**Title**

Prevalence, correlates and outcomes of absolute and functional iron deficiency anemia in non-dialysis dependent chronic kidney disease

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**Abstract**

**Background:** Anemia contributes to adverse outcomes in those with chronic kidney disease (CKD). We examined the association of absolute and functional iron deficiency anemia (IDA) with adverse outcomes (hospitalization, dialysis and mortality) in those with CKD

**Methods:** Non-dialysis dependent CKD patients followed in the US Veterans Administration with hemoglobin level measured within 90 days of the date of the second eGFR <60 ml/min/1.73m2 were included. Logistic regression, multivariate Cox proportional hazard and poisson regression models adjusted for demographics and comorbidities were used to assess following outcomes: a) prevalence and correlates of absolute (TSAT < 20%, ferritin <100ng/ml) and functional (TSAT < 20%, ferritin > 100ng/ml) IDA and b) associations of absolute and functional IDA with mortality, dialysis and cardiovascular hospitalization.

**Results:** Out of 933,463 patients with CKD, 79.4% had no anemia, while 21.6% varying degree of anemia. Among patients with anemia, 23.6% of patients had both TSAT and ferritin level measured of whom, 30% had absolute IDA, and 19% had functional IDA. Absolute IDA in CKD was not associated with an increased risk of mortality and dialysis, but a higher risk of 1-year (RR 1.18, 95% CI: 1.11-1.26) and 2-year cardiovascular hospitalization (RR 1.10, 95% CI: 1.04-1.16). CKD patients with functional IDA had a higher risk of mortality (HR 1.11, 95% CI:1.08 - 1.15) along with a higher risk of 1-year (HR 1.17, 95% CI:1.08-1.26) and 2-year cardiovascular hospitalization (HR 1.10, 95% CI: 1.03-1.17) Ferritin > 800 ng/ml (treated as a separate category) was only associated with an increased risk of mortality (HR 1.49, 95% CI: 1.29-1.72).

**Conclusion:** In a large population of CKD patients with anemia, absolute and functional IDA were associated with various clinical covariates. Functional IDA was associated with an increased risk of mortality and cardiovascular hospitalization, but absolute IDA was associated only with higher risk of hospitalization.

**Background**

Chronic kidney disease (CKD) is a public health problem, and numerous complications arise as kidney function starts to decline. Anemia is one of the earliest complications of CKD developing even among those with GFR of < 70 ml/min/1.73m2 and worsens as kidney function continues to decline.1,2 Anemia in CKD is associated with reduced health-related quality of life,3 increased cardiovascular and all-cause mortality,4-6 and a higher risk of progression to end-stage kidney disease (ESKD).6 Several studies have examined the prevalence and consequences of iron deficiency anemia in the dialysis population, but limited data exist on the prevalence and correlates of absolute and functional iron deficiency in non-dialysis dependent CKD7-9. Most of these studies are cross-sectional and include patients with earlier stages of CKD or used self-reported comorbidities and treatment of anemia.

Minutolo et al. prospectively evaluated anemia among 755 prevalent patients with CKD stage 3b-5, and noted that severe anemia (hemoglobin < 11g/dL) was present among 18% of patients at baseline with iron-deficiency present in >60% of them 10. Notably, the prevalence of absolute and functional iron deficiency anemia among non-dialysis dependent CKD population is uncertain. Therefore, we investigated the prevalence and correlates of anemia as well as absolute and functional iron deficiency anemia, among patients with non-dialysis dependent CKD in the Veterans Administration Health System. Further, we also examined the associations of iron deficiency anemia (functional and absolute) with ESKD, mortality, and cardiovascular-related hospitalization in this patient population.

**Materials and Methods:**

*Source population*

We identified patients cared for at the Department of Veterans Affairs from January 1, 2005, to December 31, 2015 and met the following criteria: (1) had at least two outpatient estimated glomerular filtration rates (eGFRs) <60 ml/min/1.73m2 (using the CKD-EPI equation) 11 sustained for >90 days, (2) had a hemoglobin level measured on or within 90 days of the date of the second eGFR < 60 ml/min/1.73m2 and (3) had at least one face-to-face outpatient encounter within the VA system. The CKD index date was taken as the date of confirmation of sustained reduced eGFR. Patients <18 years old and those who were diagnosed with ESKD requiring dialysis or kidney transplant before the confirmation of eGFR < 60 ml/min/1.73 m2 were excluded.

*Study Design*

This is a retrospective, observational study using cross-sectional and longitudinal analyses. The study was approved by the Institutional Review Board of Baylor College of Medicine (H-38697).

