

Original Article

# Prognostic parameters of pediatric acute liver failure and the role of plasma exchange



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## Key Words

acute liver failure;  
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ammonia;  
pediatric;  
plasma exchange

**Background:** This study investigated the prognostic parameters and beneficial effects of repeat plasma exchange in children with acute liver failure (ALF).

**Methods:** Twenty-three patients under 18 years of age admitted to National Taiwan University Hospital due to ALF from 2003 to 2016 were included in this retrospective analysis.

**Results:** Among the patients, 11 (48%) had native liver recovery (NLR), 9 (39.1%) died without liver transplant, and 3 (12.9%) received liver transplantation. The NLR group showed a lower proportion of idiopathic cases, lower peak ammonia level, higher peak alpha fetoprotein (AFP) level, and they had plasma exchange fewer times than the other groups. Receiver operating characteristic curve analyses yielded optimal cutoff values of plasma exchange ( $\leq 6$  times), peak ammonia level ( $< 190 \mu\text{mol/L}$ ), and peak AFP level for predicting NLR in children with ALF.

**Conclusion:** Pediatric ALF with idiopathic etiology, high peak ammonia level, and low peak AFP level are associated with fewer cases of NLR. Plasma exchange for more than six times probably offers little benefit with regard to patient survival if liver transplantation is not performed promptly.

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## 1. Introduction

Acute liver failure (ALF) is a rare but rapidly progressing and potentially fatal disease in children, with reported mortality rates ranging from 24% to 53%.<sup>1–5</sup> A nationwide retrospective study of children with ALF admitted to the referral centers in Taiwan during the period 1985–1999 indicated an overall mortality rate of 75%.<sup>6</sup>

Emergent liver transplantation remains the mainstay of therapy in children with ALF, as the short- and long-term outcomes of pediatric liver transplant have improved over the past several decades.<sup>7</sup> It is crucial to identify patients with poor prognosis to ensure timely referral for liver transplantation. Multiple indicators have been studied as prognostic factors, including peak bilirubin level, severity of hepatic encephalopathy (HE), and prothrombin time.<sup>5,6</sup> Some groups have been studying the use of scoring systems, such as the liver injury unit (LIU) scoring system<sup>8–10</sup> and Pediatric End-stage Liver Disease Model for End-stage Liver Disease (PELD-MELD) score.<sup>5,11</sup> However, there remains no optimal method for identifying patients requiring liver transplantation and determining those that will survive without a transplant.

Various methods have been developed as alternative treatment options or as bridging therapy before receiving liver transplantation or self recovery. Most bridging methods are artificial liver support devices, such as plasma exchange, molecular adsorbent recirculation system (MARS), single-pass albumin dialysis, etc. Among them, plasma exchange has been shown to improve coagulopathy and other biochemical parameters,<sup>12,13</sup> stabilize hemodynamic status,<sup>14</sup> and it may remove various toxins from the systemic circulation. In a recent randomized controlled trial, Larsen et al.<sup>15</sup> reported that high-volume plasma exchange had a survival benefit in transplant-free patients, but the trial excluded pediatric patients. In addition, the patients received plasma exchange a mean of only 2.4 times, and whether further plasma exchange would have benefited the patients remains unclear.

This retrospective study was performed to identify prognostic factors and beneficial effects of repeat plasma exchange in children with ALF.

## 2. Methods

### 2.1. Study design and patient collection

Patients under 18 years of age admitted to the National Taiwan University Hospital due to ALF between January 2003 and February 2016 were recruited. Pediatric ALF was defined in accordance with the Pediatric Acute Liver Failure (PALF) study group criteria: children with no known evidence of chronic liver disease; biochemical evidence of acute liver injury; hepatic-based coagulopathy [prothrombin time (PT)  $\geq 15$  s or international normalized ratio (INR)  $\geq 1.5$  not corrected by vitamin K in the presence of clinical HE; or PT  $\geq 20$  s or INR  $\geq 2.0$  regardless of the presence or absence of clinical HE].<sup>4</sup> Twenty-seven ALF children were diagnosed at our institute during the study period. This study was approved by the Research Ethics Committee of National Taiwan University Hospital, Taipei,

Taiwan. Patients' medical records or data were used in accordance with the relevant guidelines in Taiwan.

