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Associations of anemia persistency with medical expenditures in Medicare ESRD patients on dialysis

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Jiannong Liu[1]
Haifeng Guo[1]
David Gilbertson[1]
Robert Foley[1,2]
Allan Collins[1,2]

[1]Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, MN, USA; [2]Department of Medicine, University of Minnesota, Minneapolis, MN, USA

Abstract: Most end-stage renal disease (ESRD) patients begin renal replacement therapy with hemoglobin levels below the recommended US National Kidney Foundation Dialysis Outcomes Quality Initiative Guidelines lower level of 110 g/L. Although most patients eventually reach this target, the time required varies substantially. This study aimed to determine whether length of time with below-target hemoglobin levels after dialysis initiation is associated with medical costs, and if so, whether intermediate factors underlie the associations. US patients initiating dialysis in 2002 were studied using the Centers for Medicare and Medicaid Services ESRD database. Anemia persistence (time in months with hemoglobin below 110 g/L) was determined in a six-month entry period, and outcomes were assessed in the subsequent six-month follow-up period. The structural equation modeling technique was used to evaluate associations between persistent anemia and medical costs and to determine intermediate factors for these associations. The study included 28,985 patients. Mean per-patient-per-month medical cost was $6267 (standard deviation $5713) in the six-month follow-up period. Each additional month with hemoglobin below 110 g/L was associated with an 8.9% increment in medical cost. The increased cost was associated with increased erythropoietin use and blood transfusions, and increased rates of hospitalization and vascular access procedures in the follow-up period.

Keywords: anemia persistency, end-stage renal disease, medical costs, structural equation modeling

Introduction

For dialysis patients in the United States, hemoglobin levels have increased yearly since erythropoietin-stimulating agents (ESA) were introduced into clinical practice in 1989.[1] In early 1991, the mean hemoglobin level for end-stage renal disease (ESRD) patients was 96 g/L, and the level for 84.5% of patients was below the recommended National Kidney Foundation Dialysis Outcomes Quality Initiative (KDOQI) Guidelines lower target level of 110 g/L.[2,3] By June 2005, the mean hemoglobin level had increased to 119 g/L and levels were below 110 g/L for only 19.4% of patients.[1] In contrast to the temporal trends in the overall population, most incident patients begin dialysis treatment with hemoglobin levels below 110 g/L. In 2005, values were below 110 g/L for 67.4% of incident patients at dialysis initiation,[1] and the time required to reach the target level varies considerably. Low hemoglobin in ESRD patients is associated with increased mortality, morbidity, hospitalization, and medical costs; these associations are well documented.[4–11] One study also shows that longer time required to reach the target hemoglobin level was associated with significantly higher risk of hospitalization and mortality.[12] The present study was designed to address whether

Correspondence: Jiannong Liu
Chronic Disease Research Group, Minneapolis Medical Research Foundation, 914 South 8th Street, Suite S-253, Minneapolis, MN 55404, USA
Tel +1 612 347 7695
Fax +1 612 347 5878
Email jliu@cdrg.org

persistent anemia, measured by length of time after dialysis initiation with hemoglobin levels below 110 g/L, is associated with economic outcomes, and if so, whether intermediate factors, through which persistent anemia affects outcomes, underlie these associations?

Methods

Study population

This study includes 2002 incident US ESRD patients with hemodialysis as renal replacement therapy and Medicare as primary payer at day 91 after dialysis initiation. A six-month entry (baseline) period was defined from dialysis months 4–9. Months 1–3 were not used because data are incomplete for many patients. Patients who died, underwent transplant, changed primary payer, or whose hemoglobin was unreported or outside the range 33–183 g/L in one or more months of the six-month entry period were excluded. Patients were followed from the first day after the entry period to the first of death, undergoing transplant, changing primary payer, or six months.

Data sources and patient baselines

Data used for this study came from the Centers for Medicare and Medicaid Services (CMS) Renal Management Information System (REMIS) and CMS Standard Analytical Files. The REMIS database includes information from the CMS Medicare Enrollment Database, the United Network for Organ Sharing transplant database, the ESRD Medical Evidence Report (form CMS-2728), and the ESRD Death Notification (form CMS-2746). The Standard Analytical Files include Medicare Part A institutional claims (inpatient, outpatient, skilled nursing, home health, and hospice) and Part B physician/supplier claims.

Patient baseline information included demographic characteristics, hospital days and hemoglobin levels in the entry period, and comorbid conditions. Demographic characteristics, including age, sex, race (white, African American, other), and ethnicity (Hispanic, non-Hispanic), were obtained from the REMIS database. Duration of hospital stays in the entry period was obtained from Part A inpatient claims in the Standard Analytical Files.

