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ORIGINAL ARTICLE

Association of Hypoalbuminemia with Risk of Death in Pediatric Patients with End Stage Renal Disease undergoing Hemodialysis: A Tertiary Care Experience in Pakistan

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ABSTRACT

Background: One of the most important and common feature of chronic kidney disease is Hypoalbuminemia and is considered a poor prognostic factor. Low levels of Serum albumin are a predictor of growth failure and are strongly associated with increase death rate in pediatric patients undergoing hemodialysis with End Stage Renal Disease (ESRD), especially a challenge in underdeveloped countries.

Aim: To evaluate the association of serum albumin level with hospitalization and rate of death in ESRD hemodialyzed pediatric patients.

Study Design: Cohort study

Place and Duration of Study: Department of Pediatric Nephrology, University of Child Health Sciences, Lahore from 1st January 2018 to 31st January 2022

Methodology: Ninety two children on hemodialysis and aged 5-16 years were included. Data including patient demographics, anthropometry, date of dialysis initiation, diagnosis, systolic and diastolic blood pressure, dialysis access (HD line/AV fistula), laboratory parameters, compliance to dialysis prescription, and frequency of hospitalization and combined duration of hospital stay was recorded.

Results: The mean age at dialysis was 10.6±2.7 years with male to female ratio of 1.3:1. The mean duration on dialysis was 2.03±0.9 years. In our study, CAKUT (42.4%) was the most commonly occurring underlying etiology of end stage renal disease, followed by cystic renal disease (27.2%) and glomerular disease (15.2%) respectively. Regarding the systolic hypertension 22.9% were hypertensive and 35.8% were pre-hypertensive (BP 90th to 95th percentile). For diastolic hypertension, 18.5% were hypertensive and 42.4%were noted as pre-hypertensive. Majority of patients (87%) had hypoalbuminemia (serum albumin < 3.5 gm/dl) at dialysis initiation. In our study the value of serum albumin has inverse relationship with \risk of mortality in ESRD hemodialyzed patients even after adjustment to other factors. There is a 70% higher risk of death with each 1gm/dl decline in serum albumin value (hazard ratio=0.300(0.122-0.740) P<0.009). In addition, AVF access group has a significantly lower risk of death compared to the catheter group (hazard ratio=0.444 (0.246-0.801), P = 0.007). On generation of ROC curves, AUC obtained for serum albumin was statistically significant (AUC=0.838, 95% CI 0.758–0.918). In our study, no correlation was found between hypoalbuminemia and annual frequency of hospitalization (P<0.812) and total duration of stay (P<0.997).For mortality prediction, our study demonstrated a cut off value of albumin of 3g/dl with sensitivity of 80% and specificity of 68.7%.

Conclusion: The independent prognostic value of serum albumin in mortality prediction at a cut off value of 3g/dl. In the final model even after adjustment of other covariates, hypoalbuminemia at dialysis initiation and type of vascular access continued to be vital indicator of risk of death in pediatric ESRD patients. However, no statistically significant association was observed between hypoalbuminemia and hospitalization in dialysis patients.

Keywords: ESRD, Hypoalbuminemia, Growth failure, Haemodialysis

INTRODUCTION

Hypoalbuminemia is an important feature of chronic kidney disease[1] and is associated with adverse outcome.[2] Serum albumin is a marker of poor nutritional status, frequency of hospitallization and death rate in pediatric patients with end stage renal disease (ESRD) undergoing hemodialysis.[3]

Malnutrition is one of common cause of poor growth leading to stunted stature and poor weight gain among CKD children, which is associated with frequent hospitalization and death. Improvement of nutritional status in children on hemodialysis with ESRD can help in growth stimulation and decrease risk of intercurrent illnesses and mortality. In CKD Patients serum albumin is an important biomarker of Protein Energy Malnutrition (PEM) and inflammation in CKD.[4] As CKD is a catabolic state so these children are at increased risk of chronic inflammation and poor nutritional status. The risk of death is 20 times higher in CKD patients on dialysis, having serum albumin level <2.5g/dl as compared to value within normal range (3.5 -4.5g/dl).[5]

