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ORIGINAL ARTICLE

Etiology, outcome and prognostic indicators of acute liver failure in Asian children

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Abstract

Objective Outcome of pediatric acute liver failure (PALF) in countries with limited availability of LT is not well described. We evaluated the outcome and prognostic indicators of PALF in Malaysia where emergency LT for ALF is limited.

Methods In this retrospective review on children < 18 years with PALF, we compared clinical and laboratory parameters between survival after supportive treatment and after LT or succumbed without LT. The predictive values of Liver Injury Unit (LIU; peak laboratory values for international normalized ratio [INR], ammonia, total bilirubin) and upon admission (aLIU) on outcome of PALF was evaluated using receiver operator characteristic (ROC) curves.

Results Of 77 children (39 males [51%]; median age 2.8 years) with PALF, the overall survival was 55% ($n = 42$); 52% ($n = 40$) survived with supportive management, 2.6% ($n = 2$) after LT. As compared to children who survived without LT, children who had LT/died had lower hemoglobin, aspartate transferase, γ-glutamyl transpeptidase (GGT), and higher serum bilirubin, alkaline phosphatase, ammonia, and serum sodium ($p < 0.05$). On multivariate analysis, significant independent predictor for death or LT were peak bilirubin > 452 µmol/L and peak GGT < 96 IU/L. The C-index of LIU and aLIU score were 0.79 and 0.68, respectively, indicating that LIU score was a good model in predicting outcome of PALF.

Conclusions Overall survival of PALF remained poor. High peak bilirubin and low GGT predict poor outcome of PALF. LIU score is a good model in predicting outcome of PALF and maybe useful in selecting children for emergency LT.

Keywords Pediatric acute liver failure · Etiology · Outcome · Prognostic indicator · Spontaneous recovery · Liver transplant · Death · Dengue · Indeterminate cause · Liver injury unit

Introduction

The etiology of pediatric acute liver failure (PALF) varies according to geographical location as well as age at diagnosis [1–5]. In advanced countries, paracetamol overdose is the commonest cause [1, 2] while in developing countries, acute viral hepatitis, especially hepatitis A, is commonly seen [3–5]. In infants, gestational alloimmune liver disease-neonatal hemochromatosis (GALD-NH), mitochondrial hepatopathy, viral infection and hemophagocytic lymphohistiocytosis (HLH) are important causes [6, 7]. In up to 50% of cases, a definite cause of the liver failure cannot be established [8]. In this group of children, the prognosis is generally poor [8].

PALF is a life-threatening illness; a previously healthy child can deteriorate rapidly to develop severe hepatic dysfunction and synthetic liver failure [9]. Despite advances in therapeutic approach, up to 50% of children with PALF either succumbed to or required emergency liver transplant (LT) [9]. Prognosis is better in young infants but poorer in those with multiorgan failure as well as in cases of indeterminate diagnosis [8, 9]. To date, no specific therapies of proven benefit is available for PALF except for emergency

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LT in children with severe hepatic dysfunction. However, rapid disease progression in many cases limits the use of LT as an effective therapy, particularly when emergency LT is limited [3–5]. The overall survival of PALF without LT ranges between 56 and 73% [3, 8].

The King's College Hospital criteria (KCHC) has been used widely as a prediction model for the outcome in ALF for both children and adults [10]. However, a study by the Pediatric Acute Liver Failure (PALF) Study Group, a large multicenter, prospective cohort from the United States, Canada, and United Kingdom, showed that KCHC did not reliably predict death in non-paracetamol induced PALF [11]. Subsequently, a scoring system was derived by Lu et al. known as Liver Injury Units (LIU) score, using peak value of total bilirubin (TB), ammonia, international normalized ratio (INR) or prothrombin time (PT) collected prospectively to predict the risk of mortality in PALF. The LIU score and the score using laboratory values on admission (aLIU), evaluated by PALF Study Group, found that LIU score performed better than aLIU to predict the need for LT in children with PALF [12].

