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Pre-ESRD Hemoglobin Variability Predicts Post-ESRD Mortality in Patients Transitioning to Dialysis

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Abstract

Background—Hemoglobin variability (Hb-var) has been associated with increased mortality both in non-dialysis dependent chronic kidney disease (NDD-CKD) and end-stage renal disease (ESRD) patients. However, the impact of Hb-var in advanced NDD-CKD on outcomes after dialysis initiation remains unknown.

Methods—Among 11,872 US veterans with advanced NDD-CKD transitioning to dialysis between October 2007 through September 2011, we assessed Hb-var calculated from the residual standard deviation (SD) of at least three Hb values during the last six months before dialysis initiation (prelude period) using within-subject linear regression models, and stratified into quartiles. Outcomes included post-transition all-cause, cardiovascular, and infection-related mortality, assessed in Cox proportional hazards models and adjusted for demographics, comorbidities, length of hospitalization, medications, estimated glomerular filtration rate (eGFR), type of vascular access, Hb parameters (baseline Hb [i.e., intercept] and change in Hb [i.e., slope]), and number of Hb measurements.

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Disclosures

None of the authors have relevant conflicts of interest.

Results—Higher prelude Hb-var was associated with use of iron and antiplatelet agents, tunneled dialysis catheter use, and higher levels of baseline Hb, change in Hb, eGFR, and serum ferritin. After multivariable adjustment, higher prelude Hb-var was associated with higher post-ESRD all-cause and infection-related mortality, but not cardiovascular mortality (adjusted hazard ratios [95% CI] for the highest [vs. lowest] quartile of Hb-var, 1.10 [1.02–1.19], 1.28 [0.93–1.75], and 0.93 [0.79–1.10], respectively).

Conclusions—High pre-ESRD Hb-var is associated with higher mortality, particularly from infectious causes rather than cardiovascular causes. Further research is required to clarify the underlying mechanisms and true causal nature of the observed association.

Keywords

hemoglobin; variability; mortality; chronic kidney disease; end-stage renal disease; transition

INTRODUCTION

Anemia is a frequent complication of chronic kidney disease (CKD) and is associated with worse outcomes in patients with CKD [1]. The introduction of erythropoiesis stimulating agents (ESAs) in 1989 has given clinicians the ability to increase hemoglobin (Hb) levels, yet targeting normal Hb levels did not result in better survival, but rather in increased cardiovascular events and mortality in patients with CKD [2–4]. Maintenance of a stable Hb within the narrow range currently recommended in patients with CKD often requires frequent ESA dosing changes that, in addition to other factors such as age, intercurrent diseases, and iron therapy [5,6], result in a continuous cycling of hemoglobin levels in contrast to individuals with normal renal function whose hemoglobin levels are held constant by oxygen delivery sensing feedback upon erythropoiesis. In recent years, observational studies have shown that higher hemoglobin variability (Hb-var) is associated with adverse outcomes both in non-dialysis dependent CKD (NDD-CKD) and end-stage renal disease (ESRD) patients [7–16]. However, to the best of our knowledge, no previous studies have examined the impact of Hb-var in late stage NDD-CKD on outcomes after dialysis initiation. Given the pervasive nature of anemia in this vulnerable population who experience the highest mortality immediately after the transition to dialysis and suffer from an exceptionally high health and economic burden [1,17], the question whether high Hb-var in the immediate pre-ESRD period is associated with post-transition mortality is of particular relevance. We therefore investigated the association of Hb-var in the pre-ESRD transition period with post-ESRD all-cause, cardiovascular, and infection-related mortality, using a large nationally representative cohort of US veterans with incident ESRD.

MATERIALS AND METHODS

Study Population

We analyzed longitudinal data from the Transition of Care in CKD (TC-CKD) study, a retrospective cohort study examining US veterans with incident ESRD transitioning to dialysis from October 1, 2007 through September 30, 2011 [18–20]. A total of 52,172 US veterans were identified from the US Renal Data System (USRDS) [21] as a source

population. The algorithm for the cohort definition is shown in Supplementary Figure 1. We extracted all Hb values measured during clinical encounters in any Veterans Affairs (VA) facility; patients without Hb measurements (n = 23,088) were excluded. We also excluded patients with less than three Hb measurements recorded on different days within six months prior to dialysis initiation (i.e., six-months "prelude period") (n = 17,068) and who were missing follow-up data (n = 144), resulting in an analytical sample of 11,872 patients.

Exposure Variable

The primary exposure of interest was Hb-var over the six-month prelude period. Hb-var was defined as the residual standard deviation (SD) calculated by within-subject linear regression models using all Hb values in each patient. We categorized the Hb-var values into quartiles (<0.46, 0.46–<0.69, 0.69–<0.96, and ≥0.96 g/dL), using the lowest Hb-var quartile as reference. The Hb-var level was also treated as a continuous variable to examine nonlinear associations by using a restricted cubic spline analysis. Baseline Hb level and average change in Hb (g/dL per month) were defined as the intercept and the slope estimated from the same regression models used to calculate Hb-var.

Covariates

Data from the USRDS Patient and Medical Evidence files were used to determine patients' baseline demographic characteristics and type of vascular access at the time of dialysis initiation. Information on comorbidities was extracted from the VA Inpatient and Outpatient Medical SAS Datasets [22], using the *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic and procedure codes and Current Procedural Terminology codes, as well as from VA/Centers for Medicare and Medicaid Services (CMS) data. The Charlson Comorbidity Index score was calculated using the Deyo modification for administrative datasets, without including kidney disease [23]. Cardiovascular disease was defined as the presence of diagnostic codes for angina, coronary artery disease, myocardial infarction, or cerebrovascular disease. Medication data were collected from both CMS Data (Medicare Part D) and VA pharmacy dispensation records [24]. Patients who received at least one dispensation of medications within the six-month prelude period were recorded as having been treated with these medications. Laboratory data were obtained from VA research databases as previously described [25,26], and their baseline values were defined as the average of each covariate during the six-month prelude period preceding dialysis initiation. Estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation [27].

