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Association between repeat hospitalization and early intervention in dialysis patients following hospital discharge

Kevin E. Chan[1], J. Michael Lazarus[1], Rebecca L. Wingard[1] and Raymond M. Hakim[1]

[1]*Clinical Science Department, Fresenius Medical Care NA, Waltham, Massachusetts, USA*

Dialysis patients have a greater number of hospitalization events compared to patients without renal failure. Here we studied the relationship between different post-discharge interventions and repeat hospitalization in over 126,000 prevalent hemodialysis patients to explore outpatient strategies that minimize the risk of repeat hospitalization. The primary outcome was repeat hospitalization within 30 days of discharge. Compared to pre-hospitalization values, the levels of hemoglobin, albumin, phosphorus, calcium, and parathyroid hormone and weight were significantly decreased after hospitalization. Using covariate-adjusted models, those patients whose hemoglobin was monitored within the first 7 days after discharge, followed by modification of their erythropoietin dose had a significantly reduced risk for repeat-hospitalization when compared to the patients whose hemoglobin was not checked, nor was the dose of erythropoietin changed. Similarly, administration of vitamin D within the 7 days following discharge was significantly associated with reduced repeat hospitalization when compared to patients on no vitamin D. Therefore, it appears that immediate re-evaluation of anemia management orders and resumption of vitamin D soon after discharge may be an effective way to reduce repeat hospitalization.

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Correspondence: *Kevin E. Chan, Fresenius Medical Care NA, 920 Winter Street, Waltham, Massachusetts 02451-1457, USA. E-mail: kevin.chan@fmc-na.com*

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Over the past 15 years, the United States Renal Data System has reported modest improvements in mortality but stable hospitalization rates for patients on chronic renal replacement therapy.[1] Although new knowledge in dialysis adequacy,[2] anemia management,[3] and vitamin D therapy[4,5] may have contributed to the reduction in mortality,[1] relatively little research has focused on the prevention or reduction of hospitalization episodes, which has remained relatively stable at an annual rate of two admissions and 14 hospital days per patient-year.[1] Hospitalization remains an important outcome for the end-stage renal disease (ESRD) population, partly because patients on dialysis have a threefold increase in the number of hospitalizations when compared with the Medicare average. Per-patient per-year inpatient costs have risen by more than 30% in the past 15 years, and approximately one-third of the $26 billion in total ESRD expenditures result from hospitalization costs.[1]

Given the increasing complexity of medical disease and the continuing focus on reducing hospital length of stay, the post-hospitalization phase is increasingly being used as an 'extended period' for ongoing therapy started in the hospital. Evidence-based recommendations for the effective transfer and reevaluation of a post-hospitalized ESRD patient are almost nonexistent and, increasingly, there is recognition that this sub-population of post-hospitalized patients may benefit from additional focused monitoring and intervention.[6,7]

This study sought to determine the impact of hospitalization on commonly accepted core indicators of quality in a large, diverse population of prevalent patients undergoing chronic hemodialysis. In the second part of this study, the relationship between different post-discharge interventions and repeat hospitalization within 30 days were studied to explore the possible outpatient strategies that may minimize the risk of repeat admission to hospital.

RESULTS

Effect of hospitalization

Among incenter patients who received hemodialysis at an outpatient clinic operated by Fresenius Medical Care North America in 2007, the hospitalization rate was found to be 2.02 admissions per patient-year ($n = 162{,}389$ hospitalizations) and the median length of stay was 5 days. In all, 31% of patients in our study cohort had more than one hospitalization episode per year. The new hospitalization rate (that is, hospitalizations not preceded by another within 30 days) was found to be 1.51 admissions per patient-year ($n = 121{,}617$ hospitalizations), with 83% of these patients ($n = 100{,}835$) returning to a Fresenius facility for hemodialysis within 7 days after discharge from a new hospitalization. A total of 17% of these patients ($n = 20{,}782$) did not meet this criteria, of whom 13% were hospitalized for more than 30 days, 36% had a repeat hospitalization within 7 days, 24% died during hospitalization, 6% were transferred to a non-Fresenius clinic or to long-term care, 6% withdrew from dialysis, 3% were transplanted, 1% had renal function recovery, 0.3% changed their dialysis modality, and 9% were unknown.

Rates and characteristics of the most prevalent causes for new hospitalization are displayed in Table 1.

When compared with the most recent pre-hospitalization values, hemoglobin (mean change ± s.e.: -0.5 ± 0.01 g per 100 ml, $P < 0.0001$), albumin (mean change ± s.e.: -0.1 ± 0.002 g per 100 ml, $P < 0.0001$), phosphorus (mean change ± s.e.: -0.3 ± 0.01 mg per 100 ml, $P < 0.0001$), calcium (mean change ± s.e.: -0.1 ± 0.003 mg per 100 ml, $P < 0.0001$), parathyroid hormone (PTH) (mean change ± s.e.: -28 ± 0.2 pg/ml, $P < 0.0001$), and weight (mean change ± s.e.: -0.7 ± 0.01 kg, $P < 0.0001$) were all found to be decreased on return to outpatient dialysis after discharge from hospital. The extent of the change in these parameters was larger with an increasing length of stay (Figure 1a).

In all, 71.5% of patients had their hemoglobin checked within the first 7 days after discharge from hospital, with 23.3% of the patients receiving more EPO than their pre-hospitalization dose and 5.6% of the patients receiving less EPO. Figure 1b further shows the prevalence of post-hospitalization EPO and vitamin D usage by length of stay. In patients with post-hospitalization hemoglobin monitoring, who were found to have a hemoglobin $\leqslant$10 g per 100 ml (20.6% of the population), only 47.3% had their EPO dose increased within the 7 days after discharge. Likewise, 45.7% of post-hospitalized patients had a hemoglobin $\leqslant$11 g per 100 ml, with 43.2% of these patients receiving an increase in their EPO dose, whereas 71.6% of post-hospitalized patients had a hemoglobin $\leqslant$12 g per 100 ml with only 33.8% of these patients receiving an increase in their EPO dose.

