Anemia and Incident End-Stage Renal Disease

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ABSTRACT

Background: Chronic kidney disease (CKD) progression can be a cause and potentially a consequence of anemia. Previous studies suggesting that anemia is associated with CKD progression have not utilized 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 ESRD 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 (47.4%) had anemia at baseline. Over median follow up of 7.8 years, we observed 1,010 ESRD events and 994 deaths. In multivariable analyses, individuals with anemia had higher risk for ESRD compared to those without (HR 1.62, 95% CI 1.24-2.11). In stratified analyses, the increased risk for incident ESRD with anemia was observed in males (HR 2.15, 95% CI: 1.53-3.02) but not females (HR 1.20, 95% CI 0.82-1.78. The association between anemia and ESRD was significant among all racial/ethnic groups except non-Hispanic blacks (non-Hispanic white, HR 2.16, 95% CI 1.53-3.06; Hispanic, HR 1.92, 1.04-3.51; others, HR 2.94; 95% CI 1.16-7.44; non-Hispanic black, HR 1.39; 95% CI 0.95-2.02).

There was no association between anemia and all-cause death.

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

Anemia is common in chronic kidney disease (CKD) and its prevalence increases with the severity of CKD.\(^1\) A recent analysis of data from the African American Study of Hypertension and Kidney Disease (AASK) found that the association between estimated glomerular filtration rate (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 which 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 end stage renal disease (ESRD) using marginal structure models (MSM) to account for time-dependent confounding.
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. 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, 3,939 men and women were enrolled. Current analyses were restricted to 3,919 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, 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 (Hgb) < 12 g/dL in women and < 13 g/dL in men. 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/m²) was calculated using measured height and weight. Blood pressure measurements were obtained using the standardized American Heart Association protocol. 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. Serum cystatin C was measured using a particle-enhanced immunonephelometric assay on the BN II System (Siemens). Glomerular filtration rate 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 (mGFR). Urinary total protein and creatinine were measured using standard assays. Protein-creatinine ratios (PCR) 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; and hypertension was defined by a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications.

Outcomes

The primary outcomes were incident ESRD (defined as receipt of chronic dialysis therapy or kidney transplantation) and all-cause death. Ascertainment of ESRD was done through semiannual surveillance by study personnel, supplemented by cross-linkage with the U.S. Renal Data System, leading to no missing data for this outcome. Participant follow-up was ended at the time of death (n = 622), ESRD (n = 1010; only for incident ESRD 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 Analysis

Descriptive statistics were summarized as mean ± standard deviation for continuous variables
and frequency and proportion for categorical 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-square test for continuous and categorical
variables, respectively.

To assess the association between time-updated anemia and incident ESRD, we used marginal
structural models (MSM), which apply inverse probability weighting in a discrete time failure
model.9,17 In brief, MSM is a 2-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 2 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 blood pressure, HbA1c, BMI; phosphate, C-
reactive protein, urine protein concentration, angiotensin-converting enzyme (ACE)-
inhibitor/angiotensin receptor blocker (ARB) therapy, beta-blocker, erythropoietin stimulating agents,
and serum albumin concentration. Quadratic spline terms for urine PCR 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 ESRD) 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 blood pressure, BMI, HgbA1c, phosphate, C-reactive protein, urine protein concentration, ACE-inhibitor/ARB therapy, beta-blocker, erythroid stimulating agents, and serum albumin concentration. Time-updated variables included hemoglobin concentration, systolic blood pressure, BMI, eGFR, and proteinuria. Hazard ratio estimates using MSM and anemia status category should be interpreted as the risk for incident ESRD 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\textsuperscript{18} or by race/ethnicity.\textsuperscript{19} Stratified analyses were conducted when there was evidence of interaction. We conducted the following sensitivity analyses: a) Cox proportional hazards analysis using baseline measurement of anemia and covariates; b) Cox proportional hazards analysis using time-varying anemia and baseline covariates, and c) MSM analyses excluding individuals taking erythropoiesis-stimulating agents (ESA, n=153). All tests were 2-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 3,919 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/1.73m² and the median 24-hour urine protein was 0.19 (0.07-0.92) g/24 hours. 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 1,859 (47.4%) participants at the time of study entry. Compared to those without anemia at baseline, those with anemia were older, more likely to be non-white, had lower socioeconomic status, higher prevalence of hypertension, diabetes, and cardiovascular disease, and lower mean eGFR and higher proteinuria (Table 1). There were 1,058 individuals who had no anemia at all visits and 925 who had anemia at all visits. The proportions of males and females and of erythroid stimulating agent use by hemoglobin decile are provided in Supplementary Table 1.

