King's College Hospital Criteria for Non-Acetaminophen Induced Acute Liver Failure in an International Cohort of Children

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Objective To validate King's College Hospital criteria (KCHC) in children with non-acetaminophen induced pediatric acute liver failure (PALF) and to determine whether re-optimizing the KCHC would improve predictive accuracy.

Study design We used the PALF study group database. Primary outcomes were survival without liver transplantation vs death at 21 days following enrollment. Classification and regression tree analysis was used to determine if modification of KCHC parameters would improve classification of death vs survival.

Results Among 163 patients who met KCHC, 54 patients (33.1%) died within 21 days. Sensitivity of KCHC in this cohort was significantly lower than in the original study (61% vs 91%, $P = .002$), and specificity did not differ significantly. The positive predictive value (PPV) and negative predictive value (NPV) of KCHC for this cohort was 33% and 88% respectively. Classification and regression tree analysis yielded the following optimized parameters to predict death: grade 2-4 encephalopathy, international normalized ratio >4.02, and total bilirubin >2.02 mg/dL. These parameters did not improve PPV, but NPV was significantly better (88% vs 92%, $P < .0001$).

Conclusions KCHC does not reliably predict death in PALF. With a PPV of 33%, twice as many participants who met KCHC recovered spontaneously than died, indicating that using KCHC may cause over utilization of liver transplantation. Re-optimized cutpoints for KCHC parameters improved NPV, but not PPV. Parameters beyond the KCHC should be evaluated to create a predictive model for PALF. *(J Pediatr 2013;162:319-23)*.

Pediatric acute liver failure (PALF) is a clinical syndrome of severe liver injury, occurring in children with no prior history of liver disease. It is a life-threatening illness, which accounts for 10%-13% of all pediatric liver transplants.[1-3] In the pre-transplant era, survival following PALF occurred in only 29% of patients.[4] With improvement in supportive therapy and liver transplantation (LT), PALF survival has increased to 31%-36% in those not transplanted and to between 55%-60% in those transplanted.[5-7]

Although LT in PALF has improved short-term survival, long-term survival is poor compared with other indications for transplantation.[8] Furthermore, the ongoing shortage of viable organs heightens the need to ensure proper organ allocation.[5-7,9] Organ transplantation of children who may have recovered spontaneously would subject them to unnecessarily life-long immunosuppression, including risk of post-surgical complications and future graft failure.[10-12] Therefore, methods are needed to distinguish patients who require transplantation for survival, from those who will recover with supportive care.

Several scoring systems are available to predict mortality in non-transplanted acute liver failure (ALF) patients. The King's College Hospital criteria (KCHC), formulated in 1989, are the most extensively studied and widely applied.[13] The original derivation cohort for this model consisted of 588 patients, both children and adults in the pre-LT era. The positive predictive value (PPV) for mortality in non- acetaminophen (APAP) induced ALF was 97%, indicating a high risk of death if meeting the criteria.[14] Subsequent studies, performed primarily with adults, have demonstrated similar findings, with PPV ranging from 80%-96% and negative predictive value (NPV) ranging from 42%-82%.[15-21] As PALF differs from adult ALF in several aspects including definition, presentation, etiology, and outcome,[22-24] the KCHC may not be applicable to assess prognosis in PALF.

ALF	Acute liver failure
APAP	Acetaminophen
CART	Classification and regression tree
HE	Hepatic encephalopathy
INR	International normalized ratio
KCH	King's College Hospital
KCHC	King's College Hospital criteria
LT	Liver transplantation
NPV	Negative predictive value
PALF	Pediatric acute liver failure
PPV	Positive predictive value

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Supported by National Institutes of Health (NIH; U01-DK072146-05, UL1 RR02501-04, UL1 RR024131, UL1 RR024153) and the General Clinical Research Centers Program, National Center for Research Resources, NIH (MO1 RR00069 and MO1 RR08084). The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2012.07.002

By using the PALF Study Group database, we intend to validate the KCHC in a large cohort of children with non-APAP induced PALF and determine whether redefining the KCHC parameters would increase the predictive accuracy of this model.

Methods

Data for this study came from the PALF Study Group consisting of 20 pediatric liver transplant sites, 17 within the United States, 1 in Canada, and 2 in the United Kingdom.