Table 1 | Most prevalent primary diagnosis for new hospitalization

	New hospitalizations per patient-year	Median length of stay (days)	Probability of repeat hospitalization (%)[a]
Infection	0.22	7	25.3
Access related	0.14	4	24.1
Volume overload	0.07	4	29.4
Chest pain	0.07	4	28.1
Shortness of breath	0.06	4	30.4
Congestive heart failure	0.05	5	28.8
Cardiovascular disease[b]	0.04	5	26.2
Hypertension	0.03	4	28.0
Nausea and vomiting	0.03	4	30.3
Peptic ulcer disease	0.02	5	24.5
Abdominal pain	0.02	5	29.2
Myocardial infarction	0.02	6	28.5
Fever and chills	0.02	5	27.0
Hypotension	0.02	5	29.0
Weakness	0.02	5	28.3
Altered mental status	0.02	6	31.3
Anemia	0.02	4	31.2
Hyperkalemia	0.02	3	24.3
Coronary artery disease	0.02	5	21.8
Bleeding	0.01	5	23.9
Other causes	0.57	5	26.6

[a]Hospital visit within 30 days after discharge from a new hospitalization.
[b]Excluding myocardial infarction, congestive heart failure, and coronary artery disease.

A total of 7.1% ($n = 4814$ of 68,275) of patients who were on vitamin D before hospitalization were not on vitamin D in the 7 days after discharge. 21.7% Of patients returning from the hospital had their target dry weight modified within a week after hospital discharge.

Effect of intervention during the post-hospitalization period

Baseline patient characteristics. Baseline patient characteristics by three independent post-hospitalization interventions are shown in Table 2a–c. Not surprisingly, patients who had post-hospitalization changes in their EPO dose or target dry weight also had a longer hospital length of stay.

Post-hospitalization anemia management. In all, 28.9% of patients had a hemoglobin drawn and EPO dose modified within 1 week after discharge from hospital and return to the facility. Significant differences in the crude risk of repeat hospitalization were noted between the intervention groups ($P < 0.0001$): patients with a hemoglobin order and a subsequent change in EPO dose on return from the hospital were less likely to have a repeat hospitalization (25.4% risk for repeat hospitalization) than those with no hemoglobin monitoring and an unchanged EPO dose (29.7% risk for repeat hospitalization).

Multivariable survival analysis (Table 3) showed a 16% ($P < 0.0001$) reduction in the risk for repeat hospitalization when the EPO dose was modified in tandem with a hemoglobin order (reference: no hemoglobin order and keeping the EPO dose the same). Hazard ratios rose steeply early on after hospital discharge (Figure 2), suggesting that the effect of early intervention (that is, within 7 days after hospitalization) was immediate and diminishes over time. For example, early anemia management decreased the risk of repeat hospitalization by 28% in the first 2 weeks after discharge from hospital; however, the hospitalization benefit decreased to 15% when the follow-up period was extended to the first 30 days. The trends persisted after correction for a possible selection bias with a propensity score adjustment (Table 3), after matching for the treating facility and/or physician (Table 4), and in 41 of 46 strata in the subgroup analysis (Figure 3a), with greater benefits seen in patients who had larger pre- to post- hospitalization decreases in their hemoglobin level (Figure 3a).

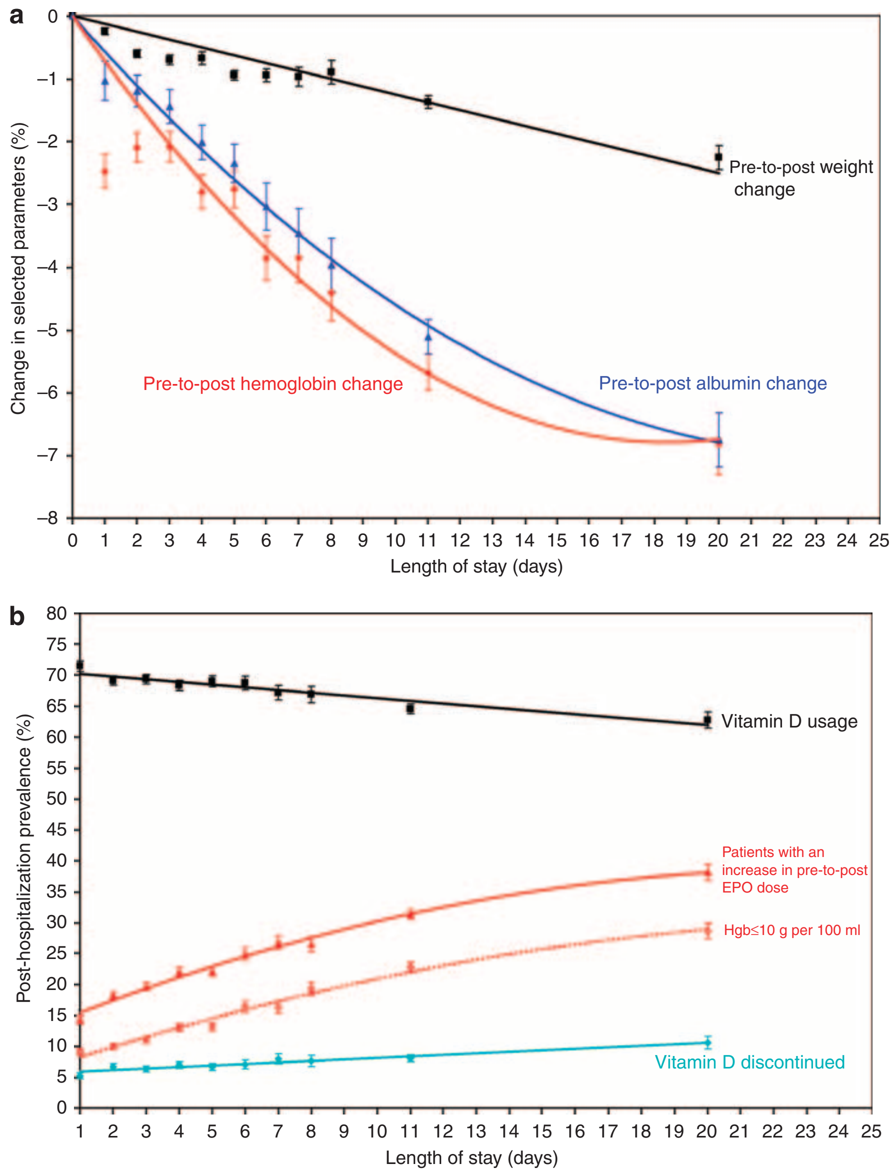

Figure 1 | Change in patient characteristics associated with hospitalization by length of hospital stay. (**a**) Impact of hospitalization on hemoglobin, albumin, and weight by length of stay. (**b**) Impact of hospitalization on the prevalence of EPO and vitamin D usage by length of stay. Note: vitamin D discontinued patients are patients who were on vitamin D before hospitalization and did not receive any vitamin D within the 7 days after hospitalization. Because of smaller sample sizes, patients with a length of stay between 8 and 14 days and between 15 and 30 days were grouped together.

