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Practical Utility of Serum Ammonia in Children With Acute Liver Failure: A Biomarker of Outcome

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Background. Hyperammonemia is a recognized biochemical abnormality in acute liver failure (ALF). Our aim was to determine a cutoff value for serum ammonia in children with ALF to predict their outcomes while conventional UK liver transplant (LT) listing criteria were applied. **Methods.** We reviewed and analyzed the data of 68 patients with ALF who presented to our center from January 2014 to December 2018; inherited defects of ammonia metabolism were excluded. Patients were divided into 3 groups: Gr 1, LT (30 patients); Gr2, native liver survival (27 patients); and Gr 3, mortality (11 patients). **Results.** Highest ammonia levels during admission before intervention were higher in the LT and mortality group than in the native liver survival group ($P = 0.011$) with levels of 140 μmol/L showing a specificity of 100% as a predictor for LT/mortality. Sixty-two percent of patients with ALF developed encephalopathy; grades 3 and 4 in almost one-third. Encephalopathy was more common in Gr1 patients, followed by Gr3, whereas Gr2 were the least likely to develop encephalopathy. Ammonia levels were significantly higher in encephalopathic patients than in nonencephalopathic ($P = 0.001$). Serum ammonia of 80.5 μmol/L predicted encephalopathy with 80% sensitivity and 75% specificity. **Conclusions.** Serum ammonia level of >80 μmol/L can be used as an alert to ongoing encephalopathy although encephalopathy signs may be missing or subtle and a surrogate marker for earlier interventions for extracorporeal therapies. Moreover, levels >140 μmol/L predict the need for LT or death.

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Pediatric acute liver failure (PALF) is a challenging dynamic illness with variable outcomes. Patients with PALF can either spontaneously recover or require a liver transplant (LT) or can die awaiting LT. The short time interval between the onset of illness and the final outcome makes it a challenging task to establish an underlying etiological diagnosis and offer timely treatment aiming for a favorable outcome.[1,2] What is more difficult and challenging, in this short time frame, is the prediction of the course and outcome of PALF particularly when LT is a therapeutic option. PALF accounts for 10%–15% of indications of LT, but the precise criteria that could predict spontaneous native liver recovery (NLR) versus death remain undefined till late when serious complications ensue.[3] Although LT has been transformational by offering survival for patients with PALF, the long-term need for immunosuppression and its associated complications and inherent risk of mortality make it a morbid condition in itself. In the absence of robust survival/mortality parameters without LT, the risk of overtransplantation is real.[3-6] Accordingly, an ideal predictive model in PALF should have high sensitivity and positive predictive value as well as high specificity and negative predictive value.[7-9] There are multiple prognostic models, most of which have been developed in adults and extrapolated to the pediatric population. There is no universally accepted predictive model for evaluating ALF outcomes in children.[9]

Currently used predictive scores incorporate factors such as age under 10 y, hepatic encephalopathy (HE) grade III/IV, decrease in serum aminotransferases, increased serum bilirubin, and severe coagulopathy.[1,10-14] Encephalopathy has been central to the diagnosis and outcome in adult patients with ALF while its early identification in children remains another challenge. Ammonia plays a pivotal role in the pathogenesis of HE in addition to other implicated toxins in patients with ALF. However, ammonia, being a measurable and modifiable factor, maybe a surrogate marker for HE and, subsequently, a predictor of outcome. Liu et al[15,16] incorporated serum ammonia in their prognostic model for PALF.

The aim of this study was to identify a cutoff value for serum ammonia in children with ALF to predict their outcome and the need for LT, while conventional UK LT listing criteria were applied.

MATERIALS AND METHODS

Patients under the age of 18 y, who presented to our center from January 2014 to December 2018 with ALF comprised the study group. PALF was defined according to the criteria used by the PALF Study Group.[17] The criteria included the following: (1) children with no known evidence of chronic liver disease, (2) biochemical evidence of acute liver injury, and (3) hepatic-based coagulopathy defined as a prothrombin time ≥15 s or international normalized ratio (INR) ≥1.5 not corrected by vitamin K in the presence of clinical HE or a prothrombin time ≥20 s or INR ≥2.0 regardless of the presence or absence of clinical HE. Patients who fulfilled UK selection criteria for pediatric super-urgent LT according to National Health Service Blood and Transplant guidelines were listed.[18] On admission to the pediatric intensive care unit, all were subjected to a unified management protocol. Continuous renal replacement therapy (CRRT) was initiated in patients with encephalopathy grade 3 or 4, hyperammonemia >150 μmol/L and not getting controlled or an absolute value of 200 μmol/L, metabolic abnormalities, oliguria, and renal dysfunction. Patients with inherited defects of ammonia metabolism were excluded.

