King's College Hospital criteria for non-acetaminophen induced acute liver failure in an international cohort of children

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Abstract

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

Study design—We utilized the PALF study group database. Primary outcomes were survival without liver transplantation (LT) versus death at 21 days following enrollment. Classification and Regression Tree (CART) analysis was used to determine if modification of KCHC parameters would improve classification of death versus 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=0.002), 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. CART 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<0.0001).

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 LT. Re-optimized cutpoints for KCHC parameters improved

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NPV, but not PPV. Parameters beyond the KCHC should be evaluated to create a predictive model for PALF.

Keywords

coagulopathy; prognosis; hepatic encephalopathy

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-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.

By utilizing 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 IRB 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 (PT)   15 seconds or

international normalized ratio (INR) 1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy (HE) or a PT 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 the 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 which 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.

Statistical Analysis

Continuous variables were expressed as a mean +/− standard deviation. 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 KCH paper was performed using tests for differences of proportions. A p-value of less than 0.05 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 versus 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 liver transplantation 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-acetaminophen 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 163 patients who met KCHC, 28 of them (17.1%) had an INR > 6.5. The remainder fulfilled the criteria by being positive for 3 of the 5 remaining parameters. Patients who met KCHC were younger (median age 1.0 years vs 4.6 years), with a greater percentage less than 1 year old (49.7 vs 29.8%). There were no significant differences in sex or ethnicity between those who did and did not meet KCHC.

Among those who met KCHC, 54 patients (33.1%) died within 21 days, and 109 patients (66.9%) survived. In the group who did not meet KCHC, 34 (11.8%) had died and 255 (88.2%) survived. The sensitivity of applying the KCHC to our cohort was significantly lower than that found in the original KCH cohort (61% vs 91%, p=0.002), but specificity did not differ significantly (70% vs 90%, p=0.17). When determining the PPV and NPV of this model, we found that 33% of patients who met the criteria died (PPV), and 88% of those not meeting criteria had survived (NPV). The PPV of 33% in our cohort was significantly lower than that of the original KCH study (96%). We did not compare NPV as the initial KCH study did not determine NPV for their cohort.

Redefining KCHC parameters

Utilizing classification and regression tree (CART) analysis, a decision tree was created to assess prognosis (survival versus mortality) utilizing optimized cut-points from the original KCHC parameters (Figure; available at www.jpeds.com). Based on our analysis, mortality was predicted based on meeting one of the following criteria: (1) grade 2–4 encephalopathy with jaundice; grade 2–4 encephalopathy with INR>4.02; and (3) grade 0–1 encephalopathy with prothrombin time>32.5s and total bilirubin >2.02 mg/dL.

The redefined parameters improved PPV from 33% to 50% (p=0.20), and NPV from 88 to 92% (p<0.0001) (Figure).

Discussion

In the era prior to LT, the natural history of pediatric acute liver failure (PALF) was either death or survival with recovery of liver function. Advances in critical care management and liver transplantation have significantly improved outcome [23, 25]. However, it is essential to assure that models utilized in the decision making process are accurate. The majority of studies validating the KCHC were performed in adults [17–21].

Our study utilized a patient cohort that best represents an uninterrupted natural history of PALF in the liver transplantation era, to explore the prognostic ability of the KCHC. Prior studies validating prognostic models in ALF/PALF often combine death and LT as one outcome. Combining death and LT will increase the sample size for analysis, but falsely assumes that the outcomes of LT and death are similar. We know patients with PALF who were listed for LT and would have undergone LT had an allograft been available. Some died on the waiting list, and others survived with their native liver and were removed from the liver transplant list. We can only assume the LT cohort is composed of children who would have lived or died had LT not interrupted the natural course of their disease. Therefore, the outcome of LT and death are not equivalent and should not be combined into one outcome, in an analysis to construct a model to predict death in PALF.

Our findings show that the KCHC does not reliably predict that a child with non-APAP acute liver failure is likely to die if the criteria are met (e.g. low sensitivity and low PPV), but is much more likely to predict spontaneous survival at 21-days if the criteria are not met (e.g. high specificity and PPV). These findings indicate that the KCHC may be useful to determine which patients will ultimately survive, and that one should consider continued supportive care rather than early LT for those patients who do not meet KCH criteria. However, reliance on the KCHC to predict death may lead to an unnecessary LT in a child who may survive without LT. With a PPV of 33%, up to two-thirds of patients who meet criteria are classified as likely to die and, thus, in need of an urgent LT would have survived to 21 days with supportive care. Use of re-optimized cut-points led to improvement in PPV to 50% and NPV to 92%. Although the PPV increased, a value at 50% implies that up to half of the patients who meet criteria may be at unnecessary risk to receive a LT.

