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Association of anemia with outcomes in men with moderate and severe chronic kidney disease

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Anemia is a common complication of chronic kidney disease (CKD), but the outcomes associated with lower hemoglobin (Hgb) levels in patients with CKD not yet on dialysis are not well characterized. Analyses exploring outcomes associated with a single baseline Hgb value also do not account for the longitudinal variation of this measure. After collecting all Hgb measurements ($N = 17\,194$, median (range): 12 (1–168)) over a median follow-up period of 2.1 years in a historical prospective cohort of 853 male US veterans with CKD Stages 3–5 not yet on dialysis, we examined the association of time-averaged Hgb levels with predialysis all-cause mortality, end-stage renal disease (ESRD), and a composite end point of both. Kaplan–Meier survival analysis and Cox models adjusted for age, race, body mass index, smoking status, blood pressure, diabetes mellitus, cardiovascular disease, categories of estimated glomerular filtration rate, serum concentrations of albumin and cholesterol, and proteinuria were examined. Lower time-averaged Hgb was associated with significantly higher hazard of the composite end point (hazard ratio (95% confidence interval) in the adjusted model for time-averaged Hgb of <110, 111–120 and 121–130, compared to >130 g/l: 2.57 (1.85–3.58), 1.97 (1.45–2.66), 1.19 (0.86–1.63), $P_{trend} < 0.001$). Lower time-averaged Hgb was associated with both significantly higher pre-dialysis mortality and higher risk of ESRD, when analyzed separately. Anemia (especially time-averaged Hgb <120 g/l) is associated with both higher mortality and increased risk of ESRD in male patients with CKD not yet on dialysis.

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KEYWORDS: anemia; chronic kidney disease; mortality; end-stage renal disease.

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Anemia is commonly present in patients with chronic kidney disease (CKD).[1] The consequences of lower hemoglobin (Hgb) levels in patients with CKD Stage 5 on dialysis are well studied, and include increased morbidity and mortality.[2–5] Fewer data exist on the effects of anemia in patients with CKD Stages 3–5 not yet on dialysis. Additionally, descriptive studies exploring the association of a single baseline Hgb value with various outcomes cannot account for the longitudinal variation of Hgb levels. We describe the association of anemia with major clinical outcomes (pre-dialysis all-cause mortality and end-stage renal disease (ESRD)) in a cohort of 853 male US veterans with CKD Stages 3–5 not yet on dialysis. We collected Hgb measurements longitudinally and examined time-averaged Hgb values to capture the temporal variation in Hgb levels.

RESULTS

Baseline characteristics divided by categories of time-averaged Hgb are presented in Table 1. Patients with higher time-averaged Hgb were more likely to be white and non-diabetic, and had higher estimated glomerular filtration rate (GFR), albumin and cholesterol levels, and lower 24 h urine protein level (Table 1). The baseline characteristics of the 36 patients lost to follow-up were not significantly different from the overall patient groups' (data not shown). The median duration of follow-up was 2.1 years and total time at risk was 2414 patient-years. Four hundred forty patients reached the composite end point (event rate (95% confidence interval (CI)): 182.2 (166.0–200.1)/1000 patient-years), with 245 patients dying and 195 patients starting dialysis. Table 2 shows the distribution of events by categories of time-averaged Hgb. Patients with lower time-averaged Hgb experienced a higher number of both the primary and the secondary events (Table 2). Figure 1 shows the hazard ratios (95% CI) for the composite end point, by categories of time-averaged Hgb, in a Cox model, both unadjusted and after adjustment for age, race, diabetes mellitus (DM), atherosclerotic cardiovascular disease (ASCVD), body mass index (BMI), smoking status, mean arterial pressure (MAP), estimated GFR, serum albumin, blood cholesterol, and 24-h urine protein level. In both models, lower time-averaged Hgb

Table 1 | Baseline characteristics of individuals stratified by categories of time-averaged hemoglobin level[a]