Outcome Assessment

The co-primary outcomes of interest were all-cause, cardiovascular, and infection-related mortality after dialysis initiation. The start of the follow-up period was the date of dialysis initiation, and patients were followed up until death or other censoring events including kidney transplantation, loss of follow-up, or the last date of available follow-up (December 27, 2012 and October 6, 2011 for all-cause and cause-specific mortality, respectively) [18–20]. All-cause mortality data, censoring events, and associated dates were obtained from VA and USRDS data sources [21]. Cause-specific mortality data were obtained from USRDS.

Statistical analysis

Baseline patient characteristics were summarized according to Hb-var quartiles, and presented as number (percent) for categorical variables and the mean ± standard deviation (SD) for continuous variables with a normal distribution or median (interquartile intervals [IQI]) for those with a skewed distribution. Differences across quartiles were assessed using analysis of variance and chi-squared tests for continuous and categorical variables, respectively. We performed multivariable linear regression to identify variables independently associated with Hb-var. Based on a priori knowledge and their availability in this study, the following explanatory variables were included: sociodemographics (age, sex, race, and marital status), comorbidities (diabetes mellitus, cardiovascular disease, congestive heart failure [CHF], peripheral vascular disease, lung disease, peptic ulcer disease, liver disease, malignancy, human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS]), Charlson comorbidity index, cumulative length of hospitalization during the six-month prelude period, medications (ESAs, intravenous or oral iron, vitamin D analogs, angiotensin-converting enzyme inhibitors [ACEIs]/angiotensin receptor blockers [ARBs], antiplatelet agents, and warfarin), vascular access type, baseline Hb, change in Hb, number of Hb measurements over the six-month prelude period, and eGFR and serum ferritin levels averaged over the six-month prelude period. Variance inflation factors were calculated to examine substantial multicollinearity among these parameters, and values >5.0 were considered to indicate collinearity. The association between Hb-var and mortality was estimated using Cox proportional hazards models. Models were incrementally adjusted for the following potential confounders based on theoretical considerations: model 1 adjusted for age, sex, race/ethnicity, and marital status; model 2 additionally accounted for comorbidities (diabetes mellitus, cardiovascular disease, CHF, peripheral vascular disease, lung disease, peptic ulcer disease, liver disease, malignancy, and HIV/AIDS), Charlson comorbidity index, and cumulative length of hospitalization during the six-month prelude period as an indicator of sickness; model 3 additionally included medications (ESAs, intravenous or oral iron, vitamin D analogs, ACEIs/ARBs, antiplatelet agents, and warfarin), eGFR, type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter), baseline Hb, change in Hb, and number of Hb measurements over the six-month prelude period. Tests for linear trend across quartiles were conducted by applying the median value of each quartile to relevant patients and modeling that variable as a continuous variable in the regression models. Restricted cubic spline models were used to investigate nonlinearity in fully adjusted associations between Hb-var and mortality.

We performed several sensitivity analyses to evaluate the robustness of our main findings. The associations of Hb-var with outcomes were examined in subgroups of patients stratified by age, race, prevalent diabetes mellitus, cardiovascular disease, and CHF, eGFR, use of ESAs and iron, and number of Hb measurements over the six-month prelude period. Potential interactions were formally tested by including relevant interaction terms. We also investigated whether accounting for serum ferritin levels further attenuates the Hb-var-mortality associations in the group of 8,605 patients with available serum ferritin measurements as an additional model (model 4). In order to account for the different Hb determinations between inpatient and outpatient settings, we further performed an additional

analysis using at least three inpatient/outpatient Hb values separately to calculate the variability.

Compared to patients in the main cohort (n = 11,872), those who were excluded from the source cohort (n = 40,300) were older (71.6 versus 66.0 years) and were less likely to be male (93.3% versus 98.0%), African-American (20.9% versus 35.4%), and diabetic (53.1% versus 71.9%). Of the variables included in multivariable models, data points were missing for race (0.2%), eGFR (0.2%), vascular access type (6.4%), and serum ferritin (22.8%). Information about cause of death was also missing in 2,831 of the 5,711 (49.6%) who died in our study population (Supplementary Table 1). Of the 11,872 patients in our study population, 11,088 (93.4%) had complete data available for the main adjusted multivariable model (model 3). Due to the relatively low proportion of missingness in the main model, missing data was not imputed. The reported P values are two-sided and reported as significant at <0.05 for all analyses. All analyses were conducted using STATA/MP Version 14 (STATA Corporation, College Station, TX). The study was approved by the Institutional Review Boards of the Memphis and Long Beach VA Medical Centers, with exemption from informed consent.

RESULTS

Baseline Characteristics

Overall, the mean±SD age at baseline was 66.0±11.1 years; 98.0% of patients were male; 35.4% were African-American; and 71.9% were diabetic. The median (IQI) eGFR level was 13.1 (9.9, 17.7) mL/min/1.73m^2. During the six-month prelude period, patients had a median (IQI) of 8 (5, 15) Hb measurements. The mean±SD prelude Hb-var was 0.75±0.45 g/dL. Baseline characteristics in the overall cohort and stratified by Hb-var quartiles are presented in Table 1. Compared to patients with lower Hb-var, those with higher Hb-var tended to have a poorer risk profile (higher prevalence of comorbidities, longer cumulative length of hospitalization, and lower serum albumin and higher serum ferritin levels) and had lower BMI and higher eGFR levels. They were also more likely to initiate dialysis therapy with a catheter and use ESAs, iron, and antiplatelet agents.

Variables associated with prelude Hb-var

Table 2 shows the association of Hb-var with patient characteristics. After multivariable adjustment, history of peptic ulcer disease or malignancy, use of iron and antiplatelet agents, dialysis catheter use, and higher baseline Hb, change in Hb, number of Hb measurements, eGFR, and serum ferritin levels were associated with higher Hb-var. In contrast, older age and use of warfarin were associated with lower Hb-var.

