



Etiologies, outcomes, and prognostic factors of pediatric acute liver failure: A single center's experience in Turkey

LIVER

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ABSTRACT

Background/Aims: Our aim was to determine the etiologies, outcomes, and prognostic indicators in children with acute liver failure.

Materials and Methods: Ninety-one patients who were followed for pediatric acute liver failure (PALF) over a 15-year period were included. Patients who survived with supportive therapy were designated as Group 1, while those who died or underwent liver transplantation were designated as Group 2.

Results: There were 37 (40.6%) patients in Group 1 (spontaneous recovery) and 54 (59.4%) patients in Group 2. Thirty-two patients (35.2%) underwent liver transplantation. Infectious and indeterminate causes were the most common etiologies (33% each). Among the infectious causes, hepatitis A (76%) was the most frequent. Hepatic encephalopathy grade 3-4 on admission and during follow-up and high Pediatric Risk of Mortality (PRISM) and Pediatric End-Stage Liver Disease (PELD) scores within the first 24 h were related with a poor prognosis. Group 2 had a more prolonged prothrombin time, higher international normalized ratio, more prolonged activated partial thromboplastin time (aPTT), and higher levels of total and direct bilirubin, ammonia, and lactate (for all, $p < 0.01$).

Conclusion: Infectious and indeterminate cases constituted the most common etiology of PALF, and the etiology was related to the prognosis in our series. Although high PELD and PRISM scores were related to poor prognoses, no sharp thresholds for individual laboratory tests could be elucidated. Liver transplantation was the only curative treatment for patients with poor prognoses and resulted in high survival rates (1-, 5-, and 10-year survival rates of 81.3%, 81.3%, and 75%, respectively) in our study.

Keywords: Acute liver failure, pediatric, prognostic factors

INTRODUCTION

Pediatric acute liver failure (PALF) is a rarely encountered condition characterized by the rapid onset of severely impaired liver function, with or without encephalopathy, and it occurs in children without any previous liver disease (1). Age and geographical location affect the etiology of PALF. In developing countries, hepatitis A is the most significant etiological agent causing acute liver failure (ALF) in children (2,3); however, infectious causes are rarely seen in developed countries (4). Pediatric ALF Study Group data (4) indicated that metabolic diseases were the most common cause of

ALF in children under 3 years. In children older than 3 years, acetaminophen intoxication was the main cause. However, the cause of ALF still remains undetermined in a large proportion of children (5). Some centers with and without liver transplantation (LT) facilities in Turkey have reported their experience of the etiology of ALF in childhood (6-9).

Despite medical therapy, the clinical outcome of PALF is poor, and the overall mortality rate is 44-67% (1,4,10,11). LT, which is lifesaving, is the only effective treatment for suitable patients. With improvement in supportive

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therapy and LT, overall survival rates have increased to 62–83% (4,10,11). Diverse combinations of age, etiologies of ALF, onset and peak grade of hepatic encephalopathy (HE), biochemical tests [prothrombin time (PT), the international normalized ratio (INR), bilirubin, ammonia, and lactate], Pediatric End-Stage Liver Disease (PELD) score, several chemokines, cytokines, and reactive nitrogen oxide species have been evaluated to assess the prognosis of PALF (2,12,13). Applying King's College Hospital Criteria to children with PALF did not predict death, and the reported positive predictive value was only 33% (14).

The PELD score predicts a high mortality risk in children with chronic liver disease listed for LT. A PELD score in ALF is reported to be useful for establishing the optimal timing for LT evaluation (15). The Pediatric Risk of Mortality (PRISM) score was developed to assess the severity of illness-related mortality in pediatric intensive care units, irrespective of the diagnosis. The PRISM score includes 14 well-defined routine clinical and laboratory variables. This scoring system has been evaluated and validated in critically ill patients and has been found to be reliable in predicting mortality. The PRISM score has been validated under various conditions, including ALF (16). The aim of this study was to determine the etiologies, outcomes, and prognostic indicators, including PELD and PRISM scores, in patients with ALF in our center and the pediatric LT unit.

MATERIALS AND METHODS

We evaluated the medical records of 91 pediatric patients with ALF who were accepted to our Pediatric Gastroenterology Unit between January 2000 and October 2015. The study was approved by the Institutional Review Board (KA 09/84). Informed consent was obtained from the parent or legal guardian of each participant.

