Section: Biochemistry

Original Research Article

STUDY OF ALBUMIN AND ELECTROLYTE VARIATIONS AMID INDIVIDUALS WITH CHRONIC LIVER DISEASE: A RETROSPECTIVE STUDY

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Received : 18/11/2025
Received in revised form : 03/01/2026
Accepted : 20/01/2026

Keywords:
Albumin, calcium, chronic liver disease.

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DOI: 10.47009/jamp.2026.8.1.59

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2026; 8 (1); 306-311

ABSTRACT

Background: Chronic liver disease(CLD) is caused due to continuous decline of the synthetic function, detoxification of harmful products as well as metabolism and excretion of bile products. Clinically it is classified as chronic if the condition occurs for more than 6 months. Serum albumin can measure the synthetic capabilities of the liver and variations in albumin as well as other electrolytes are seen in patients with CLD as well as its associated complications such as Decompensated CLD and Portal Hypertension. This study aims to better understand the importance of routine testing for albumin and electrolytes in a clinical setting. **Materials and Methods:** Serum albumin, Ionised calcium, sodium and potassium were measured at three points during the patient's hospitalisation: “at the time of admission”, “during hospitalisation” and “at the time of discharge” and this data were analyzed to find out for variations throughout the course of hospitalisation. **Result:** During the course of hospitalisation, modest but statistically significant temporal changes were observed in serum sodium as well as ionized calcium but potassium and albumin levels remained relatively stable. **Conclusion:** The routine testing of potassium and albumin may be reconsidered in the future while the importance of routine testing of sodium and ionized calcium is highlighted in this study. Further research is needed for establishing a stronger clinical association between these electrolytes and chronic liver disease.

INTRODUCTION

The defining feature of chronic liver disease (CLD) is a steady decline in the organ's ability to synthesize essential proteins, neutralize toxins, and manage the metabolism and drainage of bile. CLD is a chronic and continuous process of inflammation, destruction and regeneration of liver parenchyma, which can lead to irreversible fibrosis and cirrhosis that is severe and long-standing(>6 months).[1] Cirrhosis is the pathological manifestation of CLD, which can lead to multiple complications such as decompensated liver disease, portal hypertension, variceal bleeding amongst many others.[2] This can lead to increased morbidity and mortality.

It is a well known fact that advanced cirrhosis causes a reduction in albumin synthesis and as a result decreases its serum value. Albumin is traditionally well known for its oncotic properties but newer findings has demonstrated that albumin has other important physiologic properties such as immunomodulation, endothelial stabilisation, antioxidant effects as well as drug interactions.[3]

Calcium on the other hand shows varying levels in patients in CLD. Usually, patients with cirrhosis have decreased serum calcium due to a derangement in calcium and vitamin D homeostasis. This is due to the importance of the liver in activating Vitamin D, and decreased active vitamin D in the onset of CLD will cause decreased calcium absorption.[4] Other mechanisms include poor appetite, side effects of antiviral medication and glucocorticoid treatment.[5] Albumin binds to calcium, making it unable to participate in physiological processes. Only ionized calcium is physiologically active, and since albumin levels can be very varied in patients with CLD, only ionized calcium should be measured.[6] This has been done in this study. Hypercalcemia is a rare entity due to advanced disease or neoplasm and has a poor prognosis.[7]

Hyponatremia is the most common sodium abnormality in patients with decompensated chronic

ISSN (O): 2687-5365; ISSN (P): 2753-6556

liver disease, mainly hypervolemic (dilutional) hyponatriemia due to an excess of water relative to sodium. The main etiology behind this is increased anti-diuretic hormone(ADH) release due to circulatory dysfunction. Hyponatremia in CLD indicates increased mortality and morbidity.[8] Serum potassium can be both increased or decreased based on other concurrent symptoms, illnesses or medications(diuretics used for ascites). Nonetheless, in a study which measured potassium levels in patients with identical renal excretion, cirrhotic patients displayed a higher potassium level as compared to non-cirrhotic patients.[9]

MATERIALS AND METHODS

This study is a continuation of a previous 2024 study by Suryanarayana et al titled "Study of creatinine and electrolyte variations amid individuals with chronic liver disease". This is a secondary analysis focused on albumin and calcium, compared to the previous work which focused on creatinine and albumin.

