Association of Mortality and Hospitalization with Achievement of Adult Hemoglobin Targets in Adolescents Maintained on Hemodialysis

Sandra Amaral,* Wenke Hwang,§ Barbara Fivush,* Alicia Neu,* Diane Frankenfield,‡ and Susan Furth*†

**Department of Pediatrics, †Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, and ‡Centers for Medicare & Medicaid Services, Office of Clinical Standards and Quality, Baltimore, Maryland; and §Wake Forest University School of Medicine, Winston-Salem, North Carolina*

With the use of data from the Centers for Medicare & Medicaid Services' ESRD Clinical Performance Measures Project (October through December 1999 and 2000) linked with US Renal Data System hospitalization and mortality records, whether achieving adult target hemoglobin (Hb) levels in adolescents who are on hemodialysis (HD) was associated with decreased risk for death or hospitalization was assessed. Of 677 adolescents, 238 were hospitalized and 54 died. In bivariate analysis, 11.7% with Hb <11 g/dl at study entry died *versus* 5% of those with initial Hb ≥11 g/dl ($P = 0.001$); 40.3% with baseline Hb <11 g/dl were hospitalized *versus* 31.1% with initial Hb ≥11 g/dl ($P = 0.013$). In multivariate analysis, Hb ≥11 g/dl was associated with decreased risk for death (hazard ratio [HR] 0.38; 95% confidence interval [CI] 0.20 to 0.72) but did not show a statistically significant association with decreased risk for hospitalization (HR 0.87; 95% CI 0.66 to 1.15). When Hb was recategorized as Hb <10, ≥10 and <11, ≥11 and ≤12, and >12 g/dl, risk of mortality declined as Hb level increased. At Hb 11 to 12 g/dl (*versus* Hb <10 g/dl), mortality risk decreased by 69% (HR 0.31; 95% CI 0.14 to 0.65). Risk for mortality was similar for Hb 11 to 12 and >12 g/dl. For hospitalization, no statistically significant difference in risk between Hb categories was found. This observational study of adolescents who are on HD is consistent with adult literature showing decreased mortality in patients who have ESRD and meet adult Hb targets. Further studies in the form of randomized, clinical trials are needed to assess optimal Hb levels for adolescents who are on HD.

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The National Kidney Foundation Dialysis Outcomes Quality Initiative (DOQI) practice guidelines first were established in 1997 to create standards for dialysis care, including anemia management. In 1999, some of these guidelines were adopted by the Centers for Medicare & Medicaid Services as clinical performance measures (CPM), or therapeutic goals, for adult dialysis patients. The target range for hemoglobin (Hb) in adults is 11 to 12 g/dl. Studies in adults with ESRD have consistently demonstrated reduced risk for death and hospitalization when Hb levels are ≥11 g/dl; a lowering of Hb by 1 g/dl has been associated with a 14% increased risk for mortality in an incident adult dialysis population (1–3). Higher Hb levels have been associated with improved oxygen utilization, exercise capacity, cognitive ability, and cardiac function (4,5). Little evidence is available to assess the relevance of adult target Hb levels in pediatric patients with ESRD. This study is a preliminary analysis to examine the relationship between risk for death and hospitalization and the achievement of adult targets for Hb in adolescent patients who have ESRD and are on hemodialysis (HD). A secondary aim of this study was to assess differential risk for mortality and hospitalization among smaller Hb subcategories: <10, 10 to <11, 11 to 12, and >12 g/dl.

Materials and Methods

For this retrospective, cohort study, national data on all prevalent in-center HD patients who were aged 12 to 18 yr between October and December 1999 and October and December 2000 were obtained from the Centers for Medicare & Medicaid Services' ESRD CPM Project. This information then was linked with 3-yr hospitalization records (October 1999 through December 2002) and 4-yr mortality records (October 1999 through November 2003) of Medicare-eligible HD patients in the US Renal Data System (USRDS) by unique USRDS identification numbers.

The ESRD CPM Project collects demographic and clinical data on measures that may have an impact on quality of dialysis care, including anemia management, serum albumin, vascular access, and dialysis adequacy (6). In the ESRD CPM Project, Hb was recorded monthly during the periods of October through December 1999 and 2000; up to three separate Hb measures were available for each patient per year. The monthly levels were averaged and analyzed as means in each year. Adolescents who were on HD were categorized as failing to meet target

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Address correspondence to: Dr. Sandra Amaral, Emory University School of Medicine, Division of Pediatric Nephrology, 2015 Uppergate Drive NE, Atlanta, GA 30322. Phone: 404-727-2450, Fax: 404-727-8213; E-mail: sandra_amaral@oz.ped.emory.edu

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when mean Hb was <11 g/dl (*versus* Hb ≥11 g/dl). They then were subclassified as Hb <10, ≥10 and <11, 11 to 12, and >12 g/dl.

