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# Etiology, Outcome and Prognostic Indicators of Childhood Fulminant Hepatic Failure in the United Kingdom

*Way Seah Lee, †Patrick McKiernan, and †Deirdre Anne Kelly

**Department of Paediatrics, University of Malaya Medical Centre, Kuala Lumpur, Malaysia; and †Liver Unit, Birmingham Children's Hospital, Birmingham, United Kingdom*

**ABSTRACT**

**Objective:** To study the etiology, outcome and prognostic indicators in children with fulminant hepatic failure in the United Kingdom.

**Design:** Retrospective review of all patients <17 years with fulminant hepatic failure from 1991 to 2000. Fulminant hepatic failure was defined as presence of coagulopathy (prothrombin time >24 seconds or International Normalized Ratio >2.0) with or without hepatic encephalopathy within 8 weeks of the onset of symptoms.

**Setting:** Liver Unit, Birmingham Children's Hospital, United Kingdom.

**Results:** Ninety-seven children (48 male, 49 female; median age, 27 months; range, 1 day–192.0 months) were identified with fulminant hepatic failure. The etiologies were: 22 metabolic, 53 infectious, 19 drug-induced, and 3 autoimmune hepatitis. The overall survival rate was 61%. 33% (32/97) recovered spontaneously with supportive management. Fifty-five children were assessed for liver transplantation. Four were unstable and were not listed for liver transplantation; 11 died while awaiting liver transplantation. Liver transplantation was contraindicated in 10 children. Of the 40 children who underwent liver transplantation, 27 survived. Children with autoimmune hepatitis, paracetamol overdose or hepatitis A were more likely to survive without liver transplantation. Children who had a delay between the first symptom of liver disease and the onset of hepatic encephalopathy (median, 10.5 days versus 3.5 days), higher plasma bilirubin (299 μmol/L versus 80 μmol/L), higher prothrombin time (62 seconds versus 40 seconds) or lower alanine aminotransferase (1288 IU/L versus 2929 IU/L) levels on admission were more likely to die of fulminant hepatic failure or require liver transplantation ($P < 0.05$). On multivariate analysis, the significant independent predictors for the eventual failure of conservative therapy were time to onset of hepatic encephalopathy >7 days, prothrombin time >55 seconds and alanine aminotransferase ≤2384 IU/L on admission.

**Conclusions:** Children with fulminant hepatic failure with severe coagulopathy, lower alanine aminotransferase on admission and prolonged duration of illness before the onset of hepatic encephalopathy are more likely to require liver transplantation. Early referral to a specialized center for consideration of liver transplantation is vital. ***JPGN 40:575–581, 2005.***

**Key Words:** Fulminant hepatic failure—Etiology—Outcome—Prognostic indicators. 

## INTRODUCTION

The etiology of fulminant hepatic failure (FHF) in children differs around the world (1). In the developing world and in certain communities in developed countries, hepatitis A is the most important etiological agent causing FHF in children (2–6). Hepatitis B virus infection is the most important cause of FHF in endemic areas (7). In developed countries the cause of FHF differs according to age and geographical location (1,8). In English infants younger than 2 years, hemophagocytic lymphohistiocytosis, cryptogenic hepatitis and metabolic diseases account for 75% of cases of FHF (9). Infectious causes were rare, accounting for only two of the 45 cases studied (9). In contrast, in France, viral hepatitis and drug-induced liver injury are important causes (10,11).

With the advent of liver transplantation (LT) as an effective therapy for FHF, the importance of early reliable prognostic evaluation of patients has become critical (11–14). Etiology of FHF and patient age may be important prognostic factors. In metabolic diseases in which the liver is persistently exposed to a toxic insult, liver injury is considered irreversible and transplantation is often necessary. In an acute self-limited insult, such as hepatitis A or paracetamol overdose, exposure to liver injury may be limited and liver failure is potentially reversible. In adult patients, laboratory tests of hepatic synthetic function (plasma albumin and prothrombin time) are important prognostic indicators of FHF (14).

We reviewed 97 children admitted with FHF to one of two regional pediatric liver units in the United Kingdom over a period of 10 years to determine the etiology, outcome and prognostic indicators for survival.

