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Hemoglobin level and risk of hospitalization and mortality in children on peritoneal dialysis

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Abstract

Background—Clinical practice guidelines for management of anemia in children with end-stage kidney disease (ESKD) remain largely opinion-based. In this study, we evaluated the risk of mortality and hospitalization by hemoglobin (Hb) level in a large prevalent population of U.S. children on peritoneal dialysis (PD).

Methods—Hemoglobin levels in prevalent PD patients from the 2005 End Stage Renal Disease Clinical Performance Measures Project were linked with 5-year mortality and 4-year hospitalization records from the United States Renal Data System.

Results—Of the 468 patients included in the study, the mean age was 11 years, 55 % were male, 67 % were white, 254 (54%) were hospitalized, and 23 (5%) died. Median (interquartile range) Hb levels were 11.7 (10.7–12.6) g/dl, and 30% had Hb levels of <11 g/dl. In adjusted survival analysis, Hb thresholds of 10, 11, or 12 g/dl were not associated with a significant difference in risk of death. The incidence rate ratio (IRR) of hospitalization for patients with a mean Hb of ≥11 g/dl was 0.56 (95 % CI 0.43–0.73). Compared to a reference range of Hb of 11 to <12, Hb of ≥12 g/dl was not associated with a significant difference in hospitalization risk (IRR 0.88; 95 % CI 0.61–1.25). Using age- and sex specific cut-offs for anemia, children who were not anemic had a 27% decreased risk of hospitalization compared to those with anemia (IRR 0.73; 95 % CI 0.55–0.97). Compared to the first erythropoiesis stimulating agent (ESA) dosing quartile, higher ESA doses were associated with an increased risk of both hospitalization and mortality.

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Conclusions—U.S. children on PD with Hb levels of ≥11 g/dl were less likely to be hospitalized but had no observed difference in mortality. Children who were not anemic were also less likely to be hospitalized. Further study is necessary to elucidate whether a single optimal Hb level or a range applies to the pediatric ESKD population.

Keywords

Pediatric; End-stage kidney disease; Anemia; Peritoneal dialysis; Outcomes

Introduction

A low hemoglobin (Hb) level is a common comorbidity in children with end-stage kidney disease (ESKD) and has been associated with various adverse outcomes, including increased mortality, decreased health-related quality of life (HRQOL), and the development and progression of left ventricular hypertrophy [1–6]. Thus, anemia management is a major focus in the care of patients on dialysis. National and international clinical practice guidelines from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) recommend an Hb target of 11–12 g/dl for children on dialysis, and the European Pediatric Peritoneal Dialysis Working Group guidelines recommend a target Hb of at least 11 g/dl, with no upper limit specified. However, evidence to support these recommendations is sparse and largely based on studies of adult hemodialysis (HD) patients [7–9]. Adult HD patients have significantly different underlying etiologies of ESKD and comorbidities in comparison to children on peritoneal dialysis (PD), and all children have greater requirements for physical activity, linear growth, and cognitive development than adults; thus extrapolating anemia management guidelines from the adult population to the pediatric population may not be appropriate. Furthermore, defining an appropriate Hb target for children with chronic kidney disease (CKD) may be complicated by the fact that normal Hb levels, and definitions of anemia, vary in children by sex and age [10, 11].

Only a few large population-based studies have examined outcomes associated with Hb levels in children on dialysis. An observational study of U.S. adolescents on HD aged 12–18 years by Amaral et al. showed an increased risk of mortality associated with an Hb level of <11 g/dl, consistent with results from published adult studies [12]. Similarly, a recent study of 1,394 children on PD aged 0–20 years enrolled in the International Pediatric Peritoneal Dialysis Network (IPPN) also showed an increased risk of mortality associated with an Hb level of <11 g/dl [13]. Neither study found an association between Hb level and rate of hospitalization.

