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Serum Ammonia as an Early Predictor of Prognosis in Acute Liver Failure following Rodenticide Poisoning: A Prospective Study

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ABSTRACT

Background: Acute liver failure (ALF) due to rodenticide is associated with high morbidity and mortality, primarily from hepatic encephalopathy (HE). Early prognostic markers are vital for guiding management. This study prospectively evaluates serum ammonia as an early biomarker for ALF detection.

Methods: The prospective observational study at a Tertiary care Center enrolling 75 adult patients admitted with clinical and biochemical diagnosis of ALF due to known or suspected rodenticide exposure from 01.08.2022 to 01.03.2023 was enrolled. Serum ammonia levels were measured on admission and correlated with HE severity, laboratory parameters, treatment, and outcomes.

Results: Mean serum ammonia level among survivors was 163.4 µmol/L, while non-survivors had significantly higher levels (611.5 µmol/L). Patients with higher ammonia levels showed significantly increased risk of progressing to severe encephalopathy and poorer clinical outcomes. Serum ammonia is a strong early predictor of mortality and severity in rodenticide-related acute liver failure. Receiver Operator Characteristic (ROC) curve analysis determined prognostic cutoff values.

Conclusion: Serum ammonia is a reliable early diagnostic and prognostic marker in ALF following rodenticide. Routine measurement can facilitate early intervention and risk stratification, thereby improving clinical outcomes.

Key-words: Acute liver failure, Early detection, Prognostic marker, Rodenticide-induced Liver injury, Serum Ammonia

INTRODUCTION

Acute liver failure (ALF) is a severe clinical syndrome characterized by rapid deterioration of liver function, severe coagulopathy, and the development of hepatic encephalopathy (HE) [1-3]. This life-threatening condition represents one of the most challenging medical emergencies encountered in clinical practice, with mortality rates reaching up to 80% without appropriate intervention and transplantation.

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The condition develops rapidly, typically progressing from initial symptoms to multi-organ dysfunction within days to weeks.

The etiology of ALF varies significantly across geographic regions, reflecting differences in environmental exposures, nutritional status, and access to healthcare. In developing countries, toxins such as rodenticides are prevalent causes of acute liver failure, particularly in regions where access to rodent control measures and agricultural pesticides is widespread [4-6]. These toxin-induced cases present unique clinical challenges due to their unpredictable progression and variable response to conventional treatments. Understanding the specific etiological patterns in different populations is crucial for implementing targeted prevention strategies and developing region-specific treatment protocols.

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The pathophysiology of ALF involves complex cascading mechanisms that lead to severe hepatic dysfunction. Fundamentally, ALF involves massive hepatocyte necrosis, inflammatory cascades, and disturbances in the cerebral metabolic environment that predispose to HE and cerebral edema [7-9]. The massive destruction of hepatocytes triggers a profound inflammatory response, releasing cellular contents and activating innate immunity. This inflammatory cascade perpetuates further hepatocellular damage through oxidative stress and the release of pro-inflammatory cytokines. Additionally, the disturbance in cerebral metabolism and blood-brain barrier integrity contributes to the development of hepatic encephalopathy, which significantly worsens prognosis and functional outcomes.

Ammonia accumulation represents a central mechanism in the pathogenesis of hepatic encephalopathy associated with ALF. Ammonia accumulation due to impaired hepatic detoxification and portosystemic shunting is central to the pathogenesis of HE [7-9]. Under normal circumstances, the liver efficiently converts ammonia to urea through the urea cycle. However, in ALF, the massive loss of functional hepatic mass severely impairs this detoxification capacity. Simultaneously, the development of portosystemic collaterals and shunting of blood away from damaged hepatic tissue bypasses what little detoxification capacity remains. This results in elevated serum and cerebrospinal fluid ammonia concentrations, which directly contribute to neurological dysfunction, altered consciousness, and cerebral edema.