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Address correspondence and reprint requests to Dr. W. S. Lee, Department of Paediatrics, University of Malaya Medical Centre, 59100 Kuala Lumpur, Malaysia. (e-mail: leews@um.edu.my).

## SUBJECTS AND METHODS

The Liver Unit, Birmingham Children's Hospital, United Kingdom, was one of the two regional pediatric liver units in the United Kingdom in the 1990s. The medical records of all children younger than 17 years of age admitted to the Liver Unit, Birmingham Children's Hospital, with FHF over a period of 10 years, from January 1991 to December 2000, were reviewed.

FHF was defined as the presence of acute liver failure (coagulopathy, PT >24 seconds or International Normalized Ratio >2.0) and hepatic encephalopathy (HE) without pre-existing liver disease, within 8 weeks of the onset of clinical liver disease. As the diagnosis of HE is difficult in infants younger than 1 year, the presence of HE was not a prerequisite for inclusion in this age group. Patients with pre-existing systemic disease, such as hemophagocytic lymphohistiocytosis or leukemia were excluded.

In cases in which the symptoms and biochemical and histological features were similar to those of viral hepatitis but in which no viral markers were detected and no history of toxin or drug exposure was found, the etiology of FHF was classified as nonA-nonB-nonC hepatitis (1). Inborn metabolic defects were confirmed by measuring the relevant diagnostic metabolites in the urine or plasma or by tissue measurements of enzyme activity or mutation detection as appropriate. In some cases no specific diagnosis was reached and a metabolic disease was considered likely if there was a history of parental consanguinity or symptom-free interval, followed by clinical signs of intoxication, including vomiting, lethargy, coma, lactic acidosis, hypoglycemia or hyperammonemia (1).

The following definitions were used for staging of HE (1): grade I - alert, mood changes, slow mentation; grade II - lethargic, confused; grade III - stuporous, obeys simple commands; grade IV - unarousable, increased or flaccid muscle tone, hyper-reflexic extensive plantar response or absent reflexes. Time to HE was defined as time from first symptom to onset of encephalopathy.

Indications for LT were progressive coagulopathy or progressive HE despite supportive management (14).

### Case Ascertainment

Patients were identified from the Liver Unit database and were crosschecked with admission books and discharge summaries. Case notes were traced from the medical record department and details of the admission were extracted.

### Assessment of Prognostic Indicators

In determining the final outcome, patients were divided into two groups: group 1 included patients (n = 32) who survived without LT (spontaneous recovery with supportive management); group 2 included patients (n = 65) who received LT or died without LT. The following clinical and laboratory parameters were assessed: sex and age at onset of FHF, etiology, grade of HE, time to HE, plasma albumin and bilirubin levels, PT, alanine aminotransferase (ALT) and alkaline phosphatase.

### Statistics

Data were managed with SPSS statistical package version 11.0.0 for Windows (SPSS, Chicago, IL). Dichotomous measures were compared by means of the $\chi^2$ test. If the minimum expected frequency requirements for the $\chi^2$ test were not met, the Fisher exact test was used instead. The Mann-Whitney *U* test was used for continuous variables. Multivariate logistic regression was used to weight the parameters found to be significant in the univariate analysis. For the continuous variables, the cutoff point yielding the greatest discrimination between groups 1 and 2 was obtained by the receiver operating characteristic curve and was used as a cutoff point in the logistic regression analysis. A value of $P < 0.05$ was considered statistically significant.

## RESULTS

During the 10-year period, 97 children with FHF (48 males, 49 females) were admitted to the Liver Unit, Birmingham Children's Hospital. Twenty children were ethnic minorities from the Indian subcontinent residing in the United Kingdom; 1 was Chinese; the remaining 76 were Caucasian.

### Age Distribution

The median age of presentation with FHF was 27 months (range, 1 day–192.0 months) (Table 1). The age distribution was: <1 month, 18% (n = 17); 1 to 12 months, 23% (n = 22); 1 to 5 years, 23% (n = 22); >5 years, 37% (n = 36). Infants younger than 12 months accounted for 41% of the study population.

### Etiology

Different etiologies of FHF characteristically present at different ages (Table 1).