Association of Pre-ESRD Hb-var with Post-ESRD All-Cause Mortality

There were 5,711 all-cause deaths during a median follow-up of 2.1 years (IQI, 1.2, 3.3 years; total time at risk, 26,748 patient-years) following dialysis initiation (crude incidence rate, 213.5 per 1000 patient-years; 95% confidence interval [CI], 208.0–219.2). Table 3 shows the multivariable-adjusted hazard ratios (HRs) associated with pre-ESRD Hb-var quartiles. In the demographically adjusted model, higher Hb-var quartiles were

incrementally associated with higher all-cause mortality (*P* value for trend <0.001, Table 3). After further adjustment for other potential confounders, the association between Hb-var and all-cause mortality was substantially attenuated but remained statistically significant (adjusted HRs [95% CI] for quartiles 2 through 4 [vs. quartile 1], 0.99 [0.91–1.07], 1.08 [1.00–1.17], and 1.10 [1.02–1.19], in model 3; *P* value for trend = 0.004, Table 3). As shown in Figure 1A, higher levels of Hb-var treated as a continuous variable were monotonically associated with higher all-cause mortality.

In subgroup analyses, higher Hb-var was associated with higher all-cause mortality across most subgroups (Supplementary Figure 2). Race significantly modified the association of Hb-var with all-cause mortality, with greater association of higher Hb-var with all-cause mortality among African-Americans. Results were similar after further adjustment for serum ferritin level and using inpatient or outpatient Hb values separately to calculate the variability, albeit with borderline significance (Supplementary Tables 2A–4A).

Association of Pre-ESRD Hb-var with Post-ESRD Cardiovascular and Infection-Related Mortality

During a median follow-up of 1.3 years (IQI, 0.6, 2.3 years) following dialysis initiation, 1,045 and 382 deaths occurred from cardiovascular and infection-related causes, respectively. In the demographically adjusted model, Hb-var quartiles were incrementally associated with cardiovascular mortality, with significantly higher death risks seen in higher Hb-var quartiles. This association was considerably attenuated and no longer significant after further adjustment for other potential confounders (adjusted HRs [95% CI] for Hb-var quartiles 2 through 4 [vs. quartile 1], 0.92 [0.79–1.10], 1.03 [0.88–1.21], and 0.93 [0.79–1.10], in model 3; *P* value for trend = 0.63, Table 4A). In contrast, higher Hb-var quartiles were associated with a trend towards higher infection-related mortality in the fully adjusted multivariable model (adjusted HRs [95% CI] for Hb-var quartiles 2 through 4 [vs. quartile 1], 1.02 [0.74–1.41], 1.19 [0.87–1.63], and 1.28 [0.93–1.75], in model 3; *P* value for trend = 0.079, Table 4B). When using restricted cubic spline models, there was a weak but nonsignificant reverse U-shaped association of Hb-var with cardiovascular mortality (Figure 1B); while the pattern of association between Hb-var and infection-related mortality was qualitatively similar to that with all-cause mortality, with higher mortality seen in those with higher Hb-var (Figure 1C).

In subgroup analyses, the pattern of associations of Hb-var with cardiovascular and infection-related mortality were generally consistent across selected subgroups (Supplementary Figures 1B and 1C), with a few exceptions: the risk of infection-related mortality associated with higher Hb-var was greater in patients with eGFR <15 mL/min/1.73m^2 and those treated with ESAs, with statistically significant interactions. The associations were robust to additional adjustment for serum ferritin levels and when using inpatient or outpatient Hb values separately to calculate the variability (Supplementary Tables 2B–4C).

DISCUSSION

In this large national cohort of 11,872 US veterans with advanced NDD-CKD transitioning to dialysis, we found that higher Hb-var was independently associated with higher all-cause and infection-related mortality, but not cardiovascular mortality, following dialysis initiation. Compared with patients in the lowest Hb-var quartile (<0.46 g/dL), those in the highest Hb-var quartile (≥0.96 g/dL) had 10% and 28% higher all-cause and infection-related mortality, respectively, after adjusting for various potential confounders. During the six-month prelude period, we also found that history of peptic ulcer disease or malignancy, use of iron and antiplatelet agents, dialysis catheter use, and higher number of Hb measurements and levels of baseline Hb, change in Hb, eGFR, and serum ferritin were all associated with higher Hb-var.

These results are similar to some aspects of several previous studies that reported the association of greater Hb-var with poor survival, almost exclusively in patients undergoing maintenance hemodialysis [9–16]. Recently, a few observational studies have also demonstrated a similar Hb-var–mortality association in NDD-CKD populations [7,8], suggesting its prognostic implications throughout different stages of CKD. Most importantly, however, no previous studies have examined the Hb-var–mortality association during the ESRD transition period. The extremely high mortality experienced by incident ESRD patients immediately following transition to dialysis [17] makes the assessment of modifiable pre-transition risk factors (such as Hb-var, and others) especially important in order to find treatment targets that might have a positive effect on their survival.

Several possible explanations have been proposed for the underlying mechanisms of high Hb-var, such as differences in pharmacokinetic and bioavailability parameters among drugs that modulate Hb synthesis (e.g., ESAs and iron) [28,29], a high number of comorbidities, intercurrent events, and hospitalizations [9], anemia management practice patterns, and reimbursement policies [30]. In line with these findings, we identified several clinical factors associated with higher prelude Hb-var, including history of peptic ulcer disease or malignancy, use of iron and antiplatelet agents, dialysis catheter use, and higher number of Hb measurements and levels of baseline Hb, change in Hb, eGFR, and serum ferritin. The substantial attenuation observed in our mortality risk estimates after accounting for all of these factors may, in turn, support their potential involvement as underlying pathophysiological mechanisms in the Hb-var–mortality relationship. In fact, patients with advanced NDD-CKD have an exceptionally high burden of numerous comorbidities, and higher prelude Hb-var may merely be a marker of more severe underlying comorbid conditions with concomitant chronic anemia requiring iron and/or ESAs supplementation, which could consequently contribute to the higher risk of all-cause mortality.

