Clinical Course among Cases of Acute Liver Failure of Indeterminate Diagnosis

Ruosha Li, PhD[1], Steven H. Belle, PhD, MScHyg[2], Simon Horslen, MB, ChB[3], Ling-wan Chen, MS[4], Song Zhang, MS[5], and Robert H. Squires, MD[6], on behalf of the Pediatric Acute Liver Failure Study Group*

Objective To investigate the heterogeneity in clinical course among those with pediatric acute liver failure (PALF) of indeterminate disease etiology.

Study design We studied participants enrolled in the PALF registry study with indeterminate final diagnosis. Growth mixture modeling was used to analyze participants' international normalized ratio, total bilirubin, and hepatic encephalopathy trajectories in the first 7 days following enrollment. Participants with at least 3 values for 1 or more of the measurements were included. We examined the association between the resulting latent subgroup classification with participants' characteristics and disease outcomes. Data from participants with PALF of specified etiologies were used to investigate the potential diagnostic value of the latent subgroups.

Results In this sample of 380 participants with indeterminate final diagnosis, 115 (30%) experienced mild and quickly improving disease trajectories and another 48 (13%) started with severe disease but improved by day 7. The majority of participants (216, 57%) had disease trajectories that worsened over time. The identified patterns of disease trajectories are predictive of outcome ($P < .001$). The trajectory patterns are associated with the underlying disease etiology ($P < .001$) for the 488 participants with PALF of specified etiologies.

Conclusions The clinical courses of participants with PALF of indeterminate disease etiology exhibit distinct trajectory patterns, which have important prognostic and potentially diagnostic value. *(J Pediatr 2016;171:163-70)*.

Pediatric acute liver failure (PALF) is a life-threatening clinical syndrome in which children without previous history of liver disease suffer from rapid loss of liver function. The disease may progress quickly and lead to severe impairment of hepatic function within days or weeks, as evidenced in many children by jaundice, coagulation abnormalities, and hepatic encephalopathy (HE). The outcomes of PALF are poor, and one-half of patients die or receive liver transplantation (LTx).[1]

Medical management of PALF is largely supportive in the absence of a condition known to respond to specific therapy (eg, acute acetaminophen toxicity, herpes simplex virus). LTx becomes an option once liver function deteriorates to such an extent that recovery is judged to be unlikely. Because of the rapid progression of PALF in some patients, a timely decision to proceed to LTx is needed to interrupt damaging sequelae associated with PALF, such as cerebral edema and renal injury. Yet, it is undesirable for a patient to undergo LTx if survival with the native liver would have occurred.

Reliable prognostic tools are needed to predict the outcomes of PALF and to guide the LTx decision. The King's College Hospital Criteria (KCHC)[2] is the only predictive model for acute liver failure developed in the pre-LTx era when patient outcomes were limited to survival or death. Patients who met KCHC in the initial report had a high likelihood of death with a positive predictive value of 97% for those with nonacetaminophen acute liver failure.[2] However, when KCHC were recently applied to a cohort of PALF study participants consisting of those who died or survived with their native liver to 21 days, the positive predictive value of KCHC fell to 33%.[3]

Etiologies of PALF are diverse and include drug toxicity such as acetaminophen overdose (APAP), autoimmune liver disease, metabolic disease, and viral hepatitis.[1] Etiology is an important factor in determining outcome. For example, patients with acute APAP toxicity or herpes simplex hepatitis would be expected to have a relatively good or poor prognosis, respectively, given the known pathobiology and treatment for these conditions. Yet, individual patients with APAP

APAP	Acetaminophen overdose	INR	International normalized ratio
BIC	Bayesian information criteria	KCHC	King's College Hospital Criteria
BLRT	Bootstrap likelihood ratio test	LTx	Liver transplantation
GMM	Growth mixture modeling	MAR	Missing at random
HE	Hepatic encephalopathy	non-IND	Determined final diagnosis
IND	Indeterminate final diagnosis	PALF	Pediatric acute liver failure

From the [1]Department of Biostatistics, University of Texas School of Public Health, Houston, TX; [2]Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA; [3]Division of Gastroenterology, Seattle Children's Hospital, Seattle, WA; Departments of [4]Statistics, and [5]Biostatistics, University of Pittsburgh; and [6]Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center, Pittsburgh, PA

*List of additional members of the Pediatric Acute Liver Failure Study Group is available at www.jpeds.com (**Appendix 1**).

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toxicity do die and those with herpes simplex can survive, suggesting factors other than etiology play a role in determining outcome.

