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Role of Anemia in Dementia Risk Among Veterans With Incident CKD

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Abstract

Rationale & Objective: While some evidence exists of increased dementia risk from anemia, it is unclear if this association persists among adults with CKD. Anemia may be a key marker for dementia among adults with CKD. We therefore evaluated if anemia is associated with an increased risk of dementia among adults with CKD.

Study Design: Retrospective cohort study.

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Setting & Participants: The study included 620,095 veterans aged ≥45 years with incident stage 3 CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) between January 2005 and December 2016 in the US Veterans Health Administration system and followed through December 31, 2018 for incident dementia, kidney failure or death.

Exposures: Anemia was assessed based on the average of hemoglobin levels (g/L) during the two years prior to the date of incident CKD and categorized as normal, mild and moderate/severe anemia (≥12.0, 11.0–11.9, <11.0 g/dL, respectively for women and ≥13.0, 11.0–12.9, <11.0 g/dL for men).

Outcomes: Dementia and the composite outcome of kidney failure or death.

Analytical Approach: Adjusted cause-specific hazard ratios were estimated for each outcome.

Results: At the time of incident CKD, mean age was 72 years, 97% were male, and mean eGFR was 51 mL/min per 1.73 m^2. Over a median 4.1 years of follow-up, 92,306 (15%) veterans developed dementia before kidney failure or death. Compared to veterans with CKD without anemia, multivariable-adjusted models showed a 16% (95% confidence interval [CI] 14% to 17%) significantly higher risk of dementia for those with mild anemia and a 27% (95% CI 23% to 31%) higher risk with moderate/severe anemia. Combined risk of kidney failure or death was higher at 39% (95% CI 37% to 40%) and 115% (95% CI 112% to 119%) for mild and moderate/severe anemia, respectively, compared to no anemia.

Limitations: Residual confounding from the observational study design. Findings may not be generalizable to the broader U.S. population.

Conclusions: Anemia was significantly associated with increased risk of dementia among veterans with incident CKD, underscoring the role of anemia as a predictor of dementia risk.

Plain Language Summary

Adults with chronic kidney disease (CKD) often have anemia. Prior studies among adults in the general population suggest anemia is a risk factor for dementia, though it is unclear if this association persists among adults with CKD. In this large study of veterans in the United States, we studied the association between anemia and the risk of two outcomes: 1) dementia; 2) kidney failure or death, which are important outcomes in this population. We found that anemia was associated with a greater risk of dementia, as well as risk of kidney failure or death. The study findings therefore emphasize the role of anemia as a key predictor of dementia risk among adults with CKD.

Index Words:

chronic kidney disease; anemia; dementia; kidney failure; ESKD

Introduction

Among adults 65 years of age and older, over one third are affected by chronic kidney disease (CKD)[1] and nearly one in ten have dementia[2]. Both conditions contribute substantially to the health and financial burden of affected adults,[3–5] as well as share many risk factors such as cardiovascular disease, diabetes, hypercholesterolemia, and anemia[5,6].

While existing studies suggest anemia may be a risk factor for dementia[7], it is unclear if this association persists among adults with CKD. Anemia may play a role in the association between CKD and dementia risk. In addition to being a non-conventional risk factor for CKD[8,9], anemia may also result from CKD. As renal function worsens, erythropoietin production in the renal cortex decreases[10], resulting in decreased red blood cell production and risk of anemia. With reduced capacity to oxygenate brain tissue in the anemic state, neurodegeneration may result through increased production of β-amyloid protein implicated in the pathology of dementia, reduced cerebral blood flow, and prolonged hypoxia[7].

Few studies have examined if anemia is a risk factor for cognitive impairment or dementia among older adults with CKD. One study of adults ≥55 years old with CKD from the Chronic Renal Insufficiency Cohort (CRIC) did not find any significant association between anemia and either cross-sectional baseline cognitive function or longitudinal change in cognitive function[11]. Other studies are subject to considerable methodological limitations including cross-sectional study designs, small samples, and reporting only univariate analyses[12–16]. Further, the association of anemia and dementia is confounded by the use of erythropoietin-stimulating agents (ESA), which may confer a risk of stroke[17]. Some studies also restrict to patients with kidney failure[14,15], in whom the risk profile for health outcomes such as incident dementia may qualitatively differ due to the advanced state of the disease. Therefore, we leveraged the large longitudinal data available in the United States Veterans Health Administration (VHA), to examine the association of anemia with incident dementia among adults in mid- to late-life with CKD. As secondary analyses, we also examined this association in a subgroup with measures for transferrin saturation (TSAT) to evaluate the possible role of iron deficiency in the pathogenesis of dementia. We also assessed the risk of kidney failure or death as a composite outcome, as they are important patient-centered outcomes in this population.