	<110 (*N*=174)	111–120 (*N*=216)	121–130 (*N*=201)	>130 (*N*=262)	*P*
Age (years)	68.6±10.6	68.9±10.3	68.3±10.5	67.0±10.8	0.1
Race (% black)	55 (31.6)	61 (28.2)	46 (22.9)	47 (17.9)	0.005
DM	102 (58.6)	128 (59.3)	108 (53.7)	112 (42.7)	0.001
Hypertension	161 (92.5)	205 (94.9)	193 (96.0)	246 (93.9)	0.5
ASCVD	113 (64.9)	133 (61.6)	123 (61.2)	152 (58.0)	0.5
Smoking	48 (30.8)	46 (23.6)	55 (28.3)	66 (26.5)	0.4
BMI (kg/m^2)	28.7±6.6	28.0±5.5	29.0±5.2	29.1±5.5	0.2
MAP (mmHg)	102.1±18.6	102.1±15.9	99.9±17.7	101.1±17.2	0.5
GFR (ml/min/1.73m^2)	27.3±12.5	31.3±11.4	33.9±10.2	37.0±9.8	<0.0001
Albumin (g/l)	34±6	35±5	36±5	38±4	<0.0001
Cholesterol (mmol/l)[b]	4.52 (4.33–4.72)	4.90 (4.73–5.08)	4.83 (4.65–5.02)	4.96 (4.81–5.12)	0.004
Proteinuria (g/24 h)[b]	1.4 (1.2–1.8)	1.1 (0.8–1.4)	0.7 (0.5–0.9)	0.4 (0.3–0.5)	<0.0001

ASCVD=atherosclerotic cardiovascular disease; BMI=body mass index; DM=diabetes mellitus; GFR=glomerular filtration rate; MAP=mean arterial pressure.
Comparisons are made by ANOVA, Fisher's exact test or χ^2 test.
[a]Data presented as means±s.d., number (% of total).
[b]Geometric means (95% CI).

Table 2 | Distribution of events, by categories of time-averaged hemoglobin level[a]

	Composite (*N*=440)	Death before dialysis (*N*=245)	Dialysis (*N*=195)
<110 g/l (*N*=174)	138 (79.3%)	68 (39.0%)	70 (40.2%)
111–120 g/l (*N*=216)	139 (64.3%)	74 (34.2%)	65 (30.0%)
121–130 g/l (*N*=201)	86 (42.8%)	50 (24.9%)	36 (17.9%)
>130 g/l (*N*=262)	77 (29.4%)	53 (20.2%)	24 (9.2%)

[a]Data presented as number (% of total).

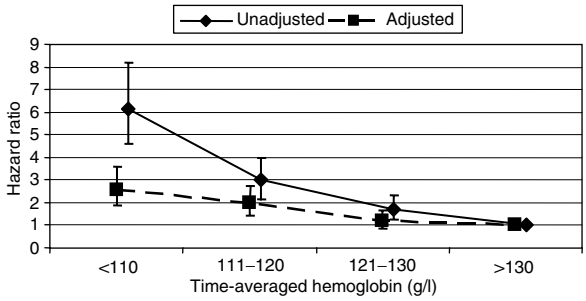

Figure 1 | Graphic representation of the hazard ratio (95% CI) of the composite outcome of pre-dialysis all-cause mortality and ESRD associated with different levels of time-averaged Hgb, unadjusted and after adjustment for age, race, DM, ASCVD, BMI, smoking status, MAP, estimated GFR, serum albumin, blood cholesterol, and 24-h urine protein. The group with time-averaged Hgb >130 g/l served as reference.