Following informed consent from a parent or legal guardian, demographic, clinical, and laboratory information were recorded daily for 7 days, starting on the date of enrollment into the study. Diagnostic evaluation and medical management were consistent with the standard of care at each site. Primary outcome measures determined at 21 days after entry into the study included death or survival with native organ. The National Institutes of Health provided a Certificate of Confidentiality to the study and institutional review board approval was secured at each site before patient enrollment.

Patients from birth through 18 years of age were eligible for enrollment if they met the following entry criteria for the PALF study: (1) children with no known evidence of chronic liver disease; (2) evidence of acute liver injury within 8 weeks of disease onset; and (3) hepatic-based coagulopathy defined as a prothrombin time ≥15 seconds or international normalized ratio (INR) ≥1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy (HE) or a prothrombin time ≥20 seconds or INR ≥2.0 regardless of the presence or absence of clinical HE.[22]

Patients with APAP induced PALF were excluded from our analysis because spontaneous recovery from APAP induced liver failure is significantly higher than in non-APAP induced PALF.[23] In our cohort specifically, of 111 patients with APAP induced PALF, 3 of them (2.7%) died and 5 (4.5%) underwent LT. The remaining patients survived with full recovery of their native liver. Therefore, we believed the study should focus on non-APAP induced liver failure, where survival is lower and more patients are considered for LT.

Patients who underwent LT were also excluded from analysis. Our primary aim was to validate KCHC in predicting the specific outcomes of death with native liver or spontaneous recovery in PALF. LT is an intervention that interrupts the natural course of PALF, and it is impossible to know the patient's natural history with certainty after LT. To validate the original KCHC analysis performed on patients in the pre-LT era, we used a cohort that represents an uninterrupted natural history of PALF to determine if KCHC reliably predicts death.

Patients were categorized as meeting KCHC if they fulfilled the parameters defined in Table I. In the original analysis, patients who met KCHC were likely to die, and those who did not meet KCHC were likely to survive. Determination of whether patients in our cohort did or did not meet KCHC was based on data recorded on the day of enrollment into the PALF Study Group database.

Table I. KCHC for predicting mortality in ALF

Non-APAP induced ALF
Prothrombin time >100 s (INR >6.5) OR Any 3 of the following (irrespective of grade of encephalopathy): • Age <10 or >40 y • Etiology: non-A/non-B hepatitis, drug-induced • Duration of jaundice to HE >7 d • Prothrombin time >50 (INR >3.5) • Serum bilirubin >300 umol/L

Statistical Analyses

Continuous variables were expressed as a mean ± SD. Categorical variables were expressed as a percentage. Prognostic value of the KCHC was determined by calculating the sensitivity, specificity, PPV, and NPV. Comparison of sensitivity, specificity, and PPV to the findings from the original King's College Hospital (KCH) paper was performed using tests for differences of proportions. A P value of less than .05 was considered significant.

Classification and regression tree (CART) analysis was used to determine whether different cutpoints of KCHC components led to better classification for 21-day mortality vs survival without LT. The PPV and NPV were compared between the KCHC and those derived from CART, using McNemar test.

Results

A total of 895 participants were enrolled in the PALF Study Group database from 1999 to 2009. Among this group, 111 patients were diagnosed with APAP induced PALF, and 784 had non-APAP induced liver failure. Of those with non-APAP induced PALF, 110 (14.0%) died, 262 (33.4%) underwent transplantation, and 412 (52.6%) were alive with their native liver at 21 days following enrollment. This yielded a 522 patient study cohort where the natural history of PALF independent of LT could be assessed. The mean age was 2.7 years, with 36.8% of patients <1 year. Males comprised 52.3% of the cohort. Approximately 69% of the participants were Caucasian.

The majority of cases of PALF were secondary to an indeterminate cause (43.1%). A total of 390 (74.7%) patients were transferred from another hospital to a PALF Study Group site, with a median time of 2.0 days from admission to transfer and 3.0 days from admission to enrollment into the database. Overall demographic and outcomes characteristics are listed in Table II.

KCHC Validation

Of 522 participants, 163 (31.2%) met the KCHC criteria that would predict death for non-APAP induced PALF, 289 (56.1%) did not meet the criteria, and 70 (13.4%) had insufficient data. The time interval between the onset of jaundice to encephalopathy was missing in 132 patients because the information was not recorded or they had no clinical evidence of encephalopathy on admission. Of the