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Death, Hospitalization, and Economic Associations among Incident Hemodialysis Patients with Hematocrit Values of 36 to 39%

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Abstract. Anemia treatment with epoetin has led to dramatic increases in hematocrit levels since 1989. Studies have demonstrated that morbidity and mortality rates are lower when hematocrit values are within the Disease Outcomes Quality Initiative (DOQI) target range (33 to 36%). Recently, clinical studies demonstrated that patients without cardiovascular disease exhibited lower morbidity rates and improved cognitive function with hematocrit values of >36%. One prospective trial, in contrast, demonstrated that normal hematocrit values among patients with cardiac disease were associated with higher mortality rates. These conflicting results have led to concerns regarding the risks and benefits associated with hematocrit values between 36 and 42%. To address these concerns, a recent cohort of 1996 to 1998 incident hemodialysis patients was studied, with assessments of the risks of death and hospitalization and the medical costs associated with hematocrit values of >36%. Patients survived at least 9 mo after dialysis initiation, and comorbidity, disease severity, and hematocrit levels were determined for months 4 to 9. Patients were grouped on the basis of hematocrit values, *i.e.*, <30, 30 to <33, 33 to <36, 36 to <39, or ≥39%, with 1 yr of follow-up monitoring. A Cox regression model was used to evaluate all-cause and cause-specific mortality and hospitalization rates. The economic evaluations included analyses with Medicare Parts A and B allowable expenditures as the dependent variable and the same clinical characteristics as independent variables. For patients with hematocrit values of ≥36%, mortality rates were not different, hospitalization rates were 16 to 22% lower, and expenditures were 8.3 to 8.5% less, compared with patients with hematocrit values of 33 to <36%. These observations do not demonstrate causality. Additional long-term studies are needed to assess the risks of higher hematocrit values among all patients and patients with cardiovascular disease.

Current recommended practices for the treatment of anemia associated with end-stage renal disease (ESRD) suggest that hematocrit values between 33 and 36% provide clinical and cost-effective outcomes (1–5). A recent study (6) demonstrated that achievement of higher mean hematocrit values of 38.5% in 6 mo was associated with lower Sickness Impact Profile scores and improved Karnofsky Scale scores for hemodialysis patients with no history of cardiovascular disease. Additional studies by McMahon and Dawborn (7) demonstrated that physical performance and electrolyte abnormalities were significantly improved among patients with hematocrit values of >36%, compared with those with hematocrit values of <36%. Pickett *et al.* (8), evaluating cognitive function in brain electrophysiologic studies, demonstrated significant enhancement of visually evoked potentials when hematocrit values were in the normal range of >36%, compared with <36%. These electrophysiologic studies were supported by a trial that demonstrated normalization of brain circulation with hematocrit values of approximately 36% (9).

These recent studies are in contrast to the prospective clinical trial by Besarab *et al.* (10), which compared patients with hematocrit levels of 30% *versus* normal hematocrit values of 42%. Those authors evaluated 1233 patients with evidence of congestive heart failure or ischemic heart disease. The study was terminated early because of an increased, but nonsignificant, incidence of nonfatal myocardial infarction or death in the normal hematocrit group when the data were analyzed by using an intent-to-treat analysis. Of note, 397 patients in the "normal" hematocrit group did not achieve a mean hematocrit level of 39.0 to 41.9% during the course of the study. For the 201 patients who actually attained hematocrit levels of 39.0 to 41.9% for at least a 6-mo period, the subsequent mortality rate was 15%, compared with a 40% mortality rate for patients maintained with lower hematocrit values. The discrepancy between the intent-to-treat results from the prospective clinical trial reported by Besarab *et al.* (10) and the findings from the

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more recent physiologic studies (reported by other investigators, as noted above) suggest that additional studies of patients with higher hematocrit values may be needed. Some concerns regarding the previous studies have centered on the inclusion of prevalent patients, because many prevalent patients have a considerable history of disease and may not adequately demonstrate the effects of anemia correction. Therefore, we evaluated only incident hemodialysis patients, with Medicare insurance, who were treated between January 1, 1996, and June 30, 1998, examining the patient outcomes for mortality rates, hospitalization rates, and Medicare-allowable expenditures during the 1-yr follow-up period. This report summarizes our findings.

Materials and Methods

Data Sources and Patient Population

We evaluated incident hemodialysis patients with Medicare insurance who were treated between January 1, 1996, and June 30, 1998. Because there are differences in Medicare data availability for the first 90 d between patients <65 yr of age and patients >65 yr of age (11), we restricted the analyses to patients surviving the first 90 d and a full 6-mo entry period. The follow-up period was a minimum of 6 mo for 1998 patients and up to 1 yr for 1996/1997 patients. Patients were excluded if they made less than four erythropoietin (EPO) and hematocrit claims during the 6-mo entry period (3,4), to ensure data consistency. Patients with secondary-pay Medicare insurance (identified from Part A and Part B claims) (12) and patients with payment amounts of less than $675/mo for dialysis (inpatient and outpatient) were also excluded, because of incomplete data on comorbidity, hematocrit values, EPO dosing, and allowed expenditures (11,13,14).

