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Hypoalbuminemia and risk of death in pediatric patients with end-stage renal disease

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Background. Although serum albumin is a marker for malnutrition and associated with a higher mortality in adult patients with end-stage renal disease (ESRD), the risk of death associated with serum albumin is unknown in pediatric patients with ESRD. We evaluated the association between serum albumin and death among pediatric patients initiating dialysis.

Methods. Data from the United States Renal Data System (USRDS) were used to identify all patients under the age of 18 who initiated dialysis between January 1, 1995 and December 31, 1998. Using the Cox proportional hazards models, the association between serum albumin obtained 45 days prior to dialysis initiation and death was estimated, controlling for demographic factors, dialysis modality, and anthropometric measures.

Results. Of 1723 patients included in the analysis, there were 93 deaths over 2953 patient-years of observation. The multivariate analysis demonstrated that each −1 g/dL difference in serum albumin between patients was associated with a 54% higher risk of death [adjusted relative risk (aRR), 1.54; 95% confidence interval (CI), 1.15 to 1.85; $P = 0.002$]. This was independent of glomerular causes for their ESRD and other potential confounding variables.

Conclusions. Pediatric patients initiating dialysis with hypoalbuminemia are at a higher risk for death. This finding persists after adjusting for glomerular causes for ESRD and other potential confounding variables. Low serum albumin at dialysis initiation is an important marker of mortality risk in pediatric ESRD patients.

The prevention of malnutrition is of paramount concern in the care of pediatric patients with end-stage renal disease (ESRD). Data from the pediatric ESRD literature have shown that improving nutritional management can stimulate growth and cognitive development [1–3]. However, little is known about the effect of nutritional status on survival within the pediatric ESRD population.

Data from adult dialysis patients suggest that indicators of nutritional status are independently associated with morbidity and mortality [4–6]. Furthermore, protein-energy malnutrition in these patients is highly prevalent and is one of the strongest predictors of morbidity and mortality [7–9]. Because of these nutritional concerns, the K/DOQI Nutritional Guidelines recommend including serum albumin as part of the routine assessment of nutritional status in maintenance dialysis patients. There is a large body of literature that defines normal serum albumin values, characterizes the multiple factors affecting serum albumin concentrations, and demonstrates the relationship between serum albumin concentrations and outcomes [10]. Hypoalbuminemia when present at the time of initiation of chronic dialysis as well as during the course of maintenance dialysis is highly predictive of future mortality risk in adult patients with ESRD [4–6, 8, 9, 11, 12].

Pediatric patients with ESRD have a significantly higher risk of death compared to the general pediatric population [13]. Though the etiology of this increased risk of death is likely multifactorial, nutritional status may play an important role. Although we have shown that abnormal anthropometric measurements are associated with risk of death, there are no studies characterizing the relationship between serum albumin and mortality among pediatric patients with renal failure [13]. We used data from the United States Renal Data System (USRDS) to estimate the risk of all-cause mortality associated with serum albumin measured within 45 days of initiating dialysis among pediatric patients.

METHODS

Patient population

The current study uses data from the USRDS, a national data system that collects information on the inci-

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dence, prevalence, treatment, morbidity and mortality of ESRD patients residing in the United States. A more in-depth discussion of the USRDS data collection techniques can be found elsewhere [14]. We identified all patients younger than 18 years of age who indicated initiation of dialysis by submitting a HCFA 2728 Medical Evidence Form between January 1, 1995 and July 31, 1998 ($N = 1937$).

Data collection

Data abstracted from the Medical Evidence Form for this study included: date of birth, date of dialysis initiation, gender, race (white, black, and other), primary cause of ESRD (congenital/inherited diseases, glomerular diseases, vasculitic/interstitial disease, nephrotoxic/tumor-related, and other), and baseline serum albumin. The reported values for serum albumin were obtained and reported within 45 days prior to the first dialysis for ESRD. The most recent value for height and weight prior to dialysis were used for the analysis. Baseline treatment modality and subsequent modality changes were abstracted from the USRDS Treatment History Standard Analysis File (SAF).

Outcome assessment

Survival status and primary cause of death were obtained from the Patients SAF of the USRDS and linked to patients in this cohort via unique patient identifiers assigned to each individual by the USRDS. Patient survival status is periodically updated in the Patients' SAF and was complete through July 1998.

