Kidney360

Anemia and Incident End-Stage Kidney Disease

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Abstract

Background CKD progression can be a cause and potentially a consequence of anemia. Previous studies suggesting that anemia is associated with CKD progression have not used methodologic approaches to address time-dependent confounding.

Methods We evaluated the association of anemia (defined using World Health Organization criteria of hemoglobin <12 g/dl in women and <13 g/dl in men) with incident ESKD and all-cause death in individuals with CKD using data from the Chronic Renal Insufficiency Cohort Study. Marginal structural models were used to account for time-dependent confounding.

Results Among 3919 participants, 1859 (47%) had anemia at baseline. Over median follow-up of 7.8 years, we observed 1010 ESKD events and 994 deaths. In multivariable analyses, individuals with anemia had higher risk for ESKD compared with those without (HR, 1.62; 95% CI, 1.24 to 2.11). In stratified analyses, the increased risk for incident ESKD with anemia was observed in males (HR, 2.15; 95% CI, 1.53 to 3.02) but not females (HR, 1.20; 95% CI, 0.82 to 1.78). The association between anemia and ESKD was significant among all racial/ethnic groups except non-Hispanic blacks (non-Hispanic white, HR, 2.16; 95% CI, 1.53 to 3.06; Hispanic, HR, 1.92; 95% CI, 1.04 to 3.51; others, HR, 2.94; 95% CI, 1.16 to 7.44; non-Hispanic black, HR, 1.39; 95% CI, 0.95 to 2.02). There was no association between anemia and all-cause death.

Conclusions In this cohort, anemia was independently associated with increased risk for incident ESKD. Future work is needed to evaluate the mechanisms by which anemia leads to CKD progression as well as the effect of novel therapeutic agents to treat anemia.

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Introduction

Anemia is common in CKD and its prevalence increases with the severity of CKD (1). A recent analysis of data from the African American Study of Kidney Disease and Hypertension found that the association between eGFR decline and decline in hematocrit was stronger in individuals with more advanced CKD (2). Anemia in CKD is due to multifactorial processes including relative erythropoietin deficiency, uremic-induced inhibition of erythropoiesis, reduced red blood cell survival, inflammation, and disordered iron homeostasis (3).

In addition to anemia being a consequence of CKD, there is accumulating evidence suggesting that anemia may be a risk factor for CKD progression. Supporting this, anemia has been reported to be associated with progression of CKD in select populations that have included individuals with diabetes (4), cardiovascular disease (5,6), veterans (7), and members of a large managed care organization (8). However, these studies did not use analytic approaches to address potential time-dependent confounding. Time-dependent confounding occurs when there is a circular relationship between a time-varying exposure (*e.g.*, anemia) and a time-varying confounder (*e.g.*, eGFR), with the confounder affecting the exposure and the exposure affecting subsequent values of the confounder (9). In a large and diverse sample of individuals enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study, we evaluated the association between anemia and incident ESKD using marginal structural models (MSMs) to account for time-dependent confounding.

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Materials and Methods

Study Population

We conducted a longitudinal analysis of participants from the CRIC Study, which is a prospective multicenter observational cohort study of adults with mild-to-moderate CKD. Details of the design and methods of the CRIC Study have been published previously (10,11). The major inclusion criteria included adults between the ages of 21–74 years old with mild-to-moderate CKD based on age-adjusted eGFR. Between June 2003 through December 2008, 3939 men and women were enrolled. Current analyses were restricted to 3919 participants with complete data for the exposures of interest. Exclusion criteria included New York Heart Association class III or IV heart failure, cirrhosis, HIV/AIDS, multiple myeloma, renal carcinoma, polycystic kidney disease, being a recipient of organ transplant, previous dialysis, history of immunotherapy for renal disease or vasculitis, and history of chemotherapy. The study was approved by the institutional review boards of the participating centers and the research was conducted in accordance with the principles of the Declaration of Helsinki. All study participants provided written informed consent.