During the 6-mo entry period, the demographic characteristics, renal diagnoses, comorbid conditions, disease severity, and hematocrit levels for the patients were assessed (3–5). Demographic information included age, race, gender, and primary renal diagnosis, which were obtained from the Identification and Medical Evidence portions of the Renal Beneficiary Utilization System (REBUS) of the Health Care Financing Administration (HCFA). Comorbid conditions were characterized on the basis of all Medicare Part A and Part B claims during the 6-mo entry period, using the International Classification of Diseases and Physicians' Current Procedural Terminology codes, as described previously (4,5). Indicators of disease severity, including the number of blood transfusions, the number of vascular access procedures, and the total number of hospital days during the 6-mo entry period, were extracted from the Medicare Part A and Part B claims files (5). EPO and hematocrit data were obtained from the Medicare EPO claims files. Claims were aggregated to a monthly level, with EPO dosage summed for the month. The last hematocrit value from the last EPO claim of the month was used, to ensure consistent data availability. The mean EPO dose and mean hematocrit value for the 6-mo entry period were computed for each patient.

Data on causes of death were obtained from the REBUS Identification and Death Notification Files, and causes of deaths were classified as cardiovascular, infectious, or other on the basis of the REBUS Death Notification Form (HCFA 2746) cause-of-death codes. Data on causes of hospitalization were obtained from the HCFA Institutional Inpatient Standard Analytical Files, and causes of hospitalization were classified as cardiovascular, infectious, or other on the basis of the principal International Classification of Diseases clinical modification code for each admission.

Financial data for the follow-up period were obtained from Medicare Part A and Part B claims and were categorized by using revenue codes for Part A claims and Current Procedural Terminology codes for Part B claims. Calculation of allowable Medicare per-member-per-month (PMPM) expenditures was performed by using the approach described by Collins *et al.* (5).

Statistical Analyses

The explanatory predictors included age (<20, 20 to 44, 45 to 64, 65 to 74, or >74 yr), race (white, black, or other), gender, primary diagnosis (diabetes mellitus *versus* non-diabetes mellitus), comorbid conditions, disease severity, and hematocrit levels. Comorbidities included atherosclerotic heart disease, congestive heart failure, peripheral vascular disease, cerebrovascular accident/transient ischemic attacks, other cardiac diseases, cancer, chronic obstructive pulmonary disease, gastrointestinal diseases with bleeding, liver disease, and gallbladder disease. Disease severity measures in the 6-mo entry period consisted of total inpatient days (0, 1 to 10, 11 to 20, or >20 d), number of blood transfusions (0, 1 or 2, or ≥3), and number of vascular access procedures (0, 1 to 4, or ≥5). Hematocrit levels were divided into five groups, *i.e.*, <30%, 30 to <33%, 33 to <36%, 36 to <39%, and ≥39%.

The study end points were all-cause death, cause-specific death, all-cause first hospitalization, and cause-specific first hospitalization during the follow-up period. Time to the event (either death or first hospitalization admission) or time to censoring was calculated. The censoring occurred at death, a modality change, loss to follow-up monitoring, renal transplantation, or the end of the follow-up period. Hospitalization end point censoring occurred at a modality change, loss to follow-up monitoring, renal transplantation, or the end of the follow-up period. Therefore, the dependent variables were either the event of death or hospitalization and the corresponding follow-up time.

To evaluate the association with hematocrit levels by controlling for patient characteristics, comorbidity, and disease severity, separate analyses of mortality and hospitalization rates were performed by using a Cox regression analysis stratified on the basis of diabetic status. The reference population consisted of white male patients 20 to 44 yr of age, without comorbidity, without disease severity indicators, and with hematocrit levels of 33 to <36% during the 6-mo entry period.

Multiple linear regression analyses were used to estimate the association between explanatory variables and allowable Medicare PMPM expenditures. The techniques were described in a previous study by Collins *et al.* (5). Because Medicare expenditures are highly skewed to the right and are not normally distributed, the data were trimmed 0.5% on the extremes and natural-logarithmically transformed, to improve the fit of the data. The smearing estimate was used to adjust for nonconstant variances and was applied to the final estimates in the retransformed data (15,16). The same sets of independent predictors were evaluated as in the survival analyses described above. The dependent variable was the natural-logarithmically transformed, allowable Medicare PMPM expenditure in the 1-yr follow-up period.