We used the Pediatric ALF Study Group criteria for defining ALF: 1) absence of a previously known history of chronic liver disease, 2) biochemical evidence of acute liver injury, and 3) hepatic-based coagulopathy defined as $PT \geq 15$ s or $INR \geq 1.5$ not corrected by vitamin K in the presence of clinical HE or $PT \geq 20$ s or $INR \geq 2$ regardless of the presence or absence of clinical HE (4).

We graded HE using the following standard criteria: Grade 1: alert, mood changes, slow mentation, inconsolable crying, disturbed sleep–awake cycle; Grade 2: lethargy, confusion, inappropriate behavior; Grade 3: somnolence, stupor; and Grade 4: comatose, increased or flaccid muscle tone (17). We did not assess the HE grade in children under 1 year.

We analyzed the medical records and data, including the clinical and laboratory parameters, namely, age; gender; PALF etiology; transaminases, gamma-glutamyl transferase, alkaline phosphatase, ammonia, albumin, lactate, and bilirubin levels; aPTT; PT; INR; fibrinogen; HE grade on admission; and the highest grade of HE during follow-up.

We calculated the PRISM scores using 14 measured physiologic variables for each patient: systolic and diastolic arterial pressures; heart and respiratory rates; PaO_2/FiO_2 ratio; $PaCO_2$; PT; total bilirubin; calcium, potassium, blood glucose, and serum bicarbonate levels; pupil response; and Glasgow coma scale (16). Using admission laboratory data, we calculated the PELD scores with an online calculator www.unos.org/resource/meldpeldcalculator (18).

We investigated infectious, metabolic, toxic, and autoimmune diseases in order to identify the cause of PALF. The laboratory tests included complete blood count; blood, urine, and stool cultures; Widal test for typhoid fever; and viral hepatitis serological tests [including HAV, HBV, HCV, HEV, EBV, CMV, HSV type 1 and 2, and parvovirus B19]. Wilson's disease was screened with 24-h urinary copper excretion and ceruloplasmin. Autoantibodies (anti-smooth muscle, anti-nuclear, and liver-kidney microsomal antibody) and metabolic screening, including tandem mass spectrometry, urine organic acid analysis and serum lactate, pyruvate, and ferritin levels, were studied. In cases where no positive viral markers, no history of toxin or drug exposure, and no metabolic cause were detected, the etiology of PALF was classified as indeterminate. All patients received medical supportive therapy for PALF (electrolyte and glucose replacement, N-acetylcysteine, oral and intravenous antibiotics, laxatives, and H₂-receptor blocker) and specific treatment for any identifiable causes and complications. Plasma exchange was performed for 68% of the patients. The indication for LT was based on progressive coagulopathy or progressive HE, despite supportive therapy including plasma exchange (19).

We divided the patients into two groups depending on the outcome in order to search for the predictors of prognosis: Group 1 included patients who had spontaneous recovery with supportive therapy; Group 2 included patients who received LT or died without LT. We assessed certain clinical and laboratory parameters between these groups: age, gender, etiology of ALF, HE grade on admission, and the highest grade of HE. On admission, the PRISM and PELD scores; bilirubin, lactate, and NH₃ levels; aPTT; PT; and INR were recorded.

Statistical analysis

Statistical analyses were performed using the SPSS for Windows version 17.0 (SPSS Inc.; Chicago, IL, USA). The mean and standard deviation were calculated for numeric variables, while counts and percentages were used for categorical variables. Continuous variables were compared using Student's *t*-test or the nonparametric Mann–Whitney rank sum test for unpaired data. Categorical variables were compared by the Chi-squared or Fisher's exact test. A *p* value of less than 0.05 was considered statistically significant. Multivariate analysis using logistic regression was performed to identify associations between the variables and risk factors for LT and death. An area under the ROC curve (AUC) of >0.8 indicates an excellent diagnostic accuracy, while a model with an AUC >0.7 may be considered

clinically useful. Variables calculated to describe the prognostic value in ALF included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the laboratory tests.

RESULTS

Demographic characteristics

We evaluated 91 children with ALF (46 males, 45 females) over a 15-year period of time. At the time of presentation, the median age of the patients was 67.9 months (range: 11 days to 17 years). The age distribution was as follows: <1 month, 1.1% (n=1); 1 to 12 months, 8.8% (n=8); 1 to 5 years, 39.6% (n=36); >5 years, 50.5% (n=46). The parents of 24 (26.3%) patients were consanguineous.