Comorbid conditions were characterized from Medicare Part A and Part B claims in the entry period, using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and Physicians' Current Procedural Terminology (CPT) codes (see Appendix for the specific codes). Conditions characterized were diabetes, atherosclerotic heart disease (ASHD), congestive heart failure (CHF), peripheral vascular disease (PVD), cerebrovascular accident/transient ischemic attack (CVA/TIA), dysrhythmia, other cardiac diseases (including pericarditis, endocarditis, myocarditis, other complications of heart disease, heart transplant, heart valve replacement, and cardiac devices), cancer, liver disease, gastrointestinal bleeding, and chronic obstructive pulmonary disease (COPD). The method used for defining comorbid conditions from claims has been previously described.[13]

Patient hemoglobin values were obtained from the Medicare recombinant human erythropoietin (EPO) claims files derived from the outpatient Standard Analytical Files. For each patient, mean hemoglobin value was computed for each entry period month and for the entire entry period. The mean number of months with hemoglobin values below 110 g/L in the entry period was calculated for the overall cohort. Anemia persistence was described by number of months with hemoglobin values below 110 g/L in the entry period. To demonstrate the robustness of the analysis, we characterized persistent anemia in 2 additional ways: whether the number of months with hemoglobin level below 110 g/L was higher than the overall cohort mean number of months, and mean hemoglobin level in the entry period.

Outcomes

In the follow-up period, total EPO dose, total number of blood transfusions, hospital days, and number of vascular access procedures were derived from Medicare Part A and Part B claims. Per-patient-per-month (PPPM) Medicare allowable costs were obtained from Medicare Part A and Part B claims. Institutional Medicare allowable costs include Medicare payment, coinsurance, deductibles, and any payment provided by a payer other than Medicare. Costs in the follow-up period were summed for each patient and divided by the number of follow-up months to obtain PPPM cost.[10]

Statistical analysis

Patient baseline characteristics were tabulated overall and by persistent anemia groups. Differences among groups were assessed using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. Means and medians of EPO dose, number of blood transfusions, number of hospitalization days, and number of vascular access procedures in the follow-up period were also tabulated by persistent anemia group, and differences among groups were tested using the Wilcoxon rank sum test.

The structural equation modeling (SEM) technique was used to evaluate the associations between persistent anemia

and medical costs and to assess the intermediate clinical factors underlying these associations. SEM is a combination of path analysis and factor analysis[14,15] that has been widely used in the psychological, behavioral, and social sciences and was introduced to medical research recently.[16–18] Because SEM allows several regression equations to be tested simultaneously, it characterizes both the overall association between independent and dependent variables and intermediate factors that describe the nature of the association.

Because SEM is most effective when data, especially endogenous (dependent) variables and latent variables (factors measured by one or more variables) indicators, are normally distributed, the continuous variables in our data were checked for normality and transformed if necessary. Instead of the original values for PPPM, EPO dose, and numbers of transfusions, hospitalization days, and vascular access procedures, the natural logarithm of PPPM expenditures and the square roots of EPO dose and numbers of blood transfusions, hospitalization days, and vascular access procedures were used in the models. Because outlier PPPM costs can cause severe skewness, patients whose costs were above the highest 0.25th percentile or below the lowest 0.25th percentile were excluded.

To reduce the number of variables in the analysis and the number of categorical variables in the model, a comorbidity score was used in the models to replace the binary comorbidity variables. To obtain the comorbidity score, a linear regression model was fit with logged PPPM as dependent variable and age, sex, race, ethnicity, number of months with hemoglobin values below 110 g/L, duration of hospitalizations in the entry period, and all individual comorbid conditions as independent variables. A weight was assigned to each comorbid condition associated with logged PPPM ($p < 0.05$ in the regression model). Weights were multiplied up relative to the smallest parameter estimate and in whole-number increments. For example, the smallest parameter estimate for the significant comorbid conditions is 0.01642 for COPD, the parameter estimate for CHF is 0.0325, and the parameter estimate for CVA is 0.04935; we assigned weight 1 to COPD, weight 2 to CHF, and weight 3 to CVA. We assigned weight 1 to ASHD, COPD, and liver disease, 2 to CHF and other cardiovascular disease, 3 to CVA and PVD, and 4 to cancer. Gastrointestinal bleeding and dysrhythmia were nonsignificant. The comorbidity score for each patient was the sum of the weights based on the presence or absence of the comorbid conditions. In SEM, all relationships between endogenous variables and the corresponding exogenous variables should be linear. Plots and regression residual plots showed that the assumptions of linearity were met.