Results

Mortality and Hospitalization

Patient Characteristics. There were 66,761 incident hemodialysis patients treated between January 1, 1996, and June 30, 1998, who survived the entry period with at least four EPO/hematocrit claims. Among this incident study population,

26,443 patients were treated in 1996, 24,910 patients in 1997, and 15,408 patients in one-half of 1998. Data for the total of 66,761 patients were as follows: the mean age was 65 yr, 51.2% of the patients were male and 48.8% were female, 58.3% were white and 35.4% were black, 44.8% had a primary diagnosis of diabetes mellitus, the mean number of hospital days during the entry period was 5.94 d, 49.3% of patients underwent vascular access procedures during the entry period, and 5.8% received blood transfusions during the entry period. Of the patients, 13.1% ($n = 8760$) exhibited hematocrit values of <30%, 36.6% ($n = 24,465$) exhibited hematocrit values of 30 to <33%, 43% ($n = 28,674$) exhibited hematocrit values of 33 to <36%, 6.5% ($n = 4307$) exhibited hematocrit values of 36 to <39%, and 0.8% ($n = 555$) exhibited hematocrit values of ≥39%.

The patient characteristics for the different hematocrit groups are presented in Table 1. The Pearson χ^2 test was used for categorical variables and the Kruskal-Wallis test for continuous variables. For each of the patient characteristics, there was a significant difference overall among the hematocrit groups (P values of <0.001 to <0.0001). For example, the mean age was older, there were more male and more white patients, and the mean number of hospital days in the 6-mo entry period was smaller for the groups with higher hematocrit values. Because there were differences among the hematocrit groups, an adjustment for these differences was made in the survival and hospitalization risk models.

Unadjusted Mortality and Hospitalization Rates. The unadjusted all-cause and cause-specific mortality rates (expressed as deaths/1000 treatment-yr) for nondiabetic, diabetic, and all patients are presented in Table 2. Cardiac-cause, other-cause, and all-cause mortality rates seemed to be lowest when patient hematocrit levels were 36 to <39%. These patterns were observed for nondiabetic patients, diabetic patients, and all study patients. Therefore, without adjustment for risk factors such as patient characteristics, comorbid conditions, and disease severity, patients with hematocrit values of 36 to <39% seem to exhibit lower mortality rates.

The unadjusted all-cause and cause-specific hospitalization rates (expressed as the number of first hospitalizations/1000 treatment-yr) for nondiabetic, diabetic, and all patients are presented in Table 3. Patients with hematocrit values of 36 to <39% exhibited the lowest unadjusted first hospitalization rates, compared with patients with lower hematocrit values. These associations were observed for all-cause and cause-specific hospitalization rates for both diabetic and nondiabetic patients.

Adjusted Mortality and Hospitalization Rates. The adjusted relative risks for death and hospitalization are presented in Figures 1 to 3 for all-cause, cardiac, and infectious events, respectively. There were statistically significant differences between groups, compared with the reference hematocrit range (33 to <36%), when the confidence intervals (CI) did not include 1 or, as demonstrated in Figures 1 to 3, when the confidence bars did not overlap the reference line. CI are reported for adjusted mortality rates but, for subsequent comparisons, readers should refer to Figures 1 to 3 for observation of significant differences.

The lower risk of death resulting from all causes in the first 1 yr of the follow-up period was associated with higher hematocrit levels, after controlling for risk factors such as patient characteristics, comorbid conditions, and disease severity (Figure 1). Compared with patients with hematocrit values of 33 to <36%, patients with hematocrit values of <30% and 30 to <33% exhibited significantly higher risks of death during the 1-yr follow-up period; the corresponding risk ratios were 1.74 (95% CI, 1.66 to 1.83) and 1.25 (95% CI, 1.20 to 1.30), respectively. However, there was no significant difference in the mortality risk between patients with hematocrit values of 33 to <36% and patients with hematocrit values of 36 to <39% (relative risk, 0.99; 95% CI, 0.92 to 1.07) or between patients with hematocrit values of 33 to <36% and patients with hematocrit values of ≥39% (relative risk, 1.05; 95% CI, 0.86 to 1.28) in the 1-yr follow-up period.

