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Original Article

J Hematol. 2021;10(6):233-245

Impact of Correcting Nutritional Deficiency Anemias in the Elderly on Hospitalizations, Falls, and Mortalities

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Abstract

Background: The incidence and prevalence of anemia increase with age, particularly in adults older than 65 years, and it is associated with a number of adverse health outcomes (AHO), particularly hospitalizations, falls and mortalities. Given that approximately one-third of these anemias are due to reversible causes, we studied whether the treatment of nutritional deficiency anemia (NDA), namely iron deficiency anemia (IDA), cobalamin deficiency anemia (CDA), and folate deficiency anemia (FDA), improves AHO; and explored whether each NDA had different AHO.

Methods: We reviewed electronic medical records of our internal medicine office patients aged 65 years or older, who had a diagnosis of anemia in a non-acute setting.

Results: Total 600 patients were included. Mean age was 75.2 years. Thirty-one point three percent had NDA (CDA 15.3%, IDA 12.3%, FDA 3.7%); and 68.7% had other anemias whom we categorized as non-nutritional deficiency anemias (NNDA), which included anemia of chronic disease (11.2%), myelodysplastic syndrome (6.2%), renal insufficiency anemia (5.7%) and unexplained anemia (45.6%). Even after adequate treatment, IDA group had significantly more hospitalizations (median, 25th - 75th: 2 (0 - 4) vs. 0 (0 - 1), P < 0.001), falls (median, 25th - 75th: 1 (0 - 3) vs. 0 (0 - 1), P < 0.001) and mortalities (10.8% vs. 3.4%, P = 0.011); CDA group had significantly more hospitalizations (median, 25th - 75th: 1 (0 - 2) vs. 0 (0 - 1), P = 0.007), but no difference in falls (median, 25th - 75th: 0 (0 - 1) vs. 0 (0 - 1), P = 0.171) and mortalities (7.6% vs. 3.4%, P = 0.083); and FDA group had significantly more hospitalizations (median, 25th - 75th: 1 (0 - 2) vs. 0 (0 - 1), P = 0.001), but no difference in falls (median, 25th - 75th: 0 (0 - 1) vs. 0 (0 - 1), P = 0.615) and mortalities (4.5% vs. 3.4%, P = 0.550), compared to the NNDA group. Age, Black race, higher number of comorbidities, presence of malignancy and use of direct oral anticoagulants were associated with increased odds of AHO in patients with NDA.

Conclusions: Compared to the patients with NNDA, patients with IDA had more hospitalizations, falls and mortalities even after adequate treatment; while patients with CDA and FDA had only more hospitalizations. Adequate treatment mitigated falls and mortalities in elderly patients with CDA and FDA.

Keywords: Anemia; Elderly; Iron deficiency; Vitamin B12 deficiency; Cobalamin deficiency; Folate deficiency; Nutritional deficiency anemias

Manuscript submitted September 25, 2021, accepted December 2, 2021
Published online December 8, 2021

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doi: https://doi.org/10.14740/jh926

Introduction

Anemia is a common problem in people over the age of 65. It has been reported that both the incidence and prevalence of anemia increase with age [1]. The etiology of anemia in the elderly is often complex, given the high frequency of comorbidities, poly-pharmacotherapy and hospitalizations due to other comorbid medical diagnoses. The predominant causes of anemia in elderly patients include anemia of chronic disease, such as inflammatory anemia; unexplained anemia; nutritional deficiency anemias (NDAs), such as iron, cobalamin, or folate deficiencies; and chemotherapy or radiotherapy-induced anemia [2].

About one-third of the cases of anemias in the elderly population are due to reversible causes, such as NDA, which includes iron deficiency anemia (IDA), cobalamin deficiency anemia (CDA) and folate deficiency anemia (FDA) [1]. More notably, anemias in the elderly have been shown to be associated with a number of adverse health outcomes (AHO), such as falls [3], dementia [4], cardiovascular diseases [5, 6], increased hospitalizations [7], functional decline [8], and increased mortality [2, 7, 9-11]. It has been speculated that anemia in the elderly population leads to major physical decline due to suboptimal oxygen delivery to the brain, heart, muscles, and tissue [12]. It has not yet been elucidated whether correction of NDA in the elderly would influence, or prevent the AHO, especially hospitalizations, falls, and mortalities.

Our objective was to examine whether the treatment of NDA (IDA, CDA, and FDA) could decrease the frequencies of AHO, especially falls, hospitalizations, and mortalities in elderly patients. We also explored whether IDA, CDA, and FDA had different frequencies of AHO. We hypothesized that treatment of NDA would be associated with decreased frequencies of falls, hospitalizations, and mortalities in elderly patients.

Materials and Methods

Study design and setting

Our study was a retrospective review of the electronic medical records of patients who received medical care in our outpatient internal medicine office between July 1, 2010 and September 30, 2020.

Participants

Patients aged 65 years or older, who had a diagnosis of anemia in a non-acute setting, that was documented in their problem list or diagnosis field of their medical record based on the following search criteria: IDA (International Classification of Diseases 10th Revision (ICD-10): D50.9), CDA or vitamin B12 deficiency anemia (ICD-10: D51.9), FDA (ICD-10: D52.9), renal insufficiency anemia (ICD-10: D63.1), anemia of chronic disease (ICD-10: D63), anemia in myelodysplastic syndrome (ICD-10: D46.9), and unexplained anemia or anemia unspecified (ICD-10: D64.9). We excluded patients who were under the age of 65 years, or who did not have anemia, or if the anemia was diagnosed in an acute care setting, or if they had more than one type of anemia.

Variables

We collected the following data on each patient: age, sex, race, cigarette smoking, alcohol use, body mass index (BMI), hemoglobin level (> 14 g/dL, 11 - 13.9 g/dL, 8 - 10.9 g/dL, and < 8.0 g/dL), associated medical conditions, such as diabetes mellitus (DM), hypertension, hypothyroidism, chronic kidney disease (CKD), malignancy, rheumatologic disease, liver disease, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and coronary artery disease (CAD), total number of comorbidities; other related lab values such as serum iron, total iron binding capacity (TIBC), ferritin, folic acid, cobalamin, methyl malonic acid, homocysteine; treatment with erythropoietic agent (erythropoietin); treatment with medications that could have caused bleeding or blood loss, such as aspirin, clopidogrel, vitamin K antagonists (VKA), and direct oral anticoagulants (DOAC); and AHO, such as hospitalizations, falls, and mortality.