Clinical characteristics that were obtained from the CPM data set were compared among the dichotomized Hb groups. Covariates that were examined included age as a continuous variable, race (white *versus* other), gender, ESRD cause (congenital/urologic *versus* other), time since most recent HD initiation (≥180 *versus* <180 d), access type (catheter *versus* graft/fistula), mean serum ferritin (≥800 *versus* <800 ng/ml), and mean serum albumin (≥3.5/3.2 *versus* <3.5/3.2 g/dl, as measured by the bromcresol green and bromcresol purple methods, respectively). The cutoffs for dialysis vintage, serum ferritin, and serum albumin were chosen from previous evidence showing differential survival and/or anemia correction between these levels (7–11). Exposure to iron (yes/no) and mean epoetin dosage (units/kg per wk) also were examined. Epoetin dosing was examined as a continuous variable and by quartiles (≤150, 150 to 250, 251 to 400, and >400 units/kg per wk). No data were available on iron dosing. In addition, presence of baseline hypertension (yes/no), estimated baseline GFR by Schwartz formula, and Medicaid/Medicare insurance coverage data were obtained from the USRDS Medical Evidence Form 2728 and were included in the analysis. Fewer than 3% of patients had diabetes, and fewer than 1% were smokers; therefore, these traditional risk factors in the adult ESRD population were not included.

Risk for death and hospitalization was analyzed by whether patients achieved the minimum target Hb (mean Hb <11 *versus* ≥11 g/dl) and then by Hb subcategories (<10, ≥10 and <11, 11 to 12, and >12 g/dl). Death and hospitalization data were obtained from the USRDS patient and hospitalization files, respectively. χ^2, Fisher exact test, ANOVA, and *t* test were used to compare dichotomized clinical characteristics and death or hospitalization (as yes/no) between baseline Hb <11 *versus* ≥11 g/dl. Nonparametric Kaplan-Meier curves with log-rank tests and semiparametric Cox proportional hazards regression models were used to compare survival, adjusting for the aforementioned covariates. Hospitalization rates were analyzed as total claims per time at risk using Poisson regression. The starting date for time at risk was either entry date of the CPM cohort (October 1, 1999, or October 1, 2000) or

entry date into USRDS if the patient entered the USRDS after the cohort entry date. The last reported death date and last hospitalization claim were used as end points for time at risk for mortality and hospitalization analyses to account for lag time between hospital admission or death notification and entry into the USRDS files. Propensity score matching also was implemented for the mortality analysis. Two sensitivity analyses were performed. The first sensitivity analysis excluded any patients who received a transplant during the study period. The second sensitivity analysis excluded any patients without reported Medicare or Medicaid coverage listed on Form 2728.

In both survival and longitudinal hospitalization analyses, patients were followed to the end of the follow-up period or death or censored at transplantation. For patients who had Hb data in both ESRD CPM Project study years, clustering by USRDS identification number was used to account for repeated measures. $P < 0.05$ was considered statistically significant. All data management and analysis were conducted using Stata 8.0 software (StataCorp, College Station, TX).

Results

Patient Characteristics

A total of 680 individual patients who were aged 12 to 18 yr were identified as common to both the ESRD CPM and USRDS databases. Three patients were dropped from this merged data set secondary to transplantation within the first 2 mo of data collection. Hb data were available for 424 patients in October through December 1999 and 430 patients in October through December 2000. A total of 177 patients remained on HD from October 1999 through December 2000 and therefore had Hb information in both years of ESRD CPM data collection (Figure 1).

Among the 677 included patients, the mean age was 16 yr (SD 1.7); 52% were male, 49% were white, and 41% were black; 41% had congenital or urologic disease; 45% were on HD for <180 d. At time of first entry, 44% of patients had Hb <11 g/dl, 47% had catheters, 19% had serum albumin <3.5/3.2 g/dl (bromcresol green/bromcresol purple), 6% had serum ferritin ≥800 ng/ml, and 34% had hypertension. Mean estimated GFR by Schwartz formula was 9.4 ml/min per 1.73 m^2 (SD 6.5). A total of 94% of patients were prescribed epoetin, and 75% were prescribed iron. A total of 50% of patients had Medicare/Medicaid coverage reported on their 2728 form at study entry; 45% of patients had an updated 2728 completed within 3 mo of the study onset; 88% of the CPM2000 cohort and 94% of the CPM2001 cohort had Medicare insurance for the entire span of data collection as based on payer history files. A total of 216 (32%) patients received a transplant during the study period.

Table 1 shows characteristics compared by Hb at study entry: <11 *versus* ≥11 g/dl. The group with Hb <11 g/dl was more likely to be on HD <180 d, have a catheter as vascular access, have lower serum albumin, and have baseline hypertension. Patients with Hb <11 g/dl also received higher mean epoetin doses.