Methods

Study Population

This study comprises veterans in the VHA, an integrated healthcare system providing care for veterans at approximately 1,300 facilities throughout the United States. Veterans were 45 years and older with incident CKD stage 3 between January 1, 2005 and December 31, 2016. The date of incident CKD, serving as the index date, was defined as the second of two estimated glomerular filtration rate (eGFR) values <60 mL/min/1.73 m^2 occurring at ≥91 days apart but within 18 months, and for the first time over the study period. The eGFR was calculated using the 2021 CKD Epidemiology (CKD-EPI) Collaboration creatinine equation that does not include the race term[18]. To maximize accuracy of the index date in representing veterans' first lifetime instance of decreased eGFR lasting ≥91 days (incident CKD), eligible veterans must have been in the VHA for at least two years before their initial eGFR value <60 mL/min/1.73m^2 recorded in the VHA database. Given this criteria, during these two years, 91% of veterans in the cohort had creatinine measurements (all eGFR values ≥60 mL/min/1.73m^2) and the remaining 9% had no creatinine measurements. To ensure accurate ascertainment of anemia status, veterans included in this cohort were regular users of the VHA, defined a priori as VHA enrollees who fulfilled two criteria: 1) utilized

VHA services that were documented in annual utilization files for the year of the index date and the prior two calendar years; 2) had at least one outpatient visit during the two years before the first of two eGFR values <60 mL/min/1.73 m^2. Veterans were excluded if they did not have any outpatient hemoglobin values within two years prior to the index date, or had a diagnosis of dementia (including secondary dementia attributed to alcohol abuse) or kidney failure before the index date. The flow chart for the cohort construction is presented in Figure S1. Institutional Review Board approval was obtained at the University of Virginia and the Salem Veterans Affairs Medical Center and the study was conducted in accordance with the Declaration of Helsinki. Informed consent was waived as the study only comprised secondary data analysis of deidentified data.

Study Variables

Follow-up period began from the index date and accrued until the first occurrence of the following events: diagnosis of dementia, kidney failure, death, loss to follow-up (defined at 18 months after the last clinical record in the VHA system), or the end of the study period (December 31, 2018). The primary outcome was incidence of dementia before kidney failure. The secondary outcome was the composite event of death or kidney failure before incidence of dementia. Dementia was identified based on the first occurrence of any qualifying International Classification of Diseases, Ninth Revision or Tenth Revision diagnosis code (ICD-9, ICD-10) code in the electronic medical record, using an algorithm adapted from a prior publication (Table S1)[19]. Secondary cases of dementia attributed to alcohol abuse were excluded due to its distinct etiology. Death status was based on the VHA Vital Status File and VHA Corporate Data Warehouse (CDW) Patient Domain. Kidney failure was determined by the initiation of kidney replacement therapy, which was recorded in the United States Renal Data System (USRDS) through linking our cohort to the USRDS.

The baseline period was defined as the two-year period prior to the index date. Baseline anemia status was measured using the average of all outpatient hemoglobin measurements during this baseline period. Thresholds to define categories of anemia status were based on World Health Organization criteria[20]. Ranges of hemoglobin levels (g/dL) for no anemia, and mild, moderate and severe anemia were as follows: ≥12.0, 11.0–11.9, 8.0–10.9, <8.0, respectively, for women and ≥13.0, 11.0–12.9, 8.0–10.9, <8.0 for men. Due to a small sample size for severe anemia, the moderate and severe categories were combined for all analyses. Follow-up anemia status was defined for each year of follow-up using the average of outpatient hemoglobin values during the previous year and with the most recent value carried forward in the absence of any measures for a given year.

Baseline demographic covariates included age (45–64, 65–84, 85–100 years) at the index date, sex, and race/ethnicity (Black, Hispanic, Other or Unknown, White). “Other” races included veterans who identified as American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, or multiple races. Additional covariates included smoking status (current, former, never), body mass index (BMI; kg/m^2), recent history of blood transfusion (based on at least one qualifying code during the two-year baseline period), urinary albumin-to-creatinine ratio (UACR; <29, 30–300, >300 mg/g), transferrin saturation (TSAT; <20%, ≥20%), medication use (ESA, angiotensin-converting-enzyme inhibitors

[ACEi], and angiotensin II receptor blockers [ARB]), and comorbidities. Comorbidities were assessed based on the presence of at least one ICD diagnosis code and included hypertension, depression, alcohol abuse, drug abuse, as well as those comprising the Charlson Comorbidity Index (CCI)[21], excluding kidney disease and dementia. These variables were defined using records during the two-year baseline period, with the exception of the calculation of the CCI, which was based on records within prior five years, to better capture long-term history of comorbidities. TSAT was based on the average of measurements over the baseline period.

All laboratory test results were obtained from the VHA CDW. As the cohort has been linked to Centers for Medicare and Medicaid Services (CMS) data, other variables were based on both VHA records and Medicare claims from the CMS. Specifically, dementia, comorbidities, and blood transfusion were based on records from both the VHA CDW and CMS Medicare Part A & Part B. Medications (ESA, ACEi and ARB) were based on records in the VHA CDW, with additional CMS Medicare Part A & Part B for ESA.