Malaysia is a middle-income country. LT is limited and was mostly performed in adult patients with chronic liver failure as an elective surgery [13]. Little is known about causes and outcome of PALF in Malaysia. In the present study, we aimed to ascertain the causes and outcome of PALF from a single referral center in Malaysia. We also evaluated the applicability of the LIU and aLIU scores in predicting the outcome of PALF in our patients.

Materials and methods

This was a retrospective, descriptive study conducted in a single pediatric liver center in Malaysia over a period of 18 years (January 2000 to December 2018). All patients younger than 18 years of age who were referred to the Department of Pediatrics, University of Malaya Medical Centre (UMMC), Kuala Lumpur, with a diagnosis of PALF were included. The present study was approved by the institutional ethical review committee of UMMC (20161122-4622). Patients were identified from the unit database, case notes were reviewed, and information was extracted. Patients who had incomplete data or unknown outcome were excluded.

Case definitions

PALF was diagnosed based on the following criteria described by Squires et al.: (a) biochemical evidence of acute liver injury, (b) no known evidence of underlying chronic liver disease, and (c) hepatic-based coagulopathy defined as PT ≥ 15 s or INR ≥ 1.5 in the presence of hepatic encephalopathy, or PT ≥ 20 s or INR ≥ 2.0 regardless of the presence or absence of clinical hepatic encephalopathy [1].

Data collection

The following data were collected: basic demography, clinical and laboratory parameters, causes of PALF and the outcome upon discharge. The underlying cause of PALF was established based on detailed clinical information and laboratory data. Inherited metabolic diseases were identified and confirmed by relevant diagnostic metabolites present in the urine or plasma, or histopathology. Cases where no identifiable cause could be ascertained despite extensive investigation were classified as indeterminate cause. The outcome was categorized into patients who (a) survived with supportive measures, or (b) requiring LT or death.

Statistics

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software for Windows version 22.0 (SPSS inc., Chicago, IL, USA.). Non-normally distributed data were expressed in median (inter-quartile range, [IQR]). Mann–Whitney *U* test was performed to compare the differences between two groups. Pearson chi-square test was performed to test for associations between categorical variables. Multiple logistic regression was used to design the risk prediction model to predict the outcome. Continuous data were categorized by utilizing median in the LT and/or death group. A p value < 0.05 was considered as statistically significant in the risk prediction model.

Prognostic indicators

Age at onset, total serum bilirubin, albumin, INR, alanine transferase (ALT) and alkaline phosphatase (ALP) were assessed using logistic regression analysis to evaluate independent predictors of the outcome. LIU score was derived from the formula using the peak value of INR, ammonia, and total bilirubin [3.057 × peak total bilirubin (mg/dL)] + (45.51 × peak INR) + (0.254 × peak ammonia), while aLIU score was derived from measurements of the three laboratory parameters on admission [12]. Since the predictive value was better for the LIU scoring using INR rather than PT [14], both LIU and aLIU scores in the current study were derived based on INR.

Receiver operating characteristic (ROC) curves were used to evaluate the discriminating ability of LIU and aLIU scores in predicting death/LT at 21 day after admission. ROC curves show the relationship between clinical sensitivity and specificity for every possible cut-off. Through the curves, the cut-off points for the measurement that maximized the rate of true positives (sensitivity) and minimized the rate of false

positives (1–specificity) were determined. The C-index (area under the ROC curve) was used to measure the discriminative ability of the test. A C-index value of < 0.5 indicates a very poor model, value > 0.7 indicates a good model, and value > 0.8 indicates a strong model [15].

Results

During the study period, a total of 84 children with PALF were admitted to the Pediatric Liver Unit of UMMC, Malaysia. Seven children were excluded: outcome unknown ($n=2$), incomplete data ($n=2$), and non-Malaysian citizens ($n=3$). Thus, data on 77 children were analyzed.

