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Hematocrit Level and Associated Mortality in Hemodialysis Patients

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Abstract. Although a number of clinical studies have shown that increased hematocrits are associated with improved outcomes in terms of cognitive function, reduced left ventricular hypertrophy, increased exercise tolerance, and improved quality of life, the optimal hematocrit level associated with survival has yet to be determined. The association between hematocrit levels and patient mortality was retrospectively studied in a prevalent Medicare hemodialysis cohort on a national scale. All patients survived a 6-mo entry period during which their hematocrit levels were assessed, from July 1 through December 31, 1993, with follow-up from January 1 through December 31, 1994. Patient comorbid conditions relative to clinical events and severity of disease were determined from Medicare claims data and correlated with the entry period hematocrit level. After adjusting for medical diseases, our results showed that patients with hematocrit levels less than 30% had significantly higher risk of all-cause (12 to 33%) and cause-specific death, compared to patients with hematocrits in the 30% to less than 33% range. Without severity of disease adjustment, patients with hematocrit levels of 33% to less than 36% appear to have the lowest risk for all-cause and cardiac mortality. After adjusting for severity of disease, the impact of hematocrit levels of 33% to less than 36% is vulnerable to the patient sample size but also demonstrates a further 4% reduced risk of death. Overall, these findings suggest that sustained increases in hematocrit levels are associated with improved patient survival.

The introduction of recombinant human erythropoietin (EPO) into clinical practice in August 1989 significantly changed the course of anemia therapy for patients with end-stage renal disease (ESRD). Numerous studies have shown the beneficial effects of anemia correction on cognitive function, patient activity, quality of life, and left ventricular hypertrophy (1). However, the optimal level of anemia correction has not been adequately defined, nor has the level of correction been shown to affect the associated mortality and morbidity.

On the basis of Food and Drug Administration (FDA) guidelines and clinical studies, the National Kidney Foundation in 1997 published the Dialysis Outcomes Quality Initiative (DOQI), suggesting a recommended target hematocrit level of 33 to 36% for anemia management in dialysis patients (1). These recommendations were developed after a review of the literature and reassessment of the previous targets used in the early 1990s following introduction of epoetin therapy. The initial target hematocrit approved by the FDA in August 1989 was from 30 to 33%, despite the fact that the target range from the Phase III clinical trial of 300 patients was 35 ± 3% (2). In June 1994, the FDA increased the target hematocrit level ranges for epoetin treatment to 30 to 36%.

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Two single-center studies have suggested that hematocrit levels higher than 33% are associated with reduced patient morbidity: Foley *et al.* in patients with cardiovascular disease (3), and Ritz *et al.* in polycystic kidney disease patients(4). Studies on the quality of life have also supported hematocrit levels in the range of 33 to 36%, compared to lower than 30% (5). In addition, exercise capacity was improved when hematocrit levels were in the range of 35 to 40% (6).

Unfortunately, few studies have been conducted to assess the impact of hematocrit levels in the 33 to 36% range on mortality. Madore *et al.* showed that in 18,792 National Medical Care hemodialysis patients, the adjusted mortality was higher in patients with hemoglobin concentrations (Hb) <100 g/L compared to those with hemoglobins from 100 to 110 g/L, and no difference in mortality was noted in patients with hemoglobins >110 g/L (7). Several factors in this study limited their ability to assess the impact of the higher hemoglobin levels. First, a 3-month entry period may have been insufficient to classify patients into stable hemoglobin ranges. Second, inclusion of patients with hemoglobin levels >120 g/L might bias the patient group with higher hemoglobins, since medical justification is required by Medicare for epoetin administration in patients with hemoglobins over 120 g/L (or hematocrits over 36%). The 120 g/L hemoglobin group would contain sicker patients than the group with 110 to 120 g/L, thereby masking a potential subgroup (hemoglobins 110 to 120 g/L), which may have a lower risk. Third, although the study included case-mix adjustment, no data were available on medical conditions and/or disease severity. Therefore, the impact of hemoglobins >110 g/L is still unclear.

To address some of the potential limitations noted above, we assessed the effect of hematocrit levels up to 36% on mortality in a period prevalent hemodialysis cohort in the latter half of 1993, with adjustment for comorbidity and disease severity. This report summarizes our findings.

Materials and Methods

Study Design and Patient Population

The study population included all prevalent Medicare hemodialysis patients surviving the period from July 1 to December 31, 1993. All patients had to survive at least 90 days to ensure homogeneous availability on medical conditions, hospitalizations, dialysis billing, and EPO/hematocrit claims. This 90-day requirement is necessary because in-center hemodialysis patients younger than 65 yr of age have a 90-day waiting period before Medicare coverage is available (8,9). The follow-up period was from January 1 to December 31, 1994. End points for the study were all-cause death and cause-specific death during the follow-up period. Cause-specific death included cardiac death and infectious death, as defined on the Health Care Financing Administration (HCFA) 2746 death notification form. Patients were censored at the time of dialytic modality switch or transplantation, when lost to follow-up, or on December 31, 1994, whichever occurred first.