We hypothesized that the relationship between persistent anemia and total (all cause) medical cost was mediated by two factors: (1) anemia treatment and (2) general severity of illness. The anemia treatment factor was measured as EPO dose and number of blood transfusions in the follow-up period. The general severity of illness factor was measured by number of inpatient hospital days and number of vascular access procedures in the follow-up period. Mathematically, our assumed model is

$$Y = X_1\beta_1 + X_2\beta_2 + \varepsilon \quad (1)$$

$$X_1 = X_2\gamma + \varepsilon_1 \quad (2)$$

where Y is log(PPPM); X_1 includes anemia treatment (the common factor of EPO dose and number of transfusions in the follow-up period) and general severity of illness (the common factor of hospitalization days and number of vascular access procedures in the follow-up period); X_2 includes age, race, sex, ethnicity, number of hospital days in the entry period, comorbidity score and persistent anemia; ε and ε_1 are residuals. A graphic expression of models (1) and (2) is displayed in Figure 1. For simplicity and clarity, all baseline variables except persistent anemia are grouped together, in a box labeled "Baseline variables." An arrow from one box to another, such as "Baseline variables" to "Medical costs," means that the baseline variables were hypothesized to affect medical costs in the follow-up period. To assess whether persistent anemia was associated with medical costs in ways other than those intermediated by anemia treatment and general severity of illness, persistent anemia was included in X_2 in regression model (1), representing the total of the direct and other indirect associations, if any, between persistent anemia and medical costs, other than associations intermediated by anemia treatment and general severity of illness.

Results

The study cohort comprised 28,985 incident patients. Figure 2 illustrates in detail the study exclusion criteria by which patients were selected. Mean number of months with hemoglobin values below the target value of 110 g/L was 1.3 (Table 1). Persistent anemia groups were defined in three ways: number of months with hemoglobin values below 110 g/L (0, 1 to 2, or ≥3); whether the number of months with hemoglobin value below 110 g/L was ≤ or >1.3, the cohort mean; and whether mean hemoglobin over the entry period was < or ≥110 g/L. Younger age, female sex, African American race, Hispanic ethnicity, hospitalization during the entry period, and each comorbid condition studied were associated with persistent anemia. In the six-month follow-up period, mean follow-up time was 5.63 months per patient, and