The data were collected anonymously as part of an audit project. It was approved by the institutional clinical audit review committee (project reference No.: CH039). Audit projects are exempted from the consent process. Demographic, clinical and laboratory data, and outcomes were analyzed. Clinical data included the underlying cause if identifiable, grade of encephalopathy (according to the Whittington scale; **Table S1, SDC,** http://links.lww.com/TXD/A735) in patients <3 y of age, whereas the standard clinical scale was used for patients 3 to 18 y of age (**Table S2, SDC,** http://links.lww.com/TXD/A735), need for circulatory and/or respiratory support, and need for renal replacement therapy. Laboratory data included liver biochemistry on presentation, peak INR, highest ammonia level during admission before intervention, and ammonia level after CRRT and kidney function tests. The outcome comprised LT, native liver survival (NLS), and death.

Continuous variables were expressed as mean (SD) or median (interquartile range, IQR) based on variable distribution and analyzed by the *t* test or the Mann-Whitney *U* test. Categorical data were expressed as frequency and percentage and analyzed using the chi-square test or the Fisher exact test. Laboratory variables showing a significant difference among the 3 outcomes in univariate analysis were identified, and a multivariable logistic regression model was performed using laboratory variables showing a *P* value of <0.05 on univariate analysis. The logistic model was performed using the forward likelihood ratio test. Receiver operating characteristic (ROC) analysis was applied to the significant variable on the logistic regression model. Data were analyzed by using SPSS software version 26.

RESULTS

Sixty-eight patients presented with PALF over a period of 5 y from 2014 to 2018. The age of patients ranged from birth to 17 y of age. PALF was the indeterminate cause in 36.2% of patients. The identifiable causes included viral-induced PALF in 12 patients (17%; 5 adenovirus induced, 4 hepatitis B virus, and 3 herpes simplex virus), autoimmune liver disease in 5 patients (7.2%), and Wilson's disease in 5 patients (7.2%; **Table S3, SDC,** http://links.lww.com/TXD/A735). The clinical and laboratory characteristics of the 68 patients with PALF are shown in Table 1.

According to the age-allocated encephalopathy grading scale (**Table S1 and S2, SDC,** http://links.lww.com/TXD/A735), 24 patients (35%) scored 0 with no encephalopathy, 13 (19%) developed grade I, 8 (11.8%) developed grade II, and 23 (34%) patients developed grade III/IV encephalopathy. The highest serum ammonia level during admission before intervention ranged from 34 to 300 μmol/L with a median (25th–75th) level of 98 μmol/L (68–140). Median ammonia levels across PALF patients with different grades of encephalopathy before intervention are shown in Figure 1.

TABLE 1.

Clinical and laboratory characteristics of 68 patients with acute liver failure

Clinical parameters	N = 68, n (%)
Encephalopathy, n (%)	42 (61.8)
CRRT, n (%)	31 (45.6)
Inotropic support, n (%)	31 (45.6)
Ventilation, n (%)	36 (52.9)
Laboratory parameters (admission levels except for INR and ammonia are peak levels)	**Median (25th–75th), range (min–max)**
Ammonia,[a] μmol/L	98 (68–140) (34–300)
Percent decrease in ammonia after 24 h of CRRT	36.7 (19.7–43) (–77 to 62.8))
WCC, $\times 10^9$/L	8.15 (5.9–12.8) (0.4–30.7)
Hb, g/L	116 (97–127) (51–211)
PLT, $\times 10^9$/L	150.5 (83.2–231) (17–488)
Total bilirubin, μmol/L	221 (81.5–320) (19–729)
ALT, U/L	1057 (186–2440) (32–9540)
AST, U/L,	1189 (258.5–3033) (41–14180)
Albumin, g/L	31.5 (26–35) (16–50)
Peak INR	4.69 (3–5.99) (2–15.1)
Urea, mmol/L	4 (2–5) (1–45)
Creatinine, μmol/L	39.5 (22–53.7) (4–285)
Peak creatinine, μmol/L	58 (32–79) (10–395)

[a]Highest ammonia level during admission before intervention.
ALT, alanine transaminase; AST, aspartate transaminase, CRRT, continuous renal replacement therapy; Hb, hemoglobin; INR, international normalized ratio; PLT, platelet; WCC, white cell count.

