

Comparison of Plasma Zinc Status in Critically ill Patients with and Without Chronic Liver Disease: A Case-Control Study

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Abstract

Background: The body needs zinc as a trace element. Both critical illness (CI) and chronic liver disease (CLD) are associated with hypozincaemia. When these situations coexist, the zinc status is unclear. In this study, we evaluated the plasma zinc levels of critically ill patients with and without chronic liver disease and examined any potential correlations between zinc levels and mortality.

Methods: This prospective study comprised 69 patients with chronic liver disease and 73 patients without chronic liver disease (Control) who were hospitalized to the intensive care unit (ICU) of GMCH, Bettiah, West Champaran, Bihar between March 2026 and July 2026. Acute Physiology and Chronic Health Evaluation III (APACHE-III), Sequential Organ Failure Assessment (SOFA), and CLD [Model For End Stage Liver Disease (MELD)] severity scores were recorded together with demographics. Plasma zinc and urine zinc levels (in patients with normal renal function) were measured, along with hematologic, renal, and liver function tests. Results from the ICU, hospital, and six months after discharge were noted.

Results: All study participants had hypozincaemia (normal range: 9.02–11.32 $\mu\text{mol/L}$). Notably, compared to critically ill patients without chronic liver disease [Control], those with chronic liver disease showed significantly lower plasma zinc levels (5.3 ± 2.2 vs. 8.1 ± 2.9 $\mu\text{mol/L}$, $P=0.0001$). Both groups had significant zinc losses in their urine. Increased mortality in the ICU (21.7% vs. 8.2%, $P=0.062$), in-hospital (37.7% vs. 16.4%, $P=0.004$), and six months after discharge (53.6% vs. 17.8%, $P=0.0001$) were all associated to hypozincaemia.

Conclusion: When compared to the critically ill control group, patients with chronic liver disease had considerably lower plasma zinc levels. Regardless of the presence of chronic liver illness, hypozincaemia was associated to higher ICU, hospital, and 6-month mortality rates. It is necessary to conduct a large trial to track zinc levels and the effectiveness of zinc supplementation on outcomes in patients with critically ill chronic liver disease.

Keywords: Zinc; Chronic Liver Disease (CLD); Critical Illness.

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Introduction

Numerous enzymatic and metabolic functions, such as gene transcription, immunoregulation, cellular repair, and protein synthesis, depend on zinc, an essential trace element in the body.[1] Zinc homeostasis is significantly influenced by the liver. Chronic liver disease (CLD) causes abnormally low zinc levels, which can result in metabolic problems such hepatic encephalopathy.[2] Higher mortality and illness severity scores are linked to

hypozincaemia, which is seen in critically ill patients.[3] Zinc deficiency in CLD patients may enhance their vulnerability to endotoxaemia by increasing intestinal barrier permeability via oxidative stress pathways.[4] Epithelial dysfunction causing intestinal hyperpermeability with modification of intestinal microbiota has also described in severe disease. This leads to local and distant tissue harm resulting in multiple organ

dysfunction syndrome.[5] Plasma zinc levels in critically ill patients with a background of CLD have not been thoroughly established. Therefore, we conducted a prospective study to investigate the plasma zinc levels in CLD patients requiring intensive care unit (ICU) admission and compared them with concurrent critically sick patients without CLD. We also studied the correlation between plasma zinc levels and outcomes in these patients.

Material and Methods

From March to July of 2026, the Department of Medicine at Government Medical College and Hospital, Bettiah, West Champaran, Bihar, carried out this prospective case-control study. This group consisted of 69 critically sick patients with chronic liver disease, while the control group consisted of 73 critically ill individuals without a history of chronic liver disease. The controls, who were concurrently admitted to the medical intensive care unit (ICU) without a history of CLD or heavy alcohol consumption, were matched for age, gender, entrance diagnosis, and the need for organ support. Patients with end stage renal failure on regular haemodialysis, receiving parenteral nutrition and with a history of receiving radiologic contrast in the previous 4 days were excluded from the study.

