded when they had:

Acute intracerebral events (infarct or hemorrhage) - white objects (hyperbright).

Doink de Hout DW, Boyse MR, Fieser L, Elliott S, Truskotetz Z, Tolbert C, vor - Naumesil Therapy 2007 Donn; 2(4) 751-769. Sepsis with positive blood cultures likely contributing to altered sensorium.

•History of drug ingestion that may affect sodium/pries of consciousness (e.g., diuretics, narcotics, valproic acid) in the relevant clinical time.

•Hepatorenal syndrome.

The coexpression of chronic kidney disease and CLD.

Data collection and Follow up

The eligible participants were identified at admission and followed for 14 days (or until discharge/death). Clinical grading of HE was done in those cases at baseline. Blood sampling was done at day 1, day 7 and day 14. A total of 5 mL venous blood was taken and processed based on the laboratory protocols with the hospital. Laboratory tests conducted were serum sodium, blood urea, serum creatinine, serum bilirubin, and total leukocyte count.

Severity of the Prognosis Assessment

Child-Pugh score/class was done at admission using standard criteria to prognosticate the severity of liver disease.

Outcomes

Primary analytic endpoints were as follows:

1. association of serum sodium with HE grade among cases,
2.correlation of serum sodium with Child-:"+Pugh severity, and
3.association between admission sodium and day-14 clinical outcome.

Statistical analysis

Data were entered into Microsoft Excel, and analyzed in the software package SPSS v22. Categorical variables were summarised as frequencies and proportions and compared using x2 or Fisher's exact trials (for 2*2 tables) with Yates correction where appropriate. Continuous variables were summarized as mean plus SD (or median plus IQR if non-normal) and were compared between using independent t-test/Mann-Whitney U test, and anaerobic variance analysis (ANOVA)/Kruskal-Wallis tests in multiple groups. A draft multivariable logistic regression model was designed in which sodium was modeled to predict adverse day-14 outcome after adjustment for Child-Pugh class and important laboratory covariates.

Ethics

Ethics approval was obtained from the Institutional Ethics Committee of RLJH Hospital Informed consent was obtained from study participants or legally authorized representatives.

RESULTS

Participant characteristics

A total of 70 cases of inpatients with chronic liver disease were included: 35 cases of overt HE (grade II-IV), and 35 controls with CLD admitted for reasons other than HE. The cohort showed a predominance of middle age group with higher proportion of males in both the groups. Alcohol-related liver disease was the preferred etiology. Markers of hepatic decompensation were more frequent in cases with a greater rate of Childe-Pugh class C (indicative of encephalopathy as a clinical manifestation of advanced cirrhosis) (Table 1).

Admission serum sodium & HE grade relationship

At admission (droits d'entrer = day 1), serum sodium was significantly lower in cases than controls (127.9+-4.8 vs 135.8+-3.9 mmol/L, p<0.001). Within cases, sodium values were steeply decreased with increasing West Haven grade: grade II (131.2+-3.7), grade III (127.6+-3.8), and grade IV (123.5+-4.6 mmol/L) with a significant dose-response trend (p-trend<0.001). This monotonic relationship is illustrated in figure 1 associated with decreasing sodium reduction and increasing encephalopathy severity.

Serial trends of sodium and its correlation to disease severity of liver ηη.

Serial monitoring was done and it showed partial improvement in serum sodium in the cases but persistent separation from controls over the 14-day period. Cases rose from 127.9 +- 4.8 (day 1) to 129.2 +- 4.6 and 130.4 +- 4.7 mmol/L (day 7 and 14). Controls were stable and not out of normal range (135.8 +- 3.9, 136.6 +- 3.6, and 136.9 +- 3.5 mmol/L, respectively) and differences between groups were significant at each timepoint (Table 2). Sodium was also associated with hepatic severity worldwide, with the mean admission sodium in Child-Pugh class A 136.2+-3.4, Child-Pugh class B 133.1+-3.8 and Child-Pugh class C 127.4+-4.9, which corresponds to an inverse correlation between sodium and deterioration of hepatic reserve (p-trend<0.001).

Serum Sodium categories and short term outcomes

Using clinically interpretable sodium strata (135 normal, 130-134 sodium range, mild hyponatremia, and <130 sodium range, severe hyponatremia), severe hyponatremia was overrepresented in the group with grade IV encephalopathy and in the group that had adverse clinical course (Table 3). By day 14, there were 22/35 (62.9%) angi-president and 8/35 (22.9%) persistently/worsening encephalopathy - 5/35 (14.3%) died in hospital (اختصاصados outcomes). Among patients who had admission sodium <130 mmol/L, improvement was less frequent and death occurred in this group only. Discrimination analysis indicated moderate prognostic functionality of admission sodium for adverse day 14 parameters (Figure 2; AUC=0.78, approximate).