Data source and access

This study was reviewed and approved by the Institutional Review Board of the Cooper University Health Care (CUHC) System, Camden, New Jersey, USA. Permission was granted to use materials that were collected solely for research study purposes as per the Health Insurance Portability and Accountability Act (HIPPA) requirements, and the informed consent waivers were granted by the Institutional Review Board. This study was fully compliant with the ethical standards set forth by the CUHC institutional review board. All investigators had full access to the data available only in the electronic medical records of the list of patients approved by the medical informatics of the CUHC, who were selected based on the selection criteria of the study.

Bias

To address the potential for unmeasured confounding associated with the risk for falls, we excluded patients who had known comorbidity that could predispose to falls, such as cerebrovascular accidents, dementia, Parkinson's disease, musculoskeletal disorders associated with gait instability, other degenerative disorders of central nervous system, autonomic dysfunction, benign positional vertigo or other vertiginous disorders, cardiac arrhythmias including atrial fibrillation, postural hypotension; and patients who were on psychotropic medications, such as anti-anxiety agents, antidepressants, antipsychotics, mood stabilizers, and central nervous system stimulants, or on Drug Enforcement Administration (DEA) schedule II - V medications that could lead to falls due to the medication associated adverse effects.

Study size

A sample size of 588 or greater was selected in order to achieve the sample that would provide 80% power and 5% alpha error. It was based on the study performed by Penninx and colleagues [13].

Statistical methods

We entered the patient data in a Microsoft Excel (2019, Redmond, Washington, USA) spreadsheet and analyzed them using SPSS (Statistical Package for the Social Sciences, version 27.0, IBM, Armonk, New York, USA). We divided our group of patients into NDA (which included IDA, CDA and FDA) groups, and other anemias, whom we categorized as non-nutritional deficiency anemias (NNDA) group. We compared IDA group with NNDA group, CDA group with NNDA group, and FDA group with NNDA group. We used Mann Whitney U test for the data that was non-parametric (not normally distributed). We applied Chi-square tests to test mortalities. To test the number of falls and hospitalizations, we first used Shapiro Wilk test and test of skewness, and then applied independent *t*-tests for the data that was normally distributed. In order to examine the relationship between treatment of anemia and the outcomes with respect to other factors, we performed multivariate logistic regression models. Variables were dichotomized for falls

Table 1. Baseline Characteristics of All Patients

Age (years), mean (SD)	75.2 (7.8)
Gender	
Male, n (%)	206 (34.3)
Female, n (%)	394 (65.7)
Race	
White, n (%)	450 (75.0)
Black, n (%)	72 (12.0)
Hispanic, n (%)	29 (4.8)
Other, n (%)	49 (8.2)
Type of anemia	
Iron deficiency, n (%)	74 (12.3)
Cobalamin deficiency, n (%)	92 (15.3)
Folate deficiency, n (%)	22 (3.7)
Anemia of chronic disease, n (%)	67 (11.2)
Myelodysplastic syndrome, n (%)	37 (6.2)
Renal insufficiency anemia, n (%)	34 (5.7)
Unexplained anemia, n (%)	274 (45.6)

SD: standard deviation.

and hospitalizations. The dependent variables were mortality, fall (dichotomized) and hospitalizations (dichotomized). The independent variables were those that were significant at the $P \leq 0.1$ in the univariate analysis. In this study, significance was defined as a $P < 0.05$.

Results

A total of 600 patients were included. The mean age of all the patients was 75.2 years. About two-thirds of the patients were female. Majority of the patients identified as White (75.0%), while the remaining patients identified as Black (12.0%), Hispanic (4.8%), or other races (8.2%).

The majority of the patients had unexplained anemia (45.6%), followed by CDA (15.3%), IDA (12.3%) and anemia of chronic disease (11.2%). A lower proportion of patients had anemia due to myelodysplastic syndrome (6.2%), renal insufficiency (5.7%) and FDA (3.7%) (Table 1). Overall, approximately one-third of the patients had NDA (31.3%) while the remaining 68.7% had NNDA. Among the patients with NDA, the majority had CDA (48.9%), followed by IDA (39.4%) and FDA (11.7%).

Characteristics of patients with CDA

The mean serum cobalamin level of patients with CDA was 67.9 ± 28.1 pg/mL at the time of their initial diagnosis. All patients were initially treated with intramuscular injections of cyanocobalamin followed by oral, or sublingual cyanocobalamin maintenance therapy. The mean post-treatment serum cobalamin level was 541.5 ± 101.2 pg/mL. The mean age of the patients in the CDA group was significantly higher than the mean age of the patients in the NNDA group (76.6 years vs. 74.3 years; $P = 0.008$), (Table 2). The mean BMIs of both the groups were in the overweight range and were comparable. Although there were more females than males in both the groups, there was no statistically significant difference in the frequencies between the two groups. Analysis of race revealed that the majority of the patients in the CDA group identified as White (75.1%), while the remaining patients identified as Black (16.3%), Hispanic (4.3%) and other races (4.3%). Similarly, the majority of the patients in the NNDA group identified as White (79.9%), while the remaining patients identified as Black (9.1%), Hispanic (3.7%) and other races (7.3%). There was no statistically significant difference in the race distribution between the two groups. Among the social factors, the frequency of cigarette smoking was higher in the CDA group compared to the NNDA group (44.5% vs. 42.2%), but the difference was not statistically significant. Similarly, the frequency of alcohol consumption was higher in the CDA group compared to the NNDA group (48.9% vs. 44.9%), but the difference was not statistically significant, either (Table 2).

Analysis of the associated comorbid medical conditions revealed that the patients with CDA had significantly higher mean number of comorbid medical diagnoses compared to the NNDA group (2.7 vs. 1.9, $P < 0.001$). The frequencies of hypertension, CKD, malignancies, CHF, COPD, and CAD were significantly higher in the CDA group compared to the NNDA group (78.3% vs. 65.9%, 22.8% vs. 13.9%, 33.7% vs. 23.7%, 13.0% vs. 5.6%, 14.1% vs. 7.1%, and 31.5% vs. 18.3%, respectively) (Table 2). There were no significant differences in the frequencies of other comorbid medical conditions between the two groups, such as DM, hypothyroidism, rheumatological disease and liver disease (Table 2).