Demographic characteristics

The ethnic distribution of the 77 patients (Malay = 42, 55%; Chinese = 26, 34%; Indian = 8, 13%; local aborigine = 1, 1.3%) reflected the ethnic distribution of Malaysian population. The gender distribution was 39 males and 36 females (males: females = 1.08:1). The median (IQR) age at diagnosis was 2.8 (7.2) years, ranged from 0 to 14 years; IQR 7.2 (Table 1). The commonest age group was 6–12 years ($n=30$; 39%), followed by early childhood (1–5 years; $n=23$, 30%). Five neonates (< 1 month; 6%) were included in the present study.

Etiology

Infection was the most common cause ($n=27$; 27.3%; Table 1), while dengue infection was the commonest etiology ($n=11$; 14%). All children who had severe dengue disease in our cohort presented with circulatory failure and shock with two having multiorgan failure. Seven patients (9%) presented with clinical sepsis and PALF, but no infective agent was identified or isolated.

Wilson's disease was the commonest metabolic disease presenting with PALF and were seen in late childhood ($n=5$; 6.5%). Other metabolic liver diseases were uncommon, seven children (9%) had paracetamol toxicity; all were secondary to unintentional overdose.

Table 1 Etiology and age at diagnosis in 77 Malaysian children with acute liver failure

	Neonatal < 2 months ($n=10$)	Infants 2–12 months ($n=11$)	Early childhood 1–5 years ($n=24$)	Late childhood 6–12 years (n = 30)	Adolescents > 12 years ($n=3$)	All
Infective						
Severe dengue	–	2 (18%)	3 (13%)	6 (20%)	–	11 (14%)
Sepsis	–	1 (9%)	5 (22%)	1 (3%)	–	7 (9%)
EBV hepatitis	1 (10%)	–	–	1 (3%)	–	2 (3%)
HSV hepatitis	–	1 (9%)	–	–	–	1 (1%)
Metabolic						
Wilson's disease	–	–	–	5 (17%)	–	5 (6%)
Isovaleric acidemia	–	–	1 (4%)	–	–	1 (1%)
SCHADD	–	–	1 (4%)	–	–	1 (1%)
Tyrosinemia	–	1 (9%)	–	–	–	1 (1%)
Immune-mediated						
Autoimmune hepatitis	–	–	–	5 (17%)	–	5 (6%)
GALD	3 (30%)	–	–	–	–	3 (4%)
Toxic injury						
Paracetamol overdose	–	1 (9%)	4 (17%)	2 (7%)	–	7 (9%)
Anti-tuberculous drug	–	–	–	1 (3%)	–	1 (1%)
Paraquat poisoning	–	–	–	1 (3%)	–	1 (1%)
Others						
Hemophagocytic lymphohistiocytosis	–	–	2 (9%)	–	1 (33%)	3 (4%)
Congestive hepatopathy	–	1 (9%)	–	–	1 (33%)	2 (3%)
Indeterminate	6 (60%)	4 (36%)	7 (30%)	8 (27%)	1 (33%)	26 (34%)
Total	10 (13%)	11 (14%)	23 (30%)	30(39%)	3 (4%)	**77**

EBV epstein-barr virus, *GALD* gestational alloimmune liver disease, *HSV* herpes simplex hepatitis, *SCHADD* short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency

In one-third ($n=26$; 34%) of the cases, no definite cause of the PALF could be identified and were classified as indeterminate cause.

Liver transplantation

Three patients (3.8%, one for Wilson's disease, and two for indeterminate cause) underwent emergency LT. One patient succumbed within four weeks after LT secondary to hepatic artery thrombosis and septicemia. Thus, only two patients survived after LT.

Outcome

The survival with native liver following supportive management was 52% ($n=40$), while the overall survival (native liver and LT) was 55% ($n=42$). ALF caused by dengue infection, paracetamol overdose, autoimmune hepatitis had a more favorable outcome with the survival rate following conservative management of 82, 86, and 60%, respectively (Table 2).