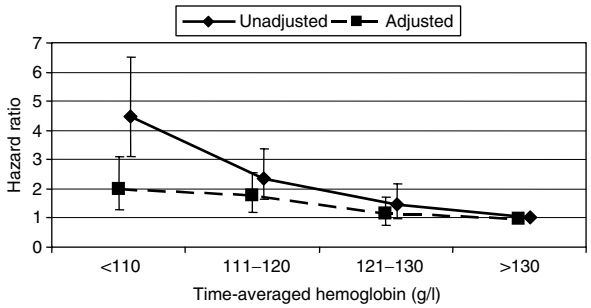

Figure 2 | Graphic representation of the hazard ratio (95% CI) of pre-dialysis all-cause mortality associated with different levels of time-averaged Hgb, unadjusted and after adjustment for age, race, DM, ASCVD, BMI, smoking status, MAP, estimated GFR, serum albumin, blood cholesterol, and 24-h urine protein. The group with time-averaged Hgb >130 g/l served as reference.

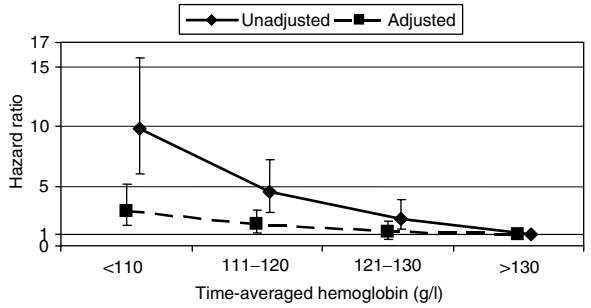

Figure 3 | Graphic representation of the hazard ratio (95% CI) of ESRD associated with different levels of time-averaged Hgb, unadjusted and after adjustment for age, race, DM, ASCVD, BMI, smoking status, MAP, estimated GFR, serum albumin, blood cholesterol, and 24-h urine protein. The group with time-averaged Hgb >130 g/l served as reference.

was associated with higher hazard ratio for the composite outcome, with a significant linear trend noted (Figure 1). In a Cox model including time-averaged Hgb as a continuous variable, a 10 g/l higher time-averaged Hgb was associated with a hazard ratio (95% CI) of 0.79 (0.73–0.85) for the composite outcome ($P<0.001$).

Figures 2 and 3 show the hazard ratios (95% CI) for pre-dialysis all-cause mortality (Figure 2) and ESRD (Figure 3), by categories of time-averaged Hgb, both unadjusted and after adjustment for age, race, DM, ASCVD, BMI, smoking status, MAP, estimated GFR, serum albumin, blood cholesterol, and 24-h urine protein. In both cases, lower time-averaged Hgb was associated with higher hazard ratios for the studied outcomes, with a significant linear trend (Figures 2 and 3). Patients with time-averaged Hgb of <110 g/l had the highest hazard ratio (95% CI) for all-cause mortality (2.06 (1.35–3.13)) and for ESRD (2.96 (1.70–5.14)), but even patients with time-averaged Hgb 111–120 g/l had significantly higher hazard ratios for both mortality (1.80 (1.23–2.63)) and

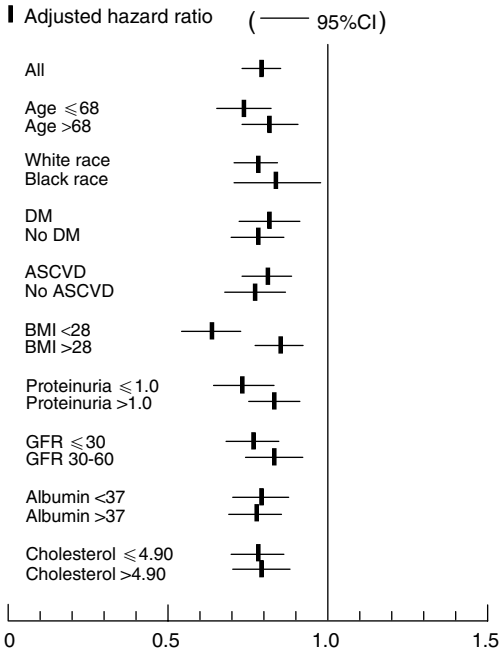

Figure 4 | Adjusted hazard of the composite end point of pre-dialysis all-cause mortality and ESRD associated with a 10 g/l higher time-averaged Hgb level, by subgroups. Models are adjusted for age, race, DM, ASCVD, BMI, smoking status, MAP, estimated GFR, serum albumin, blood cholesterol, and 24-h urine protein. CI, confidence interval; DM, diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; GFR, glomerular filtration rate.