Measurements and Variable Definition

The primary predictor was time-varying anemia, defined using the World Health Organization criteria as hemoglobin <12 g/dl in women and <13 g/dl in men (12). Hemoglobin concentration by decile was also used as a predictor. Demographic characteristics were ascertained at baseline; clinical and laboratory data were obtained at baseline and updated annually. At a baseline in-person visit, information was collected on sociodemographic variables (age, sex, race/ethnicity [non-Hispanic white, non-Hispanic black, Hispanic, or other], education, marital status, annual household income, and health insurance), medical history (hypertension, diabetes, cardiovascular disease [previous myocardial infarction, coronary revascularization, heart failure, stroke, or peripheral arterial disease]), smoking habits, and medication use. Body mass index (BMI; kg/m^2) was calculated using measured height and weight. BP measurements were obtained using the standardized American Heart Association protocol (13). Serum creatinine was measured by an enzymatic method from Ortho Clinical Diagnostics through October 2008 and by the Jaffe method from Beckman Coulter thereafter and standardized to isotope dilution mass spectrometry–traceable values (14,15). Serum cystatin C was measured using a particle-enhanced immunonephelometric assay on the BN II System (Siemens). GFR was estimated at baseline and each annual visit using a serum creatinine and cystatin C–based equation developed in a subgroup of CRIC participants with measured iothalamate GFR (16). Urinary total protein and creatinine were measured using standard assays. Protein-creatinine ratios from 24-hour and spot urine specimens were highly correlated and therefore used interchangeably. Diabetes mellitus was defined by a fasting glucose ≥126 mg/dl or use of insulin or oral hypoglycemic medications; hypertension was defined by a systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or use of antihypertensive medications.

Outcomes

The primary outcomes were incident ESKD (defined as receipt of chronic dialysis therapy or kidney transplantation) and all-cause death. Ascertainment of ESKD was done through semiannual surveillance by study personnel, supplemented by crosslinkage with the US Renal Data System, leading to no missing data for this outcome. Participant follow-up was ended at the time of death (n=622), ESKD (n=1010; only for incident ESKD analyses), withdrawal (n=213), or end of the follow-up period, whichever occurred first. Deaths were ascertained from next of kin, death certificates, obituaries, review of hospital records, and the Social Security Death Master File. Outcomes were ascertained from study entry through May 2014.

Statistical Analyses

Descriptive statistics were summarized as mean±SD for continuous variables and frequency and proportion for categoric variables. Event rates (per 100 person-years) were calculated as the ratio of the number of participants reaching the event divided by the total person-years of follow-up before an event or until censoring. Variables were compared by anemia status using the Kruskall–Wallis test or chi-squared test for continuous and categoric variables, respectively.

To assess the association between time-updated anemia and incident ESKD, we used MSMs, which apply inverse probability weighting in a discrete time failure model (9,17). In brief, MSM is a two-step approach wherein models were first fit to predict anemia status during follow-up, followed by inverse probability–weighted structural models that were fit for the outcomes. In both models, the data structure was organized so each person could contribute several records, each 1 year in length, depending on the number of annual study visits. In the first step (that is, calculating the exposure weights), the anemia status at each study visit was divided into two categories: present or absent. A logistic regression model was fit to the dichotomous anemia measure with adjustment for concurrent age; sex; race/ethnicity; education level; history of cardiovascular disease; systolic BP, hemoglobin A1c (HbA1C), and BMI; and phosphate, C-reactive protein, urine protein concentration, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy, β-blocker, erythropoiesis-stimulating agents (ESAs), and serum albumin concentration. Quadratic spline terms for urine protein-creatinine ratios and eGFR were incorporated to account for nonlinear relationships. We calculated the weights that were used in the second step based on the predicted probability of anemia during all study visits that were the same as what were seen. Patients with missing anemia status who returned for a later study visit during the analysis time period were considered to have stable anemia status from the visit at the beginning of the interval until anemia was next measured. In the second step, we fit a discrete time failure model for the outcome (*i.e.*, incident ESKD) by applying the final weight derived in the first step to the study visit-level data. We also refit the model by using hemoglobin deciles as the predictor.