After stratification by ordinals of post-hospitalization hemoglobin levels, a statistically significant decrease in repeat hospitalization was associated with an appropriate adjustment of EPO to achieve a hemoglobin level greater than 10 g per 100 ml (Figure 4a and b). Patients with a post-hospitalization hemoglobin $\leqslant$10 g per 100 ml had a 6% ($P=0.05$) decreased risk of repeat hospitalization when the EPO dose was increased (vs. same EPO dose) within the 7 days after hospitalization. Conversely, decreasing the EPO dose (vs. same EPO dose) when the post-hospitalization hemoglobin level was $\leqslant$11 g per 100 ml increased the risk of repeat hospitalization by 34% ($P<0.0001$).

Post-hospitalization vitamin D therapy. Patients administered vitamin D in the immediate post-hospitalization period also had a decreased risk for repeat hospitalization (26.0 vs 28.4% crude risk for repeat hospitalization, $P<0.0001$).

After covariate adjustment, the administration of vitamin D decreased the risk for repeat hospitalization by 6% ($P<0.0001$) when compared with no vitamin D (Table 3). Moreover, discontinuing vitamin D on return to dialysis (vs continuing vitamin D) in patients who were on it before hospitalization (4814 of 68,275 patients had vitamin D discontinued) increased the risk of repeat hospitalization by 9% ($P=0.001$).

Similar to earlier findings on anemia management, the decrease in the risk of repeat hospitalization with the timely institution of vitamin D therapy was achieved early (Figure 2). The results also withstood matched (Table 4),

Table 2a | Baseline patient characteristics by post-hospitalization anemia management status

	No Hgb, no EPO dose modification (reference)	Hgb order, EPO dose modification	*P*-value
n	19,782	29,087	
Age (years)	62.3 (0.1)	63.2 (0.08)	<0.0001
Gender (%male)	50.7 (0.2)	49.4 (0.2)	0.004
Race			
African American (%)	41.2 (0.2)	38.4 (0.2)	
Other (%)	7.0 (0.1)	6.8 (0.1)	
Caucasian (%)	51.8 (0.2)	54.8 (0.2)	<0.0001
Charlson score	5.4 (0.01)	5.5 (0.01)	<0.0001
Vintage (years)	3.4 (0.02)	3.4 (0.02)	0.55
Access			
AVF (%)	35.3 (0.2)	35.0 (0.2)	
Catheter (%)	38.3 (0.2)	39.2 (0.2)	
Graft (%)	26.0 (0.1)	25.5 (0.1)	
Unknown (%)	0.4 (0.0)	0.2 (0.02)	0.003
Length of stay (days)	3.5 (0.02)	5.9 (0.03)	<0.0001
Pre-hospitalization values			
Albumin (g per 100 ml)	3.7 (0.003)	3.7 (0.003)	0.75
Hgb (g per 100 ml)	11.7 (0.01)	11.9 (0.01)	<0.0001
EPO (1000 U)	8.9 (0.06)	7.5 (0.04)	<0.0001
Vitamin D (% use)	68.2 (0.2)	66.4 (0.2)	<0.0001
Phosphorus (mg per 100 ml)	5.5 (0.01)	5.4 (0.01)	0.0009
PTH (pg/ml)	396 (3)	373 (2)	<0.0001
Weight (kg)	77.6 (0.1)	75.8 (0.1)	<0.0001

Table 2b | Baseline patient characteristics by post-hospitalization vitamin D use

	No vitamin D order (reference)	Vitamin D order	*P*-value
n	68,658	32,177	
Age (years)	62.6 (0.08)	62.7 (0.05)	0.19
Gender (% male)	50.0 (0.1)	49.9 (0.1)	0.82
Race			
African American (%)	30.4 (0.1)	45.4 (0.1)	
Other (%)	6.6 (0.07)	6.9 (0.08)	
Caucasian (%)	63.1 (0.1)	47.7 (0.1)	<0.0001
Charlson score	5.4 (0.01)	5.5 (0.008)	0.0001
Vintage (years)	3.1 (0.02)	3.6 (0.01)	<0.0001
Access			
AVF (%)	32.6 (0.1)	36.2 (0.1)	
Catheter (%)	44.9 (0.1)	35.7 (0.1)	
Graft (%)	22.0 (0.1)	27.8 (0.1)	
Unknown (%)	0.4 (0.02)	0.2 (0.01)	<0.0001
Length of stay (days)	5.0 (0.02)	4.6 (0.01)	<0.0001
Pre-hospitalization values			
Albumin (g per 100 ml)	3.6 (0.003)	3.7 (0.002)	<0.0001
Hgb (g per 100 ml)	11.8 (0.01)	11.8 (0.006)	0.92
EPO (1000 U)	9.1 (0.04)	8.5 (0.03)	<0.0001
Vitamin D (% use)	15.0 (0.1)	92.4 (0.08)	<0.0001
Phosphorus (mg per 100 ml)	5.5 (0.01)	5.4 (0.006)	<0.0001
PTH (pg/ml)	310 (2)	419 (1)	<0.0001
Weight (kg)	75.1 (0.1)	77.7 (0.08)	<0.0001

Table 2c | Baseline patient characteristics by modification of post-hospitalization dry weight