Data taken from adult CKD also suggest that malnourishment is a strong indicator of morbidity and mortality.[6] Therefore K/DOQI Nutritional Guidelines recommend inclusion of serum albumin level as part of nutritional status assessment in chronic dialysis patients on routine basis.[7]

In an underdeveloped country like Pakistan, where repeated admissions and prolonged hospitalization place significant financial burden on already resource stricken health system. It is of utmost importance to identify correctable hospitalization risk factors that might reduce patient morbidity and mortality. Serum albumin is one such parameter with independent prognostic value used to identify high risk patients.[8] It is also easily available and cost-effective assay, especially suitable for low income setting. However, few studies have been done in children with ESRD on chronic hemodialysis focusing the relationship of hypoalbuminemia with frequent hospitalization and high mortality.[9,10] Identifying hypoalbuminemia and its causal pathways might lead to better clinical outcomes. The purpose of our study is to evaluate the association of serum albumin level with hospitalization and death rate.

MATERIALS AND METHODS

This cohort study was conducted at Department of Pediatric Nephrology, University of Child Health Sciences Lahore from 1st January 2018 to 31st January 2022. It is the largest tertiary care Centre for pediatric patients in Pakistan. Ninety two children on hemodialysis and aged 5-16 years were included. Patients who have elevated CRP, incomplete medical record and shifted to other hospital or kidney transplantation were excluded. Patients were followed in the study until they were expired from any cause, or lost follow-up or completion of the study. Data collection was approved by the Institutional Review Board of University of Child Health Sciences, Lahore. Baseline samples were collected and measured prior to dialysis initiation included hemoglobin (Hb),

albumin and serum creatinine. The blood samples were analyzed by auto-analyzer and commercial kits. Determination of serum albumin level was done by using bromocresol green method with normal reference range was 3.5–5 g/dL in hospital. CDC growth charts were used to calculate age-sex-specific height and weight standard deviation scores (SDS). Data was collected using a specially designed proforma containing patient demographics, anthropometry, date of dialysis initiation, diagnosis, systolic and diastolic blood pressure pre and post dialysis, dialysis access (hemodialysis catheter/AV fistula), laboratory parameters, compliance to dialysis prescription, frequency of hospitalization and combined duration of hospital stay and outcome.

Patients were followed in the study until they lost follow-up or had death from any cause, or completion of the study. The Cox proportional hazards mode was used to estimate the risk of death, adjusting for gender, age, height, treatment modality, systolic and diastolic blood pressure, dialysis access(Hd line/AV fistula), laboratory parameters, compliance to dialysis prescription and serum albumin. For estimation of the adjusted and unadjusted relative risk of death analysis was done to obtain Hazard ratios. In the final model other covariates were adjusted and the interpretation of the adjusted relative risks (aRR) was done to detect possible prognostic variables associated with survival. P value was set to 0.05. As frequency of hospitalization and total days of hospital stay had greater variability than expected, hence negative binomial regression model was applied to evaluate the correlation with serum albumin levels.. The receiver operating characteristics (ROC) curve was calculated by analysis of the area under the curve (AUC) which was implemented to determine the optimal cut offs of hypoalbuminemia to predict the mortality of CKD patients. The data was entered and analyzed through SPSS-24.

RESULTS

Thirty patients (34.8%) were alive at the end of study. There were 40 females and 52 males, with a mortality rate equally distributed. The mean age at dialysis initiation was 10.6±2.7 yrs and mean duration on dialysis was 2.03±0.9 years. CAKUT (42.4%) was the foremost underlying etiology of end stage renal disease, followed by cystic renal disease (27.2%) and glomerular disease (15.2%). Nephronophthisis (NPHP) constituted the main bulk (80%) of cystic/hereditary pathology group. Overall mortality at the end of study was 65.2% with the highest mortality observed in congenital renal hypoplasia/aplasia patients (88.8%) followed by glomerular causes (85.7%). In our study, the baseline value of serum albumin was 3.04±0.4g/dL (Table 1)