We adjusted for the following covariates: clinical center, age, sex, race/ethnicity, educational status, income status, cardiovascular disease, systolic BP, BMI, HbA1c, phosphate,

C-reactive protein, urine protein concentration, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy, β-blocker, ESA, and serum albumin concentration. Time-updated variables included hemoglobin concentration, systolic BP, BMI, eGFR, and proteinuria. Hazard ratio (HR) estimates using MSMs and anemia status category should be interpreted as the risk for incident ESKD for someone who had anemia at all visits compared with someone who had no anemia at all visits where the logistic regression model in the first step is replaced by a multinomial logistic regression model.

We evaluated sex and race/ethnicity as potential effect modifiers in the association between anemia and the outcomes by adding an interaction term to the fully adjusted model. These effect modifiers were chosen based upon prior literature demonstrating that anemia may have different effects on morbidity or mortality by sex (18) or by race/ethnicity (19). Stratified analyses were conducted when there was evidence of interaction. We conducted the following sensitivity analyses: (*1*) Cox proportional hazards analysis using baseline measurement of anemia and covariates, (*2*) Cox proportional hazards analysis using time-varying anemia and baseline covariates, and (*3*) MSM analyses excluding individuals taking ESAs ($n=153$). All tests were two sided, and $P<0.05$ was considered statistically significant for hypothesis testing and <0.1 for interactions. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

For the 3919 patients included in these analyses, the mean age was 58.2±11.0 years and 45% were women, 42% were non-Hispanic white, 42% were non-Hispanic black, and 13% were Hispanic. The mean eGFR was 44.9±16.9 ml/min per 1.73 m^2 and the median 24-hour urine protein was 0.19 (interquartile range, 0.07–0.92) g/24 h. The mean hemoglobin concentration was 12.6±1.8 g/dl and the distribution of hemoglobin concentration is provided in Figure 1. For multivariable regression analysis, 378 participants were excluded due to missing covariate data (including 24-hour urine protein [$n=195$], HbA1c [$n=63$], phosphate level [$n=58$], serum albumin [$n=55$], or other [$n=7$]).

Anemia was present in 1859 (47%) participants at the time of study entry. Compared with those without anemia at baseline, those with anemia were older; more likely to be nonwhite; had lower socioeconomic status; higher prevalence of hypertension, diabetes, and cardiovascular disease; and lower mean eGFR and higher proteinuria (Table 1). There were 1058 individuals who had no anemia at all visits and 925 who had anemia at all visits. The proportions of males and females and of ESA use by hemoglobin decile are provided in Supplemental Table 1.

Outcomes

Incident ESKD. During a median follow-up of 7.8 years, 1010 participants developed ESKD. A higher rate of incident ESKD was observed in participants with anemia compared with those without anemia (6.15; 95% CI, 5.70 to 6.63, versus 2.15; 95% CI, 1.94 to 2.40, per 100 person-years). In the fully adjusted model, anemia was a significant predictor of incident ESKD (HR, 1.62; 95% CI, 1.24 to 2.11). The strength of this association was of greater magnitude than that observed in sensitivity analyses using Cox proportional regression (Table 2). In addition, the association between anemia and risk of incident ESKD remained significant in a sensitivity analysis (using MSM) excluding participants treated with an ESA (fully adjusted model HR, 1.66; 95% CI, 1.26 to 2.18).