	Same target dry weight (reference)	Modification of target dry weight	*P*-value
n	78,951	21,884	
Age (years)	62.4 (0.05)	63.8 (0.1)	<0.0001
Gender (%male)	50.0 (0.1)	49.7 (0.1)	0.42
Race			
African American (%)	41.2 (0.1)	38.7 (0.1)	
Other (%)	6.8 (0.08)	6.6 (0.07)	
Caucasian (%)	52.0 (0.1)	54.8 (0.1)	<0.0001
Charlson score	5.4 (0.008)	5.5 (0.01)	<0.0001
Vintage (years)	3.5 (0.01)	3.4 (0.02)	0.001
Access			
AVF (%)	34.9 (0.1)	35.6 (0.1)	
Catheter (%)	38.6 (0.1)	38.9 (0.1)	
Graft (%)	26.2 (0.1)	25.2 (0.1)	
Unknown (%)	0.3 (0.01)	0.3 (0.01)	0.02
Length of stay (days)	4.4 (0.01)	5.8 (0.03)	<0.0001
Pre-hospitalization values			
Albumin (g per 100 ml)	3.7 (0.002)	3.6 (0.003)	<0.0001
Hgb (g per 100 ml)	11.8 (0.006)	11.6 (0.01)	<0.0001
EPO (1000 U)	8.5 (0.03)	9.1 (0.05)	<0.0001
Vitamin D (% use)	67.8 (0.1)	67.4 (0.1)	0.22
Phosphorus (mg per 100 ml)	5.5 (0.007)	5.3 (0.01)	<0.0001
PTH (pg/ml)	390 (1)	372 (2)	<0.0001
Weight (kg)	76.9 (0.07)	76.9 (0.1)	0.98

EPO, epogen; Hgb, hemoglobin; PTH, parathyroid hormone.
Results expressed as mean (s.e.).
This table compares the baseline patient characteristics of the study cohort by three independent post-hospitalization interventions (EPO dose adjustment + Hgb vs same EPO dose + no Hgb; vitamin D vs no vitamin D; dry weight modification vs no modification); *P*-values compare the individual characteristics of the patients who receive intervention after hospitalization with patients who do not receive intervention in the areas of anemia management, vitamin D therapy, and dry weight assessment.

propensity score-adjusted (Table 3), and stratified (all 46 stratum shown in Figure 3b) sensitivity analyses. No dose-dependent benefit on repeat hospitalization was observed in the case of vitamin D (P-trend$=0.13$).

Post-hospitalization target dry-weight management. Patients who had their target post-dialysis weight (estimated dry weight) modified within the first 7 days after hospitalization had a lower crude risk for repeat hospitalization (25.7% risk for repeat hospitalization) than did patients who maintained the same dry-weight target after discharge from hospital (27.1% risk for repeat hospitalization). Estimated dry weight modification (vs no modification) was associated with a 6% decrease ($P=0.0001$) in the adjusted risk for repeat hospitalization (Table 3). The effect became statistically insignificant once propensity score adjustment was added to the model ($P=0.11$).

Interaction between post-hospitalization anemia management, vitamin D therapy, and target dry-weight modification. Cross-product terms between hemoglobin monitoring and EPO adjustment, vitamin D administration, and dry-weight

Table 3 | Association between post-hospitalization intervention and the risk of repeat hospitalization

	Unadjusted model (*n*=100,835)	Adjusted model[a] (*n*=86,581)	Adjusted model with propensity scoring[b] (*n*=86,581)
Model 1 (post-hospitalization laboratory monitoring only)			
Hemoglobin (ordered vs not ordered)	0.82 (0.80–0.85)	0.83 (0.80–0.86)	0.84 (0.81–0.87)
Calcium (ordered vs not ordered)	0.88 (0.79–0.98)	0.89 (0.80–1.00)	0.92 (0.81–1.04)
Phosphorus (ordered vs not ordered)	1.09 (0.98–1.22)	1.07 (0.95–1.20)	1.04 (0.92–1.18)
Parathyroid hormone (ordered vs not ordered)	1.03 (0.99–1.06)	1.03 (0.99–1.07)	1.04 (1.00–1.08)
Model 2 (post-hospitalization intervention only)			
Modification of EPO dose post-hospitalization (vs same)	0.99 (0.96–1.01)	1.02 (0.99–1.05)	1.04 (1.01–1.08)
Vitamin D post-hospitalization (vs none)	0.90 (0.87–0.92)	0.94 (0.92–0.98)	0.94 (0.91–0.97)
Modification of dry weight post-hospitalization (vs none)	0.94 (0.91–0.96)	0.93 (0.90–0.97)	0.97 (0.94–1.01)
Model 3 (post-hospitalization laboratory monitoring and intervention)			
Hemoglobin ordered + modification of EPO dose (vs no hemoglobin ordered + same EPO dose)	0.81 (0.79–0.84)	0.84 (0.81–0.88)	0.85 (0.81–0.89)
Vitamin D post-hospitalization (vs none)	0.90 (0.87–0.92)	0.94 (0.92–0.97)	0.94 (0.91–0.97)
Modification of dry weight post-hospitalization (vs no modification)	0.94 (0.91–0.97)	0.94 (0.91–0.97)	0.97 (0.94–1.01)

[a]Model adjusted for the following covariates: age, gender, race, Charlson comorbidity index, length of stay, vintage, access, diabetic status, pre-hospitalization laboratory values (hemoglobin, phosphorus, parathyroid hormone, calcium, and albumin), and the 20 most prevalent causes for hospitalization.
[b]Model adjusted for covariates and propensity score (components of the propensity score: age, gender, race, Charlson comorbidity index, length of stay, vintage, access, diabetic status, pre-hospitalization laboratory values (hemoglobin, phosphorus, parathyroid hormone, calcium, and albumin), and the 20 most prevalent causes for hospitalization).