### 2.2. Plasma exchange protocol

Children diagnosed with ALF were initially managed with supportive care, including component therapy, vitamin K supplementation, lactulose use, and prophylactic antibiotic, fluid, and electrolyte management; at the same time, evaluations were begun for liver transplantation. Uncontrollable coagulopathy is defined according to the PALF group criteria, i.e., persistent prolonged PT or INR (PT  $\geq 15$  s or INR  $\geq 1.5$  in the presence of HE; or PT  $\geq 20$  s or INR  $\geq 2.0$  regardless of the presence or absence of HE) despite management with component therapy and vitamin K supplement in this study.<sup>4</sup> Plasma exchange was started in patients with uncontrollable coagulopathy or HE despite the above-mentioned management. A plasma separator for children under 20 kg was unavailable at our institute before May 2008, and blood exchange was performed in four of these patients during this period. To focus our study on plasma exchange, these four patients were excluded from the analyses.

Once indicated, plasma exchange was usually performed daily for the first 3 days, and then shifted to every other day or every 3 days according to the patient's condition. The exchange volume was set to 2–4 times the patient's estimated plasma volume. Ammonia, INR, total and direct bilirubin were checked before and after the plasma exchange, while alpha-fetoprotein (AFP) was checked every week.

Eventually, 23 patients were included in the analysis. Medical records were reviewed for demographic, laboratory, and clinical information.

### 2.3. Clinical and laboratory parameters

Native liver recovery (NLR) was defined as survival with native liver, while non-NLR included patients who died or received liver transplantation during the course. Clinical data were analyzed including the age at disease onset, sex, and etiology. Laboratory parameters analyzed included peak INR, peak ammonia level, peak creatinine level, trough albumin level, and peak AFP level. PELD-MELD and LIU scores were calculated according to previous reports.<sup>10,16</sup> Briefly, liver-related chemistry tests (e.g., INR and bilirubin, albumin, and creatinine levels) and relevant clinical history (e.g., age, dialysis) were used to calculate PELD-MELD score. Bilirubin levels, peak INR, and peak levels of ammonia were used to calculate LIU score.

As AFP level remains high during the first few months of life, we calculated the age-matched AFP upper limit of normal (ULN) as the mean + 1.96 standard deviation, using a regression equation developed at our hospital.<sup>17</sup> Patients younger than 1 month old were removed from the analyses, as their normal variation was wide, and they only constituted a small portion of our cohort ( $n = 2$ ). As AFP ULN calculated by the formula dropped to about the adult level at 1 year old, it was set as 20 ng/mL as the adult reference value after 1 year of age.

We standardized the AFP level by first using the age-matched normal AFP ULN to transform AFP level to “x times ULN,” and then performed log-transformation with base 10.

To assess whether liver transplantation was performed in time for those in need, the cause of mortality, reasons for not receiving liver transplantation, and the timing of liver transplantation and evaluation were also analyzed. After relevant laboratory, psychiatric, and radiological evaluations, a pre-transplantation meeting was held to discuss the feasibility and timing of the transplantation. Pre-liver transplantation evaluation was defined as “completed” after the meeting.

## 2.4. Statistical analyses

Data analyses were performed using MedCalc (version 17.2; MedCalc Software, Ostend, Belgium) and R (version 1.0.136; RStudio Inc., Boston, MA). Age, number of days before completing liver transplantation evaluation, and other laboratory parameters are given as medians and interquartile ranges (IQRs), and categorical clinical parameters are given as ratios.

Fisher’s exact test was performed for categorical variables. Wilcoxon’s rank-sum test was performed for onset age, number of plasma exchanges, median number of days before completing liver transplant evaluation, and other laboratory parameters. Due to laboratory limitations, data reaching the upper limit of our laboratory are defined as upper limit values.