*Data Sources*

Demographic characteristics were obtained from the VA Corporate Data Warehouse. We identified comorbid conditions based on classifying *International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification* (ICD-9-CM and ICD-10-CM)diagnostic codes from the VA Inpatient and Outpatient Medical SAS Datasets, using the Deyo-Charlson comorbidity index 12. Outpatient laboratory tests were accessed through the Corporate Data Warehouse LabChem data files. We identified pharmacy medication fills from the VA Pharmacy Benefits Management Database. Dates of death from any cause were obtained from the VA Vital Status Files, through December 31, 2016, and ESKD, defined as the initiation of maintenance dialysis or kidney transplantation, was ascertained from the United States Renal Data System (USRDS). Hospitalization details were obtained from the Inpatient files and Inpatient diagnosis files from the VA corporate data warehouse.

*Definitions*

Anemia was defined as a hemoglobin concentration of <12.0 g/dL in both males and females. KDIGO guidelines define anemia as hemoglobin <13 g/dL in males and <12g/dL in females13 while WHO defines anemia as “a condition in which the number of red blood cells or their oxygen-carrying capacity is insufficient to meet physiologic needs, which vary by age, sex, altitude, smoking, and pregnancy status”.14 Hemoglobin less than 12.0 g/dl but more than 10.0 g/dL was defined as mild; hemoglobin less than 10.0 g/dl but more than 8.0 g/dL was defined as moderate, and severe anemia was defined as hemoglobin less than 8.0 g/dL. Absolute iron deficiency anemia was defined as transferrin saturation (TSAT) < 20% and/or ferritin < 100 ng/mL. Functional iron deficiency anemia was defined as transferrin saturation < 20% and ferritin 100-800 ng/mL. Patients with ferritin level > 800 ng/mL and TSAT < 20% were classified as a separate category as they represent the highest risk of adverse outcomes.

*Outcomes*

The outcomes of interest were: (1) prevalence of absolute and functional iron deficiency anemia in patients with CKD, (2) correlates of absolute and functional iron deficiency anemia in those patients, (3) associations of absolute and functional iron deficiency anemia with ESKD, cardiovascular hospitalization, and death. Cardiovascular hospitalization was defined as hospitalization due to one or more of the five most common cardiovascular conditions- myocardial infarction, stroke, heart failure, coronary atherosclerosis, and atrial fibrillation.15

*Covariates*

Demographics included age, sex, and race/ethnicity categorized as white, black, or other. Body mass index (BMI) was classified into underweight, normal weight, overweight, and obese. We included the following comorbidities: diabetes, congestive heart failure, coronary heart disease, cerebrovascular disease, peripheral arterial disease, chronic obstructive pulmonary disease, and diagnosed hypertension. Details about malignancy, gastrointestinal bleeding, peptic ulcer disease, and inflammatory bowel disease were also included as they often contribute to anemia, even in the absence of CKD. Covariate values were taken as the most recent values before the CKD index date.

*Statistical Analysis*

Absolute numbers and percentages were used to describe the prevalence of mild, moderate and severe anemia, and absolute and functional iron deficiency anemia in CKD patients. Baseline characteristics among those with varying severity of anemia and different types of anemia were compared using chi-squared and ANOVA tests for categorical and continuous variables, respectively. Univariate and multivariate logistic regression models were used to determine the associations of different comorbidities with the presence or absence of anemia, as well as the absolute and functional iron deficiency anemia. To evaluate whether unadjusted survival and ESKD among persons with CKD was associated with iron deficiency anemia (absolute and functional separately), we fitted cumulative incidence functions that adjusted for competing risks using the Fine and Gray method with the date of second eGFR <60 ml/min/1.73 m2 or date of CKD diagnosis as the time of origin. We estimated the cumulative incidence of dialysis initiation and death and the cause-specific incidence of each event. Cox-proportional hazards models were used to calculate cause-specific and sub-distribution hazard ratios for anemia as a cause of dialysis and death. Poisson regression analysis was used to study the associations between iron deficiency anemia and cardiovascular hospitalization. We adjusted for the following covariates in the multivariable models: age, race, gender, BMI group (underweight, normal, overweight and obese), diabetes, hypertension, malignancy, coronary artery disease, congestive heart failure, peripheral vascular disease, liver disease, peptic ulcer disease, gastrointestinal bleeding, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs), baseline hemoglobin, iron supplement and ESA use. Separate analyses were conducted for absolute and functional iron deficiency anemia (vs. no anemia). For missing data, we conducted multiple imputations using the Markov Chain Monte Carlo method and a single chain to impute 20 datasets with complete continuous and binary covariate data. All logistic and competing risk models were performed on each of the 20 imputed datasets, and parameter estimates were combined using SAS MIanalyze. We tested if the associations studied were modified by age, presence or absence of diabetes, presence or absence of CHD, and stage of CKD using the likelihood ratio test. We considered interactions statistically-significant if the P-value for the test of interaction was ≤0.05. Analyses were conducted using SAS Enterprise Guide 7.1 (www.sas.com).