A similar pattern was observed for hospitalization risks (Figure 1). Compared to patients with hematocrit values of 33 to <36% (reference), patients with hematocrit values of <30% and 30 to <33% exhibited significantly higher risks of hospitalization. However, in contrast to mortality risks, hospitalization risk in patients with hematocrit values of 36 to <39% and

Table 1. Patient characteristics among different hematocrit groups during the 6-mo entry period[a]

	Hct < 30%	30% ≤ Hct < 33%	33% ≤ Hct < 36%	36% ≤ Hct < 39%	Hct ≥ 39%	*P* Value[b]
Patients (no.)	8760	24,465	28,674	4307	555	
Age (yr)	61.4	64.7	66.0	65.6	66.5	<0.0001
Male (%)	48.1	49.5	52.8	55.3	53.5	<0.001
White (%)	48.7	57.5	61.6	60.9	61.4	<0.001
Black (%)	45.4	36.4	32.1	31.9	31.9	<0.001
Diabetes mellitus (%)	42.3	46.0	44.7	43.6	38.7	<0.001
Hospital days	10.7	6.8	4.2	3.8	4.0	<0.0001
Mean EPO (U/mo)	66,980	53,746	42,820	38,538	40,702	<0.0001
Mean iron (vials/mo)	2.08	2.203	2.359	2.488	2.645	<0.0001

[a] Hct, hematocrit; EPO, erythropoietin.
[b] Kruskal-Wallis test for age, hospital days, mean EPO, and mean iron and χ^2 test otherwise.

Table 2. Unadjusted all-cause and cause-specific mortality rates in the 1-yr follow-up period

	Mortality Rate (deaths/1000 treatment-yr)					
	Hct < 30%	30% ≤ Hct < 33%	33% ≤ Hct < 36%	36% ≤ Hct < 39%	Hct ≥ 39%	Overall
Nondiabetics						
all-cause	357	252	183	179	195	229
cardiac	141	114	83	77	87	101
infectious	47	30	20	22	20	27
other	170	108	80	80	87	101
Diabetics						
all-cause	366	267	218	208	226	253
cardiac	158	132	109	103	84	123
infectious	64	36	27	28	26	35
other	145	99	81	78	116	95
All patients						
all-cause	361	259	199	192	207	240
cardiac	148	122	95	88	86	111
infectious	54	33	23	25	23	31
other	159	104	81	79	98	99

≥39% were significantly lower risks, compared to patients with hematocrit values of 33 to 36%.

For cardiac-cause death, a lower risk of death in the first 1 yr of the follow-up period was associated with higher hematocrit levels (Figure 2). Compared with patients with hematocrit values of 33 to <36%, patients with hematocrit values of <30% and 30 to <33% exhibited significantly higher risks of death in the follow-up period. There was no significant difference in the mortality risk between patients with hematocrit values of 33 to <36% and patients with higher hematocrit values.

A similar pattern was observed for cardiac-cause hospitalization among patients with hematocrit values of <33% (Figure 2). Compared with patients with hematocrit values of 33 to <36%, patients with hematocrit values of <33% exhibited significantly higher risks of hospitalization during the follow-up period. However, in contrast to cardiac-cause death, patients with hematocrit values of 36 to <39% exhibited significantly lower risks of cardiac-cause hospitalization, compared with patients with hematocrit values of 33 to <36%. There was no significant difference in the hospitalization risk between patients with hematocrit values of 33 to <36% and patients with hematocrit values of ≥39% during the follow-up period.

Therefore, patients with hematocrit values of 36 to <39% exhibited lower risks of cardiac-cause hospitalization during

Table 3. Unadjusted all-cause and cause-specific hospitalization rates

	Hospitalization Rate (no. of first hospitalizations/1000 treatment-yr)					
	Hct < 30%	30% ≤ Hct < 33%	33% ≤ Hct < 36%	36% ≤ Hct < 39%	Hct ≥ 39%	Overall
Nondiabetics						
all-cause	1401	1041	763	568	652	909
cardiac	379	326	253	183	230	286
infectious	350	215	144	112	89	187
other	672	500	365	273	332	436
Diabetics						
all-cause	1617	1213	908	696	683	1067
cardiac	434	349	284	203	218	315
infectious	372	242	164	135	94	209
other	812	623	461	359	371	544
All patients						
all-cause	1488	1117	825	621	664	977
cardiac	401	336	266	191	226	298
infectious	359	227	153	121	91	196
other	728	554	406	309	347	482