*Metabolic Causes.* Twenty-two children had a metabolic cause for FHF. Inherited metabolic disease was diagnosed mainly in infants younger than 12 months. Neonatal hemochromatosis was seen exclusively in neonates younger than 4 weeks. Wilson disease was found in two older children aged 8.5 and 10 years.

In 4 cases, the nature of the underlying metabolic disorder could not be determined despite extensive investigation. The first was a 2-year-old girl from the Indian subcontinent whose parents were first cousins. She had moderate developmental delay and a history of HE (altered sleep rhythm and changes in behavior) and jaundice for 2 months. Magnetic resonance imaging of the brain and visual evoked responses showed poor myelination for her age, indicating a generalized involvement. The second child was a 6-month-old boy from the Indian subcontinent whose parents were first cousins. There was a history of 3 stillbirths and early infant deaths in his family. He presented with coagulopathy, hypoglycemia and status epilepticus and developed acute renal failure on admission. Because of the general nature of the disease, LT was deemed inappropriate in both cases. The third case was a 10-month-old girl of Indian origin with

**TABLE 1.** *Etiology, according to age, of 97 children with fulminant hepatic failure in the United Kingdom*

| | Neonatal <1 month (n = 17) | Infancy 1–12 month (n = 22) | Early childhood 1–5 yr (n =22) | Late childhood >5 yr (n = 36) |
|---|---|---|---|---|
| Metabolic (n =22) | | | | |
| Neonatal hemochromatosis (n = 7) | 7 | – | – | – |
| Mitochondrial disorders (n = 4) | 2 | 2 | – | – |
| Tyrosinemia (n = 2) | – | 2 | – | – |
| Wilson's Disease (n = 2) | – | – | – | 2 |
| Other metabolic disorders (n = 7) | 1* | 3† | 3‡ | – |
| Infective (n = 53) | | | | |
| Hepatitis B (n = 2) | – | 2 | – | – |
| Hepatitis A (n = 9) | – | 1 | 4 | 4 |
| nAnBnC hepatitis (n = 36) | 2 | 10 | 11 | 13 |
| Other infections (n = 6) | 5§ | – | 1 | – |
| Drugs (n = 19) | | | | |
| Paracetamol overdose (n = 14) | – | 2 | 1 | 11 |
| Drug-induced hepatotoxicity (n = 5) | – | – | – | 5‖ |
| Autoimmune hepatitis (n = 3) | – | – | 2 | 1 |

*Galactosemia; †undefined (x3); ‡fatty acid oxidative disorder, carnitine deficiency, undefined; §one each for herpes simplex virus type 2, echovirus 12, *Eschecheria coli* sepsis, liver abscess, generalised sepsis; ‖carbamazepine (x2); Sodium Valproate, methotrexate, isoniazid.

consanguineous parents. She had developmental delay and presented with drowsiness, hypotonia, hyporeflexia and coagulopathy. The serum and cerebrospinal fluid lactate values were high, suggestive of mitochondrial disorder, but this was not confirmed by respiratory chain enzyme assay. She recovered with conservative management. The fourth case was a 6-month-old girl with a Caucasian father and Asian mother. Delayed development had been suspected before her illness. She was found collapsed with status epilepticus, apnea, bradycardia, severe hypoglycemia and hyperammonemia. She had progressive coagulopathy and was listed for LT but died before receiving a liver graft.

*Infective Causes.* There were 53 children with an infectious cause for FHF. Four of 9 patients with FHF attributed to hepatitis A were ethnic minorities from Asia; 1 was from an institution for children with developmental delay. Thirty-six cases were classified as having nonA-nonB-nonC hepatitis.

*Drugs.* Nineteen children had FHF attributed to hepatotoxic drugs, either overdose or idiosyncratic toxicity; this was seen in older children. Deliberate self-overdose with paracetamol was seen in 10 adolescents (median age, 15 years), but 4 children, including 2 infants, were deliberately poisoned with paracetamol by a caregiver.

## Clinical Presentation and Hepatic Encephalopathy

The commonest presenting features on admission were jaundice (n = 69, 71%), hepatomegaly (n = 52, 54%), splenomegaly (n = 19, 20%) and ascites (n = 10, 10%) (Table 2). HE was present in all children older than 1 year. HE could not be staged in 8 cases. Two were sedated before transfer and data were incomplete in six.