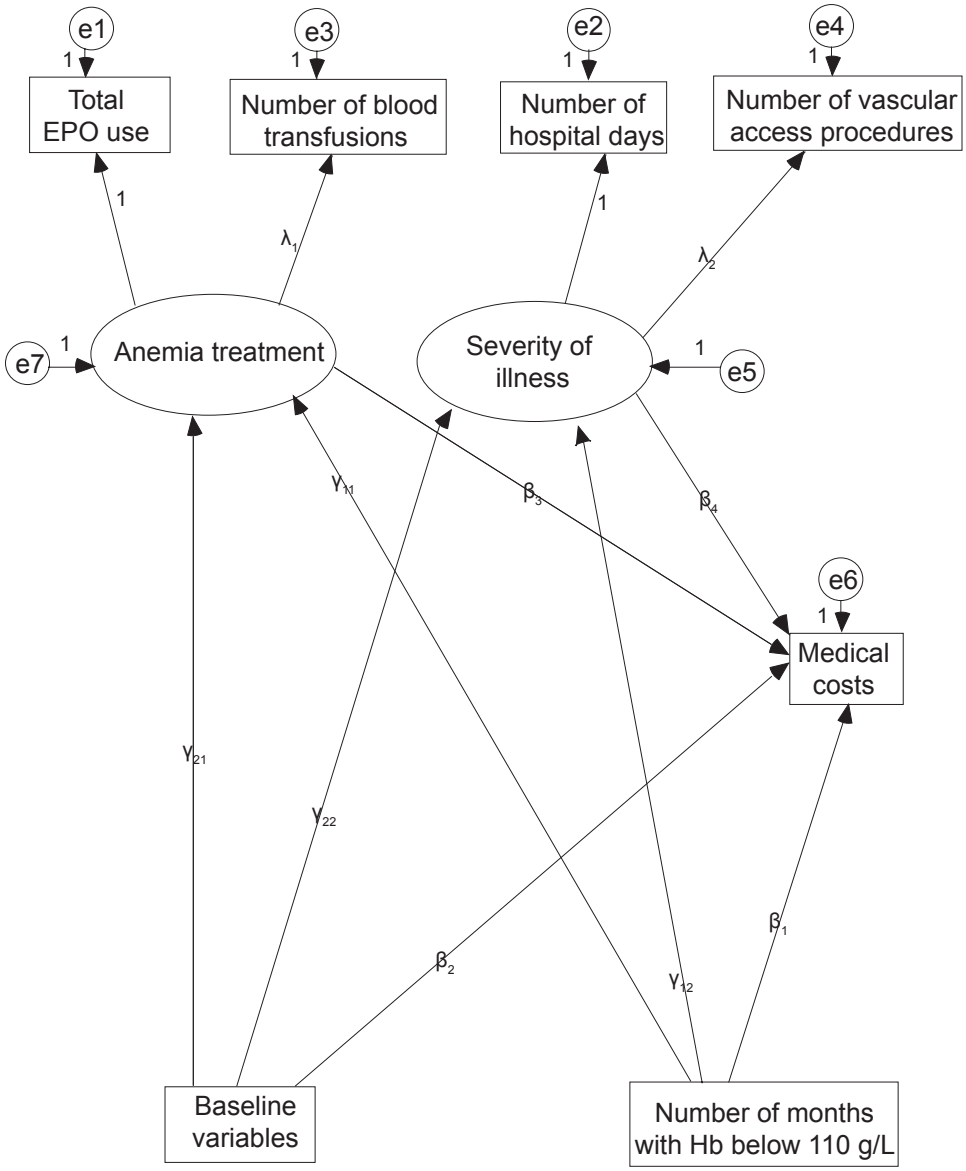

Figure 1 Graphical expression of assumed model. For simplicity and clarity, all baseline variables except persistent anemia appear together in a box labeled "Baseline variables." An arrow from one box to another, such as "Baseline variables" to "Medical costs," means that the baseline variables were hypothesized to affect medical costs in the follow-up period. The e_1–e_7 are residuals.

average medical cost was $6267 per patient per month in the follow-up period.

Among persistent anemia groups, compared with the zero-month group, the one-to-two months group and ≥ three-months group had mean values that were 47.6% and 155.1% higher for EPO doses, 41.2% and 252.9% higher for number of blood transfusions, 26.9% and 98.4% higher for number of hospital days, and 16.2% and 39.1% higher for number of vascular access procedures, respectively, in the follow-up period (Table 2). The corresponding cost showed the same relationship with persistent anemia. Results were similar for the other anemia persistency measures.

Compared with PPPM cost for patients with zero months with hemoglobin level below 110 g/L, mean PPPM costs for patients with one to two months and ≥ three months below 110 g/L were 14.9% and 47.8% higher, respectively (Table 3). The incremental costs were 29.3% higher for the >1.3-months group than for the ≤1.3-months group, and 43.7% higher for the group with mean hemoglobin below 110 g/L than for the group with mean hemoglobin above 110 g/L.

The β_1 in the structural equation model in Figure 1 was tested nonsignificant (the estimate is –0.006 and the p-value is 0.622). Thus, except for associations intermediated by