Data on patient characteristics, which included date of ESRD onset, age, gender, race (black, white, Native American, and other), causes of ESRD, date of death, and cause(s) of death, were obtained from the HCFA ESRD Program Management and Medical Information System (PMMIS) files. The hemodialysis treatment was determined from revenue codes 82X on the HCFA institutional outpatient claims filed on HCFA Uniform Bill forms (UB82) throughout the entire entry and follow-up period.

Data on the hematocrit levels were obtained from HCFA EPO files, which were compiled from the HCFA outpatient dialysis claims submitted to Medicare for EPO reimbursement by treatment facilities (10,11). The hematocrit levels on these claims reflect only those hemodialysis patients receiving EPO to sustain their hematocrit levels. Patients with spontaneously higher hematocrits above 36% and not receiving EPO were not reported on these claims and therefore were not included in the analysis. Furthermore, no predialysis hematocrit levels were included. To characterize the patients by hematocrit levels that would also be representative of the 6-mo entry period, only patients with four or more EPO/hematocrit claims were included. This criterion ensured a minimum of 3 mo with EPO claims during the 6-mo entry period, with an average 5.1 mo of EPO coverage. Furthermore, patients with average hematocrit levels above 36% were excluded from most analyses in the study due to potential selection bias of these patients, whose medical justification is required by Medicare for their EPO administration. Specific analysis with the hematocrit group greater than 36% included demographics of the patients and a single Cox regression, as noted below.

Comorbidity and Severity of Disease

The comorbid conditions were determined longitudinally from The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes on the HCFA institutional claims (from Uniform Bill UB82/92 forms; Medicare Part A 1984–1993) and Physicians' Current Procedural Terminology (CPT) codes on the HCFA physician/supplier claims (from HCFA 1500 forms; Medicare Part B 1991–1993). The major medical conditions were defined as atherosclerotic heart disease, congestive heart failure, peripheral vascular disease, cerebrovascular accident/transient ischemic attacks, other cardiac diseases (consisting of valvular heart disease, arrhythmias, and pacemakers), cancer (including malignant melanoma but excluding other skin malignancies), chronic obstructive pulmonary disease, liver disease, gallbladder disease, gastrointestinal diseases, and gastrointestinal tract diagnoses associated with bleeding (12).

Severity of medical conditions was summarized during the 6-mo entry period by quantifying acute blood loss events (such as blood transfusions and vascular access procedures) and hospital length of stay. Vascular access procedures were determined from the CPT codes in physician/supplier claims and all blood transfusions from both inpatient and outpatient claims. Additionally, disease severity was defined by accounting for the total of all inpatient lengths of stay (in days) for each patient during the entry period (from the date of admission to the date of discharge on the inpatient claims). The total entry period hospital days provided a current degree of "illness." These severity of disease measures were used as preexisting conditions before the follow-up period to assess patient outcomes.

Statistical Analyses

Patient age and years of prior ESRD exposure were calculated at the beginning of the entry period (July 1, 1993), for the following age groups: under 45, 45 to 64, 65 to 74, and 75 yr and older. Prior ESRD exposure (in years) was classified as <1, 1 to 2, 3 to 5, and >5 yr. All of the comorbid conditions were summarized from the first available claim up to the beginning of the 6-mo entry period. Severity of disease during the entry period was characterized by the number of vascular access procedures performed (none, 1 to 3, and 4 or more), blood transfusions (none, 1 to 3, and 4 or more), and total length of stay in days (none, 1 to 3, 4 to 10, 11 to 20, and 21 or more). Average hematocrit values during the entry period were categorized into five hematocrit groupings: less than 27%, 27% to less than 30%, 30% to less than 33%, 33% to less than 36%, and 36% and greater.

Among all hemodialysis patients who survived the entire 6-mo entry period, comparisons of patient characteristics were tested by χ^2 analysis among those with none, three or less EPO claims, and those with four or more EPO claims. These comparisons were performed to ensure a clear definition of the variables in the study population (four or more EPO claims), compared to the excluded patients. For the study population, the distribution of patient characteristics was also examined among the five hematocrit groups for significant differences using χ^2 analysis among the hematocrit groups. Percent deaths and unadjusted death rates (number of deaths per 1000 hemodialysis treatment-years) were computed for all-cause mortality as well as for cardiac and infectious cause-specific mortality.

The impact of hematocrit levels, patient demographics, prior ESRD exposure, comorbidity, and severity of disease indicators was evaluated using a Cox proportional hazards model (13). The time of prior ESRD exposure was included to reduce the potential bias from left truncation in the prevalent cohort (14). To avoid the potential nonproportionality between renal diagnoses, the Cox regression analysis was stratified on diabetic status, as defined from primary cause of ESRD as diabetes or diabetic complications before the study entry. To assess the influence of severity of disease, separate Cox regression analyses were performed both with and without these factors. The end points for the Cox regression analyses were all causes of death as well as cardiac death and infectious death. The baseline population consisted of white male patients younger than 45 yr, with less than 1 yr of ESRD exposure, without comorbidity, with no blood transfusions, no vascular access procedures, no hospital stays, and with hematocrit levels of 30% to less than 33%. An additional Cox regression analysis

on all-cause and cause-specific death was performed by including patients with hematocrit levels above 36% to contrast their mortality with those having hematocrit levels under 36%.