In comparison with adults on HD in the CPM2000 and CPM2001 cohorts as described in the annual reports, adolescents who were on HD were more likely to be on HD for <6 mo and more likely to have catheters as vascular access; these adolescents also were more likely to have Hb <11 g/dl (44 *versus* 32% adults). The adult HD CPM patients were more likely to have diabetes (40%) and had higher mean serum ferritin (489 to 529 ng/ml) (12,13).

During the designated follow-up period for hospitalization, 238 (35%) of the 677 included patients were hospitalized. Hospitalized patients comprised 165 patients who had >3 yr of hospitalization time at risk (October 1999 through December 2002) and 73 patients who were exclusively in CPM2001 and had >2 yr of hospitalization time at risk (October 2000 through December 2002; Figure 1). Mean follow-up time for hospitalization analysis was 1.7 yr (±0.9). Only 3.9% of hospitalizations had infection reported as one of the top three diagnoses.

There were 54 deaths during a 4-yr mortality follow-up period. Of those deaths, 26 occurred in patients with Hb data exclusively in CPM2000, 18 deaths occurred in patients with data exclusively in CPM2001, and 10 deaths occurred in patients with Hb data from both periods (Figure 1). Causes of death on the ESRD death notification form included 14 cardiac events, six vascular events, 10 infectious causes, eight other, and 16 unknown or missing. Mean follow-up time for mortality analysis was 2.1 yr (±1.3).

Bivariate Analysis

Survival. In bivariate analysis, 11.7% of patients with Hb <11 g/dl at study entry died *versus* 5% of those with initial Hb

Table 1. Clinical characteristics of cohort at study entry, Hb <11 *versus* ≥11 g/dl, $N = 677$[a]

Baseline Clinical Characteristics	Hb < 11 g/dl (n = 298; 44%; n [%] or Mean [SD])	Hb ≥ 11 g/dl (n = 379; 56%; n [%] or Mean [SD])
Age (yr)	15.9 (±1.8)	16 (±1.6)
White race	140 (47)	190 (50)
Male gender	144 (48)	210 (55)
Congenital/urologic cause of ESRD	123 (41)	154 (41)
HD initiation ≥ 180 d[b]	125 (42)	245 (65)
HD access type: catheter[b]	177 (59)	140 (37)
Medicare/Medicaid coverage	152 (51)	188 (50)
Serum albumin ≥ 3.5/3.2 g/dl[b,c]	212 (71)	339 (89)
Mean serum ferritin (ng/ml)	261.9 (±359)	259 (±272)
Presence of baseline HTN[b]	112 (38)	117 (31)
eGFR by Schwartz (ml/min per 1.73 m^2)	9.2 (±6.9)	9.6 (±6.2)
Iron use (yes)	216 (72)	295 (78)
Mean epoetin dosage (units/kg per wk)[b]	370.6 (±265.4)	254.6 (±203)
Patients who received transplant during study	87 (29)	129 (34)

[a]BCG/BCP, Bromcresol green/Bromcresol purple; eGFR, estimated GFR; Hb, hemoglobin; HD, hemodialysis; HTN, hypertension.
[b]$P \leq 0.05$ (χ^2 or ANOVA).
[c]BCG/BCP.

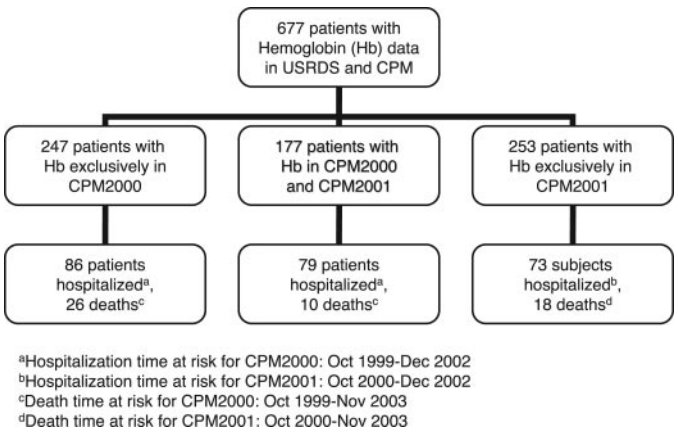

Figure 1. Study population subsets by time at risk.

≥11 g/dl ($P = 0.001$). Patients with Hb <11g/dl had five *versus* 1.9 deaths per 100 patient-years in the Hb ≥11 g/dl group ($P = 0.0009$; Table 2). Of the covariates examined, dialysis vintage was the only covariate that was associated with differential mortality rates. Thirty-seven (10%) patients who were initiated on hemodialysis ≥180 d before study entry died *versus* 17 (5.5%) patients who were on HD <180 d ($P = 0.033$).

Kaplan-Meier curves and log rank testing also were used to assess survival risk. Log rank tests demonstrated a statistically significant improved survival in patients with mean Hb ≥11 g/dl ($P = 0.0003$). The only other covariate that demonstrated a statistically significant association with improved survival by log rank testing was serum albumin ≥3.5/3.2 g/dl ($P = 0.0247$).