## Outcome

The overall survival rate (survival with and without LT) was 61%. The rate of spontaneous recovery with supportive management was 33% (32 cases) (Table 3, Fig. 1). The survival rate for those who underwent LT was 68%.

## Death Before and After LT

*Death Before LT*

(a) LT was contraindicated in 10 children, including 2 with an undefined metabolic disorder and 4 with mitochondrial disorders. All had multisystem involvement

**TABLE 2.** *Stage of hepatic encephalopathy and outcome in 58 children aged 12 months and above with fulminant hepatic failure*

| Clinical features | All (n = 58) | Group 1 (n = 19) | Group 2 (n = 39) | *P* value* |
|---|---|---|---|---|
| Encephalopathy | | | | |
| Grade 1 | 9 (16) | 4 (21) | 5 (13) | 0.844 |
| Grade 2 | 18 (31) | 10 (53) | 8 (21) | 0.038 |
| Grade 3 | 14 (24) | 3 (16) | 11 (28) | 0.548 |
| Grade 4 | 9 (15) | 0 (0) | 9 (23) | 0.072 |
| Encephalopathy grade 1 + 2 | 27 (47) | 14 (52) | 13 (48) | 0.015 |
| Encephalopathy grade 3 + 4 | 23 (38) | 3 (13) | 20 (87) | 0.033 |
| Encephalopathy undetermined† | 8 | 2 (25) | 6 (75) | 0.988 |

Values are expressed as number (%).

Group 1 = survived spontaneously without liver transplantation; Group 2 = liver transplantation or died without liver transplantation.

†Hepatic encephalopathy present, but the stage of encephalopathy was undetermined in 6, sedated on transfer 2.

*$P$ values obtained by chi-square test with Yate's correction, group 1 + 2 versus group 3 + 4.

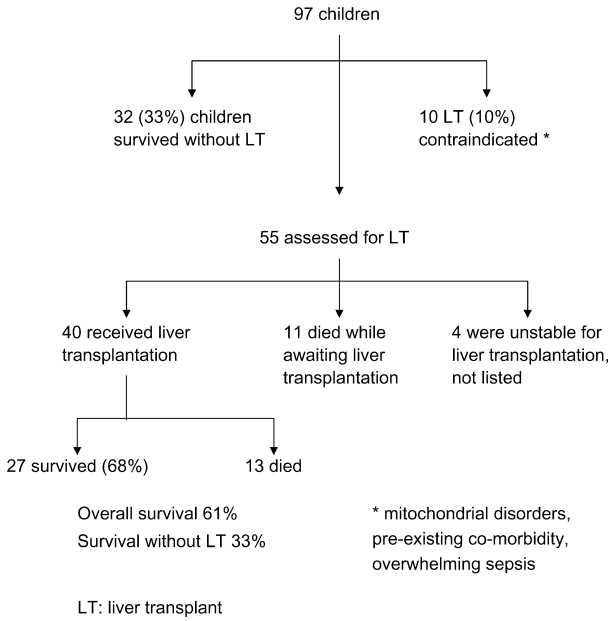


**FIG. 1.** Outcome of 97 children with fulminant hepatic failure admitted to Birmingham Children's Hospital, 1991–2000.

and died of multiorgan failure. Of the remaining 4 patients, 1 child had an Alper-like syndrome, and FHF was precipitated by sodium valproate therapy. The second child had severe developmental delay and developed fulminant hepatitis A. The third child had *Escherichia coli* septicemia and died of sepsis, renal failure and severe coagulopathy. The fourth child died of FHF with multiple hepatic and myocardial abscesses.

(b) Four children were considered for LT but were not listed because of multiorgan failure. These included 1 child with nonA-nonB-nonC hepatitis and a severe neurologic deficit attributable to cerebral edema. The second child with hepatitis A had a cardiopulmonary arrest. The third child with galactosemia and severe coagulopathy died of extensive bleeding after a femoral line insertion. The fourth child had nonA-nonB-nonC hepatitis and died with renal failure.