Statistical analysis

To standardize height, weight, and body mass index (BMI; defined as weight in kilograms per meter of height squared) with respect to age and sex, the measurements were reported as standard deviation scores (SDS), as described previously [13]. Normative data were obtained from the Third National Health and Nutrition Examination Survey (NHANES III), a cross-sectional survey of the United States (US) civilian, non-institutionalized population, aged two months and older [15]. SDS were calculated using the following formula:

$$\text{SDS} = \frac{(\text{ESRD patient measurement}) - (\text{mean US value for age and sex})}{(\text{standard deviation of mean US value for age and sex})}$$

The resulting SDS reflects the number of standard deviations the measurement for an ESRD patient lies above or below the mean value in the general population matched by age and gender.

For selected analyses, differences between patient groups were compared using chi-square tests for categorical variables. The risk of all-cause mortality was estimated using a Cox proportional hazards model, adjusting for age, sex, race, glomerular cause of ESRD (yes vs. no), treatment modality, height SDS, weight SDS, and serum albumin.

Patients were followed in the study until they had the event of interest, death from any cause, or were censored due to a loss to follow-up or to termination of the study (July 31, 1998). Patients were not censored at the time of transplant because a major assumption of the Cox proportional hazards model requires that censoring, or removing patients from the analysis, is not associated with the end point, in this case, death [16]. Removing patients from the analysis at the time of transplant may have violated this assumption, because transplanted patients are generally healthier and less likely to die than those remaining on dialysis [17–19]. In order to account for changes in ESRD treatment modality over time and retain individuals that were subsequently transplanted over the course of the study, treatment modalities (hemodialysis, peritoneal dialysis, transplant) were modeled as time-dependent covariates [16, 17, 20].

Adjustment factors were included in the model if they were shown to be associated with death, thought to confound the relationship between albumin and death, or considered an adjustment factor a priori. All adjustment variables used in the model satisfied the assumption of proportional hazards. The proportionality of hazards for all models was verified via formal hypothesis tests and visual inspection of the scaled Schoenfeld residuals.

Hazard ratios obtained from the analysis were used to estimate the adjusted and unadjusted relative risk of death. After adjustment for other covariates in the final model, the adjusted relative risks (aRR) were interpreted as the risk for death among pediatric ESRD patients associated with each variable of interest. The estimated standard error of the coefficients from the Cox regression analysis was used to estimate confidence intervals (CI's) for the aRR. The threshold of statistical significance was set to 0.05. Results were reported as aRRs with 95% CI's and two-tailed P values. Computations were performed using S-PLUS (Mathsoft, Seattle, WA, USA).

RESULTS

Between January 1, 1995 and December 31, 1998, 1937 pediatric patients initiated dialysis. Of these patients, 1723 patients had a serum albumin level available for analysis. Two hundred fourteen patients whose serum albumin data were missing were excluded. Characteristics of the study population and those excluded from the analysis are summarized in Table 1. Comparing patients with and without serum albumin data, there were no differences between the groups with regard to gender, race, cause of ESRD, or proportion of deaths. However, patients with missing data were more likely to be in the 15 to 18 year age group. Comparing patients with a normal serum albumin to those with a serum albumin <3.5

Table 1. Characteristics of the study population stratified by baseline albumin[a]