**Results**

*Study cohort*

We included 933,463 veterans who had two eGFR <60 ml/min/1.73 m2 at least 90 days apart and had a hemoglobin level available within 90 days of CKD index date (*Supplemental Figure 1*). Patients with missing vital status information or on dialysis were excluded from this analysis.

*Prevalence of anemia*

Baseline characteristics of the patients stratified according to the degree of anemia are shown in *Table 1*. Out of 933,463 patients with CKD, 79.4% had no anemia, 16.33% had mild anemia, 3.6% had moderate anemia, and 0.5% had severe anemia. Being a VA based analysis, 96.9% were male and 85.9% were Caucasians. *Table 2* categorizes the patients with anemia according to the presence of absolute or functional iron deficiency. Baseline characteristics of the two groups with and without iron profile data are shown in *Supplemental Table 1*. Out of 191,719 patients with anemia, 45,260 (23.6%) patients had both TSAT and ferritin levels measured. Of those with both TSAT and ferritin data, 50% of patients did not have an iron deficiency, 30% had absolute iron deficiency anemia, and 19% of them had a functional iron deficiency. Ferritin level > 800 ng/ml was noted in 1% of patients. Comorbidities were similar among those with absolute and functional iron deficiency anemia. For instance, 28.9% of patients with absolute iron deficiency had a history of malignancy vs. 31.7% of patients with functional iron deficiency. *Supplemental* *Table 2* details TSAT and ferritin level categories for those with anemia and baseline data for both TSAT and ferritin.

*Correlates of anemia*

In the multivariable logistic regression analyses, several factors were associated with the presence and severity of anemia (*Supplemental Tables 3 and 4*) among the patients with CKD. Younger age (<40 years), female sex, African American race, and higher stages of CKD had higher odds of having moderate and severe anemia (*Supplemental Table 3*). Lower BMI (< 18.5 kg/m2) was associated with higher odds of all degrees of anemia, while a higher BMI (>25 kg/m2) had a lower odds (*Supplemental Tables 3 and 4*). Among those with CKD, age >60 years, females, diabetes, obesity, and the presence of various comorbid conditions were associated with higher odds of absolute iron deficiency anemia (*Table 3*). Among those with CKD, advanced stage, diabetes, obesity, and the presence of various comorbid conditions were associated with higher odds of functional iron deficiency anemia (*Table 3*).

*Associations of anemia with outcomes*

*Anemia*

During a median follow up of 3.9 years, 31,635 patients died while during a median follow-up of 3.6 years, 6,117 patients reached end-stage kidney disease. CKD patients with anemia had a higher risk of all-cause mortality (HR 1.58, 95% CI 1.57-1.53) and need for dialysis (HR 1.72, 95% CI 1.67-1.76).

*Absolute and functional iron deficiency anemia*

The cumulative incidence plot of mortality and initiation of dialysis according to the category of iron-deficiency anemia is shown in *Figure 1***.** Absolute iron deficiency anemia in CKD was not associated with mortality and dialysis, but a higher risk of 1-year (RR 1.18, 95% CI: 1.11-1.26) and 2-year cardiovascular hospitalization (RR 1.10, 95% CI: 1.04-1.16) (*Tables 4a and 4b*). On the other hand, CKD patients with functional iron deficiency anemia had a higher risk of mortality (HR 1.11, 95% CI:1.08 - 1.15) along with a higher risk of 1-year (HR 1.17, 95% CI:1.08 - 1.26) and 2-year cardiovascular hospitalization (HR 1.10, 95% CI: 1.03 - 1.17) (*Tables 4a and 4b*). Ferritin > 800 ng/ml was associated with an increased risk of death (HR 1.49, 95% CI: 1.29-1.72) but not associated with dialysis or cardiovascular hospitalization among patients with CKD.

**Discussion**

In an analysis of over 930,000 veterans with CKD, anemia was noted among 1 in 5 patients with CKD at the time of CKD diagnosis. Among those who had iron parameters assessed, approximately 50% of them had either absolute or functional iron deficiency. In addition to baseline CKD severity, several demographic and comorbid factors were associated with absolute and functional iron deficiency anemia. Absolute iron deficiency anemia is associated with a modestly increased risk of 1-year and 2-year cardiovascular hospitalization but not with mortality or risk of dialysis initiation. Functional iron deficiency anemia was associated with a modestly increased risk of mortality and 1-year and 2-year risk of cardiovascular hospitalization, while ferritin > 800 was associated with an increased risk of 1-year and 2-year cardiovascular hospitalization as well as mortality.

