# Health Related Quality of Life and Neurocognitive Outcomes in the First Year after Pediatric Acute Liver Failure

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**Objective** To determine health-related quality of life (HRQoL) and neurocognitive impairment in survivors of pediatric acute liver failure (PALF).

**Study design** A longitudinal prospective study was conducted. At 6 and 12 months after PALF presentation, surveys of HRQoL were completed for 2- to 19-year-olds and executive functioning for ages 2-16 years. At 12 months, patients 3-16 years of age completed neurocognitive testing. HRQoL scores were compared with a healthy, matched sample. Neurocognitive scores were compared with norms; executive functioning scores were examined categorically.

**Results** A total of 52 parent-report HRQoL surveys were completed at 6 months, 48 at 12 months; 25 patients completed neurocognitive testing. The median age at 6 months was 7.9 years (range 3.5-15.0), and final diagnosis was indeterminate for 46.2% (n = 24). Self and parent-report on Pediatric Quality of Life Inventory Generic and Multidimensional Fatigue scales fell below the healthy sample at 6 months and 12 months (almost all $P < .001$). Children reported lower mean scores on cognitive fatigue at 12 months (60.91 ± 22.99) compared with 6 months (73.61 ± 27.49, $P = .006$) . The distribution of Behavior Rating Inventory of Executive Function scores was shifted downward on parent-report (preschool) for all indices at 6 months (n = 14, $P \leq .003$); Global Executive Composite and Emergent Metacognition at 12 months (n = 10, $P = .03$). Visual Motor Integration (VMI-6) Copying (mean = 90.3 ± 13.8, $P = .0002$) and VMI-6 Motor Coordination (mean = 85.1 ± 15.2 $P = .0002$) fell below norms, but full scale IQ (Wechsler Scales) and Attention (Conners' Continuous Performance Test) did not.

**Conclusions** Survivors of PALF appear to show deficits in motor skills, executive functioning, HRQoL, and evidence for worsening cognitive fatigue from 6 to 12 months following PALF presentation. *(J Pediatr 2018;■■:■■-■■).*

Pediatric acute liver failure (PALF) is a rare, devastating condition affecting often previously healthy children and associated with 50% spontaneous survival. Rapid clinical deterioration frequently occurs, with hepatic encephalopathy (HE) and multisystem organ failure. Cerebral edema associated with advanced injury can result in intracranial hypertension and brain herniation.[1-3] A small case series of children surviving PALF secondary to viral hepatitis demonstrated significant cognitive deficits that improved in parallel with indicators of cerebral edema and circulating proinflammatory cytokine levels.[4]

Prospective neurocognitive testing has been lacking in a cohort of PALF survivors of varied etiology. Many PALF patients who require liver transplantation report cognitive fatigue affecting day-to-day function.[5] Spontaneous survivors of PALF are also likely at increased risk for cognitive fatigue, but clinical follow-up after discharge is inconsistent. Despite resolution of HE in survivors, there may be residual subclinical neurologic injury compromising neurocognitive

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| ABAS-II | Adaptive Behavior Assessment System-Second Edition |
| APAP | Acetaminophen |
| BRIEF | Behavior Rating Inventory of Executive Function |
| CDI-2 | Children's Depression Inventory, Second Edition |
| CPT-II | Conners' Continuous Performance Test II |
| HE | Hepatic encephalopathy |
| HRQoL | Health-related quality of life |
| K-CPT | Conners' Kiddie Continuous Performance Test |
| PALF | Pediatric acute liver failure |
| PALFSG | Pediatric acute liver failure study group |
| PedsQL MFS | PedsQL Multidimensional Fatigue Scale |
| PedsQL | Pediatric Quality of Life Inventory 4.0 Generic Core Scales |
| PTSD | Post-traumatic stress disorder |
| VMI-6 | Beery-Buktenica Developmental Test of Visual-Motor Integration, Sixth Edition |
| WISC-IV | Wechsler Intelligence Scales for Children, Fourth edition |
| WPPSI-IV | Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition |

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

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function, including cognitive fatigue. Cognitive fatigue has been operationally defined as a "decline in alerting, orienting, and executive attention performance" as distinct from general fatigue (eg, feeling tired).[6]

Health-related quality of life (HRQoL) in these survivors may also be lower than expected compared with healthy children. Detailed assessment of neurocognitive function, cognitive fatigue, and HRQoL is critical to understanding the full impact of PALF.