Despite significant advances in critical care medicine and supportive therapies, early prognostic markers to identify patients at high risk of neurological deterioration remain limited [10-14]. Current prognostic scoring systems, while useful, often lack sensitivity in identifying patients who will develop severe encephalopathy or require urgent intervention. This diagnostic gap represents a critical challenge in ALF management, as early identification of high-risk patients could guide treatment decisions and transplantation listing.

Serum ammonia has emerged as a promising marker for early diagnosis and prognostication but requires further validation in rodenticide toxin-induced ALF cohorts [10-14]. Preliminary studies suggest that ammonia concentrations correlate with encephalopathy grade and neurological outcomes, making it a potentially valuable point-of-care diagnostic and prognostic tool. However, standardization of ammonia measurement techniques and validation in specific toxin-induced ALF populations remain necessary [15-18].

This study aims to prospectively evaluate the role of serum ammonia concentration in the early detection of HE and prognosis in patients with ALF following rodenticide ingestion. By establishing the diagnostic and prognostic utility of serum ammonia in this specific patient population, this research could provide clinicians with an evidence-based tool for risk stratification, treatment optimization, and improved patient outcomes in developing countries where rodenticide-induced ALF represents a significant public health challenge.

MATERIALS AND METHODS

Research Design- A prospective observational study was conducted at Thanjavur Government Medical College, Tamil Nadu, India. The study included patients who were admitted with Acute Liver Failure as a result of intake or exposure to rodenticide in the ICU under the Medicine Department from 1st August 2022 to 31st March 2023. Purposive sampling was used to select study participants. A total of 75 patients who satisfied the Inclusion criteria were enrolled in the study.

Inclusion criteria

- Age > 20 years
- ALF due to Rodenticide exposure
- Patient, who developed Hepatic Encephalopathy without prior liver disease.

Exclusion criteria

- Patient with chronic liver disease and severe systemic illnesses.
- Patient admitted with ALF other than rodenticide poisoning.

Methodology- Serum ammonia levels were measured within 24 hours of admission using an Enzymatic assay standardized in our clinical laboratory. Clinical assessment of HE was done following the West Haven criteria by trained physicians. Biochemical parameters, including Total Bilirubin, INR, Prothrombin time, Liver aminotransferases, and Renal function tests, were concurrently obtained. We followed standard

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Institutional protocols, including supportive care and ammonia-lowering therapies such as lactulose and plasma exchange, as appropriate.

Statistical Analysis- Data were entered into an MS Excel sheet and analyzed using SPSS version 27. Continuous variables were expressed as mean±standard deviation or median (interquartile range), as appropriate, and compared using Mann-Whitney U tests. Categorical variables were compared by chi-square or Fisher's exact test. Pearson's correlation coefficient was used to assess relationships between serum ammonia and other clinical parameters. Receiver-operating characteristic (ROC) curve analysis was performed to determine the optimal serum ammonia cutoff for mortality prediction. Statistical significance was set at $p<0.05$.

Ethical approval- Ethics approval for the study was obtained from the Institutional Review Board under protocol number 996/2022.

RESULTS

Patient demographics indicated a mean age of 31.37±13.68 years and a predominantly male population (70.7%). The majority of the patients presented with rodenticide exposure, principally yellow phosphorus (73.3%) (Table 1).

Table 1: Baseline characteristics of study population

Parameters		Frequency (n)	Percentage (%)
Sex	Male	22	29.3
	Female	53	70.7
Chemical Composition	Bromadiolone	12	16
	Yellow Phosphorous	55	73.3
	Zinc Phosphide	8	10.7
Treatment	Pharmacological	30	40
	Pharmacological + FFP	4	5.3
	Pharmacological+ FFP + Plasmapheresis	41	54.7
Grading of Encephalopathy	Grade 1	6	8.0
	Grade 2	4	5.3
	Grade 3	3	4.0
	Grade 4	32	42.7
Outcome	Discharged	45	60
	Expired	30	40

Serum ammonia levels were significantly higher in patients with hepatic encephalopathy compared with those without hepatic encephalopathy (518.18±282.4 µmol/L vs 79.3±85.9 µmol/L, $p<0.0001$) (Fig. 1).