In an effort to monitor and improve the quality of care delivered to patients with ESKD in the USA, the United States Renal Data System (USRDS) and End Stage Renal Disease Clinical Performance Measures Project databases routinely collect clinical data, including records of hospitalizations and mortality on all children receiving dialysis in the USA. Using these databases, we examined the association between various Hb levels/anemia status and rate of hospitalization/ mortality in a national cohort of children on PD to provide further evidence to inform best practices in anemia management in children with ESKD.

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Methods

The Center for Medicare and Medicaid Services' 2005 ESRD Clinical Performance Measures (CPM) Project collected demographic and clinical measures on all prevalent PD patients in the USA who were aged 0–18 years between October 2004 and March 2005. In our retrospective cohort study, data from children on PD included in the CPM project were linked with 4-year hospitalization records (October 2004–December 2008) and 5-year mortality records (October 2004–September 2009) in the USRDS by USRDS identification numbers common to each patient in both datasets.

The ESRD CPM Project includes yearly demographic and clinical data that may inform the quality of dialysis care, including anemia management, serum albumin, and dialysis adequacy. To examine anemia management, CPM recorded up to three separate Hb measurements for each PD patient during the period of October 2004 through March 2005 for the 2005 CPM project year. If a patient was censored during the data collection period, only Hb measurements obtained prior to censorship were used. Available levels were averaged, and mean Hb levels were categorized in several different ways: (1) thresholds of ≥10 (vs. <10) g/dl, ≥11 (vs. <11) g/dl, or ≥12 (vs. <12) g/dl; (2) categories of <10, 10 to <11, 11 to <12, and ≥12 g/dl; (3) anemic versus non-anemic, based on age- and sex-specific definitions [10, 11].

Certain clinical data derived from the 2005 CPM Project were categorized as follows: race (white vs. other), ESKD cause (congenital/urologic vs. other), time since most recent PD initiation (≥180 vs. <180 days), calculated total weekly Kt/V urea (≥1.8 vs. <1.8), mean serum albumin (≥3.5/3.2 vs. <3.5/3.2 g/dl, as measured by the bromcresol green/ bromcresol purple laboratory methods, respectively), mean serum ferritin (≥800 vs. <800 ng/ml), iron use (yes/no), and eythropoiesis-stimulating agent (ESA; epoetin alfa or darbepoetin) dose quartiles. Total weekly Kt/V urea values were calculated from the raw data provided using anthropometric total body water prediction equations established by Morgenstern et al. [14] The cutoffs for dialysis vintage, ferritin, albumin, and Kt/V were chosen from previous studies of dialysis patients having demonstrated differential survival or anemia prevalence based on these levels [15–21]. Differences in clinical and demographic data of patients with an Hb level of ≥11 versus <11 g/dl were determined by the *t*-test for continuous data and chi-squared test of proportions for categorical data.

Risk for hospitalization or death was analyzed with the described Hb thresholds and categories. Of 326 patients who had a mean Hb level of >11 g/dl, 109 (33 %) were defined as being anemic, and thus mortality and hospitalization risk were also analyzed comparing those who were anemic versus those not anemic and in association with increasing Hb standard deviation score (SDS), calculated using age and sex referent means.

Hospitalization risk was examined by looking at the number of hospital admissions per time at risk using Poisson regression modeling, with adjustment for covariates of interest. All models were tested for goodness of fit, and overdispersed data that fit poorly in Poisson models were analyzed with generalized linear modeling with the Poisson function. Mortality risk was examined using adjusted survival analysis with Cox regression. Proportional

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hazards assumption was confirmed by performing the test of proportionality on Schoenfeld residuals. The start date for time at risk for both mortality and hospitalization analysis was entry date into the ESRD CPM cohort (October 1, 2004). The date of last reported death (September 2009) and of last reported hospitalization (December 2008) were used as endpoints for mortality and hospitalization analyses, respectively. Patients were followed to the end of the follow-up period, loss of follow-up, or death, or were censored at transplantation or switch to HD.