Characteristic	Albumin <3.5 g/dL	Albumin ≥3.5 g/dL	Missing albumin
Total patients	987 (100%)	736 (100%)	214 (100%)
Sex			
Male	502 (50.9%)	443 (60.2%)	111 (51.9%)
Age			
0 to 2 years	89 (9%)	53 (7.2%)	13 (6.1%)
3 to 5 years	128 (13.0%)	62 (8.4%)	20 (9.3%)
6 to 14 years	393 (39.8%)	341 (46.3%)	76 (35.5%)
15 to 18 years	377 (38.2%)	280 (38.0%)	105 (49.1%)
Race			
White	556 (56.3%)	456 (62.0%)	126 (58.9%)
Black	294 (29.8%)	189 (25.7%)	63 (29.4%)
Other	137 (13.9%)	91 (12.4%)	25 (11.7%)
Height SDS[b]			
Less than −2	350 (36.5%)	298 (41.4%)	78 (36.8%)
−2 to 0	404 (42.1%)	314 (43.6%)	81 (38.2%)
Greater than 0	205 (21.4%)	108 (15.0%)	53 (25.0%)
Weight SDS[b]			
Less than −2	88 (9.2%)	64 (8.8%)	13 (6.2%)
−2 to 0	680 (71.0%)	542 (74.9%)	141 (67.5%)
Greater than 0	190 (19.8%)	118 (16.3%)	55 (26.3%)
BMI SDS[b]			
Less than −2	25 (2.7%)	22 (3.1%)	3 (1.5%)
−2 to 0	630 (67.0%)	470 (65.9%)	135 (65.5%)
Greater than 0	286 (30.4%)	221 (31.0%)	68 (33.0%)
Cause of ESRD			
Glomerular diseases	524 (53.1%)	195 (26.5%)	101 (47.2%)
Congenital/inherited	234 (23.7%)	356 (48.4%)	64 (29.9%)
Vasculitis/interstitial diseases	61 (6.2%)	80 (10.9%)	14 (6.5%)
Nephrotoxic/tumor related	18 (1.8%)	8 (1.1%)	2 (0.9%)
Other	83 (8.4%)	44 (6.0%)	20 (9.3%)
Unknown	67 (6.8%)	53 (7.2%)	13 (6.1%)
Cause of death ($N = 103$)			
All causes	69	24	10
Cardiovascular	14 (20.3%)	4 (16.7%)	1 (10.0%)
Infection	14 (20.3%)	2 (8.3%)	3 (30.0%)
Cerebrovascular/anoxia	3 (4.3%)	2 (8.3%)	1 (10.0%)
Hemorrhage	1 (1.4%)	1 (4.2%)	0 (0%)
Gastrointestinal	3 (4.3%)	1 (4.2%)	0 (0%)
Fluid overload	1 (1.4%)	0 (0%)	2 (20.0%)
Neoplasm	5 (7.2%)	3 (12.5%)	0 (0%)
Other	28 (40.6%)	11 (45.8%)	3 (30.0%)

[a] Statistics presented are frequency (%)
[b] Numbers may vary from total due to missing data

g/dL, there were no significant differences by age, gender, race, height, weight, or BMI. Hypoalbuminemic pediatric patients were more likely to have glomerular diseases as their cause of ESRD compared to patients who were not hypoalbuminemic (53.1 vs. 26.5%; $P < 0.0001$).

Among the pediatric ESRD patients in the study, there were 93 deaths over 2953 patient-years of observation. This yielded a mortality rate of 31.5 deaths per 1000 patient-years. The mortality rates stratified by serum albumin are presented in Figure 1. The risk of pediatric ESRD death was inversely related to the level of serum albumin. From the highest to lowest categories of serum albumin, the rate of death per 1000 patient-years of observation was 18.4 for patients with a serum albumin of >3.5 g/dL, 33.2 for patients with a serum albumin between 3.5 to 3.1 g/dL, and 46.9 for patients with a serum albumin between 3.0 to 2.1 g/dL. The mortality rate was

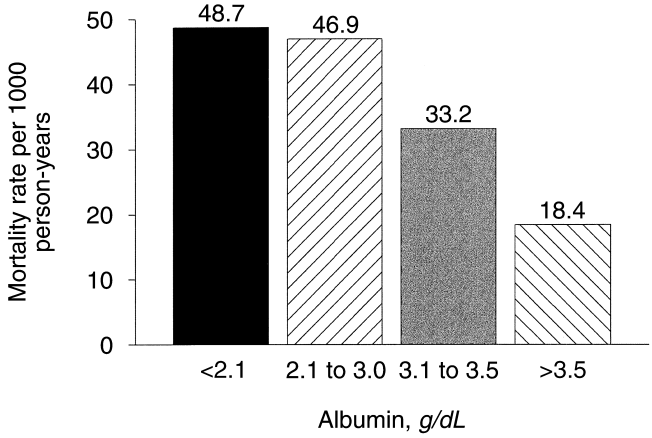

Fig. 1. Pediatric end-stage renal disease (ESRD) mortality rate per 1000 person-years by level of serum albumin.