All statistical analyses were performed using the Statistical Analysis System (SAS) statistical package, version 6.12 (SAS Institute, Cary, NC). The descriptive results are presented as a percentage of patients, except as indicated, and the results from the Cox regression are presented as relative risks (RR) with 95% confidence intervals (CI). All of the probability values are two-tailed.

Results

Patient Characteristics

During the entry period from July 1 to December 31, 1993, a total of 96,369 hemodialysis patients survived the entire 6-mo entry period. Of these, 1,096 patients (approximately 1%) had at least one hematocrit greater than 36%. This small group of patients was restricted to only selected analyses due to insufficient power to evaluate their mortality risks. Of the remaining 95,273 patients, approximately 14% of patients ($n = 13,488$) had no EPO claims at all; 8% ($n = 7,187$) had one to three EPO claims; and 78% ($n = 75,283$) had four or more EPO claims. Descriptive comparisons of all patient characteristics among these three subpopulations are shown in the first three columns of Table 1. For each of the characteristics listed, there is a significant difference by χ^2 test ($P < 0.0001$) among the three types of EPO claim groupings.

Compared with those patients having three or less claims, it appears that patients with four or more EPO claims were more likely to be older, female, a minority race, and have relatively longer ESRD exposure before study entry (July 1, 1993) than the included study group (with four or more EPO claims). Patients with four or more EPO claims had significantly more diabetes and hypertension, higher percentages of comorbid conditions, received more vascular access procedures and blood transfusions, and had more hospital days. Thus, patients with three or fewer EPO claims were younger and relatively healthier patients. Our study population was slightly older, had more black patients, and had slightly fewer diabetics and 1% more hypertensive patients, compared with the United States Renal Data System (USRDS) in-center hemodialysis patients between 1991 and 1995, as shown in the fourth column of Table 1 (9).

Of the 75,283 patients in the study population, there were twelve percent in the hematocrit group less than 27%, thirty percent in the hematocrit group 27% to less than 30%, forty-four percent in the hematocrit group 30% to less than 33%, and thirteen percent in the hematocrit group 33% to less than 36%. The group greater than 36% accounted for 1%, or 685 patients. The distributions of patient characteristics by the five hematocrit groups are shown in Table 2, and they were all significantly different among the five hematocrit groups by the χ^2 test ($P < 0.05$). Specifically, older, male, and white patients were more likely to have hematocrits greater than 30%. The results in Table 2 also show the significant differences in comorbid conditions and disease severity measurements among the hematocrit groups. Although the results were not completely consistent across all medical conditions, patients with more comorbidity and longer hospital lengths of stay in the entry period tended to have lower hematocrit levels. The hematocrit group 36% and above had significantly greater prevalence of congestive heart failure, other cardiac disease, liver disease, gallbladder disease, and gastrointestinal bleeding history. Increasing prevalence of congestive heart failure and other cardiac diseases was also noted as the hematocrit levels decreased in the groups under 36%. Similar patterns existed in patients with liver disease and diseases associated with gastrointestinal bleeding. There was also a monotonic decrease in the number of access procedures, blood transfusions, and hospital days as the hematocrit levels increase. Therefore, there appears to be a strong association between hematocrit level and comorbidity as well as disease severity, and these confounding effects should be adjusted in the Cox regression analyses. The hematocrit group 36% and greater had more comorbidity, which may reflect the medical justification biasing secondary to HCFA payment rules.

Unadjusted Mortality

For each of the hematocrit ranges, the percentages of all-cause, cardiac, and infectious death are shown in Table 3, separated by diabetic status. The hematocrit group 36% and above was not assessed secondary to the small sample size. The percentages of deaths decreased as the hematocrit levels increased in both nondiabetic and diabetic patients, and they were significantly different among the remaining four hematocrit groups ($P < 0.001$), except for cardiac deaths in nondiabetic patients ($P = 0.168$). Table 4 shows the unadjusted all-cause and cause-specific death rates (as deaths per 1000 hemodialysis treatment-years) by diabetic status. Because of the selection criterion that patients had to survive at least 6 mo, the overall mortality was slightly lower than that in the general U.S. hemodialysis population, reported at 275 and 211 deaths per 1000 treatment-years for diabetic and nondiabetic patients, respectively (Table D4, pages D-22 and D-23 of the 1997 USRDS Annual Data Report (9)). The death rate in the diabetic population was much higher than that in nondiabetics, but the patterns with respect to hematocrit levels were the same. That is, all-cause and cause-specific mortality decreased monotonically as the hematocrit level increased. The unadjusted mortality showed that increasing the hematocrit from the level of less than 27% to the level of 33% to less than 36% was associated with a twenty-six percent and thirty-two percent all-cause mortality reduction in nondiabetics and diabetics, respectively. A similar pattern held for cause-specific death: a fourteen percent and twenty-four percent reduction for cardiac death, and a forty-six percent and forty percent reduction for infectious death in nondiabetics and diabetics, respectively. Therefore, without risk adjustment other than diabetic status, higher hematocrits were associated with lower all-cause and cause-specific mortality, and this trend was consistent in both nondiabetic and diabetic patients.