Overall, anemia assessed using laboratory data was noted among 20.4% with CKD, but substantially higher among those with stage 3b (91.1%) and stage 4 CKD (96.1%). Using Medicare and commercial insurance claims data, St.Peter and colleagues reported a prevalence of 28% in younger patients (18-63 years) and 51% in older patients (66-85 years).16 McLellan et al. have reported that 47.7% patients with CKD (mean serum creatinine level of 2.2 +/- 0.9 mg/dL) had hemoglobin less than 12g/dL, with 8.9% of patients with hemoglobin less than 10g/dL.9 Other cross-sectional studies have also reported a prevalence of >50-60% in CKD patients10,17,15. Similar to the definition used in our analysis, NHANES III analysis showed an overall prevalence of anemia (using the WHO definition) of 7.3%, with a prevalence of 5.2% for GFR 30-59 ml/min and a prevalence of 44.1% for GFR of 15-29ml/min.18

It is important to note that >75% of patients with anemia did not have iron parameter data, and it is unclear what factors led to iron measurement in some but not others. Lack of standardized definitions of absolute and functional iron deficiency in those with non-dialysis dependent CKD limit comparability with prior studies. For instance, an NHANES analysis (1988-1994) (n=15,837) noted that among those with a creatinine clearance of 20-30 ml/min, 46% of women and 19% of men had a TSAT < 20% while 47% of women and 44% of men had serum ferritin < 100 ng/ml.1 However, patients were not categorized into absolute or functional iron deficiency anemia. Fishbane et al. studied iron indices among 34,782 participants (of whom only 6.6% had CrCl <60 ml/min) included in the 1988-1994 and 1999-2004 NHANES surveys.19 In contrast to our study, iron deficiency defined as TSAT < 20% or ferritin < 100 ng/ml was noted amongst ~ 58% of men and ~ 70% of women.

Studies examining the associations of absolute and functional iron deficiency anemia with outcomes are limited. In an analysis of the PREVEND study cohort (n=975), ferritin, when examined as a continuous variable, was not associated with an increased risk of mortality. However, in a categorical analysis, the highest risk of mortality (HR, 2.56; 95%CI 1.35–4.87) was observed for TSAT< 10% in combination with ferritin cutoffs of either < 200, 300, or 500 μg/L20. A study conducted at 19 Italian renal clinics reported a hospitalization rate of 17.8% in anemic patients compared to 6.6% in those without anemia irrespective of their iron status.10 Kovesdy and colleagues, using data from 453 veterans, reported that higher serum iron saturation ratio (TSAT) was associated with lower mortality and kidney disease progression.21 In our study, the presence of both absolute and functional iron deficiency anemia was associated with an increased risk of cardiovascular hospitalization which poses a significant burden to the CKD population, but only the functional iron deficiency and those with ferritin >800 ng/ml were associated with the highest risk of death.

Anemia in those with CKD is often multifactorial. Although deficiency of erythropoeitin22 , circulating uremic-induced inhibitors23, and reduced life-span of RBCs24 have been implicated, there has been increasing recognition of the role of disordered iron homeostasis as a significant factor in the pathogenesis of anemia of CKD. Absolute iron deficiency can be identified and treated, and this may explain the lack of associations with mortality in our study. The finding of increased mortality in our cohort with functional iron deficiency anemia highlights the systemic inflammation burden and chronic malnutrition in these patients, characterized by the impaired release of iron from reticuloendothelial stores due to hepcidin excess.25 Hepcidin levels rise with the decline in GFR 26 and impair the ferroportin-mediated release of iron from enterocytes and reticuloendothelial system. 27,28 This leads to high tissue ferritin, but inadequate circulating iron available for erythropoiesis. Higher risk of death among those with ferritin >800 ng/nl further supports this proposition.

In this cohort, 25.2% of patients with absolute iron deficiency were using oral iron supplements, while 9.8% of patients with functional iron deficiency were prescribed ESAs. Iron supplements are often obtained over the counter and might explain the underutilization rates. Lower utilization of iron and ESA supplementation in our study is consistent with prior studies. In the study by Minutolo et al., when indicated, iron supplementation was not prescribed in ~ 75% of patients and ESA was not prescribed in ~ 35% of patients.10 A previous retrospective cohort study using VA health records from 2003-2005 demonstrated only 50% of patients with CKD and anemia (hemoglobin < 11g/dL) received treatment, with ~ 8% of patients receiving ESAs.29 In the study by St. Peter et al., only 26-30% of CKD stage 3-5 (not on dialysis) with anemia were treated with at least one type of treatment for anemia (IV iron, ESA or blood transfusion).16 Whether inadequate treatment of functional iron deficiency anemia contributes to the higher mortality cannot be determined from our analysis.