A retrospective cohort study was conducted at PSG Institute of Medical Sciences and Research, Coimbatore between September 2021 to February 2022. Institutional Ethical Committee's approval was obtained (Ref. No.: PSG/IHEC/2022/Appr/Exp/012). In compliance with the Institutional Health Insurance Portability and Accountability Act(HIPPA) policy, patient protected health information(PHI) was not collected nor documented. Case sheets of all patients who presented to PSG hospitals between September 2021 to February 2022 who were diagnosed with chronic liver disease were reviewed and data were collected at 3 points during the course of hospitalization: "at the time of admission", "during hospitalisation" and "at the time of discharge".[10]

Out of 600 reports collected, 492 were selected after filtering through the inclusion and exclusion criteria. Only adult patients, those above 19 years of age, who presented with chronic liver disease whose signs and symptoms were present for a duration longer than 6 months with an etiology of alcoholic, post-infective, autoimmune and non-alcoholic steatohepatitis were chosen for this study. Patients with already pre-existing gastrointestinal diseases or malignancies, underlying kidney diseases, acute liver failure and liver cell failure due to septicemia or endotoxemia other than primary liver cause were not selected and excluded from the study. The data were then analysed and the results were interpreted.[10]

The mean age of individuals in our study was 48.5 years, with majority of the patients in the 40-49 years range(313 patients, 63.6%), followed by 50-59 years range(178 patients, 36.2%). As for the gender variations, we had 475 males (96.55%) compared to 17 females(3.45%). This is predominantly due to the most common etiology in our CLD cases which was alcoholic liver disease (267 patients, 54.3%). All the females presented with nonalcoholic steatohepatitis with no incidence of alcoholic liver disease. This could be due to behaviour patterns in males with regards to alcohol consumption as supposed to women. Hence, due to the gender and age based statistics, it would be safe to extrapolate our data to middle aged male population between 40-49 years old.[10]

RESULTS

Table 1: Mean and Standard Deviation of parameters with respect to time points in hospitalization

	At the time of admission					During hospitalization					At the time of discharge				
Parameter	**N**	**Mean**	**Median**	**IQR**	**SD**	**N**	**Mean**	**Median**	**IQR**	**SD**	**N**	**Mean**	**Median**	**IQR**	**SD**
Na+ (mEq/L)	434	133.02	134	130, 137	8.79	217	131.69	132	129, 136	1.5	244	132.76	134	130, 137	9.85
K+ (mEq/L)	440	4.4	4.06	3.62, 4.5	6.12	227	4.55	4	3.56, 4.5	7.47	247	4.04	4.05	3.6, 4.41	0.666
Ca 2+ (ionised)	428	1.38	1.09	1.03, 1.15	4.99	213	1.09	1.09	1.05, 1.14	0.091	244	1.12	1.11	1.05, 1.16	0.22
Albumin	401	2.84	2.7	2.3, 3.2	1.26	118	2.6	2.55	2.3, 2.8	0.742	175	2.64	2.6	2.25, 2.9	0.567

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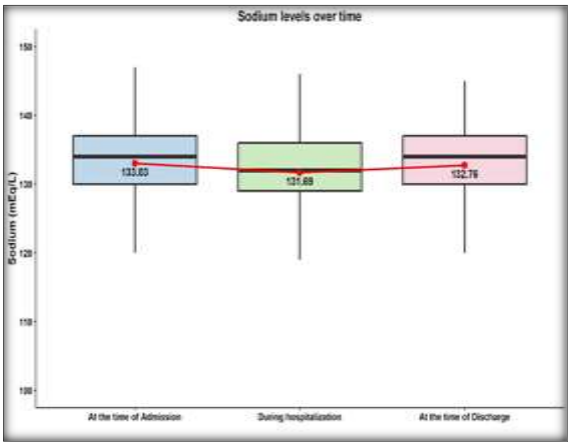

Diagram 1 Parameter Trends and Descriptive Statistics

The mean sodium level started at 133.02mEq/L at admission, decreased to 131.69mEq/L during hospitalisation and increased to 132.76mEq/L at discharge.

