Pretransplant Serum Albumin Is an Independent Predictor of Graft Failure in Pediatric Renal Transplant Recipients

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Objectives To determine the prevalence of hypoalbuminemia in children listed for renal transplantation and to evaluate the effect of pretransplant hypoalbuminemia on posttransplant outcomes.

Study design Retrospective cohort analysis of children receiving their first kidney transplant in the US between January 2000 and December 2010 obtained through the Organ Procurement and Transplantation Network. The primary outcome measure was time to graft failure. Cox regression analyses were used to estimate the independent effect of serum albumin on event incidence.

Results Of the 6032 children who received transplants, 308 (5.1%) had a very low serum albumin level at registration; rates of transplantation in such children varied significantly across geographic regions (χ^2, $P < .001$) ranging from 2.1% to 8.7%. Serum albumin was inversely associated with graft failure; each 1-g/dL increase in serum albumin was associated with a 19% reduction in risk of graft failure (adjusted hazard ratio 0.81, 95% CI 0.75-0.88, $P < .001$).

Conclusions Considerable regional variation exists in the US with respect to transplantation in children with hypoalbuminemia. Severe hypoalbuminemia is an independent risk factor for graft failure. Transplant centers as well as patients need to be aware of this risk and make informed decisions regarding the optimal timing of transplantation. Whether graft failure is a consequence of the low serum albumin or the reflection of a higher inflammatory milieu remains to be explored. *(J Pediatr 2014;164:602-6)*.

Low serum albumin is a predictor of mortality in the general population[1] and in patients admitted to the hospital with acute illnesses.[2] In adults with chronic kidney disease (CKD), including those on dialysis, hypoalbuminemia is an independent predictor of death.[3,4] Data pertaining to children are much more limited. In a recent prospective study of children with CKD stages 2-4, 47% of the studied population had a low serum albumin (≤4 g/dL), and this was an independent predictor of disease progression.[5]

Within the adult renal transplant population, posttransplantation hypoalbuminemia is a well-documented risk factor for patient and graft loss.[6] Very limited data have been published on the impact of pretransplantation hypoalbuminemia on post-transplant outcomes in adults, and none to our knowledge in children. In one study pretransplantation hypoalbuminemia was associated with postoperative wound complications[7]; another recent study showed that adult patients with hypoalbuminemia receiving hemodialysis in the pretransplantation period had worse graft and patient survival and a higher incidence of delayed graft function (DGF).[8]

The objective of our study was to determine the prevalence of moderate (2.5-3.4 g/dL) and severe hypoalbuminemia (serum albumin < 2.5 g/dL) in pediatric transplant recipients and to investigate the impact of pretransplantation serum albumin on posttransplant outcomes. Our hypothesis was that children would very commonly have hypoalbuminemia pretransplantation. Knowing that hypoalbuminemia is a surrogate marker for inflammation,[9] we also hypothesized that children with albuminemia receiving renal transplants would have a lower graft survival and that this would be mediated by a higher incidence of DGF and acute rejection (AR). This is a question of critical importance because if our hypotheses were proven to be true, one approach to address hypoalbuminemia could be to delay transplantation until measures are instituted to normalize the serum albumin. This potentially could prolong wait times of patients, which could itself adversely affect graft survival.[10]

Methods

We conducted a retrospective analysis of the Organ Procurement and Transplantation Network (OPTN) database, as of March 2, 2012, to identify children (age

AR	Acute rejection
CKD	Chronic kidney disease
DGF	Delayed graft function
FSGS	Focal segmental glomerulosclerosis
HLA	Human leukocyte antigen
OPTN	Organ Procurement and Transplantation Network

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<18 years at the time of transplantation) who had received their first kidney-only standard criteria transplant between January 1, 2000, and December 31, 2010. The study was granted an exempt status from the University of California Davis Institutional Review Board.

To be included in the study, we also required that the child have a functioning graft on postoperative day 1 and information available on serum albumin, human leukocyte antigen (HLA) mismatch level, and whether patients had received pretransplant dialysis. The primary outcome measure was time to graft failure or death. Secondary outcome measures were the incidence of DGF, which was defined as the receipt of dialysis within the first week after transplantation, treatment for AR at 1 year, and graft failure or death at 1 year. Multivariate (Cox event-history and logistic) regression analyses were performed to determine the independent effect of serum albumin at the time of registration on the OPTN wait list (the only time point when serum albumin data were collected in the registry) on the outcome measures. Serum albumin was analyzed both as a continuous variable and as a categorical variable: severe hypoalbuminemia <2.5 g/dL, moderate hypoalbuminemia 2.5-3.4 g/dL, and normal albumin ≥3.5 g/dL.