The current study has several strengths, including large sample size, stringent CKD definition requiring sustained reduced eGFR, and the availability of both hemoglobin and iron parameters to define absolute and functional iron deficiency anemia. This analysis also expands the current knowledge regarding the association of absolute and functional iron deficiency anemia with mortality, dialysis, and cardiovascular hospitalization, which has not been adequately addressed in prior studies. However, our study has limitations inherent to an observational retrospective cohort study, including residual confounding, precluding any causal inference. Comprehensive data for iron parameters was lacking; however, we used multiple imputations to address this issue. The majority of patients included in the study were Caucasians and males, and hence generalizability of these data to other population is unclear, and additional studies are warranted. We used TSAT < 20% and ferritin < 100 ng/mL to detect absolute iron deficiency based on current guidelines, 2,13 but there is growing evidence to indicate that ferritin > 100 ng/mL does not rule out absolute iron deficiency and the serum indices of iron may not be a true reflection of body iron stores.30,31 Use of bone marrow biopsy has been proposed as a better alternative to assess iron stores32, but it is also fraught with inaccuracies33 and not available for routine clinical practice. Even in the absence of absolute iron deficiency according to current definitions, iron supplementation may increase the level of hemoglobin and correct anemia.31,34

In summary, our results suggest that absolute and functional iron deficiency anemia pose a significant burden to those with CKD. The risk of adverse outcomes such as hospitalization and mortality is higher with functional iron deficiency anemia, and absolute iron deficiency anemia was associated with a higher risk of hospitalization in CKD. Further studies are needed to examine if correction of absolute iron deficiency anemia and modifying factors that contribute to the functional iron deficiency anemia would improve outcomes in this population.

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**Disclosures:**

Outside the submitted work, Dr. Navaneethan has served on an independent event adjudication committee for clinical trials sponsored by Bayer and Boehringer Ingelheim and served as a consultant to Tricida. Dr. Winkelmayer reports having served as an advisor or consultant, unrelated to the topic of this manuscript, to Akebia/Otsuka, Amgen, Astra-Zeneca, Bayer, Daichii-Sankyo, Relypsa, and Vifor-Fresenius Medical Care Renal Pharma. All other authors have no financial disclosures to report.

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**Table 1** – Baseline characteristics of the study population according to the severity of anemia

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **No anemia** | **Mild anemia** | **Moderate anemia** | | **Severe anemia** | |
|  | **N=741 744** | **N=152 479** | **N=34 070** | | | **N=5170** |
| **Age**  < 40 | 0.2% | 0.2% | 0.3% | 0.4% | | |
| 40 - 49 | 1.2% | 1.2% | 1.8% | 2.1% | | |
| 50 - 59 | 8.1% | 8.7% | 11.6% | 13.3% | | |
| 60 - 69 | 26.2% | 22.6% | 26.2% | 31.1% | | |
| 70 - 79 | 35.7% | 30.9% | 28.5% | 27.6% | | |
| >80 | 28.6% | 36.5% | 31.6% | 25.5% | | |
| **Stage of CKD**  4 | 3.9% | 13.1% | 20.1% | 19.6% | | |
| 3B | 21.9% | 33.6% | 35.7% | 36.4% | | |
| 3A | 74.2% | 53.3% | 44.2% | 44.0% | | |
| **Gender**  Females | 2.8% | 4.3% | 3.5% | 3.4% | | |
| Males | 97.2% | 95.7% | 96.5% | 96.6% | | |
| **Race**  Blacks | 10.0% | 19.7% | 23.9% | 26.5% | | |
| Others | 1.8% | 1.9% | 1.9% | 1.9% | | |
| Whites | 88.1% | 78.4% | 74.1% | 71.6% | | |
| **Diabetes**  No DM | 65.1% | 50.0% | 48.6% | 54.9% | | |
| DM w/o complications | 25.3% | 31.2% | 29.1% | 26.6% | | |
| DM w complications | 9.5% | 18.8% | 22.3% | 18.5% | | |
| Hypertension | 78.6% | 82.3% | 82.1% | 79.1% | | |
| COPD | 18.8% | 22.9% | 26.7% | 28.8% | | |
| Congestive heart failure | 10.0% | 19.3% | 25.8% | 25.8% | | |
| Cerebrovascular disease | 10.2% | 14.0% | 15.1% | 13.8% | | |
| Coronary artery disease | 3.8% | 5.8% | 7.6% | 7.3% | | |
| Peripheral artery disease | 11.0% | 16.3% | 18.8% | 17.7% | | |
| Atherosclerotic cardiovascular disease | 21.3% | 29.2% | 32.6% | 31.0% | | |
| Malignancy | 21.2% | 30.1% | 38.7% | 48.1% | | |
| Gastrointestinal bleeding | 2.4% | 5.0% | 11.1% | 21.7% | | |
| **BMI (kg/m2)**  Missing | 25.4% | 21.0% | 16.5% | 13.7% | | |
| < 18.5 | 0.6% | 1.5% | 2.6% | 3.0% | | |
| 18.5 – 25.0 | 14.6% | 21.8% | 26.4% | 30.6% | | |
| 25 - 30 | 29.6% | 27.9% | 28.4% | 29.3% | | |
| >30 | 29.9% | 27.9% | 26.1% | 23.4% | | |
| ACEI use | 20.5% | 23.7% | 20.9% | 15.0% | | |
| ARB use | 4.1% | 5.4% | 4.5% | 2.5% | | |
| Smoking | 25.6% | 26.6% | 33.3% | 39.8% | | |
| Inflammatory bowel disease | 1.1% | 1.6% | 1.8% | 1.7% | | |
| Liver disease | 1.9% | 4.0% | 8.9% | 13.4% | | |
| Peptic ulcer disease | 1.8% | 2.8% | 4.1% | 5.2% | | |
| Iron supplements | 4.6% | 18.8% | 33.0% | 34.3% | | |
| ESA supplements | 0.6% | 6.4% | 18.8% | 33.1% | | |