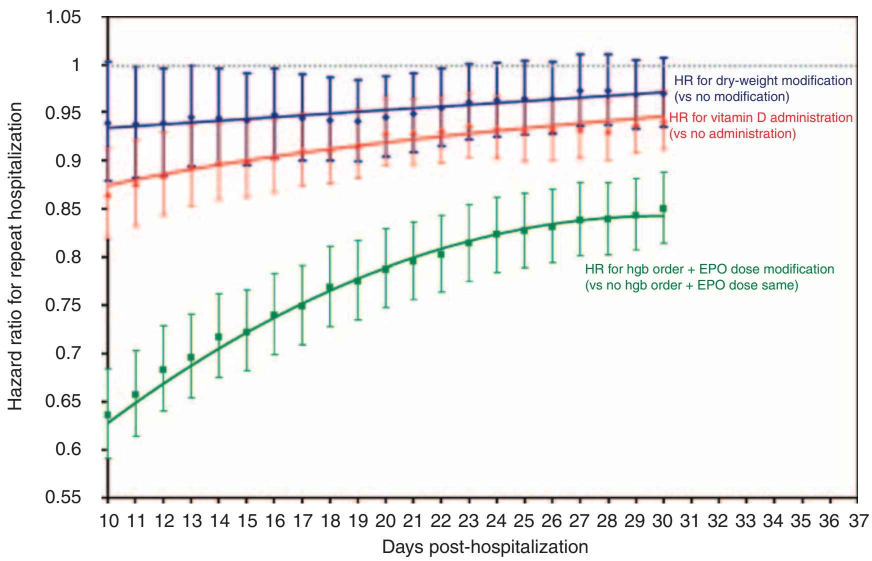

Figure 2 | Hazard ratios for repeat hospitalization within the specified number of days after discharge from hospital. This graph illustrates the time-sensitive relationship between early post-hospitalization anemia management and vitamin D administration with the risk of repeat hospitalization. Hazard ratios become less profound over time, which suggest excess repeat hospitalizations when anemia management or vitamin D administration is delayed. Hazard ratios have been covariate and propensity-score adjusted.

modification were insignificant ($P > 0.05$), indicating that there was no evidence of effect modification between anemia intervention, the administration of vitamin D, and the adjustment of target dry weight on the risk of repeat hospitalization.

DISCUSSION

This retrospective study in a large ESRD population demonstrated that hospitalization was associated with significant decreases in albumin, hemoglobin, and phosphorus, which become worse with increasing length of stay. Appropriate anemia management and the administration of vitamin D within the first 7 days after discharge from hospital and on return to a dialysis facility were each independently associated with a decreased risk of repeat hospitalization. When examined over a 1-year period, the clinical significance of early intervention is likely to be greater, given that the benefit is potentially cumulative in patients who experience multiple hospitalizations per year (>30% of the study cohort).

Table 4 | Hazard ratios for repeat hospitalization after matching on the specified variables

Matched variable[a]	n	Unadjusted model	Adjusted model[b]	Adjusted model + propensity scoring[c]
HR for hgb order + EPO dose modification (vs no hgb order + same EPO dose)				
Facility	33,054	0.82 (0.79–0.85)	0.86 (0.83–0.91)	0.90 (0.82–0.99)[d]
Physician	33,160	0.81 (0.78–0.84)	0.84 (0.81–0.88)	0.88 (0.80–0.97)[d]
Facility + physician	27,096	0.82 (0.78–0.85)	0.85 (0.81–0.90)	0.92 (0.83–1.02)[d]
HR for vitamin D (vs no vitamin D)				
Facility	60,552	0.90 (0.87–0.93)	0.95 (0.92–0.98)	0.95 (0.92–0.98)[e]
Physician	59,510	0.90 (0.88–0.93)	0.95 (0.92–0.98)	0.96 (0.92–0.99)[e]
Facility + physician	51,786	0.91 (0.88–0.94)	0.96 (0.93–1.00)	0.97 (0.93–1.00)[e]

EPO epogen; hgb, hemoglobin; HR, Hazard ratio.
[a]Each 'vitamin D' patient was paired with a 'non-vitamin D' patient in the same facility, under the care of the same attending nephrologist, and then under the care of the same attending nephrologist in the same facility. This ensured that all facility and/or physician factors in the case and control groups were balanced in the analysis.
[b]Model adjusted for the following covariates: age, gender, race, Charlson comorbidity index, length of stay, vintage, access, diabetic status, pre-hospitalization laboratory values (hgb, phosphorus, parathyroid hormone, calcium, and albumin), and the 20 most prevalent causes for hospitalization.
[c]Model adjusted for covariates and propensity score (components of the propensity score: age, gender, race, Charlson comorbidity index, length of stay, vintage, access, diabetic status, pre-hospitalization laboratory values (hgb, phosphorus, parathyroid hormone, calcium, and albumin), and the 20 most prevalent causes for hospitalization).
[d]c-Statistic for propensity score=0.86.
[e]c-Statistic for propensity score=0.67.

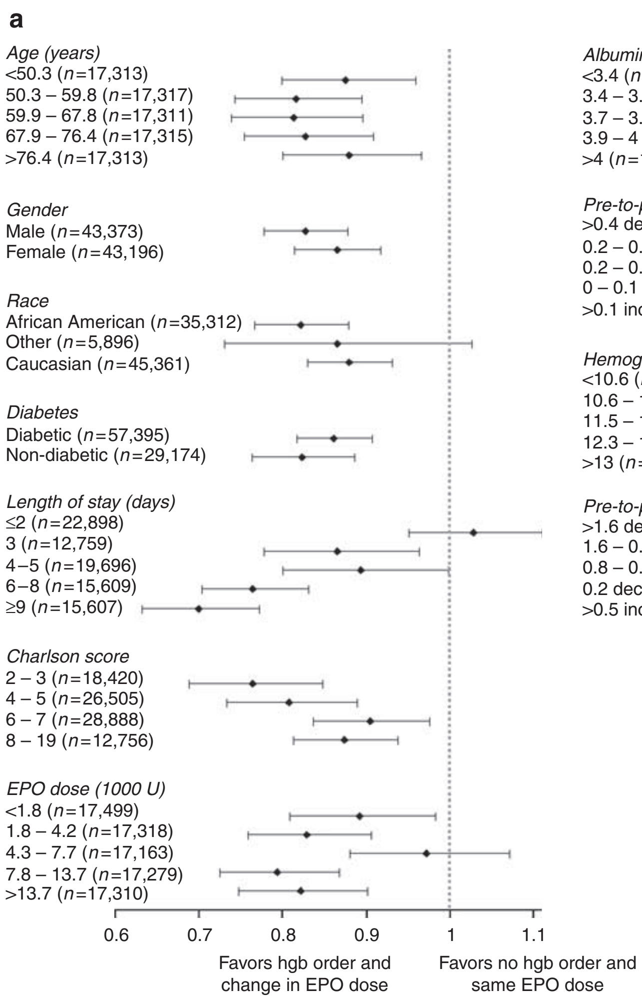

Figure 3 | Hazard ratios for repeat hospitalization associated with early post-hospitalization intervention, stratified by characteristics of the patient. (**a**) Hazard ratios for repeat hospitalization associated with post-hospitalization hemoglobin monitoring + EPO dose modification (vs no hemoglobin monitoring and the same EPO dose), with stratification according to patient characteristics. (**b**) Hazard ratios for repeat hospitalization associated with vitamin D administration (vs none), with stratification according to patient characteristics.