Table 1. Distribution of patient characteristics (%)[a]

Characteristic[b]	No EPO Claims (n = 13,488)	1 to 3 EPO Claims (n = 7,187)	≥4 EPO Claims (n = 75,283)	USRDS Hemo 1991-1995
Age				
under 45	24.8	24.2	18.6	18.7
45 to 64	43.7	43.1	35.3	36.1
65 to 74	20.3	22.5	29.4	27.6
≥75	11.2	10.2	16.7	17.6
Female	38.2	42.2	51.4	
Race				
white	56.6	50.4	49.3	54.8
black	36.0	42.2	41.3	39.2
Native American	1.1	1.4	1.4	1.5
other	6.3	6.0	8.1	4.5
Primary renal diagnosis				
diabetes mellitus	25.8	29.8	31.1	33.2
hypertension	27.0	28.2	31.1	30.1
GN	18.8	17.5	16.4	13.9
other	28.4	24.6	21.4	22.8
Prior ESRD exposure				
<1 yr	26.5	25.7	23.0	
1 to 2 yr	15.8	20.4	19.6	
2 to 5 yr	25.3	26.7	33.9	
≥5 yr	32.5	27.2	23.5	
Comorbid conditions				
ASHD	26.1	34.8	40.4	
CVA/TIA	16.4	24.5	29.2	
PVD	38.0	52.9	61.7	
CHF	33.2	47.3	56.2	
cardiac other	41.6	58.0	66.1	
COPD	14.9	20.6	23.3	
cancer	16.7	20.9	25.3	
liver	12.5	20.1	22.9	
gallbladder	6.7	9.1	10.9	
GI	15.5	24.0	29.1	
No. of access procedures				
no procedures	85.4	71.8	67.8	
1 to 3 procedures	10.4	19.3	20.6	
≥4 procedures	4.2	8.9	11.5	
No. of transfusions				
no blood transfusion	95.9	90.2	87.7	
1 to 2 pints	1.8	4.3	6.4	
≥3 pints	2.3	5.4	6.0	
Length of stay				
no hospital stay	75.1	58.2	54.6	
1 to 3 days	7.6	9.9	11.6	
3 to 10 days	9.1	13.7	16.2	
11 to 20 days	4.4	7.9	9.1	
>20 days	3.8	10.3	8.5	

[a] EPO, erythropoietin; USRDS, U.S. Renal Data System; GN, glomerulonephritis; ESRD, end-stage renal disease; ASHD, atherosclerotic heart disease; CVA/TIA, cerebrovascular accident/transient ischemic attacks; PVD, peripheral vascular disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

[b] All χ^2 tests are significant with P value <0.001 among the left three columns.

Table 2. Distribution of patient characteristics in the study population (%)[a]

Characteristic (n = 75,283)	<27% (n = 9,130)	27% to <30% (n = 22,217)	30% to <33% (n = 33,122)	33% to <36% (n = 10,129)	≥36% (n = 685)	P Value
Age						
under 45	27.2	19.8	16.5	15.1	18.0	0.001
45 to 64	38.5	36.5	34.3	33.2	38.0	
65 to 74	23.4	28.4	30.8	32.2	29.2	
≥75	10.9	15.2	18.5	19.5	15.0	
Female	52.6	53.4	51.5	46.0	39.7	0.001
Race						
white	37.1	45.4	52.6	57.7	53.6	
black	54.7	45.2	37.6	32.5	33.7	0.001
Native American	1.4	1.4	1.4	1.7	4.1	
other	6.8	8.1	8.4	8.1	8.6	
Prior ESRD exposure						
<1 yr	21.6	22.9	23.5	23.0	20.0	0.001
1 to 2 yr	19.0	19.6	19.8	19.5	17.2	
2 to 5 yr	34.1	34.3	33.7	33.5	32.6	
≥5 yr	25.3	23.2	23.1	24.0	30.2	
Primary renal diagnosis						
diabetes mellitus	27.2	31.2	32.1	31.3	31.4	0.001
hypertension	32.6	31.6	30.8	29.8	27.6	
GN	16.2	16.2	16.2	17.6	19.1	
other	24.0	21.0	20.9	21.4	21.9	
Comorbid conditions						
ASHD	35.4	57.6	55.4	53.1	43.1	0.001
CVA/TIA	28.8	30.0	29.1	28.1	24.8	0.002
PVD	61.8	63.0	61.2	60.0	60.2	0.001
CHF	59.2	57.6	55.4	53.1	55.6	0.001
cardiac other	68.0	67.8	65.2	63.6	64.1	0.001
COPD	21.9	23.9	23.3	23.3	22.5	0.002
cancer	24.1	25.4	25.3	26.0	20.4	0.024
liver	26.7	23.3	22.2	21.1	24.7	0.001
gallbladder	11.2	11.8	10.7	9.7	10.1	0.001
GI	34.1	31.2	27.5	25.0	27.2	0.001
No. of access procedures						
no procedures	61.1	63.9	70.2	74.8	73.3	0.001
1 to 3 procedures	24.1	22.6	19.5	17.0	18.4	
≥4 procedures	14.8	13.6	10.3	8.2	8.3	
No. of transfusions						
no transfusion	74.9	84.1	91.3	94.5	96.1	0.001
1 to 2 pints	11.3	8.5	4.7	3.0	2.2	
≥3 pints	13.8	7.4	4.0	2.1	1.8	
Length of stay						
no hospital stay	42.4	48.4	58.2	67.5	67.7	0.001
1 to 3 days	11.4	12.1	11.7	10.3	10.4	
3 to 10 days	19.4	17.8	15.5	12.3	11.5	
11 to 20 days	13.0	11.1	7.8	5.7	5.8	
>20 days	13.9	10.7	6.9	4.3	4.5	
Hematocrit (mean ± SD)	25.04 ± 2.06	28.69 ± 0.84	31.40 ± 0.84	33.88 ± 0.72	37.57 ± 1.62	0.001