An interaction between anemia and sex for incident ESKD was observed ($P=0.07$). In fully adjusted stratified analyses, the association between anemia and risk for incident ESKD

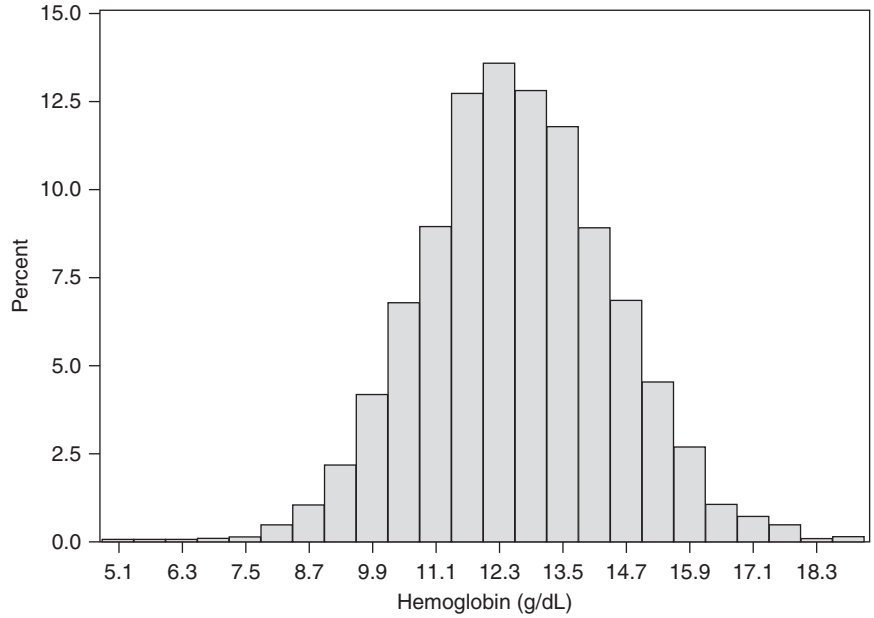

Figure 1. | **Baseline hemoglobin concentration was normally distributed.**

Table 1. Baseline characteristics of Chronic Renal Insufficiency Cohort Study participants by anemia status

Characteristic	No Anemia (n=2060)	Anemia (n=1859)
Age, yr	57.6 (11.1)[a]	58.8 (10.9)
Women	901 (44%)	869 (47%)
Race/ethnicity		
Non-Hispanic white	1067 (52%)[a]	564 (30%)
Non-Hispanic black	713 (35%)	925 (50%)
Hispanic	183 (9%)	313 (17%)
Other	97 (5%)	57 (3%)
Income ≤$20,000	500 (24%)[a]	729 (39%)
Education less than high school	285 (14%)[a]	536 (29%)
Health insurance	1736 (93%)	1491 (91%)
Nephrology care	1289 (63%)[a]	1296 (70%)
Hypertension	1675 (81%)[a]	1698 (91%)
Diabetes	700 (34%)[a]	1198 (64%)
Cardiovascular disease	591 (29%)[a]	717 (39%)
Current smoker	284 (14%)[b]	229 (12%)
Medications		
ACE inhibitor or ARB	1304 (64%)[a]	1372 (74%)
β-Blocker	936 (46%)[a]	984 (53%)
Aspirin or antiplatelet	866 (42%)[a]	928 (50%)
Statin	1013 (50%)[a]	1128 (61%)
Erythropoiesis-stimulating agent	38 (2%)[a]	115 (6%)
Iron	87 (4%)[a]	257 (14%)
Systolic BP, mm Hg	124.7 (20.9)[a]	132.7 (22.8)
Body mass index (kg/m^2)	31.7 (7.1)[a]	32.54 (8.49)
Transferrin saturation, %	25[a]	22
Ferritin, ng/ml, median (IQR)	156.8 (86.0–276.5)[a]	159.4 (80.6–299.3)
Serum albumin	4.1 (0.4)[a]	3.8 (0.5)
Hemoglobin A1c	6.4 (1.4)[a]	7.0 (1.7)
LDL cholesterol, mg/dl	106.8 (35.0)[a]	98.3 (35.8)
Calcium, mg/dl	9.3 (0.5)[a]	9.1 (0.5)
Phosphate, mg/dl	3.6 (0.6)[a]	3.9 (0.7)
Total parathyroid hormone, pg/ml	46.3 (32.0–73.0)[a]	65.6 (39.8–114.0)
C-reactive protein, mg/L	2.4 (1.1–5.7)[a]	2.8 (1.1–7.4)
eGFR, ml/min per 1.73 m^2	50.3 (17.4)[a]	38.9 (14.0)
Urine protein, g/24 h, median (IQR)	0.13 (0.07–0.61)[a]	0.3 (0.08–1.40)
Hemoglobin, g/dl	13.9 (1.2)[a]	11.2 (1.1)
Mean cell volume, fl	89.1 (5.0)[a]	87.3 (6.6)