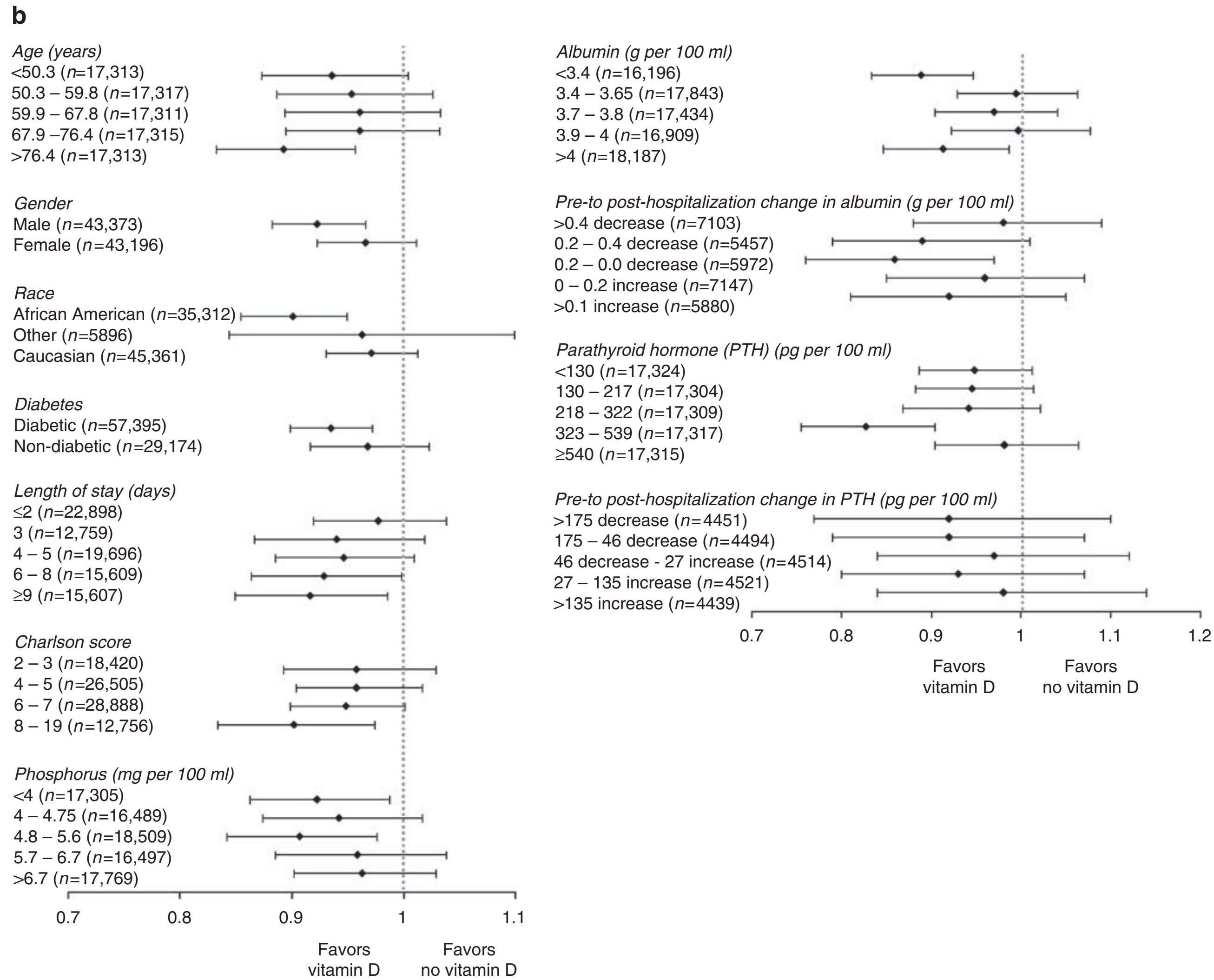

Figure 3 | Continued.

The rate of hospitalization is high for all dialysis patients who, as a group, have a high prevalence of comorbid conditions and treatment-related complications.[1,8–10] The transition from being an inpatient in a hospital to going back to the facility is an important period for patients to recover from a possible acute decline in their baseline health status. Unfortunately, a discontinuity between inpatient and outpatient care is common,[11] which can hinder the recovery process through a preventable medication error,[11] adverse events,[12–14] and re-hospitalization.[11,15] In many cases, dialysis patients returning to their outpatient facility have their routine orders reinstated ('resume previous orders') with no additional modification or monitoring. In fact, post-hospitalized patients with no EPO dose modification and no hemoglobin monitoring had a risk of repeat hospitalization that was equivalent when compared to anemic post-hospitalized patients (hemoglobin <10 g per 100 ml) who do not receive an increase in their EPO dose (Hazard ratio $=0.97$; 95% confidence interval 0.92–1.03). Although an increased physician–patient contact time has been shown to reduce morbidity and mortality of dialysis patients in general, frequent patient evaluation, specifically after hospitalization, remains unproven.[16–18] Using physician's orders, this study examined the possible impact of timely medical intervention on the risk of repeat hospitalization. The results suggest that the appropriate and timely reassessment of a post-hospitalized dialysis patient may be an effective strategy to interrupt the cascade of repeated hospitalizations and the subsequent downward spiral.[19]

Overall, the peri-hospitalization period could be described by an acute inflammation-malnutrition syndrome characterized by significant decreases in weight, albumin, and phosphorus (followed by decrements in PTH values), with increasing EPO resistance. Although the decrease in phosphorus may be a beneficial 'unintended consequence' of hospitalization, particularly in patients with hyperphosphatemia, it is important to analyze the factors that may have led to or are associated with this improvement: if it is due to an improved prescription or compliance with phosphate binders, it is indeed a beneficial outcome; however, if it