[a] Abbreviations as in Table 1.

Table 3. Percentage of all-cause and cause-specific death

Group and Causes of Death	Hematocrit Level				Overall
	<27%	27% to <30%	30% to <33%	33% to <36%	
Nondiabetics (n = 36,905)					
all-cause death	18.5	16.8	15.1	14.3	15.9
cardiac death[a]	6.9	6.8	6.3	6.1	6.5
infectious death	2.6	2.0	1.6	1.4	1.8
other death	9.0	8.0	7.1	6.7	7.6
Diabetics (n = 37,693)					
all-cause death	28.1	25.1	22.2	20.3	23.5
cardiac death	12.1	11.5	10.3	9.7	10.8
infectious death	4.5	3.3	2.9	2.9	3.2
other death	11.5	10.3	9.0	7.7	9.5

[a] The χ^2 test is not significant (P = 0.168); all other P values <0.001.

Table 4. Unadjusted all-cause and cause-specific mortality rates (deaths/per 1000 treatment-years)

Group and Causes of Death	Hematocrit Level				Overall
	<27%	27% to <30%	30% to <33%	33% to <36%	
Nondiabetics					
all-cause death	214.66	192.00	170.61	161.37	181.02
cardiac death	80.10	77.84	71.78	68.97	74.18
infectious death	30.07	23.04	18.47	16.27	20.94
other death	104.50	91.11	80.36	76.13	85.90
Diabetics					
all-cause death	342.70	298.23	258.34	234.59	276.77
cardiac death	147.90	135.91	119.67	112.71	126.84
infectious death	54.63	39.67	33.28	32.94	37.58
other death	140.17	122.65	105.38	88.94	112.35

Mortality Adjusted for Risk Factors, without Severity of Disease

Table 5 shows the results of the Cox regression analyses adjusting for demographics and comorbidity but without adjusting for disease severity measures, including the number of access procedures, blood transfusions, and prior hospital days for all causes of death as well as cardiac and infectious death. As expected, each increase in age group is associated with higher all-cause and cause-specific mortality. Female patients had better outcomes for all-cause and cardiac death than male patients. Compared with whites, blacks and other minorities (except Native Americans) had significantly lower all-cause and cause-specific mortality. Only Native Americans had lower infectious mortality. The impact of prior years of ESRD exposure varied for all-cause and cause-specific mortality, where longer exposures were associated with higher cardiac and infectious mortality. Comorbid conditions before the study entry significantly affected the outcomes. All of the cardiovascular risks, including atherosclerotic heart disease, peripheral vascular disease, congestive heart failure, cerebrovascular accident/transient ischemic attacks, and other cardiac disease were consistently associated with higher mortality, especially cardiac mortality. Liver and gallbladder diseases were nonsignificant risk factors for higher mortality. Patients with gastrointestinal bleeding complications had a seventeen percent higher risk for all-cause death and a thirty-one percent higher risk for infectious death.

After adjusting for patient demographics and comorbidity, the levels of hematocrit greatly impacted all-cause and cause-specific mortality. Compared with patients in the hematocrit range 30% to less than 33%, patients with hematocrit levels less than 27% had a fifty-one percent higher risk (RR = 1.51; 95% CI, 1.44 to 1.59) for all-cause death, and patients with hematocrits in the 27% to less than 30% range had a twenty percent higher risk (RR = 1.20; 95% CI, 1.16 to 1.25). In contrast, patients in the hematocrit range 33% to less than 36% had a ten percent lower risk (RR = 0.90; 95% CI, 0.85 to 0.95) for all-cause death.

Similarly, hematocrit levels had a significant impact on cardiac death, with a forty percent higher risk (RR = 1.40; 95% CI, 1.30 to 1.52) in the group with hematocrits less than 27%; an eighteen percent higher risk (RR = 1.18; 95% CI, 1.12 to 1.25) in the 27% to less than 30% group; and an eight percent lower risk (RR = 0.92; 95% CI, 0.85 to 0.99) in the

Table 5. The impact of patient characteristics and hematocrit levels on mortality without adjusting for severity of disease measures[a]

