Evaluation of the Liver Injury Unit Scoring System to Predict Survival in a Multinational Study of Pediatric Acute Liver Failure

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Objective To examine the predictive value of the Liver Injury Units (LIU) and admission values (aLIU) of bilirubin and prothrombin time and international normalized ratio scores in a large cohort from the Pediatric Acute Liver Failure (PALF) Study Group, a multinational prospective study.

Study design LIU and aLIU scores were calculated for 461 and 579 individuals, respectively, enrolled in the PALF study from 1999 to 2008. Receiver operator characteristic curves were used to evaluate the scores with respect to survival without liver transplantation (LT), death, or LT by 21 days after enrollment.

Results At 21 days, 50.3% of participants were alive without LT, 36.2% underwent LT, and 13.4% died. The c-indices for transplant-free survival were 0.81 based on the LIU score with the international normalized ratio (95% CI, 0.78-0.85) and 0.76 based on the aLIU score (95% CI, 0.72-0.79). The LIU score predicted LT better than it predicted death (c-index for LT 0.84, c-index for death 0.76).

Conclusion Based on data from a large, multicenter cohort of patients with PALF, the LIU score was a better predictor of transplant-free survival than was the aLIU score. The LIU score might be a helpful, dynamic tool to predict clinical outcomes in patients with PALF. *(J Pediatr 2013;162:1010-6)*.

Pediatric acute liver failure (PALF) is a life-threatening illness in which a previously healthy child rapidly progresses to severe hepatic dysfunction and synthetic liver failure within 8 weeks of onset of symptoms.[1] Although the diagnosis of acute liver failure (ALF) in adults requires the presence of hepatic encephalopathy, this is difficult to assess in young children and is not always present and thus it is not included in the diagnostic criteria for PALF.[2] For many years, the characterization of PALF was based on the experience of single centers, which may introduce bias if generalized to all cases of PALF because of different center populations, varying definitions of PALF, and different time periods. In 1999, the PALF Study Group was created to overcome these deficiencies by collecting demographic, clinical, laboratory, and short-term outcome data in a uniform matter and with standardized nomenclature for pediatric cases of PALF from 24 pediatric centers (21 in the US, 2 in the United Kingdom, and 1 in Canada).[2] Despite current therapeutic approaches, PALF results in death or liver transplantation (LT) in up to 45% of pediatric patients. The ability to predict PALF clinical outcomes and the need for LT, to stratify patients for clinical trials, and to determine the severity of illness is currently limited[2] and is an unmet need in the clinical care and research priorities of PALF.

A promising scoring system for predicting LT-free survival in PALF was derived using objective laboratory data based on a single-center experience[3] and validated in a second, independent cohort of patients with PALF from the same center.[4] This system was named the Liver Injury Units (LIU) Scoring System, with LIU = [3.584 × peak total bilirubin (mg/dL)] + [1.809 × peak prothrombin time (PT) (seconds)] + [0.307 × peak ammonia (μmol/L)]. Alternatively, substituting international normalized ratio (INR) for PT, the score was calculated as LIU = (3.507 × peak total bilirubin) + (45.51 × peak INR) + (0.254 × peak ammonia). An attempt to develop a scoring system using admission laboratory values demonstrated that only serum bilirubin and PT/INR were significantly associated with outcome; however, the admission LIU (aLIU) score did not have strong predictive ability.[4] A number of other studies have identified the degree of cholestasis, coagulopathy, hepatic encephalopathy, or

ALF	Acute liver failure
aLIU	Admission Liver Injury Units
hdLIU	Highest daily Liver Injury Units
INR	International normalized ratio
LIU	Liver Injury Units
LT	Liver transplantation
MELD	Model of End-stage Liver Disease
PALF	Pediatric acute liver failure
PELD	Pediatric End-stage Liver Disease
PT	Prothrombin time
ROC	Receiver operating characteristic

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blood ammonia as predictors of death or LT; however, none have been validated for clinical decision making.[2,5-9] The LIU score was validated at a single center,[4] so there is a need to examine its applicability across multiple centers and in a larger sample. The objective of this study was to determine the predictive accuracy of the LIU and aLIU scores in participants enrolled in the PALF Study Group database, which includes >700 participants from 24 sites. Secondary aims included determining if the LIU score could be used on a daily basis and determining the relative predictive strength of the LIU score for LT versus death.