Unadjusted and adjusted estimates for relative risk of death associated with the covariates of interest are presented in Table 2.There is no correlation between risk of death and age or gender. Patients who had vascular access through AV fistula had 56%lower risk of death compared with those with dialysis catheter. Patients who had glomerular cause of ESRD have a higher risk of mortality as compared to non- glomerular cause (RR,0.791; 95% CI (0.420-1.491); P=0.469). Assessment of anthropometric measures revealed an inverse correlation between height and weight SDS and risk of death, however, the association was not statistically significant in final adjusted model. Majority of patients had elevated systolic (58.7%) and diastolic blood pressure (60.9%). Majority of patients (87%) were hypoalbuminemia (serum albumin <3.5 gm/dl) at dialysis initiation. After adjustment to other factors, the value of serum albumin has inverse correlation with risk of death. 70% higher risk of death [0.300 (0.122-0.740) P<0.009] with each 1 g/dL decline in serum albumin value. There are no other substential risk factors related to pediatric ESRD survival demonstrated by the multivariate analysis. The annual hospitalization rate and cumulative hospital stay were 2.11±1.0 per year and 6.30±5.0 days per patient-year, respectively. Using negative binomial regression model, statistically no significant association in relation to baseline serum albumin (Table 3). On generation of ROC curves, AUC obtained for serum albumin was statistically significant. Hence demonstrates to be a good prognosticator of mortality (AUC=0.775, 95% CI 0.68–0.87 (Fig. 1)

Table 1: Etiology of end stage renal disease

Diagnosis	Alive	Death	Total
Cystic/hereditary diseases	8	15	25 (27.2%)
CAKUT 39 (42.4%)			
Cong. renal hypoplasia	1	8	9 (9.8%)
VUR	6	5	11 (11.9%)
Obstructive uropathy	7	12	19 (20.6%)
Inherited and acquired stone disease	7	4	11 (11.9%)
Glomerular disease	2	12	14 (15.2%)
Unknown	1	2	3(3.3%)
Total	32	60	92

Table 2: Cox regression analysis: unadjusted and adjusted estimates for relative risk of death

Covariates		Alive	Death	Unadjusted		Adjusted	
				Relative risk (95% CI)	P value	Relative risk (95% CI)	P value
Age	≤8 years	11	11	1	0.736	1.639(0.777-3.460)	0.194
	>8 years	21	49	1.123 (0.573-2.202)			
Gender	Male	19	33	1	0.882	0.840(0.438-1.612)	0.600
	Female	13	27	0.962(0.577-1.604)			
Diagnosis	Glomerular	2	12	1	0.469	1.576(0.758-3.277)	0.224
	Non-glomerular	30	48	0.791(0.420-1.491)			
Access	Hd line	12	21	1	0.014	0.444(0.246-0.801)	0.007
	AV fistula	30	39	0.505(0.292-0.873)			
Compliance to treatment	Compliant	28	40	1	0.115	0.874(0.480-1.593)	0.661
	Non-compliant	4	20	1.508(0.904-2.514)			
Systolic blood pressure	<90th centile	13	24	1	0.463	1	0.236
	90th-95th centile	9	24	1.133(0.640-2.003)	0.668	1.134(0.268-4.793)	0.864
	>95th centile	10	12	0.729(0.363-1.463)	0.374	0.355(0.046-2.765)	0.323
Diastolic blood pressure	90th centile	12	24	1	0.470	1	0.743
	90th-95th centile	12	27	1.033(0.588-1778)	0.936	1.366(0.326-5.734)	0.670
	>95th centile	8	9	0.648(0.300-1.403)	0.271	2.309(0.263-20.250)	0.450
Height (SDS)	Less than -3	8	34	1	0.030	1	0.095
	-3 to -1	14	19	0.638(0.363-1.119)	0.117	0.621(0.322-1.196)	0.154
	Greater than -1	10	7	0.360(0.159-0.814)	0.014	0.401(0.164-0.982)	0.046
Weight (SDS)	Less than -2	5	24	1	0.067	1	0.230
	-2 to 1	14	21	0.625(0.346-1.128)	0.118	60(0.339-1.288)	0.223
	Greater than 1	13	13	0.475(0.246-0.914)	0.026	0.548(0.264-1.139)	0.107
Hemoglobin (mg/dl)	8.52±1.5			0.957(0.810-1.129)	0.600	1.068(0.880-1.296)	0.507
S. creatinine (mg/dl)	6.46±3.1			1.023(0.954-1.098)	0.519	1.035(0.936-1.144)	0.506
Serum albumin	2.967±0.4			0.365(0.200-0.667)	0.001	0.300(0.122-0.740)	0.009

