Lactate and Lactate: Pyruvate Ratio in the Diagnosis and Outcomes of Pediatric Acute Liver Failure

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Objectives To assess the accuracy of blood lactate and lactate: pyruvate molar ratio (L:P) as a screen for mitochondrial, respiratory chain, or fatty acid oxidation disorders in children with pediatric acute liver failure (PALF); to determine whether serum lactate ≥ 2.5 mmol/L or L:P ≥ 25 correlated with biochemical variables of clinical severity; and to determine whether lactate or L:P is associated with clinical outcome at 21 days.

Study design Retrospective review of demographic, clinical, laboratory, and outcome data for PALF study group participants who had lactate and pyruvate levels collected on the same day.

Results Of 986 participants, 110 had lactate and pyruvate levels collected on the same day. Of the 110, the etiology of PALF was a mitochondrial disorder in 8 (7%), indeterminate in 65 (59%), and an alternative diagnosis in 37 (34%). Lactate, pyruvate, and L:P were similar among the 3 etiologic groups. There was no significant association between the initial lactate or L:P and biochemical variables of clinical severity or clinical outcome at 21 days.

Conclusions A serum lactate ≥ 2.5 mmol/L and/or elevated L:P was common in all causes of PALF, not limited to those with a mitochondrial etiology, and did not predict 21-day clinical outcome. *(J Pediatr 2017;182:217-22).*

Trial registration ClinicalTrials.gov: NCT00986648

Pediatric acute liver failure (PALF) is a rare and potentially fatal illness caused by heterogeneous insults including infections, drugs and toxins, autoimmune liver disease, genetic/metabolic diseases, ischemia/reperfusion injury, and, in a relatively large proportion, a cause is not identified.[1] PALF continues to have a high rate of mortality and is the third leading indication in childhood for liver transplantation.[2] Primary mitochondrial disorders, including mitochondrial DNA (mtDNA) depletion syndromes, occur in 1 in 5000 live births and are a known cause of PALF in children <2 years of age.[3-5] One of the biochemical features suggestive of a mitochondrial disorder is a serum lactate concentration ≥ 2.5 mmol/L, especially in cases with respiratory chain alterations or mtDNA depletion syndrome.[6] Elevated blood lactate levels, however, can be caused by factors other than primary mitochondrial function, including poor collection technique, tissue hypoxia/ischemia, thiamine deficiency, or secondary mitochondrial dysfunction.[7,8] Conversely, patients with certain mitochondrial diseases, such as DNA polymerase gamma (*POLG1*)-associated disease, *MPV17* deficiency, Leber hereditary optic neuropathy, Leigh disease, Kearns-Sayre syndrome, and complex I deficiency, may have normal or minimally elevated lactate levels even in the setting of a metabolic crisis.[9] The lactate to pyruvate molar ratio (L:P) is proposed to be a better screening test for mitochondrial disorders, because the L:P reflects the equilibrium between the product and substrate of the reaction catalyzed by lactase dehydrogenase and indirectly reflects the NADH:NAD+ cytoplasmic redox state.[10] When cellular respiration or mitochondrial oxidative metabolism is impaired, such as in inborn errors of components of the mitochondrial respiratory chain, there is an increase in reducing equivalents (excess NADH and absence of NAD+) that results in an elevated L:P. In the past an L:P ≥ 25 has been considered to be highly suggestive of respiratory chain dysfunction[11]; however, an elevated lactate or an elevated L:P also could represent secondary mitochondrial dysfunction occurring as a result of severe liver disease. Therefore, we sought to understand whether lactate and the L:P could be used to distinguish accurately primary mitochondrial causes of PALF. We also sought to determine whether elevated lactate and an elevated L:P represented more severe liver disease and thus predicted poor clinical outcomes.

The Mitochondrial Liver Diseases Working Group of the Childhood Liver Disease Research Network (ChiLDReN) recently recommended screening for mitochondrial disorders in infants and children with severe liver dysfunction, including those presenting with PALF, by examining for elevated blood lactate and the L:P[12]; however, the role and utility of these screening tests for mitochondrial disorders in

ALT	Alanine aminotransferase	L:P	Lactate: pyruvate molar ratio
AST	Aspartate aminotransferase	mtDNA	Mitochondrial DNA
INR	International normalized ratio	PALF	Pediatric acute liver failure

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patients with PALF have not been determined systematically. We hypothesized that an elevated serum lactate ≥ 2.5 mmol/L in combination with an elevated L:P ≥ 25 would identify patients with primary mitochondrial causes of PALF and that these elevated laboratory values early during the onset of PALF would be predictive of clinical outcomes. To address these hypotheses, we used the PALF Study Group dataset to (1) assess the accuracy of blood lactate and L:P as a screen for mitochondrial, respiratory chain, or fatty acid oxidation disorders in children with PALF; (2) determine whether serum lactate ≥ 2.5 mmol/L or L:P ≥ 25 correlated with biochemical variables that reflect clinical severity in children with PALF; and (3) determine whether lactate level or L:P is associated with clinical outcomes at 21 days in patients with PALF.