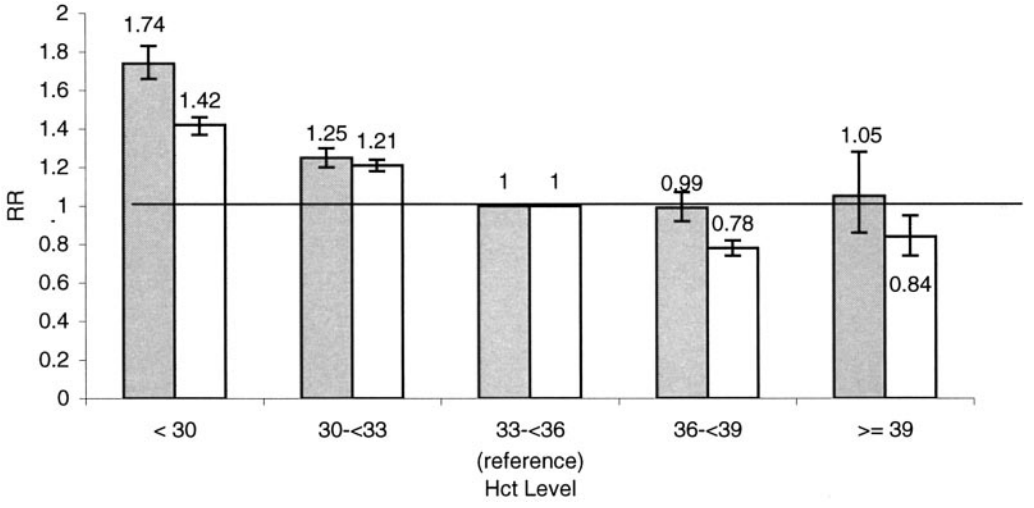

Figure 1. Relative risks (RR) of death (□) and hospitalization (□) from all causes [with 95% confidence intervals (CI)]. Hct, hematocrit.

the follow-up period, compared with patients with hematocrit values of 33 to <36%. The lower risk of hospitalization was statistically significant, but the lower risk of death was not statistically significant at the 95% confidence level.

For infectious-cause death, patients with hematocrit values of <33% exhibited significantly higher risks of death during the follow-up period, compared with patients with hematocrit values of 33 to <36% (Figure 3). There was no significant difference in the risk of death between patients with hematocrit values of 33 to <36% and patients with hematocrit values of ≥36% in the follow-up period.

However, for infectious-cause hospitalization, patients with hematocrit values of <33% exhibited significantly higher risks of hospitalization and patients with hematocrit values of >36% exhibited significantly lower risks of hospitalization, compared with patients with hematocrit values of 33 to <36% (Figure 3).

Expenditure Results

Unadjusted Allowable PMPM Expenditures. The economic associations between allowable Medicare PMPM expenditures in the follow-up period and the clinical predictors of death and hospitalization, with censoring at a modality change, were evaluated. Table 4 presents the unadjusted allowable PMPM expenditures corresponding to patient hematocrit levels. Total allowable Medicare PMPM expenditures for patients with hematocrit values of <30% were 32.8% more, for patients with hematocrit values of 30 to <33% were 14.3% more, for patients with hematocrit values of 36 to <39% were 5.8% less,

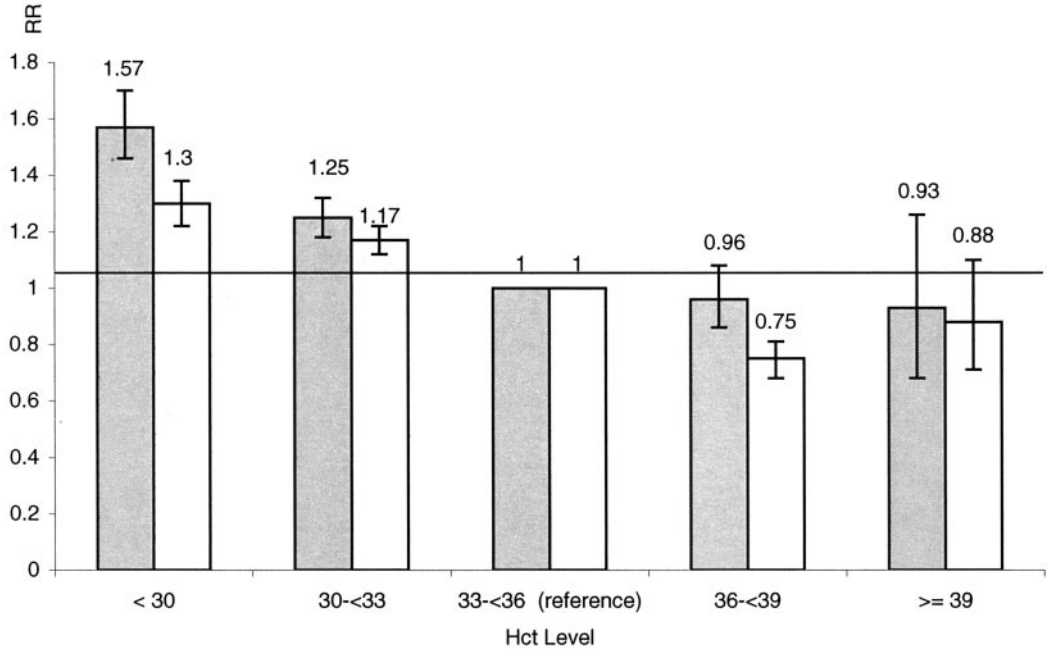

Figure 2. Relative risks (RR) of death (□) and hospitalization (□) from cardiac causes (with 95% CI). Hct, hematocrit.