Statistical Analysis

Baseline characteristics were summarized by baseline anemia status using counts and proportions for categorical variables, mean and standard deviation for normally distributed continuous variables, and median and interquartile range for non-normal continuous variables. The association between anemia status and incident dementia was examined with cause-specific hazard models[22] using dementia before kidney failure as the event of interest. Patients were censored if they developed the competing risk, the composite outcome of kidney failure or death, before developing dementia. Because anemia status may change over time, in addition to evaluating the potential effect of baseline anemia status, we also performed cause-specific hazard models with annual anemia status modeled as a time-varying covariate. Similarly, cause-specific hazard models were performed for the secondary outcome, the composite event of death or kidney failure before incidence of dementia, as the event of interest. Patients were therefore censored if they developed the competing risk, incident dementia, before kidney failure or death. We obtained both unadjusted and adjusted hazard ratios (HR) for mild and moderate/severe anemia, respectively, compared with no anemia. Variables used for adjustment included the following: age, sex, race/ethnicity, BMI, smoking status, eGFR, ESA use, ACEi use, ARB use, blood transfusion, CCI, hypertension, depression, alcohol abuse, drug abuse, and year of incident CKD. The proportional hazards assumption was assessed using the cox.zph function from the survival package in R.

To evaluate iron deficiency as a potential confounder of the association between anemia and each outcome, we performed additional analyses in a subcohort of veterans (n=112,334, 18% of the overall cohort) who had available TSAT data. We obtained the adjusted HRs with and without further adjustment for TSAT by adding TSAT to the previous adjusted models used in the primary analysis. Lastly, the primary analysis was replicated in subgroups of select baseline covariates to assess potential effect modification and p values for the corresponding interaction tests were reported. We also examined the availability of TSAT measurement as an effect modifier. SAS 9.4 (SAS Institute Inc., Cary, NC) and R Statistical

Software (version 4.1.2, R Foundation for Statistical Computing) were used to conduct statistical analyses.

Results

Characteristics of the 620,095 veterans are presented in Table 1. The mean age at index date was 72 years (standard deviation [SD]: 10 years); 600,568 (97%) were male and the majority were White (437,030 [71%]). Compared with veterans without anemia at baseline, those with moderate or severe anemia were more likely to be older, identify as Black, have a lower mean eGFR, have had a blood transfusion, be ESA users, and have more prevalent comorbidities. Over a median follow-up of 4.1 years (interquartile range [IQR]: 2.4 – 7.0 years), 92,306 (15%) veterans developed dementia before kidney failure, with an incidence rate of 30.6 cases per 1,000 patient-years. A total of 201,686 (33%) veterans developed kidney failure or died without developing dementia, with an incidence rate of 66.6 cases per 1,000 patient-years. Of the veterans who developed dementia before kidney failure, the median age at dementia diagnosis was 83 years (IQR: 76 – 88), reflecting a predominance of late-onset dementia among observed cases.

Among veterans with incident CKD, both mild and moderate/severe anemia at baseline were significantly associated with an increased risk of both the primary outcome of dementia before kidney failure and the secondary composite outcome of kidney failure or death (Table 2). In multivariable-adjusted models, mild and moderate/severe anemia were significantly associated with a 16% (HR [95% CI]: 1.16 [1.14–1.17]) and 27% (HR [95% CI]: 1.27 [1.23–1.31]) increased risk of dementia, respectively. For the composite outcome of kidney failure or death, anemia was a stronger risk factor than for dementia, with a 39% (HR [95% CI]: 1.39 [1.37–1.40]) and 115% (HR [95% CI]: 2.15 [2.12–2.19]) significantly increased risk for mild and moderate/severe anemia, respectively, compared with no anemia. For the above findings, although p values for testing the proportional hazards assumption were less than 0.001, the tests were likely over-sensitive to slight deviations from the assumption due to the large sample size, as the time-varying HRs did not deviate substantially from the average HR over the course of follow-up and the direction of association did not change. When considering time-varying anemia status, the hazard ratios showed a similar trend but of a higher magnitude as compared to anemia status at baseline. In the subgroup of veterans with available TSAT measurements, results from the primary analysis were slightly attenuated but did not substantively change (Table S2).

Within select baseline subgroups (Figure 1), the significantly increased risks of both outcomes (dementia and the composite outcome of kidney failure or death) from anemia were seen across the subgroups. P-values from tests for interaction ranged from <0.001 to 0.75. For both the dementia and kidney failure or death outcomes, the interaction between anemia status and age group was significant ($p<0.001$), while it was not significant for sex, with the latter finding potentially attributed to greater variability in estimates due to small numbers of female veterans in anemia subgroups. The majority of the remaining interaction tests were statistically significant, particularly for the composite outcome of kidney failure or death.