A prior cross-sectional study of neurocognitive and HRQoL outcomes in PALF survivors with varied etiology was conducted by the Pediatric Acute Liver Failure Study Group (PALFSG). Thirty-six patients aged 6-16 years were assessed 1-6 years after presentation. This study demonstrated average IQ, but greater than expected impairments in motor skills, attention, executive functioning, HRQoL and cognitive fatigue in long-term survivors.[7]

The goal of the present longitudinal prospective study, also conducted by the PALFSG, was to characterize more fully in PALF survivors during the first year following presentation and to validate findings from our cross-sectional study. We hypothesized HRQoL and cognitive fatigue would be lower at 6 and 12 months after PALF presentation compared with a matched healthy sample, but would improve from 6 to 12 months. We also hypothesized neurocognitive function (specifically motor, attention, and executive functioning) would be lower compared with test norms at 12 months after PALF.

## Methods

PALFSG inclusion criteria are age birth to <18 years, biochemical evidence of acute liver injury without chronic liver disease, and coagulopathy not corrected by parenteral vitamin K or other intervention. Registry participants must have liver synthetic failure with international normalized ratio ≥1.5 associated with HE, or international normalized ratio ≥2.0 with or without HE.

Eligible patients for the present longitudinal study were drawn from the PALFSG (N = 158) and recruited at 12 medical centers in the US and Canada between May 2012 and December 2014, with 1-year follow-up testing through December 2015. None of the patients in the current sample participated in the previously published cross-sectional study.[7] Specific eligibility criteria differed slightly for HRQoL and neurocognitive/executive functioning testing because primarily of the measures used. Therefore, the samples overlap, but are not the same. The **Figure** (available at www.jpeds.com) details the recruitment algorithm and the reasons for nonparticipation.

### HRQoL and Fatigue

Eligible patients from 2 to 19 years of age enrolled in the PALFSG completed age-appropriate HRQoL and cognitive fatigue surveys at 6 months (N = 52; 81% of eligible) and 12 months (N = 48; 84% of eligible) following PALF presentation. Subject and parent/guardian were fluent in English or Spanish.

The healthy sample was derived from 2 previously completed studies[8,9] and randomly matched by age, sex, and race/ethnicity to the PALF sample separately for child self-report and parent-proxy report given age differences between the 2.

### Executive Function and Neurocognitive Function

Surveys assessing executive functioning were completed by parents of eligible patients age 2-16 years at 6 months (N = 31; 89% of eligible) and 12 months (N = 25; 89% of eligible) after PALF presentation. Eligible patients age 3-16 years completed neurocognitive testing 12 months after PALF presentation (N = 25; 89% of eligible). In addition, participants (≥8 years old) and parents completed the depression and posttraumatic stress disorder (PTSD) surveys along with the neurocognitive testing battery.

Eligibility for the present study was assessed at the PALFSG visit. Therefore, if the visit was missed, eligibility could not be determined. Participants and parent/guardian were fluent in English. Exclusions included unstable medical status at time of testing (eg, hospitalizations within 4 weeks prior to testing, awaiting liver transplantation, uncontrolled seizures) or medical factors that could independently affect functioning or invalidate testing (ie, cancer diagnosis; weakness or abnormality of muscle tone or coordination, sufficiently severe that it impaired the ability to perform the physical tasks required for testing; no intelligible speech and/or inability to follow simple commands.) Fourteen children met exclusion criteria at the 12 months visit: non-English speaking (n = 5), hospitalized or listed for liver transplantation (n = 5), impaired speech or muscle weakness (n = 3), and previous cancer diagnosis (n = 1).

### Study Design

Participants meeting inclusion criteria were identified by the Data Coordinating Center, which provided weekly reports to site coordinators and investigators of those patients who were due for their 6- and 12-month follow-up visits. The report served as a notice for coordinators to begin scheduling the patient for an in-person follow-up visit with the appropriate amount of time and resources for the visit specific measures to be completed. The 12-month neurocognitive tests were performed or supervised by licensed psychologists.

Written, informed consent was obtained from the child's parent/legal guardian before participation in the PALFSG. Assent was obtained from children as required by individual institutions. The study protocol was approved by the institutional review boards at all PALFSG sites.

### Instruments

**HRQoL and Fatigue (Completed at 6- and 12-Month Visit).** The child self-report (only for ≥5 years old) and parent proxy-report versions of the 23-item Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL, Mapi Research Institute, Lyon, France)[8] and the PedsQL Multidimensional Fatigue Scale (MFS)[10,11] were administered at both the 6- and 12-month follow-up visits. Items are reverse-scored and linearly transformed to a 0-100 scale, so that higher scores indicate better HRQoL. The PedsQL encompasses (1) physical functioning (8 items), (2) Emotional Functioning (5 items), (3) Social Functioning (5 items), and (4) School Functioning (5 items) and



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