Hospitalization. Of the 677 patients, 40.3% with Hb <11 g/dl at study entry were hospitalized *versus* 31.1% of patients with Hb ≥11 g/dl ($P = 0.013$). Patients with Hb <11 g/dl averaged 0.45 hospital admissions per year at risk *versus* 0.31 visits per year at risk for those with Hb ≥11 g/dl ($P = 0.013$; Table 2). A total of 39% of patients who were on HD for ≥180 d were hospitalized *versus* 31% of those who were on HD <180 d ($P = 0.024$). A total of 39% of patients with baseline Medicare/Medicaid coverage were hospitalized *versus* 28% of those without this coverage ($P = 0.009$). Patients who received a transplant were less likely to be hospitalized (20% *versus* 42% of patients who did not receive a transplant; $P = 0.000$). Patients with baseline hypertension also had decreased risk for hospitalization (28 *versus* 37% of those without hypertension; $P = 0.004$).

Multivariate Analysis

Survival. Cox proportional hazard regression models were constructed with adjustment for the aforementioned covariates (Table 3). In crude models, Hb ≥11 g/dl was associated with a 63% decreased risk for mortality (hazard ratio [HR] 0.37; 95% confidence interval [CI] 0.21 to 0.65), and serum albumin ≥3.5/3.2 g/dl was associated with a 50% decreased risk for mortality (HR 0.50; 95% CI 0.27 to 0.93). All epoetin quartiles showed a more than double increased risk for mortality in crude analysis; however, this association seemed statistically significant only for epoetin 151 to 250 units/kg per wk. The full adjusted model demonstrated decreased risk for death (HR 0.38; 95% CI 0.20 to 0.72) for patients with Hb ≥11 g/dl After covariate adjustment, the association between albumin and mortality no longer was statistically significant. All epoetin quartiles continued to show increased risk for mortality; however, only epoetin 151 to 250 units/kg per wk was statistically significant. In both crude and adjusted models, epoetin as a continuous variable showed no statistically significant associa-

Table 2. Bivariate analysis: Risk for death and hospitalization, Hb <11 *versus* ≥11 g/dl, $N = 677$

Parameter	Hb <11 g/dl ($n = 298$)	Hb ≥11 g/dl ($n = 379$)	P
Deaths per 100 patient-years	5	1.9	0.0009[a]
Hospitalizations per year at risk (±SD)	0.45 (±0.87)	0.31 (±0.76)	0.0128[b]

[a]Log rank.
[b]ANOVA.

tion with mortality (HR 1.00; 95% CI 0.99 to 1.00). Dialysis vintage was statistically significant in the full model: Patients who were on HD ≥180 d were at greater risk for mortality (HR 1.91; 95% CI 1.03 to 3.52). Because there were multiple covariates and few events, propensity score matching also was performed. Adjusting for all covariates, propensity score matching yielded an HR of 0.36 for decreased risk for mortality in patients with Hb ≥11 g/dl (95% CI 0.19 to 0.67), consistent with the unadjusted and full models (Table 3).

Hospitalization. Hospitalization was examined by hospital admissions per time at risk using Poisson regression. In the crude model, Hb ≥11 g/dl was associated with decreased risk for hospitalization (incidence rate ratio [IRR] 0.74; 95% CI 0.56 to 0.96). In unadjusted analyses, mean serum albumin ≥3.5/3.2 g/dl was associated with decreased risk for hospitalization (IRR 0.65; 95% CI 0.46 to 0.92), and serum ferritin ≥800 ng/ml was associated with increased risk (IRR 1.21; 95% CI 1.00 to 1.47). All epoetin quartiles were associated with increased risk for hospitalization; however, the associations at quartiles 151 to 250 and >400 units/kg per wk (*versus* <150 units/kg per wk) were statistically significant (Table 4).

In multivariate analysis, although the point estimate suggested decreased risk for hospital admissions per time at risk in patients with Hb ≥11 g/dl, this association was no longer statistically significant (IRR 0.87; 95% CI 0.66 to 1.15). After adjustment for the aforementioned covariates, only epoetin 151 to 250 and >400 units/kg per wk (*versus* < 150 units/kg per wk) were statistically associated with increased risk for hospitalization.