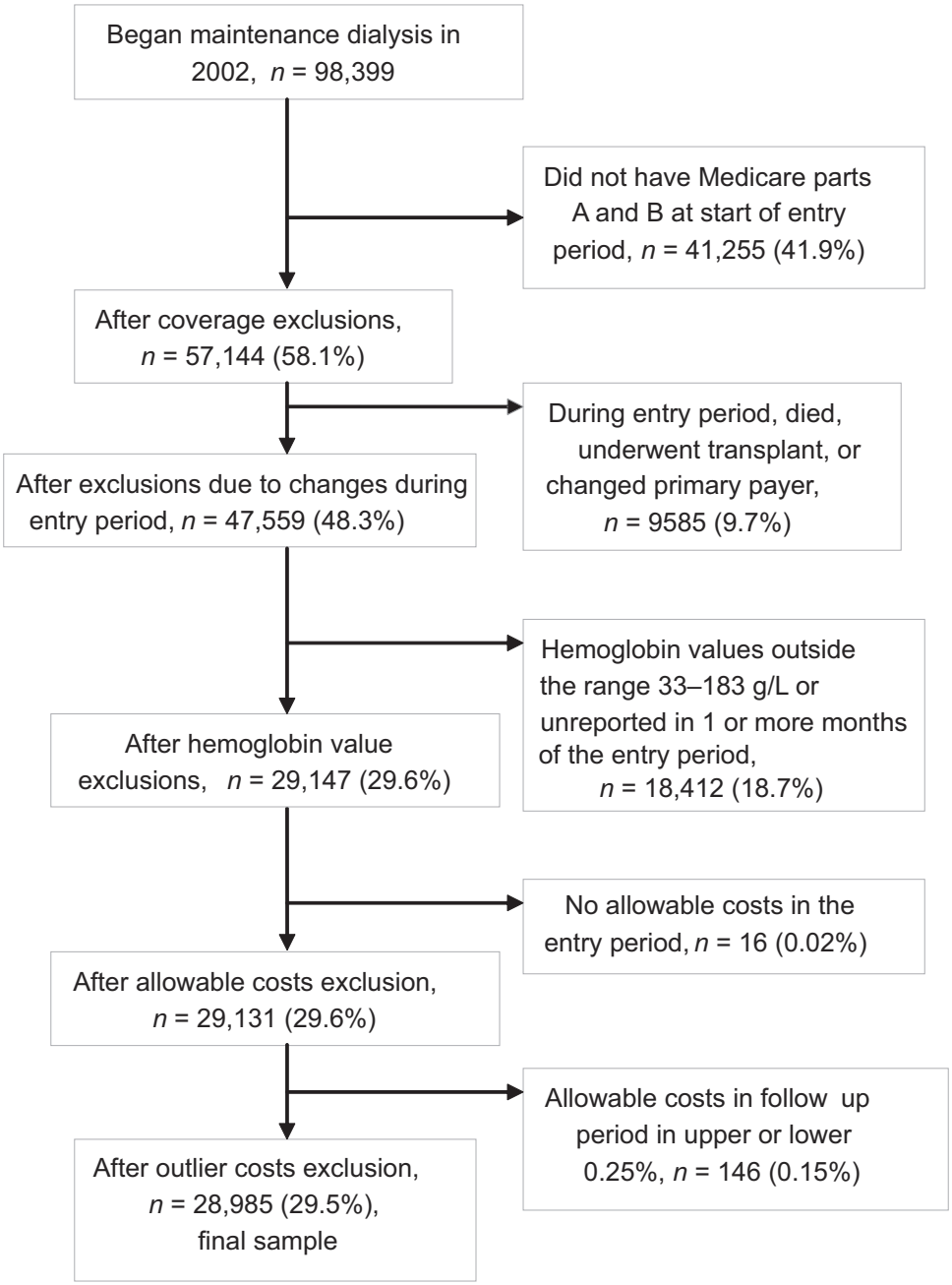

Figure 2 Flow chart for patient selection from the Centers for Medicare and Medicaid Services end-stage renal disease database.

anemia treatment and general severity of illness in the follow-up period, there is no other association between persistent anemia and medical costs, or it is too small to detect. Except β_1, all associations on paths from persistent anemia to medical cost are significant (all p-values are < 0.0001). The model was rerun with $\beta_1 = 0$. The model fits the data very well. The R-square for logged PPPM is 0.812; Goodness of Fit Index = 0.976, Normed Fit Index = 0.91, Root Mean Square Error Approximation = 0.057. Table 4 summarizes findings from structural equation models assessing associations between medical costs and persistent anemia. Persistent anemia was associated with future medical costs, an association that persisted when adjustment was made for age, sex, race, ethnicity, diabetes, comorbid conditions, and baseline length of hospital stay. Each additional month with hemoglobin below 110 g/L was associated with an 8.9% cost increment (because the log scale was used for costs, the total percent change has a multiplicative, not an additive relationship, here $1.036 \times 1.051 \approx 1.089$ [95% confidence