Table 2. Cox regression results analysis: Unadjusted and adjusted estimates for relative risk of death

Covariate	Observed deaths	Deaths per 1000 patient-years	Unadjusted Relative risk (95% CI)	Unadjusted *P* value	Adjusted[a] Relative risk (95% CI)	Adjusted[a] *P* value
Sex						
Female	49	33.8	1.0		1.0	
Male	54	28.8	0.87 (0.59, 1.27)	0.46	0.82 (0.53, 1.27)	0.37
Age			0.95 (0.92, 0.99)	0.009	0.96 (0.91, 1.00)	0.07
0 to 2 years old	16	42.5	1.0		1.0	
3 to 14 years old	53	30.8	0.52 (0.30, 0.91)	0.02	0.39 (0.21, 0.75)	0.005
15 to 18 years old	34	26.4	0.45 (0.25, 0.82)	0.009	0.39 (0.19, 0.80)	0.01
Race						
White	58	29.5	1.0		1.0	
Black	31	33.4	1.12 (0.72, 1.73)	0.61	1.20 (0.72, 2.00)	0.47
Other	14	32.7	1.10 (0.61, 1.98)	0.75	0.97 (0.50, 1.91)	0.94
Treatment modality						
HD	39	37.2	1.0		1.0	
PD	40	35.2	0.94 (0.60, 1.46)	0.78	0.79 (0.47, 1.30)	0.35
Transplant	13	11.9	0.29 (0.15, 0.57)	<0.001	0.32 (0.16, 0.66)	0.002
Primary cause of ESRD						
Not GN related	58	30.6	1.0		1.0	
GN related	45	31.6	1.03 (0.70, 1.53)	0.86	0.86 (0.52, 1.42)	0.56
Height SDS[b]			1.30 (1.18, 1.43)	<0.001	1.28 (1.14, 1.43)	<0.001
Less than −3	42	66.5	1.0		1.0	
−3 to −1	29	21.3	0.32 (0.2, 0.51)	<0.001	0.35 (0.21, 0.59)	<0.001
Greater than −1	27	21.6	0.32 (0.2, 0.52)	<0.001	0.23 (0.10, 0.54)	0.001
Weight SDS[c]				0.005		0.12
Less than −1	56	36.5	1.0		1.0	
−1 to 3	41	25.1	0.69 (0.46, 1.03)	0.07	1.11 (0.65, 1.89)	0.70
Greater than 3	3	45.3	1.24 (0.39, 3.95)	0.72	2.75 (0.79, 9.53)	0.11
Albumin *g/dL*[d]			1.54 (1.23, 1.92)	<0.001	1.47 (1.15, 1.85)	0.002
3.5 g/dL or greater	24	18.4	1.0		1.0	
Less than 3.5 *g/dL*	69	41.8	2.25 (1.41, 3.58)	0.001	1.90 (1.16, 3.10)	0.01

[a] Adjusted for age, gender, race, treatment modality, glomerular cause of ESRD, height SDS, weight SDS, and albumin
[b] Modeled as a continuous variable decreasing by 1 SDS
[c] Weight SDS was modeled with a quadratic term; corresponding *P* values apply to a joint likelihood ratio test for both the linear and quadratic term
[d] Modeled as a continuous variable decreasing by 1 g/dL

highest at 48.7 deaths per 1000 patient-years among patients initiating dialysis with a serum albumin <2.1 g/dL.

Univariate relative risks of death associated with the covariates of interest are presented in Table 2. There were no differences in risk of death by sex or race. Risk of death was inversely proportional to age. The youngest patients from 0 to 2 years of age had the highest rate of mortality at 42.5 deaths per 1000 patient-years. Compared to the youngest age group, patients initiating dialysis at 3 to 14 years of age had a 48% lower risk of death (RR = 0.52; 95% CI 0.30 to 0.91; $P = 0.02$). Those initiating dialysis between 15 and 18 years of age had a 54% lower risk of death compared to patients in the youngest age category (RR = 0.45; 95% CI 0.25 to 0.82; $P = 0.009$). Patients who were transplanted had an estimated 81% lower risk of death compared to hemodialysis patients (RR = 0.29; 95% CI 0.15 to 0.57; $P < 0.001$). Compared to patients who did not have a glomerular cause of ESRD, patients with a glomerular cause of ESRD did not have a higher risk of death (RR, 1.03; 95% CI, 0.70 to 1.53; $P = 0.86$). Analyzing anthropometric measures, we found an inverse association between height SDS and pediatric risk of death. Additionally, extremes in weight SDS, either too high or too low, were associated with a higher risk of death. However, the evaluation of BMI SDS demonstrated no association with risk of death in this cohort of pediatric ESRD patients (data not shown).