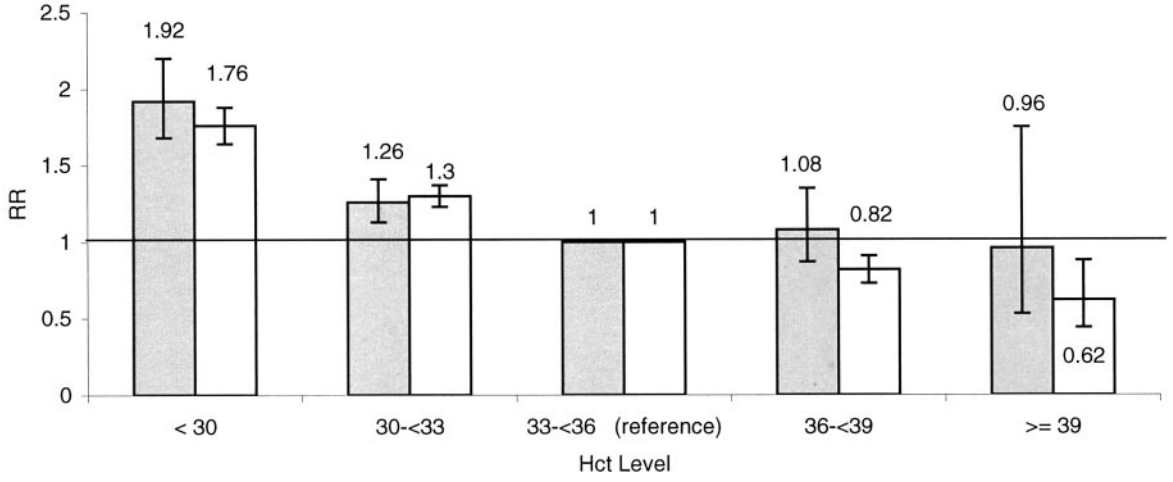

Figure 3. Relative risks (RR) of death (■) and hospitalization (□) from infectious causes (with 95% CI). Hct, hematocrit.

and for patients with hematocrit values of ≥39% were 6.7% less, compared with patients with hematocrit values of 33 to <36% (reference). The EPO expenditures for patients with hematocrit values of <30% were 89.5% more, for patients with hematocrit values of 30 to <33% were 36.9% more, for patients with hematocrit values of 36 to <39% were 27.3% less, and for patients with hematocrit values of ≥39% were 38.5% less, compared with patients with hematocrit values of 33 to <36%. The unadjusted results demonstrated the association of lower total allowable Medicare EPO expenditures with higher hematocrit levels.

Adjusted Allowable PMPM Expenditures. The adjusted percent changes in allowable Medicare PMPM expenditures for patients with different hematocrit levels were compared and estimated by using ordinary least-squares estimates. The modified Levene test (17) demonstrated significant heteroscedasticity across hematocrit groups; therefore, the comparisons were performed on the basis of the smeared estimates (15,16). Total Medicare allowable expenditures in the follow-up period for patients with hematocrit values of <30% were 24.1% more, for patients with hematocrit values of 30 to <33% were 10.6% more, for patients with hematocrit values of 36 to <39% were 8.3% less, and for patients with hematocrit values of ≥39% were 8.5% less, compared with patients with hematocrit values of 33 to <36% (reference).

The adjusted percent change in allowable PMPM EPO expenditures was also estimated by using the ordinary least-squares method with the dependent variable being the natural logarithm of allowable PMPM EPO expenditures. The results from the smeared estimate, with the assumption of heteroscedasticity, demonstrated that EPO expenditures in the follow-up period for patients with hematocrit levels of <30% were 82.1% more, for patients with hematocrit levels of 30 to <33% were 35.8% more, for patients with hematocrit levels of 36 to <39% were 26.6% less, and for patients with hematocrit levels of ≥39% were 39.4% less, compared with patients with hematocrit levels of 33 to <36%, after controlling for risk factors (5).