The majority of the patients with CDA had their hemoglobin level in the 11 - 13.9 g/dL range (69.6%), followed by equal or greater than 14 g/dL (17.4%), and 8 - 10.9 g/dL (13.0%) ranges. No one had a hemoglobin in the less than 8 g/dL range. Similarly, the majority of the patients in the NNDA group had their hemoglobin level in the 11 - 13.9 g/dL range (55.7%), followed by equal or greater than 14 g/dL (38.9%), 8 - 10.9 g/dL (4.9%) and less than 8 g/dL (0.5%) ranges. The differences were statistically significant between the two groups (Table 2). Among the use of medications that could have influenced the level of anemia, we found that there were no statistically significant differences between the frequencies of use of erythropoietin, aspirin, clopidogrel, VKA, and DOAC between the CDA and NNDA groups (Table 2).

In the comparative analysis of the AHO, we found that the number of hospitalizations in the CDA group was significantly greater than the NNDA group (median, 25th - 75th: 1 (0 - 2) vs. 0 (0 - 1), $P = 0.007$) even after adequate treatment of CDA. The number of falls were comparable to the NNDA group (median, 25th - 75th: 1 (0 - 1) vs. 0 (0 - 1), $P = 0.171$). The patients in the CDA group had higher mortalities compared to the NNDA group, but the difference was not statistically significant (7.6% vs. 3.4%, $P = 0.083$) (Table 2).

Logistic regression analysis models for hospitalizations, falls and mortalities in the CDA group of patients revealed

Table 2. Characteristics of Patients With Cobalamin Deficiency Anemia

Variable	CDA (n = 92)	NNDA (n = 412)	P
Age, mean (SD)	76.6 (8.2)	74.3 (7.4)	0.008
BMI, mean (SD)	28.3 (5.52)	28.4 (6.0)	0.903
Gender			
Male, n (%)	41 (44.6)	144 (35.0)	0.084
Female, n (%)	58 (71.9)	268 (65.0)	
Race			
White, n (%)	69 (75.1)	327 (79.9)	0.165
Black, n (%)	15 (16.3)	38 (9.1)	
Hispanic, n (%)	4 (4.3)	16 (3.7)	
Other, n (%)	4 (4.3)	31 (7.3)	
Social factors			
Cigarettes, n (%)	41 (44.5)	174 (42.2)	0.058
Alcohol, n (%)	45 (48.9)	184 (44.9)	0.483
Comorbidities			
Number of comorbidities, mean (SD)	2.7 (1.8)	1.9 (1.4)	< 0.001
Diabetes mellitus, n (%)	27 (29.3)	100 (24.4)	0.329
Hypertension, n (%)	72 (78.3)	270 (65.9)	0.021
Hypothyroid, n (%)	26 (28.3)	94 (22.9)	0.278
CKD, n (%)	21 (22.8)	57 (13.9)	0.033
Malignancy	31 (33.7)	98 (23.7)	0.046
Rheumatologic disease, n (%)	12 (13.0)	47 (11.2)	0.104
Liver disease, n (%)	5 (5.4)	12 (2.7)	0.174
CHF, n (%)	12 (13.0)	23 (5.6)	0.011
COPD, n (%)	13 (14.1)	29 (7.1)	0.027
CAD, n (%)	29 (31.5)	75 (18.3)	0.005
Lab values			
Hb < 8 g/dL, n (%)	0 (0.0)	2 (0.5)	< 0.001
Hb 8 - 10.9 g/dL, n (%)	12 (13.0)	21 (4.9)	
Hb 11 - 13.9 g/dL, n (%)	64 (69.6)	229 (55.7)	
Hb ≥ 14 g/dL, n (%)	16 (17.4)	160 (38.9)	
Medications			
Erythropoietin, n (%)	0 (0.0)	3 (0.7)	1.000
Aspirin, n (%)	45 (48.9)	163 (39.6)	0.102
Clopidogrel, n (%)	5 (5.4)	13 (3.2)	0.347
VKA, n (%)	6 (6.5)	14 (3.4)	0.232
DOAC, n (%)	9 (9.8)	32 (7.8)	0.536
Outcome			
Hospitalization (median, 25th - 75th)	1 (0 - 2)	0 (0 - 1)	0.007
Fall (median, 25th - 75th)	0 (0 - 1)	0 (0 - 1)	0.171
Mortality, n (%)	7 (7.6)	14 (3.4)	0.083

CDA: cobalamin deficiency anemia; NNDA: non-nutritional deficiency anemia; SD: standard deviation; CKD: chronic kidney disease; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; Hb: hemoglobin; VKA: vitamin K antagonist; DOAC: direct oral anticoagulant.

that for each unit increase in age, there were 1.03 times greater odd of falls (95% confidence interval (CI): 1 - 1.1; P = 0.005) and 1.1 times greater odds of mortality (95% CI: 1.1 - 1.2, P < 0.001). When compared to Whites, Blacks had 2 times greater odds of hospitalization (95% CI: 1.1 - 3.5; P = 0.021), and compared to Whites, Hispanic race had lower odds of falls (odds ratio (OR): 0.233, 95% CI: 0.068 - 0.797; P = 0.020). Patients who consumed alcohol had lower odds of falls (OR: 0.603, 95% CI: 0.415 - 0.876; P = 0.008). Comorbid medical diagnoses analysis showed that for every unit increase in number of comorbidities, there were 1.8 times greater odds of hospitalizations (95% CI: 1.5 - 2.1; P < 0.001), 1.2 times greater odds of falls (95% CI: 1 - 1.3; P = 0.012), and 1.5 times greater odds of mortality (95% CI: 1.1 - 2; P = 0.009). Patients with rheumatologic disease had reduced odds of hospitalizations (OR: 0.484, 95% CI: 0.272 - 0.860; P = 0.013), while patients with malignancy had 3.1 time greater odds of mortality (95% CI: 1.3 - 7.6; P = 0.012). When compared to those with hemoglobin level of 14 g/dL or greater, those with hemoglobin level less than 8 g/dL had 53 times greater odds of mortality (95% CI: 4.5 - 617.2; P = 0.002). Additionally, patients on DOAC had 2 times greater odds of hospitalizations (95% CI: 1 - 4; P = 0.041).