Mean (SD or %) or median (interquartile ranges) are provided for normally and non-normally distributed variables, respectively. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; IQR, interquartile range.
[a]P<0.01.
[b]P<0.05.

was significant in men (HR, 2.15; 95% CI, 1.53 to 3.02) but was not significant in women (HR, 1.20; 95% CI, 0.82 to 1.78). In addition, we found evidence of interaction between anemia and race/ethnicity (P=0.098). The association between anemia and incident ESKD was significant in all groups except non-Hispanic blacks (non-Hispanic white, HR, 2.16; 95% CI, 1.53 to 3.06; Hispanic, HR, 1.92; 95% CI, 1.04 to 3.51; others, HR, 2.94; 95% CI, 1.16 to 7.44; non-Hispanic black, HR, 1.39; 95% CI, 0.95 to 2.02).

For hemoglobin concentrations below the eighth decile (<13.6 g/dl), there was a graded and inverse association between decile of hemoglobin and rates of incident ESKD, where the lowest decile of hemoglobin had the highest rates (Figure 2). In multivariable models using the tenth decile as the referent categoric, a hemoglobin of <13.1 g/dl was associated with a higher risk of incident ESKD (Figure 3).

All-Cause Mortality. During follow-up, there were 994 deaths. A higher rate of all-cause death was observed in participants with anemia compared with those without anemia (4.3; 95% CI, 4.0 to 4.7, versus 2.4; 95% CI, 2.2 to 2.7, per 100 person-years). In the fully adjusted model, anemia was not associated with an increased risk for death (HR, 0.95; 95% CI, 0.78 to 1.16) (Table 2). Sensitivity analyses were consistent with this finding.

For hemoglobin concentrations below the eighth decile (<13.6 g/dl), there was a graded and inverse association between decile of hemoglobin and rates of death, where the lowest decile of hemoglobin had the highest rates Figure 2. On multivariable analyses, there was no consistent association between decile of hemoglobin concentration and risk for death (Figure 4).

Discussion

Using MSMs to take into account time-dependent confounding, we found a strong association between anemia and incident ESKD in a large, racially diverse, prospective cohort of persons with mild-to-moderate CKD. In particular, we observed a >60% increased risk of incident ESKD among those with anemia compared with those without anemia. Furthermore, we found that sex and race/ethnicity were important effect modifiers of this association.

Table 2. Hazard ratio (95% CI) for the association of anemia (versus no anemia) with incident ESKD and death

Outcome	MSM with Time-Varying Anemia and Time-Varying Covariates[a]	Cause-Specific Hazards Model with Baseline Anemia and Baseline Covariates[a]	Cause-Specific Hazards Model with Time-Varying Anemia and Baseline Covariates[a]
ESKD	1.62 (1.24 to 2.11)	1.26 (1.08 to 1.47)	1.31 (1.12 to 1.54)
Death	0.95 (0.78 to 1.16)	0.97 (0.83 to 1.13)	1.01 (0.87 to 1.17)

Time-updated variables included anemia status, BP, body mass index, eGFR, and proteinuria. Hazard ratio for MSM estimates reflect the risk for outcome of incident ESKD for the scenario in which anemia status was unchanged at all study visits. MSM, marginal structural model; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
[a]Covariates: clinical site, age, sex, race/ethnicity, education, income, cardiovascular disease, systolic BP, body mass index, hemoglobin A1c, phosphate level, c-reactive protein, eGFR, 24-h urine protein, ACEi/ARB therapy, β-blocker therapy, erythropoiesis-stimulating agents, serum albumin.