Table 1 Patient characteristics: All and by persistent anemia group

	All	Baseline months with hemoglobin < 110 g/L						Baseline mean hemoglobin		
Characteristics		**0**	**1–2**	**≥3**	***P*[a]**	**≤1.3[b]**	**>1.3[b]**	***P*[a]**	**≥110 g/L**	**<110 g/L**	***P*[a]**
n	**28,985**	**11,450**	**12,154**	**5,381**		**18,580**	**10,405**		**25,315**	**3670**	
Baseline mean (SD)											
Number of months below	1.30		1.41	3.80		0.38	2.93		0.90	4.02	
Hemoglobin target	(1.46)	0	(0.49)	(1.01)	<0.001	(0.49)	(1.16)	<0.001	(1.00)	(1.20)	<0.001
Baseline mean (SD)											
Hemoglobin, g/L	119 (10)	126 (7)	119 (5)	107 (9)	<0.001	124 (7)	111 (9)	<0.001	122 (7)	103 (8)	<0.001
Baseline mean (SD)	6106	5016	6280	8034		5391	7383		5748	8575	
Medical cost, dollars	(3700)	(2677)	(3578)	(4825)	<0.001	(2983)	(4439)	<0.001	(3306)	(5076)	<0.001
Baseline mean (SD) EPO	2.41	1.87	2.40	3.58		2.02	3.12		2.19	3.96	
Dose (1000 U per day)	(1.78)	(1.23)	(1.60)	(2.45)	<0.001	(1.35)	(2.19)	<0.001	(1.50)	(2.60)	<0.001
Age, yr					<0.001			<0.001			<0.001
Mean	65.6	66.7	65.6	63.4		66.4	64.2		66	62.7	
Median	69	70	68	66		69	67		69	66	
Age groups, yr, percent					<0.001			<0.001			<0.001
0–44	10.1	8.4	10.2	13.6		9.0	12.2		9.4	14.9	
45–64	27.8	26.5	27.8	30.5		26.7	29.8		27.3	31.0	
65–74	31.2	32.0	31.2	29.2		31.8	30.0		31.5	28.8	
≥75	31.0	33.2	31.0	26.6		32.6	28.0		31.8	25.3	
Sex, percent					<0.001			<0.001			<0.001
Men	51.1	53.7	50.0	48.0		52.5	48.6		51.5	48.2	
Women	48.9	46.3	50.0	52.0		47.5	51.4		48.5	51.8	
Race, percent					<0.001			<0.001			<0.001
White	63.2	64.3	63.3	60.4		64.1	61.4		63.7	59.2	
African American	31.9	30.8	31.5	35.0		30.8	33.7		31.2	36.3	
Other	5.0	4.9	5.2	4.6		5.1	4.9		5.1	4.5	
Ethnicity, percent					<0.001			0.075			0.369
Non-Hispanic	88.1	89.0	87.7	87.4		88.4	87.7		88.2	87.7	
Hispanic	11.9	11.0	12.3	12.6		11.6	12.3		11.8	12.3	
Baseline hospital days					<0.001			<0.001			<0.001
Mean	5.6	3	5.9	10.6		3.9	8.8		4.7	11.8	
Median	0	0	1	5		0	3		0	6	

Baseline hospital day groups, percent					<0.001			<0.001			<0.001
0[c]	50.3	62.7	46.2	33.0		57.3	37.8		53.3	29.4	
1–7	26.2	24.7	27.9	25.7		26.1	26.5		26.3	25.6	
>7	23.5	12.6	25.9	41.3		16.6	35.8		20.4	45.0	
Baseline comorbid conditions, percent											
Atherosclerotic heart disease	35.5	31.7	37.2	39.7	<0.001	33.6	38.9	<0.001	34.7	40.8	<0.001
Congestive heart failure	32.9	27.0	34.2	42.6	<0.001	29.0	39.9	<0.001	31.2	44.8	<0.001
Diabetes mellitus	60.8	59.0	61.6	63.0	<0.001	59.7	62.9	<0.001	60.6	62.7	0.012
CVA/TIA	11.7	9.0	12.8	15.0	<0.001	10.1	14.7	<0.001	11.2	15.2	<0.001
Peripheral vascular disease	25.6	20.6	27.9	33.0	<0.001	22.6	31.0	<0.001	24.4	34.5	<0.001
Other cardiovascular disease	20.0	14.6	21.1	29.3	<0.001	16.7	26.1	<0.001	18.4	31.6	<0.001
COPD	14.1	11.4	14.5	18.8	<0.001	12.3	17.2	<0.001	13.2	19.8	<0.001
Gastrointestinal bleeding	6.6	3.7	7.3	11.1	<0.001	4.7	9.8	<0.001	5.7	12.8	<0.001
Liver disease	8.1	7.6	8.1	8.9	0.014	7.8	8.7	0.007	7.8	10.0	<0.001
Dysrhythmia	22.0	18.9	22.8	26.7	<0.001	20.2	25.2	<0.001	21.1	28.2	<0.001
Cancer	7.0	5.4	6.9	10.6	<0.001	5.8	9.2	<0.001	6.4	11.3	<0.001

Notes: [a]*P* values obtained by χ^2 test for categorical variables and Wilcoxon rank-sum test for continuous variables. [b]The cohort mean number of months with hemoglobin values below 110 g/L is 1.3. [c]0 days means no hospitalization. About half of hospitalized patients were hospitalized for ≤7 days and about half for >7 days; thus, 7 days was chosen as the cut point.

Abbreviations: COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; EPO, erythropoietin; SD, standard deviation.