The 40%-50% of cases of PALF with an indeterminate cause present a formidable challenge in predicting outcome as underlying causes or treatment strategies are not known.[4,5] Patients with indeterminate PALF were more likely to receive LTx than are patients with PALF with specified etiologies.[4] Importantly, those with an indeterminate diagnosis have inherent heterogeneity likely involving the unknown underlying etiology, pathobiology, and outcomes.

The goal of this analysis was to determine whether PALF dynamics, as measured by trajectories of disease markers, could aid in the prognosis following PALF of indeterminate etiology. Hence, this analysis attempts to determine if disease trajectory over up to 7 days of observation can aid with determining who should undergo LTx and who may be able to wait for signs of spontaneous improvement.

Methods

The PALF study group is a multicenter collaborative study formed in 1999 to investigate the diagnosis, etiology, prognosis, and management of PALF.[1] The first phase of the PALF study was an ancillary to the adult acute liver failure study group, which was sponsored by the National Institutes of Health-National Institute of Diabetes, Digestive, and Kidney disease. During this initial phase, the study included 22 pediatric sites and a data coordinating center at the University of Texas Southwestern Medical School. The PALF study transitioned to its second phase in 2005, when the pediatric consortium received independent funding from the National Institutes of Health-National Institute of Diabetes, Digestive, and Kidney disease. The second phase of the PALF study consisted of 20 sites and a data coordinating center at the University of Pittsburgh. There were 986 participants enrolled in the PALF study between 1999 and 2010. The inclusion/exclusion criteria and primary aims were identical for the 2 phases of the PALF study.

The PALF study group created a registry database including demographic, clinical, laboratory, and outcome data among pediatric participants with acute liver failure. Inclusion criteria were less than 18 years of age, no evidence of chronic liver disease, biochemical evidence of acute liver injury, and coagulopathy not corrected by vitamin K. Patients could be recruited to the study if the they had international normalized ratio (INR) $\geq$1.5 (or prothrombin time $\geq$15 seconds) in the presence of clinical HE or INR $\geq$2 (or prothrombin time $\geq$20 seconds) regardless of presence or absence of HE.[1]

The study was observational because patient management, including the decision regarding LTx, was determined by treating clinicians who followed the local standard of care. The PALF study did not have any treatment protocols outside of a clinical trial of NAC for non-APAP caused PALF.[6] Clinical measurements and laboratory test results were recorded daily for up to 7 consecutive days following enrollment. In phase 1, the earliest outcome (hospital discharge, death, LTx, survival without transplantation) 21 days following enrollment was recorded. Any of these outcomes that occurred up to 1 year following enrollment was recorded in phase 2. The daily maximum of the HE grade was recorded.

The site principal investigator determined a primary etiology at the time of study enrollment and a final diagnosis at the time of the outcome event. An indeterminate etiology was assigned if the participant could not be classified into any specific etiology.

Statistical Analyses

To explore the heterogeneity in the clinical course among participants with an indeterminate final etiology, participants were classified into latent subgroups based on the dynamic trajectories of several key clinical and laboratory measurements using growth mixture modeling (GMM), a multilevel random effect modeling framework.[7-10] The GMM assumes that the heterogeneous study population, exemplified by the indeterminate cohort, is comprised of homogeneous latent subgroups that can be identified by similar dynamic trajectories of data elements. Each latent subgroup features its own set of variables, which defines a pattern of changing clinical course for those in the same subgroup. Therefore, the GMM serves as a powerful tool for clustering subjects into unobserved subgroups and for estimating the dynamic disease trajectories within different subgroups. Subject-specific random effect terms were used to account for the within subject correlation across study days.

The GMM variables can be estimated via maximum likelihood methods. The maximum likelihood estimators accommodate the "missing at random" (MAR) mechanism, allowing use of a participant's data even if his/her measures were not available for each of the 7 days of data collection or until an outcome was reached. The MAR assumption allows the probability of data missing to depend on observed data.

Rigorous model selection procedures were conducted to determine the number of subgroups and the shape of the trajectories. For model selection, we considered statistical measures (ie, the Bayesian information criteria [BIC], entropy, the Lo, Mendell, and Rubin likelihood ratio test, and the bootstrap likelihood ratio test [BLRT]), and the clinical meaningfulness of the resulting classifications.[9,10] The BIC is a penalized-likelihood model selection criterion that accounts for both the model fit and the number of variables, whereby models with smaller BIC values are often preferred. Entropy is a measure of the classification quality, where entropy values close to 1 suggest good discrimination among the latent subgroups.[11] Entropy values of 0.8 or higher implies adequate separation among latent subgroups. The Lo, Mendell, and Rubin likelihood ratio test and BLRT are hypothesis testing procedures, for which significant test results suggest that the K-subgroup GMM is better than the (K-1)-subgroup GMM. Here, K is an integer that denotes the