Outcomes

Incident ESRD

During a median follow up of 7.8 years, 1010 participants developed ESRD. A higher rate of incident ESRD was observed in participants with anemia compared to those without anemia (6.15; 95% CI 5.70-6.63 vs 2.15; 95% CI 1.94-2.40 per 100 person-years). In the fully adjusted model, anemia was a significant predictor of incident ESRD (HR 1.62; 95% CI, 1.24-2.11). 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 ESRD remained significant in a sensitivity analysis (using MSM) excluding participants treated with an ESA (fully adjusted model HR 1.66; 95% CI, 1.26-2.18).

An interaction between anemia and sex for incident ESRD was observed (P =0.07). In fully adjusted stratified analyses, the association between anemia and risk for incident ESRD was significant in men (HR 2.15; 95% CI, 1.53-3.02) but was not significant in women (HR 1.20; 95% CI, 0.82-1.78). In addition, we found evidence of interaction between anemia and race/ethnicity (p=0.098). The association between anemia and incident ESRD was significant in all groups except non-Hispanic blacks (non-Hispanic white, HR 2.16, 95% CI 1.53-3.06; Hispanic, HR 1.92, 1.04-3.51; others, HR 2.94; 95% CI 1.16-7.44; non-Hispanic black, HR 1.39; 95% CI 0.95-2.02).

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 ESRD, where the lowest decile of Hb had the highest rates (Figure 2). In multivariable models using the tenth decile as the referent categorical, a hemoglobin of less than 13.1 g/dL was associated with a higher risk of incident ESRD (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 to those without anemia (4.3, 95% CI 4.0-4.7 vs. 2.4. 95% CI 2.2-2.7 4.3 vs. 2.45 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 - 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 Hb and rates of death, where the lowest decile of Hb 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 marginal structural models to take into account time-dependent confounding, we found a strong association between anemia and incident ESRD in a large, racially diverse, prospective cohort of persons with mild-to-moderate CKD. In particular, we observed a greater than 60% increased risk of incident ESRD among those with anemia compared to those without anemia. Furthermore, we found that sex and race/ethnicity were important effect modifiers of this association.

Although previous studies have reported an association between anemia and CKD progression, these studies have not utilized methods which account for time-dependent confounding. Furthermore, most of these studies have examined only baseline anemia status.\textsuperscript{4,6,20,21} For example, in the Reduction in 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 ESRD as compared to the highest quartile.\textsuperscript{4} Similarly, a post-hoc analysis of a trial evaluating the impact of enalapril in patients with heart failure, baseline anemia was associated with a more rapid eGFR decline.\textsuperscript{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, which utilized time-updated anemia status.\textsuperscript{7,8} Both of these studies reported a significant association between anemia and incident ESRD. However, these studies used Cox models and did not evaluate time-varying covariates. Using marginal structural models, we found that the strength of the association between anemia and incident ESRD was more robust with this approach than the traditional cause-specific hazards models. Since marginal structure models address time-varying
confounding, our findings provides 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\textsuperscript{22,23} resulting kidney scarring, as well as increased sympathetic activity.\textsuperscript{24} Interestingly, we found that even a mild decrement of hemoglobin concentration (hemoglobin concentration less than 13.1 gm/dL) was associated with increased risk. Other studies have also found that mild decrements in hemoglobin were associated with increased risk.\textsuperscript{4}

We found that anemia was a significant predictor of incident ESRD 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 ESRD.\textsuperscript{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 ESRD need to be explored further. We also observed sex associated differences, in particular, anemia was associated with incident ESRD outcome in men but not women. We are not aware of other studies which 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.\textsuperscript{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 ESRD. Furthermore, our findings did not change in a sensitivity analysis excluding individuals treated with ESA. 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, in the fully adjusted multivariable model, we did not find a significant association. This in contrast to other studies which 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, whereas another study focused on a non-CKD population.