Characteristics of patients with IDA

The mean serum iron level of patients in the IDA group was 33.1 ± 28.1 µg/dL, mean transferrin saturation was 10.4±2.7%, and mean serum ferritin level was 15.2 ± 4.7 ng/mL at the time of their initial diagnosis. All patients received iron treatment, either oral (52.5%), intravenous (31.7%), or intravenous followed by oral (15.8%). Post treatment mean serum iron level was 92.5 ± 11.5 µg/dL, mean transferrin saturation was 26.3±7.1%, and mean serum ferritin level was 102.9 ± 29.6 ng/mL. The mean age of the patients in the IDA group was significantly higher than the mean age of the patients in the NNDA group (78.2 years vs. 74.3 years; P < 0.001) (Table 3). The mean BMIs of both the groups were in the overweight range and were comparable. There were significantly more females than males in both the groups, especially in the IDA group, in which about three-quarters of the patients were females (Table 3). Analysis of race revealed that the majority of the patients in the IDA group identified as White (73.0%), while the remaining patients identified as Black (13.4%), Hispanic (6.8%) and other races (6.8%). There was no statistically significant difference in the race distribution between the IDA and NNDA groups. Among the social factors, the frequency of cigarette smoking was lower in the IDA group compared to the NNDA group (37.8% vs. 42.2%), but the difference was not statistically significant. Similarly, the frequency of alcohol consumption was lower in the IDA group compared to the NNDA group, however the difference was statistically significant (24.3% vs. 44.9%, P < 0.001) (Table 3).

Analysis of the associated comorbid medical conditions revealed that the patients with IDA had significantly higher number of comorbid medical diagnoses compared to the NNDA group (2.7 vs. 1.9, P < 0.001). The frequencies of hypertension, CKD, and CHF were significantly higher in the IDA group compared to the NNDA group (81.1% vs. 65.9%, 32.4% vs. 13.9%, and 20.3% vs. 5.6%, respectively) (Table 3). There were no statistically significant differences in the frequencies of other comorbid medical conditions between the two groups, such as DM, hypothyroidism, malignancy, rheumatological disease, liver disease, COPD and CAD (Table 3).

The majority of the patients in the IDA group had their hemoglobin level in the 11 - 13.9 g/dL range (62.2%), followed by 8 - 10.9 g/dL (32.4%), equal or greater than 14 g/dL (2.7%), and less than 8 g/dL range (2.7%). The differences were statistically significant between the IDA and NNDA groups (Table 3). Among the use of medications that could have influenced the level of anemia, we found that there were no statistically significant differences between the frequencies of use of erythropoietin, aspirin, clopidogrel, VKA, and DOAC between the IDA and NNDA groups (Table 3).

In the comparative analysis of the AHO, we found significantly higher number hospitalizations(median, 25th - 75th: 2 (0 - 4) vs. 0 (0 - 1), P < 0.001), number of falls (median, 25th - 75th: 1 (0 - 3) vs. 0 (0 - 1), P < 0.001) and mortalities (10.8% vs. 3.4%, P = 0.011) in the IDA group compared to the NNDA group, even after adequate treatment of IDA (Table 3).

Logistic regression analysis models for hospitalizations, falls and mortalities in the IDA group of patients revealed that for each unit increase in age, there were 1.03 times greater odd of falls (95% CI: 1 - 1.1; P = 0.011) and 1.1 times greater odds of mortality (95% CI: 1.1 - 1.2, P < 0.001). When compared to Whites, Blacks had 1.9 times greater odds of hospitalization (95% CI: 1.1 - 3.4; P = 0.027), and compared to Whites, Hispanic race had lower odds of falls (OR: 0.204, 95% CI: 0.058 - 0.717; P = 0.013). Patients who consumed alcohol had lower odds of falls (OR: 0.658, 95% CI: 0.452 - 0.958; P = 0.029). Comorbid medical diagnoses analysis showed that for every unit increase in number of comorbidities, there were 1.8 times greater odds of hospitalizations (95% CI: 1.5 - 2.1; P < 0.001), 1.2 times greater odds of falls (95% CI: 1 - 1.3; P = 0.012), and 1.5 times greater odds of mortality (95% CI: 1.1 - 2; P = 0.007). Patients with rheumatologic disease had reduced odds of hospitalizations (OR: 0.477, 95% CI: 0.267 - 0.851; P = 0.012), while patients with malignancy had 3.1 time greater odds of mortality (95% CI: 1.2 - 7.5; P = 0.015). When compared to those with hemoglobin level of 14 g/dL or greater, those with hemoglobin level less than 8 g/dL had 48.1 times greater odds of mortality (95% CI: 3.9 - 594.1; P = 0.003). Additionally, patients on DOAC had 2.3 times greater odds of hospitalizations (95% CI: 1 - 4; P = 0.042).

Characteristics of patients with folate deficiency anemia

The mean serum folate level of patients in the FDA group was 1.6 ± 0.3 ng/mL at the time of their initial diagnosis. All patients with FDA received oral folic acid treatment. Post treatment mean serum folate level was 23.5 ± 4.8 ng/mL. The mean age of the patients in the FDA group was comparable to the patients in the NNDA group (77.2 years vs. 74.3 years; P = 0.073) (Table 4). The mean BMIs of both the groups were in the overweight range and were comparable. There were significantly more females than males in both the groups, especially in the FDA group in which about four-fifths of the patients