(c) Eleven children were listed but died awaiting LT (Table 3, Fig. 1). Three died of hemorrhage (spontaneous cerebral hemorrhage, cerebral hemorrhage after insertion of cerebral pressure monitoring device and pulmonary hemorrhage). The fourth child died of cerebral edema. The fifth child with carnithine palmitoyl transferase deficiency died of progressive metabolic acidosis and pericardial effusion resulting in cardiac tamponade. The sixth child was a 6-month-old Caucasian girl who was found collapsed, apneic, bradycardic with severe hypoglycemia and coagulopathy, possibly resulting from an undefined metabolic disorder. She died of progressive encephalopathy and renal failure while awaiting LT. Five children had acute renal failure and multiorgan failure (2 myocardial dysfunction, 3 HE, cerebral edema or an intracerebral bleed). One child had acute pancreatitis complicating the terminal illness.

Nine of the 25 children (36%) who died without LT had acute renal failure complicating FHF during the course of their illness.

*Death after LT* Of the 13 children who died after LT, 1 child had 2 transplants and 2 had 3 transplants. In the 10 children who died after a single LT, the median duration between LT and death was 7 days. The underlying causes of death were: cerebral edema in 3, multi-organ failure in 3, persistent severe neurologic dysfunction after LT in 2, hepatic artery thrombosis, cerebral abscess and small bowel necrosis (1 case each). One child died of acute renal failure, disseminated intravascular coagulopathy and intracerebral hemorrhage. Another child died after 3 LTs (primary graft non-function in the first, arterial and

**TABLE 3.** *Outcome of 97 children with fulminant hepatic failure in the United Kingdom, according to underlying cause*

| | Total (n = 97) | Survived without LT (n = 32) | LT, alive (n = 27) | LT, died (n = 13) | Died, no LT (n = 25) |
|---|---|---|---|---|---|
| Metabolic (n = 22) | | | | | |
| Neonatal hamochromatosis | 7 | 3 | 2 | 1 | 1 |
| Mitochondrial disorders | 4 | – | – | – | 4 |
| Tyrosinemia | 2 | 2 | – | – | – |
| Wilson's Disease | 2 | – | 2 | – | – |
| Other metabolic disorders | 7 | 2 | – | – | 5 |
| Infective (n = 53) | | | | | |
| Hepatitis B | 2 | – | – | 1 | 1 |
| Hepatitis A | 9 | 4 | 3 | – | 2 |
| nAnBnC hepatitis | 36 | 8 | 16 | 6 | 6 |
| Other infections | 6 | 2 | 2 | – | 2 |
| Drugs (n = 19) | | | | | |
| Paracetamol overdose | 14 | 7 | 1 | 4 | 2 |
| Drug-induced hepatotoxicity | 5 | 2 | 1 | 1 | 1 |
| Autoimmune hepatitis | 3 | 2 | – | – | 1 |

LT, liver transplantation.

venous thrombosis of the graft in the second and graft dysfunction and sepsis in the third).

### Prognostic Indicators

*Age and Sex.* Age and sex at diagnosis were not a significant prognostic indicator for survival with supportive management (age; $\chi^2$ for trend: 0.863) (Tables 2, 4 and 5). The survival rate with supportive management was 29% (14 of 48) in male patients and 37% (18 of 49) in female patients ($P = 0.72$).

*Etiology.* Children with FHF from autoimmune hepatitis, paracetamol overdose and hepatitis A had a higher survival with supportive management (autoimmune hepatitis, 2 of 3, 67%; paracetamol overdose, 7 of 14, 50%; hepatitis A, 4 of 9, 44%; remaining, 25.6%), but the advantage to these patients was not statistically significant.

*Hepatic Encephalopathy.* Children with HE grades 1 and 2 on admission were more likely to recover without LT than those with HE grades 3 and 4 (grade 1 + 2 versus 3 + 4: 52% versus 13%; $P < 0.033$; Table 2). The elapsed time between the first clinical symptom of FHF and the onset of HE was longer in children who died or required a LT than in those who recovered without LT (10.5 days versus 3.5 days, $P = 0.001$).

*Laboratory Parameters.* Children with higher plasma bilirubin were more likely to die of FHF or undergo LT (mean plasma bilirubin on admission of group 2 versus group 1; 299 μmol/L versus 80 μmol/L, $P = 0.000$). Group 2 children also had lower mean ALT (1466 IU/L versus 2929 IU/L, $P = 0.031$) on admission than those children who survived without LT. The combination of rising bilirubin and falling transaminases was a poor prognostic indicator.