ESRD (1.81 (1.07–3.05)) compared to the group with time-averaged Hgb >130 g/l. There was no significant difference in outcomes between the time-averaged Hgb 121–130 and >130 g/l groups (Figures 2 and 3). In Cox models including time-averaged Hgb as a continuous variable, a 10 g/l higher time-averaged Hgb was associated with a hazard ratio (95% CI) of 0.86 (0.78–0.95) for all-cause mortality ($P=0.001$) and 0.74 (0.65–0.84) for ESRD ($P<0.001$). Older age, prevalent ASCVD, lower MAP, lower albumin, lower cholesterol, lower proteinuria, and lower GFR were also associated with significantly higher risk of all-cause mortality and younger age, prevalent DM, higher proteinuria and lower GFR were also associated with significantly higher risk of ESRD in the Cox models.

The associations between time-averaged Hgb and the studied outcomes remained significant in all the examined subgroups (Figure 4). Inclusion of interaction terms in the statistical model also revealed no significant interaction with any of the studied covariates. The associations between time-averaged Hgb and the studied outcomes were similar when analyses were performed including non-imputed data only and also after inclusion of the eight female patients (results not shown).

DISCUSSION

We examined the association of anemia with clinical outcomes (pre-dialysis all-cause mortality and ESRD) in a cohort of male US veterans with moderate and severe CKD. As blood Hgb concentration varies longitudinally in patients with CKD as a result of changing kidney function,[1] treatment measures[6,7] and various states of illness, using a single baseline measure does not provide an accurate assessment of the individual patients' exposure to the effects of anemia over time. To account for this, we used the time-averaged Hgb in each individual patient, a value that makes it possible to assess the longitudinal burden of anemia by averaging all the individual measurements and accounting for the duration of any individual measurement value. We found that time-averaged Hgb values below 120 g/l were associated with significantly higher hazard ratios for both pre-dialysis all-cause mortality and ESRD, with a significant linear trend toward higher hazard ratios with lower time-averaged Hgb levels. This association was consistent in all studied subgroups, suggesting that low Hgb is an independent risk factor for the above outcomes, rather than a surrogate marker of another concomitant condition.

Anemia is a frequent complication of CKD,[1] and the prevalence of anemia increases as kidney function declines.[1] Studies in dialysis patients have shown an increased mortality with lower Hgb levels,[2–4] but relatively little is known about this in patients who have CKD but are not yet on dialysis. In a middle-aged community-based population, anemia was associated with higher incidence of coronary events[8] and stroke[9] in patients with elevated serum creatinine levels. Anemia and CKD were also shown to be risk factors for death in hospitalized patients with congestive heart failure[10] and acute myocardial infarction.[11] Treatment of anemia prior to initiation of dialysis confers a survival advantage after the start of dialysis,[12,13] it ameliorates left ventricular hypertrophy and it improves quality of life and various health measures.[14–17] Anemia was also associated with higher all-cause and cardiovascular mortality in a sample of patients with CKD pooled from various prospective studies.[18] The patients in this study, however, had less advanced CKD (mean estimated GFR 51 ml/min/1.73m^2), and the study used a single baseline Hgb to define anemia.[18] Our study is to our knowledge the first to examine pre-dialysis mortality in an unselected patient group with moderate and advanced CKD, and also account for the longitudinal variation of Hgb levels, whereas addressing the confounding effects of multiple other potential risk factors.