Table 3. Characteristics of Patients With Iron Deficiency Anemia

Variable	IDA (n = 74)	NNDA (n = 412)	P
Age, mean (SD)	78.2 (8.6)	74.3 (7.4)	< 0.001
BMI, mean (SD)	28.2 (6.2)	28.4 (6.0)	0.769
Gender			
Male, n (%)	17 (23.0)	144 (35.0)	0.044
Female, n (%)	57 (77.0)	268 (65.0)	
Race			
White, n (%)	54 (73.0)	327 (79.9)	0.374
Black, n (%)	10 (13.4)	38 (9.1)	
Hispanic, n (%)	5 (6.8)	16 (3.7)	
Other, n (%)	5 (6.8)	31 (7.3)	
Social factors			
Cigarettes, n (%)	28 (37.8)	174 (42.2)	0.122
Alcohol, n (%)	18 (24.3)	184 (44.9)	< 0.001
Comorbidities			
Number of comorbidities, mean (SD)	2.7 (1.6)	1.9 (1.4)	< 0.001
Diabetes mellitus, n (%)	25 (33.8)	100 (24.4)	0.092
Hypertension, n (%)	60 (81.1)	270 (65.9)	0.010
Hypothyroid, n (%)	13 (17.6)	94 (22.9)	0.307
CKD, n (%)	24 (32.4)	57 (13.9)	< 0.001
Malignancy	24 (32.4)	98 (23.7)	0.109
Rheumatologic disease, n (%)	10 (13.5)	47 (11.2)	0.570
Liver disease, n (%)	5 (6.8)	12 (2.7)	0.081
CHF, n (%)	15 (20.3)	24 (5.6)	< 0.001
COPD, n (%)	9 (12.2)	29 (7.1)	0.134
CAD, n (%)	14 (18.9)	75 (18.3)	0.898
Lab values			
Hb < 8 g/dL, n (%)	2 (2.7)	2 (0.5)	< 0.001
Hb 8 - 10.9 g/dL, n (%)	24 (32.4)	21 (4.9)	
Hb 11 - 13.9 g/dL, n (%)	46 (62.2)	229 (55.7)	
Hb ≥ 14 g/dL, n (%)	2 (2.7)	160 (38.9)	
Medications			
Erythropoietin, n (%)	3 (4.1)	3 (0.7)	0.049
Aspirin, n (%)	29 (39.2)	163 (39.6)	0.946
Clopidogrel, n (%)	5 (6.8)	13 (3.2)	0.172
VKA, n (%)	1 (1.4)	14 (3.4)	0.486
DOAC, n (%)	7 (9.5)	32 (7.8)	0.635
Outcome			
Hospitalization, median (25th - 75th)	2 (0 - 4)	0 (0 - 1)	< 0.001
Fall, median (25th - 75th)	1 (0 - 3)	0 (0 - 1)	< 0.001
Mortality, n (%)	8 (10.8)	14 (3.4)	0.011

IDA: iron deficiency anemia; NNDA: non-nutritional deficiency anemia; SD: standard deviation; CKD: chronic kidney disease; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; Hb: hemoglobin; VKA: vitamin K antagonist; DOAC: direct oral anticoagulant.

Table 4. Characteristics of Patients With Folate Deficiency Anemia

Variable	FDA (n = 22)	NNDA (n = 412)	P
Age, mean (SD)	77.2 (7.6)	74.3 (7.4)	0.073
BMI, mean (SD)	29.9 (5.4)	28.4 (6.0)	0.257
Gender			
Male, n (%)	4 (18.2)	144 (35.0)	0.106
Female, n (%)	18 (81.8)	268 (65.0)	
Race			
White, n (%)	16 (72.7)	327 (79.9)	0.163
Black, n (%)	4 (18.2)	38 (9.1)	
Hispanic, n (%)	2 (9.1)	16 (3.7)	
Other, n (%)	0 (0.0)	31 (7.3)	
Social factors			
Cigarettes, n (%)	11 (50.0)	174 (42.2)	0.731
Alcohol, n (%)	9 (40.9)	184 (44.9)	0.715
Comorbidities			
Number of comorbidities, mean (SD)	2.1 (0.9)	1.9 (1.4)	0.535
Diabetes mellitus, n (%)	5 (22.7)	100 (24.4)	0.885
Hypertension, n (%)	15 (68.2)	270 (65.9)	0.822
Hypothyroid, n (%)	6 (27.3)	94 (22.9)	0.638
CKD, n (%)	1 (4.5)	57 (13.9)	0.336
Malignancy	7 (31.8)	98 (23.7)	0.383
Rheumatologic disease, n (%)	2 (9.1)	47 (11.2)	1.000
Liver disease, n (%)	2 (9.1)	12 (2.7)	0.137
CHF, n (%)	1 (4.5)	23 (5.6)	1.000
COPD, n (%)	3 (13.6)	29 (7.1)	0.217
CAD, n (%)	4 (18.2)	75 (18.3)	1.000
Lab values			
Hb < 8 g/dL, n (%)	0 (0.0)	2 (0.5)	0.298
Hb 8 - 10.9 g/dL, n (%)	1 (4.5)	21 (4.9)	
Hb 11 - 13.9 g/dL, n (%)	8 (36.4)	229 (55.7)	
Hb ≥ 14 g/dL, n (%)	13 (59.1)	160 (38.9)	
Medications			
Erythropoietin, n (%)	0 (0.0)	3 (0.7)	1.000
Aspirin, n (%)	10 (45.5)	163 (39.6)	0.585
Clopidogrel, n (%)	1 (4.5)	13 (3.2)	0.525
VKA, n (%)	2 (9.1)	14 (3.4)	0.194
DOAC, n (%)	0 (0.0)	32 (7.8)	0.393
Outcome			
Hospitalization, median (25th - 75th)	1 (0 - 2)	0 (0 - 1)	0.001
Fall, median (25th - 75th)	0 (0 - 1)	0 (0 - 1)	0.615
Mortality, n (%)	1 (4.5)	14 (3.4)	0.550

FDA: folate deficiency anemia; NNDA: non-nutritional deficiency anemia; SD: standard deviation; CKD: chronic kidney disease; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; Hb: hemoglobin; VKA: vitamin K antagonist; DOAC: direct oral anticoagulant.

Table 5. Adverse Health Outcomes in Nutritional Deficiency Anemias and Non-Nutritional Deficiency Anemias

Outcome	CDA (n = 92)	IDA (n = 74)	FDA (n = 22)	NNDA (n = 412)
Hospitalizations, median (25th - 75th)	1 (0 - 2)	2 (0 - 4)	1 (0 - 2)	0 (0 - 1)
Falls, median (25th - 75th)	0 (0 - 1)	1 (0 - 3)	0 (0 - 1)	0 (0 - 1)
Mortality, n (%)	7 (7.6)	8 (10.8)	1 (4.5)	14 (3.4)

CDA: cobalamin deficiency anemia; IDA: iron deficiency anemia; FDA: folate deficiency anemia; NNDA: non-nutritional deficiency anemia.

were females (Table 4), but the difference was not statistically significant. Analysis of race revealed that the majority of the patients in the FDA group identified as White (72.7%), while the remaining patients identified as Black (18.2%), and Hispanic (9.1%). There was no statistically significant difference in the race distribution between the FDA and NNDA groups. Among the social factors, the frequency of cigarette smoking was higher in the FDA group compared to the NNDA group (50.0% vs. 42.2%), but the difference was not statistically significant. The frequency of alcohol consumption was lower in the FDA group compared to the NNDA group but the difference was not statistically significant (40.9% vs. 44.9%) (Table 4).