Methods

Enrollment in the PALF study cohort began in December 1999. The PALF study protocol has been described in detail.[2] Institutional review board approval was secured at each of the 24 clinical sites. Briefly, after informed consent was provided, demographic, clinical, and laboratory information was recorded daily on case report forms for up to 7 days after enrollment, and outcome was assessed at 21 days.[2] Diagnostic evaluation and medical management were consistent with the standard of care at each site. Data were collected until LT, death, or 21 days after enrollment. The LIU score was not used in treatment decisions, although components of the LIU score may have been used in clinical decisions at individual centers. Treatment recommendations were not part of the PALF study protocol. Completed data forms were coded and forwarded to the Data Coordinating Center at the University of Pittsburgh. Participants from birth through 17 years of age were eligible for enrollment if they met the following criteria: (1) no known evidence of chronic liver disease; (2) biochemical evidence of acute liver injury; and (3) hepatic-based coagulopathy defined as PT $\geq$15 seconds or INR $\geq$1.5 not corrected with vitamin K in the presence of hepatic encephalopathy or PT $\geq$20 seconds or INR $\geq$2.0 regardless of the presence or absence of clinical hepatic encephalopathy. The underlying cause of PALF, based on standard laboratory tests obtained clinically at each center and investigator judgment, included indeterminate, acetaminophen toxicity, autoimmune liver disease, infectious, non acetaminophen drug-induced liver disease, metabolic liver disease, shock, and other (Budd-Chiari, hemophagocytic syndrome, leukemia, neonatal iron storage disease, and veno-occlusive disease).

Calculation of the LIU Score

For this study, both the LIU and aLIU scores were calculated for all PALF Study Group participants with available data, excluding those from the University of Colorado/Children's Hospital Colorado, which provided the study population for the original and replicate analysis of the LIU score.[3,4] Although the criteria to define the PALF causes were the same at the University of Colorado and for the PALF Study, there were differences in data collection between the original derivation study and the current study. The original LIU score derivation was based on the peak laboratory values (total bilirubin, blood ammonia, PT/INR), defined as the highest recorded values during the entire PALF hospitalization (ending at transplantation if relevant), whereas the PALF study data were limited to laboratory values for the first 7 days after enrollment into the study. For each case, the highest values were obtained from available laboratory data, which were not available every day for all cases. In the original derivation, the aLIU score was calculated from admission values of total serum bilirubin and PT/INR (ammonia was not independently predictive and was not included in the aLIU calculation) obtained at the time the participant first met study criteria for PALF. In the PALF Study, the admission values were obtained on the day of enrollment into the PALF Study, which may have occurred after the day of admission or after entry criteria for the PALF Study were met. Outcomes of death before transplantation, transplantation, and alive with native organ were assessed at 3 weeks after enrollment in the PALF Study Group, compared with 16 weeks in the original derivation of the LIU and aLIU scores.[3,4] In the original derivation, individual receiver operating characteristic (ROC) curves of the LIU/aLIU scores were generated for the combined end point of death or LT at 4 weeks after admission to hospital, as opposed to outcomes recorded at 3 weeks after enrollment in the PALF Study Group.[4] Additional subcohort post hoc analyses included examining the LIU score based on cause (indeterminate vs known cause) and in participants at least 6 months old. Additional predictive analysis of the LIU score included using laboratory values obtained on the same day as opposed to during a 7-day period and they were called the highest daily laboratory values (highest daily LIU [hdLIU] score).

Statistical Analyses

SAS (SAS Institute, Cary, North Carolina), Stata (StataCorp, College Station, Texas), and R (CRAN) (http://cran.r-project.org/) were used for the analyses. Pearson χ^2 test for association (without continuity correction) or Fisher exact test was used to compare categorical demographic and clinical characteristics between inclusion and exclusion groups and by outcomes, and the nonparametric Wilcoxon rank sum test was used to compare continuous lab values. ROC curves for the LIU score (and for the aLIU score) for 21-day outcomes were generated and c-indices (areas under the ROC curve) were compared using a nonparametric test.[10] The product-limit method[11] was used to estimate survival curves (alive without LT vs death or LT) for each quartile of LIU (or aLIU) score, and a log-rank test[12] was used to determine whether they differed significantly. Because death without LT and LT are not equivalent events, they are preclusive and related to each other, the cumulative incidences of LT and of death without LT were also estimated and compared in a competing risk model.[13] A value of $P < .05$ was considered to be statistically significant.

Results

From December 1999 through October 2008, the PALF Study Group registry included 709 participants, of whom 461 had

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