Prognostic indicators

Table 3 shows factors associated with a poor outcome, either LT or death. Multiple logistic regression analysis (Table 4) showed that independent predictors for poor outcome were peak total serum bilirubin ≥ 452 µmol/L (OR = 0.13 [95% CI 0.02—0.74], $p=0.022$) and peak γ-glutamyl transpeptidase (γGT) < 96 IU/L (OR = 11.97 [95% CI 1.73—82.73], $p=0.012$).

LIU and aLIU score

In applying LIU and aLIU scores in our cohort, 12 patients were excluded due to missing peak ammonia value. Another patient was excluded when applying aLIU score due to missing of INR on admission. C-index for both LIU (Fig. 1) and aLIU (Fig. 2) scores were 0.79 (95% CI 0.67–0.91) and 0.68 (95% CI 0.55–0.81), respectively.

Table 2 Outcome at discharge in 77 Malaysian children with acute liver failure

Etiology	Survival with native liver	Death or liver transplant	*p* value
Age group			
< 2 months	4 (44%)	5 (56%)	0.421
2–< 12 months	6 (55%)	5 (46%)	
1–< 5 years	14 (58%)	10 (42%)	
5–< 12 years	16 (53%)	14 (47%)	
12 years and above	0	3 (100%)	
Metabolic			
Wilson's disease	1 (2.5%)	4 (10.8%)	0.187
Isovaleric acidemia	1 (2.5%)	0	
SCHADD	1 (2.5%)	0	
Tyrosinemia	1 (2.5%)	0	
Immune-mediated			
Autoimmune hepatitis	3 (7.5%)	2 (5.4%)	0.18
GALD	0	3 (8.1%)	
Toxic injury			
Paracetamol overdose	6 (15%)	1 (2.7%)	0.42
Non-paracetamol poisoning	1 (2.5%)	1 (2.7%)	
Hemophagocytic lymphohistiocytosis	0	3 (8.1%)	
Congestive hepatopathy	0	2 (5.4%)	
Indeterminate	11 (27.5%)	15 (40.5%)	0.17
Total	**40 (52%)**	**37 (48%)**	

EBV epstein-barr virus, *GALD* gestational alloimmune liver disease, *HSV* herpes simplex hepatitis, *LT* liver transplant, *SCHADD* short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency

[#]*p* value acquired from Chi-square test of association

Table 3 Comparison of clinical characteristics age at diagnosis, laboratory parameters and outcome of children with pediatric acute liver failure in a single center

	Recover ($N=40$)	Liver transplant and/or death ($N=37$)	p value*
Age at diagnosis, years	2.7 [7.0]	4.0 [7.9]	0.710
Hemoglobin (admission), g/dL	11.2 [3.7]	10.5 [3.5]	0.029
White blood cell (admission), $\times 10^9$/L	10.4 [9.0]	9.5 [11.3]	0.919
Platelet (admission), $\times 10^9$/L	145.5 [206.5]	118.0 [155.0]	0.217
Total serum bilirubin (peak), µmol/L	91.5 [176.3]	452.0 [467.0]	<0.001
Albumin (lowest), g/L	22.5 [6.5]	23 [8.5]	0.327
Alkaline phosphatase (peak), IU/L	333.0 [196.3]	425.0 [439.5]	0.028
Alanine aminotransferase (peak), IU/L	1618.5 [5171.3]	1082.0 [2446.5]	0.039
Aspartate aminotransferase (peak), IU/L	2391.5 [8530.3]	1700.0 [4715.5]	0.195
Gamma-glutamyl transferase (peak), IU/L	175.0 [239.0]	96.0 [90.8]	0.005
International normalized ratio (peak)	2.8 [2.3]	3.9 [3.9]	0.127
Ammonia (peak), µmol/L	132.8 [89.7]	159.9 [147.0]	0.033
Sodium (admission), mmol/L	135.0 [6.5]	137.0 [6.0]	0.040

Median *IQR* inter-quartile range

*p value obtained from Mann–Whitney U test of comparison between groups

Table 4 Predictors of mortality and/or liver transplant in 77 Malaysian children with acute liver failure