Discussion

In a large national cohort of veterans with incident CKD, anemia was associated with an increased risk of dementia in addition to the composite outcome of kidney failure or death. Furthermore, observed associations with dementia risk were greater in magnitude when using a time-varying measure of anemia status, suggesting that the recent presence or severity of anemia may be a stronger indicator of dementia risk than baseline anemia. More recent anemia may be an indication of anemia accelerating the progression of dementia, since the pathology underlying dementia develops years or decades before clinical diagnosis[23]. In contrast, the larger magnitude of association using time-varying anemia status may also be attributed to reverse causation, as dementia can lead to cognitive and functional deficits resulting in malnutrition and anemia. The association between anemia status and kidney failure or death was stronger, which may be at least partially attributed to anemia as a marker of worsening CKD, as reflected by lower baseline eGFR among veterans with anemia compared with those without anemia. Additionally, the anemia-CKD relationship may also be bidirectional, as anemia may contribute to progression to kidney failure from hypoxic injury in tubular cells[24]. However, such mechanisms are unlikely to have meaningfully contributed to the observed results as patients with CKD are at substantially greater risk of cardiovascular death than kidney failure.

While the risk of kidney failure or death was higher than the risk of dementia, approximately 15% of veterans with CKD still developed dementia over a median follow-up of 4.1 years. Moreover, this value is likely an underestimate, given the tendency to under-ascertain dementia when using administrative data[25]. Additionally, with increasing prescription drug coverage[26] and availability of newer treatments[27], the survival rate among individuals with CKD continues to increase[26], therefore increasing the probability of developing other conditions prevalent in late-life such as dementia. Furthermore, compared with VHA users, the burden of dementia risk may be greater in the general population due to the larger proportion of women, who are at greater risk of dementia than men[28]. Collectively, these findings underscore the risk of dementia among adults with CKD. The current findings also highlight the importance of recognizing anemia as a potential marker of dementia risk in this population.

Our results were further enhanced by adjusting for iron deficiency status using TSAT, suggesting that the anemic state itself and/or other causes of anemia are likely driving the observed results. However, while demographic and clinical characteristics were similar between patients with and without TSAT measurements, patients selected for TSAT measurements in a clinical setting might still differ from the general patient population by other unmeasured factors. Regardless, rather than iron deficiency, a more prevalent cause of anemia may be anemia of chronic disease or inflammation from CKD itself and/or other conditions such as cancer, autoimmune disease, and acute or chronic infections[29,30]. It is unknown to what extent the anemia observed in our cohort is attributed to CKD, from these inflammatory conditions, or from other potential causes such as vitamin B12 or folate deficiency. Thus, it is possible that the observed anemia in our cohort is a proxy measure of underlying risk factors of dementia that include cardiometabolic, inflammatory, nutritional, environmental and psychosocial factors. Randomized trials have not shown any

reduction in risk of death or major cardiovascular events among adults with CKD when administered ESA[17,31,32], emphasizing the likely role of anemia as a predictive but not a causative risk factor for adverse health outcomes. Similarly, as adjustment for TSAT in the current study did not affect results, correction for iron deficiency may not reduce risk of dementia. Therefore, given the collective evidence, it may be most important to identify and target those factors contributing most to the anemic state to reduce the risk of outcomes such as dementia, kidney failure, or death among adults with CKD. Lastly, the biologic mechanisms by which anemia can contribute to neurodegenerative processes are yet to be fully explored. Current hypotheses include chronic brain hypoxia contributing to increased inflammation and formation of β-amyloid protein[7,33], and decreased activation of neuroprotective erythropoietin receptors in the brain[34].

A prior study among adults with CKD has evaluated the longitudinal association between anemia and dementia or other measures of cognitive function. Among 692 participants ≥55 years old (mean age=64 years) with prevalent CKD from the CRIC study[11], no significant association was found between anemia status and longitudinal change in cognitive function as measured by any of six neuropsychological tests. Though a neuropsychological battery may provide more information on cognitive function than diagnosis codes, the CRIC study might have been underpowered and CRIC volunteer study participants, on average, were younger and more likely to be healthier than VHA users[35]. Therefore, although the CRIC study findings did not show statistical significance, the results may be difficult to compare due to differences in study design, sample size and participant characteristics.

Strengths of the current study include the large national cohort with available data on clinical diagnoses, laboratory measures and pharmaceutical treatment, and the use of an incident CKD cohort at baseline which may reduce confounding by disease stage. Moreover, the use of both VHA records and Medicare claims to measure variables such as dementia and comorbidities likely provide greater validity than using VHA data alone as is commonly done in other studies. Additionally, time-dependent and subgroup analyses were conducted to illustrate the robustness of results. Limitations include the observational study design, as residual confounding from unmeasured variables such as socioeconomic status may have affected results. Since findings are derived from a cohort of predominately male veterans, the results may not be generalizable to the U.S. population. Non-differential misclassification of anemia status may result from measurement error of hemoglobin levels[36], although using the average of multiple measurements may reduce the impact of any misclassification. Lastly, the use of ICD codes in place of direct neuropsychological assessment to identify incident dementia may result in under-ascertainment.