At the time of admission, patient demographic information was gathered, including age, gender, admission diagnosis, physiologic parameters, and clinical features. Scores from the Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation III (APACHE-III) were noted. The Model For End Stage Liver Disease (MELD) score, which uses blood

creatinine, bilirubin, and prothrombin time to predict survival, was used to assess the severity of liver disease.[6]

Blood samples were taken from each patient upon admission in order to measure their hemoglobin, white blood cell count, platelet count, coagulation profile, including the international normalized ratio (INR), C-reactive protein, liver function, and renal function. Zinc levels were measured at the time of ICU admission in order to be included in the study. All patients had their blood drawn for zinc levels at the same time (0600) in metal-free vacutainer tubes. Mass spectrometry, which has a verified normal range of 9.02–11.32 $\mu\text{mol/L}$, was used to detect plasma zinc.[7] In both groups, a subgroup of patients with normal renal function (36% of critically sick chronic liver disease patients and 33% of control) had their 24-hour urine zinc levels tested. A specialized metal-free container containing 50 milliliters of diluted nitric acid was used to collect urine. Using hospital patient information systems, all patients were monitored throughout the duration of their ICU and hospital stays as well as for death in the ICU, within the hospital, and six months after discharge.

The continuous variables are shown as mean $\pm$ standard deviation (SD), while the categorical variables are shown as absolute frequency and percentages. The Pearson's chi-squared test or Fisher's exact test for categorical variables and the Student's t-test for continuous variables were used to compare the clinical characteristics of the two groups: critically ill patients with chronic liver disease and the control group (critically ill without chronic liver disease).

Results

Table 1: Demographics, laboratory parameters and diagnosis on admission in Critically ill chronic liver disease (CI-CLD) and critically ill without chronic liver disease patients [CI-CONTROL]

Parameter	CI-CLD (n=69)	CI-CONTROL (n=73)	P value
Male, %[n]	62.3% [43]	65.8% [48]	0.86
Age (years), mean (SD)	53.7 $\pm$ 11.0	54.0 $\pm$ 13.4	0.89
Weight (kg), mean (SD)	80.4 $\pm$ 22.4	79.5 $\pm$ 17.9	0.80
Current/former smoker, %[n]	69.6% [48]	56.2% [41]	0.12
Insulin dependent diabetes mellitus, %[n]	21.7% [15]	17.8% [13]	0.51
SOFA score, mean (SD)	8.8 $\pm$ 3.5	4.4 $\pm$ 3.3	0.0001
APACHE-III score, mean (SD)	87.4 $\pm$ 31.1	73.8 $\pm$ 35.5	0.02
MELD score, mean (SD)	26.4 $\pm$ 7.8	—	—
Albumin(g/L), mean (SD)	22.2 $\pm$ 5.7	26.2 $\pm$ 7.4	0.001
Serum bilirubin ($\mu\text{mol/L}$), mean (SD)	120.5 $\pm$ 125.7	23.4 $\pm$ 44.4	0.001
Ammonia ($\mu\text{mol/L}$), mean (SD)	114.5 $\pm$ 69.7	—	—
C-reactive protein (mg/L), mean (SD)	60.5 $\pm$ 53.3	121.5 $\pm$ 106.3	0.001
Serum creatinine ($\mu\text{mol/L}$), mean (SD)	144.3 $\pm$ 105.4	116.8 $\pm$ 99.9	0.10
Platelets ($\times 10^9/\text{L}$), mean (SD)	83.3 $\pm$ 59.4	214.7 $\pm$ 140.4	0.001
Community acquired pneumonia, %[n]	17.4% [12]	19.2% [14]	0.78
Septic shock, %[n]	21.7% [15]	23.3% [17]	0.82
Surgical without sepsis, %[n]	5.8% [4]	16.4% [12]	0.04
Haemorrhagic/hypovolemic shock, %[n]	30.4% [21]	23.3% [17]	0.30
Neurological failure/encephalopathy, %[n]	24.6% [17]	17.8% [13]	0.32

SD; standard deviation; SOFA, Sequential Organ Failure Assessment; APACHE III, Acute Physiology and Chronic Health Evaluation III; MELD, model for end-stage liver disease

The admission diagnoses and patient demographics matched well (Table 1). The CLD group had high mean MELD scores of 26.4 ± 7.8 , indicating considerably higher APACHE-III and SOFA scores (Table 1). The CI-CLD group had both hypoalbuminemia and hyperammonaemia. There was no difference in serum creatinine across the

groups (Table 1). In both study groups, the need for organ support with vasopressors, mechanical breathing, and renal replacement therapy was comparable. As expected, there was a statistically significant difference in coagulopathy between the CI-CLD and CI-CONTROL groups (mean INR 2.3 vs. 1.5 , $P=0.010$) (Table 2).