There are several reasons why the KCHC may differ in accuracy between adults and children. First, HE is difficult to assess in children and may not even become clinically apparent in PALF [1]. This finding has actually led to revision of the definition of ALF in children to exclude HE as a necessary criterion, if the patient has severe, uncorrectable, liver-based coagulopathy [22]. Secondly, the KCH also relies on etiology of ALF in determining prognosis. However, the etiology of ALF in children differs greatly from that in adults. In children, 50% of the cases are from an indeterminate cause making it a less discriminate independent variable [22, 23]. Furthermore, several etiologies of PALF are rarely or not reported in adult ALF, including metabolic defects and enzyme defects within mitochondria and infectious agents such as EBV, CMV, parvovirus, enteroviruses and herpes viruses [26–28]. Finally, none of the 29 children in the original KCHC study were less than age 1 or had metabolic induced liver failure [14].

Ciocca et al also evaluated the KCHC using a cohort entirely of children with PALF. In their retrospective review of 210 patients, they found a PPV and NPV of 96% and 82%, respectively, in predicting mortality and a PPV and NPV of 95% and 82%, in predicting LT [19]. Although these findings indicate better prognostic accuracy than ours, there are two important differences between these studies. First, the majority of their patients (61%) had PALF secondary to hepatitis A, and the majority of our patients (45.1%) had PALF secondary to an indeterminate cause [19]. This distinction is important as it is easier characterize the natural history of hepatitis A induced PALF, which has a common set of clinical signs and symptoms, due to a single, underlying etiology. In contrast, indeterminate PALF has a number of potential causes including congenital metabolic defects, infections which may not be diagnosed, or medications/toxins which may not be detected, all of which have different clinical presentations [22, 23]. In addition, the study by Ciocca et al excluded those younger than 1 year of age, and, in our cohort, 27.4% of the patients were less than 1 year old [19]. Exclusion of this patient subset can alter the results of a study validating the KCH model, by eliminating those with the highest percentage of PALF secondary to inborn errors of metabolism, and by excluding those in whom it is most difficult to characterize HE. Given these differences in study design, the findings of the study by Ciocca et al may not be applicable to the broad and heterogeneous population of PALF patients represented by our cohort.

The primary limitation of our study was that information was recorded beginning on the date of enrollment into the study, as opposed to the date of admission. It is possible that certain laboratory values may have improved compared with on admission, due to supportive management. In particular, the INR is subject to improvement with administration of fresh frozen plasma or vitamin K. Therefore it is possible that some patients who would have fulfilled KCHC, based on having an elevated INR on admission, may have been incorrectly categorized due to improvement in the INR at the time of study enrollment. Additional

limitations of the study include reliance on variables such as grade of encephalopathy and presence of jaundice, which are based on the subjective opinion of the physician, and incorporating prothrombin time into the reoptimized model because prothrombin time may vary among different centers[29].

In summary, given the shortage of donor organs and the life-altering nature of liver transplantation, we need an accurate model to determine prognosis in PALF patients. The KCHC does have utility in predicting survival in both its original form and with redefined cutpoints. However, it cannot be relied upon to predict death, as it may lead to over-utilization of LT in patients who would otherwise survive despite meeting criteria. Though redefining the KCHC parameters improves the PPV, unnecessary transplantation may still occur in half of the patients who meet KCH criteria. We recommend further investigation with incorporation of a dynamic set of parameters into future models, as it is unlikely that an algorithm from a single time point will sufficiently predict survival or mortality.

Acknowledgments

Abbreviations

PALF	pediatric acute liver failure
LT	liver transplantation
KCHC	King's College Hospital criteria
APAP	acetaminophen
PPV	positive predictive value
NPV	negative predictive value
CART	classification and regression tree
INR	international normalized ratio