Clinical parameters	Adjusted OR [95% CI]	p value
Hemoglobin < 10.5 G/DL	1.07 [0.22–5.17]	0.932
Platelet < 118 × 10^9/L	3.24 [0.65–16.08]	0.150
Total bilirubin (peak) ≥ 452 µmol/L	8.23 [1.33–50.97]	**0.023**
Alkaline phosphatase (peak) ≥ 428 IU/L	5.44 [0.72–40.93]	0.100
Alanine aminotransferase (peak) < 1082 IU/L	0.84 [0.12–5.72]	0.861
Aspartate aminotransferase (peak) < 1700 IU/L	0.43 [0.05–4.10]	0.463
γ-glutamyl transpeptidase (peak) < 96 IU/L	13.49 [1.85–98.43]	**0.012**
International normalized ratio (peak) ≥ 3.9	2.22 [0.44–11.12]	0.334
Plasma ammonia (peak) ≥ 160 µmol/L	1.46 [0.23–9.29]	0.688
Serum sodium (admission) ≥ 137 mmol/L	1.17 [0.22–6.10]	0.853

*Multiple logistic regression

Discussion

Despite significant advances in the research and management, ALF in children remains a rapidly progressing disease with high mortality rate, ranging from 25 to 55% [1, 2, 6, 12, 16, 17]. The overall mortality is higher in settings where emergency LT is not readily available [18]. The present study on children with ALF admitted to a single tertiary center in Malaysia showed an overall spontaneous recovery rate of 52%. The result is comparable to a study by Alam et al. from India who studied 109 patients with PALF and found that 48% of patients survived with native liver at day 90 of presentation and an overall mortality of 42% [19]. In another study from India involving 43 children, Kaur et al. reported a spontaneous recovery rate of 56% and an overall mortality rate of 44% [5]. In the developed world, Lee et al. from the United Kingdom reported a spontaneous recovery rate of 33% and an overall mortality of 39% [2]. A multicenter study involving 348 patients by PALF Study Group reported a spontaneous recovery rate of 53%, while the overall mortality rate was 16% [1]. In the present study, the spontaneous recovery rate was similar to the rates reported by Lee et al. [2] and PALF group but the overall mortality rate was much higher. This can be attributed to lack of timely emergency LT in children with ALF in Malaysia.

Although the etiology of PALF varies according to geographical location, acute viral hepatitis, metabolic liver diseases as well as drug-induced liver injuries (DILI) remained the three main identifiable causes [2, 4, 5, 17, 19–21]. Underlying cause of the liver failure is an important factor in determining the outcome. Spontaneous recovery was most likely in children with paracetamol toxicity while prognosis is worse in children with

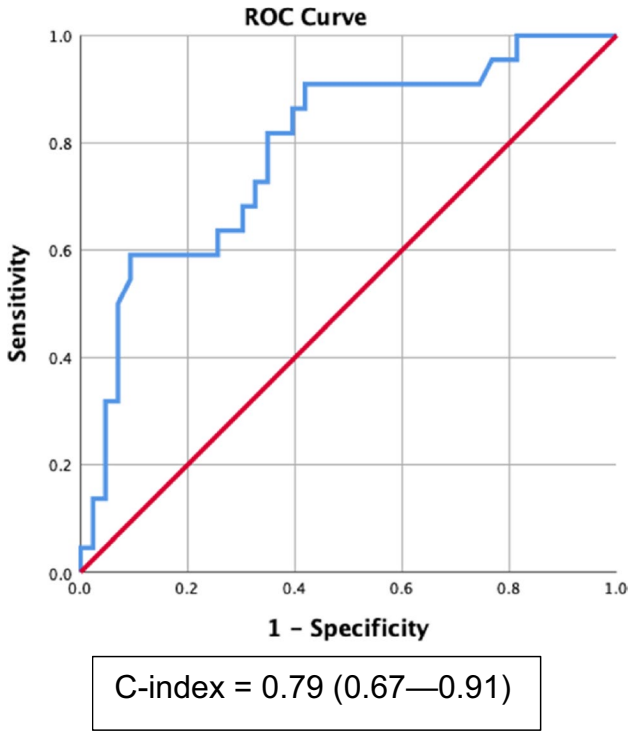

Fig. 1 Receiver operating characteristic curve of liver injury unit (LIU) score using international normalized ratio (INR) in predicting 21-day outcome in children with acute liver failure ($n=65$)