Etiology

The etiologies of PALF, including 33% (n=30) infectious, 33% (n=30) indeterminate, 15.4% (n=14) toxic, 12.1% (n=11) metabolic, 3.3% (n=3) hemophagocytic syndrome, 2.2% (n=2) cardiac causes, and 1.1% (n=1) autoimmune causes, are given in Figure 1. We determined different etiologies for ALF in the different age groups (Table 1).

Clinical presentation, laboratory analysis, and outcome

The most common clinical findings during presentation were jaundice (n=84, 92.3%), hepatomegaly (n=64, 70.3%), splenomegaly (n=32, 35.2%), ascites (n=18, 19.8%), edema (n=12, 13.1%), and fever (n=12, 13.1%). The HE grade could not be assessed in 9 (9.8%) patients due to young age, while HE was not seen in 13 (14.3%) patients on admission and during follow-up. During follow-up, mild HE (grade 1–2) was present in 24.2% (22/91) patients, of whom 68.1% spontaneously survived, and 31.8% received LT or died. Moderate to severe HE (grade 3–4) was present in 51.6% (47/91) patients, of whom 14.8% spontaneously survived, and 85.1% received LT or died. The HE grades on admission and during follow-up are listed in Table 2.

The rate of spontaneous recovery with supportive therapy was 40.6% (n=37), while 24.2% (n=22) died, and 35.2% (n=32) received LT. Fifteen patients who died without LT were considered and listed for LT; however, the patients died while awaiting suitable donors due to multiorgan failure and/or sepsis. LT was contraindicated in seven children due to irreversible neurologic damage secondary to very late referral. Thirty-two patients received LT (Figure 2); however, seven (22%) patients died following LT. The mean duration of follow-up after LT was 3515±359 days (range: 434–4610 days). One-, 5-, and 10-year survival rates of liver transplanted patients were 81.3%, 81.3%, and 75% respectively (Figure 3).

Concomitant infections and conditions

Patients with positive blood or urine cultures or with pulmonary infiltration on admission or during follow-up were also investigated. The microorganisms that were isolated from the

blood cultures of patients who spontaneously survived were *coagulase negative Staphylococcus* (CONS) in three patients and *Staphylococcus aureus* in two. *Escherichia coli* was isolated from urine culture in one patient and three patients had pulmonary infiltration. As a result, the frequency of infection was deter-

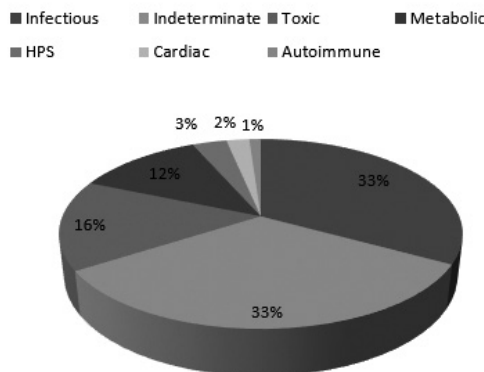


Figure 1. Etiology of acute liver failure (HPS: hemophagocytic lymphohistiocytosis)

Table 1. Etiologies of ALF according to age

	Neonatal <28 days (n=1)	Infancy 1–12 months (n=8)	Early childhood 1–5 years (n=36)	Childhood >5 years (n=46)
Infectious causes, total (n=30)				
Hepatitis A (n=23)	-	-	12	11
EBV (n=3)	-	-	2	1
Adenovirus (n=1)	-	-	1	-
Hepatitis B (n=1)	-	-	-	1
Salmonellosis (n=1)	-	-	-	1
Klebsiella sepsis (n=1)	1	-	-	-
Indeterminate, total (n=30)				
Metabolic causes, total (n=11)				
Fulminant Wilson's disease (n=7)	-	-	-	7
Tyrosinemia (n=1)	-	1	-	-
Fatty acid oxidation defect (n=2)	-	-	2	-
N. hemochromatosis (n=1)	-	1	-	-
Toxic causes, total (n=14)				
Mushroom poisoning (n=6)	-	-	3	3
Drugs (n=6)	-	-	1	5
Firework poisoning (n=2)	-	-	1	1
Autoimmune hepatitis (n=1)				
Other causes, total (n=5)				
Hemophagocytic syndrome (n=3)	-	-	2	1
Myocarditis/cardiomyopathy (n=2)	-	-	1	1

ALF: acute liver failure; EBV: Epstein-Barr virus

mined as 16.2% in Group 1. The microorganisms that were isolated from the blood cultures of patients in Group 2 were CONS in three patients, *Klebsiella pneumoniae* in two patients, and *Streptococcus mitis* in one patient. Seven patients had positive urine culture; *Escherichia coli* was isolated in four samples, *Klebsiella pneumoniae* was isolated in two samples, and *Klebsiella oxytoca* was isolated in one sample. As a result, the frequency of infection was determined as 31.25% in Group 2.