Time to onset of HE, plasma bilirubin and albumin, PT, ALT, alkaline phosphatase and age at onset were assessed using logistic regression analysis to evaluate independent predictors of the outcome. Time to onset of HE $>$ 7 days, PT $>$ 55 seconds and ALT $\leq$ 2384 IU/L were significant independent prognostic indicators for eventual death or the likelihood of requiring a LT.

## DISCUSSION

The currently accepted definition of FHF is the development of coagulopathy and HE within 8 weeks of the first symptoms of liver disease (8). There are difficulties in applying this definition to the pediatric population, particularly to very young infants, in whom features of HE may be difficult to ascertain and in whom presentation may occur late in the course of illness (1,8). Most investigators have not regarded the presence of HE as a prerequisite for the diagnosis of FHF in neonates and young infants (8,9,12). The second difficulty with this definition is the requirement that pre-existing liver disease be absent. Many authors include liver failure that occurs with an underlying primary systemic disease, such as hemophagocytosis, acute leukemia and inborn errors of metabolism as part of FHF (9,12). In this study, children with pre-existing systemic illness and liver failure were excluded.

In infants younger than 12 months, the main cause of FHF is metabolic disease (9,12). Durand et al. noted neonatal hemochromatosis and mitochondrial cytopathy as important causes of neonatal FHF (12), whereas Mieli-Vergani et al. noted hemophagocytic lymphohistiocytosis as the most important cause (9). In our study, neonatal hemochromatosis was the most important cause of FHF in the neonatal period. The reason for these differences in the etiology of FHF is not apparent but could be attributable to differences in the patterns of referral.

There are no reliable criteria on which to determine the prognosis in a child with FHF (15,16). Many attempts have been made to correlate clinical variables and laboratory data with outcome (17–19). We did not find the sex of the child a significant factor influencing the outcome of FHF (17). In adult patients with non-paracetamol-induced FHF, O'Grady et al. found the most important prognostic indicators were age and etiology (14,19). In this study, spontaneous recovery rate was better in FHF

**TABLE 4.** *Clinical factors, laboratory investigations and outcome in 97 children with fulminant hepatic failure*

| Clinical factors and laboratory investigations | All (n = 97) | Group 1 (n = 32) | Group 2 (n = 65) | *P* value |
|---|---|---|---|---|
| Age at diagnosis (months) | 27.0 (0.03–192.0) | 25.0 (0.06–192.0) | 30.0 (0.03–191.2) | 0.561 |
| Time to onset of HE (days) | 5.5 (1.0–58.5) | 3.5 (1.0–21.0) | 10.5 (1.0–58.5) | 0.001 |
| Albumin (g/L) | 30.0 (22.0–49.0) | 33.0 (22.0–49.0) | 30.0 (18.0–40.0) | 0.081 |
| Prothrombin time (s) | 50.0 (24.0–200) | 40.0 (24.0–127) | 62.0 (24.0–200) | 0.010 |
| Plasma bilirubin (μmol/L) | 217.5 (20–731) | 80.0 (24.0–731) | 299.0 (20–697) | 0.000 |
| Alkaline phosphatase (IU/L) | 516 (90–3400) | 512 (195–2200) | 575 (90–3400) | 0.622 |
| Alanine aminotransferase (IU/L) | 1591 (23–15153) | 2929 (23–15153) | 1446 (38–10000) | 0.031 |

Values are expressed as median ($2.5^{th}$ – $97.5^{th}$ percentile).
HE = hepatic encephalopathy; Time to onset of HE = duration of first symptom to onset of HE.
Group 1 = survived with conservative management alone; Group 2 = subsequent liver transplantation, or died without liver transplantation.
*P* values are for group 1 versus group 2 (obtained by Mann-Whitney *U*-test).
For age at diagnosis, 1 day of life = 0.03 month, 2 days = 0.06 month.