Characteristic	All-Cause Death		Cardiac Death		Infectious Death	
	RR	95% CI	RR	95% CI	RR	95% CI
Age						
under 45 (ref)	1.00		1.00		1.00	
45 to 64	1.67	(1.56 to 1.78)	1.67	(1.51 to 1.85)	1.77	(1.46 to 2.13)
65 to 74	2.21	(2.07 to 2.37)	2.17	(1.96 to 2.40)	2.21	(1.83 to 2.68)
≥75	3.11	(2.90 to 3.34)	2.90	(2.61 to 3.23)	3.29	(2.70 to 3.99)
Female	0.94	(0.91 to 0.97)	0.86	(0.82 to 0.91)	1.02	(0.93 to 1.12)
Race						
white (ref)	1.00		1.00		1.00	
black	0.73	(0.70 to 0.76)	0.66	(0.63 to 0.70)	0.81	(0.73 to 0.89)
Native American	0.83	(0.72 to 0.97)	0.82	(0.65 to 1.02)	0.55	(0.33 to 0.92)
other	0.87	(0.82 to 0.92)	0.89	(0.81 to 0.97)	0.80	(0.67 to 0.95)
Prior ESRD exposure						
<1 year (ref)	1.00		1.00		1.00	
1 to 2 years	1.07	(1.02 to 1.12)	1.06	(0.99 to 1.14)	1.06	(0.92 to 1.21)
2 to 5 years	1.11	(1.06 to 1.16)	1.16	(1.09 to 1.24)	1.22	(1.08 to 1.38)
≥5 years	1.12	(1.06 to 1.18)	1.16	(1.07 to 1.25)	1.37	(1.19 to 1.58)
Comorbid conditions						
ASHD	1.11	(1.07 to 1.15)	1.31	(1.24 to 1.38)	1.06	(0.96 to 1.17)
CVA/TIA	1.23	(1.19 to 1.27)	1.15	(1.09 to 1.21)	1.32	(1.20 to 1.45)
PVD	1.21	(1.16 to 1.25)	1.20	(1.13 to 1.27)	1.37	(1.23 to 1.53)
CHF	1.42	(1.36 to 1.48)	1.62	(1.52 to 1.73)	1.34	(1.20 to 1.50)
cardiac other	1.16	(1.11 to 1.21)	1.22	(1.14 to 1.30)	1.14	(1.01 to 1.29)
COPD	1.24	(1.20 to 1.29)	1.23	(1.16 to 1.29)	1.17	(1.06 to 1.29)
cancer	1.03	(1.00 to 1.07)	0.93	(0.88 to 0.99)	0.99	(0.89 to 1.09)
liver	1.00	(0.96 to 1.04)	0.98	(0.92 to 1.04)	1.04	(0.94 to 1.16)
gallbladder	1.03	(0.98 to 1.08)	1.06	(0.99 to 1.52)	1.08	(0.95 to 1.24)
GI	1.17	(1.13 to 1.21)	1.11	(1.04 to 1.16)	1.31	(1.19 to 1.44)
Hematocrit						
<27%	1.51	(1.44 to 1.59)	1.40	(1.30 to 1.52)	1.82	(1.59 to 2.08)
27% to <30%	1.20	(1.16 to 1.25)	1.18	(1.12 to 1.25)	1.25	(1.12 to 1.39)
30% to <33% (ref)	1.00		1.00		1.00	
33% to <36%	0.90	(0.85 to 0.95)	0.92	(0.85 to 0.99)	0.94	(0.81 to 1.10)

[a] RR, relative risk; CI, confidence interval.

33% to less than 36% group. As for infectious deaths, patients in the 27% to less than 30% hematocrit range had a twenty-five percent increased risk (RR = 1.25; 95% CI, 1.12 to 1.39). Patients with hematocrits less than 27% had an eighty-two percent increased risk (RR = 1.82; 95% CI, 1.59 to 2.08) of infectious death. There was no significant beneficial impact on infectious deaths in patients with hematocrit levels 33% to less than 36%. For all other causes of death other than cardiac and infectious, the impact of hematocrit level was virtually the same as that for all-cause death.

To contrast patients having hematocrit levels 36% and above with those having hematocrits under 36%, Cox regression analyses were performed on all-cause, cardiac, and infectious deaths. The relative risk of all-cause mortality for those patients with hematocrits 36% and above is 1.06 ($P = 0.4935$), with 95% confidence interval 0.89 to 1.27, compared to those patients with hematocrits from 30% to less than 33%. Similarly, the relative risk of cardiac death is 1.15, with 95% confidence interval 0.90 to 1.47, and the relative risk of infectious death is 1.04, with 95% confidence interval 0.62 to 1.73. Therefore, all-cause and cause-specific mortality in patients with hematocrits 36% and above is not significantly different from those in the 30% to less than 33% group. These indeterminate results could represent insufficient numbers of patients in the 36% and greater hematocrit group.