Four patients (7.4%) in Group 2 had acute renal failure complicating PALF during the course of their illnesses. Four patients who were diagnosed with fulminant Wilson’s disease had severe Coombs negative hemolytic anemia. Two patients (one with EBV hepatitis and one with indeterminate cause) had aplastic anemia. One patient recovered and the other one underwent bone marrow transplantation. Generalized convulsions were seen in seven patients and one patient had acute pancreatitis.

Table 2. Demographic, clinical, and laboratory findings of patients with ALF

	Group 1 (n=37)	Group 2 (n=54)	p
	Spontaneous recovery	Received LT or died	
Sex (male) ^a	16 (43.2%)	30 (55.5%)	0.347
Age, months ^b	60.3±49.8	79.1±49.4	0.078
HE (on admission) ^a			<0.001
None	11 (29.7%)	2 (3.7%)	
Grade 1+2	19 (51.4%)	23 (42.6%)	
Grade 3+4	3 (8.1%)	24 (44.4%)	
Not assessed	4 (10.8%)	5 (9.3%)	
HE (peak level) ^a			<0.001
None	11 (29.7%)	2 (3.7%)	
Grade 1+2	15 (40.5%)	7 (13%)	
Grade 3+4	7 (18.9%)	40 (70.1%)	
Not assessed	4 (10.8%)	5 (9.3%)	
PRISM score ^c	10.78±6.78	17.5±9.57	<0.001
PELD score ^c	21.07±9.09	33.59±10.56	<0.001
Total bilirubin (mg/dL) ^c	12.96±12.13	26.03±13.91	<0.001
Direct bilirubin (mg/dL) ^c	9.16±8.71	16.85±10.41	<0.001
Ammonia (µmol/L)	103.61±99.11	118.05±96.58	<0.001
Lactate (mmol/L)	2.85±2.04	5.19±3.90	<0.001
aPTT (s) ^c	48.21±22.74	58.23±29.08	0.006
PT (s) ^c	32.30±12.76	46.47±23.86	<0.001
INR ^c	3.26±1.67	5.05±3.30	<0.001

^aValues are given as percentage.

^bValues are given as median and range.

^cValues are given as mean±standard deviation.

LT: liver transplantation; ALF: acute liver failure; HE: hepatic encephalopathy; PRISM: Pediatric Risk of Mortality; PELD: Pediatric End-Stage Liver Disease; aPTT: activated partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio

Prognostic indicators

The age of patients who received LT or died and who survived with supportive therapy was similar (p=0.078). Children with PALF from toxic causes (11 of 14 patients, 78.5%) and hepatitis A (12 of 23 patients, 52.1%) had higher survival rates with supportive therapy; however, patients with fulminant Wilson’s disease (none of 7 patients) and those with an indeterminate etiology (6 of 30 patients, 20%) had lower survival rates without LT (Table 2).

Patients with grade 1 and 2 HE on admission and follow-up were more likely to recover without LT than those with grade 3 and 4 HE (both, p<0.001). The mean values for the PRISM and PELD scores on admission were significantly higher in Group 2 than in Group 1 (17.53±9.57 vs 10.78±6.78, p<0.001 and 33.59±10.56 vs 21.07±9.09, p<0.001, respectively). The mean values for serum total bilirubin, direct bilirubin, ammonia, lactate, aPTT, PT, and INR were significantly different between groups 1 and 2 (Table 3).