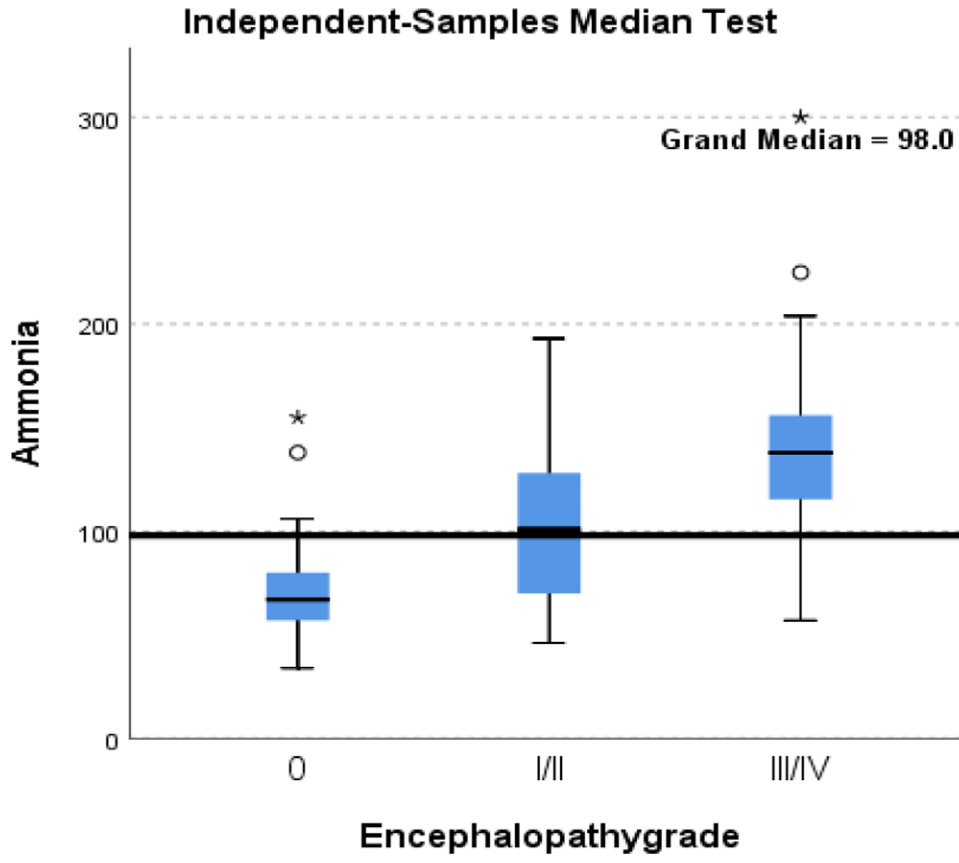

FIGURE 1. Median ammonia levels in ALF patients with no encephalopathy, grade I/II, and grade III/IV encephalopathy. ALF, acute liver failure.

The median (25th–75th) serum ammonia level was 121 (89.25–151.75) in encephalopathic patients, which was significantly higher than in nonencephalopathic patients (median [25th–75th] = 67 [57–89]). ROC analysis was applied to serum ammonia level to determine cutoff values as a predictor for encephalopathy (area under the curve [AUC] = 0.821, P = 0.000; Figure 2). Serum ammonia level of 80.5 µmol/L was a predictor for encephalopathy with 80% sensitivity and 75% specificity.

CRRT was commenced in 31 patients (45%) with a median (25th–75th) percent decrease in ammonia level of 36.7 (19.7–43). The serum ammonia level did not decline in 2 patients, and both died. Nineteen patients with ALF who were on CRRT were transplanted, whereas 12 patients were not transplanted (5 survived their native liver and 7 succumbed).

Fifty-three patients (78%) required pediatric intensive care unit management. Twenty-seven patients with ALF (39.7%) recovered spontaneously with NLS, 30 patients (48.5%) were transplanted and survived, and 11 patients (16.2%) died (Figure 3). Deaths included 3 after LT (severe intracranial hypertension in 2 patients, graft versus host and fulminant Epstein-Barr virus infection on a background of X-linked lymphoproliferative disease in one patient) and 8 died without LT (4 had multisystem organ failure and deteriorated quickly and could not be listed, 2 patients were listed but could not make it to LT, and 2 patients were not a candidate for LT).

Clinical and laboratory data were analyzed among the 3 groups of outcomes: Gr1 LT (30 patients), Gr2, NLS (27 patients), and Gr 3, mortality (11 patients) through univariate analysis (Table 2).

