Impact of Anemia on Physical Function and Survival Among Patients with Coronary Artery Disease

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ABSTRACT

Background: Anemia is a purported risk factor for adverse outcomes, particularly among patients with cardiac disease. Although anemia at the time of discharge has been associated with poor functional status and survival, its impact over time is not clear.

Hypothesis: Among patients with significant coronary artery disease (CAD), anemia (hemoglobin <11 g/dL) is prevalent, and is associated with poor physical function (PF) and survival over time.

Methods: Patients with significant CAD at the time of cardiac catheterization (n = 1,821) were enrolled into a single-center, observational, and prospective study. All patients were followed for up to 1 y for clinical events and self-reported PF. Prevalence of anemia at discharge and its' associations with outcomes over time were examined.

Results: Anemia at the time of discharge was very common (40.4%), and was associated with increased odds of death at 12 mo (odds ratio [OR] 1.55, 95% confidence interval [CI] 1.12–2.15), yet other clinical factors accompanying anemia accounted for this association (adjusted OR 1.13, 95% CI 0.79–1.62). Discharge anemia was also associated with significantly lower self-reported PF at 6 and 12 mo (p < 0.05 for both); however, other clinical factors accompanying anemia also accounted for these associations.

Conclusions: Although discharge anemia is highly prevalent, its association with adverse outcomes is largely explained by baseline patient characteristics. Further research is needed to clarify the relationship between anemia and outcomes in this population and to identify subpopulations that do not recover independently and for whom available therapies may be beneficial.

Key words: coronary artery disease, anemia, mortality, physical function

Introduction

Anemia is a common comorbidity among patients with coronary artery disease (CAD).^{1–5} If present at admission or discharge, it has been demonstrated to have important prognostic implications for physical function (PF) and mortality. In patients with acute coronary syndromes, admission hemoglobin levels <11 g/dL have been associated with increased risk of death and ischemic complications at 30 d.^{3,5} This same hemoglobin threshold at discharge continues to predict worse all-cause mortality over the subsequent 2 y.⁴ Many therapies used during hospitalization for acute coronary syndromes are associated with increased risk of bleeding, so anemia is likely to develop or worsen in this setting.^{6,7} As a result, patients with anemia at discharge may be different than those with anemia at the time of admission. However, the extent to which discharge anemia remains important over time with respect to both PF and survival is unclear. Therefore, using a population with significant CAD defined at the time of cardiac catheterization, we evaluated the prevalence of discharge anemia and the impact of anemia on long-term outcomes. Specifically, we assessed the following: (1) the frequency of discharge anemia; (2) association with baseline, 6 mo, and 12 mo

functional outcomes; and (3) associations with 6 mo and 12 mo mortality.

Methods

The study population was drawn from patients who were enrolled in a longitudinal study that sought to assess functional status and quality of life. These patients were treated at Duke University Medical Center (Durham, NC, USA) between August 1998 and April 2001, and were found to have significant CAD (≥ 1 vessel with $>75\%$ stenosis) by elective diagnostic catheterization. Patients with any of the following were excluded from the study: prior coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) <6 mo, congenital heart disease, heart transplant, primary valvular disease, or inability to provide consent. After the study protocol was approved by the Duke University Institutional Review Board, eligible patients were approached to participate and informed consent was obtained from 2,073 participants. From this cohort of eligible participants, patients were included in the present study if they had baseline and discharge hemoglobin values, as well as a baseline serum creatinine (n = 1,821).