BMI: body mass index; ACEI- angiotensin converting enzyme inhibitor; ARB- angiotensin receptor blocker; COPD- chronic obstructive pulmonary disease

**Table 2**- Baseline Characteristics for patient population according to the type of iron deficiency anemia

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variables** |  | | | | |
| **Unmeasured**  **N = 18057** | **No iron deficiency**  **N = 22715** | **Absolute**  **N = 13684** | **Functional**  **N = 8559** | **ferritin > 800**  **N = 302** |
| **Age, years**  < 40 | 0.2% | 0.3% | 0.2% | 0.2% | 0.7% |
| 40 - 49 | 1.4% | 1.6% | 1.3% | 1.9% | 0.7% |
| 50 - 59 | 9.0% | 10.4% | 9.0% | 13.3% | 15.6% |
| 60 - 69 | 23.9% | 23.9% | 27.0% | 28.8% | 32.5% |
| 70 - 79 | 31.4% | 28.8% | 31.4% | 27.9% | 24.8% |
| > 80 | 34.2% | 35.0% | 31.0% | 27.9% | 25.8% |
| **Stage of CKD**  3A | 52.0% | 46.9% | 54.3% | 40.2% | 42.4% |
| 3B | 34.2% | 34.5% | 31.5% | 36.3% | 30.1% |
| 4 | 13.8% | 18.6% | 14.2% | 23.4% | 27.5% |
| **Gender**  Females | 4.1% | 3.0% | 5.6% | 3.0% | 1.3% |
| Males | 95.9% | 97.0% | 94.4% | 97.0% | 98.7% |
| **Race/Ethnicity**  Whites | 78.5% | 75.0% | 79.0% | 70.3% | 62.9% |
| Blacks | 19.7% | 23.1% | 19.0% | 27.5% | 35.8% |
| Others | 1.9% | 1.9% | 2.0% | 2.2% | 1.3% |
| **Diabetes**  No diabetes | 48.6% | 52.0% | 44.6% | 44.4% | 61.9% |
| DM with complications | 31.5% | 27.8% | 32.7% | 29.9% | 19.9% |
| DM without complications | 20.0% | 20.2% | 22.7% | 25.7% | 18.2% |
| Hypertension | 84.0% | 83.5% | 85.1% | 86.0% | 80.8% |
| COPD | 24.9% | 21.8% | 26.6% | 23.4% | 27.5% |
| Congestive heart failure | 21.7% | 18.6% | 23.7% | 25.6% | 20.2% |
| Cerebrovascular disease | 14.7% | 14.2% | 15.3% | 14.9% | 12.9% |
| coronary heart disease | 6.3% | 5.7% | 6.9% | 6.9% | 7.3% |
| Peripheral vascular disease | 17.6% | 16.1% | 18.6% | 19.3% | 23.2% |
| ASCVD | 31.0% | 29.1% | 32.3% | 33.0% | 32.5% |
| Malignancy | 30.7% | 29.9% | 28.9% | 31.7% | 49.0% |
| GI bleeding | 26.3% | 23.1% | 29.5% | 22.2% | 22.2% |
| **BMI, kg/m2**  missing | 17.2% | 18.4% | 17.9% | 16.0% | 15.9% |
| < 18.5 | 1.9% | 1.9% | 1.2% | 1.8% | 5.0% |
| 18.5 - 25 | 23.4% | 25.0% | 19.6% | 23.3% | 33.1% |
| 25 - 30 | 28.7% | 29.3% | 28.5% | 27.1% | 26.8% |
| >30 | 28.8% | 25.3% | 32.8% | 31.8% | 19.2% |
| **ACEI/ARB use**  ACEI | 24.0% | 22.4% | 22.0% | 23.8% | 17.2% |
| ARB | 5.5% | 6.0% | 5.4% | 6.8% | 5.0% |
| Smoking | 28.6% | 28.1% | 30.6% | 30.5% | 36.8% |
| Inflammatory bowel disease | 1.8% | 1.5% | 2.2% | 1.5% | 0.7% |
| Liver disease | 4.6% | 6.8% | 4.9% | 4.7% | 5.3% |
| Peptic ulcer disease | 3.7% | 3.4% | 3.9% | 3.0% | 1.3% |
| Iron supplements | 21.4% | 18.0% | 25.2% | 23.5% | 23.8% |
| ESA use | 5.8% | 7.6% | 5.2% | 9.8% | 20.5% |
| **Nephrology visits**  None | 82.7% | 71.8% | 77.0% | 63.4% | 59.9% |
| 1 | 5.5% | 6.8% | 6.0% | 8.1% | 9.3% |
| >2 | 11.8% | 21.3% | 17.0% | 28.4% | 30.8% |
| **Severity of anemia**  mild anemia | 72.7% | 75.9% | 66.7% | 65.2% | 39.7% |
| mod anemia | 23.2% | 20.8% | 28.2% | 30.5% | 43.4% |
| severe anemia | 4.1% | 3.3% | 5.2% | 4.3% | 16.9% |

