

Acute liver failure in Chinese children: a multicenter investigation

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BACKGROUND: Currently, no documentation is available regarding Chinese children with acute liver failure (ALF). This study was undertaken to investigate etiologies and outcomes of Chinese children with ALF.

METHODS: We retrospectively enrolled 32 pediatric patients with ALF admitted in five hospitals in different areas of China from January 2007 to December 2012. The coagulation indices, serum creatinine, serum lactate dehydrogenase, blood ammonia and prothrombin activity were analyzed; the relationship between these indices and mortality was evaluated by multivariate analysis.

RESULTS: The most common causes of Chinese children with ALF were indeterminate etiology (15/32), drug toxicity (8/32), and acute cytomegalovirus hepatitis (6/32). Only 1 patient (3.13%) received liver transplantation and the spontaneous mortality of Chinese children with ALF was 58.06% (18/31). Patients who eventually died had higher baseline levels of international normalized ratio ($P=0.01$), serum creatinine ($P=0.04$), serum lactate dehydrogenase ($P=0.01$), blood ammonia ($P<0.01$) and lower prothrombin activity ($P=0.01$) than those who survived. Multivariate analysis showed that the entry blood ammonia was the only independent factor significantly associated with mortality (odds ratio=1.069, 95% confidence interval 1.023-1.117,

$P<0.01$) and it had a sensitivity of 94.74%, a specificity of 84.62% and an accuracy of 90.63% for predicting the death. Based on the established model, with an increase of blood ammonia level, the risk of mortality would increase by 6.9%.

CONCLUSIONS: The indeterminate causes predominated in the etiologies of ALF in Chinese children. The spontaneous mortality of pediatric patients with ALF was high, whereas the proportion of patients undergoing liver transplantation was significantly low. Entry blood ammonia was a reliable predictor for the death of pediatric patients with ALF.

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KEY WORDS: acute liver failure; children; etiology; mortality; prognosis

Introduction

Acute liver failure (ALF) is a rare but life-threatening syndrome. Although definitions of ALF in adults include the presence of hepatic encephalopathy (HE), HE in younger children is difficult to assess. Hence it may not be essential to the diagnosis of ALF in children.^[1] Additionally, the etiologic spectrum and the clinical features of pediatric patients with ALF differ from those of adults with ALF.^[2, 3] It is very necessary to do studies in children with ALF.

The etiologies of pediatric patients with ALF showed worldwide variations. In the United States, most cases are indeterminate,^[1] but viral infections are the leading cause in India.^[4] In China, the national diagnostic and treatment guidelines for liver failure were issued by the *Chinese Society of Hepatology* in late 2006.^[5] From then on, the diagnosis of ALF was standardized. As this result, we enrolled pediatric patients with ALF from January 2007. To our knowledge, this is the first report of a multicenter study on Chinese pediatric patients with ALF.

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Methods

Patient collection

ALF in pediatric patients in the present study was defined by coagulopathy [prothrombin activity (PTA) $\leq 40\%$ or international normalized ratio (INR) ≥ 1.5 , excluding hematologic diseases] and jaundice [serum total bilirubin (TBil) $\geq 171 \mu\text{mol/L}$] within 4 weeks in a child without pre-existing liver diseases. Patients (≤ 12 years old) with ALF from January 2007 to December 2012 were included in this study.

To ensure the representativeness and comparability of the data, we selected five tertiary military hospitals in different areas of China: Beijing 302 Hospital, General Hospital of the PLA, Changhai Hospital, General Hospital of Jinan Military Region and General Hospital of Lanzhou Military Region.

Ethical approval

The study was approved by the ethics committee of each hospital. All procedures were in accordance with the ethical guidelines of the 1975 *Declaration of Helsinki*. Informed consent was obtained from all patients or their guardians.

Data extraction and assessment

The following variables were obtained from the electronic medical records and follow-up documents: causes, outcomes (death, survival, transplantation), gender, age, body mass index (BMI), white blood cell (WBC) count, hemoglobin, platelet count, PTA, INR, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), cholinesterase, lactate dehydrogenase (LDH), TBil, albumin, creatinine, urea nitrogen, glucose, Na^+ , K^+ , Cl and blood ammonia (BLA).

The etiology of ALF in the pediatric patients was ascertained by historical review and clinical, radiographic and laboratory evaluations. It was considered indeterminate when the evaluations failed to indicate a specific cause.

Statistical analysis

Data analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA). Continuous data were expressed as median (interquartile range) or mean \pm SD. Categorical data were expressed as the number of subjects. Group comparisons were performed using Wilcoxon's rank-sum test or Student's *t* test for continuous variables, and the Chi-square test for categorical variables. Logistic regression was used for evaluating the prognostic predictors of ALF in children.

Receiver operating characteristic (ROC) curve was used for analysis of prognostic accuracy of the method. All the tests were two-tailed, and a *P* value of less than 0.05 was considered statistically significant.

Results

Causes, mortality and transplantation

Thirty-two children with ALF were finally included in this study. Of them, 15 (46.88%) had indeterminate cause, 8 (25.00%) had drug toxicity, 6 (18.75%) had acute cytomegalovirus (CMV) hepatitis, 2 (6.25%) had Wilson's disease, and 1 (3.13%) had malignant extrahepatic metastasis.

In the drug-related cases, 3 were due to acetaminophen, 2 were attributed to herbal remedies, 2 were caused by antibiotics, and 1 was due to antiallergic drug.

Only one patient received liver transplantation in this study, but died eventually. In the other 31 patients without liver transplantation, 13 (41.94%) survived and 18 (58.06%) died. The causes and outcomes of children with ALF are shown in Fig. 1.

Baseline characteristics on admission

Table summarizes the clinical characteristics of the pediatric patients with ALF on admission according to the outcomes (death or survival). The median levels of INR ($P=0.01$), serum creatinine ($P=0.04$), serum LDH ($P=0.01$) and BLA ($P<0.01$) in non-survivors were significantly higher than those in survivors, and

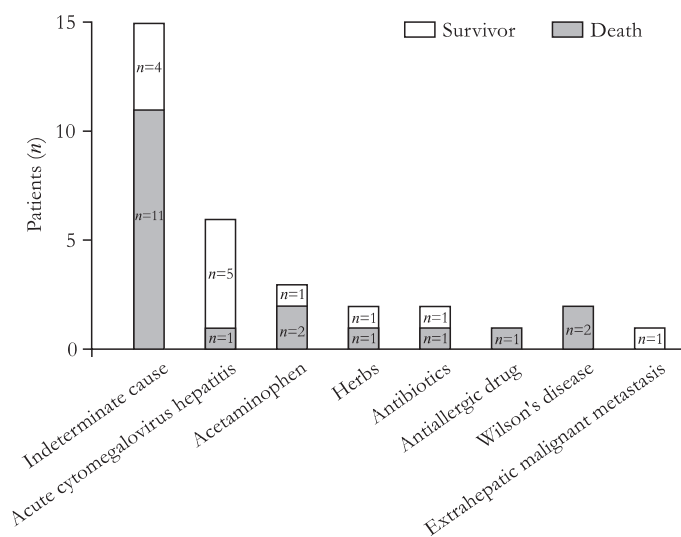


Fig. 1. Etiologies and outcomes of 32 pediatric patients with acute liver failure in China. Indeterminate etiology, drug toxicity and acute cytomegalovirus hepatitis were the most common causes of pediatric acute liver failure.

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