It has been suggested that increased Hb-var can also serve as a potential direct mediator of organ dysfunction or injury by repeated episodes of relative ischemia to vital organs and Hb overshoot, the former causing left ventricular dilation or hypertrophy through the development of pathologic changes of myocardium [31,32], the latter resulting in elevated blood pressure with risk for hypertensive encephalopathy [33], increased thrombotic events [2], and accelerated left ventricular dysfunction and hypertrophy [34], mostly in patients

receiving hemodialysis. In the range of Hb levels typically encountered in the NDD-CKD population, anemia as a cause of solid organ dysfunction mediated by ischemia would be unusual, which could explain why we observed less contributions of prelude Hb-var to the risk of cardiovascular mortality than infection-related mortality following dialysis initiation. This seemingly counterintuitive observation might also be partly explained by survivorship bias in this unique study population, such that patients who had suffered from the abovementioned cardiovascular complications and had higher Hb-var may have died before reaching ESRD.

Meanwhile, our findings on the association between Hb-var and infection-related mortality are generally consistent with a few previous studies that investigated the relationship between Hb-var and incidence of infectious diseases [9,16]. Although we cannot infer a causal relationship from observational studies, there are some plausible explanations linking higher Hb-var to the risk of infection. In the present study, despite almost identical levels of baseline Hb across Hb-var quartiles, we observed higher serum ferritin levels and a higher prevalence of patients who used iron and ESAs in higher (vs. lower) Hb-var quartiles, which may have reflected underlying systemic inflammation due to infections among patients with higher Hb-var. Increase in systemic inflammation may inhibit erythropoiesis and result in a blunted or absent response to ESAs despite its high-dose administration. This ESA hyporesponsiveness, which itself is also an independent risk factor for poor survival [35], may trigger the use of more iron because of the low transferrin saturation levels which result from inflammatory blockade of reticuloendothelial stores of iron [36]. Iron administration is highly effective in replenishing iron stores to accelerate erythropoiesis, but its excessive use may in turn result in impaired host innate immune response [37,38]. Indeed, iron overload has been shown to promote apoptosis of helper $CD4^+$ T lymphocytes through iron-induced oxidative stress [39,40] and impair phagocytic and bactericidal capacities of polymorphonuclear leukocytes [41–43]; thereby increasing susceptibility to infections. These underlying mechanisms could synergistically contribute to a higher risk of infection-related mortality. In our study, however, the association of Hb-var with infection-related mortality still remained statistically significant even after accounting for serum ferritin levels and use of ESAs and iron as well as various potential confounders, suggesting that higher prelude Hb-var could be a harbinger of future deaths from infectious causes independent of known risk factors. Given the considerable uncertainties about the physiological mechanism of Hb-var and the optimal approach to anemia management in the transition period, the effect of such interventions toward reducing Hb-var on patient outcomes may deserve further investigation.

Our study results must be interpreted in light of several limitations. First, our cohort consisted predominantly of male US veterans; hence, generalization of the results to women or patients from other geographical areas needs to be undertaken cautiously. Second, the effect of longitudinal changes in Hb-var and other potential confounders such as ESA use and iron status over the post-ESRD follow-up period was not accounted for; therefore, it is possible that such time-dependent factors might affect the observed associations. However, given the unique nature of this study which examined the impact of pre-ESRD Hb-var on post-ESRD outcomes, the observed results with the use of fixed prelude baseline covariates would still be of value, providing potential prognostic implications for post-ESRD outcomes

in patients with advanced NDD-CKD. Finally, as with all observational studies, we cannot eliminate the possibility of unmeasured confounders such as proteinuria.

In conclusion, in this large national cohort of US veterans with advanced NDD-CKD transitioning to dialysis, a greater pre-ESRD Hb-var was associated with higher post-ESRD mortality, especially with infection-related mortality. Our findings broaden the recognition of the prognostic importance of Hb-var in the immediate pre-ESRD period on post-ESRD outcomes and suggest the need for careful attention to high Hb-var in CKD patients during the transition period. Further research is required to clarify the underlying mechanisms and to test whether modification of pre-ESRD Hb-var can improve clinical outcomes in incident ESRD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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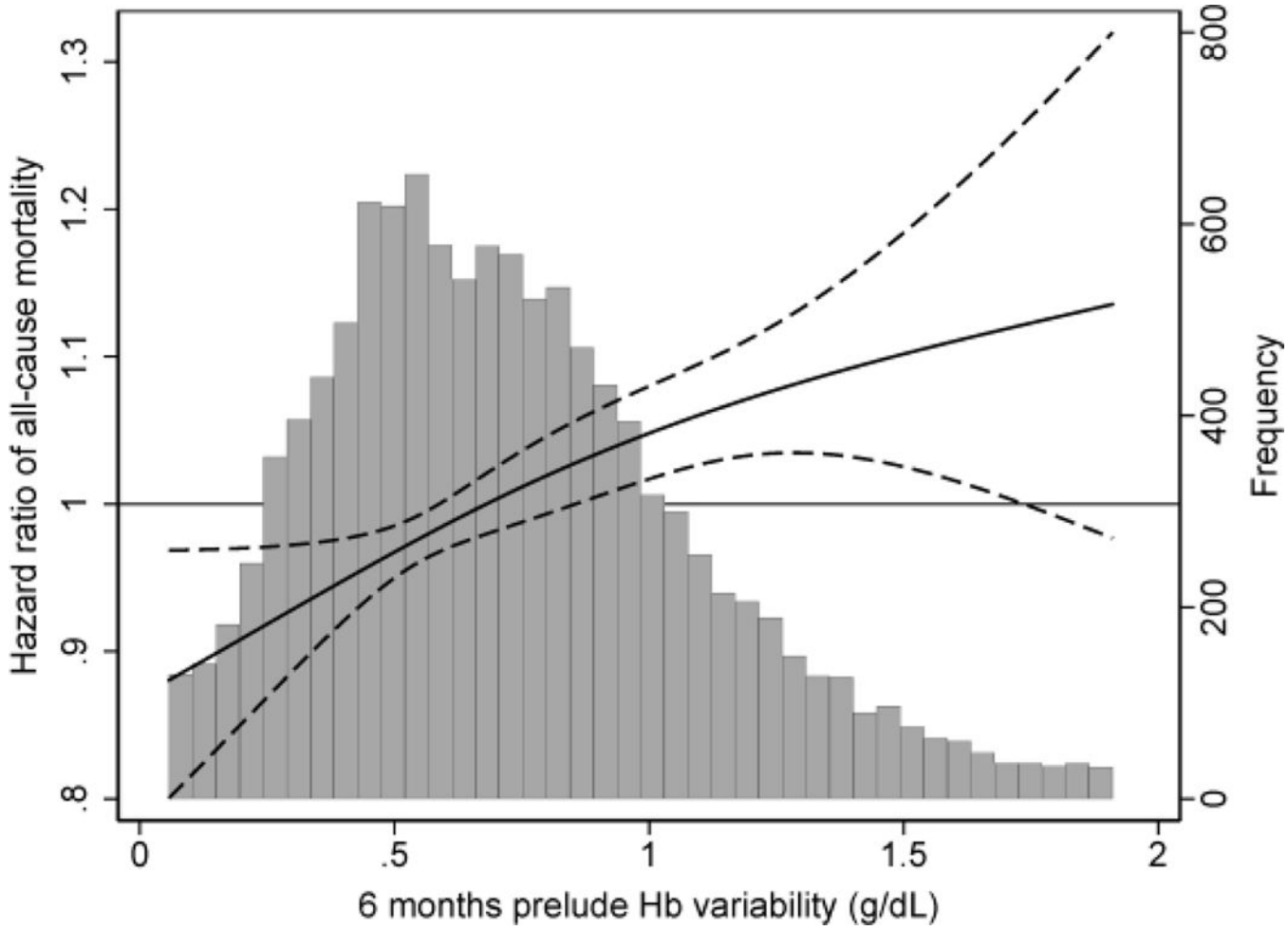