In conclusion, our findings suggest that anemia is a predictor for dementia in a national cohort of veterans with incident CKD. Future studies are warranted to identify what factors leading to anemia play the largest role in the etiology of dementia. Identification of modifiable risk factors would have the greatest potential public health impact in reducing dementia risk among adults with CKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States, 2021. US Department of Health and Human Services. Accessed October 12, 2022. https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html
2. Farina MP, Zhang YS, Kim JK, Hayward MD, Crimmins EM. Trends in Dementia Prevalence, Incidence, and Mortality in the United States (2000–2016). J Aging Health. Jan 2022;34(1):100–108. doi:10.1177/08982643211029716 [PubMed: 34233528]
3. Wang V, Vilme H, Maciejewski ML, Boulware LE. The Economic Burden of Chronic Kidney Disease and End-Stage Renal Disease. Semin Nephrol. Jul 2016;36(4):319–30. doi:10.1016/j.semnephrol.2016.05.008 [PubMed: 27475662]
4. Cantarero-Prieto D, Leon PL, Blazquez-Fernandez C, Juan PS, Cobo CS. The economic cost of dementia: A systematic review. Dementia (London). Nov 2020;19(8):2637–2657. doi:10.1177/1471301219837776 [PubMed: 30909718]
5. Deckers K, Camerino I, van Boxtel MP, et al. Dementia risk in renal dysfunction: A systematic review and meta-analysis of prospective studies. Neurology. Jan 10 2017;88(2):198–208. doi:10.1212/WNL.0000000000003482 [PubMed: 27974647]
6. Sarnak MJ. Cardiovascular complications in chronic kidney disease. Am J Kidney Dis. Jun 2003;41(Suppl 5):11–17. doi:10.1016/s0272-6386(03)00372-x [PubMed: 12776309]
7. Kung WM, Yuan SP, Lin MS, et al. Anemia and the Risk of Cognitive Impairment: An Updated Systematic Review and Meta-Analysis. Brain Sci. Jun 11 2021;11(6):777. doi:10.3390/brainsci11060777 [PubMed: 34208355]
8. Saraf SL, Hsu JY, Ricardo AC, et al. Anemia and Incident End-Stage Kidney Disease. Kidney360. Jul 30 2020;1(7):623–630. doi:10.34067/kid.0000852020 [PubMed: 33117990]
9. Iseki K, Kohagura K. Anemia as a risk factor for chronic kidney disease. Kidney Int Suppl. Nov 2007;(107):S4–9. doi:10.1038/sj.ki.5002481 [PubMed: 17943141]
10. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. PLoS One. 2014;9(1):e84943. doi:10.1371/journal.pone.0084943 [PubMed: 24392162]
11. Kurella Tamura M, Vittinghoff E, Yang J, et al. Anemia and risk for cognitive decline in chronic kidney disease. BMC Nephrol. Jan 28 2016;17:13. doi:10.1186/s12882-016-0226-6 [PubMed: 26823182]
12. Aggarwal HK, Jain D, Bhavikatti A. Cognitive Dysfunction in Patients with Chronic Kidney Disease. Saudi J Kidney Dis Transpl. Jul-Aug 2020;31(4):796–804. doi:10.4103/1319-2442.292313 [PubMed: 32801240]