Anemia could increase mortality by its effect on the development of left ventricular hypertrophy, which is a risk factor for mortality in patients on dialysis.[19] Lower Hgb is associated with left ventricular hypertrophy and treatment of anemia was shown to result in regression of left ventricular hypertrophy.[14,15]

An association of anemia with progression of CKD has been proposed in the past, as treatment of anemia ameliorated the loss of kidney function and progression to ESRD.[17,20,21] Our findings are in agreement with these results, as we found that lower time-averaged Hgb values were associated with higher hazard ratios for ESRD, even after adjustment for several confounders. The mechanisms

involved in the association of anemia with progression of CKD may involve hypoxia-induced tubulointerstitial fibrosis, and treatment with recombinant human erythropoietin may have additional benefits beyond decreasing tissue hypoxia, such as antiapoptotic and antioxidant effects.[22]

Several shortcomings of our study need to be stressed. Our cohort was derived from a single medical center, and we examined an exclusively male group of patients; hence, our findings may not apply to females or patients from other geographic locations. We did not have cause of death available for our analyses, hence we could not test the hypothesis that anemia could increase mortality by impacting on cardiovascular disease-related factors such as left ventricular hypertrophy. Given the retrospective nature of our study, associations, but no cause–effect relationships can be established from it. While we tried to account for several potential confounding risk factors, the presence of residual confounding cannot be excluded. Even so, the uniformity of the detected associations across a wide array of subgroups, and the lack of any significant interactions make it more likely that anemia is an independent risk factor for the studied outcomes. Another shortcoming of our study is that we did not account for the effects of therapeutic interventions with recombinant human erythropoietin or angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers. The major effect of recombinant human erythropoietin treatment is an increase in Hgb levels,[6] and by collecting longitudinal Hgb values, we would have captured such a benefit. Additionally though, there could be other benefits of treatment with EPO that go beyond increasing Hgb levels.[22] Although the effects of such benefits would have been missed in our study, this is only a theoretical concern, as the mentioned benefits have not yet been proven in human studies. Therapy with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers could have impacted the examined associations in different ways: first, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers has been shown to favorably impact the progression of CKD,[23–25] and second, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers have been shown to lower Hgb concentrations in polycythemic patients;[26–28] hence, a negative effect of such therapies on time-averaged Hgb levels in our study cannot be ruled out. Additionally, we could not assess the impact of changing therapeutic practices on outcomes, given the shift in general usage patterns for both recombinant human erythropoietin and angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers during the studied time period. Finally, the use of a single time-averaged value of Hgb did not allow for capturing dynamic changes in Hgb levels (such as the direction of change over time) and their effects on outcomes, even though it made possible to account for overall temporal variations.

CONCLUSION

We have found that anemia is independently associated with higher risk of pre-dialysis mortality and ESRD in male patients with CKD Stages 3–5 not yet on dialysis. Patients with time-averaged Hgb values <120 g/l had significantly higher relative risks of these outcomes, and the benefit of a time-averaged Hgb >120 g/l appeared to have no upper limit. Our findings could serve as basis for randomized controlled studies in order to establish an ideal therapeutic goal for the treatment of anemia in pre-dialysis CKD.

MATERIALS AND METHODS

Study population

We examined patients referred for evaluation to a single Nephrology clinic at Salem Veterans Affairs Medical Center between January 1, 1990 and December 31, 2004. After patients with a kidney transplant, patients on dialysis and patients referred for problems other than CKD were excluded, 960 patients with CKD not yet on dialysis were identified. GFR was estimated using the abbreviated equation developed for the Modification of Diet in Renal Disease Study,[29] and patients were classified according to the Kidney/Dialysis Outcome Quality Initiative Clinical Practice Guidelines for CKD: Evaluation, Classification and Stratification.[30] Ninety nine patients with CKD Stages 1 and 2 were excluded. As there were only eight female patients left in the remaining cohort, they were also excluded from further analyses, leaving the final number of patients available for analysis at 853.