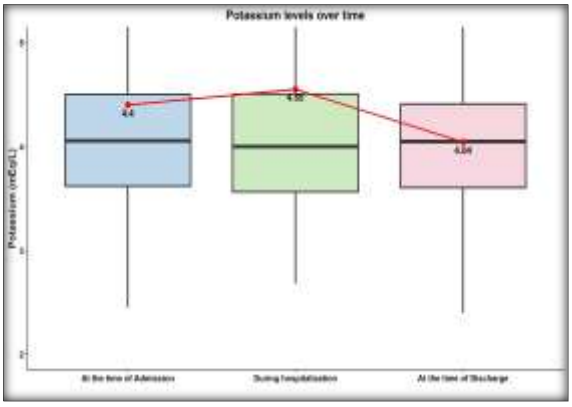

Diagram 2

The mean potassium level started at 4.4mEq/L at admission, increased to 4.55mEq/L during hospitalisation, and decreased to 4.04mEq/L at discharge.

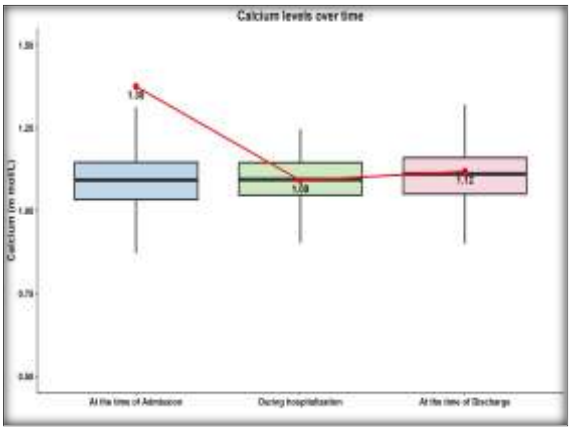

Diagram 3

The mean ionised calcium level started 1.38 mmol/L at admission, decreased to 1.09 mmol/L during hospitalisation and had a slight increase to 1.12 mmol/L at discharge.

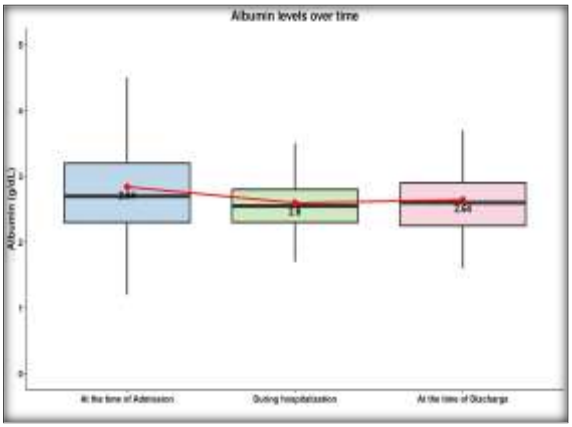

Diagram 4

The mean albumin level started at 2.84g/dL at admission, decreased to 2.6g/dL during hospitalisation, and stayed relatively stable at 2.64g/dL at discharge.

Table 2: Friedman Test

	N	Chi-square	P value	Kendall W
Na+ (mEq/L)	164	6.9309	0.0312	0.0211
K+ (mEq/L)	172	5.9327	0.0514	0.0172
Ca 2+ (ionised)	162	9.972	0.0068	0.0308
Albumin	92	5.6437	0.0594	0.0307

The Friedman test was used to determine if the change across the course of hospitalisation were statistically significant: Sodium ($p = 0.00312$) and ionised Calcium ($p = 0.0068$) were statistically significant with a $p<0.05$, while potassium ($p = 0.0514$) and albumin ($p = 0.0594$), were not statistically significant with a $p>0.05$.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 3: Post-hoc pairwise comparisons (Wilcoxon signed-rank test)