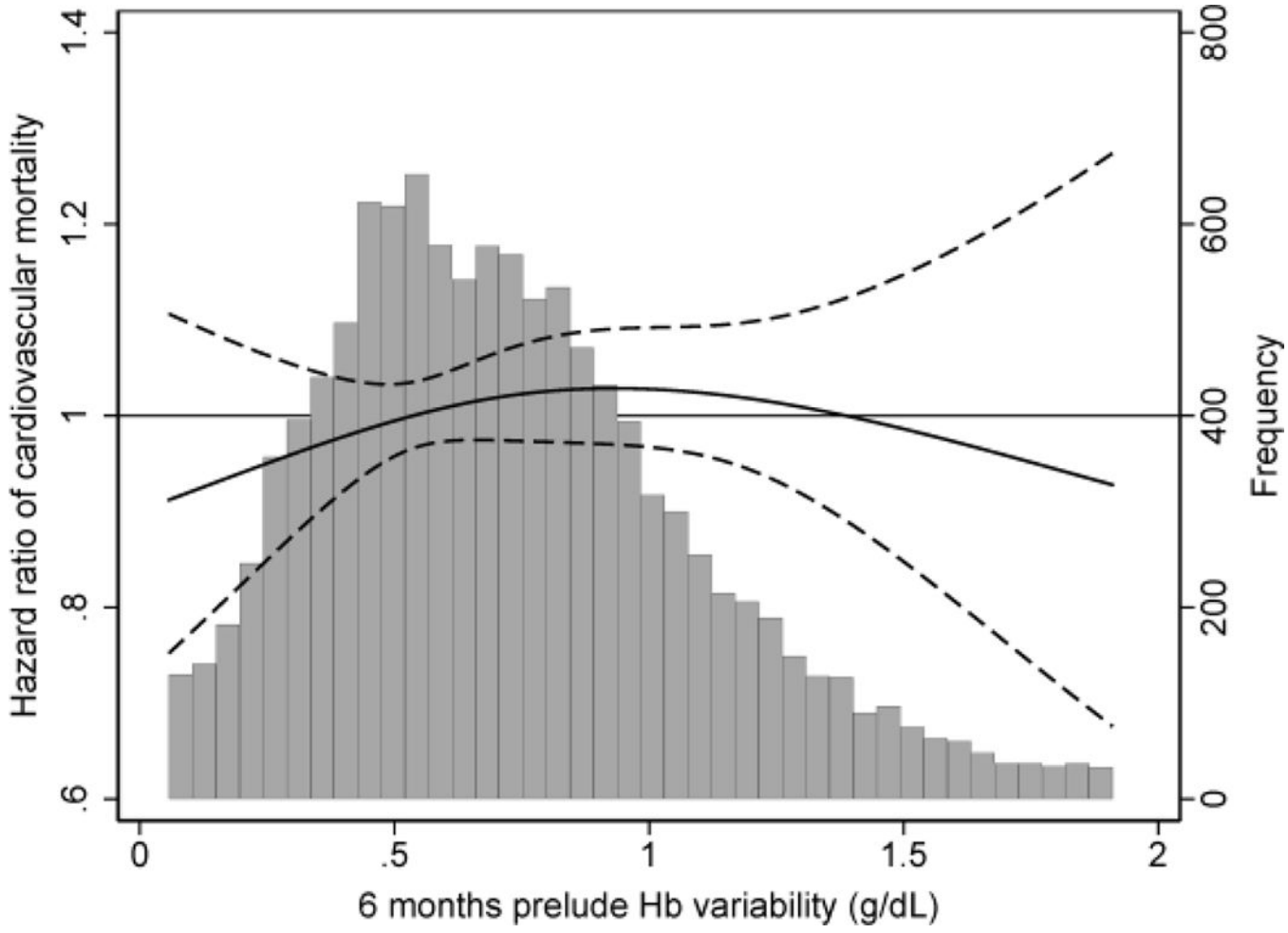

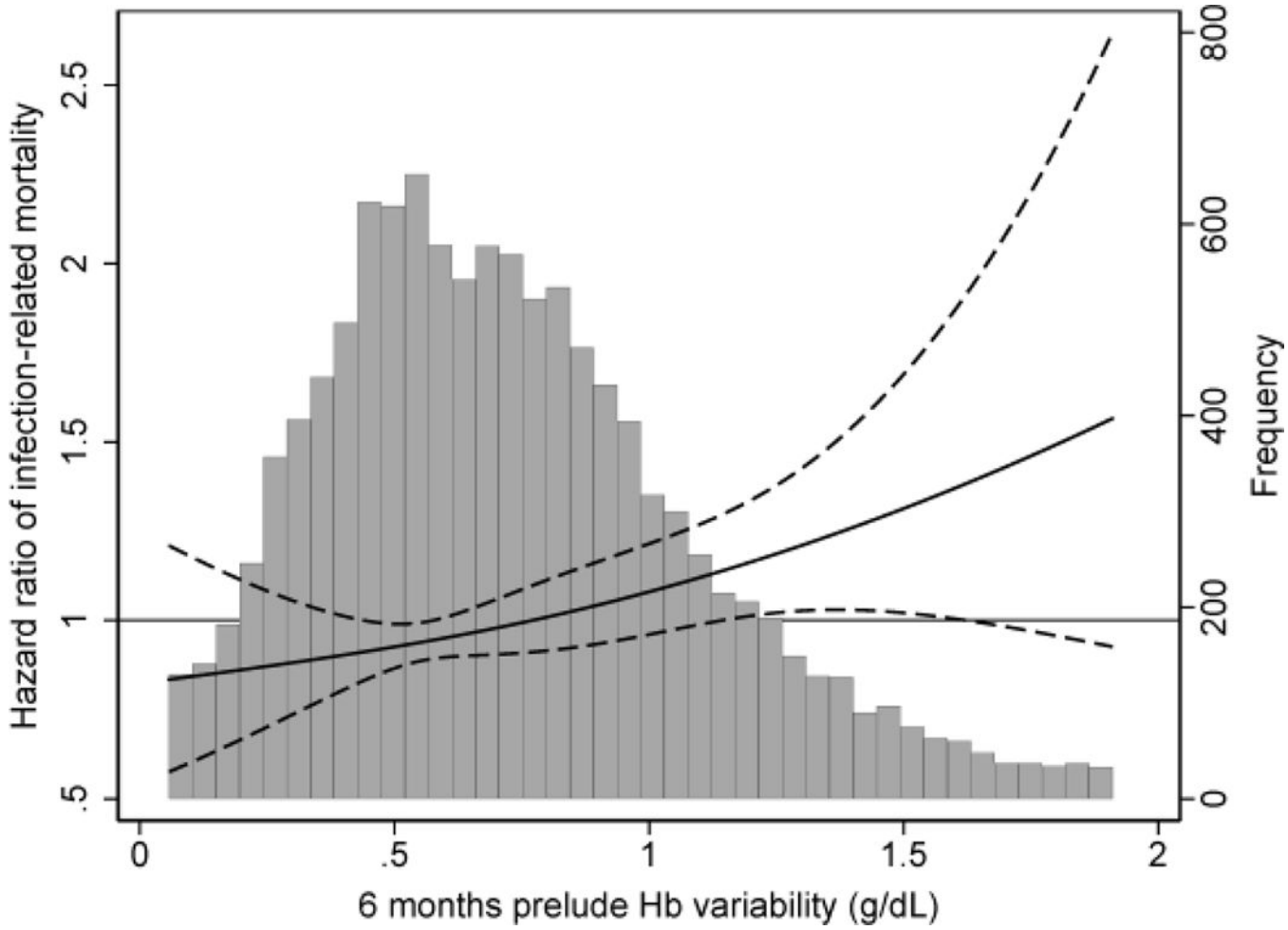

Figure 1. Association of prelude Hb variability with (A) all-cause, (B) cardiovascular, and (C) infection-related mortality after dialysis initiation

Solid and dashed lines represent hazard ratio and 95% CI, respectively.

A hazard reference ratio of 1 (solid horizontal line) and a histogram of observed Hb variability values are overlaid.

The x-axis shows Hb variability levels, trimmed at 2% and 98%.

Model is adjusted for age, sex, race/ethnicity, marital status, comorbidities (diabetes mellitus, cardiovascular disease, congestive heart failure, peripheral vascular disease, lung disease, peptic ulcer disease, liver disease, malignancy, and HIV/AIDS), Charlson comorbidity index, cumulative length of hospitalization, medications (ESAs, intravenous or oral iron, vitamin D analogs, ACEIs/ARBs, antiplatelets, and warfarin), eGFR levels averaged over the six-month prelude period, type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter), Hb variability parameters (baseline Hb level and change in Hb), and number of Hb measurements during the six-month prelude period.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immunodeficiency syndrome; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; ESA, erythropoietin stimulating agent; Hb, hemoglobin; HIV, human immunodeficiency virus

Table 1

Baseline patient characteristics according to quartiles of prelude Hb variability