Discussion

Determination of the appropriate target hematocrit level for patients undergoing hemodialysis continues to be a controversial area. Recently, significant improvements in the quality of life and functional status of patients with normalized hematocrit levels were demonstrated in a prospective study of selected patients who were undergoing hemodialysis and receiving epo-

Table 4. Unadjusted allowable Medicare PMPM expenditures in the 1-yr follow-up period, censored at modality change

	Hct < 30%	30% ≤ Hct < 33%	33% ≤ Hct < 36%	36% ≤ Hct < 39%	Hct ≥ 39%	All
Total patients[a]	7759	22,274	26,271	3864	486	60,654
Total allowable PMPM expenditures ($)	6283	5405	4730	4456	4415	5167
change (%)	32.8	14.3	Reference	−5.8	−6.7	
EPO allowable PMPM expenditures ($)	774	559	408	297	251	505
change (%)	89.5	36.9	Reference	−27.3	−38.5	

[a] The patient numbers are different from those in Table 1 because some patients had previous hospitalizations at the end of the follow-up period. When we calculated the per-member-per-month (PMPM) expenditures, we excluded patients with Medicare as a secondary payer.

etin treatment (6). That study involved hemodialysis patients without cardiovascular disease, who attained a mean hematocrit level of 38.5 ± 2.5% after 6 mo of treatment. Quality-of-life measurements with the Sickness Impact Profile decreased and measurements with the Karnofsky scale increased (lower scores are better with the Sickness Impact Profile and higher scores are better with the Karnofsky scale), after 6 mo of follow-up monitoring, with increased hematocrit values. The number of hospitalizations was reduced after 6 mo of follow-up monitoring, compared with baseline values, and the rate of adverse cardiovascular effects was low (6).

Previous studies conducted by our research group (3,4) demonstrated an association between lower probabilities of death and hospitalization and higher hematocrit levels among prevalent hemodialysis patients with Medicare insurance. Ma *et al.* (4) demonstrated that patients with hematocrit levels in the range of 33 to <36% seemed to exhibit a lower risk of death, compared with patients with hematocrit values in the range of 30 to <33%. Xia *et al.* (3) demonstrated that patients with hematocrit levels in the range of 33 to <36% exhibited less risk of hospitalization, compared with patients with lower hematocrit levels. Because there were insufficient patients with higher hematocrit levels in those studies, which were performed using a 1993 long-term dialysis cohort (1% of patients demonstrated hematocrit values of ≥36%), a comparison of clinical outcomes between patients with hematocrit levels of 33 to <36% and patients with hematocrit levels of 36 to <39% was not performed.

In this study, we examined a more recent incident dialysis cohort (patients treated between January 1, 1996, and June 30, 1998), which contained sufficient patients with hematocrit levels of ≥36%. Our study cohort included 6.45% of patients ($n = 4307$) with hematocrit levels of 36 to <39% overall, and there were 11.67% of patients with hematocrit levels of 36 to <39% in the 1998 cohort. The larger number of patients with hematocrit values of 36 to <39% was associated with a lower first-hospitalization risk, compared with patients with hematocrit levels of 33 to <36% (reference group). The risk of death for patients with hematocrit levels of 36 to <39% was not significantly different from that for patients with hematocrit levels of 33 to 36%.

Our findings are consistent with results from the prospective trials reported by McMahon and Dawborn (7), Metry *et al.* (9), and Pickett *et al.* (8). Our recent study results and the national trends in increasing hematocrit values and lower mortality rates are consistent with the national trends in first-year mortality rates for incident dialysis patients (11), in contrast to the results of the study by Besarab *et al.* (10). The reasons for the differences in outcomes between the latter study and our work should be carefully considered. The study by Besarab *et al.* (10) was a prospective randomized trial of patients undergoing long-term dialysis, with hematocrit value groups of 30% *versus* 42% (10). To achieve the target hematocrit level of 42%, patients required larger doses of EPO and intravenously administered iron. Our observational study was conducted with incident dialysis patients and demonstrated that patients with hematocrit values of 36 to <39% and ≥39% used lower doses of EPO, compared with patients with lower hematocrit values. Our findings most likely reflect selection bias, because patients with more sensitivity to EPO may be more likely to achieve higher hematocrit levels. The study by Besarab *et al.* (10) evaluated patients with cardiac disease (New York Heart Association class I, II, or III congestive heart failure or ischemic heart disease), compared with our observational study that evaluated all hemodialysis patients with Medicare insurance who survived the 6-mo entry period, regardless of cardiac status. In addition, our study evaluated incident dialysis patients with hematocrit levels achieved early in their ESRD history. The incident dialysis patients in our study had survived the first 9 mo of ESRD treatments, compared with the patients undergoing long-term dialysis studied by Besarab *et al.* (10), who exhibited a mean ESRD time of 3.2 yr. The observational question our study attempts to answer is whether there is an adverse mortality or hospitalization risk in the next 1 yr of follow-up monitoring, if an incident dialysis patient survives the first 9 mo of treatment and exhibits hematocrit values in the 36 to <39% range during the entry period. In fact, there seems to be no mortality advantage or disadvantage, compared with patients with values of 33 to <36%, but a lower associated hospitalization risk and lower Medicare allowable expenditures were observed.