Table 2: Organ Supports and parameters of organ dysfunction in CI-CLD and CI-CONTROL

Parameter	CI-CLD	CI-CONTROL	P value
Vasopressor, % [n]	23.5% [16]	25.6% [19]	0.694
Mechanical ventilation, % [n]	52.9% [36]	39.2% [29]	0.610
Renal replacement therapy, % [n]	4.3% [3]	8.2% [6]	0.343
Coagulopathy, mean INR (SD)	2.3 ± 0.87	1.5 ± 0.74	0.010

SD; standard deviation; INR, international normalised ratio; CI, critically ill patients with; CLD, chronic liver disease

One-third of the study group ($n = 49$) had their urine zinc levels measured over a 24-hour period. Compared to CI-CONTROL, urinary zinc losses were greater but not statistically significant (39.4 ± 38.3 vs. 28.0 ± 32.1 $\mu\text{mol}/24\text{ h}$, $P=0.26$) in the CI-CLD group (Table 3).

Table 3: Zinc levels in CI-CLD and CI-CONTROL

Parameter	CI-CLD	CI-CONTROL	P value
Plasma zinc ($\mu\text{mol/L}$), mean (SD) [n]	5.3 ± 2.2 [69]	8.1 ± 2.9 [73]	0.0001
24-hour urinary zinc losses ($\mu\text{mol}/24\text{h}$), mean (SD) [n]	39.4 ± 38.3 [25]	28.0 ± 32.1 [24]	0.26

SD; standard deviation; CI, critically ill patients with; CLD, chronic liver disease

In the ICU (21.7% vs. 8.2%, $P=0.062$), hospital (37.7% vs. 16.4%, $P=0.004$), and six-month follow-up (53.6% vs. 17.8%, $P=0.0001$), our data showed a significant increase in the unconditional mortality rate linked to hypozincaemia (Table 4).

Table 4: Outcome results in CI-CLD and CI-CONTROL

Parameter	CI-CLD (n=69)	CI-CONTROL (n=73)	P value
LOS ICU (days), mean (SD)	6.8 ± 6.5	10.8 ± 17.0	0.02
LOS hospital (days), mean (SD)	21.0 ± 22.7	20.9 ± 24.3	0.73
ICU mortality, % [n]	21.7% [15]	8.2% [6]	0.062
Hospital mortality, % [n]	37.7% [26]	16.4% [12]	0.004
6-month mortality, % [n]	53.6% [37]	17.8% [13]	0.0001

SD; standard deviation; LOS, length of stay; ICU, intensive care unit; CI, critically ill patients with; CLD, chronic liver disease

SOFA score, plasma zinc levels, and site were found to be predictors of 6-month survival using a multivariate Cox model (Table 5).

Table 5: Multivariate Cox analysis for predictors of mortality

Predictor	Hazard ratio	Lower 95%CI	Upper 95%CI	P value
SOFA score	1.300	1.200	1.407	0.004
Plasma zinc	0.835	0.739	0.943	0.004
Site 2 vs. Site 1	0.505	0.328	0.902	0.021

Discussion

In contrast to modest levels in the CI-CONTROL group, this prospective investigation shows quantitatively severe hypozincaemia in CI-CLD. Although the literature now in publication recognizes the presence of hypozincaemia in critical illness [2,10] and CLD [2,9], little of it describes the state of zinc levels when these two disorders combine.

Up to 83% of patients with CLD have been shown to be zinc deficient (9). Zinc is typically absorbed

in the small intestine, with 11% being deposited in the skin and liver before being eliminated by the kidneys. Zinc transporters are essential for zinc transport, absorption, and excretion (4,11). Reduced zinc absorption, altered zinc transport, decreased zinc concentration in the liver, and increased zinc excretion in the urine are all present in patients with CLD. [9]

95% of ICU patients had hypozincaemia, as seen in CI-CONTROL.[12] This is linked to a lower chance of survival and is partially caused by greater tissue sequestration of zinc as an acute phase

response in critical disease.[9] Subacute zinc shortage was linked to increased organ damage, mortality, and systemic inflammation in an experimental mouse model of polymicrobial sepsis.[13] Important proteins may be harmed by suboptimal zinc concentrations in critical disease with elevated oxidative stress and inflammatory indicators.[14]

The considerable disparity in plasma zinc levels between the two study groups could be explained by both impaired zinc homeostasis during acute illness and chronic zinc shortage in CLD.