Table 3: Correlation with serum albumin (p value) with hospitalization rates using negative binomial regression model means p value

Hospitalization (number of days)	6.30±5.0	0.997
Number of admissions/year	2.11±1.0	0.812

Table 4: ROC analysis of serum albumin related to all-cause mortality

Area under the curve	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower bound	Upper bound
0.838	0.041	.000	0.758	0.918

Albumin cut off value	sensitivity	Specificity
3.05g/dl	80%	68.7%

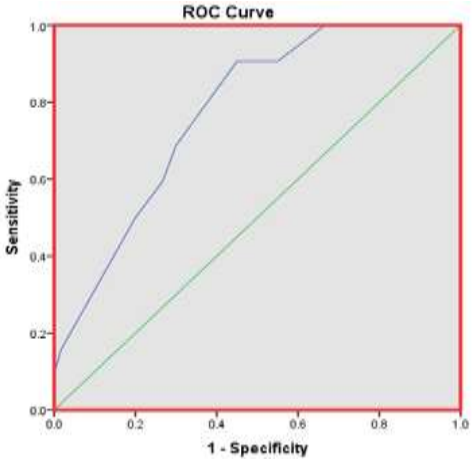

Fig. 1: Diagonal segments are produced by ties

On generation of ROC curves, AUC obtained for serum albumin was statistically significant. Hence, demonstrates to be a good prognosticator of mortality (AUC = 0.775, 95% CI 0.68–0.87)

DISCUSSION

In the present study, 10.6±2.7 years were the mean age at dialysis initiation; with male: female ratio of 1.3:1. This gender distribution is similar to another study done in Pakistan at another tertiary care centre by Shah et al[11] reported mean age was 8.71±3.96 years. According to their study, small size kidneys were present in 46.5% patients with majority reporting polyuria (53.5%). This is consistent with our study as Nephronophthisis (34.5% in our study) presents with small sized kidneys, polyuria and nocturia. High prevalence of NPHP is explained by high consanguinity rate in our country. Hari et al[12] reported CKD etiologies according to age in a tertiary centre in India. According to them, younger age group (0-5) presented mainly with obstructive etiology, while older age group had chronic glomerulonephritis. Among the obstructive causes, posterior urethral valve were in 45 (46.4%), pelviureteric junction obstruction or hydronephrosis in 41 cases respectively. However, all these etiologies come under the domain of CAKUT. In a 10 year cohort study conducted in Karachi[13], CAKUT was the most reported etiology (49% cases).

Patients with systolic hypertension, 22.9% were hypertensive and 35.8% were prehypertensive (BP 90th to 95th percentile) and for diastolic hypertension, 18.5% were hypertensive and 42.4%% were prehypertensive respectively. Flynn et al[14] studied the prevalence of hypertension in pediatric CKD patients. He reported hypertension in 14% patients (both systolic and diastolic), which seems to be an underestimation compared to other studies. However, as pediatric hypertension is labile, so this research was limited to its small sample size due to cross-sectional design.