MULTINOMINAL LOGISTIC REGRESSION WAS CARRIED OUT USING SIGNIFICANT LABORATORY VARIABLES AS PREDICTORS FOR LT

The multinomial log-odds of having a transplant would be expected to increase by 0.031 units if ammonia increases by one point while holding all other variables in the model constant. For LT relative to NLS, ammonia as a predictor was associated with a P value of 0.001, and hence, the regression coefficient for ammonia was statistically significant for LT to NLS, given that platelet, urea, and alkaline phosphatase are in the model. In this regression model, the relative risk for having an LT to NLS would be expected to increase by a factor of 1.031, given the other variables in the model are held constant if ammonia increases by one unit. Therefore, patients are more likely to have an LT rather than NLS if they have a higher ammonia level. The same was deduced for mortality relative to NLS, where patients were likely to die if they had a higher ammonia (P = 0.012). For mortality relative to LT, patients were more likely to die if they had a lower platelet count and higher urea (P = 0.035 and 0.044, respectively).

ROC analysis was applied to the highest serum ammonia during admission before intervention as a predictor for the need for LT/mortality, and different ammonia cutoff values were identified (AUC = 0.77, P = 0.000; Figure 4). An ammonia level of 93.5 µmol/L predicted LT/mortality with a sensitivity of 67.5% and a specificity of 68%. A higher ammonia level of 121 µmol/L was more specific (specificity 92%) and less sensitive (sensitivity 55%) in predicting LT/mortality. Interestingly, a serum level of ammonia of 140 µmol/L was

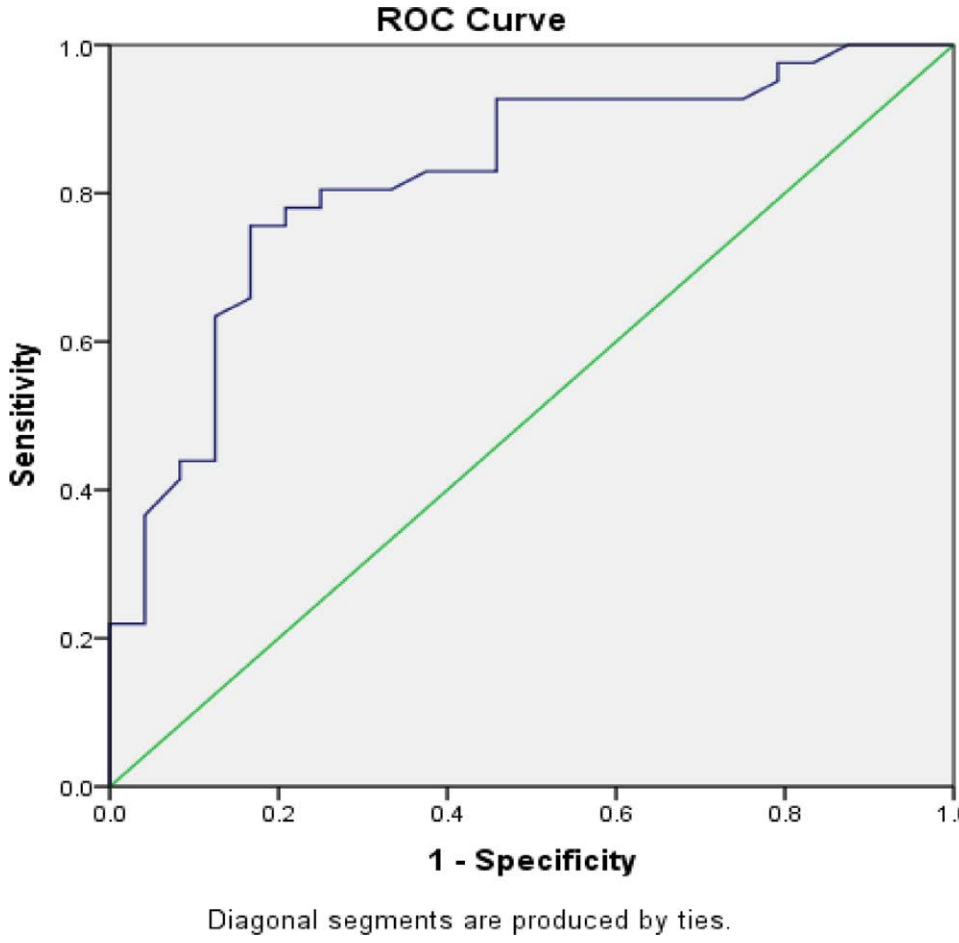

FIGURE 2. ROC analysis for serum ammonia as a predictor for encephalopathy. ROC, receiver operating characteristic.