Table 2 Mean and median erythropoietin dose, number of blood transfusions, number of vascular access procedures, and hospitalization days in the follow-up period, by persistent anemia group (n = 28,985)

	Baseline months with hemoglobin <110 g/L							Baseline mean hemoglobin		
Means[a] and medians	**0**	**1 to 2**	**≥3**	***P*[b]**	**≤1.3[c]**	**>1.3[c]**	***P*[b]**	**≥110 g/L**	**<110 g/L**	***P*[b]**
EPO dose (1000 U/day)				<0.001			<0.001			<0.001
Mean (SD)	1.47 (1.11)	2.17 (1.69)	3.75 (3.06)		1.67 (1.27)	3.11 (2.67)		1.89 (1.53)	4.28 (3.36)	
Median	1.19	1.73	2.84		1.33	2.33		1.48	3.3	
Numbers of transfusions per patient-year				<0.001			<0.001			<0.001
Mean	0.17	0.24	0.6		0.12	0.45		0.21	0.71	
Median	0	0	0		0	0		0	0	
All-cause hospital days per patient-year				<0.001			<0.001			<0.001
Mean	11.54	14.64	22.89		12.38	19.47		13.46	25.27	
Median	0	2	7.98		0	5.99		0	9.98	
Numbers of vascular access procedures per patient-year				<0.001			<0.001			<0.001
Mean	1.97	2.29	2.74		2.06	2.56		2.16	2.81	
Median	0	0	2		0	2		0	0	

Notes: [a]Weighted mean with follow-up time as weight. [b]*P* values obtained by Wilcoxon rank-sum test. [c]The cohort mean number of months with hemoglobin values below 11 g per dL is 1.3.
Abbreviations: EPO, erythropoietin; SD, standard deviation.

Table 3 Mean, median, 25th and 75th percentiles of per patient per month costs in dollars in the follow-up period by persistent anemia group

	Baseline months with hemoglobin <110 g/L							Baseline mean hemoglobin		
Per patient per month costs, $	**0**	**1 to 2**	**≥3**	***P*[a]**	**≤1.3[b]**	**>1.3[b]**	***P*[a]**	**≥110 g/L**	**<110 g/L**	***P*[a]**
n	11,450	12,154	5381		18,580	10,405		25,315	3670	
				<0.001			<0.001			<0.001
Mean[c] (SD)	5461 (494)	6276 (554)	8070 (691)		5684 (511)	7349 (643)		5958 (530)	8562 (737)	
Median	4180	4919	6802		4376	5985		4616	7390	
25th–75th percentiles	3092–6671	3481–8051	4399–10,998		3188–7037	3954–9954		3293–7498	4763–11,946	

Notes: [a]*P* values obtained by Wilcoxon rank-sum test. [b]The cohort mean number of months with hemoglobin values below 110 g/L is 1.3. [c]Weighted mean with follow-up time as weight.
Abbreviation: SD, standard deviation.

interval 8.2%–9.4%]). Similarly, each one-unit increase in mean hemoglobin in the entry period was associated with an 11.8% decrease in medical costs (95% confidence interval 10.1%–12.4%). Medical costs for the >1.3-months group were 22.0% higher than for the ≤ 1.3-months group. The adjusted difference between the > and ≤1.3-months groups was smaller than the unadjusted difference (22.0% vs 29.3%) because the >1.3-months group was more ill, with more comorbid conditions and more hospital days in the entry period (see Table 1).

Discussion

This study shows that persistent anemia after dialysis therapy initiation is followed by increased medical costs and that the association between persistent anemia and future medical costs was mainly explained by associations with future EPO doses, blood transfusions, hospitalizations, and vascular access procedures in the follow-up period. Hospitalization and vascular access (the indirect costs) appeared to be the more important component of the anemia/cost relationship.

Our finding that persistent anemia is associated with higher medical costs is consistent with previous studies,[9–11] but our methodology may represent a level of robustness not seen in other observational studies. Structural equation modeling is attractive because it can incorporate complex relationships among the endogenous and exogenous variables. It not only models the association between persistent anemia and medical costs, but also assesses the intermediate factors for

Table 4 Association between persistent anemia and medical costs from structural equation models

Association	**Months with hemoglobin <110 g/L**		
	Continuous variable[a]	**>1.3[b]**	**Mean hemoglobin**
γ_{11} (SE)	0.044 (0.001)	0.09 (0.003)	–0.64 (0.002)
γ_{12} (SE)	0.321 (0.016)	0.79 (0.043)	–0.474 (0.023)
β_3 (SE)	0.789 (0.048)	0.822 (0.065)	0.789 (0.049)
β_4 (SE)	0.158 (0.004)	0.157 (0.004)	0.158 (0.004)
Effect through anemia treatment			
Effect at log scale	0.035	0.074	–0.05
Percentage change at the original scale	3.6	7.7	–4.9
Effect through general severity of illness			
Effect at log scale	0.05	0.124	–0.075
Percentage change at the original scale	5.1	13.2	–7.2
Total effect (SE)[c]			
Effect at log scale	0.085 (0.003)	0.198 (0.008)	–0.125 (0.004)
Percentage change at the original scale	8.9 (0.027)	22.0 (0.176)	–11.8 (0.047)