Data on demographics, comorbidities, and clinically relevant variables were collected from patient medical

records. Demographic variables included age, gender, race, marital status, and education. Comorbid conditions included diabetes, hypertension, congestive heart failure (CHF), history of smoking, dementia, and depression. Clinically relevant variables included the number of diseased vessels, ejection fraction, serum hemoglobin values, and baseline serum creatinine, from which an estimated glomerular filtration rate (GFR) was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) study formula.⁸ Catheterization data was obtained through the Duke Information System for Cardiovascular Care database. Hemoglobin values were obtained from all patients at baseline (drawn prior to cardiac catheterization) and discharge (last value prior to hospital discharge, or if outpatient status for catheterization, last value up to 30 d following cardiac catheterization). Anemia was defined categorically as hemoglobin <11 g/dL.^{3,4} Finally, health-related quality of life assessments were conducted by trained interviewers for all patients at baseline (24 h from cardiac catheterization), 6 mo, and 1 y using the validated Medical Outcomes Study Short-form 36 (SF-36).⁹ Physical function was assessed by self-report using the SF-36 PF subscale in which higher scores indicate better health (scale 0–100).^{9,10} Vital status at 1 y was obtained directly from patient contact or clinical records for all study participants.

Descriptive statistics summarizing baseline characteristics were stratified based on the patient's anemia status at discharge and presented as percentages for discrete variables, and means and standard deviations for continuous variables. Comparisons between those with and without anemia at discharge were made using chi-square tests for categorical variables and Wilcoxon's tests for non-normally distributed continuous variables, and were considered significant at a level of $p < 0.05$. To evaluate the independent relationship between discharge anemia and study outcomes, multivariable models were used. When model covariates had missing values, these observations were dropped resulting in slightly different numbers of patients included in the various models. Backward stepwise regression was used with a criterion of $p < 0.10$ for inclusion of secondary predictors described above and included in Table 1. However, variables that were felt to be important potential confounders were forced into all models including demographics (age, gender, and race) and treatment groups (CABG, PCI, or medical therapy). All analyses were performed using SAS version 8.2 (SAS, Cary, NC, USA).

Results

Among the 1,821 study participants, 40.4% ($n = 735$) were anemic at discharge. Compared with those who were not anemic at discharge, anemic patients were more likely to be older, female, non-Caucasian, unmarried, and more educated (Table 1). Clinical characteristics of this cohort revealed a population with a greater burden of CAD and comorbid conditions including chronic kidney disease, diabetes, and CHF. As expected, patients anemic at discharge were more likely to have been managed with CABG therapy ($p < 0.0001$). In addition, a larger proportion

Figure 1: Unadjusted and risk-adjusted mortality at 6 mo and 1 y according to Discharge Anemia Status. Models included 1,810 observations adjusted for age, gender, race, education, marital status, GFR category, depression, smoking, hypertension, diabetes, history of CHF, and medical treatment group.

of those with discharge anemia as compared with those without were also anemic at baseline (34.0 versus 5.9%, $p < 0.0001$).

When compared with those who were not anemic, patients with discharge anemia had lower baseline PF at all study time points (Table 2). While mean PF scores at baseline, 6 mo, and 1 y were all significantly lower among those with discharge anemia, differences in PF scores were no longer present after multivariable adjustment for potential confounders. For example, unadjusted PF scores were significantly different between those with and without discharge anemia at 1 y. After patient-level adjustment, the differences were significantly attenuated.

Finally, the death rate was higher among those with discharge anemia (7.6% at 6 mo and 10.9% at 1 y) compared with those without discharge anemia (5.2% at 6 mo and 7.4% at 1 y). Accordingly, patients with discharge anemia were found to have increased odds of death at 6 mo (odds ratio [OR] 1.48) and 12 mo (OR 1.55) (Figure 1). However, neither of these associations persisted after patient-level adjustment (OR 1.01 and OR 1.19 at 6 and 12 mo, respectively).

Discussion

Our study confirms that anemia at discharge is common among patients with significant CAD following cardiac catheterization. In this population, we found that discharge anemia was associated with significantly worse PF and higher mortality at 6 mo and 1 y. However, these associations were partially explained by other clinical characteristics that were included in the multivariable models.