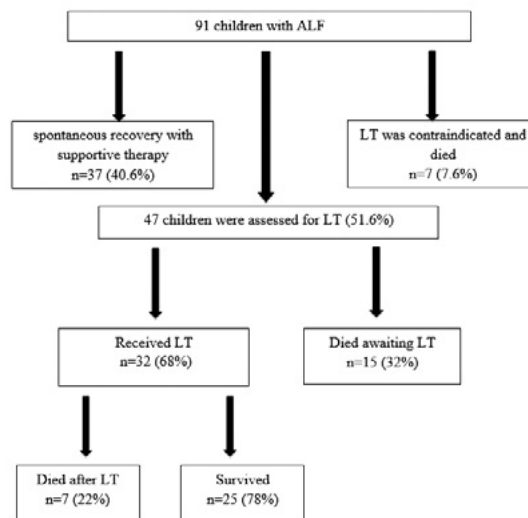


Figure 2. Study assignment and outcomes of patients with ALF

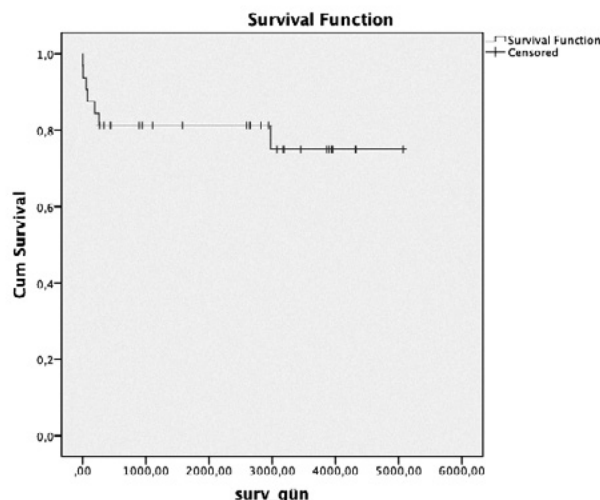


Figure 3. Postoperative cumulative survival rate of patients with ALF who underwent liver transplantation at 1, 5, and 10 years (81.3%, 81.3%, and 75%)

Table 3. Survival according to the etiologies of ALF

	Total (n=91)	Supportive therapy (n=37)	Survival with transplantation (n =26)	Died after transplantation (n=6)	Died before transplantation (n=22)
Infectious causes (n=30)					
Hepatitis A	23	12	6	2	3
EBV	3	1	-	-	2
Adenovirus	1	-	-	1	-
Hepatitis B	1	-	-	1	-
Salmonellosis	1	1	-	-	-
Klebsiella sepsis	1	-	-	-	1
Indeterminate (n=30)	30	6	11	2	11
Metabolic causes (n=11)					
Fulminant Wilson's disease	7	-	6	-	1
Tyrosinemia	1	1	-	-	-
Fatty acid oxidation defect	2	2	-	-	-
<i>N. hemochromatosis</i>	1	-	-	-	1
Toxic causes (n=14)					
Mushroom poisoning	6	5	1	-	-
Drugs	6	4	1	-	1
Firework poisoning	2	2	-	-	-
Autoimmune hepatitis (n=1)	-	1	-	-	-
Other causes (n=5)					
Hemophagocytic syndrome	3	1	1	-	1
Myocarditis	1	-	-	-	1
Dilated cardiomyopathy	1	1	-	-	-

ALF: acute liver failure; EBV: Epstein-Barr virus

Hepatic encephalopathy on admission to the hospital and the highest grade of HE during follow-up, the PRISM and PELD scores on admission, bilirubin levels, ammonia, lactate, aPTT, PT, and INR were assessed using logistic regression analysis to evaluate independent predictors of the outcome. The following factors remained independently associated with poor prognosis: developing grade 3–4 HE (OR; 12.86, 95% CI, 1.29–128.34), higher total bilirubin levels (OR; 1.17, 95% CI, 1.05–1.18), and prolonged PT (OR; 1.05, 95% CI, 1–1.18). A cutoff of 32.1 s in PT levels using the receiver operating characteristic curves showed 70.3% specificity and 70.4% sensitivity for a poor outcome (PPV 77.6% and NPV 61%; AUC 0.728); while a cutoff of 8.4 mg/dL total bilirubin levels using the receiver operating characteristic curves showed 56.8% specificity and 92.6% sensitivity for a poor outcome (PPV 75.8% and NPV 84%; AUC 0.779). Although the PELD and PRISM scores were significantly different between groups, we found them ineffective in predicting a poor prognosis in logistic regression analysis.