Receiver operating characteristic (ROC) curves of total number of plasma exchanges, peak level of ammonia, and peak standardized levels of AFP were plotted, and the cutoff values with the best sensitivity and specificity for predicting NLR were calculated. In all analyses,  $P < 0.05$  was taken to indicate statistical significance.

## 3. Results

### 3.1. Clinical characters

In total, 23 ALF patients were analyzed (Table 1). The patients ranged in age from 3 days to 15 years old, and the median age was 1.39 years old. Eighteen patients received plasma exchange, and five did not receive plasma exchange in this study. The etiologies of ALF included infection, metabolic disease, immunological disease, drug toxicity, and idiopathic etiology. Eleven (48%) patients had NLR, and nine (39.1%) died without liver transplant. Three (12.9%) subjects received liver transplantation, while one died afterward due to post-transplant lymphoproliferative disease.

Cerebral edema was the main reason for mortality among the nine patients that died ( $n = 5$ , 55.6%). The remaining causes were pulmonary hemorrhage ( $n = 2$ ), intracranial hemorrhage ( $n = 1$ ), and sepsis ( $n = 1$ ).

All patients underwent evaluation for liver transplantation. The median time from disease onset to completing liver transplantation evaluation was 16 days (IQR: 13.25–25.25 days). Two patients received liver transplantation 1 and 20 days after evaluation at our institute, and another foreign patient received liver

**Table 1** Clinical parameters of ALF patients.

Clinical parameters	Native liver recovery group (n = 11)	Non-native liver recovery group (n = 12) <sup>a</sup>	P-value*
Male, n (%)	4 (36.36%)	9 (75.00%)	0.10
Onset age (year), median (IQR)	0.29 (0.15–9.88)	1.52 (0.42–9.25)	0.36
Etiology, n (%)			
Idiopathic	4 (36.36%)	10 (83.33%)	0.04
Infection <sup>b</sup>	4 (36.36%)	0 (0%)	
Metabolic <sup>c</sup>	1 (9.09%)	1 (8.33%)	
Immunologic <sup>d</sup>	1 (9.09%)	1 (8.33%)	
Toxin	1 (9.09%) <sup>e</sup>	0 (0%)	
Total number of plasma exchanges, median (IQR)	3 (0–4.75)	9 (4.50–18.50)	<0.01
Days before finishing liver transplant evaluation, median (IQR)	16 (11.00–25.30)	15.5 (14.00–23.50)	0.90
Death, n (%)	–	9 (75.00%) <sup>a</sup>	–
Cerebral edema, n (% of all deaths)	–	5 (55.56%)	
Pulmonary hemorrhage, n (% of all deaths)	–	2 (22.22%)	
Intracranial hemorrhage, n (% of all deaths)	–	1 (11.11%)	
Sepsis, n (% of all deaths)	–	1 (11.11%)	

\*The  $P$ -values of categorical variables (i.e., sex, etiology) were calculated using a Fisher’s exact test. The  $P$ -values for continuous numerical variables (i.e., onset age, total number of plasma exchanges, days before finishing transplant evaluation) were calculated using a Wilcoxon’s rank-sum test.

<sup>a</sup> Among the three patients who received liver transplantation, one died due to post-transplantation lymphoproliferative disease.

<sup>b</sup> One coxsackie virus B3, two hepatitis b, one cytomegalovirus.

<sup>c</sup> Native liver recovery group—congenital error of bile acid synthesis; non-native liver recovery group—Wilson’s disease.

<sup>d</sup> Native liver recovery group—neonatal hemochromatosis; non-native liver recovery group—infection-associated hemophagocytic syndrome.

<sup>e</sup> Graves disease with propylthiouracils overdose.

transplantation abroad 57 days after evaluation. Among the nine patients that died without liver transplant, the transplantation was canceled or postponed in six (66.6%) due to poor or deteriorating clinical condition (progressing brain edema,  $n = 4$ ; persistent infection,  $n = 1$ ; massive hemorrhage,  $n = 1$ ). The families of two of the patients refused to allow liver transplantation after understanding their poor neurological outcome. A suitable living donor

could not be found for one patient, who died while waiting for a cadaveric liver.