Although several studies have examined the relationship between anemia and outcomes in patients with CAD, the results have been mixed. Adverse outcomes, such as worse PF or increased mortality, have been demonstrated in diverse cardiac populations (e.g., acute coronary syndrome,

TABLE 1: Baseline characteristics of study participants according to discharge anemia status

	Overall n = 1,821	No discharge anemia n = 1,086	Discharge anemia n = 735	p-value
Age, y	68±11	67±11	69±11	0.0002
Female, n (%)	694 (38.1)	377 (34.7)	317 (43.1)	0.0003
Race, n (%)				
Caucasian	1,355 (74.4)	831 (76.5)	524 (71.3)	0.012
Non-Caucasian	466 (25.5)	255 (23.5)	211 (28.7)	
Marital status, n (%) ^a				
Married/living as married	1,219 (66.9)	755 (69.5)	464 (63.1)	
Divorced/separated/never married	217 (11.9)	126 (11.6)	91 (12.4)	0.007
Widowed	383 (21.0)	203 (18.7)	180 (24.5)	
Education, n (%) ^a				
Less than ninth grade	651 (35.8)	403 (37.1)	248 (33.7)	
Some or all high school	804 (44.2)	486 (44.8)	318 (43.3)	0.017
Some college or more	355 (19.5)	188 (17.3)	167 (22.7)	
No. of diseased vessels, n (%)				
0	36 (2.0)	27 (2.5)	9 (1.2)	
1	638 (35.0)	437 (40.2)	201 (27.4)	
2	520 (28.6)	326 (30.0)	194 (26.4)	<0.0001
3	627 (34.4)	296 (27.3)	331 (45.0)	
Ejection fraction, %	53±15	53±16	53±14	>0.5
Baseline creatinine, mg/dL	1.31±1.27	1.20±0.97	1.47±1.61	0.0002
Baseline MDRD GFR ^b , n (%)				
>60	1,229 (67.5)	788 (72.6)	441 (60.0)	
30–60	501 (27.5)	269 (24.8)	232 (31.6)	<0.0001
<30 or dialysis	91 (5.0)	29 (2.7)	62 (8.4)	
Baseline hemoglobin, g/dL	12.9±1.9	13.4±1.6	12.0±2.0	<0.0001
Baseline anemia, n (%)	314 (17.2)	64 (5.9)	250 (34.0)	<0.0001
Discharge hemoglobin, g/dL	11.6±1.9	12.8±1.3	9.7±0.8	<0.0001
Treatment group				
Medical	435 (23.9)	301 (27.7)	134 (18.2)	
PCI	728 (40.0)	523 (48.2)	205 (27.9)	<0.0001
CABG	658 (36.1)	262 (24.1)	396 (53.9)	
Comorbid conditions, n (%)				
Diabetes	579 (31.8)	311 (28.6)	268 (36.5)	0.0004
Hypertension	1,275 (70.0)	758 (69.8)	517 (70.3)	>0.5
Congestive heart failure	353 (19.4)	189 (17.4)	164 (22.3)	0.009
Smoking	960 (52.7)	597 (55.0)	363 (49.4)	0.02
Dementia	17 (0.9)	9 (0.8)	8 (1.1)	>0.5
Depression	119 (6.5)	76 (7.0)	43 (5.9)	0.33

Unless specified otherwise, values are mean±SD. ^aTotals different from overall n because of missing values. ^bMDRD formula for GFR in ml/min/1.73 m². *Abbreviations:* CABG = coronary artery bypass graft; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; PCI = percutaneous coronary intervention; SD = standard deviation.