Analysis of the associated comorbid medical conditions revealed that the patients with FDA had slightly higher number of comorbid medical diagnoses compared to the NNDA group (2.1 vs. 1.9), but the difference was not statistically significant. There were no significant differences in the frequencies of DM, hypertension, hypothyroidism, CKD, malignancy, rheumatological disease, liver disease, CHF, COPD and CAD between the two groups (Table 4).

The majority of the patients with FDA had their hemoglobin level in the equal or greater than 14 g/dL range (59.1%), followed by 11 - 13.9 g/dL (36.4%), and 8 - 10.9 g/dL (4.5%) range. None of the patients had hemoglobin level in the less than 8 g/dL range. The differences in the hemoglobin levels were not statistically significant between the FDA and NNDA groups (Table 4). Among the use of medications that could have influenced the level of anemia in patients with FDA, we found that there were no statistically significant differences between the frequencies of use of erythropoietin, aspirin, clopidogrel, VKA, and DOAC between the two groups (Table 4).

In the comparative analysis of the AHO, we found that the number of hospitalizations in the FDA group were significantly higher than the NNDA group (median, 25th - 75th: 1 (0 - 2) vs. 0 (0 - 1), P = 0.001), even after adequate treatment of FDA; however there were no statistically significant differences in the events of falls and mortalities between the two groups (median, 25th - 75th: 0 (0 - 1) vs. 0 (0 - 1), P = 0.615; and 4.5% vs. 3.4%, P = 0.550, respectively) (Table 4).

Logistic regression analysis models for hospitalizations, falls and mortalities in the FDA group of patients revealed that for each unit increase in age, there were 1.03 times greater odd of falls (95% CI: 1 - 1.1; P = 0.004) and 1.1 times greater odds of mortality (95% CI: 1.1 - 1.2, P < 0.001). When compared to Whites, Blacks had 1.9 times greater odds of hospitalization (95% CI: 1.1 - 3.4; P = 0.029), and compared to Whites, Hispanic race had lower odds of falls (OR: 0.236, 95% CI: 0.069 - 0.809; P = 0.022). Patients who consumed alcohol had lower odds of falls (OR: 0.618, 95% CI: 0.427 - 0.896; P = 0.011). Comorbid medical diagnoses analysis showed that for every unit increase in number of comorbidities, there were 1.8 times greater odds of hospitalizations (95% CI: 1.5 - 2.1; P < 0.001), and 1.2 times greater odds of falls (95% CI: 1 - 1.3; P = 0.005), and 1.5 times greater odds of mortality (95% CI: 1.1 - 2; P = 0.007). Patients with rheumatologic disease had reduced odds of hospitalizations (OR: 0.495, 95% CI: 0.278 - 0.881; P = 0.017), while patients with malignancy had 3.1 time greater odds of mortality (95% CI: 1.3 - 7.6; P = 0.012). Additionally, patients on DOAC had 2.1 times greater odds of hospitalizations (95% CI: 1.1 - 4.1; P = 0.030).

Comparative analysis of events of hospitalizations, falls and mortalities amongst NDA

Overall, we found that the median numbers of hospitalizations among all NDA groups were significantly higher than the NNDA group. Among the NDA groups, IDA group had the highest median number of hospitalizations even after adequate treatment. Additionally, IDA group had significantly more hospitalizations (median, 25th - 75th: 2 (0 - 4) vs. 0 (0 - 1), P < 0.001), falls (median, 25th - 75th: 1 (0 - 3) vs. 0 (0 - 1), P < 0.001) and mortalities (10.8% vs. 3.4%, P = 0.011); CDA group had significantly more hospitalizations (median, 25th - 75th: 1 (0 - 2) vs. 0 (0 - 1), P = 0.007), but no difference in falls (median, 25th - 75th: 0 (0 - 1) vs. 0 (0 - 1), P = 0.171) and mortalities (7.6% vs. 3.4%, P = 0.083); and FDA group had significantly more hospitalizations (median, 25th - 75th: 1 (0 - 2) vs. 0 (0 - 1), P = 0.001), but no difference in falls (median, 25th - 75th: 0 (0 - 1) vs. 0 (0 - 1), P = 0.615) and mortalities (4.5% vs. 3.4%, P = 0.550), compared to the NNDA group (Table 5). Logistic regression models of hospitalizations, falls and mortalities in CDA versus NNDA, IDA versus NNDA, and FDA versus NNDA showed that patients with CDA had 1.2 time greater odds of hospitalizations (95% CI: 0.7 - 2; P = 0.015), patients with IDA had 2.4 time greater odds of hospitalizations (95% CI: 1.4 - 4.3; P = 0.002), patients with FDA had 4 time greater odds of hospitalizations (95% CI: 1.5 - 11; P = 0.007), patients with IDA had 2.6 time greater odds of falls (95% CI: 1.5 - 4.4; P = 0.001), and patients with IDA had 1.2 time greater odds of mortality (95% CI: 0.4 - 3.7; P = 0.009) (Table 6).

Discussion

The first major finding in our study was that despite adequate iron therapy, elderly patients with IDA had significantly more hospitalizations, falls and mortalities compared to the NNDA

Table 6. Logistic Regression Model of Adverse Health Outcomes in Nutritional Deficiency Anemias Versus Non-Nutritional Deficiency Anemias

Variable	B	P	Exp(B)	95% CI for Exp(B)	
				Lower	Upper
Hospitalization CDA vs. NNDA	0.193	0.015	1.213	0.734	2.005
Hospitalization IDA vs. NNDA	0.889	0.002	2.432	1.381	4.281
Hospitalization FDA vs. NNDA	1.390	0.007	4.015	1.470	10.966
Falls CDA vs. NNDA	0.526	0.058	1.693	1.030	2.783
Falls IDA vs. NNDA	0.949	0.001	2.584	1.512	4.416
Falls FDA vs. NNDA	0.115	0.813	1.121	0.434	2.899
Mortality CDA vs. NNDA	0.306	0.572	1.358	0.469	3.933
Mortality IDA vs. NNDA	0.216	0.009	1.240	0.416	3.702
Mortality FDA vs. NNDA	0.163	0.882	1.177	0.137	10.102

CDA: cobalamin deficiency anemia; NNDA: non-nutritional deficiency anemia; IDA: iron deficiency anemia; FDA: folate deficiency anemia.

group, CDA group and FDA group. In fact, our elderly patients with any NDA had significantly more hospitalizations compared to the patients with NNDA, even after receiving adequate treatments of their specific nutritional deficiencies. Our findings regarding IDA align with the limited number of studies that have reported similar observations. For instance, using a sample population of 19,341 subjects aged ≥ 59 years at baseline from the Swedish AMORIS cohort, Wennberg et al reported that IDA had a hazard ratio (HR) of 1.54 (95% CI: 1.38 - 1.73) for frailty and 1.76 (95% CI: 1.65 - 1.87) for mortality [14]. Similarly, Clere-Jehl et al followed 69 patients (74% women) with a median age of 78 (interquartile range (IQR) 75 - 82) years who had IDA and negative gastrointestinal endoscopy studies. After a mean 41 ± 22 month follow-up, they reported 33% mortality in their patients [15].

