No Child Left Behind: Liver Transplantation in Critically Ill Children

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BACKGROUND: Advances in critical care prolong survival in children with liver failure, allowing more critically ill children to undergo orthotopic liver transplantation (OLT). In order to justify the use of a scarce donor resource and avoid futile transplants, we sought to determine survival in children who undergo OLT while receiving pre-OLT critical care.

STUDY DESIGN: We analyzed 13,723 pediatric OLTs using the United Network for Organ Sharing (UNOS) database from 1987 to 2015, including 6,746 recipients in the Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease (MELD/PELD) era (2002 to 2015). There were 1,816 recipients (26.9%) admitted to the ICU at the time of transplantation. We also analyzed 354 pediatric OLT recipients at our center from 2002 to 2015, one of the largest institutional experiences. Sixty-five recipients (18.3%) were admitted to the ICU at the time of transplantation. Kaplan-Meier, volume threshold, and multivariable analyses were performed.

RESULTS: Patient survival improved steadily over the study period, (66% 1-year survival in 1987 vs 92% in 2015; $p < 0.001$). Our institutional experience of ICU recipients in the MELD/PELD era had acceptable outcomes (87% 1-year survival), even among our sickest recipients with vasoactive medications, mechanical ventilation, dialysis, and molecular adsorbent recirculating system requirements. Volume analysis revealed inferior outcomes (hazard ratio [HR] 1.68; 95% CI 1.11 to 2.51) in low-volume centers (<5 annual cases). Identifiable risk factors (previous transplantation, elevated serum sodium, hemodialysis, mechanical ventilation, body weight < 6 kg, and low center volume) increased risk of mortality.

CONCLUSIONS: This analysis demonstrates that the use of advanced critical care in children and infants with liver failure is justified because OLT can be performed on the sickest children and acceptable outcomes achieved. It is an appropriate use of a scarce donor allograft in a child who would otherwise succumb to a terminal liver disease. (J Am Coll Surg 2017;224:671–677. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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In a short span of time, pediatric critical care has made tremendous strides.[1] Critically ill children, who once were destined for death, are now surviving longer and often recovering. This is demonstrated in the plummeting mortality rates for children with sepsis, cardiac arrest, and traumatic brain injury.[2] Free-standing pediatric hospitals and round-the-clock ICU coverage have further reduced pediatric ICU mortality.[3,4] The overall mortality rate for children in the pediatric ICU is reported to be under 2%.[1] The same trend is true for children with liver failure. A recent study reported a 75% survival for children with acute liver failure without transplantation compared with just 15% in 1985.[5] Also, for chronic liver failure, we have seen improvements in waitlist survival for candidates

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Abbreviations and Acronyms

GFR	= glomerular filtration rate
HR	= hazard ratio
MARS	= molecular adsorbent recirculating system
MELD score	= Model for End-Stage Liver Disease score
OLT	= orthotopic liver transplant
PELD	= Pediatric End-Stage Liver Disease
TCH	= Texas Children's Hospital
TPE	= therapeutic plasma exchange
UNOS	= United Network for Organ Sharing

awaiting orthotopic liver transplantation (OLT).[6] These improved critical care outcomes in children make it possible for more sick children with liver failure to survive long enough to be afforded the option of life-saving OLT.

Hand-in-hand with improved care for critically ill children with liver failure, post-transplant critical care has made tremendous strides.[7-12] Our recipients have gotten sicker while our postoperative outcomes have improved.[10] The question then becomes, have our operative skills and postoperative critical care management kept up with the abilities to keep sick children with liver failure alive? Just because transplantation is now possible in our sickest children, is it justified? We hypothesized that post-transplant patient survival among ICU-bound children justifies the use of a scarce donor liver allograft, both in the national and our institutional experiences.

METHODS

National experience: Study population

We performed a retrospective analysis of United Network for Organ Sharing (UNOS) deidentified patient-level data of all recipients of OLT between September 1, 1987 and June 30, 2015. Our analysis used the liver registry with data collected by the Organ Procurement and Transplantation Network (OPTN). We included all transplant recipients younger than 18 years old. Donor and recipient characteristics were reported at the time of liver replacement. Follow-up information was collected at 6 months and then yearly after transplantation. Patients undergoing combined or multivisceral transplants (n = 956), with the exception of those receiving liver-kidney transplants (n = 266), were excluded from the study. All patients were followed from the date of transplantation until either death (n = 2,525) or the date of last known follow-up (n = 11,198). We analyzed 13,723 recipients, including 6,746 recipients in the Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease (MELD/PELD) era (2002 to 2015); 1,816 recipients were admitted to the ICU at the time of transplantation.

National experience: Study period

Because we demonstrated improving outcomes over time, we divided our study period into eras. The MELD/PELD era was defined as March 1, 2002 to June 30, 2015 due to the significant shift in policy about the use of MELD and PELD scores for liver allocation. The remote era was from September 1, 1987 to March 1, 2002. Because of the significant improvement in outcomes over time, we restricted our multivariable, center volume, and institutional analyses to the MELD/PELD era.

National experience: Definition of critical illness

There are several potential definitions of critical illness in transplant recipients. We decided to incorporate all candidates admitted to the ICU at the time of transplantation and then include more objective definitions as covariates in our multivariable regression analysis. Objective markers included dialysis dependence, PELD score, renal insufficiency, status 1 listing, serum sodium, serum albumin, and mechanical ventilator dependence. In the investigation of survival outcomes improvements over time, analyses using alternative definitions of critical illness, including dialysis and mechanical ventilator dependence, were conducted.

National experience: Statistical analysis

Data were analyzed with a standard statistical software package, Stata 12.1 (Stata Corp). Continuous variables were reported as mean ± standard deviation and compared using the Student's *t*-test. Contingency table analysis was used to compare categorical variables. Results were considered significant when $p < 0.05$. All reported p values were 2-sided. The primary outcome measure was patient death. Time to death was assessed as the time elapsed from the date of transplantation to the date of death. All death dates were verified with Social Security Death Master Files. Kaplan-Meier analysis with log-rank test and Cox regression was used for time-to-event analysis. Risk factors that were significant in univariable analysis ($p < 0.05$) were included in the multivariable analysis. Multivariable Cox regression was performed combining 100 bootstraps. Patients lost to follow-up or alive on June 30, 2015 were censored at the date of last known follow-up. Model discrimination was assessed using the area under the receiver operating characteristic curve.

We defined the center volume groups as follows: more than15 annual transplants, 10 to 15 annual transplants, 5 to 9 annual transplants, and less than 5 annual transplants, based on a previously published analysis that explored volume relationships in pediatric OLT.[13] The