Methods

Data were obtained from the PALF Study Group registry, a National Institutes of Health–supported, multicenter, prospective study initiated in 1999 that collects data and specimens on children <18 years of age with PALF from 24 participating centers in the US, Canada, and the United Kingdom (ClinicalTrials.gov: NCT00986648). Definitions used and study methodology have been reported previously.[1,13] The enrollment criteria for PALF required (1) the presence of severe hepatic dysfunction occurring within 8 weeks of onset of illness, (2) no known underlying chronic liver disease, and (3) a liver-based coagulopathy (not corrected with vitamin K) with an international normalized ratio (INR) ≥ 1.5 or prothrombin time ≥ 15 seconds in patients with encephalopathy or an INR ≥ 2.0 or prothrombin time ≥ 20 seconds in patients without encephalopathy. Enrollment occurred as soon as possible after hospital admission to the study site. The study protocol was approved by the individual centers' institutional review boards. Evaluation and management of each participant was based on local standard of care; however, the PALF study group had agreed-on guidelines for optimal evaluation of PALF at different ages.[1] Data collected by each site were transmitted to a central data-coordinating center for data editing and quality control procedures.

Participants in the PALF study dataset who had a serum lactate and pyruvate concentration obtained on the same day (within 7 days of study enrollment) were identified. Demographic information including sex, race, ethnicity, age at enrollment, was collected. Laboratory data used in this analysis included the following: the first serum lactate and pyruvate levels drawn on the same day, the resulting calculated L:P, and aspartate aminotransferase (AST), alanine transaminase (ALT), and INR drawn on the same day as the lactate and pyruvate levels. Minimum glucose during the first 7 days of enrollment also was used in analysis. Participants were classified into 3 diagnosis groups based on the final determination of the underlying etiology of PALF: (1) primary mitochondrial disease diagnosis, (2) other confirmed cause (eg, infectious, toxic or drug-induced [including acetaminophen], autoimmune, genetic, ischemia and others), and (3) indeterminate cause (no other etiology determined). For this analysis, the term primary mitochondrial disease includes subjects with a final diagnosis of mitochondrial, respiratory chain, or fatty acid oxidation disorders. Clinical outcome at 21 days (alive without liver transplant, death without transplant, or liver transplantation) was recorded for each participant.

Statistical Analyses

Descriptive statistics were used to characterize the participants by age at enrollment, sex, race, ethnicity, and baseline laboratory values. Because of a small sample size, the power to detect clinically meaningful differences between the 3 diagnosis groups is minimal; therefore, *P* values are not shown for the comparison among the 3 diagnostic categories. Spearman correlations were used to estimate the association between lactate, the L:P, and laboratory values within each diagnostic group. The exact Pearson χ^2 test was used to determine whether the proportion of outcomes differed between the 2 lactate groups (<2.5 or ≥2.5) and the 2 L:P groups (ratio <25 or ≥25). All statistical analyses were performed with SAS 9.3 software (SAS Institute, Cary, North Carolina).

Results

For this study, data were analyzed for participants enrolled between December 27, 1999, and December 31, 2010. Of 986 participants in the PALF Study dataset, 537 had a serum lactate level recorded and, of these, 110 had both serum lactate and pyruvate drawn on the same day and were included in this analysis. The median time between hospital admission and enrollment in the PALF Study was 2 days (IQR 1-4 days). Likewise, the median time between hospital admission and lactate and pyruvate measurement was 2 days (IQR 1-4 days). Of these 110, 74 (67%) had a lactate level ≥ 2.5 mmol/L (**Figure 1**; available at www.jpeds.com). The median age at enrollment of these participants was 2.0 years (IQR 0.5-4.8 years), and 63 (57%) were male. Eight (7.3%) participants had a final diagnosis of a mitochondrial disorder, 37 (33.6%) had another confirmed diagnosis (other diagnosis group), and 65 (59.1%) had an indeterminate diagnosis. Of the 8 participants with a final diagnosis of mitochondrial disorder, 3 had mitochondrial disease, 3 had a respiratory chain disorder, and 2 had drug-induced liver injury (nonacetaminophen) plus mitochondrial disease. Age, sex, race, and Hispanic ethnicity were similar among the 3 diagnosis groups (**Table I**). Baseline AST and ALT were lower in the mitochondrial diagnosis group.

Lactate, Pyruvate, and the L:P Were Similar in All Diagnostic Groups

When we examined the distribution of lactate and pyruvate levels by diagnosis group, lactate tended to be greater in the mitochondrial disease group, but there was considerable overlap among the 3 groups (**Figure 2**). Pyruvate values were comparable among the 3 groups (**Figure 2**). The L:P was elevated in subjects in all 3 groups (**Figure 2** and **Table I**). Surprisingly, only 25% (2/8) of the participants in the mitochondrial group had an elevated L:P (≥25), whereas 46% (17/37) in the other diagnosis group and 48% (31/65) in the indeterminate