The presence of high-grade hepatic encephalopathy (Grade IV) was significantly more common among non-survivors (93.8%) than among survivors, demonstrating the strong association between encephalopathy severity and mortality (Fig. 2).

Biochemical parameters showed markedly higher total bilirubin levels (6.2±2.2 mg/dL vs 1.7±0.9 mg/dL), prolonged prothrombin time (28.2±6.3 s vs 16.7±3.6 s), and elevated INR (2.9±3.2 vs 1.3±0.2) in the expired group compared with survivors ($p<0.0001$) (Fig. 3).

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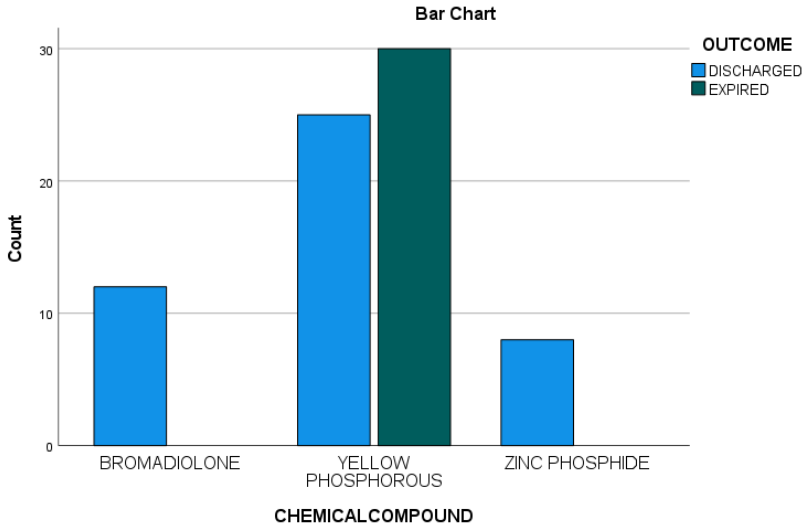