Mortality Adjusted for Risk Factors, with Severity of Disease

In addition to all of the risk factors in Table 5, severity of disease measures in the entry period (including blood transfusions, vascular access procedures, and hospital length of stay) were included in the Cox regression analysis to fully evaluate

Table 6. The impact of severity of disease measurements and hematocrit levels on mortality risk[a]

Characteristic	All-Cause Death		Cardiac Death		Infectious Death	
	RR	95% CI	RR	95% CI	RR	95% CI
1993 Cohort						
no. of access procedures						
no procedures (ref)	1.00		1.00		1.00	
1 to 3 procedures	1.01	(0.97 to 1.05)	1.00	(0.94 to 1.06)	1.10	(0.98 to 1.23)
≥4 procedures	0.93	(0.89 to 0.98)	0.94	(0.87 to 1.01)	1.03	(0.90 to 1.18)
no. of transfusions						
no transfusion (ref)	1.00		1.00		1.00	
1 to 2 pints	1.03	(0.97 to 1.09)	1.05	(0.96 to 1.15)	1.07	(0.91 to 1.25)
≥3 pints	1.20	(1.13 to 1.27)	1.15	(1.05 to 1.25)	1.19	(1.03 to 1.39)
length of stay						
no hospital stay (ref)	1.00		1.00		1.00	
1 to 3 days	1.23	(1.17 to 1.31)	1.22	(1.12 to 1.32)	1.26	(1.06 to 1.49)
4 to 10 days	1.47	(1.41 to 1.55)	1.42	(1.32 to 1.52)	1.62	(1.41 to 1.85)
11 to 20 days	1.92	(1.82 to 2.03)	1.85	(1.70 to 2.01)	2.29	(1.97 to 2.66)
>20 days	2.57	(2.44 to 2.72)	2.42	(2.23 to 2.63)	3.42	(2.96 to 3.96)
hematocrit						
<27%	1.33	(1.26 to 1.40)	1.25	(1.15 to 1.35)	1.53	(1.33 to 2.75)
27% to <30%	1.12	(1.08 to 1.17)	1.11	(1.05 to 1.17)	1.13	(1.02 to 1.26)
30% to <33% (ref)	1.00		1.00		1.00	
33% to <36%	0.96	(0.91 to 1.01)	0.97	(0.90 to 1.05)	1.02	(0.88 to 1.19)
1992 & 1993						
33% to <36%	0.96	(0.92 to 0.99)				

[a] The result from the combined cohorts is compared to that from the 1993 cohort only in the 33% to <36% group. The relative risk is the same 0.96, but the confidence interval is significant. This combined analysis was based on 16,000 patient observations compared to 10,129 in 1993 only. Therefore, the hematocrit group 33% to <36% outcome is sensitive to the number of patients and patient observations in the analysis.

the association of hematocrit levels with mortality. Even with severity of disease adjustments, the impact of patient demographics, prior ESRD exposure, and the ten major comorbid conditions were similar to the results shown in Table 5. The relative risks of severity of disease measures and the adjusted relative risks of hematocrit levels are shown in Table 6. There was no significant impact on all-cause and cause-specific mortality if patients had less than three access procedures during the entry period, but receiving more than three procedures was associated with a seven percent lower risk of all-cause death, and a six percent lower risk of cardiac death. Patients who had three or more units of blood transfused had a fifteen to twenty percent higher risk of all-cause and cause-specific death than those who received less than three units of blood. Hospital length of stay during the entry period was also a significant predictor of patient survival in the follow-up period: The longer the prior hospital stay, the higher the mortality risk for all-cause and specific causes in the future. There was at least a twenty percent higher risk for patients staying in the hospital 1 to 3 days and a fifty percent higher risk for those staying 4 to 10 days. The risk of dying during the follow-up period was more than double for patients with hospital stays of greater than 10 days during the 6-mo entry period. Therefore, medical conditions that were severe enough to require hospitalization before the follow-up period were highly predictive of future mortality.

Once adjustments were made for the severity of disease measures in the analyses, the absolute value of the relative risks of hematocrit level on patient mortality was less than that without adjusting for disease severity. Patients with hematocrits less than 30% still had significantly higher risks of death compared to patients in the 30% to less than 33% range, but the magnitude of the impact was reduced from that in Table 5. For example, after adjusting for disease severity, the relative risk of all-cause death decreased from 1.51 to 1.33 for patients in the hematocrit group less than 27%, and from 1.20 to 1.12 for patients in the 27% to less than 30% hematocrit group. Patients in the hematocrit group 33% to less than 36% had marginally better survival (after severity adjustment) than those in the 30% to less than 33% group for all-cause and cardiac deaths, but not significantly different for infectious deaths.

Sensitivity Analysis

The reduced effect of hematocrit levels on mortality, especially in the 33% to less than 36% group, may be due to the complex confounding effect of interactions between hematocrit level, comorbidity, and severity of disease. It was hypothesized that adjustment for all of these confounding effects would

require more patients to detect the true impact of hematocrit level. To verify this hypothesis, we constructed a similar period prevalent cohort in 1992 ($n = 61,797$) and added it to the 1993 cohort. This resulted in a total of 136,395 patient observations of the 1992 and 1993 combined prevalent cohort.

The Cox regression analyses were performed on this combined cohort for all-cause death, with adjustment for all of the risk factors described in the previous section. The relative risks of death for demographics, comorbidity, and severity of disease were very similar to those in Table 6 and are not repeated. The magnitude of relative risks for hematocrit levels from the combined cohort were virtually identical to those from the 1993 prevalent cohort alone, but their corresponding confidence intervals became narrower (with smaller *P* values) compared to that in Table 6. For example, the relative risk of all-cause death from both the 1993 cohort only and the combined cohort was 0.96 for patients in the hematocrit group 33% to less than 36%, but the probability was not significant ($P \leq 0.0956$) for the 1993 cohort only. The probability in the combined 1992 and 1993 cohorts was significant ($P = 0.0385$; 95% CI, 0.92 to 0.99). This demonstrated the influence of sample size when many confounding factors associated with disease complexity and hematocrit were adjusted in the same analyses, which could mask the true effect of the hematocrit levels on patient mortality.