Additional Analyses

To assess the differential risk of mortality and hospitalization among smaller Hb subcategories, we classified Hb as <10, ≥10 and <11, 11 to 12, and >12 g/dl and repeated the analyses (Tables 5 and 6). Using these classifications, in adjusted analyses, there was a trend toward both decreased hospitalization (HR 0.95; 95% CI 0.85 to 1.07) and decreased mortality (HR 0.58; 95% CI 0.42 to 0.81) as Hb level increased. Hb 11 to 12 g/dl (*versus* Hb <10 g/dl) was associated with a 69% decreased risk for mortality (HR 0.31; 95% CI 0.14 to 0.65). At Hb >12 g/dl (*versus* Hb <10 g/dl), mortality risk was decreased by 72% (HR 0.28; 95% CI 0.13 to 0.61). Kaplan-Meier curves for the varying Hb groups showed a significant difference in survival between Hb <10 g/dl and the other Hb categories ($P = 0.0007$, log rank;

Table 3. Cox proportional hazard: Risk for mortality, Hb <11 *versus* ≥11 g/dl[a]

Covariates	HR, Crude (95% CI)	HR, Adjusted (95% CI)
Hb ≥ 11 g/dl (*versus* Hb < 11 g/dl)	0.37 (0.21 to 0.65)[b]	0.38 (0.20 to 0.72)[b]
Age (yr)	1.13 (0.93 to 1.37)	1.14 (0.93 to 1.41)
White race	1.06 (0.62 to 1.81)	1.01 (0.56 to 1.82)
Male gender	0.87 (0.51 to 1.46)	0.98 (0.53 to 1.83)
Congenital/urologic cause of ESRD	1.30 (0.76 to 2.21)	1.58 (0.83 to 3.00)
HD initiation ≥ 180 d	1.32 (0.73 to 2.39)	1.91 (1.04 to 3.50)[b]
HD access type: catheter	1.27 (0.81 to 1.98)	1.11 (0.68 to 1.80)
Medicare/Medicaid coverage	0.91 (0.63 to 1.32)	1.05 (0.64 to 1.74)
Serum albumin ≥ 3.5/3.2 g/dl (BCG/BCP)	0.50 (0.27 to 0.93)[b]	0.60 (0.28 to 1.28)
Serum ferritin ≥ 800 ng/ml	1.00 (0.68 to 1.48)	0.96 (0.60 to 1.54)
Presence of HTN	0.91 (0.67 to 1.24)	0.89 (0.59 to 1.32)
eGFR by Schwartz (ml/min per 1.73 m^2)	1.03 (0.99 to 1.06)	1.02 (0.98 to 1.06)
Iron use (yes)	0.97 (0.51 to 1.84)	0.73 (0.36 to 1.50)
Epoetin (units/kg per wk)		
151 to 250	2.57 (1.00 to 6.57)[b]	2.63 (1.05 to 6.60)[b]
251 to 400	2.32 (0.88 to 6.08)	2.11 (0.77 to 5.73)
>400	2.46 (0.96 to 6.29)	2.04 (0.77 to 5.38)

[a]CI, confidence interval; HR, hazard ratio.
[b]$P < 0.05$.

Table 4. Poisson regression: Risk for hospitalization, Hb <11 *versus* ≥11 g/dl[a]

Covariates	IRR, Crude (95% CI)	IRR, Adjusted (95% CI)
Hb ≥ 11 g/dl (*versus* Hb < 11 g/dl)	0.74 (0.56 to 0.96)[b]	0.87 (0.66 to 1.15)
Age (yr)	1.01 (0.93 to 1.09)	1.01 (0.94 to 1.10)
White race	0.89 (0.68 to 1.16)	0.90 (0.68 to 1.19)
Male gender	0.93 (0.71 to 1.21)	0.97 (0.73 to 1.29)
Congenital/urologic cause of ESRD	1.03 (0.79 to 1.36)	0.98 (0.73 to 1.32)
HD initiation ≥ 180 d	1.11 (0.84 to 1.47)	1.24 (0.92 to 1.68)
HD access type: catheter	1.17 (0.92 to 1.48)	1.13 (0.87 to 1.45)
Medicare/Medicaid coverage	1.13 (0.94 to 1.35)	1.24 (0.96 to 1.60)
Serum albumin ≥ 3.5/3.2 g/dl (BCG/BCP)	0.65 (0.46 to 0.92)[b]	0.78 (0.54 to 1.12)
Serum ferritin ≥ 800 ng/ml	1.21 (1.00 to 1.47)[b]	1.21 (0.98 to 1.49)
Presence of HTN	0.95 (0.81 to 1.12)	0.87 (0.71 to 1.08)
eGFR by Schwartz (ml/min per 1.73 m^2)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.03)
Iron use (yes)	1.17 (0.86 to 1.60)	1.19 (0.84 to 1.69)
Epoetin (units/kg per wk)		
151 to 250	1.64 (1.08 to 2.48)[b]	1.68 (1.11 to 2.54)[b]
251 to 400	1.27 (0.82 to 1.99)	1.29 (0.83 to 2.00)
>400	2.07 (1.38 to 3.13)[b]	1.89 (1.23 to 2.89)[b]

[a]IRR, incidence rate ratio.
[b]$P < 0.05$.