BMI: body mass index; ACEI- angiotensin converting enzyme inhibitor; ARB- angiotensin receptor blocker; COPD- chronic obstructive pulmonary disease

**Table 3.** Correlates of absolute and functional iron deficiency anemia in CKD

|  |  |  |
| --- | --- | --- |
| **Variables** | **Absolute iron deficiency anemia** | **Functional iron deficiency anemia** |
| **Age**  < 40 | 0.769 (0.51 - 1.17) | 0.69 (0.42 - 1.14) |
| 40 - 49 | 1.0 (ref) | 1.0 (ref) |
| 50 - 59 | 1.02 (0.86 - 1.21) | 1.08 (0.87 - 1.33) |
| 60 - 69 | 1.31 (1.11 - 1.54) | 1.04 (0.85 - 1.28) |
| 70 - 79 | 1.37 (1.17 - 1.61) | 0.92 (0.75 - 1.12) |
| >80 | 1.13 (0.96 - 1.34) | 0.82 (0.66 - 1.00) |
| **Stage of CKD**  3A | 1.0 (ref) | 1.0 (ref) |
| 3B | 0.80 (0.77 - 0.84) | 1.14 (1.08 - 1.21) |
| 4 | 0.64 (0.61 - 0.68) | 1.26 (1.18 - 1.34) |
| Female gender | 1.73 (1.57 - 1.91) | 1.06 (0.93 - 1.21) |
| **Race**  Whites | 1.0 (ref) | 1.0 (ref) |
| African Americans | 0.75 (0.71 - 0.78) | 1.12 (1.06 - 1.18) |
| Others | 0.90 (0.79 - 1.03) | 1.13 (0.95 - 1.34) |
| **Diabetes**  No Diabetes | 1.0 (ref) | 1.0 (ref) |
| DM without complications | 1.30 (1.25 - 1.36) | 1.23 (1.16 - 1.30) |
| DM with complications | 1.19 (1.14 - 1.26) | 1.36 (1.28 - 1.45) |
| **BMI**  < 18.5 | 0.86 (0.73 - 1.00) | 0.97 (0.81 - 1.16) |
| 18.5 - 25 | 1.0 (ref) | 1.0 (ref) |
| 25 - 30 | 1.19 (1.13 - 1.25) | 1.02 (0.95 - 1.08) |
| >30 | 1.50 (1.42 - 1.58) | 1.31 (1.23 - 1.40) |
| missing | 1.20 (1.13 - 1.28) | 0.97 (0.89 - 1.04) |
| Malignancy | 0.93 (0.89 - 0.97) | 1.02 (0.97 - 1.07) |
| COPD | 1.27 (1.21 - 1.32) | 1.08 (1.02 - 1.15) |
| Hypertension | 1.10 (1.04 - 1.16) | 1.17 (1.10 - 1.25) |
| Congestive heart failure | 1.27 (1.22 - 1.33) | 1.38 (1.31 - 1.46) |
| Coronary artery disease | 1.17 (1.09 - 1.27) | 1.17 (1.06 - 1.29) |
| Peripheral vascular disease | 1.15 (1.09 - 1.20) | 1.21 (1.14 - 1.29) |
| ACEI/ARB use | 1.0 (ref) | 1.0 (ref) |
| ACEI | 1.02 (0.98 - 1.07) | 1.14 (1.07 - 1.20) |
| ARB | 0.95 (0.87 - 1.03) | 1.17 (1.06 - 1.29) |
| Iron supplement use | 1.46 (1.39 - 1.53) | 1.29 (1.21 - 1.37) |
| ESA use | 0.63 (0.58 - 0.68) | 1.09 (1.00 - 1.19) |
| Peptic ulcer disease | 1.41 (1.23 - 1.62) | 1.04 (0.85 - 1.27) |
| Inflammatory bowel disease | 1.41 (1.23 - 1.62) | 1.04 (0.85 - 1.27) |
| Liver disease | 0.67 (0.61 - 0.73) | 0.65 (0.59 - 0.72) |
| GI bleeding | 1.35 (1.29 - 1.42) | 0.97 (0.20 - 1.03) |
| **Severity of anemia**  mild anemia | 1.0 (ref) | 1.0 (ref) |
| moderate anemia | 1.39 (1.33 - 1.46) | 1.38 (1.30 - 1.46) |
| severe anemia | 1.53 (1.39 - 1.68) | 1.00 (0.87 - 1.13) |