Discussion

A number of clinical studies have shown that increased hematocrit levels are associated with improved cognitive function, reduced left ventricular hypertrophy, increased exercise tolerance and improved quality of life(1). The hematocrit levels achieved in these studies, however, were usually in the range of 30 to 33%. Higher hematocrit levels in the 33% to less than 36% range have not been previously shown to be associated with further reduction in mortality.

Our study included prevalent Medicare hemodialysis patients with a 6-mo exposure to a sustained hematocrit level during 1993 with follow-up into 1994. This 6-mo entry period enabled us to characterize the patient population by a profile of clinical events and to assess severity of disease. Our results showed a progressively higher risk of death as the hematocrit level declined below 30%, both with and without disease severity adjustment. Patients in the hematocrit group 33% to less than 36% had significantly lower risks of death compared to the hematocrit group 30% to less than 33% without adjusting for disease severity, and marginally lower risk after adjusting for disease severity. When combining 1992 and 1993 cohorts, the impact of higher hematocrits becomes significant even after adjusting for disease severity. The reduced mortality effect noted in the 33% to less than 36% group was demonstrated when the number of patient observations was increased to 16,000 by the analysis of the 1992 and 1993 cohorts together.

Our findings are consistent with the Madore *et al.* study (7), which used hemoglobin level as the predictive variable. The pattern of higher mortality risk with hemoglobin levels less than 100 g/L are similar in absolute value to our results. The lower relative risks in our study may actually reflect an underestimation, since hematocrit level determined by measurement of mean cell size is less precise compared with the direct hemoglobin concentration method. In addition, cell swelling from delayed measurement of hematocrit will falsely elevate hematocrit levels, thereby artificially changing patient hematocrit groups. The Madore *et al.* findings of no improvement in outcomes associated with hematocrit ranges above 33% (or hemoglobins greater than 110 g/L) may reflect a low sample size. Our sensitivity analysis demonstrated that up to 16,000 patient observations may be needed in the 33% to less than 36% group to detect the lower risk. The Madore *et al.* study had only approximately 2100 patient observations.

The association of higher infectious death in the hematocrit group less than 27% compared to all-cause and cardiac death raises concerns about the relationship. Lower hematocrits are typically associated with chronic inflammatory states and infectious processes. The chronic inflammatory states produce cytokines, which interfere with bone marrow responsiveness to EPO (15–19), thereby leading to lower hematocrits. These chronic inflammatory conditions may predispose patients to increased risks of infectious death by inadequate host defenses. In this case, the lower hematocrits only play a passive role and are not a primary causal factor. The lower hematocrit levels and reduced EPO responsiveness may also be involved in the potential associations between the risks of iron overload, poor white blood cell function, and reduced bacterial killing(20). Unfortunately, since the two possibilities are confounded and cannot be separated by the observational analysis, the causality cannot be determined. Additional data on the history of infectious complications and the use of dialysis catheters, which can increase infections(21), would be useful but were beyond the scope of this study. Further evaluation in this area is indicated to clarify these associations.

Dialysis therapy and nutritional status, both of which have been shown to affect patient outcomes, were not included in the current study due to unavailability of the data. The Madore *et al.* study did assess the impact of dialysis therapy (urea reduction ratio) and biochemical data relative to hematocrit results and showed an impact only when the hemoglobin was less than 90 g/L. Therefore, although we did not evaluate these parameters, it appears that dialysis therapy may have less impact than nutritional factors and only at lower hematocrit levels. The nutritional status of patients was not directly assessed, since biochemical data were unavailable. In our study, the strong association of comorbidity and hospital length of stay in the entry period with future mortality has the same magnitude of impact as albumin on patient survival(22) and a similar absolute impact as in the Madore *et al.* study. Thus, we believe that nutritional status was indirectly adjusted through the comorbidity and severity of disease measurements, which influence nutritional status.

Conclusion

We developed an epidemiologic model to study the association of hematocrit level and patient mortality, with patients exposed to a sustained hematocrit during a 6-mo entry period. This entry period enabled us to use administrative claims data

to characterize patient demographics, clinical conditions, and severity of disease measures. After adjusting for these confounding patient characteristics, our results showed that patients with hematocrit levels less than 30% have significantly higher risk of all-cause and cause-specific death, compared to patients with hematocrit levels of 30% to less than 33%. Without severity of disease adjustment, patients with hematocrits in the 33% to less than 36% range have the lowest risk for all-cause and cardiac mortality. After adjusting for severity of disease, the impact of hematocrit levels in the 33% to less than 36% range becomes vulnerable to the number of patients included but still demonstrates a further 4% reduced risk of death. Overall, our findings suggest that sustained increases in hematocrit levels are associated with improved patient survival.

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