Besarab *et al.* (10) performed an intent-to-treat analysis, according to their study protocol. The results suggested that there was a trend toward a higher mortality rate and a higher rate of nonfatal myocardial infarctions for the high-hematocrit group. However, only 201 of 598 patients achieved mean hematocrit values of 39.0 to 41.9%. When those authors reanalyzed the data using achieved hematocrit values, they observed that patients who actually reached the target "normal" hematocrit value exhibited lower mortality rates in the follow-up period, compared with patients in lower-hematocrit groups. Therefore, the results of their secondary analysis are consistent with our study results, which demonstrated that the hospitalization risk was lower among patients who actually achieved hematocrit values of >36%. Our study did not demonstrate a mortality advantage for the patients with hematocrit values of 36 to <39%, compared with the 33 to <36% group, which is different from the lower mortality rate noted in the study by Besarab *et al.* (10) for patients who achieved normal hematocrit values.

More importantly, it may be inappropriate to compare an observational study with a randomized prospective trial, because the study design and controls are quite different. We attempted to adjust for medical conditions and disease severity in our study, which only strengthened the findings, compared with the unadjusted event rates.

Hematocrit levels observed for dialysis patients have steadily improved in the past decade (2,18). The percentage of in-center hemodialysis patients with hematocrit values of ≥30% increased from 46% in late 1993 to 83% in late 1998 (18). The percentage of patients with hematocrit values of <30% decreased from 64.7% in 1990 to 11.6% in 1998. The percentage of patients with hematocrit values of 30 to <33% was 28% in 1990, increased to 46.4% in 1994, and then

decreased to 33.4% in 1998. The percentage of patients with hematocrit values of 33 to <36% increased from 6.4% in 1990 to 46.4% in 1998. The percentage of patients with hematocrit values of 36 to <39% increased from 0.7% in 1990 to 7.3% in 1998, thus confirming the HCFA clinical performance data (19). Although other factors, such as dialysis therapy, have also improved in the past decade, the continued decrease in the mortality rate extended into 1998, while the urea reduction ratio has increased only marginally.

After adjustment for many factors, including the number of hospital days in the entry period, we observed that the relative risks for infectious causes of hospitalization were decreased when patients achieved hematocrit values of >36%. It is unclear why higher hematocrit values lead to lower infectious-cause hospitalization rates, but there are at least two possible explanations. Patients with infectious diseases, cancer, and other inflammatory conditions respond less readily to EPO, because of increased levels of cytokines and other inflammatory mediators. Therefore, patients with lower hematocrit values in general may exhibit more infectious problems, which we did not specifically examine in this analysis. In addition, patients with higher hematocrit values may have improved blood delivery to tissues, which may improve the response of the body to infection. Unfortunately, the two possible mechanisms cannot be distinguished in this type of observational study.

In addition to the analyses of clinical outcomes, we performed an expenditure analysis. The results presented here confirmed our previous findings (5) and demonstrated that patients with hematocrit values of 36 to <39% exhibited significant associated savings, in either total or EPO Medicare allowable expenditures, in the 1-yr follow-up period. Our earlier work and the economic analysis presented here also noted higher expenditures for patients with hematocrit values of <30%.

Our findings may reflect selection bias, because our study protocol required patients to survive the first 9 mo of ESRD. However, our findings are consistent with the lower first-year mortality rates reported by the United States Renal Data System for 1996 to 1998, during a time of increasing hematocrit levels in the dialysis population as a whole (11,18). The early hematocrit transition period is a clinical reality, with patients beginning with mean hematocrit values of 28% (as documented on Medical Evidence Forms) and achieving mean hematocrit values of 34% by 4 to 6 mo after dialysis initiation (11). This early hematocrit transition period should be evaluated more carefully to establish whether the increase in mean hematocrit values from 28 to 34% yields lower risks, compared to those associated with changes from 30 to 42% (10). Given the important clinical concern regarding adverse events among patients with cardiac disease but the favorable effects on cerebral function, cognitive function, and quality-of-life parameters, caution should be used in extrapolating our results. We think it may be premature to suggest a change in target hematocrit values to 36 to <39% on the basis of this observational study. Further analyses and additional trials are needed to confirm our results. In addition, we used a follow-up period of only up to 1 yr. Longer-term studies to evaluate the effects of sustained high hematocrit values should be considered. Given the difficulty of maintaining stable hematocrit values in the Disease Outcomes Quality Initiative target range of 33 to 36% for several months, whether hematocrit values reach the 36 to <39% range may be of less concern than previously considered. Additional research on patients with symptomatic cardiac disease and on outcomes in the early hematocrit transition period is needed to address these areas of concern.

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