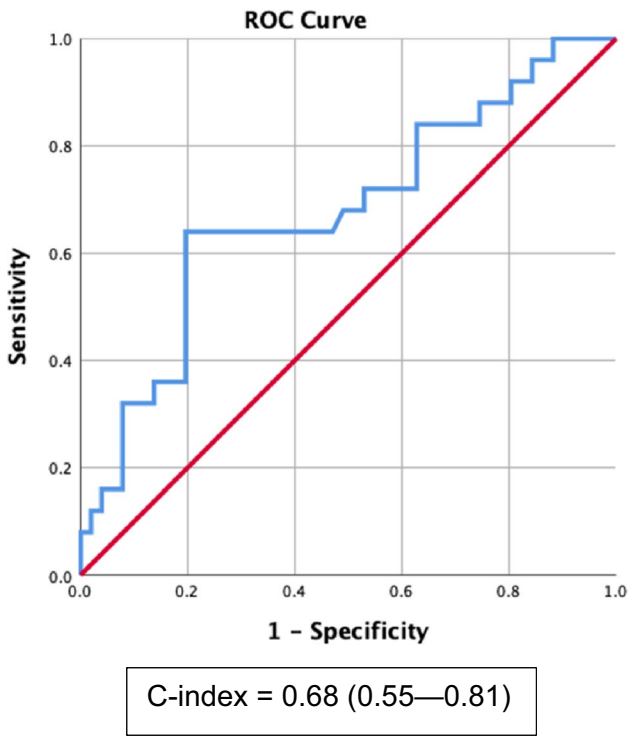

Fig. 2 ROC curve of aLIU score using INR for predicting 21-day outcome of death or LT versus LT-free survival ($n=76$)

indeterminate cause [1]. In the present study, we observed that ALF caused by paracetamol poisoning has the best outcome.

Dengue infection is the commonest identifiable cause of ALF in the present study. Dengue-induced hepatitis is common in South and Southeast Asia as dengue is endemic in this region [22]. Liver is commonly affected in dengue infection, but patients are mostly asymptomatic clinically despite elevated liver transaminases [23]. Dengue-induced ALF is not uncommon and has been reported in both children and adults [23–25]. It was associated with significant mortality of between 50 and 66%, especially in younger age group [26]. The mortality rate in the present study was 18%, comparable to a local study by Lum et al. which reported a mortality rate of 12.5% [23].

To improve the outcome of PALF, a ready access to emergency LT is important [26]. Unfortunately, this service is not readily available in Malaysia. Thus, there is an urgent need to formulate a prognostic scoring for PALF which would ensure that only patients who are most likely to succumb without transplant can be assessed immediately for emergency LT.

Many prognostic factors, including peak serum bilirubin level, PT or peak INR, alanine aminotransferase, peak ammonia level and degree of hepatic encephalopathy have been studied [1, 2, 16, 17, 21, 26]. Scoring systems such as LIU scoring system, Pediatric End-stage Liver Disease Model–Model for End-stage Liver Disease (PELD-MELD) score have also been evaluated [12, 16, 17]. But none of the prognostic indicators or scoring systems have been uniformly reproduced or widely used.

In the current study, we observed that peak bilirubin level of ≥ 452 µmol/L and γGT level of <96 IU/L were significant independent prognostic indicators for death or the need for LT. This is consistent with the study by Rajanayagam et al. [17] and Dhawan et al. [27]. Lee et al. [2] found that a higher plasma bilirubin level was more likely to be associated with death or LT but was not a significant prognostic indicator after multiple logistic regression analysis. On the other hand, Rajanayagam et al. [17] and Squires et al. [1] found that a higher peak of INR was a significant predictor for death or LT. However, we were unable to reproduce their findings in our study.