DISCUSSION

The aim of this study was to determine the etiological characteristics and prognostic outcomes of patients who were

treated for PALF during January 2000 to October 2015 in our hospital. To date, pediatric ALF has been evaluated in certain reports from Turkey (6-8). In our series, infectious (33%) and indeterminate etiologies (33%) were the most common underlying causes, while among the infectious causes, hepatitis A (76.6%) was the most frequent one. Viral hepatitis accounted for less than 10% of cases of ALF (10,20) in developed countries. However, a previous Turkish study conducted between 1997 and 2003 showed that an infectious etiology (35%) (hepatitis A constitutes 71% of infectious causes) was the most common cause of ALF (6). In a study from Argentina (2) of 210 children with ALF, the authors showed that the main cause of ALF was HAV infection (61%). In the past few years, a study from the pediatric LT center in France (21) showed infectious etiology, particularly hepatitis A, was the main cause of ALF (22%) and accounted for 10% of LT performed at this center. Sanitation, high socioeconomic standards, and vaccination play an important role in the protection against HAV infection. A national vaccination program for HAV was initiated in October 2012 in Turkey, and we believe that achieving a high percentage of vaccination will reduce the incidence of HAV infection and ALF

secondary to hepatitis A. HBV infection has also been reported to be an important cause of ALF, with a prevalence of 8.8% in southern Asia (22). Kayaalp et al. (9) reported that hepatitis B was the most common etiology (34.6%) of ALF in adults in Turkey, which was much more frequent than the etiology of ALF in children (2.3%). Previous studies from Turkey (6,7) reported pediatric ALF cases caused by HBV; however, in our study we identified only one case (1.1%) of hepatitis B. The low rate of hepatitis B in children may possibly be attributed to the successful national HBV vaccination program, which has been in effect since 1998. In most countries in northern Europe, and in North and South America (2,4,10,23,24), indeterminate causes predominate in ALF in childhood, whereas acetaminophen toxicity was the most common identifiable cause of ALF in older children. In our study, etiology remained indeterminate in 33% of patients.

Metabolic causes for PALF have higher rates in infants than in older children (4,25). The series of Lee et al. (10) showed that neonatal hemochromatosis, while that of Durand et al. (25) reported that mitochondrial respiratory chain disorders, were the most frequent causes in neonates. Our study included only one neonatal ALF case diagnosed with Klebsiella sepsis and two cases secondary to neonatal hemochromatosis and tyrosinemia in early infancy. A study from Turkey (7) found that metabolic causes were the most common etiology in children with ALF; likewise, fulminant Wilson's disease was the most common metabolic cause in children aged 5–12 years. Similarly, in our series, fulminant Wilson's disease was the most common metabolic cause of ALF in the late childhood period. However, other metabolic diseases were rarely recorded in our ALF cases. This finding could be secondary to the low percentage of infants in our series. The low referral rate of young infants to our hospital could be explained with the referral of these groups of patients to other centers that have a department of pediatric metabolic diseases.

The Pediatric ALF Study Group showed that the toxic causes of ALF, particularly acute acetaminophen toxicity, were the most common identifiable causes of ALF in children older than 3 years (4). Drug-related ALF cases were seen in six patients in our study, and atomoxetine, acetaminophen, anti-tuberculous drugs, and isoflurane were suspected as the causative agents of ALF (26). Mushroom poisoning was the most common toxic cause of ALF in our study. A systematic review reported that mushroom intoxication was the most frequent factor of toxic liver failure for both adults and children (13%) in Turkey (9). This can lead to ALF with high mortality, which is likely due to late presentation (27). The molecular adsorbent recirculating system has been used to enable native liver recovery and as a bridging treatment to LT (28). In the present study, five of the six patients with mushroom poisoning recovered with early supportive therapy that included charcoal hemadsorption and plasma exchange, while only one patient received LT. Increased community and medical awareness are important to

reduce the frequency, morbidity, and mortality of mushroom and firework (yellow phosphorus) poisoning (29).

The prognosis is influenced by several factors, including age, etiology, and laboratory findings in ALF. Rajanayagam et al. (30) observed ages below 3 months to be associated with poor prognoses. In our series, age was not related to the poor prognosis. The etiology was the other most important prognostic indicator in the literature (4,30). In our study, the spontaneous survival rate was higher in ALF, secondary to hepatitis A and toxic causes. However, fulminant Wilson's disease and indeterminate cases had lower survival rates without LT.