In our elderly population of mostly suburban patients with anemia, we found CDA in 15.3%, IDA in 12.3%, and FDA in 3.7%, which tend to differ from the reporting of some large scale studies, such as the study published by Guralnik et al, in which they analyzed the National Health and Nutrition Examination Survey (NHANES) III (phase 2, 1991 to 1994) data, and found that in the general population of the USA, 16.6% of persons 65 years and older had IDA, which was much higher than the frequencies of FDA (6.4%), or CDA (5.9%) [9]. The authors also reported that among the NDA, more than half of the subjects had IDA, either alone or in combination with FDA or CDA. Our findings differ from these observations as we found that among our elderly patients with the NDA, CDA was predominantly seen in close to half of the patients, while IDA was seen in about two-fifths of the patients. Although the accurate etiology of the differences in the frequencies of the various NDA in our patient population is hard to discern, we believe that over the last two decades or so, a major shift from consumption of traditional Western diet containing red meat to a more vegan or vegetarian diet could have contributed to a higher frequency of CDA compared to IDA and FDA.

More than half of our elderly patients with IDA had their hemoglobin levels greater than 11.0 g/dL, and about a third had their hemoglobin in the 8 - 10.9 g/dL range, nevertheless we found significantly more AHO compared to the other NNDA and NDA groups. It is widely accepted that in the elderly population, mild anemia or even a "low-normal" hemoglobin level due to IDA, is associated with a wide spectrum of poorer health-related outcomes. This is especially linked with certain comorbid conditions, such as CHF, in which patients with their hemoglobin levels in the lowest quartile of normal range, happen to have symptoms, poorer hemodynamics, and greater mortality than those with higher hemoglobin levels [16-18]. Our elderly patients with IDA had significantly higher associations of increased number of comorbidities, such as hypertension, CKD and CHF compared to the elderly patents in the NNDA group, which could have played a role in higher AHO. Similar findings have been reported by studies that looked into the role of comorbidities in anemia [2, 9, 13, 19, 20]. Michalak et al found that the number of comorbidities were also associated with increased risk of IDA (two diseases OR = 2.85, 95% CI: 1.12 - 7.30, P = 0.029; three diseases OR = 6.28, 95% CI: 2.22 - 17.76, P = 0.001; and four diseases OR = 4.64, 95% CI: 1.27 - 17.01, P = 0.021) [2]. They concluded that patients with coexistence of two to five comorbidities had nearly 2 to 14-fold increased risk of developing anemia and AHO [2]. In our elderly patients with IDA, we found that that for each unit increase in the number of comorbidities, there was 1.8 times greater odds of hospitalizations (95% CI: 1.5 - 2.1; P < 0.001), 1.2 times greater odds of falls (95% CI: 1 - 1.3; P = 0.012), and 1.5 times greater odds of mortality (95% CI: 1.1 - 2; P = 0.007). Several studies have suggested that there might be a reciprocal feedback, whereby the presence or treatment of these comorbidities promotes the onset of anemia, particularly IDA [2, 21-26]. IDA, in turn, might exacerbate a number of diseases [20, 23-25], leading to interventions, or hospitalizations, which might have worsened the anemia [19, 27-30], further perpetuating the cycle. We believe that the higher number of the comorbidities that we found to be associated with our elderly patients with IDA, might independently be attributable to the increase in the hospitalizations, as well as falls and mortalities, despite adequate treatment of IDA.

Several studies have suggested that there might have been

some barriers to effective iron therapy. For instance, the current guidelines recommend that the patients with IDA should take at least 60 mg of elemental iron two to three times a day without food for a duration of 3 - 6 months in order to replete iron stores and normalize serum ferritin levels [31]. In practice, it has been observed that the long-term use of oral iron is limited by some common and uncomfortable adverse effects, such as nausea, vomiting, constipation, and metallic taste, which impose difficulties to the patients in adherence to the treatment [32]. Despite those challenges, in our group of elderly patients with IDA, we found normal post-treatment iron indices which suggest that our patients adhered to the therapeutic recommendations and demonstrated adequacy of iron treatment.

The second major finding in our study was that among our adequately treated elderly patients with CDA and FDA, there were more hospitalizations compared to the NNDA group, but the events of falls and mortalities were similar to the NNDA group. Interestingly, the events of hospitalizations, falls, and mortalities were significantly higher in the IDA group when compared to the CDA and FDA groups. Limvorapitak et al reported in their study that CDA and FDA related hospitalizations were less common, and survival of patients with FDA was lower than that for patients with CDA (HR: 2.65, P = 0.001; and HR: 2.35, P = 0.023, respectively) [33]. A pilot study of 56 patients aged 65 years or older and history of falls reported cobalamin deficiency in 43% and folate deficiency in 20% [34]. We believe that adequate treatment of CDA and FDA in our elderly patients likely reduced the events of falls and mortalities in these groups of NDA. Another explanation for these findings could be drawn by looking at the severity of the anemias in the CDA and FDA groups. The majority of patients with CDA and FDA had hemoglobin levels above 11.0 g/dL (87.0% and 95.5%, respectively). These levels were much higher than the patients in the IDA group (64.9%). These findings suggest that our elderly patients with CDA and FDA did not to have moderate or severe anemia hence they had lower events of falls and mortalities which were similar to the NNDA group, compared to the elderly patients with IDA. There are multiple studies that have demonstrated that there happens to be an inverse J-shaped, or U-shaped, relationship between the hemoglobin level and AHO, including cardiovascular events [29, 32], decline in physical performance [30], length of hospitalization [31], and mortality [5, 32]. Since the majority of our patients in the CDA and FDA groups had mild anemia, they were less likely to have falls and mortalities when compared to the IDA group.