Without adjustment for other factors, serum albumin determined within 45 days of initiating dialysis was inversely associated with risk of death. Each 1 g/dL lower serum albumin was associated with an estimated 54% higher risk of death (RR, 1.54; 95% CI, 1.23 to 1.92; $P < 0.001$). When patients were divided into two groups by serum albumin, patients with a serum albumin <3.5 g/dL had over a twofold greater risk of death compared patients with a normal serum albumin ≥3.5 g/dL (RR, 2.25; 95% CI, 1.41 to 3.58; $P = 0.001$).

After adjustment for age, gender, race, treatment modality, glomerulonephritis as a cause of ESRD, height SDS and weight SDS, serum albumin continued to be a significant predictor for death (Table 2). Comparing two patients who are similar for the above factors with the exception of serum albumin, the patient initiating dialysis with a lower serum albumin by 1 g/dL was estimated to experience a 47% greater risk of death (aRR, 1.47; 95% CI, 1.15 to 1.85; $P = 0.002$). After adjusting for the above

factors, patients with a serum albumin below 3.5 g/dL had an estimated 90% greater risk of death compared to patients with a serum albumin level ≥3.5 g/dL (aRR, 1.90; 95% CI, 1.16 to 3.10; $P = 0.01$). Age-specific interactions with serum albumin were not statistically significant ($P = 0.43$), nor were modality-specific interactions (albumin * HD = referent; albumin * PD, $P = 0.16$; albumin * transplant, $P = 0.88$).

The multivariate analysis demonstrated other significant risk factors associated with pediatric ESRD survival. In addition to albumin, age, ESRD modality, and height SDS continued to be associated with mortality. Compared to the youngest group of patients (0 to 2 years of age) who were at the highest risk for death, older children in both groups 3- to 14-year-olds and 15- to 18-year-olds had an estimated 61% lower risk for death (respectively, aRR, 0.39; 95% CI, 0.21 to 0.75; $P = 0.005$ and aRR, 0.39; 95%CI, 0.19 to 0.80; $P = 0.01$). Transplanted patients had a 68% lower mortality risk compared to the risk for hemodialysis patients (aRR, 0.32; 95% CI, 0.16 to 0.66; $P = 0.002$). There was no significant difference in mortality risk of peritoneal dialysis patients compared to hemodialysis patients. Height SDS was inversely related to mortality risk. For each decrement in height SDS by 1 the adjusted relative risk for death was estimated to be 28% higher (aRR, 1.28; 95% CI, 1.14 to 1.43; $P < 0.001$). After adjustment, weight SDS was not significantly associated with pediatric ESRD mortality. The association between glomerular cause of ESRD and risk of death in the multivariate analysis was not significant.

DISCUSSION

The results of this study demonstrate that hypoalbuminemic pediatric patients who are initiating dialysis have a higher risk of death compared to those starting dialysis with a normal serum albumin. These findings are independent of conditions such as glomerulonephritis in which proteinuria may contribute to hypoalbuminemia, and other potentially confounding factors. Low serum albumin is an important marker for mortality risk in pediatric ESRD patients.

Even though glomerular cause of ESRD was not associated with higher risk of death, we included glomerular associated diseases as an a priori adjustment factor in the multivariate analysis. By adjusting for the glomerular causes of ESRD, we in essence evaluated the association between risk of death and serum albumin among groups of patients with glomerular causes of ESRD and among groups who did not have a glomerular cause of ESRD. Hypothetically, if the increased risk of death was a manifestation of the underlying renal disease and hypoalbuminemia was a marker for this condition, then the adjustment for glomerular causes of ESRD would have accounted for the potential bias and the multivariate analysis would have demonstrated no association between serum albumin and risk of death. However, even after including glomerular cause of ESRD in the multivariate analysis, a low serum albumin was still found to be associated with a higher risk of death.