Although previous studies have reported an association between anemia and CKD progression, these studies have not used methods which account for time-dependent confounding. Furthermore, most of these studies have examined only baseline anemia status (4–6,20,21). For example, in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study, the lowest quartile of baseline hemoglobin concentration was associated with 1.87-fold increased risk of ESKD as compared with the highest quartile (4). Similarly, a *post hoc* analysis of a trial evaluating the effect of enalapril in patients with heart failure, baseline anemia was associated with a more rapid eGFR decline (5). In contrast, we are aware of at least two studies, one in veterans and the other in members of a large health care organization, that used time-updated anemia status (7,8). Both of these studies reported a significant association between anemia and incident ESKD. However, these studies used Cox models and did not evaluate time-varying covariates. Using MSMs, we found that the strength of the association between anemia and incident ESKD was more robust with this approach than the traditional cause-specific hazards models. Because MSMs address time-varying confounding, our findings provide new evidence of a potential causal effect of anemia on CKD progression.

The mechanisms underlying the association of anemia with CKD progression are not clear. However, it has been hypothesized that anemia may result in tissue hypoxia and subsequently lead to cytokine release (22,23), resulting kidney scarring, as well as increased sympathetic activity (24). Interestingly, we found that even a mild decrement of hemoglobin concentration (hemoglobin concentration <13.1 g/dl) was associated with increased risk. Other studies have also found that mild decrements in hemoglobin were associated with increased risk (4).

We found that anemia was a significant predictor of incident ESKD in non-Hispanic whites but not in non-Hispanic blacks. A study in Medicare recipients and another in veterans did not see racial differences in the association of between anemia and incident ESKD (6,7). Our contrasting findings may have been related to differences in the characteristics of the samples and analytic approaches. The clinical implications of this finding are not clear and reasons for race-associated differences in the association of anemia with incident ESKD need to be explored further. We also observed sex-associated differences, in particular, anemia was associated with incident ESKD outcome in men but not