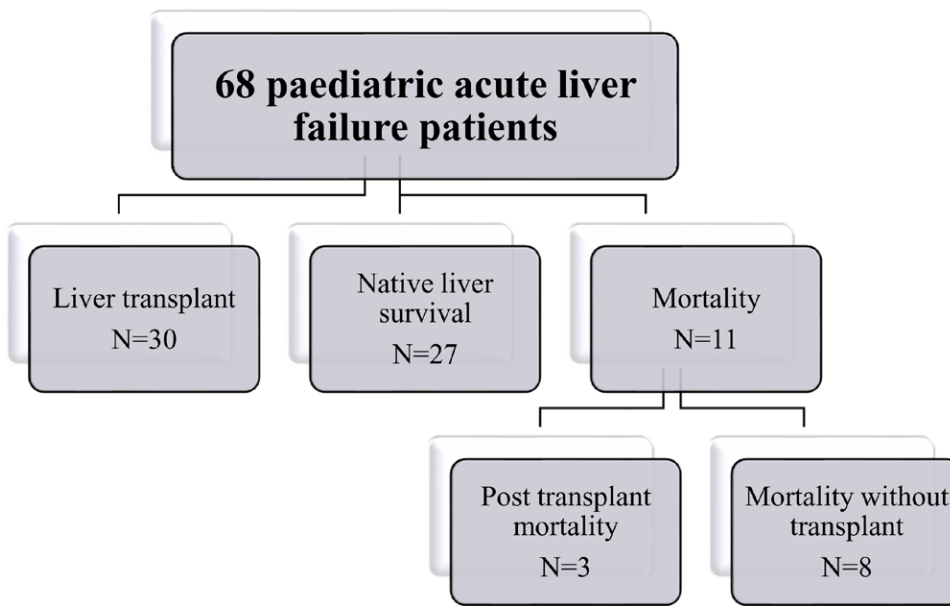

FIGURE 3. Outcome in 68 patients with pediatric acute liver failure patients.

100/% specific for LT/mortality with a positive predictive value of 100%. Nevertheless, this ammonia level had a low sensitivity of 40%, negative predictive value of 51%, and a diagnostic accuracy of 63%. Sixteen patients had ammonia level >140. Thirteen patients underwent LT and 3 patients died; 2 of them died after LT.

TABLE 2.

Univariate analysis for clinical and laboratory data among patients with liver transplant, native liver survival, and mortality group of patients

Clinical data	Liver transplant (N = 30), n (%)	Native liver survival (N = 27), n (%)	Mortality (N = 11), n (%)	*P*
Indeterminate cause	12 (40)	7 (25.9)	6 (54.5)	0.224
Encephalopathy, n (%)	24 (80)	12 (44.4)	6 (54.5)	0.019
CRRT, n (%)	16 (53.3)	5 (18.5)	10 (90.9)	0.000
Inotropic support, n (%)	14 (46.7)	6 (22.2)	11 (100)	0.000
Ventilation, n (%)	18 (60)	7 (25.9)	11 (100)	0.000
Length of hospital stay, median (25th–75th)	38.5 (30.7–61.2) (13–153)	12.5 (8–18) (5–25)	11 (3–61) (1–171)	0.000
Laboratory parameter, median (25th–75th), range (min–max)				
Ammonia,[a] µmol/L	151 (133–196) (97–204)	113 (95.5–133.5) (92–138)	148 (78.5–267) (62-300)	0.011
Total bilirubin, µmol/L	246 (106.5–373) (74–451)	79.5 (62–226.7) (60–272)	252 (95.5–536.7) (75–600)	0.21
ALT, U/L	1226 (249–2115) (111–2319)	4073 (796–8265) (250–9117)	1376 (251–2937.7) (87–3247)	0.75
AST, U/L	1925 (363–3719) (151–6386)	1736 (722–11 161) (507–14180)	1370.5 (401.5–5524.7) (245–6743)	0.56
ALP, U/L	341 (174.5–471.5) (27–1344)	407 (195.2–635) (109–1157)	163 (103–239) (59–423)	0.006
GGT, U/L	75 (40.7–105.2) (18–365)	78 (42.5–165.7) (17–506)	86 (49–237) (26–341)	0.9
Albumin, g/L	31 (27.5–34) (22–39)	33.5 (29.2–38.5) (29–39)	34.5 (27.7–37.5) (26–38)	0.87
Peak INR	4.8 (4—6.3) (3–13.6)	3.37 (2.5–5.14) (2–14.9)	7.2 (4.7–9) (3.3–15.1)	0.06
Urea, mmol/L	3 (1.3–3.5) (1–4.9)	4.35 (2.1–5.5) (1.6–5.7)	3.95 (3–15.4) (2.9–19.2)	0.015
Peak creatinine, µmol/L	49 (38–66) (31–112)	65.5 (40–80) (34–82)	44.5 (21.7–92.7) (21–102)	0.09
WCC, $\times 10^9$/L	4.89 (3.2–8.9) (0.35–15)	6.6 (5.1–8.7) (4.86–9.2)	10.2 (4–16) (2.8–16.9)	0.87
Hb, g/L	103 (93.5–130) (86–143)	107.5 (97–119) (97–120)	107 (91.25–120.5) (88–123)	0.08
PLT, $\times 10^9$/L	112 (57–264) (29–409)	184.5 (89.2–225) (64–232)	65.5 (39.5–254.2) (38–310)	0.012

[a]Highest ammonia level during admission before intervention.