Sensitivity analyses were performed: (1) excluding patients who were transplanted during the study period; (2) excluding patients who switched to HD; and (3) excluding the Kt/V covariate, allowing for the inclusion of more subjects in the final adjusted analysis. $P<0.05$ was considered to be statistically significant for all analyses. All management and analysis of data were completed using Stata 11.0 software (StataCorp, College Station, TX).

Results

Patient characteristics

A total of 761 pediatric patients whose data had been submitted to the 2005 ESRD CPM Project were identified as receiving PD in the USA, of whom 468 had complete data available for inclusion in final adjusted analysis. The majority of patients excluded were those who were missing the data required to calculate Kt/V urea (Fig. 1). Patients included in the final adjusted analysis had a mean age of 11.1 ±5.4 (SD) years, 55 % were male, 67 % were white, 36 % had a congenital or urologic disease as underlying cause of ESKD, and 40 % were on PD for <180 days. The mean Hb level was 11.7±1.4 g/dl. Fifty-three percent of the children were anemic based on age- and sex-specific definitions. Three unique Hb values were available for 90% of patients. The intra-patient coefficient of variability for Hb was 0.10±0.07. With regards to the prescribed route of iron administration, 79% ofpatients were prescribed oral iron supplementation, 4% received intravenous iron supplementation, 3 % had both oral and intravenous iron supplementation, and 14% were missing data. All patients received an ESA, with 9% prescribed darbepoetin and 91% epoetin alfa.

The clinical characteristics of the entire cohort stratified by Hb category are shown in Table 1. PD patients of white race or Hispanic ethnicity were more likely to have an Hb level of ≥11 g/dl, as were those with higher serum albumin levels and those receiving lower mean ESA doses.

During the follow-up period, 254 (54 %) of patients were hospitalized one or more times, with a total of 889 hospitalizations for the entire cohort. Twenty-three deaths occurred among the 468 patients, and 338 patients (72%) were transplanted during the 4-year follow-up period, with 287/338 being censored at transplant and 51/338 censored at switch to HD prior to transplantation. The switch to HD led to censoring in 106/468 patients (23 %). Given censoring, the mean follow-up time was 1.8±1.2 years for the hospitalization analyses and 1.9±1.4 years for the mortality analyses.

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Unadjusted analysis

Hospital admission and mortality rates are provided in Table 2. Lower Hb categories (<11 g/dl) were associated with more deaths and hospitalizations per 100 patient-years. The unadjusted hospitalization incidence rate ratio (IRR) for an Hb level of <10 versus 11 to <12 g/dl was 1.74 (95 % CI 1.16–2.61), and for an Hb level of 10 to <11 versus 11 to <12 g/dl, the IRR was 1.78 (95 % CI 1.24–2.58). The hospitalization IRR for an Hb level of ≥12 versus 11–12 g/dl was not significant (0.89; 95 % CI 0.62–1.26). Unadjusted risks of death for patients across the Hb subcategories were not significant. An Hb level of ≥11 (vs. <11) g/dl was associated with a 47 % lower rate of hospitalizations (IRR 0.53; 95 % CI 0.41–0.68) and a 57 % lower risk of death [hazard ratio (HR) 0.43; 95 % CI 0.19–0.99; data not shown in Table 2).

Multivariate analysis

Table 3 shows the hospitalization and mortality risk by various Hb thresholds. The hospitalization IRR for patients with a mean Hb level of ≥11 versus <11 g/dl was 0.56 (95% CI 0.43–0.73). Children who were not anemic had a 27% lower rate of hospitalization per time at risk (IRR 0.73; 95% CI 0.55–0.97). Each +1 increase in Hb SDS corresponded with a 14% lower hospitalization risk (IRR 0.86; 95% CI 0.79–0.93) (data not shown in Table 3). No Hb threshold was associated with risk for mortality.