	All	Hb variability (g/dL)				*P*
		Q1 (lowest) <0.46	Q2 0.46–<0.69	Q3 0.69–<0.96	Q4 (highest) ≥0.96	
	(*N* = 11,872)	(*n* = 3,039)	(*n* = 2,942)	(*n* = 2,971)	(*n* = 2,920)	
Age (years)	66.0±11.1	66.3±11.2	65.8±11.2	66.2±11.0	65.7±10.9	0.12
Gender (male)	11,629 (98.0)	2,988 (98.3)	2,883 (98.0)	2,907 (97.8)	2,851 (97.6)	0.29
Race (African-American)	4,201 (35.4)	1,027 (33.8)	1,078 (36.6)	1,076 (36.2)	1,020 (34.9)	0.005
Marital status (married)	5,628 (47.4)	1,525 (50.2)	1,401 (47.6)	1,371 (46.1)	1,331 (45.6)	0.011
Body mass index (kg/m^2)	29.8±6.8	30.9±6.9	30.5±6.9	29.6±6.6	28.2±6.5	<0.001
Diabetes mellitus	8,538 (71.9)	2,152 (70.8)	2,135 (72.6)	2,205 (74.2)	2,046 (70.1)	0.002
Hypertension	11,550 (97.3)	2,946 (96.9)	2,885 (98.1)	2,907 (97.8)	2,812 (96.3)	<0.001
Cardiovascular disease[a]	5,116 (43.1)	1,173 (38.6)	1,253 (42.6)	1,354 (45.6)	1,336 (45.8)	<0.001
Congestive heart failure	6,379 (53.7)	1,498 (49.3)	1,607 (54.6)	1,725 (58.1)	1,549 (53.0)	<0.001
Peripheral vascular disease	4,600 (38.7)	1,105 (36.4)	1,137 (38.6)	1,205 (40.6)	1,153 (39.5)	0.007
Lung disease	5,095 (42.9)	1,201 (39.5)	1,260 (42.8)	1,367 (46.0)	1,267 (43.4)	<0.001
Peptic ulcer disease	849 (7.2)	191 (6.3)	177 (6.0)	226 (7.6)	255 (8.7)	<0.001
Liver Disease	1,684 (14.2)	352 (11.6)	391 (13.3)	457 (15.4)	484 (16.6)	<0.001
Malignancy	2,830 (23.8)	629 (20.7)	639 (21.7)	769 (25.9)	793 (27.2)	<0.001
HIV/AIDS	200 (1.7)	45 (1.5)	40 (1.4)	48 (1.6)	67 (2.3)	0.026
Charlson Comorbidity Index	5 [3, 7]	4 [3, 6]	5 [3, 6]	5 [3, 7]	5 [3, 7]	<0.001
Cumulative length of hospitalization (days)	17 [6, 39]	10 [2, 27]	14 [5, 34]	20 [8, 45]	23 [10, 51]	<0.001
Vascular access type (catheter)	8,184 (68.9)	1,897 (62.4)	1,999 (67.9)	2,120 (71.4)	2,168 (74.2)	<0.001
Medications						
ESAs	5,690 (47.9)	1,081 (35.6)	1,392 (47.3)	1,549 (52.1)	1,668 (57.1)	<0.001
Iron	6,018 (50.7)	1,259 (41.4)	1,528 (51.9)	1,620 (54.5)	1,611 (55.2)	<0.001
Vitamin D analogs	4,340 (36.6)	1,207 (39.7)	1,111 (37.8)	1,049 (35.3)	973 (33.3)	<0.001
ACEIs/ARBs	6,267 (52.8)	1,526 (50.2)	1,581 (53.7)	1,645 (55.4)	1,515 (51.9)	<0.001
Antiplatelets	5,998 (50.5)	1,248 (41.1)	1,478 (50.2)	1,669 (56.2)	1,603 (54.9)	<0.001
Warfarin	1,062 (8.9)	236 (7.8)	287 (9.8)	278 (9.4)	261 (8.9)	0.042

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	All	Hb variability (g/dL)				*P*
		Q1 (lowest) <0.46	Q2 0.46–<0.69	Q3 0.69–<0.96	Q4 (highest) ≥0.96	
	(*N* = 11,872)	(*n* = 3,039)	(*n* = 2,942)	(*n* = 2,971)	(*n* = 2,920)	
Laboratory parameters						
Serum Albumin (g/dL)[b]	3.3±.6	3.4±0.6	3.3±0.6	3.2±0.6	3.2±0.6	<0.001
eGFR (mL/min/1.73m^2)[b]	13.1 [9.9, 17.7]	12.2 [9.2, 16.2]	12.6 [9.5, 16.7]	13.5 [10.2, 18.5]	14.0 [10.5, 19.8]	<0.001
Serum ferritin (ng/mL)[b]	206 [110, 374]	183 [100, 318]	189 [104, 341]	207 [114, 382]	253 [125, 469]	<0.001
Baseline Hb (g/dL)	10.9±1.8	11.0±1.7	11.0±1.6	10.9±1.8	10.9±2.1	0.015
Change in Hb (g/dL/month)	−0.22 [−0.53, 0.05]	−0.20 [−0.51, 0.04]	−0.23 [−0.51, 0.01]	−0.23 [−0.53, 0.05]	−0.22 [−0.58, 0.11]	0.003
Number of Hb measurements	8 [5, 15]	5 [4, 7]	8 [5, 13]	11 [7, 19]	13 [7, 24]	<0.001

Data are presented as number (percentage), mean ± standard deviation, or median [interquartile interval].

[a] Cardiovascular disease include coronary artery disease, angina, myocardial infarction, or cerebrovascular disease.

[b] Laboratory results averaged over the six-month prelude period.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immunodeficiency syndrome; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; ESA, erythropoietin stimulating agent; Hb, hemoglobin; HIV, human immunodeficiency virus

Table 2

Variables associated with prelude Hb variability

Characteristics	Coefficient*	95% CI	*P* value
Age (per 1 year)	−0.001	−0.002 to −0.0007	0.001
Sex (male vs. women)	0.055	−0.007 to 0.12	0.08
Race (African-American vs. white)	−0.003	−0.022 to 0.017	0.79
Marital status (married vs. non-married)	−0.007	−0.025 to 0.01	0.42
Comorbidities (yes vs. no)			
Diabetes mellitus	−0.020	−0.047 to 0.008	0.16
Cardiovascular disease[a]	0.013	−0.009 to 0.035	0.25
Congestive heart failure	0.002	−0.019 to 0.022	0.88
Peripheral vascular disease	0.012	−0.008 to 0.033	0.23
Lung disease	−0.008	−0.028 to 0.012	0.42
Peptic ulcer disease	0.047	0.012 to 0.082	0.008
Liver disease	0.014	−0.014 to 0.042	0.33
Malignancy	0.030	0.003 to 0.058	0.031
HIV/AIDS	0.034	−0.046 to 0.11	0.40
Charlson Comorbidity Index (per 1 unit)	0.003	−0.004 to 0.010	0.45
Cumulative length of hospitalization (per 1 day)	−0.0001	−0.0003 to 0.00008	0.27
Medications (yes vs. no)			
ESAs	0.094	0.075 to 0.113	0.27
Iron	0.030	0.011 to 0.049	0.002
Vitamin D analogs	−0.014	−0.032 to −0.005	0.16
ACEIs/ARBs	−0.009	−0.027 to 0.009	0.30
Antiplatelet agents	0.026	0.007 to 0.045	0.007
Warfarin	−0.052	−0.085 to −0.020	0.002
Vascular access type (catheter vs. others)	0.032	0.012 to 0.052	0.002
Laboratory parameters			
Baseline Hb (per 1 g/dL)	0.014	0.008 to 0.019	0.002
Change in Hb (per 1 g/dL/month)	0.0004	0.0003 to 0.0007	<0.001
Number of Hb measurements	0.006	0.005 to 0.006	<0.001
eGFR (per 1 mL/min/1.73m^2)[b]	0.002	0.0009 to 0.003	<0.001
Serum ferritin (per 1 ng/mL)[b]	0.00010	0.00008 to 0.00012	<0.001