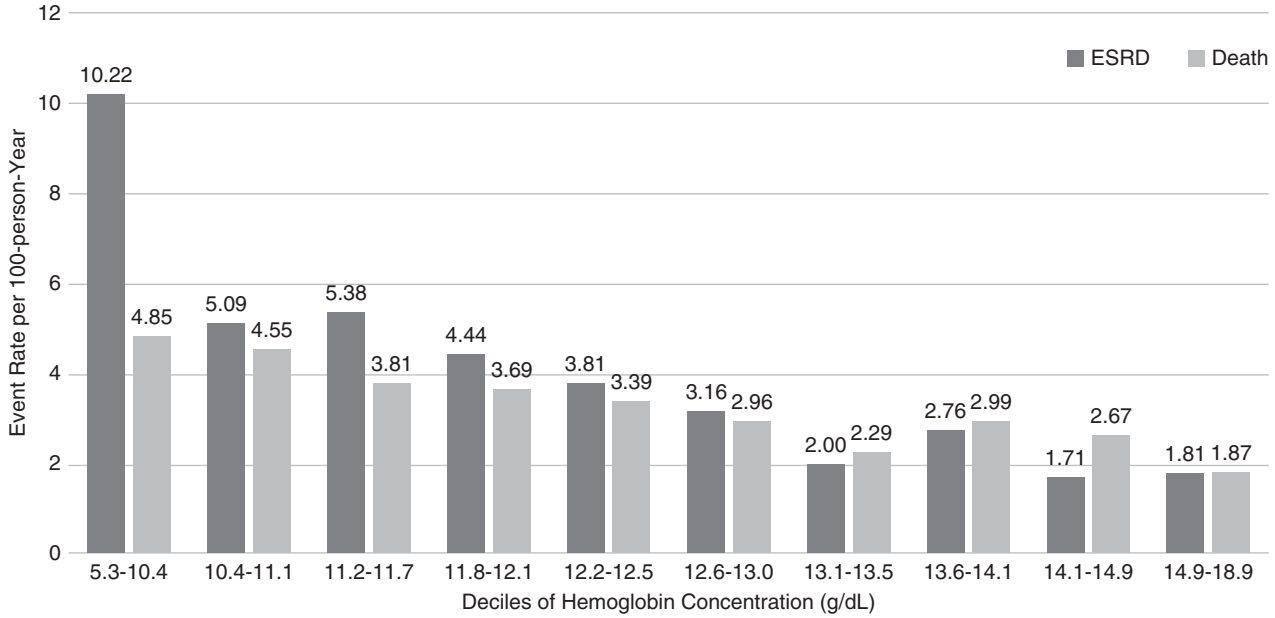

Figure 2. | Higher rates of incident ESKD and all-cause death were seen for lower deciles of hemoglobin concentration.

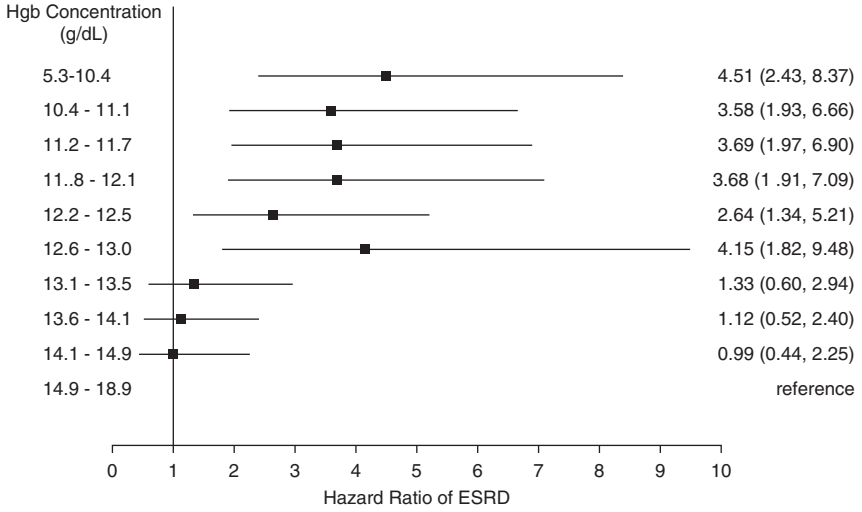

Figure 3. | In multivariable models using the tenth decile as referent, a hemoglobin (Hgb) of <13.1 g/dl was associated with a higher risk of incident ESKD.

women. We are not aware of other studies that have found this sex-related difference. However, there is increasing evidence that there are important differences in risk of CKD progression between men and women, as well as differences in risk factor profiles (25).

Our finding regarding the strong association between anemia and CKD progression raises the question of whether treatment of anemia might ameliorate the risk for CKD progression. However, prior studies have not shown that correction of anemia with ESA is associated with improved kidney outcomes. In a meta-analysis including 27 clinical trials, there was no significant association between ESA treatment and ESKD (26). Furthermore, our findings did not change in a sensitivity analysis excluding individuals treated with ESAs. Future studies are needed to evaluate the effect of newer agents to treat anemia.

Although we found that anemia was associated with higher rates of death, we did not find a significant association in the fully adjusted multivariable model. This in contrast to other studies that reported a significant association. Reasons for this difference are not clear but may be related to differences in the populations. For example, one study included only male veterans (7), whereas another study focused on a non-CKD population (8).