13. Kurella Tamura M, Xie D, Yaffe K, et al. Vascular risk factors and cognitive impairment in chronic kidney disease: the Chronic Renal Insufficiency Cohort (CRIC) study. Clin J Am Soc Nephrol. Feb 2011;6(2):248–56. doi:10.2215/CJN.02660310 [PubMed: 20930087]
14. Leinau L, Murphy TE, Bradley E, Fried T. Relationship between conditions addressed by hemodialysis guidelines and non-ESRD-specific conditions affecting quality of life. Clin J Am Soc Nephrol. Mar 2009;4(3):572–8. doi:10.2215/CJN.03370708 [PubMed: 19261828]
15. Murray AM, Tupper DE, Knopman DS, et al. Cognitive impairment in hemodialysis patients is common. Neurology. Jul 25 2006;67(2):216–23. doi:10.1212/01.wnl.0000225182.15532.40 [PubMed: 16864811]
16. Zhu J-J, Chen Y-J, Chen L-L, Zhao L-J, Zhou P Factors that contribute to the cognitive impairment in elderly dialysis patients. Therapeutic Apheresis and Dialysis. 2021;doi:10.1111/1744-9987.13740
17. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. Nov 19 2009;361(21):2019–32. doi:10.1056/NEJMoa0907845 [PubMed: 19880844]
18. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. New England Journal of Medicine. 2021;385(19):1737–1749. doi:10.1056/NEJMoa2102953 [PubMed: 34554658]
19. Moura L, Festa N, Price M, et al. Identifying Medicare beneficiaries with dementia. J Am Geriatr Soc. Aug 2021;69(8):2240–2251. doi:10.1111/jgs.17183 [PubMed: 33901296]
20. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. 2011. Accessed October 12, 2022. https://apps.who.int/iris/handle/10665/85839
21. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. Nov 1994;47(11):1245–51. doi:10.1016/0895-4356(94)90129-5 [PubMed: 7722560]
22. Li L, Yang W, Astor BC, Greene T. Competing Risk Modeling: Time to Put it in Our Standard Analytical Toolbox. J Am Soc Nephrol. Dec 2019;30(12):2284–2286. doi:10.1681/asn.2019101011 [PubMed: 31732615]
23. Beason-Held LL, Goh JO, An Y, et al. Changes in brain function occur years before the onset of cognitive impairment. J Neurosci. Nov 13 2013;33(46):18008–14. doi:10.1523/JNEUROSCI.1402-13.2013 [PubMed: 24227712]
24. Rossert J, Froissart M. Role of anemia in progression of chronic kidney disease. Semin Nephrol. Jul 2006;26(4):283–9. doi:10.1016/j.semnephrol.2006.05.004 [PubMed: 16949466]
25. Hayat S, Luben R, Khaw KT, Wareham N, Brayne C. Evaluation of routinely collected records for dementia outcomes in UK: a prospective cohort study. BMJ Open. Jun 15 2022;12(6):e060931. doi:10.1136/bmjopen-2022-060931
26. Johansen KL, Chertow GM, Gilbertson DT, et al. US Renal Data System 2021 Annual Data Report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2022;79(4)(suppl 1):A8–A12. doi: 10.1053/j.ajkd.2022.02.001 [PubMed: 35331382]
27. Persson F, Borg R, Rossing P. A narrative review of new treatment options for chronic kidney disease in type 2 diabetes. Ann Transl Med. Apr 2021;9(8):716. doi:10.21037/atm-20-4841 [PubMed: 33987414]
28. Andrew MK, Tierney MC. The puzzle of sex, gender and Alzheimer's disease: Why are women more often affected than men? Womens Health (Lond). 2018;14 doi:10.1177/1745506518817995
29. Nemeth E, Ganz T. Anemia of inflammation. Hematol Oncol Clin North Am. Aug 2014;28(4):671–81, vi. doi:10.1016/j.hoc.2014.04.005 [PubMed: 25064707]
30. Madu AJ, Ughasoro MD. Anaemia of Chronic Disease: An In-Depth Review. Med Princ Pract. 2017;26(1):1–9. doi:10.1159/000452104 [PubMed: 27756061]
31. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. Nov 16 2006;355(20):2085–98. doi:10.1056/NEJMoa065485 [PubMed: 17108343]
32. Drüeke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. Nov 16 2006;355(20):2071–84. doi:10.1056/NEJMoa062276 [PubMed: 17108342]

33. Andreev A, Erdinc B, Shivaraj K, et al. The Association Between Anemia of Chronic Inflammation and Alzheimer's Disease and Related Dementias. J Alzheimers Dis Rep. Sep 18 2020;4(1):379–391. doi:10.3233/ADR-200178 [PubMed: 33163899]

34. Gattas BS, Ibetoh CN, Stratulat E, et al. The Impact of Low Hemoglobin Levels on Cognitive Brain Functions. Cureus. Nov 8 2020;12(11):e11378. doi:10.7759/cureus.11378 [PubMed: 33312780]

35. Agha Z, Lofgren RP, VanRuiswyk JV, Layde PM. Are patients at Veterans Affairs medical centers sicker? A comparative analysis of health status and medical resource use. Arch Intern Med. Nov 27 2000;160(21):3252–7. doi:10.1001/archinte.160.21.3252 [PubMed: 11088086]

36. Stawschenko E, Schaller T, Kern B, et al. Current Status of Measurement Accuracy for Total Hemoglobin Concentration in the Clinical Context. Biosensors (Basel). Dec 8 2022;12(12)doi:10.3390/bios12121147