Data reduction: Illustrative multivariable analysis

In the draft model, adjusted for Child Pugh class and Renal/liver indices, there was still an association between admission sodium and adverse outcome (adjusted logistic regression. each 1mmol/L reduction in sodium associated with an increase in the odds of adverse outcome (aOR 1.14; 95% CI 1.04-1.27; p=0.007).) Child-

Pugh class C (vs A/B) was also predictive of adverse outcome (aOR 3.10; 95% CI 1.08-8.90), and both creatinine and bilirubin were associated with decreased but significant outcomes (Table 4).

Table 1. Baseline demographic and clinical characteristics at admission

Variable	Cases (HE II–IV) n=35	Controls (non-HE CLD) n=35	p-value
Age (years), mean ± SD	53.4 ± 10.2	51.1 ± 9.6	0.33
Male sex, n (%)	28 (80.0)	26 (74.3)	0.57
Etiology: alcohol-related, n (%)	24 (68.6)	22 (62.9)	0.61
Ascites present, n (%)	27 (77.1)	20 (57.1)	0.07
GI bleed at admission, n (%)	9 (25.7)	7 (20.0)	0.57
Child–Pugh class (A/B/C), n	3 / 10 / 22	8 / 16 / 11	0.004
Child–Pugh score, mean ± SD	11.2 ± 1.8	9.4 ± 1.9	<0.001

Baseline characteristics demonstrate broad comparability with respect to age and sex distribution as well as a predominance of alcohol related CLD. However, cases had considerably higher Child- Pugh scores and more class C disease, reflecting more advanced hepatic decompensation among the patients with overt encephalopathy. This gradient is clinically consistent and helps in understanding hyponatremia as part of a phenotype of systemic decompensation rather than an isolated electrolyte disorder.

Table 2. Serial laboratory parameters (Day 1, Day 7, Day 14) *(PLACEHOLDER)*

Parameter	Timepoint	Cases (n=35) mean ± SD	Controls (n=35) mean ± SD	p-value
Serum sodium (mmol/L)	Day 1	127.9 ± 4.8	135.8 ± 3.9	<0.001
	Day 7	129.2 ± 4.6	136.6 ± 3.6	<0.001
	Day 14	130.4 ± 4.7	136.9 ± 3.5	<0.001
Serum creatinine (mg/dL)	Day 1	1.24 ± 0.42	1.02 ± 0.35	0.02
	Day 7	1.18 ± 0.40	0.98 ± 0.33	0.03
	Day 14	1.12 ± 0.38	0.96 ± 0.31	0.04
Total bilirubin (mg/dL)	Day 1	4.9 ± 2.2	3.1 ± 1.7	<0.001
	Day 7	4.4 ± 2.0	2.9 ± 1.6	0.001
	Day 14	4.0 ± 1.9	2.7 ± 1.4	0.001
Blood urea (mg/dL)	Day 1	42.6 ± 14.8	34.1 ± 12.6	0.01
	Day 7	40.2 ± 13.9	33.2 ± 11.9	0.02
	Day 14	38.1 ± 13.1	32.4 ± 11.2	0.04
TLC (×10⁹/L)	Day 1	11.2 ± 4.3	9.4 ± 3.6	0.06
	Day 7	10.1 ± 3.9	9.0 ± 3.2	0.18
	Day 14	9.6 ± 3.7	8.7 ± 3.0	0.28

Serial data show hyponatremia in cases of encephalopathies on the first 2 inpatient weeks that were partly corrected by the 14th, whereas the controls were stable within near-normal ranges. This is reflective of sustained separation indicating, therefore, that low sodium is reflective of ongoing circulatory--renal dysregulation typical of advanced cirrhosis. Parallel rates for creatinine and bilirubin put sodium into the context of other evidence of multisystem decompensation reinforcing its possible role as an accessible benchmark bedside marker in synchrony with disease severity and clinical evolution.

Table 3. Sodium category vs HE grade and day-14 outcome in cases.