Strengths of our study include the large diverse population of individuals with CKD, the prospective design of the study, and use of time-updated variables and MSMs. However, our findings should be interpreted in the context of observational studies that may be subject to residual confounding bias. The low hemoglobin may have been due to smaller renal mass and adjusting for eGFR alone may not have completely captured residual renal capacity, leading to

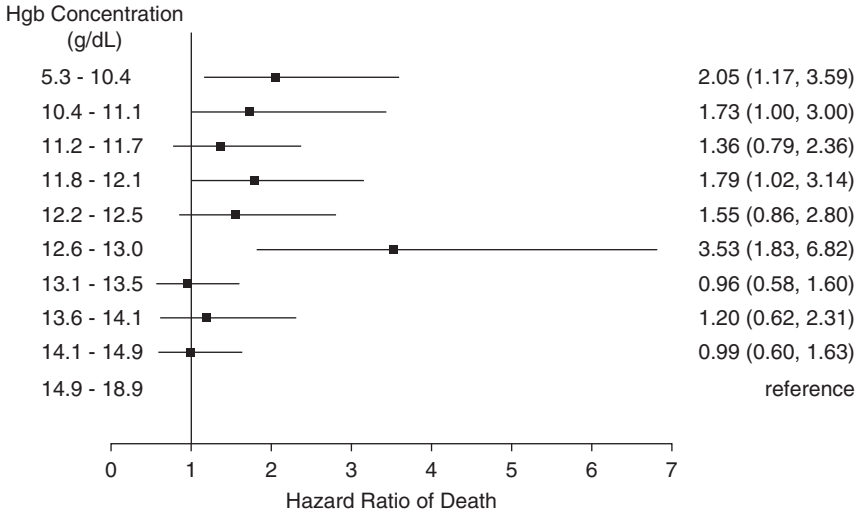

Figure 4. | No consistent association between decile of hemoglobin (Hgb) concentration and risk for death was seen on multivariable analyses.

residual confounding. In addition, we lacked information regarding nutritional causes of anemia (*i.e.*, folate and vitamin B12), other treatments of anemia (*e.g.*, blood transfusions), and urinary biomarkers of hypoxia that may help highlight mechanisms for how anemia leads to more rapid kidney disease progression. Use of ESAs was too low in this cohort to analyze their effects on anemia and outcome, and the effect of strategies to improve anemia on kidney disease progression and mortality will need to be investigated in future studies.

In summary, using MSMs to account for time-varying confounding, we found that anemia was associated with an increased risk for incident ESKD. Our findings reinforce the clinical importance of anemia and the need for future studies to identify alternative therapies to treat anemia in CKD.

Author Contributions

J. Hsu was responsible for data curation and validation; J. Hsu, J. Lash, A. Ricardo, S. Saraf, and X. Zhang were responsible for investigation; J. Hsu and X. Zhang were responsible for formal analysis; and all authors conceptualized the study, were responsible for methodology, wrote the original draft, and reviewed and edited the manuscript.

Disclosures

R. Mehta reports other from Abbot Laboratories, other from AbbVie Inc., personal fees from Akebia/Oksuba, and other from Teva Pharmaceuticals Industries, outside the submitted work. S. Saraf reports personal fees from Global Blood Therapeutics and personal fees from Novartis outside the submitted work. M. Weir reports personal fees and other from Astra Zeneca, personal fees and other from Boehringer Ingelheim, personal fees and other from Janssen, personal fees and other from Merck, and personal fees and other from Vifor/Relypsa, outside the submitted work. M. Wolf reports personal fees and other from Akebia, personal fees from Ardelyx, personal fees from Astrazeneca, and personal fees from Pharmacosmos, outside the submitted work. All remaining authors have nothing to disclose.

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Supplemental Material

This article contains supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000852020/-/DCSupplemental.

Supplemental Table 1. Hemoglobin by deciles.

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