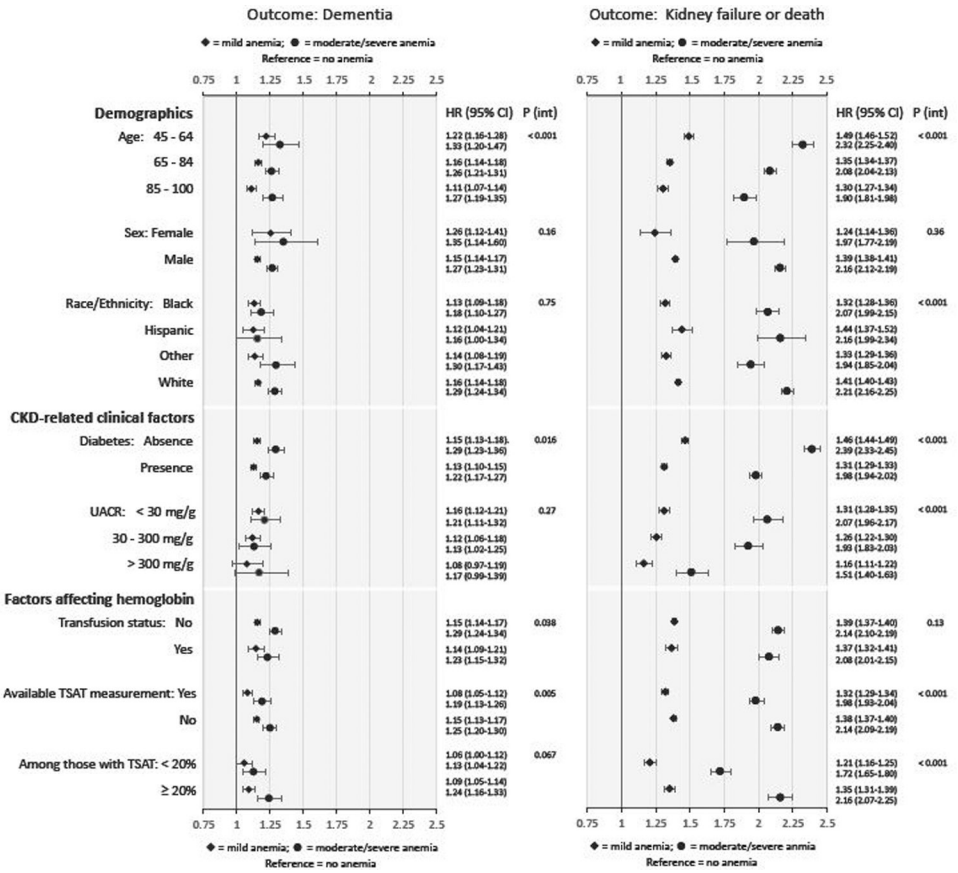

Figure 1.

Association between anemia at baseline and outcome in select baseline subgroups. Hazard ratios are stratified by levels of subgroups for age, sex, race/ethnicity, diabetes status, urinary albumin-to-creatinine ratio (UACR), transfusion status, availability of transferrin saturation (TSAT) measurement (yes/no), and TSAT (<20% / ≥20%) (among those with available TSAT), adjusting for all covariates included in the adjusted models shown in Table 2, provided it is not the stratifying variable. The rhombus symbol indicates the hazard ratios (HR) for mild anemia versus no anemia and the circle symbol indicates the HRs for moderate/severe versus no anemia. Abbreviations: P(int) = p value for the interaction test.

Table 1.

Baseline characteristics of veterans, by anemia status

Characteristic	Overall (n=620,095)	Baseline anemia status		
		Normal (n=416,582)	Mild (n=168,469)	Moderate or severe (n=35,044)
Age at CKD onset, years, mean ± SD	72 ± 10	72 ± 10	74 ± 10	73 ± 11
Age category at CKD onset, n (%)				
45–64 years	153,731 (25)	106,986 (26)	37,624 (22)	9,121 (26)
65–84 years	401,999 (65)	273,461 (66)	107,789 (64)	20,749 (59)
≥ 85 years	64,365 (10)	36,135 (9)	23,056 (14)	5,174 (15)
Male, n (%)	600,568 (97)	401,558 (96)	165,430 (98)	33,580 (96)
Race and ethnicity, n (%)				
Black	102,360 (17)	61,705 (15)	32,611 (19)	8,044 (23)
Hispanic	23,828 (4)	14,651 (4)	7,445 (4)	1,732 (5)
White	437,030 (71)	302,458 (73)	112,466 (67)	22,106 (63)
Other or unknown	56,877 (9)	37,768 (9.1)	15,947 (10)	3,162 (9)
BMI, kg/m^2, mean ± SD	29.8 ± 6.0	30.0 ± 5.8	29.5 ± 6.4	28.6 ± 6.7
Smoking, n (%)				
Current	138,128 (22)	97,905 (24)	32,853 (20)	7,370 (21)
Former	342,184 (55)	224,230 (54)	97,692 (58)	20,262 (58)
Never	139,783 (23)	94,447 (23)	37,924 (23)	7,412 (21)
eGFR at onset, mL/min per 1.73 m^2, mean ± SD	51 ± 8	52 ± 7	50 ± 9	46 ± 11
Blood transfusion, n (%)	48,106 (8)	15,165 (4)	20,182 (12)	12,759 (36)
ESA use, n (%)	6,152 (1)	563 (0.1)	2,787 (2)	2,802 (8)
ACEi use, n (%)	351,917 (57)	230,154 (55)	101,439 (60)	20,324 (58)
ARB use, n (%)	82,267 (13)	52,425 (13)	24,908 (15)	4,934 (14)
Charlson score, median (IQR)	2 (1–4)	2 (1–3)	3 (1–4)	4.0 (2–6)
Hypertension, n (%)	561,485 (91)	372,704 (90)	156,466 (93)	32,315 (92)
Depression, n (%)	181,712 (29)	119,641 (29)	50,573 (30)	11,498 (33)
Alcohol abuse, n (%)	55,297 (9)	33,956 (8)	16,375 (10)	4,966 (14)
Drug abuse, n (%)	35,916 (6)	22,753 (6)	10,342 (6)	2,821 (8)
Diabetes, n (%)	303,872 (49)	184,040 (44)	98,654 (59)	21,178 (60)
Heart failure, n (%)	145,429 (234)	81,051 (20)	50,925 (30)	13,453 (38)
Coronary artery disease, n (%)	280,572 (45)	176,155 (42)	86,363 (51)	18,054 (52)
Cardiac dysrhythmia, n (%)	207,783 (34)	128,007 (31)	64,916 (39)	14,860 (42)
Other cardiac disease, n (%)	187,874 (30)	112,237 (27)	60,836 (36)	14,801 (42)
CVA/TIA, n (%)	128,241 (21)	78,507 (19)	40,739 (24)	8,995 (26)
PVD, n (%)	171,268 (28)	102,468 (25)	55,498 (33)	13,302 (38)
COPD, n (%)	183,493 (30)	115,692 (28)	54,603 (32)	13,198 (38)