This study shows that there is a higher risk of death of patients with hypoalbuminemia at initiatind dialysis (AUC for albumin=0.838).This is consistent with literature involving adult and pediatric CKD patients. Wong and colleagues[15] studied relationship of albumin with risk of death in ESRD patients in a multivariate analysis involving 1700 patients. They demonstrated a 54% higher risk of death with decrease of each 1g albumin in CKD patients. In this study, we observed that each 1 g/dL lower serum albumin was associated with 70% higher risk of death (hazard ratio=0.300(0.122-0.740) P<0.009). Compared to Huang et al. who found higher risk for 1-year mortality when blood albumin levels were below 3.4 g/dL, our study demonstrated a cut off of 3g/dl with sensitivity of 80% and specificity of 68.7%. The lower albumin value can be partly explained by the fact that LMICs have widespread malnutrition.

On the contrary, in a recent study done by Alves et al[16], they argued that even though death risk rate was higher in stage 5 chronic kidney disease patients with hypoalbuminemia and high CRP, as compared to patients with low albumin and normal CRP. Their study findings suggest that inflammatory status should be considered when using S-albumin for risk assessment in CKD patients. Similar studies[17,18] show that low Serum albumin rather depicts a state of chronic inflammation with limited value as a indicator of nutritional status. However, these results cannot be generalized as these studies have been done in resource rich countries, where primary malnutrition is a thing of the past.

In a retrospective cohort study of children 1–17 years old with end-stage renal disease receiving therapy in a large US dialysis organization, Okuda et al[8] studied the association of serum albumin value with frequency and total stay of hospitalization using negative binomial regression. They reported U-shaped association as both high (>4.5g) and low (<3g) serum albumin were associated with hospitalization in incident dialysis patients. Similarly in an adult study done in Karachi, Pakistan, hypoalbuminemia along with anemia, cardiovascular disease and high TLC were observed as important risk factors for hospitalization in CKD patients. However, in our study, no correlation was found between hypoalbuminemia and frequency and duration of hospitalization. This can be explained as in developing countries, most common reasons[19] for hospitalization include pulmonary edema (19.1%), and catheter related infection (17%), and hypertensive urgency and emergency (14%). These complications are related to compliance to dialysis regimen and CKD medication, alongwith prolonged usage of temporary HD line access compared to perm catheters and AV fistulas. Due to poor resources and lack of dialysis centres, patient often need to travel long distances for dialysis, hence decreasing compliance. Our study model demonstrated association between low compliance group and all-cause mortality however, it did not reach standard statistical significance [hazard ratio=1.508 (0.904-2.514)], p value 0.115). Overall mortality was significantly lower among AV access group compared to the catheter group, even after adjusting for other covariates. [hazard ratio=0.444 (0.246-0.801), P = 0.007]. Vascular access type could have a confounding effect, however, even on adjusting data on the basis of vascular access and compliance, hypoalbuminemia continued to be associated with increased mortality (p<0.008). This shows the independent prognostic value of hypoalbuminemia on mortality.

CONCLUSION

Mortality rate of pediatric CKD patients in Pakistan continues to be high in the face of widespread malnutrition and scarcity of resources. Our observation suggests that both hypoalbuminemia at dialysis initiation and type of vascular access for dialysis appear to be the major determinants of survival among ESRD patients. In Pakistan, majority of pediatric ESRD patients are catered by the Government and donor-based institutions. The ever-increasing healthcare cost of the dialysis has become a major hurdle for the Government based institutions to accommodate the burden of ESRD patients. Because frequent and prolonged hospitalization has a substantial impact on health cost, identifying patients who

require nutritional rehabilitation early in the course of disease could modify disease progression among this population.

Limitations of Study: Relatively small sample size and research done in a single hospital setting limit our research's ability to generalize the results. Also, to reduce bias, sampling criteria should include only those patients who are compliant to dialysis regimen. Though our study demonstrated independent prognostic value of albumin in mortality predication, yet an important confounding variable in the form of inflammatory marker like CRP was excluded from the study. More studies need to be performed in LMICs to study the impact of albumin on survival of ESRD patients

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