Patients were further divided into NLR ( $n = 11$ ) and non-NLR ( $n = 12$ ) groups. There were no differences between these groups with regard to sex (male ratio: 36.4% vs. 75.0%, respectively,  $P = 0.10$ ), median onset age (0.29 vs. 1.52 years of age, respectively,  $P = 0.36$ ), or time to finishing liver transplantation evaluation (16 vs. 15.5 days, respectively,  $P = 0.90$ ). There were fewer cases of idiopathic ALF in the NLR group than the non-NLR group (36.4% vs. 83.3%, respectively,  $P = 0.04$ ).

### 3.2. Plasma exchange

The median number of plasma exchanges was lower in the NLR group than the non-NLR group (3 vs. 9 times, respectively,  $P < 0.01$ ). In ROC curve analyses, the area under the curve (AUC) was 0.852. For the best prediction of NLR, the cutoff criterion was  $\leq 6$  times, with a sensitivity of 100% and a specificity of 66.7% (Table 3, Fig. 2a). The odds ratio for NLR when total number of plasma exchanges exceeded six times was 0.023 (95% CI: 0.001–0.488,  $P = 0.02$ ).

### 3.3. Laboratory parameters

There were no significant differences in peak bilirubin level, peak INR, peak creatinine level, or trough albumin level between the two groups (Table 2). Significant differences were seen in peak ammonia and AFP levels, which are discussed below.

### 3.4. Ammonia

Peak ammonia level (148 vs. 302  $\mu\text{mol/L}$ ,  $P < 0.01$ ) was significantly lower in the NLR group (Table 2). In ROC curve analyses, the AUC was 0.924. For the best prediction of NLR, the cutoff criterion was  $< 190 \mu\text{mol/L}$ , with a sensitivity of 90.9% and a specificity of 83.3% (Table 3, Fig. 2b).

### 3.5. AFP level

Peak AFP levels were higher in the NLR group than the non-NLR group (4.52 vs. 2.66  $\log_{10} \text{ ng/mL}$ , respectively,  $P < 0.01$ ). After excluding patients less than 1 month old and standardizing the AFP value to a ratio of age-matched upper limit of normal, the NLR group still had higher peak AFP levels than the non-NLR group (2.09 vs. 0.89  $\log_{10} \text{ ng/mL}$ , respectively,  $P < 0.01$ ; Table 2 and Fig. 1). In ROC curve, the area under curve was 0.848. For the best prediction of NLR, the cutoff criteria was  $> 1.20$  in  $\log_{10}$  ratio, with a sensitivity of 100% and a specificity of 58.3% (Table 3, Fig. 2c).

### 3.6. Scoring system

The PELD score was not significantly different between the NLR group and non-NLR group (39 vs. 41, respectively,  $P = 0.76$  by Wilcoxon's rank-sum test). Only three patients were older than 12 years of age, and therefore the MELD score was not used in the analyses.

**Table 2** Laboratory parameters of acute liver failure patients.

Laboratory values, median (IQR)	Reference value	Native liver recovery group (n = 11)	Non-native liver recovery group (n = 12)	P-value*
Peak total bilirubin (mg/dL)	0.2–1.2	27.32 (12.19–31.66)	28.43 (21.77–41.18)	0.30
Peak international normalized ratio (INR)	0.85–1.15	6.39 (2.51–10.00)	5.23 (4.28–9.23)	0.66
Peak creatinine (mg/dL)	0.6–1.3	0.6 (0.52–0.64)	0.7 (0.40–0.94)	0.67
Trough albumin (g/dL)	3.5–5.0	3.10 (2.68–3.35)	2.90 (2.64–3.50)	0.73
Peak ammonia ( $\mu\text{mol/L}$ )	9–33	148.00 (116.75–166.75)	302.00 (204.00–383.00)	$< 0.01$
Peak standardized AFP <sup>a</sup>	Age-related <sup>a</sup>	2.09 (1.56–2.47)	0.89 (0.01–1.55)	$< 0.01$

\*P-values were calculated using a Wilcoxon's rank-sum test.