Table 4 shows hospitalization and mortality risk among smaller Hb subcategories, with an Hb reference category of 11 to <12 g/dl. An Hb level of 10 to <11 g/dl was associated with an increased hospitalization rate (IRR 1.76; 95% CI 1.22–2.56), and an Hb level of ≥12 g/dl was not associated with a significant difference in hospitalization risk. Risk of mortality among the Hb subcategories, with Hb 11 to <12 g/dl as referent, was not significant.

In our multivariable analysis, adjusting for Hb level, the third and fourth ESA dosing quartiles were associated with significant increases in the risk of both hospitalization and death. With the first quartile as referent, the third and fourth dosing quartiles were associated with a 68 and 58 % increased risk of hospitalization, respectively (IRR 1.68; 95 % CI 1.16–2.42, and IRR 1.58; 95% CI 1.09–2.3, respectively). The HR for mortality was 6.3 (95% CI 1.23–32.44) for the third quartile and 5.9 (95 % CI 1.12–30.58) for the fourth quartile.

Additional analyses

Associations of Hb thresholds with risk of hospitalization did not significantly change in any of our sensitivity analyses: (1) excluding patients who were censored at transplant, perhaps representing a healthier subset of patients; (2) excluding those who switched to HD; (3) excluding the Kt/V variable, which allowed for a significant increase in the sample size.

Discussion

To help inform best clinical practices in anemia management in children on dialysis, we assessed whether achieving specific Hb targets, including the current KDOQI and KDIGO target of 11–12 g/dl, was associated with decreased mortality and hospitalization in children on PD in the USA. This retrospective cohort study showed that achieving a mean Hb of ≥11

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(vs. <11) g/dl was associated with a 44 % lower hospitalization rate and that achieving a mean Hb level of ≥12 (vs. <12) g/dl was associated with a 35 % lower rate. When Hb level was further subcategorized, a mean Hb of 10 to <11 g/dl compared to that of 11 to <12 g/dl was associated with a higher hospitalization risk, suggesting that Hb levels of <11 g/dl may not be appropriate for children on PD. Hb levels ≥12 g/dl versus those of 11 to <12 g/dl were not associated with a significant difference in risk of hospitalization. Patients with a mean Hb greater than the 5th percentile for age and sex had a 27% lower risk of hospitalization compared to their anemic counterparts. None of the Hb thresholds or subcategories examined in this study was associated with a significant difference in mortality risk.

Studies in adults on HD have consistently demonstrated reduced risk of death and hospitalization when Hb levels are ≥11 g/dl, with conflicting evidence of risk and benefit of Hb levels of ≥12 g/dl [22–24]. In comparison, there is a relative paucity of data in adults on PD. Li et al. studied the outcomes of incident adult PD patients between 1991 and 1998 and found an increased risk of both hospitalization and mortality when the Hb level was <11 g/dl, as well as no significant benefit or risk for an Hb of ≥12 g/dl [25]. Evidence supporting a pediatric Hb target in children maintained on dialysis is limited. Staples et al. found that pediatric CKD patients (pre-dialysis) with anemia (hematocrit <33 %) had a significantly increased risk for hospitalization during the first year of follow-up when compared with non-anemic CKD patients [odds ratio 1.55; 95 % confidence interval (CI) 1.23–1.94]. Hematocrit levels above either 36 or 39 % were not associated with increased risk of hospitalization in this study of pre-ESKD children [26]. Warady and Ho demonstrated an association between a hematocrit of <33 % 30 days after initiation of dialysis and increased risk for prolonged hospitalization and death of pediatric patients, irrespective of dialysis modality [4]. In a study of prevalent adolescent HD patients, Amaral et al. showed that an Hb level of ≥11 g/dl was associated with decreased mortality, with a similar mortality risk for an Hb of 11 to ≤12 g/dl and >12 g/dl. These authors found no statistically significant difference in the risk of hospitalization by Hb levels [12]. More recently, a study by the IPPN evaluated the relationship between Hb level and hospitalization and death in a prospective cohort of international pediatric PD patients enrolled in a voluntary registry. The findings of this study revealed an association between an Hb level of <11 g/dl and death [13]. The risk of patient death on PD was inversely associated with Hb level (HR 0.23; $P<0.003$) and serum albumin levels (HR per g/L 0.87; $P<0.0001$) and was positively associated with the use of high ESA doses (HR per 1,000 IU/m^2 per week 1.33; $P<0.01$). No relationship between Hb level and hospitalization was found.