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CRRT, continuous renal replacement therapy; GGT, gamma glutamyl transferase; Hb, hemoglobin, INR, international normalized ratio, PLT, platelet; WCC, white cell count.

DISCUSSION

PALF is a challenging disease with many identifiable etiologies, some of which are medically treatable, and others not, yet there is still a significant proportion with indeterminate cause. In our cohort, 36% were of indeterminate cause where there is no room for outcome modification by applying a specific treatment. Moreover, in treatable conditions, we still cannot predict the outcome and response to treatment in the setting of a limited time frame and rapid deterioration of the condition. Therefore, all efforts have been made to predict the course and outcomes of PALF, aiming at LT at the right timing in patients who will die without an LT, as well as avoid unnecessary transplants in patients who can survive their native livers. LT was performed in 33 patients (48.5% of our patients with PALF), and spontaneous recovery with NLS was performed in 40% of patients.

The PALF Study database highlighted that 10% of all patients listed for emergency LT were delisted because of death or spontaneous recovery in 20% and 80% of patients, respectively.[17] Hence, predictors are important for the timely management and appropriate allocation of organs.

Patients were more likely to have LT/mortality rather than NLS if they had a higher ammonia level. Different cutoff values for ammonia, as a predictor for LT, have been identified on ROC analysis based on the sensitivity and specificity of the proposed cutoff value. Higher ammonia levels provide more specificity as a predictor of LT/mortality, yet they will have lower sensitivity. Interestingly, serum ammonia levels of >140 before intervention had 100% specificity in predicting the need for a LT. That is to say all patients with serum ammonia of >140 µmol/L were either transplanted or died and hence this level should be considered deleterious and needs prompt intervention and timely transplant and are unlikely to survive with their native livers.

Ammonia cutoff values have been proposed before in adult patients. Niranjan-Azadi et al, 2016 mentioned that admission ammonia >120 µmol/L is associated with higher mortality. It has been reported that ammonia seems to be a better prognostic parameter for children than for adults in the setting of ALF.[19] Zhao et al[20] showed in their study, which included 32 children and 177 adults with ALF, that ammonia levels were significantly higher in children, and the outcome was worse with higher ammonia levels. The liver injury units (LIU) scoring model has incorporated ammonia as it had a significant association with death or need for LT. LIU has been evaluated in different studies, including the multinational study done on the PALF Study database for validation of LIU, which showed that LIU score predicted LT better than it predicted death (AUC for LT 0.84, AUC for death 0.76).[16] Another pediatric study done in Germany, including 44 patients with PALF, showed lower ammonia levels in NLS and AUC for peak ammonia, which was 0.79; however, no cutoff values were reported.[21] In 2018, Chien et al[22] enrolled 23 patients with PALF to identify the predictors of NLR. Peak ammonia levels were lower with NLR, and ROC analysis yielded a cutoff value of <190 mmol/L, with a sensitivity of 90.9% and a specificity of 83.3% in the prediction of NLR in children with ALF.

Not only can ammonia be helpful in predicting LT/mortality, but it can also aid with early identification of encephalopathy, allowing timely management and preventing further deterioration. Encephalopathy is an established criterion in ALF in the adult population; nevertheless, it is not the case in pediatrics, where signs of encephalopathy can be subtle and