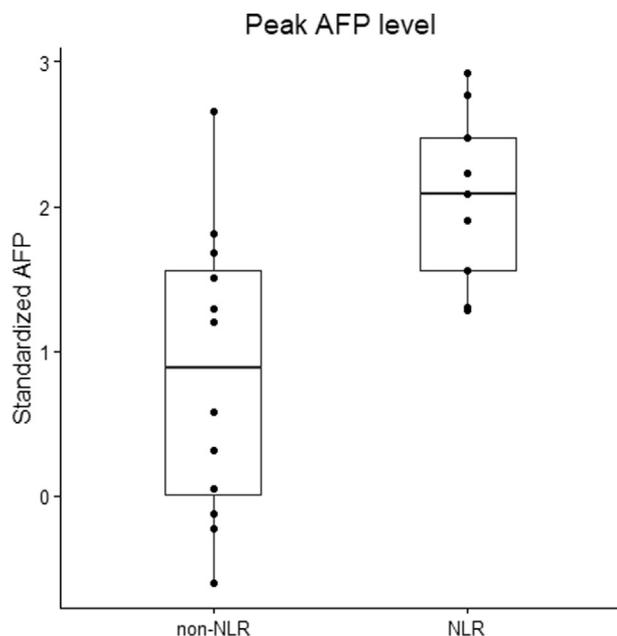
<sup>a</sup> AFP: alpha-fetoprotein. As the normal AFP level is related to age, it was standardized by first transforming to "x times upper limit of normal" according to age-related reference, and then log-transformed with base 10. Patients less than 1 month old (two in the native liver recovery group) were excluded from analyses of AFP. See "Clinical and laboratory parameters" in the Methods section for details.

LIU scores were categorized into "low-risk group" and "median/high-risk group" according to a previous study,<sup>10</sup> and the percentage of patients with median/high risk was not significantly different between the NLR group and non-NLR group (63.6% vs. 91.7%, respectively,  $P = 0.16$  by Fisher's exact test).

**Table 3** Characteristics of the receiver operating characteristic curves and cutoff criteria.

Predicting native liver recovery	Area under the curve	Cutoff criterion	Sensitivity	Specificity
Plasma exchanges	0.852	$\leq 6$	100%	66.7%
Peak ammonia ( $\mu\text{mol/L}$ )	0.924	$< 190$	90.9%	83.3%
Peak standardized AFP <sup>a</sup>	0.852	$> 1.20$	100%	58.3%

<sup>a</sup> AFP: alpha-fetoprotein. As the normal AFP level is related to age, it was standardized by first transforming to "x times upper limit of normal" according to age-related reference, then log-transformed with base 10. Patients less than 1 month old were excluded from analyses. See "Clinical and laboratory parameters" in the Methods section for details.



**Figure 1** Box plot of standardized peak alpha-fetoprotein levels using the age-matched normal AFP reference to transform the patient's AFP level to "x times upper limit of normal," followed by log-transformation with base 10. The native liver recovery (NLR) group had higher standardized peak AFP levels than the non-NLR group (median 2.09 vs. 0.89, respectively,  $P < 0.01$ ).

#### 4. Discussion

Despite recent advances, ALF remains a rare disease with a high mortality rate. In this study, only 48% of the patients recovered without liver transplantation, which is similar to previous reports indicating spontaneous recovery rates of ~24–53%.<sup>1–5</sup>

Fewer studies of liver support devices have focused on pediatric patients than on adults, and those that have are mainly case series or retrospective studies. Those studies reported improvements in biochemical parameters, neurological status, and hemodynamic stability in children,<sup>12,14,18,19</sup> but no randomized controlled trials have supported the benefits of any liver support devices.