While the data from our study and from that by Borzych-Duzalka et al. [13] may be difficult to compare directly given the different study designs and follow-up periods, both datasets demonstrate an decreased risk of adverse outcomes with an Hb level of ≥11 g/dl. Borzych-Duzalka et al. revealed a decrease in mortality associated with a mean achieved Hb level of ≥11 g/dl [13]. In comparison, while our analysis suggested a decreased risk of death associated with an Hb level of ≥11 g/dl, the effect estimate was not statistically significant and potentially limited by the low number of deaths and smaller cohort size. Borzych-Duzalka et al. noted no associations between Hb level and hospitalization; our analysis demonstrated a decreased risk of hospitalization both in patients with a mean Hb level of ≥11 g/dl and those who were not anemic. While hospitalization is a less severe adverse

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effect relative to mortality, it is associated with decreased HRQOL and increased healthcare costs. For these reasons, identifying factors that may be associated with rate of hospitalization may be of significant benefit in this population.

Normative Hb values in children vary significantly depending on age and sex, arguing that a common Hb target for all pediatric patients may not be sufficient. For example, the 5th percentile Hb value, defining anemia, for males aged 1–2 years and 15–19 years is 10.7 and 13.5 g/dl, respectively. Furthermore, because atherosclerosis is less clinically apparent in childhood, compared to adulthood, and as children's requirements for linear growth and neurocognitive development may put them at increased risk for the adverse effects of anemia [27–29], we hypothesized that achieving higher Hb levels in childhood may not pose the same risk for mortality and morbidity as described in adult HD and CKD literature [30, 31], and instead may be associated with additional benefit. Indeed, our analysis demonstrated that mean Hb levels above the 5th percentile for age and sex, including Hb levels of greater than the 11 to <12 g/dl range, and an increase in Hb SDS, were associated with a decreased risk of hospitalization. However, we were not able to distinguish a difference in outcomes based on age- and sex-specific Hb targets in comparison to a fixed Hb target or range, possibly due to sample size limitations and the range of Hb data. Clinically, targeting age- and sex-specific Hb targets in children with CKD/ESKD is possible, and given the known biologic variation, further study of the impact of Hb level by age and sex is of interest.

In adults, observational studies and the secondary analysis of two trials, TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) and CHOIR (Correction of Hemoglobin in the Outcomes in Renal Insufficiency), have shown that higher ESA doses independently predict mortality [32–34]. Potential mechanisms of adverse outcomes include ESA-induced activation of platelets, upregulation of endothelial cell pro-thrombotic molecules, and direct vasoconstriction, with a possible increase in thrombotic events when used in patients with underlying cardiovascular morbidity [35, 36]. Borzych-Duzalka et al. described for the first time an association between mortality and higher ESA dose in children and in a PD population [13]. Our study found a similar association in U.S. children on PD, as well as an increased risk of hospitalization, with higher ESA dose in this cohort. In both our study and that by the Borzych-Duzalka [13], the association of ESA dose with adverse outcomes was independent of Hb level. Further study is needed to determine if this association persists in prospective analyses, and if so, whether it represents a direct effect of ESA or rather is a marker of systemic inflammation and/or comorbidities that contribute to both ESA resistance and adverse outcomes, such as hospitalization and death.