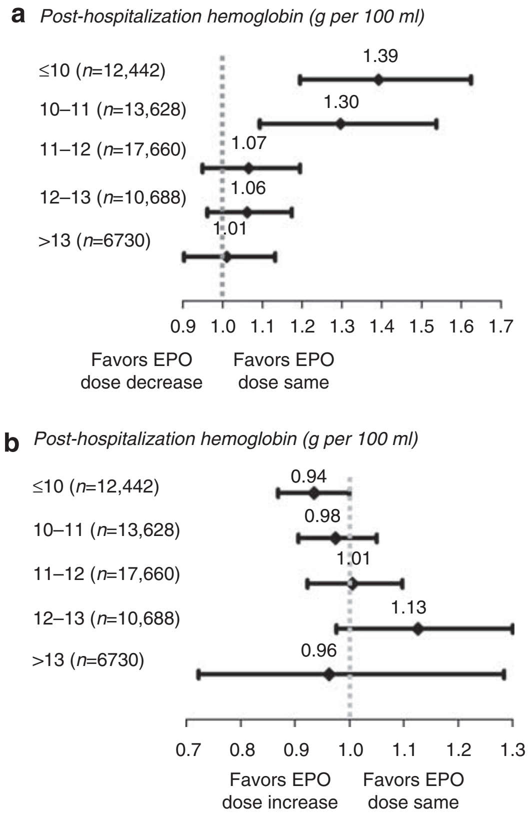

Figure 4 | Hazard ratios for repeat hospitalization associated with increasing or decreasing EPO dose, stratified by post-hospitalization hemoglobin level. (**a**) Adjusted hazard ratios for repeat hospitalization with a decrease in pre- to post-EPO dose (vs same EPO dose) stratified according to post-hospitalization hemoglobin level. (**b**) Adjusted hazard ratios for repeat hospitalization with an increase in pre- to post-EPO dose (vs same EPO dose) stratified according to pre to post–hospitalization hemoglobin level. **a** and **b** suggest the adjustment of post-hospitalization EPO dose to target a hemoglobin level >10 mg per 100 ml. In patients with a post-hospitalization hemoglobin level $\leqslant 10$ g per 100 ml, an increase in EPO dose was associated with a decreased risk of repeat hospitalization (**b**). Decreasing EPO dose was associated with an increased risk of repeat hospitalization in patients with a post-hospitalization hemoglobin level $\leqslant 11$ g per 100 ml (**a**). No statistically significant relationship could be demonstrated between EPO dose adjustment and repeat hospitalization in patients with a post-hospitalization hemoglobin of 11 g per 100 ml or greater. Hazard ratios are covariate and propensity-score adjusted.

reflects a decreased oral intake, then it may not be. Unfortunately, the Fresenius electronic medical records are not linked to hospital systems, and we did not have access to information about the patient when in the hospital to incorporate into the analysis.

This study confirms that hospitalization in ESRD patients is associated with a significant decline in hemoglobin, as reported in two previous analyses.[20,21] Lower hemoglobin levels have been shown to increase the risk of hospital admissions, although the optimal target hemoglobin level remains somewhat controversial. This study found that patients with a post-hospitalization hemoglobin level $\leqslant 10$ g per 100 ml (14% of patients discharged from hospital) significantly benefited from an increase in the EPO dose on discharge from hospital, which is consistent with the latest Food and Drug Administration recommendation for anemia patients with chronic renal failure.[22] Given the number of patients with such a hemoglobin level, routine hemoglobin monitoring on a return to dialysis would seem to be a reasonable first strategy to decrease the risk of repeat hospitalization.

This study also found that patients who did not receive vitamin D after hospitalization had worse outcomes when compared with patients who did receive vitamin D. The risk of repeat hospitalization was greater in patients who had their vitamin D discontinued after discharge from hospital. Although the changes in the mineral-metabolism parameters (calcium, phosphorus, PTH) were modest, they were also decrements and unlikely to be viewed as a contraindication to restarting vitamin D therapy on return from hospital. Overall, these results are consistent with current studies that demonstrate a survival benefit with vitamin D therapy,[5] which, in the aggregate, suggest that the impact of vitamin D is more pervasive than being merely for the control of the PTH in a dialysis population[23]

Although the reduction in the frequency of repeat hospitalization with changes in the EPO dose and with the reinstitution of vitamin D was statistically significant, we should nevertheless emphasize that these are not our current recommendations, which should await prospective clinical trials.

This study also highlights the fact that hospitalization is associated with significant decreases in serum albumin and weight; nevertheless, it was not possible to explore the impact of post-hospitalization interventions to ameliorate malnutrition and inflammation because such data were not collected at the time of the study and interventions to address this are not well defined. However, considering the robust relationship between albumin concentration with hospitalization[24–26] and mortality,[27] it is reasonable to conclude that early intervention—for example, through the encouragement of oral intake, use of nutritional supplements, treatment of any infection, and avoidance of catheters—may also help in reducing the rate of repeat hospitalization in such patients.

Our study also did not report a significant association between repeat hospitalization with target dry-weight modification or with the monitoring of calcium, phosphorus, and the PTH. Consequently, clinical judgment should be used for mineral-metabolism monitoring and volume management in the immediate post-hospitalization period.

Potential residual confounding from unmeasured patient characteristics is likely to be the study's biggest limitation. For example, there was no charting of a phosphate binder prescription that could have confounded the effect of vitamin D. We also could not formally quantify a patient's true volume status to determine how a dilution from the excess extracellular volume could have affected the decrement in laboratory parameters associated with hospitalization. Confounding by indication was likely to be minimal, given that sicker patients who are discharged from hospital are more likely to receive early intervention, which could bias the result toward the null hypothesis. Finally, changes in the Epogen package insert guidelines by the Food and Drug Administration or the Erythropoietin-monitoring policy (EMP) by CMS during 2007 may have also contributed to the residual confounding.

In conclusion, hospitalization represents a change of patient status, which impacts laboratory markers that are associated with mortality in ESRD. Although the administration of vitamin D and the proper treatment of anemia are known to improve survival, this study suggests that the timely evaluation of these therapies, as examples of post-hospitalization care, may result in a significant reduction in the risk of repeat hospitalization.

MATERIALS AND METHODS

Study population

A retrospective cohort study was conducted that enrolled all prevalent, outpatient hemodialysis patients at the Fresenius Medical Care North America from 1 January 2007 to 31 December 2007 ($n = 80,578$ patient years). All data for the study were derived from the Fresenius clinical data systems, which prospectively collect laboratory, medication, demographic, hospitalization, and comorbidity information for all patients receiving chronic renal replacement therapy in over 1500 clinics in the United States.