Fig. 1: Type of Rodenticide and Patient Outcome

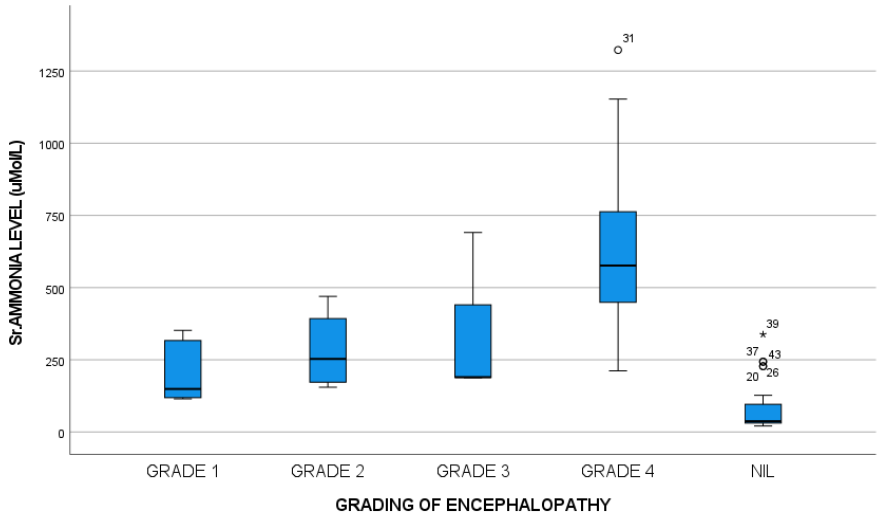

Fig. 2: Boxplot-Grades of Hepatic Encephalopathy with Serum Ammonia Level

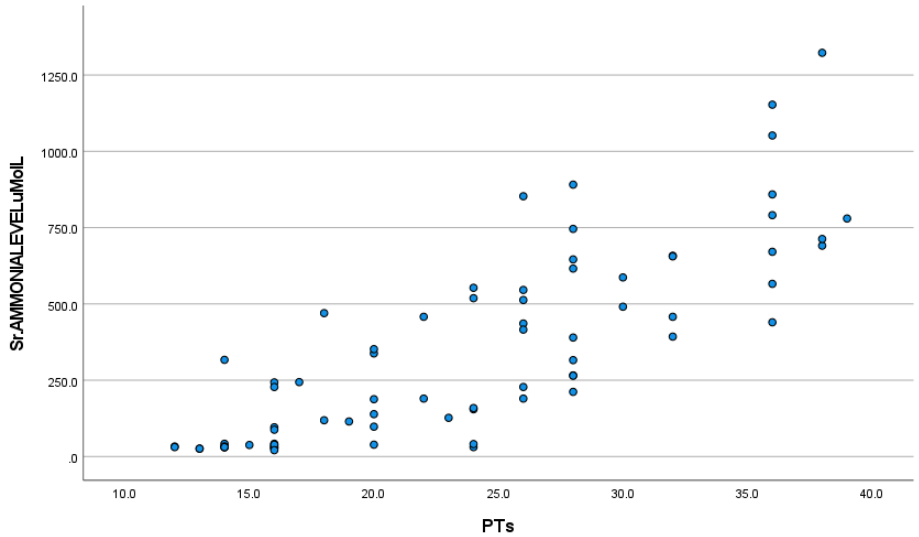

Fig. 3: Scatter plot between Serum Ammonia Level and Prothrombin Time

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Correlation analysis revealed strong positive associations between serum ammonia and markers of hepatic injury, including total bilirubin (r=0.89, p<0.0001), prothrombin time (r=0.81, p<0.0001), and INR (r=0.23, p=0.03). Treatment with ammonia-lowering methodologies, such as therapeutic plasma exchange, was associated with reduced ammonia levels, which correlated with improved survival rates (p=0.01) (Table 2).

Table 2: Correlation of serum ammonia levels with various Hepatic injury markers in Rodenticide poisoning

Correlation of serum ammonia (umol/L) with	Pearson's "r"	p-value
High TB (mg/dL)	0.89	<0.0001*
High SGOT (U/L)	0.87	<0.0001*
High SGPT (U/L)	0.87	<0.0001*
Average SGOT (U/L)	0.82	<0.0001*
Average SGPT (U/L)	0.81	<0.0001*
Prothrombin time(s)	0.81	<0.0001*

The strength of association between serum Ammonia level and Hepatic injury markers was assessed using the Pearson correlation coefficient, represented by the 'r' value.
**indicates p<0.05 and is considered statistically significant.*

ROC curve analysis demonstrated the predictive capability of serum ammonia, with an area under the curve (AUC) of 0.92 (95% CI: 0.86-0.99, p<0.0001). The optimal cutoff level for mortality prediction was 92.5 µmol/L with 100% sensitivity and 51% specificity (Fig. 4).