**TABLE 5.** *Assessment of prognostic factors on admission in 97 children with fulminant hepatic failure*

| Indicator | β coefficient (SE) | *P* value | Odds ratio (95% confidence interval) |
|---|---|---|---|
| Age at diagnosis <3.5 months | 0.41 (1.51) | 0.794 | 1.51 (0.079–28.95) |
| Time to onset of HE >7 days | 3.00 (0.87) | 0.001 | 20.06 (3.62–111.03) |
| Plasma bilirubin >156 μmol/L | 0.75 (1.10) | 0.491 | 2.11 (0.25–17.85) |
| Albumin ≤32 g/L | 0.036 (0.83) | 0.966 | 1.04 (0.20–5.31) |
| Prothrombin time >55 s | 2.56 (0.85) | 0.002 | 12.89 (2.46–67.54) |
| Alanine aminotransferase ≤2384 IU/L | 1.74 (0.76) | 0.023 | 5.67 (1.27–25.27) |
| Alkaline phosphatase >685 IU/L | −0.017 (0.82) | 0.984 | 0.91 (0.20–4.90) |

HE = hepatic encephalopathy, duration between first symptom and the onset of HE. Only 58 children were included in the analysis, excluding infants aged less than 1 year.

Assessment performed with stepwise multiple logistic regression.

secondary to autoimmune hepatitis, hepatitis A and paracetamol overdose compared with other causes of childhood FHF. These data were not statistically significant because of the small numbers in our study. In 1989, O'Grady et al. noted that children younger than 10 years with FHF had a worse prognosis than older age groups (19). We did not find any significant difference between the different age groups and the rate of survival without LT, but this may have been a result of the much younger median age in this study (2 years) or because of advances in medical management since 1989.

Some authors have noted absence of prognostic significance in the duration of illness before the onset of HE and the degree of HE at the time of presentation (12,20). Rivera-Penera et al., however, noted that children with a shorter duration of HE after the onset of clinical disease were more likely to survive without LT (17). They also noted that children with stage IV HE on admission had a better chance of surviving without LT. The number of patients who had stage IV HE in that study was small (17). In this study, we found that children who recovered spontaneously had a shorter interval between the onset of first symptoms and the onset of HE and had less severe HE on admission.

Laboratory parameters correlate with the degree of liver necrosis and outcome but provide little reliable predictive power. A very prolonged activated partial thromboplastin time has been found to be a predictor of a fatal outcome in FHF (14,21). Rivera-Penera et al. noted that in children who did not receive LT, the non-survivors had significantly higher mean peak total bilirubin and lower ALT and aspartate aminotransferase levels than did survivors (17). In our study, children who died or required LT tended to have higher plasma bilirubin and lower ALT levels. We also noted that children with worse hepatic synthetic function (lower albumin and a more deranged PT) were less likely to recover spontaneously. In addition, children who had lower transaminase levels with increased bilirubin and prolonged PT and activated partial thromboplastin time were more likely to require LT. This was confirmed by multivariate analysis (Table 5); a lower ALT (≤2384 IU/L) and a prolonged PT (>55 seconds), together with a longer time between first symptom and onset of HE (>7 days), were significant independent prognostic indicators.

FHF in children has a poor prognosis with multiorgan failure as the main cause of death (17). The overall survival without LT in this study was only 33%, which is not significantly different from the 29% from King's College Hospital published 20 years ago (21), indicating that there has been no improvement in supportive management for this fatal disease. In the last 2 decades, LT has significantly advanced the management of FHF, improving the survival rate to 60%, which is comparable with other pediatric and adult series (11,13). However, not all children with FHF may be suitable candidates for LT (22,23), and pre-transplant neurologic status (13,17), severe sepsis, multiorgan failure, especially as a result of mitochondrial cytopathy, and infiltrative diseases may all be contraindications for LT in FHF (24). In addition, LT was not always successful in FHF (11–13), as HE and severe neurologic dysfunction may persist after LT (11), leading to death.

In conclusion, FHF is a rare but fatal condition. The prognosis is better for those with FHF resulting from paracetamol overdose or hepatitis A. Children with severe coagulopathy, lower ALT on admission and a prolonged duration of illness before the onset of HE are more likely to require LT. LT is life saving in those with progressive disease, and early recognition and referral to a specialist center for consideration for LT is essential.

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