Patients were eligible for the analysis if they were receiving outpatient hemodialysis at the time of new hospitalization (see below) and returned to a Fresenius facility for outpatient hemodialysis within 7 days after discharge from hospital (immediate post-hospitalization period). The cohort represented a patient population in which health-care professionals would have an adequate opportunity to evaluate a recently hospitalized patient with laboratory testing and modify orders to meet or improve quality outcome parameters as suggested by the Kidney Disease Outcomes Quality Initiative (K/DOQI).[28]

Patients whose hospital length of stay was greater than 30 days were excluded as these patients were discharged from the dialysis facility with a closure of their active hospitalization record as per company policy (1.3% of hospitalization episodes).

Hospitalization, baseline characteristics, and exposures

For the purpose of this study, new hospitalization was defined as a hospital admission that was not preceded by a previous hospital encounter within the past 30 days. The immediate post-hospitalization period was defined as the 7-day period immediately after a patient was discharged from the hospital, during which time, any intervention in the treatment of anemia, administration of vitamin D, and change in the target dry weight was documented. The impact of these interventions on repeat hospitalization, defined as a hospitalization admission within 30 days of discharge from the most recent hospitalization, was sought.

The documentation of hospitalization data (hospital admission date, length of stay, and primary and secondary hospitalization diagnosis) in the Fresenius Medical Care clinical data system was reconciled at the time of patient discharge. Primary and secondary discharge diagnoses were obtained from physician-written discharge summaries. Details of the database can be found in previous publications.[29,30]

During the study period, Fresenius Medical Care maintained a post-hospitalization policy that required physician's reconciliation of all outpatient orders when patients returned to the dialysis facility after more than 1 week of hospitalization. Most laboratory monitoring occurred at regular monthly intervals (and in some facilities, hemoglobin was ordered routinely every 2 weeks), and additional laboratory monitoring after a hospitalization was at the request of the treating nephrologist.

Baseline patient characteristics and laboratory values were defined as the most recent reading within 30 days before a new hospitalization event. Post-hospitalization interventions, laboratory readings, and treatment orders were evaluated within 7 days immediately after the discharge from hospital and return to facility. An analysis comparing data at 30 days and 60 days before a new hospitalization did not show a significant difference (not shown).

The hospitalization rate was calculated by dividing the total number of hospital admissions over the total number of patient years of incenter hemodialysis at Fresenius in 2007. The denominator did not include days when the patient was in hospital.

Impact of hospitalization on laboratory, treatment, and process parameters

To determine the impact of hospitalization on subsequent laboratory and treatment parameters, the absolute and percent change in albumin, hemoglobin, calcium, phosphorus, PTH, dialysis weight, and EPO dose, which occurred after a new hospitalization, were calculated for each patient. On average, laboratory readings were measured 14 days before hospitalization and 3 days after discharge from hospital. Paired t-tests were used to determine if there was a significant change in the last value measured before hospital admission, with the value measured in the 7 days after discharge from hospitalization. The extent of change (pre- to post-hospitalization) was calculated for hospitalizations of differing lengths of stay. Owing to smaller sample sizes, patients with a length of stay between 8 and 14 days and between 15 and 30 days were grouped together.

Impact of intervention during the post-hospitalization period on repeat hospitalization: primary analysis

The primary outcome of the intention-to-treat analysis was the extent of repeat hospitalization (hospitalization within 30 days of an earlier admission). Three separate Cox regression analyses were performed to test whether there was an association between repeat hospitalization and interventions that occurred in the 7 days after discharge from hospital. More specifically, we determined the association between repeat hospitalization, with the following predictor variables entered into the survival equation: (Model 1) hemoglobin (ordered within 7 days after hospitalization vs not ordered), calcium (ordered vs not ordered), phosphorus (ordered vs not ordered), and PTH (ordered vs not ordered); (Model 2) EPO dose modification (yes vs no), vitamin D administration (yes vs no), and target dry-weight change (yes vs no) within 7 days after hospitalization; and (Model 3) ordering of post-hospitalization hemoglobin in tandem with EPO dose modification (vs no hemoglobin order and carrying over pre-hospitalization EPO dose), vitamin D administration (yes vs no), and target dry-weight change (yes vs no) within the 7 days after hospitalization.

Hazard ratios with 95% confidence intervals were calculated for our predictor variables using Cox models that were unadjusted and then adjusted for baseline covariates: age (years), gender, race (Caucasian, African American, others), access (fistula, graft, catheter, unknown), the Charlson comorbidity index,[31–33] vintage, primary hospital discharge diagnosis, length of stay, diabetic status, and pre-hospitalization values for albumin, hemoglobin, calcium, phosphorus, and PTH. A robust sandwich estimator of variance[34] was used to correct for correlations of observations within each patient over time as the same patient could have multiple new hospitalizations with repeated enrollment in the study. Cross-product terms between EPO modification, vitamin D administration, and dry-weight modification were entered into the model to detect significant interaction effects.

Impact of intervention during the post-hospitalization period on repeat hospitalization: sensitivity analysis

Several follow-up analyses were also carried out to validate the findings of our primary analysis. To account for potential unmeasured confounding and selection bias effects, propensity score-based risk-adjustment for multiple groups[35,36] was implemented. To quantify the degree of possible bias, multinomial logistic regression was initially used to model the probability of intervention as a function of 15 variables and the 20 most prevalent causes of hospitalization. The probability for treatment was incorporated into our Cox models as inverse weights to correct for possible confounding by indication.[37,38]

To account for potential bias from unmeasurable confounders from the treating physician or facility,[39,40] each case (hemoglobin order with EPO modification) was matched to a control (no hemoglobin order with the same EPO dose) from the same dialysis unit and/or nephrologist. Unadjusted and covariate-adjusted hazard ratios for repeat hospitalization were then determined for the matched cohort with weighting by propensity for intervention.[35]

Stratum-specific hazard ratios by prespecified categories (baseline characteristics and by the degree of pre- to post-hospitalization change in albumin, hemoglobin, and PTH) were also determined to examine the effectiveness by different subgroups. *P* for trend was calculated by quintiles of vitamin D dose to determine the dose–response relationship between repeat hospitalization and vitamin D dose in users. Doxercalciferol and calcitriol doses were converted into their paricalcitol equivalent[41] for this analysis. All statistical analyses were carried out using SAS version 9.1 (Cary, North Carolina).

DISCLOSURE

Dr Chan, Lazarus, Wingard, and Hakim are employees of Fresenius Medical Care North America.

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