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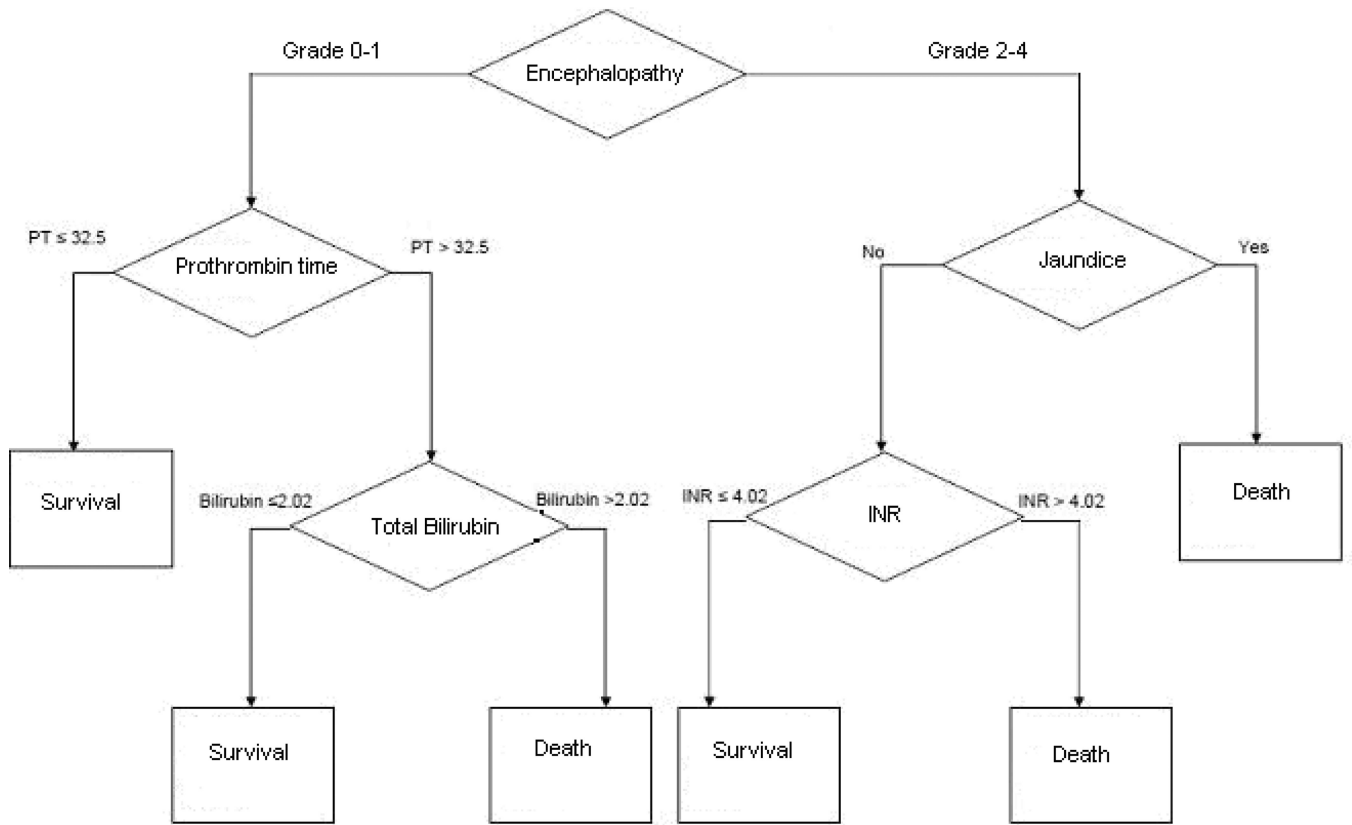
Figure.
Redefined KCHC parameters to predict survival versus mortality

Table 1

King's College Hospital Criteria for predicting mortality in acute liver failure

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

Table 2

Demographic and outcomes characteristics of the study cohort (non-transplanted) and transplanted patients

	Study Cohort (n = 522)		Transplanted Patients (n = 262)	
	N	%	N	%
Sex				
Male	273	52.3	149	56.9
Female	249	47.7	113	43.1
Ethnicity				
Not Hispanic or Latino	421	80.7	205	78.2
Hispanic or Latino	101	19.3	57	21.8
Race				
Caucasian	355	68.9	187	71.4
Non-white	167	31.1	57	21.8
Age (years)				
Mean	2.7		5.5	
Range	0.0 – 17.9		0.0–17.9	
<1 year	192	36.8	48	18.3
1–2.9 years	78	14.9	42	16.0
3–9.9 years	120	23.0	95	36.3
10–17.9 years	132	25.3	77	29.4
Final Diagnosis				
Indeterminate	225	43.1	179	68.3
Budd-Chiari	2	0.4	1	0.4
Hemophagocytic Syndrome	17	3.3	2	0.8
Ischemia	29	5.6	1	0.4
Neonatal Iron Storage	17	3.3	5	1.9
Veno-occlusive disease	10	1.9	1	0.4
Wilson's disease	11	2.1	23	8.8
Metabolic disorder	49	9.4	8	3.1
Viral hepatitis	55	10.5	12	4.6
Autoimmune hepatitis	45	8.6	15	5.7
Drug-induced	19	3.6	6	2.3
Mushroom toxicity	2	0.4	2	0.8
Other	25	4.8	4	1.5
Outcomes				
21-day mortality	110	21.1		
Recovery	412	78.9		

Table 3

Outcomes data for individual King's College Hospital Criteria parameters applied to PALF cohort

King's College Hospital Criteria Parameter	Total (n=522)	Met criteria	Death*	PPV	NPV	SENSITIVITY	SPECIFICITY
1.a) INR > 6.5 or prothrombin time > 100 s	521	n=28	n=8	29%	80%	7%	95%
1.b) INR > 3.5 or prothrombin time > 50 s	521	n=119	n=45	38%	84%	41%	82%
2.a) Age < 10 years old	522	n=390	n=85	22%	81%	77%	26%
Age < 1 year old	522	n=192	n=49	26%	82%	45%	65%
2.b) Etiology not hepatitis A or B (can be indeterminate)	522	n=515	n=110	21%	100%	100%	2%
Duration of jaundice to encephalopathy 2.c) > 7 days	390	n=22	n=7	32%	86%	12%	95%
2.d) Serum bilirubin > 17.6 mg/dl	502	n=100	n=26	26%	80%	25%	81%
Number meeting KCH criteria: (INR > 6.5 or prothrombin time > 100 s) OR meet any of three criteria (1.b, 2.a, 2.b, 2.c, 2.d) Number not meeting criteria Number unknown whether criteria were met	452	n=163 n=289 n=70	n=54	33%	88%	61%	70%

*
Death among those who met each individual criteria.