A critical issue that should be considered during the management of pediatric ALF patients is the accessibility of liver transplantation. In previous studies, the liver transplantation rate for ALF ranged from 21% to 41%.<sup>1–5</sup> Among those listed for emergent liver transplantation, the time from listing to transplantation was mostly within 1 week.<sup>13,18,20–23</sup> In the present study, only three (12.9%) subjects received liver transplantation at 1, 20, and 57 days after completing liver transplantation evaluation. Unlike Western countries, most pediatric liver transplantation in Taiwan received living-related liver graft donation.<sup>24,25</sup> The shortage of organ sources may have resulted in a lower transplantation rate and longer waiting time in our cohort.

On the other hand, plasma exchange is more readily available, exposing the patient to only minimal risks associated with blood product transfusion. Plasma exchange

can be performed in patients with poor condition, and it may stabilize the patient until spontaneous recovery can occur or liver transplantation becomes available. However, there are concerns regarding the overuse of plasma exchange. For example, two of the patients in our cohort who were contraindicated for liver transplantation had undergone plasma exchange more than 20 times, with a median of nine times in the non-NLR group. In previous studies, regardless of which artificial liver support system was used (e.g., plasma exchange, plasmapheresis, albumin dialysis, or continuous veno-venous hemodiafiltration), the number of sessions was mostly in the range of 1–13.<sup>12–14,18,21–23</sup>

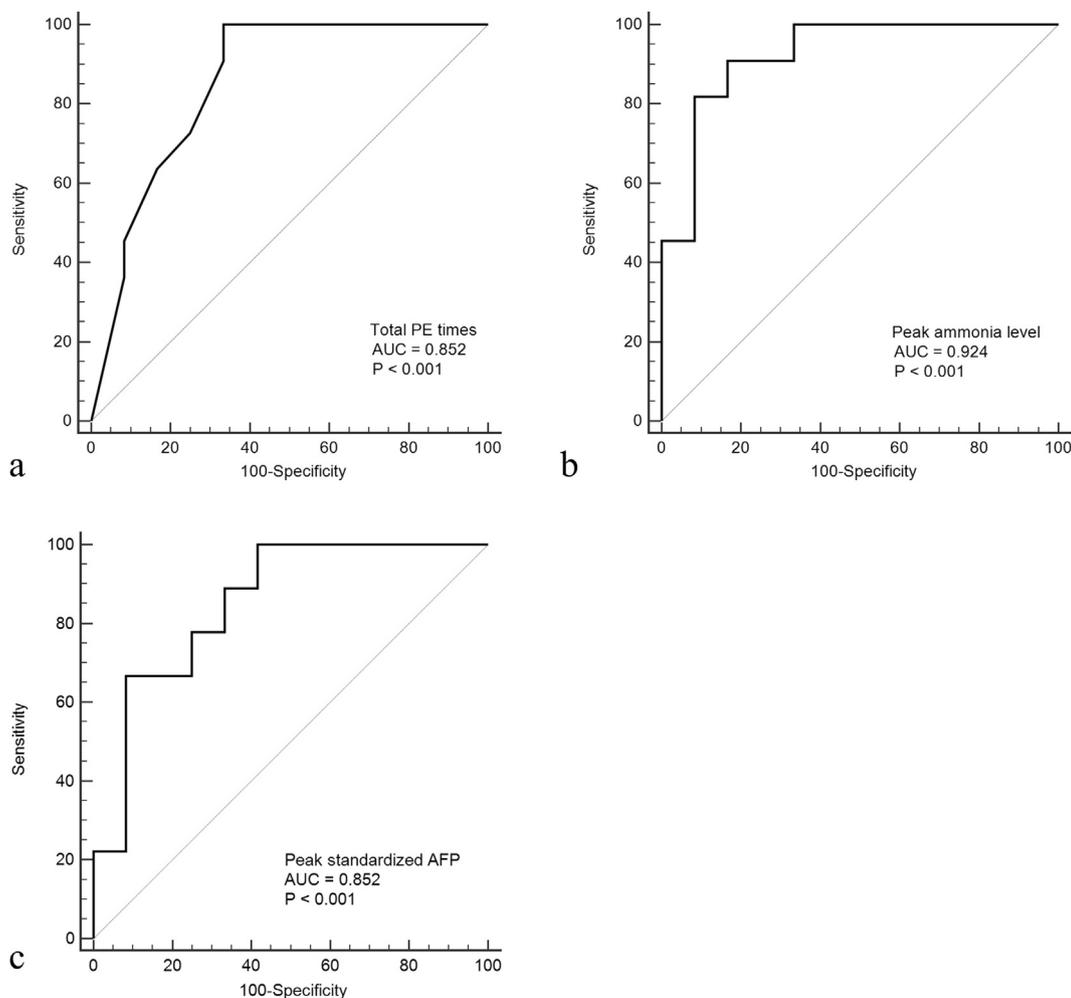
In a large randomized controlled trial that examined whether molecular adsorbent recirculating system (MARS) therapy improved survival in ALF, the authors reported no survival benefit, but the study was confounded by a short delay to liver transplantation (median, 16.2 h).<sup>26</sup> Patients in a randomized controlled trial by Larsen et al. had only a limited number of plasma exchange treatments.<sup>15</sup> In our study, the time to liver transplantation was long, and the number of treatments was large enough to allow us to examine the survival benefit of plasma exchange after several sessions.