Notes: [a]Number of months with hemoglobin value below 110 g/L. [b]The cohort mean number of months with hemoglobin values below 110 g/L is 1.3. [c]Bootstrap standard error.
Abbreviation: SE, standard error.

the association. A 6-month follow-up period, much shorter than most other studies, was used because hemoglobin levels change frequently over even short time periods,[19] and these changes during the follow-up period could affect outcomes if the follow-up time were longer. Assessing the effect of persistent anemia on medical cost would thus be impossible. Our shorter follow-up period avoids this problem.

For incident ESRD patients starting dialysis, minimizing time with hemoglobin values below 110 g/L may need to be balanced against the potential for exceeding target hemoglobin levels, which appears to be common.[1] Although the higher hemoglobin levels, like the levels below 110 g/L, may be transient, safety concerns related to higher targeted hemoglobin levels were reported in the Normal Hematocrit Study[20] and the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study.[21] Adverse morbidity and mortality outcomes occurred in the higher hemoglobin target group, a finding that should be carefully considered. Conversely, the lower hemoglobin levels are also of concern because they also appear to be linked to morbidity and costs. Time within the target hemoglobin range of 110 to 120 g/L may be the best measure of successful anemia treatment.

Because more than 90% of patients had at most three months with hemoglobin values below 110 g/dL, the effect of patients with more than three months on the parameter estimate was weak. Therefore, interpretation of results should focus on patients with hemoglobin values below 110 g/L for three months or less. Similarly, interpretation of the results should focus on patients with mean hemoglobin values between 100 and 130 g/L, because mean hemoglobin values for most patients fell in this range. It should be noted that achieved patient hemoglobin levels are the result of the target hemoglobin level, treatment, and patient health status. The target range was likely 110–130 g/L for most of patients, because that was the KDOQI recommended target range during the study period. The results of this study are consistent with results in the Normal Hematocrit Study[20] in the sense that for each target group, those with higher hematocrit had better outcomes.

The limitations of this study are related to its retrospective design and its reliance on administrative claims. Though the results are adjusted for numerous baseline patient factors, residual confounding remains possible and likely. Also, the results are adjusted for patient comorbid conditions, but condition severity, which might be associated with both persistent anemia and medical costs, is not available in the data. Survival for nine months (three months before the entry period and six months during the entry period), primary coverage by Medicare Parts A and B, and six months of hemoglobin reports in the entry period were study entry criteria, and the findings may not be generalizable to all incident patients numerically; however, the pattern of associations should be the same.

Disclosure

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Appendix

International Classification of Diseases, Ninth Revision, *Clinical Modification* (ICD-9-CM) Codes, Current Procedural Terminology (CPT) Codes, and V-Codes Used to Define Comorbid Conditions and Vascular Access

Condition/Access	ICD-9-CM Code/CPT Code	V-code
Atherosclerotic heart disease	410.xx–414.xx	V45.81; V45.82
Congestive heart failure	398.91; 422.xx; 425.xx; 428.xx; 402.x1; 404.x1; 404.x3	V42.1
Cerebrovascular accident/transient ischemic attack	430.xx–438.xx	
Peripheral vascular disease	440.xx–444.xx; 447.xx; 451.xx–453.xx; 557.xx	
Cardiac (other)	420.xx–421.xx; 423.xx–424.xx; 429.xx; 785.0–785.3	V42.2; V43.3
Chronic obstructive pulmonary disease	491–494; 496.xx; 510.xx	
Gastrointestinal bleeding	456.0–456.2; 530.7; 531–534; 569.84; 569.85; 578	
Liver disease	570.xx; 571.xx; 572.1; 572.4; 573.1–573.3	V42.7
Dysrhythmia	426.xx–427.xx	V45.0x; V53.3x
Cancer	140.xx–172.xx; 174.xx–208.xx; 230.xx–231.xx; 233.xx–234.xx	
Diabetes	250.xx; 357.2; 362.0x; 366.41	
Vascular access	CPT code 36800 alone; CPT codes 36488, 36489, 36490, 36491, 36533 associated with diagnosis codes 250.xx, 403.xx, 593.xx, V56.x, 996.1, 996.62, 996.73, V45.1, or 580.xx–589.xx	