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 marginal structural models. However, our findings should be interpreted in the context of observational studies which 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 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 which 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 impact of strategies to improve anemia on kidney disease progression and mortality will need to be investigated in future studies.

In summary, using marginal structural models to account for time-varying confounding, we found that anemia was associated with an increased risk for incident ESRD. 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:**

S Saraf: Conceptualization; Investigation; Methodology; Writing - original draft; Writing - review and editing

J Hsu: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Writing - original draft; Writing - review and editing

A Ricardo: Conceptualization; Investigation; Methodology; Writing - original draft; Writing - review and editing

R Mehta: Conceptualization; Methodology; Writing - original draft; Writing - review and editing

J Chen: Conceptualization; Methodology; Writing - original draft; Writing - review and editing

T Chen: Conceptualization; Methodology; Writing - original draft; Writing - review and editing

M Fischer: Conceptualization; Methodology; Writing - original draft; Writing - review and editing

L Hamm: Conceptualization; Methodology; Writing - original draft; Writing - review and editing

J Sondheimer: Conceptualization; Methodology; Writing - original draft; Writing - review and editing

M Weir: Conceptualization; Methodology; Writing - original draft; Writing - review and editing
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Disclosures:
S. Saraf reports personal fees from Novartis and personal fees from Global Blood Therapeutics outside the submitted work. R. Mehta reports other from Abbot Laboratories, other from AbbVie, Inc, other from Teva Pharmaceuticals Industries, and personal fees from Akebia/Oksuba outside the submitted work. M. Weir reports personal fees and other from AstraZeneca, 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 Astrazeneca, personal fees from Pharmacosmos, and personal fees from Ardelyx outside the submitted work. All remaining authors have nothing to disclose.

REFERENCES
Table 1. Baseline characteristics of CRIC participants by anemia status