Table 5. Mortality risk by Hb level

Parameter	Hb ≥ 11 g/dl (*versus* <11 g/dl; *n* = 379; HR [95% CI])	Hb ≥10 and <11 g/dl (*versus* <10 g/dl; *n* = 137)	Hb 11 to 12 g/dl (*versus* <10 g/dl; *n* = 195)	Hb > 12 g/dl (*versus* <10 g/dl; *n* = 184)
Crude model (*n* = 677)	0.37 (0.21 to 0.65)[c]	0.58 (0.29 to 1.15)	0.31 (0.14 to 0.65)[c]	0.28 (0.13 to 0.61)[c]
Full model[a] (*n* = 641)	0.38 (0.20 to 0.72)[c]	0.46 (0.20 to 1.04)	0.30 (0.19 to 0.74)[c]	0.20 (0.07 to 0.56)[c]
Full model, excluding those without baseline Medicare or Medicaid (*n* = 340)	0.30 (0.13 to 0.71)[c]	0.17 (0.05 to 0.58)[c]	0.15 (0.04 to 0.53)[c]	0.11 (0.03 to 0.39)[c]
Full model, excluding patients who received a transplant (*n* = 461)	0.38 (0.20 to 0.72)[c]	0.47 (0.21 to 1.06)	0.29 (0.12 to 0.74)[c]	0.20 (0.07 to 0.56)[c]
Full model, excluding those with repeated measures (*n* = 466)	0.35 (0.17 to 0.73)[c]	0.54 (0.23 to 1.26)	0.28 (0.10 to 0.81)[c]	0.23 (0.08 to 0.66)[c]
Inflammatory model[b] (*n* = 641)	0.39 (0.21 to 0.75)[c]	0.55 (0.27 to 1.14)	0.34 (0.15 to 0.80)[c]	0.24 (0.10 to 0.61)[c]

[a]Adjusted for age, race, gender, ESRD cause, dialysis vintage, vascular access type, Medicare/Medicaid insurance status, serum albumin level, serum ferritin level, baseline hypertension, baseline eGFR by Schwartz, iron use, and epoetin quartiles.
[b]Serum albumin level, serum ferritin level, iron use, and epoetin quartiles.
[c]$P < 0.05$.

Figure 2). For hospitalization, differences among Hb groups were not statistically significant.

To address possible ascertainment bias from unreported claims of patients without Medicare or Medicaid, we performed a sensitivity analysis excluding patients who did not have Medicare/Medicaid at study entry. For the remaining 340 patients with baseline Medicare or Medicaid coverage, Hb ≥11 g/dl demonstrated a 70% decreased risk for mortality (IRR 0.30; 95% CI 0.13 to 0.71). Hb 11 to 12 *versus* Hb <10 g/dl showed an 85% decreased risk for mortality (IRR 0.15; 95% CI 0.04 to 0.53). The hospitalization analysis continued to show no statistically significant difference among Hb groups.

Initial analyses censored patients at time of transplantation. Because patients who received a transplant may have represented a healthier subset of the adolescent ESRD population, a sensitivity analysis was performed excluding those 216 patients. For both survival and hospitalization analyses, the exclusion of patients who received a transplant did not significantly change the point estimates.

We also considered survival bias in the patients with re-

Table 6. Hospitalization risk by Hb level

Parameter	Hb ≥ 11 g/dl (*versus* <11 g/dl; *n* = 379; IRR [95% CI])	Hb ≥10 and <11 g/dl (*versus* <10 g/dl; *n* = 137)	Hb 11 to 12 g/dl (*versus* <10 g/dl; *n* = 195)	Hb > 12 g/dl (*versus* <10 g/dl; *n* = 184)
Crude model (*n* = 677)	0.74 (0.56 to 0.96)[c]	0.93 (0.64 to 1.35)	0.76 (0.53 to 1.09)	0.66 (0.47 to 0.93)[c]
Full model[a] (*n* = 641)	0.87 (0.66 to 1.15)	1.15 (0.77 to 1.72)	1.00 (0.68 to 1.48)	0.89 (0.61 to 1.31)
Full model, excluding those without baseline Medicare or Medicaid (*n* = 340)	0.72 (0.51 to 1.03)	1.07 (0.64 to 1.79)	0.78 (0.46 to 1.30)	0.73 (0.44 to 1.21)
Full model, excluding patients who received a transplant (*n* = 461)	0.87 (0.64 to 1.18)	1.18 (0.75 to 1.86)	1.00 (0.64 to 1.55)	0.91 (0.59 to 1.40)
Full model, excluding those with repeated measures (*n* = 466)	0.77 (0.54 to 1.09)	1.24 (0.75 to 2.06)	0.95 (0.57 to 1.56)	0.79 (0.48 to 1.30)
Inflammatory model[b] (*n* = 641)	0.88 (0.66 to 1.16)	1.14 (0.76 to 1.69)	1.00 (0.68 to 1.46)	0.88 (0.61 to 1.27)

[a]Adjusted for age, race, gender, ESRD cause, dialysis vintage, vascular access type, Medicare/Medicaid insurance status, serum albumin level, serum ferritin level, baseline hypertension, baseline eGFR by Schwartz, iron use, and epoetin quartiles.
[b]Serum albumin level, serum ferritin level, iron use, and epoetin quartiles.
[c]$P < 0.05$.