*Coefficient for multivariable linear regression models. Value of coefficient represents change in Hb variability (g/dL) per 1 unit change in each factor. Positive and negative numbers indicate higher and lower Hb variability per 1 unit change in factors, respectively. The variance inflation factors of these parameters were all less than 5.

[a]Cardiovascular disease include coronary artery disease, angina, myocardial infarction, or cerebrovascular disease.

[b]Laboratory results averaged over the six-month prelude period.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immunodeficiency syndrome; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; ESA, erythropoietin stimulating agent; Hb, hemoglobin; HIV, human immunodeficiency virus

Table 3

Adjusted hazard ratios (95% CI) for all-cause mortality after dialysis initiation by Hb variability quartiles over the six-month prelude period

	Quartile of prelude Hb variability (g/dL)				
	Q1 (lowest) <0.46	**Q2 0.46–<0.69**	**Q3 0.69–<0.96**	**Q4 (lowest) ≥0.96**	***P* for trend[a]**
Participants (*n*)	3,039	2,942	2,971	2,920	
Events	1,323 (43.5)	1,290 (43.8)	1,521 (51.2)	1,577 (54.0)	
Model 1	1 [reference]	1.05 (0.97–1.13)	1.29 (1.20–1.39)	1.37 (1.28–1.48)	<0.001
Model 2	1 [reference]	0.99 (0.92–1.07)	1.17 (1.08–1.26)	1.23 (1.14–1.32)	<0.001
Model 3	1 [reference]	0.99 (0.91–1.07)	1.08 (1.00–1.17)	1.10 (1.02–1.19)	0.004

Data are presented as number (percentage) or hazard ratio (95% CI) unless otherwise specified.

Models are as follows: model 1 is adjusted for age, sex, race/ethnicity, and marital status; model 2 is adjusted for the variables in model 1 plus comorbidities (diabetes mellitus, cardiovascular disease, congestive heart failure, peripheral vascular disease, lung disease, peptic ulcer disease, liver disease, malignancy, and HIV/AIDS), Charlson comorbidity index, and cumulative length of hospitalization; and model 3 is adjusted for the variables in model 2 plus medications (ESAs, intravenous or oral iron, vitamin D analogs, ACEIs/ARBs, antiplatelets, and warfarin), eGFR levels averaged over the six-month prelude period, type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter), Hb variability parameters (baseline Hb level and change in Hb), and number of Hb measurements during the six-month prelude period.

[a]Linear trend across the quartiles using the median Hb variability value of each quartile.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immunodeficiency syndrome; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; ESA, erythropoietin stimulating agent; Hb, hemoglobin; HIV, human immunodeficiency virus

Table 4

Adjusted hazard ratios (95% CI) for (A) cardiovascular and (B) infection-related mortality after dialysis initiation by Hb variability quartiles over the six-month prelude period

	Quartile of prelude Hb variability				
	Q1 (lowest) <0.46	**Q2 0.46–<0.69**	**Q3 0.69–<0.96**	**Q4 (lowest) ≥0.96**	***P* for trend[a]**
Participants (*n*)	3,039	2,942	2,971	2,920	
(A) Cardiovascular					
Events	333 (11.0)	322 (10.9)	389 (13.1)	361 (12.4)	
Model 1	1 [reference]	1.03 (0.88–1.20)	1.28 (1.11–1.49)	1.20 (1.04–1.40)	0.003
Model 2	1 [reference]	0.96 (0.82–1.12)	1.15 (0.99–1.33)	1.07 (0.92–1.24)	0.15
Model 3	1 [reference]	0.92 (0.79–1.10)	1.03 (0.88–1.21)	0.93 (0.79–1.10)	0.63
(B) Infection-related					
Events	77 (2.5)	81 (2.8)	105 (3.5)	119 (4.1)	
Model 1	1 [reference]	1.11 (0.81–1.51)	1.46 (1.09–1.96)	1.71 (1.28–2.28)	<0.001
Model 2	1 [reference]	1.07 (0.78–1.46)	1.36 (1.00–1.82)	1.53 (1.15–2.05)	0.001
Model 3	1 [reference]	1.02 (0.74–1.41)	1.19 (0.87–1.63)	1.28 (0.93–1.75)	0.079

Data are presented as number (percentage) or hazard ratio (95% CI) unless otherwise specified.

Models are as follows: model 1 is adjusted for age, sex, race/ethnicity, and marital status; model 2 is adjusted for the variables in model 1 plus comorbidities (diabetes mellitus, cardiovascular disease, congestive heart failure, peripheral vascular disease, lung disease, peptic ulcer disease, liver disease, malignancy, and HIV/AIDS), Charlson comorbidity index, and cumulative length of hospitalization; and model 3 is adjusted for the variables in model 2 plus medications (ESAs, intravenous or oral iron, vitamin D analogs, ACEIs/ARBs, antiplatelets, and warfarin), eGFR levels averaged over the six-month prelude period, type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter), Hb variability parameters (baseline Hb level and change in Hb), and number of Hb measurements during the six-month prelude period.

[a]Linear trend across the quartiles using the median Hb variability value of each quartile.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIDS, acquired immunodeficiency syndrome; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; ESA, erythropoietin stimulating agent; Hb, hemoglobin; HIV, human immunodeficiency virus