For multiple regression models, directed acyclic graphs were used to encode the investigators' judgments about possible interrelationships among the variables. These formed the basis of selecting available covariates from the OPTN datasets to minimize confounding of the estimated associations of serum albumin level with the primary and secondary outcomes of interest. For these outcomes, the following recipient-, donor-, and transplant-related characteristics were accounted for in the multivariate models: recipient age, sex, ethnicity, cause of CKD, OPTN region where transplant occurred, year of transplant, receipt of pretransplantation dialysis, time on the deceased donor wait list, donor source (deceased or living), donor age and cause of death, HLA mismatch level, and cold ischemia time. Cause of CKD and donor cause of death were categorical variables derived using both forced-choice and open-text responses (all derived variable definitions are available on request). Also, for the outcome measures related to graft failure, additional Cox regression analyses were performed that included the intermediate outcomes of AR and DGF as time-varying explanatory variables.

To characterize determinants of serum albumin level, we conducted univariate analyses to investigate associations of recipient characteristics with serum albumin. Multiple logistic and linear regression variables were then built that included only the exogenous recipient characteristics listed above (age, sex, ethnicity, cause of CKD), the OPTN region, year of transplantation, and any other factors that were significant in the univariate analyses.

Sensitivity analyses were performed to assess whether the observed associations between serum albumin and graft failure depended on 4 potentially biasing factors. First, we assessed whether the association varied according to time on the wait list, a possible source of information bias given that that our albumin measurement was collected at registration, not immediately before transplantation. Second, we assessed whether the association was modified by whether the patient had focal segmental glomerulosclerosis (FSGS) as the cause of CKD, a potential effect modifier given the strong association of FSGS with low albumin levels and posttransplant complications. Third, we assessed whether the association was modified by mode of dialysis (none vs hemodialysis vs peritoneal dialysis) received up to the time of listing, a potential effect modifier (given physiological considerations related to protein losses and/or breakdown as a consequence of dialysis) that is not included in the primary analysis because information on mode of pretransplantation dialysis stopped being collected in 2006. In a fourth analysis, we added pretransplantation dialysis duration, a potential confounder that also was not included in the primary model due to moderate levels of missing data. To maximize statistical power, the continuous measure of serum albumin was used in sensitivity analyses. For sensitivity analyses assessing effect modification, an interaction term for the continuous measure and the candidate effect modifier was added to the Cox regression model, and the coefficient and Wald test statistic associated with the interaction were assessed for clinical and statistical significance.

Results

Using the OPTN database, we identified 7474 children who would have met the study's inclusion criteria; 6032 (81%) of them had serum albumin data available and were included in the study. The recipient mean (SD) age was 10.9 (5.2) years; 41% were female. The largest 3 recipient ethnic categories were white, 53%; Hispanic, 23%; and black, 19%. Twenty-eight percent of the recipients had not received pretransplantation dialysis. Among the 3505 patients with information on the type of dialysis they had received up to the time of listing (data that were last collected in 2006), 34% had received hemodialysis, 34% had received peritoneal dialysis, and 31% had not received any pretransplantation dialysis. The mean and median wait times on the transplant list were 241.8 and 152 days, respectively, for the 4296 recipients with 0 or more days on the wait list. Living donor transplantation accounted for 48% of all transplants, including all 1736 transplants from patients with missing wait times. The causes of CKD were typical for the pediatric population: congenital/structural causes in 47%, FSGS in 14%, other glomerular diseases in 26%, malignancies in 1%, other causes in 7%, and unknown cause in 5%. DGF was encountered in 7% of the recipients; at 1 year, 13.9% of the patients had experienced AR and 5% had experienced graft failure.

Prevalence and Predictors of Hypoalbuminemia

Five percent of all transplant recipients had severe hypoalbuminemia, 23% had moderate hypoalbuminemia, and 72% had a normal serum albumin level at registration. On univariate analyses, compared with patients with a normal serum albumin level, those with severe hypoalbuminemia were younger at registration (9.3 vs 10.7 years, $P < .001$, Student t-test), were more often female (46% vs 40%, $P = .04$, χ^2