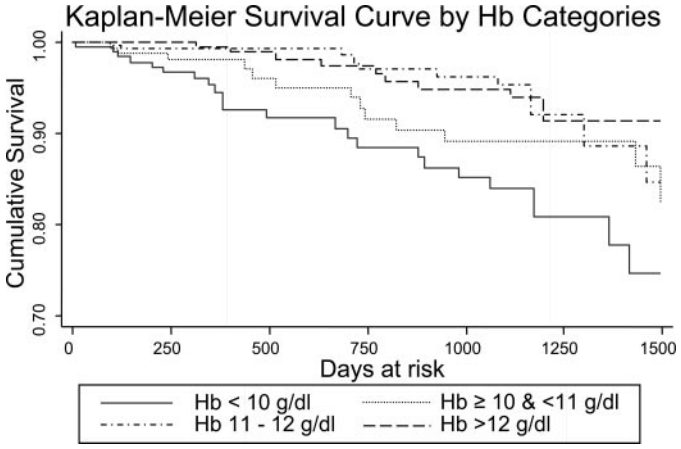

Figure 2. Cumulative survival by hemoglobin categories (P = 0.0007, log rank).

peated measures. To examine this possibility, we repeated the analysis excluding the 177 patients who had Hb data in both CPM cohorts. The results of mortality and hospitalization analyses were not significantly altered by this exclusion. In addition, we performed χ^2 analysis to examine whether there was difference in the probability of survival or hospitalization in patients with repeated measures on the basis of whether their Hb increased, decreased, or stayed the same over time. We were unable to detect a statistically significant difference on the basis of direction of Hb change for either mortality (P = 0.372) or hospitalization (P = 0.762).

To examine the contribution of inflammation toward the relationship between anemia and mortality or hospitalization, we composed a model that was limited to the surrogates of inflammation that were available in our data set—mean serum albumin and ferritin—and we adjusted for iron use and epoetin quartiles. Using this model, neither the association between Hb level and mortality nor the association between Hb level and hospitalization was significantly changed.

Discussion

The National Kidney Foundation DOQI practice guidelines for anemia management were based primarily on adult studies. There is limited evidence to support use of these adult targets in pediatric patients who are on HD. Warady and Ho (14) demonstrated an association between baseline hematocrit <33% at 30 d after initiation of dialysis and increased risk for prolonged hospitalization and death in incident ESRD patients who were younger than 18 yr and from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) registry. We sought to assess whether meeting the specific adult Hb target of 11 to 12 g/dl is associated with decreased hospitalization and mortality risk in prevalent adolescents who are on HD. Our study included the mean of Hb measures over 3 mo in each year and incorporated all prevalent in-center HD patients who were aged 12 to 18 yr in the ESRD CPM Project and USRDS, including patients who were cared for in nonpediatric centers and would not have been included in NAPRTCS. We looked at Hb as a dichotomized measure (<11 *versus* ≥11 g/dl) and as a categorical variable (<10, >10 and <11, 11 to 12, and >12 g/dl).

Our analysis demonstrated a consistent and strong positive association between achievement of adult target Hb ≥11 g/dl and improved survival in up to 4 yr of follow-up for adolescent HD patients. Hb ≥11 g/dl was associated with a 60 to 70% decreased risk for mortality across multiple models and with propensity score matching. Poisson regression demonstrated a 12 to 28% decreased risk for hospitalization across varying models; however, this association was not statistically significant.

We also tried to assess differential risk for mortality and hospitalization among smaller Hb subcategories. In adult studies, the optimal target Hb remains controversial. Higher Hb levels have been associated with increased access thrombosis, hypertension, and cardiovascular events. In 2004, the Cochrane Renal Group performed a meta-analysis of randomized, clinical trials to evaluate the harms and benefits of various Hb targets in patients with chronic kidney disease; they found lower risk for all-cause mortality with Hb <12 *versus* >13 g/dl (relative risk 0.84; 95% CI 0.71 to 1.00) (15). In 1998, Besarab *et al.* (16) halted a randomized, clinical trial in adults who had cardiac disease, were on HD, and were receiving epoetin to achieve a hematocrit of 42 *versus* 30%. The group with higher hematocrit experienced decreased event-free survival. A longitudinal study of HD patients over 6 mo found no increased risk for mortality or hospitalization associated with Hb 12 to <13 *versus* ≥11 and <12 g/dl but did demonstrated increased risk for mortality and hospitalization with Hb <9 *versus* ≥11 and <12 g/dl (2). More recently, Volkova and Arab (17) performed an evidence-based literature review of the relationship between Hb and/or hematocrit and mortality in dialysis patients. They concluded that "most observational studies supported the increased mortality associated with Hb levels less than the reference range [of 11 to 12 g/dl]. . . . Evidence of risks or benefits of Hb levels greater than 11 to 12 g/dl is variable."