Data collection

We collected baseline data from medical records (paper and electronic) at the time of the initial encounter in the Nephrology clinic, including demographic and anthropometric information, comorbidities, blood pressure measurements, and laboratory measures. BMI was calculated as the weight in kilogram divided by the square of the height in meters. DM was defined as the presence of an abnormal fasting glucose level or antidiabetic therapy. Hypertension was defined as the presence of an abnormal blood pressure measurement (defined as a systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg) or antihypertensive therapy. ASCVD was defined as a previous history of cardiovascular, cerebrovascular or peripheral vascular disease, based on chart review. Additionally, we collected all Hgb measurements longitudinally from the time of the initial encounter until the end of follow-up (total of 17 194 measurements, median (range): 12 (1–168)), and calculated time-averaged values for each patient individually, using the following formula:

$$\text{Time}-\text{averaged Hgb} = \frac{1}{2(t_n - t_0)} \sum_{i=1}^{n} (\text{Hgb}_i + \text{Hgb}_{i-1})(t_i - t_{i-1}),$$

where Hgb values Hgb_0, Hgb_1, …, Hgb_n were measured at time points t_0, t_1, …, t_n.

Outcomes

We followed patients until death or loss of follow-up, or until June 16, 2005. We considered a patient lost to follow-up if no contact with the medical center was documented for more than 6 months. Thirty-six patients (4.2%) were lost to follow-up. Our outcome measures of interest were mortality and ESRD. We recorded deaths from the VA centralized patient record system, which uses a combination of sources including national databases from the Veterans Health Administration, direct notifications from family

members and obituaries to ascertain the death of an enrolled veteran. No data was available on cause of death; hence, the studied outcome measure was all-cause mortality. ESRD was defined as the initiation of dialysis (hemodialysis or peritoneal dialysis), and was ascertained from local medical records.

Statistical analysis

After descriptive statistics, variables with skewed distribution were transformed to their natural logarithm. We imputed missing data points for 24-h urine protein (3.9% missing), blood cholesterol (1.2% missing) and serum albumin (1.0% missing) using linear regression with all other patient characteristics serving as independent variables. Given the large number of missing data points for BMI (24.3% missing), we categorized this variable by using quartiles and adding a 'missing' category as a fifth group. Similarly, we analyzed smoking status (6.8% missing) as a categorical variable with three categories (non-smoker, active smoker and 'missing smoking status'). Analyses were repeated with the inclusion of the female participants and using non-imputed data only.

Survival modeling. The starting time for survival analysis was the date of the initial encounter and the main outcome measure was the composite of pre-dialysis all-cause mortality and ESRD. Secondary outcome measures were mortality and ESRD analyzed separately. We censored patients lost to follow-up at the date of the last documented contact with the medical center. Event rates were calculated using the person-years approach. We analyzed the unadjusted association of categorized time-averaged Hgb with all-cause mortality using Kaplan–Meier plots and the log-rank test. To examine the effect of potentially confounding variables, we adjusted in a multivariable Cox model for patient age, race, DM, ASCVD, BMI, smoking status, MAP, estimated GFR, serum albumin, blood cholesterol, and 24-h urine protein levels. We performed subgroup analyses in groups divided by age, race, DM, ASCVD, smoking status and levels of MAP, BMI, estimated GFR, albumin, cholesterol and proteinuria, and we explored potential interactions by inclusion of interaction terms. We tested the proportionality assumption using plots and interaction terms with time. We considered *P*-values of less than 0.05 significant. Statistical analyses were performed using STATA statistical software Version 8 (STATA Corporation, College Station, TX, USA).

The study protocol was approved by the Research and Development Committee and the Human Studies Sub-Committee at the Salem Veterans Affairs Medical Center.

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