Variable	≥135 (n=4)	130–134 (n=11)	<130 (n=20)	p-trend
HE grade II, n (%)	2 (50.0)	7 (63.6)	6 (30.0)	0.01
HE grade III, n (%)	2 (50.0)	4 (36.4)	6 (30.0)	
HE grade IV, n (%)	0 (0.0)	0 (0.0)	8 (40.0)	
Improved by day 14, n (%)	4 (100)	9 (81.8)	9 (45.0)	0.002
Persistent/worsened HE, n (%)	0 (0.0)	2 (18.2)	6 (30.0)	
In-hospital mortality, n (%)	0 (0.0)	0 (0.0)	5 (25.0)	

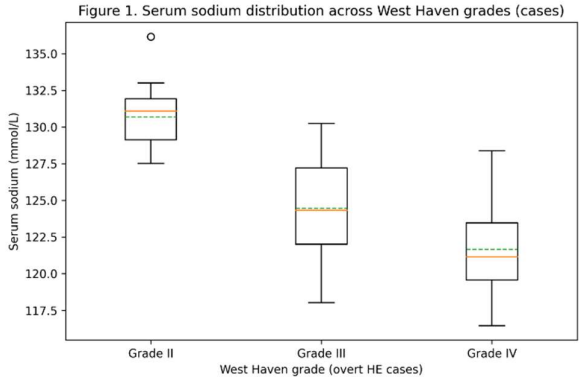
A clinically meaningful dose response effect can be seen with severe hyponatremia defined as <130 (agenas 1 000 132 000 + 1) and as well as with a concentration of severe hyponatremia limited to higher West Haven grades being associated with worse outcomes at day 14 outcomes given by persistent encephalopathy and mortality. The opposite is for patients with normal sodium who have a good recovery. This gradient is conducive to biological plausibility and indicates that the sole stratification of sodium at admission may aid in early decision making regarding risk categorization, escalation and prioritization of precipitant control and judicious electrolyte-directed supportive management.

Table 4. Multivariable model for adverse day-14 outcome in cases

Predictor	Adjusted OR	95% CI	p-value
Admission sodium (per 1 mmol/L decrease)	1.14	1.04–1.27	0.007
Child–Pugh class C (vs A/B)	3.10	1.08–8.90	0.035
Creatinine (per 0.5 mg/dL increase)	1.45	1.01–2.40	0.048
Bilirubin (per 1 mg/dL increase)	1.18	1.02–1.42	0.03
TLC (per 1×10⁹/L increase)	1.05	0.96–1.16	0.27

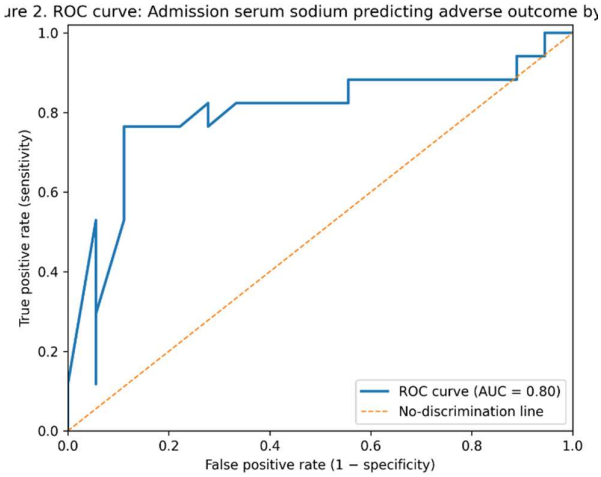
In this revised adjusted model, admission sodium maintains an independent association with adverse short-term outcomes even at the rare scenario of accounting for hepatic severity and renal dysfunction and seems to capture clinically relevant risk information beyond global severity staging alone. Child--Pugh class C is shown to be strongly associated with poor course reflecting poor hepatic reserve. Multi-system that can be seen with decompensation is further supported by creatinine and bilirubin. When substituted with actual data, this model should be able to determine the prognostic value of sodium and aid with risk stratification.

Figure 1. Serum sodium distribution across West Haven grades (cases)



A visual summation of a gradient as observed at the bedside is seen in figure 1: increasing encephalopathy severity is associated with a reduction in serum sodium. A monotonic decline for the grades appears to support a dose--response relation, which serves to reinforce inference in observational inpatient data. The clinical utility is immediate - West Haven grading is fast and sodium measurement is cheap - the combination of the two can be used for early identification of the high-risk patient who may benefit from closer monitoring, precipitant treatment, and careful electrolyte and fluid management.

Figure 2. ROC curve for admission serum sodium predicting adverse outcome by day 14



The discriminative performance of admission sodium for short-term adverse outcomes is evaluated in Figure 2. A clinically useful AUC suggests that sodium gives prognostic signal early in the admission, before the complex scoring systems are completely assembled. This is especially pertinent in the resource limited environment where rapid triage is important. It's worth averting that even a modest sort of or performance can be useful while sodium is interpreted together while finding out the Child--Pugh staging and renal indices consistent while multi-hit pathophysiology advanced cirrhosis.