Low alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level predicting unfavorable outcome of PALF are well described in the literature [2, 16, 17]. However, the role of γGT level has not been well studied and described. In the current study, instead of ALT and AST, we found lower peak of GGT is more likely to be associated with death or LT.

The KCHC which is the most widely used prognostic indicators for ALF in adult patients does not predict death in PALF reliably. The positive predictive value (PPV) of KCHC

was only 33% [11]. Thus, there are no ideal parameter(s) or criteria which can be generalized to all patients to predict the outcome of PALF. In addition, using peak value can be problematic given the uncertainty of the exact timing for the value to be achieved [28].

Our study found that LIU score is useful in prognosticating PALF. It is even more important in setting where LT is not readily available by assisting the managing team in deciding if referral to a transplant center is necessary based on the score which may indicate whether a patient will likely to need a transplant surgery due to the risk of mortality in the next 21 days after initial diagnosis.

When applying LIU and aLIU scores in our cohort, we observed that LIU score with a C-index of 0.79 was a good model in predicting transplant-free survival while aLIU score with a C-index of 0.68 was moderate. This was similar to the study by Lu et al. [12] where the C-index was 0.81 and 0.76 for LIU and aLIU, respectively. The study population from Lu et al. was from PALF study group, with slightly different etiology of PALF compared to current study. Current study finding further confirms that LIU score is applicable in different settings. From a practical perspective, aLIU score is more applicable and provides time for planning for LT if required especially in a resource-poor country. Further studies are needed to ascertain the strength of both the scoring systems to assist in decision making and management of PALF.

There are a few limitations in this study. First, this was a retrospective study with a small sample size performed in a single center. It is potentially underpowered in detecting some prognostic factors. Second, some of the potentially important prognostic indicators such as timing of onset and degree of encephalopathy, as well as serum ammonia level were not appropriately documented, making further analysis not possible. A well-designed and structured multicenter prospective study is needed to further evaluate the prognostic indicators for PALF.

In conclusion, optimal prognostic indicator to identify the outcome of children with ALF with or without LT has yet to be identified. Peak serum bilirubin level of ≥ 452 μmol/L and peak γGT level of < 96 IU/L appeared to be significant in predicting death or LT independently, as shown in many studies. LIU score also seems to be promising but further multicenter prospective studies are needed to confirm their significance in predicting the outcome of PALF. Currently, clinical course and the trajectory pattern of the disease progression are still the mainstay for timely decision for intervention.

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Declarations

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Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

References

1. Squires RH Jr, Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewicz MR, 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
2. Lee WS, McKiernan P, Kelly DA. Etiology, outcome and prognostic indicators of childhood fulminant hepatic failure in the United kingdom. J Pediatr Gastroenterol Nutr. 2005;40:575–581
3. Latif N, Mehmood K. Risk factors for fulminant hepatic failure and their relation with outcome in children. J Pak Med Assoc. 2010;60:175–178
4. Bravo LC, Gregorio GV, Shafi F, Bock HL, Boudville I, Liu Y, et al. Etiology, incidence and outcomes of acute hepatic failure in 0–18 year old Filipino children. Southeast Asian J Trop Med Public Health. 2012;43:764–772
5. Kaur S, Kumar P, Kumar V, Sarin SK, Kumar A. Etiology and prognostic factors of acute liver failure in children. Indian Pediatr. 2013;50:677–679
6. Durand P, Debray D, Mandel R, Baujard C, Branchereau S, Gauthier F, et al. Acute liver failure in infancy: a 14-year experience of a pediatric liver transplantation center. J Pediatr. 2001;139:871–876
7. Taylor SA, Whitington PF. Neonatal acute liver failure. Liver Transpl. 2016;22:677–685
8. Kulkarni S, Perez C, Pichardo C, Castillo L, Gagnon M, Beck-Sague C, et al. Use of Pediatric Health Information System database to study the trends in the incidence, management, etiology, and outcomes due to pediatric acute liver failure in the United States from 2008 to 2013. Pediatr Transpl. 2015;19:888–895