Parameter	Pairwise comparisons	P value adjusted
Na+ (mEq/L)	Admission vs Hospitalization	0.805
	Admission vs Discharge	0.013
	Hospitalization vs Discharge	0.036
K+ (mEq/L)	Admission vs Hospitalization	0.058
	Admission vs Discharge	0.492
	Hospitalization vs Discharge	1
Ca 2+ (ionised)	Admission vs Hospitalization	0.292
	Admission vs Discharge	0.008
	Hospitalization vs Discharge	0.333
Albumin	Admission vs Hospitalization	0.799
	Admission vs Discharge	1
	Hospitalization vs Discharge	0.096

Post-hoc pairwise comparison can be done to identify where the specific differences occured:
Sodium for admission vs discharge & hospitalisation vs discharge as well as ionised calcium for admission vs discharge.

Statistical Analysis

Continuous biochemical parameters, including serum sodium (Na^+), potassium (K^+), ionised calcium (Ca^{2+}), and albumin, were measured at three time points: at admission, during hospitalization, and at discharge. As these measurements represented repeated observations on the same individuals and the distributions were non-normal, a non-parametric approach was chosen. Overall differences across the three time points were assessed using the Friedman test, a rank-based non-parametric test appropriate for comparing related samples measured on more than two occasions. This method does not assume normality and accounts for within-subject pairing. As the Friedman test requires complete observations across all time points, analyses were restricted to complete cases for each parameter, and the corresponding sample sizes are reported. When the Friedman test indicated a statistically significant overall difference, post-hoc pairwise comparisons were performed using the Wilcoxon signed-rank test. To control for inflation of Type I error due to multiple comparisons, Bonferroni adjustment was applied to the p values. To quantify the magnitude of observed differences across time points, Kendall's coefficient of concordance (W) was calculated as an effect size measure for the Friedman test. Kendall's W ranges from 0 to 1, with higher values indicating greater differences across repeated measurements. All statistical analyses were performed using R software (4.5.0), and a two-sided p value of <0.05 was considered statistically significant.

Friedman's test was used to compare changes in biochemical parameters measured at admission, during hospitalization, and at discharge (Table 2). A statistically significant difference across time points was observed for serum sodium (Na^+) levels ($\chi^2(2) = 6.93$, $p = 0.031$), although the effect size was small (Kendall's $W = 0.021$). Similarly, ionised calcium (Ca^{2+}) demonstrated a significant overall difference across the three time points ($\chi^2(2) = 9.97$, $p = 0.007$), with a small effect size (Kendall's $W = 0.031$). In contrast, potassium (K^+) levels ($\chi^2(2) = 5.93$, $p = 0.051$) and serum albumin ($\chi^2(2) = 5.64$, $p = 0.059$) did not show statistically significant differences across time, although both showed trends toward significance. Effect sizes again were small for both parameters.

Post-hoc pairwise comparisons using Wilcoxon signed-rank tests with Bonferroni adjustment are presented in Table 3. For sodium, significant differences were observed between admission and discharge ($p = 0.013$) and between hospitalization and discharge ($p = 0.036$), whereas no difference was found between admission and hospitalization ($p = 0.805$). For ionised calcium, a significant difference was noted between admission and discharge ($p = 0.008$), with no significant differences between admission and hospitalization ($p = 0.292$) or between hospitalization and discharge ($p = 0.333$). No statistically significant pairwise differences were observed for potassium or albumin levels across any of the time-point comparisons after adjustment for multiple testing. Overall, these findings suggest modest but statistically significant temporal changes in serum sodium and ionised calcium during the course of hospitalization, while potassium and albumin levels remained relatively stable.

DISCUSSION

Chronic liver disease, with the onset of cirrhosis as well as complications such as decompensated liver cirrhosis has a poor prognosis with an overall survival of 2-4 years, which is worse than many cancers. Patients often present with hypoalbuminemia, and inculcating albumin infusion as a management tool is very helpful in cirrhotic patients, since it reduces many complications associated with cardiocirculatory dysfunction and spontaneous bacterial peritonitis.[11] Our studies have shown that the mean and median value for albumin is 2.84g/dL and 2.7g/dL respectively (Table 1, at admission), showing that there is a substantial decrease in serum albumin compared to the normal range of 3.5-5.0 g/dL. Looking at the calcium levels throughout the course of hospitalisation, we can infer that it remains relatively stable (Diagram 4), indicating that the treatments done throughout hospitalisation have not significantly affected the levels. Hence while the measurements of albumin