Our results demonstrate that low serum albumin at initiation of dialysis in the pediatric ESRD population is a marker for poor outcome, independent of other known risk factors for death. Although there are no comparable data among pediatric ESRD patients, our findings are consistent with the preponderance of studies in the adult dialysis population demonstrating that low serum albumin is a risk factor for death [5, 7–9, 11, 21]. The magnitude of the relative risk of death associated with different levels of serum albumin in our study is similar to values reported by Leavey et al [9] and Iseki et al [5], but lower in magnitude compared to the estimated two- to seven-fold higher risk of death for patients with a serum albumin <3.5 g/dL reported by Lowrie and Lew [7, 22]. The differences among the studies regarding the magnitude of the relative risk for death associated with serum albumin may be due to differences in the study design or analytic methods. For example, the variability or imprecision in the determination of serum albumin may attenuate the estimated magnitude of the risk for death associated with low serum albumin in our study [23]. The determination of serum albumin was not performed by one single laboratory for the whole cohort, but by multiple laboratories for patients in this cohort. Furthermore, as an additional source of variation, no single uniform method was used for the measurement of serum albumin. The technique to measure serum albumin was not requested for the HCFA 2728 form and thus the method for serum albumin determination was not available in the data. Recent studies have examined the variation in measurement of serum albumin commonly performed by two different analytic methods: bromocresol green (BCG) and bromocresol purple (BCP) [24, 25]. It has been established that for a given measurement of serum albumin the BCG method will report a higher value compared to BCP. Therefore, a patient with hypoalbuminemia might be misclassified as having a higher serum albumin value if the serum albumin was determined by the BCG analysis. How might such a difference in serum albumin determination affect the results of this study? Assuming that some patients with hypoalbuminemia might have been misclassified to groups with a higher serum albumin, the magnitude of the "true" relative risk for death associated with hypoalbuminemia would be underestimated by the analysis due to this source of variability. Another possible explanation for the differences in the estimate of the relative risk between serum albumin and mortality may lie in the differences between adult and pediatric ESRD populations. Changes in serum albumin may have a greater

magnitude of difference in the associated risk for adults due to co-morbid factors—such as smoking, diabetes, and coronary artery disease—which are not generally present in children. Despite the differences, the above studies demonstrate that low serum albumin is associated with poor outcome in adult and pediatric patients with ESRD.

Consistent with previously published data, we identified other known risk factors for death in the pediatric ESRD population. We demonstrated that the youngest patients initiating dialysis had the highest rate of death, confirming previous observations [26–29]. Recent reports have demonstrated that in the youngest patients undergoing dialysis co-morbid non-renal disease, in particular pulmonary hypoplasia, was a risk factor for death [27, 29]. The findings of our study demonstrates that low serum albumin is also a risk factor for death in this young ESRD population. In our study, age-specific interaction terms with serum albumin were used to test if the association between low serum albumin and poor outcome depended on the age of the patient. This analysis showed no significant differences by age, suggesting that the relationship between a low serum albumin and higher risk of death were no different in young children compared to other age groups. A study using the data from Pediatric Growth and Development Special Study of the USRDS demonstrated that height SDS was inversely associated with risk of death [13]. The analysis in the present study demonstrated that height SDS and serum albumin were independently associated with death. Even though height SDS was included as an adjustment factor in the analysis, low serum albumin remained an independent risk factor for death. This raises the possibility that factors contributing to growth impairment and hypoalbuminemia in this population may act through separate pathophysiologic mechanisms contributing independently to the risk of death.

Serum albumin obtained at initiation of dialysis is a marker for children who are at risk for poor outcome regardless of subsequent renal replacement modality. This single measurement of serum albumin remained strongly associated with risk of death, even after adjustment for renal replacement modality. Furthermore, the modality-specific interaction terms with serum albumin demonstrated no significant differences, suggesting that the magnitude of association between serum albumin at initiation of dialysis and risk of death was similar among pediatric patients treated with peritoneal dialysis, hemodialysis, and renal transplantation. These findings suggest that low serum albumin at the initiation of dialysis is an important indicator of subsequent mortality risk among pediatric ESRD patients.