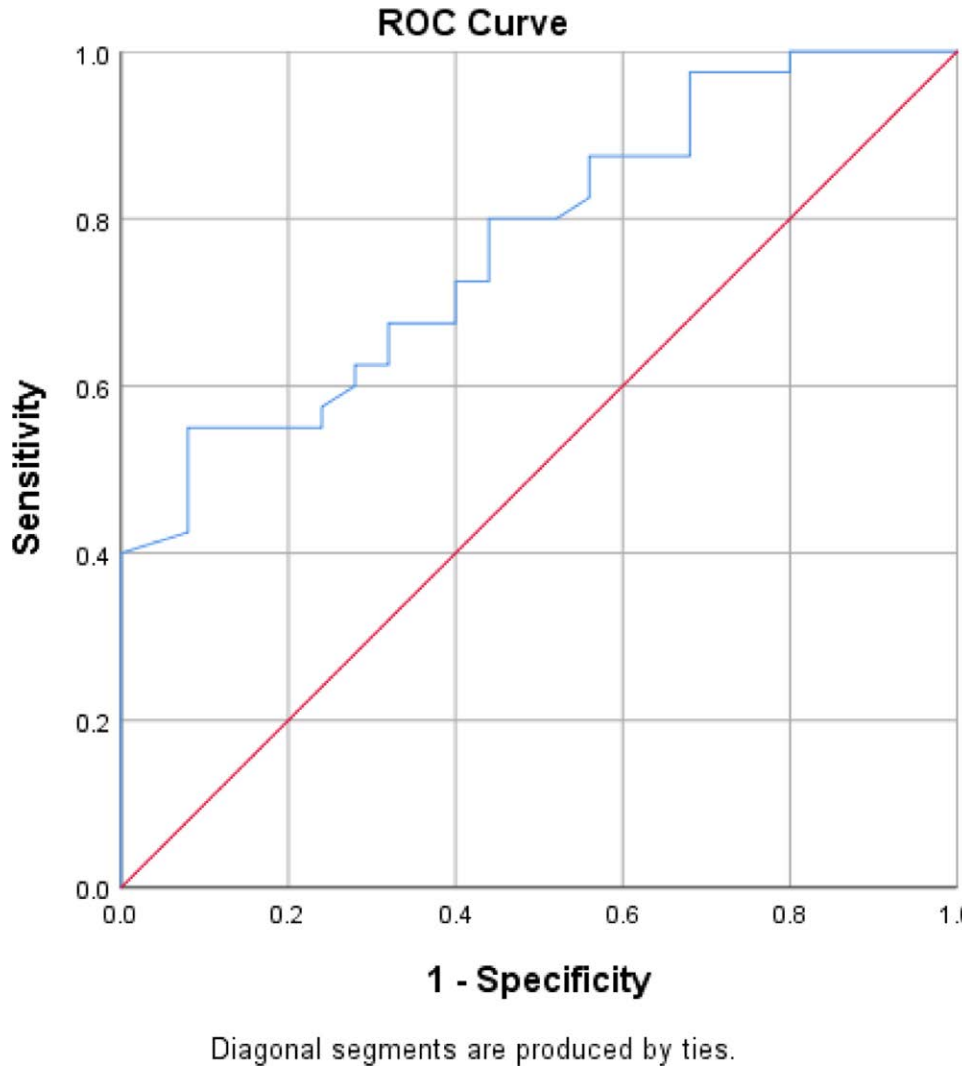

FIGURE 4. ROC analysis for serum ammonia as a predictor for liver transplant/mortality in pediatric acute liver failure. ROC, receiver operating characteristic.

may be overlooked and not identified except late in the disease course. Ammonia is not the only toxin responsible for encephalopathy, but it is the only measurable and modifiable factor. Measuring arterial ammonia is the ideal method; however, it is not practical in pediatrics and is usually replaced by a free-flowing venous sample and transported on ice to the laboratory, and using trends of ammonia is recommended rather than 1 single value.[6]

Ammonia level correlated with clinical encephalopathy and serum ammonia level of 80.5 μmol/L can be a predictor of encephalopathy with 80.5% sensitivity and 75% specificity. Accordingly, it can be a fair representative of encephalopathy. It can be used as a biomarker to institute early neuroprotection protocol (such as normoglycemia, serum sodium of 145–150, head up to 30 degrees, neck in a neutral position, and monitoring for raised intracranial pressure per local facilities and practices). Different threshold values have been proposed in the adult population for ammonia as a predictor of encephalopathy and increased intracranial tension. Ammonia of 75 mmol/L has been considered as a threshold below which patients rarely develop intracranial hypertension, and admission ammonia levels of >100 mmol/L as an independent risk factor for high-grade HE[23] and a level of >200 mmol/L is strongly associated with cerebral herniation.[24]

Encephalopathy and hyperammonemia were among the indications of the commencement of CRRT in our patients, and CRRT was successful in lowering the ammonia level except in 2 patients whose hyperammonemia was refractory, and both died in 3 d. Therefore, the inability to lower ammonia even after the initiation of CRRT was a poor prognostic sign.

Limitations of the study: it is a single-center retrospective study that included patients from birth to 18 y and we do not have a nomogram for the ammonia levels in different age groups, and the values may vary according to the age. Arterial ammonia is the ideal method of measuring ammonia; however, this was not feasible in all cases, and free-flowing venous samples were mostly used. There was difficulty following the trend of ammonia once the patient was on extracorporeal liver support like CRRT.