The duration of illness before the onset of HE and the degree of HE at the time of presentation have been extensively investigated in numerous studies (2,25,31). Patients with the rapid development of HE after the onset of clinical disease were found to more likely survive without LT. A study from Argentina (2) showed that one of the most significant indicators of a poor prognosis was grade 3 to 4 HE. Our study revealed that patients who survived with supportive therapy had a less severe HE grade (1 or 2) on admission and follow-up. Some studies have evaluated the prognostic accuracy of the PELD and PRISM scores upon hospital admission (15,16,30). Sanchez and D'Agostino (15) showed that PELD scores on admission were significantly higher among non-survivors (39.8 ± 9.5) and LT recipient (39 ± 7.1) than among those who survived without LT (31.3 ± 3) ($p < 0.001$), and they emphasized that PELD scores on admission could significantly determine a poor outcome. In our study, the presence of higher values of PELD scores on admission was related to a poor prognosis. However, Rajanayagam et al. (30) reported that instead of a single PELD score on admission, serial PELD scores and peak values during follow-up were superior for an evaluation of the prognosis. However, we did not examine serial PELD scores in our study. The reason for this was because our supportive therapies, including plasmapheresis, interacted with the PELD score variables. The PRISM score was investigated in patients with ALF (16,32). Tissières et al. (32) observed that the PRISM score is an accurate means of severity assessment in pediatric ALF; however, the assessment of mortality by the PRISM score has a low predictive value. We also found that PRISM scores were significantly higher in those who received LT or with those who died than in those who survived with supportive therapy. The findings of this study suggest that the PELD and PRISM scores obtained upon admission may be helpful to ascertain the prognosis. Sanchez and D'Agostino (33) reported that a cutoff of 33 in the PELD score showed 81% specificity and 86% sensitivity for a poor outcome. Although the PELD and PRISM scores were significantly different between the groups, we could not determine a cutoff to indicate a poor prognosis in our study.

Several laboratory parameters, such as PT(2), serum bilirubin (2,33), serum phosphate (8), lactate (35), ammonia (36), albumin (37), and factor V and factor VII38, were assessed to identify a poor prognosis. In the present study, patients who died or

received LT tended to have higher serum total bilirubin, direct bilirubin, ammonia and lactate levels, aPTT, PT, and INR. After using logistic regression analysis, advanced HE, serum total bilirubin, and higher PT indicated death and the need for LT. $PT \geq 32.1$ s and a total bilirubin level ≥ 8.4 mg/dL were shown to be risk factors for a poor outcome. The cutoff for bilirubin is different than that reported previously in another center from Turkey, where Bariş et al. (7) reported that a total bilirubin level of >5.35 mg/dL was associated with an increased risk of mortality. This difference between bilirubin levels could be attributed to the differences in the etiologies of PALF between the centers, whereby infectious and indeterminate etiologies predominated in our study, while metabolic diseases were the most common causes of PALF in the other center.

Spontaneous survival without LT was 40.6% in the patients included in our study, which is higher than that in previous reports (28%, 32.4%, 33%, respectively) (2,7,10). Early referral of patients with PALF and improved intensive care supportive treatment lead to an increased spontaneous survival rate (14). LT significantly improves the prognosis of ALF (39). Before, the post-transplant outcome of children with ALF was considered to be poor when compared with patients with chronic liver disease. However, recently, improved outcomes have been reported, with cumulative survival rates of the grafts at 1 and 5 years of 81.9% and 79.2%, respectively (40). In our series, the 1-, 5-, and 10-year survival rates of patients with PALF who underwent LT were 81.3%, 81.3%, and 75%, respectively, which are comparable with those in other centers.

In conclusion, PALF is a life-threatening condition. For this reason, referring the patient to the LT center on time, estimating the likelihood of spontaneous survival, and identifying patients who cannot recover without LT are necessary.

Although prognostic factors that predict mortality and the need for early LT are vigorously required in children, they have not been determined yet. However, the presence of the following factors was found to predict a poor prognosis: a higher HE grade, a higher bilirubin level, and severe coagulopathy. Children with PALF should be closely monitored with all relevant clinical and laboratory parameters together. LT can achieve considerable long-term success for patients who would otherwise die secondary to liver failure and its complications.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Başkent University Institutional Review Board (KA 09/84).

Informed Consent: Written informed consent was obtained from patients and patients' parents who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.Ö.; Design - F.Ö.; Supervision - F.Ö., Z.B.; Materials - E.K.Ö., O.C.; Data Collection and/or Processing - E.K.Ö.,

O.C.; Analysis and/or Interpretation - E.K.Ö.; Literature Review - E.K.Ö., F.Ö., Z.B.; Writer - E.K.Ö., F.Ö.; Critical Review - F.Ö., G.M., M.H.

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