This study has a number of limitations. An averaged Hb level at the beginning of the observation period was used to categorize patients for a subsequent rate of hospitalization. As Hb is known to vary in some patients over time, some misclassification is possible. To help address this limitation, we also used multivariable Cox regression to analyze time to first hospitalization and found that associations did not significantly change. In terms of looking at death as an outcome, follow-up time was relatively short, however, comparable to that in studies examining the same associations in adults [22–25]. Another limitation of this study was the absence of markers of fluid overload, a factor which could impact both Hb levels and hospital admissions and mortality. Because of the observational design of this

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study, we cannot infer causality. The association of low Hb level with observed outcomes instead may reflect surrogacy with other variables, such as underlying disease, inflammation, and/or poor adherence, causing both anemia and adverse outcomes. Clinically, we can apply this evidence by using level of Hb as a potential marker for worse outcome and look more closely at the comorbid conditions and risk factors in those patients with severe anemia, while optimizing anemia management.

This study is notable in that it includes all prevalent children on PD in the USA at the time of data collection and included 4 or more years of hospitalization and mortality data. As such, it represents one of the most comprehensive examinations of pediatric PD patients to date.

Conclusion

An Hb level of ≥11 g/dl in children on PD in the USA was associated with a 44 % lower risk of hospitalization but no observed difference in mortality. Compared to Hb levels of 11 to <12 g/dl, levels ≥12 were not associated with a significantly decreased risk of hospitalization. However, a 27 % decreased risk of hospitalization for children whose mean Hb level was above the 5th percentile for age and sex (not anemic), including Hb levels greater than the 11–12 g/dl range, was also observed in this study. Further prospective studies or randomized clinical trials would be useful to determine the optimal Hb level(s) and the impact of ESA dose in children with CKD/ ESKD.

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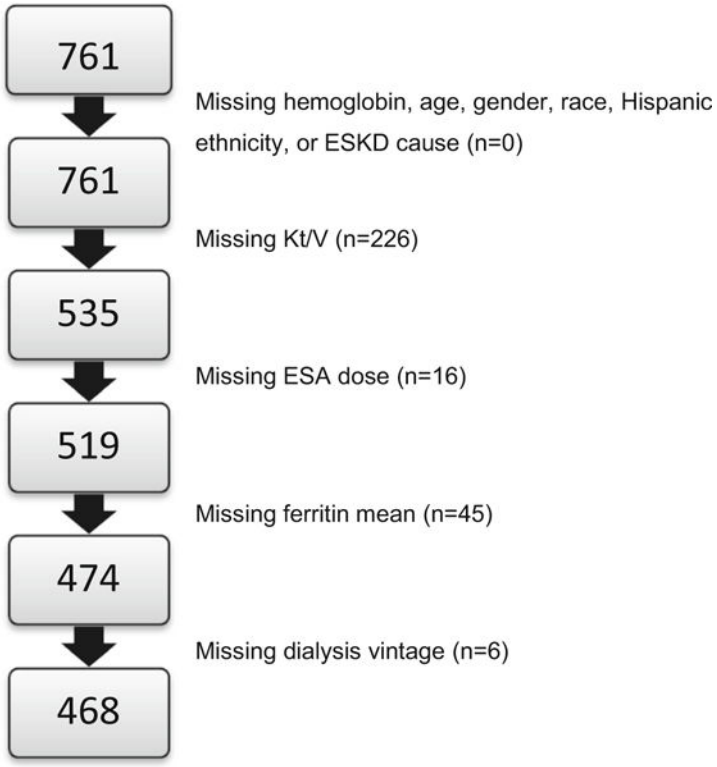

Fig. 1.

Flow diagram of exclusion of study subjects due to missing data. *ESKD* End-stage kidney disease, *ESA* erythropoiesis stimulating agent

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Pediatr Nephrol. Author manuscript; available in PMC 2019 June 10.