ISSN (O): 2687-5365; ISSN (P): 2753-6556

may not indicate statistical significance, the importance of albumin measurement in the clinical settings will have to be much more extensively researched and correlated clinically before deciding on its efficacy in routine treatment. Another important point to consider is that there is a qualitative abnormality in cirrhotic patients as well, in which the albumin structurally misfolding such that its oncotic and other physiological properties are affected.[12] This aspect of albumin abnormality was not considered in this study and can be of relevance in future studies.

Ionised calcium on the other hand has demonstrated significant change throughout the course of hospitalisation (Diagram 3). The mean and median for ionised calcium were both 1.38mmol/L and 1.09mmol/L respectively (Table 1, at admission). The median value was slightly below the normal range of 1.12mmol/L to 1.32mmol/L, indicating hypocalcemia, which correlates with existing studies mentioning hypocalcemia due to hypovitaminosis D due to decreased liver function.[13] The mean calcium was above the normal range on the other hand, well outside the interquartile range(1.03-1.15mmol/L, Table 1), indicating that were a small number of patients with high calcium levels bringing the mean values up. This could indicate hypercalcemia in a small number of patients, which could be due to hepatocellular carcinoma or other rare coexisting underlying cause, which has been reported to be associated with a poor prognosis, with hospital mortality rates of 21%.[14] Hence hypercalcemia is an alarming sign in patients with CLD, and the underlying etiology has to be identified and treated immediately. Throughout the course of hospitalisation, ionised calcium has demonstrated a statistically significant change (Diagram 3), further highlighting the importance of its routine measurement at various points of admission. Mean and median levels of calcium at admission which were both above and below normal range were within normal range at discharge, potentially indicating that adequate correction has been done in both the majority of hypocalcemic patients and minority of hypercalcemic patients (Table 1) Additionally, albumin binds with calcium, and in CLD patients who predominantly have hypoalbuminemia, it is important that ionized calcium(physiologically active) is tested rather than total calcium which may be deranged but might not reflect an accurate clinical picture.[15]

Hyponatremia would be commonly seen in patients with chronic liver disease, especially dilutional(hypervolemic) hyponatremia due to hypoalbuminemia and its associated free water clearance. This can also be clearly seen in our patients, in which the serum sodium has stayed below 135mEq/L throughout the course of hospitalisation (Diagram 1). Hyponatremia is also associated with complications such as hepatic encephalopathy and spontaneous bacterial peritonitis.[16] Routine measurement of sodium and timely intervention can help in the management and prognosis of the patient. Potassium on the other hand was within the normal range throughout the course of hospitalisation, and also did not show any statistically significant change throughout the course of hospitalisation. Literature also shows that CLD patients can show both hyperkalemia,[9] or hypokalemia,[17] and that the etiology due to either condition would be due to the various underlying cause such as poor nutrition or kidney disease. Hence, while our study does not show a statistical significance in measuring the potassium values, it could be useful in figuring out other underlying disease or condition that could cause a derangement in the serum potassium value and routine monitoring could help in earlier management in correcting the potasssium abnormality.

Limitations[10]: The data collected were from patients in a tertiary care centre in south india among a small group of individuals. Regional and societal variations with respect to etiologies were not considered in the analysis of this study, and hence the findings cannot be used to precisely reflect the disease profile of the larger community. A larger, multicentric study in the future can help yield more conclusive findings.

CONCLUSION

Overall, ionised calcium and sodium showed a statistically significant change over the course of hospitalisation while potassium and albumin values have stayed fairly constant throughout the course of hospitalisation. Hence we could potentially reconsider unnecessary testing for potassium and albumin in the future for CLD patients. However, further studies with regards to clinical correlation has to be established to substantiate our claim and to achieve more conclusive evidence. A future study could incorporate specific data analysis for the different etiologies causing CLD, helping us identify if certain derangements of albumin and electrolytes could be attributed to certain etiologies. This could help in the management of CLD patients in the clinical settings.

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