9. Squires RH Jr. Acute liver failure in children. Semin Liver Dis. 2008;28:153–166
10. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology. 1989;97:439–445
11. Sundaram V, Shneider BL, Dhawan A, Ng VL, Im K, Belle S, et al. King's college hospital criteria for non-acetaminophen induced acute liver failure in an international cohort of children. J Pediatr. 2013;162:319–23.e1
12. Lu BR, Zhang S, Narkewicz MR, Belle SH, Squires RH, Sokol RJ. 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
13. Lee WS, Chai PF, Lim KS, Lim LH, Looi LM, Ramanujam TM. Outcome of biliary atresia in Malaysia: a single-centre study. J Paediatr Child Health. 2009;45(5):279–285
14. Lu BR, Gralla J, Liu E, Dobyns EL, Narkewicz MR, Sokol RJ. Evaluation of a scoring system for assessing prognosis in pediatric acute liver failure. Clin Gastroenterol Hepatol. 2008;6:1140–1145
15. Meyers LS, Gamst G, Guarino AJ. Applied multivariate research: design and interpretation. Thousand Oaks: SAGE Publications, Inc.; 2017. p. 367–376
16. Kathemann S, Bechmann LP, Sowa JP, Manka P, Dechêne A, Gerner P, et al. Etiology, outcome and prognostic factors of childhood acute liver failure in a German single center. Ann Hepatol. 2015;14:722–728
17. Rajanayagam J, Coman D, Cartwright D, Lewindon PJ. Pediatric acute liver failure: etiology, outcomes, and the role of serial pediatric end-stage liver disease scores. Pediatr Transpl. 2013;17:362–368
18. Squires JE, Rudnick DA, Hardison RM, Horslen S, Ng VL, Alonso EM, et al. Liver transplant listing in pediatric acute liver failure: practices and participant characteristics. Hepatology. 2018;68:2338–2347
19. Alam S, Khanna R, Sood V, Lal BB, Rawat D. Profile and outcome of first 109 cases of paediatric acute liver failure at a specialized paediatric liver unit in India. Liver Int. 2017;37:1508–1514
20. Dhawan A. Etiology and prognosis of acute liver failure in children. Liver Transpl. 2008;14:S80–S84
21. Zhao P, Wang CY, Liu WW, Wang X, Yu LM, Sun YR. Acute liver failure in Chinese children: a multicenter investigation. Hepatobiliary Pancreat Dis Int. 2014;13:276–280
22. Chongsrisawat V, Hutagalung Y, Poovorawan Y. Liver function test results and outcomes in children with acute liver failure due to dengue infection. Southeast Asian J Trop Med Public Health. 2009;40:47–53
23. Lum L, Lam S, George R, Devi S. Fulminant hepatitis in dengue infection. Southeast Asian J Trop Med Public Health. 1993;24:476–471
24. Tan S-S, Bujang MA. The clinical features and outcomes of acute liver failure associated with dengue infection in adults: a case series. Braz J Infect Dis. 2013;17:164–169
25. Poovorawan Y, Hutagalung Y, Chongsrisawat V, Boudville I, Bock HL. Dengue virus infection: a major cause of acute hepatic failure in Thai children. Ann Trop Paediat. 2006;26:17–23
26. Chien M-M, Chang M-H, Chang K-C, Lu F-T, Chiu Y-C, Chen H-L, et al. Prognostic parameters of pediatric acute liver failure and the role of plasma exchange. Pediatr Neonatol. 2019;60:389–395
27. Dhawan A, Cheeseman P, Mieli-Vergani G. Approaches to acute liver failure in children. Pediatr Transplant. 2004;8:584–588
28. Li R, Belle SH, Horslen S, Chen LW, Zhang S, Squires RH. Clinical course among cases of acute liver failure of indeterminate diagnosis. J Pediatr. 2016;171:163–170 (**e1–3**)