Table 1

Clinical characteristics at study entry for entire cohort and by hemoglobin category (*n*=468)

Clinical characteristics	Hb <11 g/dl (*N*=142; 30%)	Hb ≥11 g/dl (*N*=326; 70%)	All patients (*N*=468)
Age (years)	10.8(5.2)	11.2 (5.4)	11.1 (5.4)
Male	54	56	55
White race[a]	61	70	67
Hispanic ethnicity[a]	18	32	28
ESKD cause, congenital/urologic	32	37	36
Dialysis vintage ≥180 days	59	61	60
Mean albumin ≥3.5/3.2 g/dl[a,b]	65	75	72
Mean Kt/V urea ≥1.8	84	89	88
Mean ferritin, ≥800 ng/ml	11	9	10
Iron use, yes	87	85	86
Mean ESA dose			
Epoetin[a] units/kg/week (*N*=428)	307 (284)	198 (170)	230 (215)
Darbepoetin mcg/kg/week (*N*=40)	0.034 (0.028)	0.024 (0.025)	0.028 (0.026)

[a] $P<0.05$; according to the X^2-test or *t* test

[b] Bromcresol green/bromcresol purple

Data in all columns are presented as the percentage of patients in that category, or as the mean with the standard deviation (SD) in parenthesis Hb, Hemoglobin; ESKD, end-stage kidney disease; ESA, erythropoiesis stimulating agent

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Table 2

Events by hemoglobin level (unadjusted)

Hb level (g/dl)	Mean Hb level within group (±SD)	Number of deaths	Deaths per 100 patient-years	Number of hospitalizations	Hospitalizations per 100 patient-years
<10 (*N*=60)	9.3 (0.6)	4	3.6	163	153
≥10 to <11 (*N*=82)	10.5 (0.3)	7	4.5	234	156
≥11 to <12 (*N*=131)	11.5 (0.3)	3	1.2	205	88
≥12 (*N*=195)	13.0 (0.8)	9	2.3	287	78
All patients (*N*=468)	11.7(1.4)	23	2.6	889	103

Hb, Hemoglobin

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Table 3

Mortality and hospitalization risk by Hb level[a]

Mortality and hospitalization (*N*=468)	≥10 vs. <10 g/dl	≥11 vs. <11 g/dl	≥12 vs. <12 g/dl	Not anemic vs. Anemic
Risk for mortality, HR (95 % CI)[b]	1.28(0.41–4.01)	0.69(0.28–1.70)	1.16(0.46–2.94)	0.84 (0.35–2.04)
Risk for hospitalization, IRR (95 % CI)[c]	0.75 (0.53–1.07)	0.56 (0.43–0.73)*	0.65 (0.49–0.87)*	0.73 (0.55–0.97)*

*P<0.05

CI, Confidence interval; HR, hazard ratio; IRR incidence rate ratio; Hb, Hemoglobin; ESKD, end-stage kidney disease; ESA, erythropoiesis stimulating agent

[a]Adjusted for age, gender, race, Hispanic ethnicity, ESKD cause, dialysis vintage, serum albumin level, serum ferritin level, Kt/V, iron use, and ESA dose quartile

[b]Cox proportional regression

[c]General linear modeling with Poisson function

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Table 4

Mortality and hospitalization risk by Hb level[a]

Mortality and hospitalization risk	<10 vs. 11 to <12 g/dl (*N*=191)	10 to <11 vs. 11 to <12 g/dl (*N*=213)	≥12 vs. 11 to <12 g/dl (*N*=255)
Risk for mortality, HR (95 % CI)[b]	1.67(0.33–8.44)	3.38(0.76–14.28)	2.16(0.52–9.02)
Risk for hospitalization, IRR (95 % CI)[c]	1.50(0.99–2.27)	1.76(1.22–2.56)*	0.88(0.61–1.25)

*P<0.05

Hb, Hemoglobin; ESKD, end-stage kidney disease

[a]Adjusted for age, gender, race, Hispanic ethnicity, ESKD cause, dialysis vintage, serum albumin level, serum ferritin level, Kt/V, iron use, and ESA dose quartile

[b]Cox proportional regression

[c]General linear modeling with Poisson function

Pediatr Nephrol. Author manuscript; available in PMC 2019 June 10.