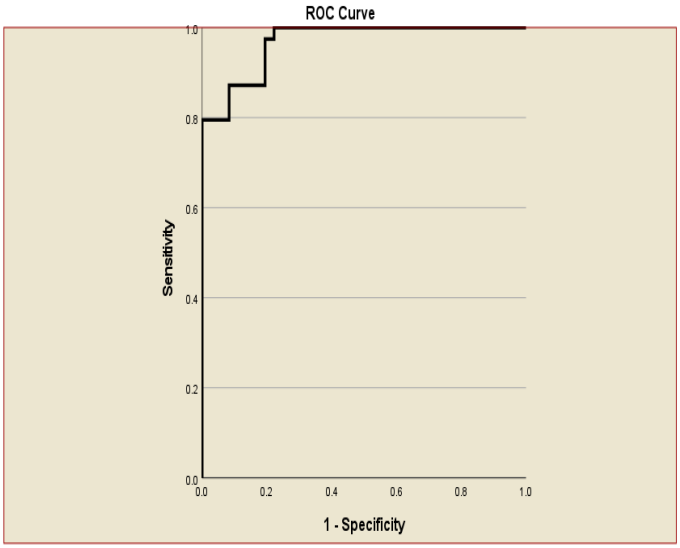

Fig. 4: ROC curve of serum ammonia for the prediction of mortality

DISCUSSION

In this prospective study, serum ammonia demonstrated a significant association with disease severity and clinical outcomes in patients presenting with rodenticide-induced acute liver failure (ALF). The demographic pattern, characterized by a young mean age and predominance of yellow phosphorous ingestion, parallels earlier regional reports and underscores the continued public health impact of easily accessible rodenticides in India.

The study findings highlight the strong relationship between elevated serum ammonia levels and the development of hepatic encephalopathy (HE). Patients with HE exhibited markedly higher ammonia concentrations compared to those without neurological involvement, supporting the well-established role of ammonia in the pathogenesis of cerebral edema and astrocyte dysfunction in ALF. The observation that nearly all non-survivors presented with Grade IV encephalopathy emphasizes the prognostic significance

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of early ammonia elevation and its potential to signal rapid clinical deterioration, which is similar to a study conducted by Ravi *et al.* in Mumbai [19].

Biochemical parameters reflective of hepatic failure, total bilirubin, prothrombin time, and INR, were significantly deranged in the expired group. The strong positive correlations between serum ammonia and these markers indicate that ammonia levels parallel the progression of hepatic injury. These findings align with an existing study by Murugesan *et al.* in South India [5] and Vivek *et al.* in Lucknow [20].

The mode of treatment showed a statistically significant association with clinical outcome. Patients receiving therapeutic plasma exchange demonstrated improved survival, likely attributable to enhanced ammonia clearance and stabilization of hepatic function. This observation reinforces the role of extracorporeal liver support systems in ALF and suggests that ammonia monitoring may help identify patients who could benefit from early initiation of such therapies. These findings are similar to the study done by Vivek *et al.* in Lucknow [20].

The ROC analysis further supports the predictive utility of ammonia in mortality risk stratification. An AUC of 0.929 indicates excellent discriminatory capability, and the identified cutoff of 92.5 µmol/L achieved perfect sensitivity [21]. Although the specificity was modest, the high sensitivity is advantageous for emergency triage, where prompt recognition of high-risk patients is essential for timely intervention found similar to the study done by Chenxia *et al.* [22].

Collectively, these findings demonstrate that serum ammonia is a valuable and readily accessible biomarker for early prognostication in rodenticide-induced ALF. Routine incorporation of ammonia measurement into initial assessment protocols may enhance clinical decision-making by identifying patients at greatest risk for neurological deterioration and mortality. Early identification of high-risk individuals may facilitate appropriate improvement in care, including intensive monitoring and ammonia-lowering treatment strategies, thereby improving overall patient outcomes.

LIMITATIONS

Limitations include the single-center design, a moderate sample size, and the lack of longitudinal ammonia measurements, which offer avenues for future multicenter and mechanistic research.

CONCLUSIONS

Serum ammonia emerged as a sensitive early marker of physiological decompensation in patients with rodenticide-induced acute liver failure. Increasing ammonia concentrations showed a significant association with the progression to hepatic encephalopathy and with poorer clinical outcomes. These findings highlight the clinical utility of ammonia estimation as a rapid and adjunctive tool for early risk stratification. Integrating serum ammonia testing into routine assessment protocols may enable earlier escalation of care and improve management and survival in this high-risk population.

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