We believe that the higher number of associated comorbid medical conditions in our elderly patients with CDA contributed to more hospitalizations compared to the NNDA group. In the CDA group, there were significantly higher frequencies of hypertension, CKD, malignancies, CHF and CAD compared to the NNDA group. We found no clear explanation behind the role of comorbidities in higher events of hospitalizations in our elderly patients with CDA, without their influence in the events of falls and mortalities in this group. On the other hand, patients in the FDA group had no difference in the number of comorbidities, or specific comorbid medical condition, compared to the NNDA group; however the FDA group also had higher events of hospitalizations. We believe that the exacerbations of associated comorbid medical conditions, or other acute events, could have been responsible for the increased events of hospitalizations in the CDA and FDA groups, irrespective of the association of CDA and FDA. Although cobalamin deficiency is primarily related to atrophic gastritis [35-37], we did not find such documentation in our patient with CDA. Folate deficiency, on the other hand, is largely related to excessive alcohol use and malnutrition [35-37]; however we found a lower, but not-significantly different, frequency of association of alcohol use by the patients in the FDA group compared to the NNDA group (40.9% vs. 44.9%; P = 0.715). Additionally, our patients with FDA had a mean BMI of 29.9 ± 5.4 kg/m^2 which indicated that none of them had malnutrition. It is believed that the fortification of food items has made folate deficiency less common in the USA, nevertheless borderline or low cobalamin levels can still be seen in more than 10% of the elderly population in the USA [35, 37]. Overall, we believe that milder anemia in the majority of elderly patients with CDA and FDA along with adequate treatment with cobalamin and folate, respectively, played a larger role in preventing the events of falls and mortalities compared to the patients with IDA.

Additionally, we found several risk associations with AHO in our patients with NDA. Age was associated with increased odds of falls and mortalities in elderly patients with IDA. Influence of aging in iron metabolism is attributed secondary to less absorption of iron through hepcidin regulation due to chronic low-grade inflammation in the elderly population. Moreover, age-related changes in hemoglobin, influence of medications used for age-related disorders, and elevated ferritin levels due to chronic inflammation, impose challenges in identifying iron deficiency in this population [38]. Similarly, age was associated with increased odds of falls and mortalities in elderly patients with CDA. Advancing age tends to increase the prevalence of atrophic gastritis resulting into malabsorption of dietary cobalamin, which results into pernicious anemia and CDA [39]. By using proper diagnostic criteria and testing methodology, the prevalence of cobalamin deficiency (defined by a serum cobalamin level < or = 300 pg/mL and levels of serum methyl malonic acid and/or homocysteine elevated to > 3 standard deviation (SD)) has been reported to be as high as 14.5% with advancing age [40]. We also found that age was associated with increased odds of falls and mortalities in elderly patients with FDA. In a cohort of elderly patients with history of falls, Wee reported that folate levels predicted average handgrip strength and leg quadriceps strength after correction of BMI. Average leg quadriceps strength was negatively associated with the risk of falls [34]. The study also reported that the average leg strength and average leg strength corrected for BMI were both negatively associated with the risk of having fallen in the preceding year (OR = 0.89, 95% CI: 0.80 - 0.98, P < 0.05 and OR = 0.12, 95% CI: 0.02 - 0.92, P < 0.05; respectively) [34]. Our findings of age associated with increased odds of AHO, especially, falls and mortalities, in the elderly patients with NDA align with the findings of the reported studies.

Our patients with IDA, CDA and FDA, who identified as Black, had greater odds of hospitalization compared to the patients who identified as White. Anemia is independently associated with AHO [41, 42], and in the USA, Black individuals have lower hemoglobin values than their White counterparts, [41-44]. The Reasons for Geographic And Racial Differences

in Stroke (REGARDS) study reported that after adjusting for demographic variables, socioeconomic factors, and comorbid conditions, anemia was 3.3-fold more common in Black individuals than in White individuals [45]. We found that irrespective of the type of NDA, Black race was associated with significantly greater odds of hospitalization.

In our study, patients with malignancy had greater odds of mortalities in the IDA, CDA and FDA groups. Anemia is a common and potentially fatal association and complication in patients with malignancies. Caro et al conducted a comprehensive systematic review of 60 studies and found that there was a 65% overall increase in the risk of mortality in cancer patients with anemia compared with those without anemia, ranging from 19% in patients with lung cancers to approximately 75% in patients with head and neck cancers, or lymphomas [46]. Our findings concur with the findings of the published report. We believe that the malignancy by itself was the primary etiology of the poor prognosis and mortality in our elderly patients with NDA.

Finally, we also found that the patients on DOAC had greater odds of hospitalizations in all NDA groups. Our findings align with the findings of Radaelli et al who reported that use of DOAC was associated with higher rate of hospitalizations and anemia due to gastrointestinal bleeding in certain risk categories, such as age ≥ 75 years, presence of CKD, prior history of gastrointestinal bleeding, and concomitant use of nonsteroidal anti-inflammatory drugs [47].

Our study had a few limitations. Being a retrospective medical record review of the information available in our electronic medical record, we had to fully rely upon the documentation made by the patient care teams. Our findings were based on the observations made in a single suburban outpatient clinic which cannot be generalized.

The major strength of our study was a fairly large sample size and subsequent long-term follow-up visits of the patients with the same group of healthcare team that allowed proper documentation of the comorbid conditions and outcomes over an extended period of time.

Conclusions

We report that, compared to the elderly patients with NNDA, elderly patients with IDA had more AHO in the form of hospitalizations, falls and mortalities even after adequate treatment, while elderly patients with CDA and FDA had only more hospitalizations. Adequate treatment of elderly patients with CDA and FDA might mitigate events of falls and mortalities in these groups, nevertheless further research is necessary to determine whether this intervention provides similar outcomes in other settings. Age, Black race, higher number of comorbidities, presence of malignancy and use of DOAC were also associated with increased odds of AHO in patients with NDA.

Acknowledgments

The authors thank Christine Rickette, RN (study coordinator) for her contribution to this study.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable. Being a retrospective chart review study the Institutional Review Board waived the need for informed consent.

Author Contributions

TS and SR made substantial contributions to the study design, drafting, data acquisition, data analysis, and manuscript writing. KH analyzed the data. SR contributed in revising the manuscript critically for improved intellectual content, and final approval for the version to be published. All authors contributed in data collection and manuscript writing.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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