Low AFP level is associated with poor outcome, while increasing AFP level during the clinical course is related to better outcome,<sup>27–29</sup> but the application of AFP level as a prognostic parameter in pediatric patients is limited by the fact that it is naturally high in infants and neonates.<sup>17,30,31</sup> By standardizing the data with age-related normal reference values, we demonstrated that elevated AFP was related to better outcome and may be useful as a prognostic factor in pediatric ALF. To the best of our knowledge, this is the first study to have used standardized AFP levels to predict the outcome of pediatric ALF, and it may be of benefit for predicting the prognosis of ALF in patients less than 1 year old. Since different mechanisms may associate with different severity of liver damage,<sup>32–36</sup> the clinical outcome of different etiologies may be different. The NLR in idiopathic ALF subjects is 28.57% in this cohort, and the phenomenon highlights the importance of aggressive preparation for liver transplant in idiopathic ALF children.<sup>36</sup>

PELD-MELD and LIU scores were tested in our cohort, but their associations with outcome were not significant. This may have been due to our small sample size with inadequate statistical power, and further validation of these score systems is needed.

The limitation of our study is the relatively small sample size. For an alpha-level of 0.05, beta-level of 0.20, and a ratio of sample sizes in negative group/positive groups of 1, nine positive cases and nine negative cases are required to reject the null hypothesis (AUC = 0.50, which means no discrimination power) for ROC analyses with an AUC of 0.85. As the AUCs of the parameters tested were large, our sample size was sufficient to show the significance of their prognostic value.

This was a retrospective study with a small sample size performed at a single institute, and it may therefore have been underpowered to detect some of the prognostic factors. Further studies in larger cohorts are needed to elucidate the efficacy of plasma exchange.



**Figure 2** Receiver operating characteristic (ROC) curve for accuracy of various factors in predicting native liver recovery (NLR): (a) ROC curve of total number of plasma exchanges. For a cutoff value  $\leq 6$  times, sensitivity was 100%, specificity was 66.7%. (b). ROC curve of peak ammonia level. For a cutoff value  $< 190 \mu\text{mol/L}$ , sensitivity was 90.9% and specificity was 83.3%. (c). ROC curve of standardized peak AFP levels. For a cutoff value  $> 1.20$ , sensitivity was 100% and specificity was 58.3%.

In conclusion, idiopathic etiology, high peak ammonia level, and low peak AFP level were associated with fewer cases of NLR. Plasma exchange more than six times probably offers little benefit with regard to patient survival if liver transplantation is not performed promptly.

### Conflict of interest

The authors declare that they have no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pedneo.2018.09.006>.