Given the prognostic value of serum albumin at dialysis initiation, factors that determine hypoalbuminemia during chronic renal failure may have a significant influence on subsequent survival after dialysis initiation. Hypoalbuminemia may be influenced by multiple factors during chronic renal insufficiency. Pediatric patients with chronic renal insufficiency are at risk for malnutrition and poor growth [3, 30–32]. Malnutrition in this cohort might be indicated by hypoalbuminemia. The uremic milieu of chronic renal insufficiency is characterized by several factors leading to protein-energy malnutrition and hypoalbuminemia including anorexia, acidosis, and alterations in metabolism secondary to hormonal derangements [33–37]. Furthermore, hypoalbuminemia may reflect other co-morbid conditions associated with either decreased synthesis of serum albumin due to inflammation, infection, or liver disease; or increased losses secondary to persistent proteinuria [38].

Although this study demonstrates a strong association between hypoalbuminemia and poor outcome, the pathophysiologic mechanism between the two remain unclear. A number of investigators have suggested that pro-inflammatory cytokines play a key role in both mediating hypoalbuminemia and increasing atherogenic processes that may increase the risk of cardiovascular-specific events [12, 39–42]. Other mechanisms that have been proposed include generalized immunologic dysfunction and chronic inflammation, decreased bioactivity of insulin-like growth factor-1, and altered drug kinetics [13, 33, 43–47]. Additional studies are warranted to define the causal pathway contributing to mortality in pediatric ESRD patients with hypoalbuminemia.

We acknowledge the marked differences in the natural history of disease between dialysis and transplant modalities. However, excluding transplant recipients would have limited the generalizability of our results. In addition, censoring subjects at the time of transplant from our analysis would have biased our results [18, 19, 48]. Healthier dialysis patients are more likely to have a normal serum albumin and may be preferentially selected for transplantation. If these patients were censored at the time of transplantation, they would no longer accumulate time at risk and therefore fewer deaths would be observed among patients with higher albumin. Therefore, dialysis patients who were subsequently transplanted after the start of the study were not censored, but remained in the study.

To account for the possibility of bias due to subsequent transplantation, it was necessary to adjust for renal replacement modality. We were able to adjust for the inherent differences between dialysis and transplantation by using time-dependent covariates [16, 17, 20]. Time-dependent covariates allow patients to contribute time at risk for death for a given modality as they changed from one form of renal replacement therapy to another, more precisely modeling the risk for death associated with each modality.

Given that this is an observational study, there may

be unmeasured factors that could introduce bias into the analysis. Furthermore, a selection bias may have been introduced since only patients who had a documented serum albumin were included in the analysis. Eleven percent of the patients in the original cohort were missing values for serum albumin and thus were excluded from the analysis. Those who were missing serum albumin were more likely to be of older age, between 15 and 18 years. Therefore, the findings of the analysis may be more generalizable to a younger population of patients initiating dialysis. Furthermore, pediatric-specific co-morbid conditions are not reported to the USRDS on the HCFA 2728 Medical Evidence Form and thus were not available for this study. Lastly, only the serum albumin at dialysis initiation was available in the data, hence it was not possible to determine if subsequent changes in serum albumin was associated with survival. Although there were no data on subsequent serum albumin, the serum albumin at the index course of dialysis provides clinicians relevant information regarding risk of death with data from an easily identifiable time point.

Despite the limitations of this study, our results show that hypoalbuminemia at the initiation of dialysis is a strong marker of poor survival among pediatric patients with ESRD. Furthermore, as a population-based study, the results are not a reflection of dialysis unit specific practices and thus can be generalized to the US pediatric ESRD population.

At dialysis initiation in the US pediatric population, hypoalbuminemic patients are at higher risk for death compared to patients initiating dialysis with a normal serum albumin. Even after adjusting for glomerular causes leading to ESRD, demographic factors, and ESRD treatment modality, serum albumin continued to be associated with risk of death in this population. Further studies are warranted to determine if efforts to prevent or ameliorate hypoalbuminemia at dialysis initiation may improve survival in pediatric patients with ESRD.

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