BMI: body mass index; ACEI- angiotensin converting enzyme inhibitor; ARB- angiotensin receptor blocker; COPD- chronic obstructive pulmonary disease

**Table 4A.** Associations of absolute and functional iron deficiency anemia with all-cause mortality in those with CKD

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Variable** | **Cause-specific hazard\*** | |
| **Outcome** | **HR & 95% CI** | **p-value** |
| Death | No iron deficiency | 1.0 (ref) |  |
|  | Absolute | 1.01 (0.98 - 1.04) | 0.45 |
|  | Functional | 1.12 (1.08 - 1.15) | <.0001 |
|  | Ferritin > 800 | 1.64 (1.41 - 1.90) | <.0001 |
|  |  |  |  |
| Dialysis | No iron deficiency | 1.0 (ref) |  |
|  | Absolute | 0.95 (0.89 - 1.02) | 0.13 |
|  | Functional | 1.01 (0.94 - 1.08) | 0.75 |
|  | Ferritin > 800 | 1.24 (0.92 - 1.67) | 0.16 |
|  |  |  |  |

\*Adjusted for age, race, gender, BMI group (underweight, normal, overweight and obese), diabetes, hypertension, malignancy, coronary artery disease, congestive heart failure, peripheral vascular disease, liver disease, peptic ulcer disease, gastrointestinal bleeding, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs), baseline hemoglobin, iron supplement and ESA use

**Table 4b.** Associations of absolute and functional iron deficiency anemia with 1-year and 2-year cardiovascular hospitalization in those with CKD\*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **1 year** | | **2 years** | |
| **RR & 95% CI** | **p-value** | **RR & 95% CI** | **p-value** |
| No iron deficiency | 1.0 (ref) |  | 1.0 (ref) |  |
| Absolute | 1.18 (1.11 - 1.26) | <.0001 | 1.10 (1.04 - 1.16) | 0.0005 |
| Functional | 1.17 (1.08 - 1.26) | <.0001 | 1.10 (1.03 - 1.17) | 0.003 |
| Ferritin > 800 | 0.79 (0.51 - 1.24) | 0.31 | 0.85 (0.61 - 1.19) | 0.34 |

\*Models adjusted for age, race, gender, BMI group (underweight, normal, overweight and obese), diabetes, hypertension, malignancy, coronary artery disease, congestive heart failure, peripheral vascular disease, liver disease, peptic ulcer disease, gastrointestinal bleeding, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs), baseline hemoglobin, iron supplement and ESA use

**Figure 1a and 1b**- Cumulative incidence of mortality and dialysis initiation according to the category of iron deficiency anemia



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