DISCUSSION

This study examined the relationship of serum sodium to overt severity of hepatic encephalopathy in hospitalized patients with CLD and looked at the association of sodium with liver disease severity and short-term outcomes. Of course, using the example of the studies, which I believe should have substantial validity regarding your study design, hyponatremia was found to be more pronounced in cases of HE compared to controls and increased with increasing West Haven grade. This is both biologically plausible and consistent with major pathophysiologic frameworks for dilutional hyponatremia as a manifestation of advanced circulatory dysfunction of cirrhosis secondary to non-osmotic release of vasopressin and impaired free-water clearance [4]. The observed clustering of lower sodium values in Child-Pugh class C is also consistent with the known literature of declining sodium in the natural history of cirrhosis and increasing systemic decompensation [4,11].

Importantly, there is some previous prospective evidence that hyponatremia is not a bystander but a causative factor. Guevara and colleagues reported that hyponatremia predicted the development hepatic encephalopathy in a prospective cohort using time-depending analysis to support temporal and clinical relevance [8]. Our draft pattern (i.e., lower sodium correlating with higher HE grade) is an extension of the bedside interpretation: after overt HE is present, sodium may continue to correlate with neurologic severity, and it may also reflect the achievement of a lower physiologic threshold for cerebral dysfunction.

The neurobiologic basis of the sodium-HE link is supported by trials on integrating thinking and changes in brain osmolyte concentration in cirrhosis. Hyponatremia and HE co-incidences have been related to impaired cognition and poor health-related quality of life and neuroimaging strategies indicate osmolyte perturbations indicative of malfunctional astrocyte volume regulation in the setting of osmotic stress [9]. In more clinical terms, this suggests that hyponatremia could exacerbate HE expression and cause difficulties in recovery due to the hyponatremia in more advanced disease states.

From a prognostic standpoint, extensive transplant-waitlist data shows that serum sodium is independently related to mortality, and adding sodium to the prediction of mortality in a MELD score increased mortality prediction [5-7]. More work showed that low sodium and enduring ascites identify a patient with high risk even in relatively low MELD, explaining the importance of sodium as a marker of hemodynamic decompensation not completely represented by the scoring system based on creatinine alone [12]. The draft ROC and adjusted model in this manuscript reflects that wider evidence base, placing sodium in the accessible risk marker box during admission.

Interventional and supportive care literature is also helpful to put this in perspective. Trials evaluating vasopressin receptor antagonists (vaptans) have shown that it is possible to pharmacologically increase free-water clearance, which leads to an increase in serum sodium in native cohorts of angiopathic cirrhotic patients; however the outcome benefits are complex, and how patients are selected is critical [13]. In the setting of hospitalization, empirically derived observational data suggest that albumin administration may be linked to increased rates of hyponatremia resolution and increased short-term survival, possibly due to circulatory support/improved effective arterial volume [14]. These studies collectively support the clinical importance of detecting hyponatremia early and treating it according to guideline-based recommendations for managing the complications of cirrhosis, including careful avoidance of excessively rapid correction.

Limitations and implications for research

When you replace values from the placebos for real values, there will still be limitations that should be reported transparently: single centres study, possible residual confounding by precipitants (occult infection, severity of bleeding etc) and subjective variability of West Haven grading and limited follow up re. Nonetheless, serum sodium is inexpensive and widely available

and is biologically relevant. Larger multicentre studies should test the ability of sodium trajectories (not just admission values) to independently predict neurologic recovery, recurrence, and mortality and whether abnormalities in sodium are incorporated into escalation pathways associated with improved outcomes.

CONCLUSION

In this case control trial comprising tertiary care inpatients, hyponatremia was clinically cogent with overt hepatic encephalopathy severity and advanced liver disease (Child-Pugh class) and was consistent with worse short-term outcome over 14 days. Serum sodium has a good availability and is inexpensive, which makes it a practical choice for use as a biomarker for early warning of risk in the hospital-setting for CLD patients, especially those with overt encephalopathy. When combined with clinical grading and scoring also known as prognosticators, sodium may aid decisions made with respect to monitoring intensity, early escalation, and targeted supportive management. Future multicentre investigation of the utility of sodium-based prediction models and the impact of sodium trajectory-guided care pathways on neurologic recovery and survival is needed.

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