<table>
<thead>
<tr>
<th></th>
<th>No Anemia (n = 2060)</th>
<th>Anemia (n = 1859)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.6 (11.1)†</td>
<td>58.8 (10.9)</td>
</tr>
<tr>
<td>Women</td>
<td>901 (43.7%)</td>
<td>869 (46.7%)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>1067 (51.8%)†</td>
<td>564 (30.3%)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>713 (34.6%)</td>
<td>925 (49.8%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>183 (8.9%)</td>
<td>313 (16.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>97 (4.7%)</td>
<td>57 (3.1%)</td>
</tr>
<tr>
<td>Income ≤ $20,000</td>
<td>500 (24.3%)†</td>
<td>729 (39.2%)</td>
</tr>
<tr>
<td>Education less than high school</td>
<td>285 (13.8%)†</td>
<td>536 (28.8%)</td>
</tr>
<tr>
<td>Health insurance</td>
<td>1736 (93.0%)</td>
<td>1491 (91.4%)</td>
</tr>
<tr>
<td>Nephrology care</td>
<td>1289 (62.6%)†</td>
<td>1296 (69.7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1675 (81.3%)†</td>
<td>1698 (91.3%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>700 (34.%)†</td>
<td>1198 (61.1%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>591 (28.7%)†</td>
<td>717 (38.6%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>284 (13.8%)†</td>
<td>229 (12.3%)</td>
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<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>1304 (63.8%)†</td>
<td>1372 (74.3%)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>936 (45.8%)†</td>
<td>984 (53.3%)</td>
</tr>
<tr>
<td>Aspirin or antiplatelet</td>
<td>866 (42.3%)†</td>
<td>928 (50.3%)</td>
</tr>
<tr>
<td>Statin</td>
<td>1013 (49.5%)†</td>
<td>1128 (61.1%)</td>
</tr>
<tr>
<td>Erythropoiesis-stimulating agent</td>
<td>38 (1.9%)†</td>
<td>115 (6.2%)</td>
</tr>
<tr>
<td>Iron</td>
<td>87 (4.3%)†</td>
<td>257 (13.9%)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>124.7 (20.9)†</td>
<td>132.7 (22.8)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>31.7 (7.1)†</td>
<td>32.54 (8.49)</td>
</tr>
<tr>
<td>Transferrin saturation, %</td>
<td>24.8†</td>
<td>21.5</td>
</tr>
<tr>
<td>Ferritin, ng/ml, median (IQR)</td>
<td>156.8 (86.0-276.5)†</td>
<td>159.4 (80.6-299.3)</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>4.1 (0.4)†</td>
<td>3.8 (0.5)</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>6.4 (1.4)†</td>
<td>7.0 (1.7)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>106.8 (35.0)†</td>
<td>98.3 (35.8)</td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>9.3 (0.5)†</td>
<td>9.1 (0.5)</td>
</tr>
<tr>
<td>Phosphate, mg/dL</td>
<td>3.6 (0.6)†</td>
<td>3.9 (0.7)</td>
</tr>
<tr>
<td>Total parathyroid hormone, pg/mL</td>
<td>46.3 (32.0-73.0)†</td>
<td>65.6 (39.8-114.0)</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>2.4 (1.1-5.7)†</td>
<td>2.8 (1.1-7.4)</td>
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<tr>
<td>Estimated GFR, mL/min/1.73 m²</td>
<td>50.3 (17.4)†</td>
<td>38.9 (14.0)</td>
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<td>Urine protein, g/24 hours, median (IQR)</td>
<td>0.13 (0.07-0.61)†</td>
<td>0.3 (0.08-1.40)</td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>13.9 (1.2)†</td>
<td>11.2 (1.1)</td>
</tr>
<tr>
<td>Mean cell volume, fL</td>
<td>89.1 (5.0)†</td>
<td>87.3 (6.6)</td>
</tr>
</tbody>
</table>

*p<0.05, †p<0.01

Mean (standard deviation) or median (interquartile ranges) are provided for normally and non-normally distributed variables, respectively. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; LDL, low density lipoprotein; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate
Table 2: Hazard Ratio (95% CI) for the association of anemia (vs. no anemia) with incident End-Stage Renal Disease and Death

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MSM with time-varying anemia and time-varying covariates*</th>
<th>Cause-Specific hazards model with baseline anemia and baseline covariates*</th>
<th>Cause-specific hazards model with time-varying anemia and baseline covariates*</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-Stage Renal Disease</td>
<td>1.62 (1.24-2.11)</td>
<td>1.26 (1.08-1.47)</td>
<td>1.31 (1.12-1.54)</td>
</tr>
<tr>
<td>Death</td>
<td>0.95 (0.78-1.16)</td>
<td>0.97 (0.83-1.13)</td>
<td>1.01 (0.87-1.17)</td>
</tr>
</tbody>
</table>

*Clinical site, age, sex, race/ethnicity, education, income, cardiovascular disease, systolic blood pressure, body mass index, Hemoglobin A1c, phosphate level, c-reactive protein, eGFR, 24 hour urine protein, ACEi/ARB therapy, beta-blocker therapy, erythroid stimulating agents, serum albumin

Time updated variables included anemia status, blood pressure, body mass index, eGFR, and proteinuria. MSM, marginal structural models

Hazard ratio for MSM estimates reflect the risk for outcome of incident ESRD for the scenario in which anemia status was unchanged at all study visits.
Figure 1. Baseline hemoglobin concentration was normally distributed.
Figure 2. Higher rates of incident ESRD 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 of less than 13.1 g/dL was associated with a higher risk of incident ESRD.
Figure 4. No consistent association between decile of hemoglobin concentration and risk for death was seen on multivariable analyses.