Characteristic	Overall (n=620,095)	Baseline anemia status		
		Normal (n=416,582)	Mild (n=168,469)	Moderate or severe (n=35,044)
Cancer, n (%)	144,551 (23)	83,376 (20)	47,924 (28)	13,251 (38)
GI bleeding disorders, n (%)	64,653 (10)	32,564 (8)	23,372 (14)	8,717 (25)
Liver disease, n (%)	27,094 (4)	13,874 (3)	9,412 (6)	3,808 (11)
HIV/AIDS, n (%)	4,374 (0.7)	2,746 (0.7)	1,286 (0.8)	342 (1)
UACR, n (%)				
<30 mg/g	93,171 (15)	62,706 (15)	26,245 (16)	4,220 (12)
30–300 mg/g	50,306 (8)	29,936 (7)	16,678 (10)	3,692 (11)
>300 mg/g	15,993 (3)	8,419 (2)	5,919 (4)	1,655 (5)
Missing	460,625 (74)	315,521 (76)	119,627 (7)	25,477 (73)
TSAT, n (%)				
≥20%	66,134 (11)	29,064 (7)	28,986 (17)	8,084 (23)
<20%	46,200 (8)	13,101 (3)	23,735 (14)	9,364 (27)
Missing	507,761 (82)	374,417 (90)	115,748 (69)	17,596 (50)
Hemoglobin (g/dL), mean ± SD	13.6 ± 1.6	14.4 ± 1.0	12.2 ± 0.5	10.2 ± 0.7

Abbreviations: ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disorder; CVA/TIA = cerebrovascular accident/transient ischemic attack; eGFR = estimated glomerular filtration rate; ESA = erythropoiesis stimulating agent, GI = gastrointestinal; HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome; IQR = interquartile range; PVD = peripheral vascular disease; SD=standard deviation TSAT=transferrin saturation; UACR = urinary albumin-to-creatinine ratio

Note: Blood transfusion status, medication use, and comorbidities were based on their presence in the two years prior to the date of incident CKD.

Table 2.

Association between anemia and study outcomes

Baseline anemia status	Event rate, per 1000 patient-years	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]	Time-varying anemia status	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Outcome: Dementia						
Normal	27.4	Reference	Reference	Normal	Reference	Reference
Mild	38.2	1.44 (1.42–1.46)	1.16 (1.14–1.17)	Mild	1.67 (1.65–1.70)	1.30 (1.28–1.31)
Moderate/severe	44.4	1.73 (1.68–1.78)	1.27 (1.23–1.31)	Moderate/severe	2.35 (2.30–2.40)	1.68 (1.65–1.72)
Outcome: Kidney failure or death						
Normal	51.9	Reference	Reference	Normal	Reference	Reference
Mild	93.5	1.82 (1.81–1.84)	1.39 (1.37–1.40)	Mild	2.57 (2.54–2.59)	2.10 (2.08–2.12)
Moderate/severe	184.6	3.63 (3.58–3.69)	2.15 (2.12–2.19)	Moderate/severe	7.32 (7.24–7.40)	5.15 (5.09–5.22)

HR = Hazard ratio.

[a]Model adjusted for baseline age, sex, race and ethnicity, BMI, smoking, eGFR, ESA use, transfusion status, ACEi use, ARB use, Charlson score, hypertension, depression, alcohol abuse, drug abuse, and year of incident CKD.