In cases of acute severe dietary zinc insufficiency, urinary zinc excretion is typically blocked (15). On the other hand, both research groups had high urine zinc levels. Regardless of zinc consumption, increased urinary zinc losses are caused by tissue zinc redistribution, hypoalbuminemia, and diuretic use—all of which are frequent in both critical illness and CLD. [16,17] In hypoalbuminemia, unbound zinc has a higher affinity for amino acids such as α -2-macroglobulin, an acute phase reactant, which increases the excretion of zinc.[18] Because of this strong correlation, hypoalbuminemia is utilized as a stand-in for an underlying zinc shortage in CLD.[19]

As expected, the CI-CLD group had hyperammonaemia ($114.5 \pm 69.7 \mu\text{mol/L}$, reference range $<50 \mu\text{mol/L}$).[20] Since Prasad et al. unintentionally found hyperammonaemia in volunteers who ate a zinc-free diet in 1978, zinc deficiency has been associated with altered ammonia metabolism.[21] Zinc deficiency lowers the activity of hepatic ornithine transcarboxylase, an essential urea cycle enzyme needed for ammonia metabolism. Zinc supplementation has been shown to lower ammonia levels in CLD patients, according to data from randomized control trials.[22] Zinc limits the enterohepatic circulation of bilirubin, resulting in increased total circulating bilirubin levels in zinc deficiency. Our investigation revealed a negative connection between hyperbilirubinemia and plasma zinc content in CLD [19].[23] Therefore, in certain high-risk patient groups, zinc supplementation is utilized to treat hyperbilirubinemia (24). Although its etiology is unknown, hyperbilirubinemia is also frequently seen in critical disease and associated with higher mortality.[25] Vanwijngaerden et al. found no correlation between cholestasis and inflammation in critically ill patients, but they did confirm a strong correlation between the pro-inflammatory state of critical illness and hyperbilirubinemia, which has been linked to zinc deficiency and is probably caused by altered bile acid handling. [24,26]

In the past, declining plasma zinc levels were linked to higher ICU mortality and illness severity

scores for severe infections (27, 28). It supports our findings that zinc levels and the SOFA score are predictive of survival at six months. Hypozincaemia has been linked to higher mortality, which may indicate its prognostic significance. Reduced survival in the CI-CLD group may be explained by disruption of zinc's vital involvement in immunoregulation, DNA repair, and antioxidant defense in CLD patients (29), which is made worse by critical illness. Our small study population and case-mix were likely contributing factors to the research site variation in outcome prediction.

The importance of zinc in preserving homeostasis and the detrimental effects of zinc shortage are well-documented.[8, 11, 13, 14] Nevertheless, it is still unknown and has not been studied how zinc supplementation affects CI-CLD patients.

There are no explicit recommendations for zinc supplementation in the current guidelines. Diglio et al.'s systematic analysis found that, with the probable exception of hepatic encephalopathy, zinc supplementation in CLD did not enhance clinical outcomes or stop the disease's progression.[22, 30] Similarly, the clinical outcome of critically ill mechanically ventilated patients with multisystem organ failure was not improved by additional antioxidants.[31]

This study has certain limitations even though, to the best of our knowledge, it is the first to evaluate the zinc levels in CLD patients experiencing acute critical illness. The results cannot be generalized because only one-third of the patients had urine zinc analyzes. Only patients with hepatic disease had their ammonia levels measured. Risk factors for non-hepatic sources of hyperammonaemia may be present in critically unwell populations.[32] The results of the study may have been impacted by our limited sample size, the recruitment of more CI-CONTROL from a single site, and variations in the case-mix. Zinc levels were not checked again after being discharged from the intensive care unit to see if they had improved after the acute sickness had subsided. While controls may have normal baseline zinc levels and only have an acute decline during sickness, CLD patients who are predisposed to chronically low zinc levels may experience a further reduction during an acute episode.

Conclusion

In comparison to hypozincaemia observed in other critically ill patients, this study concludes that acutely ill patients with CLD have much lower plasma zinc levels. According to our data, hypozincaemia is linked to higher ICU, hospital, and 6-month mortality rates. To assess the function of monitoring zinc levels and maintaining normal zinc levels with supplementation in CI-CLD patients, a sizable clinical research is needed.

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