In conclusion, ammonia could be a useful biomarker in the setting of PALF with levels >140 μmol/L suggestive of adverse outcomes of either LT or mortality. In addition, persistent hyperammonemia, even after starting extracorporeal therapy, predicts poor survival.

REFERENCES

1. Whitington PF, Alonso EM. Fulminant hepatitis and acute liver failure. In: *Diseases of the Liver and Biliary System in Children*, 2nd ed; Deirdre, K., ed. Oxford, UK: Wiley-Blackwell; 2003:pp. 107–126.
2. Gilbert Pérez JJ, Jordano Moreno B, Rodríguez Salas M. Aetiology, outcomes and prognostic indicators of paediatric acute liver failure. *An Pediatr*. 2018;88:63–68.
3. Sanchez MC, D'Agostino DE. Pediatric end-stage liver disease score in acute liver failure to assess poor prognosis. *J Pediatr Gastroenterol Nutr*. 2012;54:193–196.
4. Wlodzimirow KA, Eslami S, Chamuleau RA, et al. Prediction of poor outcome in patients with acute liver failure-systematic review of prediction models. *PLoS One*. 2012;7:e50952.
5. Saluja V, Sharma A, Pasupuleti SS, et al. Comparison of prognostic models in acute liver failure: Decision is to be dynamic. *Indian J Crit Care Med*. 2019;23:574–581.
6. Squires JE, Alonso EM, Ibrahim SH, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the Diagnosis and Management of Pediatric Acute Liver Failure. *J Pediatr Gastroenterol Nutr*. 2022;74:138–158.
7. O'Grady JG. Prognostication in acute liver failure: A tool or an anchor? *Liver Transpl*. 2007;13:786–787.
8. D'Agostino D, Diaz S, Sanchez MC, et al. Management and prognosis of acute liver failure in children. *Curr Gastroenterol Rep*. 2012;14:262–269.
9. Jain V, Dhawan A. Prognostic modeling in pediatric acute liver failure. *Liver Transpl*. 2016;22:1418–1430.
10. Bansal S, Dhawan A. Acute liver failure. *Curr Paediat*. 2006;16:36–42.
11. Bhatia V, Singh R, Acharya SK. Predictive value of arterial ammonia for complications and outcome in acute liver failure. *Gut*. 2006;55:98–104.
12. Bernal W, Auzinger G, Dhawan A, Wendon, J. Acute liver failure. *Lancet*. 2010;376:190–201.
13. Du WB, Pan XP, Li LJ. Prognostic models for acute liver failure. *Hepatobiliary Pancreat Dis Int*. 2010;9:122–128.
14. Mishra A, Rustgi V. Prognostic models in acute liver failure. *Clin Liver Dis*. 2018;22:375–388.
15. Liu E, MacKenzie T, Dobyns EL, et al. Characterization of acute liver failure and development of a continuous risk of death staging system in children. *J Hepatol*. 2006;44:134–141.
16. Lu BR, Zhang S, Narkewicz MR, et al; Pediatric Acute Liver Failure Study Group. Evaluation of the liver injury unit scoring system to predict survival in a multinational study of pediatric acute liver failure. *J Pediatr*. 2013;162:1010–1016.
17. Squires RH Jr, Shneider BL, Bucuvalas J, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. *J Pediatr*. 2006;148:652–658.
18. NHS Blood and Transplant. Liver Advisory Group on behalf of NHSBT (2022) POL195/14—liver transplantation: selection criteria and recipient registration. Available at https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/27372/pol195-120822.pdf. Accessed February 1, 2025.
19. Niranjan-Azadi AM, Araz F, Patel YA, et al. Ammonia level and mortality in acute liver failure: a single-center experience. *Ann Transplant*. 2016;21:479–483.
20. Zhao P, Wang C, Liu W. Can Experience from adults regarding acute liver failure fit children? *Indian J Pediatr*. 2014;81:501–503.
21. Kathemann S, Bechmann LP, Sowa JP, et al. Etiology, outcome and prognostic factors of childhood acute liver failure in a German Single Center. *Ann Hepatol*. 2015;14:722–728.
22. Chien MM, Chang MH, Chang KC, et al. Prognostic parameters of pediatric acute liver failure and the role of plasma exchange. *Pediatr Neonatol*. 2019;60:389–395.
23. Bernal W, Hall C, Karvellas CJ, et al. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. *Hepatology*. 2007;46:1844–1852.
24. Clemmesen JO, Larsen FS, Kondrup J, et al. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. *Hepatology*. 1999;29:648–653.