We hypothesized that because cardiovascular damage in adolescents tends to reflect uremic arteriopathy and metabolic dysregulation rather than traditional atherogenic risk factors, achieving higher Hb in adolescents with ESRD may not pose the same risk for mortality and cardiovascular events as in the adult ESRD population (18). In addition, pediatric norms for Hb vary by age with peaks in infancy and adolescence; mean Hb values for male and female adolescents who are aged 12 to 18 yr are 14.5 (±0.75) and 14.0 g/dl (±1), respectively (19). We considered that adolescents who had ESRD and were on HD actually may require higher Hb levels than the current adult target to meet increased metabolic needs.

When we recategorized Hb as <10, ≥10 and <11, 11 to 12, and >12 g/dl, the greatest risk for mortality was at Hb <10 g/dl, and risk for mortality was similar between Hb 11 to 12 and >12 g/dl (*versus* Hb <10 g/dl; Table 5). The mean Hb in the subcategory of Hb >12 g/dl was 12.8, which may explain our inability to detect a difference between Hb 11 to 12 and >12 g/dl. Sixty-five patients had Hb >13 g/dl, and among those, there was only one death.

The model that excluded those without Medicare/Medicaid coverage at study entry was the only model that differed from the other models for mortality risk. This model showed overall lower point estimates at all Hb levels (*i.e.*, showed a greater degree of decreased risk for mortality at all Hb categories above Hb <10 g/dl). This model was composed of patients who were more likely to be on HD longer because there is a waiting period to become Medicare eligible. These results suggest that patients who have Hb <10 g/dl and have been on HD >6 mo are at greatest risk for mortality.

Because of the observational nature of this study, we cannot infer causality. Patients with more severe anemia and longer HD duration may have more severe hyperparathyroidism or a greater degree of long-standing uremia or may be hyporesponsive to epoetin. In our study population, we were unable to detect a statistically significant dose-dependent relationship between epoetin dosing and mortality. We did not see a relationship between being prescribed iron and mortality; however, we did not have available data on iron dosing. It also is possible that the patients in our data set who had Hb <10 g/dl and were on HD ≥180 d represented patients who were most medically nonadherent and were not presenting for HD and therefore not receiving their prescribed epoetin or iron. We are limited by the available covariates to explain whether this observed association between Hb <10 g/dl and increased mortality is causal or whether higher hemoglobin is a marker for healthier patients with better compliance and/or less inflammation, for example. Clinically, however, we can apply this evidence by recognizing the risk that is associated with low Hb and looking more closely at these patients with more severe anemia. Increasing epoetin dosing alone may not be effective because other factors that limit epoetin response may be at work. Each patient's comorbid conditions and risk factors must be assessed using their level of Hb as a potential marker for poorer outcome.

For hospitalization analysis, we did not detect a statistically significant association between Hb level and risk for hospitalization. None of the covariates was statistically significant in the full adjusted model, with the exception of two of the four epoetin quartiles. The relationship between epoetin and risk for hospitalization did not seem dose dependent and therefore is difficult to interpret.

In crude analyses, serum albumin <3.5/3.2 g/dl and mean serum ferritin ≥800 ng/ml both were associated with increased risk for hospitalization. We used serum albumin and ferritin as surrogates for inflammation. In our database, we did not have data on specific acute or chronic inflammatory markers. A chronic inflammatory state was demonstrated previously in pediatric patients who were on HD (20). An inflammatory state may modify the relationship between anemia and hospitalization; however, we were unable to detect this association.

Conclusion

Patients with Hb ≥11 g/dl consistently demonstrated a 60 to 70% decreased risk for mortality across multiple models and with propensity score matching. Within Hb subcategories, Hb 11 to 12 *versus* <10 g/dl also was strongly associated with decreased risk for mortality (HR 0.30; 95% CI 0.19 to 0.74). Risk for mortality was similar between Hb 11 to 12 g/dl and >12 *versus* <10 g/dl. Therefore, in our population of adolescents who had ESRD and were on HD, those who failed to achieve the KDOQI target of Hb 11 to 12 g/dl showed increased risk for mortality. Because of the observational nature of our study and limited numbers of patients in each subcategory, we cannot conclude that Hb above the current adult KDOQI target is beneficial for adolescents who have ESRD and are on HD. We also are unable to infer any causal relationship between anemia and mortality or hospitalization. Further study in the form of randomized, clinical trials is necessary to investigate causality

and to elucidate optimal Hb levels in this particular subset of patients with ESRD.

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