TABLE 2: Physical function outcomes at baseline, 6 mo, and 1 y according to discharge anemia status

Physical function	No discharge anemia (mean [95% CI])	Discharge anemia (mean [95% CI])
Baseline		
Unadjusted	47.1 (45.7–48.5)	42.8 (41.1–44.6)
Adjusted ^a	46.0 (44.5–47.5)	44.5 (42.7–46.4)
6 mo		
Unadjusted	52.7 (51.3–54.2)	48.7 (46.9–50.5)
Adjusted ^b	51.6 (50.1–53.1)	50.4 (48.6–52.3)
1 y		
Unadjusted	53.0 (51.5–54.4)	49.1 (47.3–50.9)
Adjusted ^b	52.0 (50.5–53.5)	50.5 (48.6–52.4)

^aModel included 1,676 observations adjusted for age, gender*, race*, education*, GFR category*, depression, smoking*, hypertension, diabetes*, history of CHF*, and medical treatment group*. ^bModel included 1,648 observations adjusted for age*, gender*, race, marital status*, education*, GFR category*, depression*, hypertension*, diabetes*, history of CHF*, and medical treatment group*. * $p \leq 0.05$. Abbreviations: CHG = congestive heart failure; CI = confidence interval; GFR = glomerular filtration rate.

chronic kidney disease, and CHF).^{3,11–17} Most of the studies that report strong associations between anemia and adverse outcomes characterized anemia at baseline.^{3,11–16} However, associations with baseline anemia may be confounded by underlying patient comorbidities that mediate the apparent association with adverse outcomes.^{15,16} In addition, definitive conclusions from several of these studies are limited because of cross-sectional examination of associations without longitudinal analyses,¹¹ inclusion of short-term outcomes (in-hospital or 30 d),^{3,14} or inclusion of patients with CHF that may further confound the relationship between anemia and outcomes.^{12,13} This confounding may have accentuated the associations between survival and discharge anemia.

Discharge anemia is often followed closely by clinicians because it may be modified by treatment with either blood transfusion or erythrocyte-stimulating agents.^{18–20} To our knowledge, only 1 other study has clearly examined the association between survival and anemia at discharge.⁴ After multivariable adjustment, Vaglio et al.⁴ found that discharge anemia was significantly associated with higher 2-y mortality, while admission anemia was not. In the current study, after multivariable adjustment, we found that the associations between anemia and higher 6-mo and 1-y mortality were significantly attenuated. Although our results demonstrate that other factors may indeed confound the association between anemia and outcome, the tight collinearity of several measures (e.g., anemia and renal function) makes it somewhat difficult to determine which factor is more closely linked to the causal pathway of adverse outcomes. Indeed, other studies have also suggested that associations between anemia and mortality were due to residual confounding.^{1,21}

A similar pattern was observed when we examined the impact of discharge anemia and PF. In particular, we found

lower PF at baseline, 6 mo, and 12 mo among those with discharge anemia; however, these differences also did not persist after multivariable adjustment. Our findings differ from others that have demonstrated independent associations with reduced PF.^{11,22–24} Discrepancies between our results and those of other studies may be due to our focus on the longitudinal impact of discharge anemia on PF rather than cross-sectional analyses alone.

Nonetheless, anemia among patients with CAD following cardiac catheterization was quite common in our study; affecting 2 out of every 5 patients. This prevalence is somewhat higher than that observed by Vaglio et al.⁴ (24%), but is likely explained by differences in our cohort that included older patients with more comorbidities. Given our mean cohort age of 68 y of age, such a high prevalence is not surprising since up to 20% of the US population over the age of 75 y has chronic anemia attributable to nutritional deficiencies, chronic inflammation, renal disease, or other causes.²⁵ Other comorbid conditions that likely contributed to anemia in our cohort include CHF^{17,26} and chronic kidney disease.^{8,12,13,18} In addition, up to 10% of patients with cardiac disease have major bleeding episodes during their hospitalization,^{6,7} which further contributes to discharge anemia.

Therefore, despite a high prevalence of anemia at discharge among patients with CAD and the presence of effective therapies, our findings raise questions about the premise for treatment of this common comorbidity in a CAD population. We highlight that associations between anemia and adverse outcomes are in large part due to other patient-level characteristics. However, there may be subpopulations for whom anemia treatment is beneficial. For instance, some patients with discharge anemia will not recover independently and they may have persistently worse outcomes. Unfortunately, we were unable to assess

the impact of anemia nonrecovery in our study due to inconsistent and incomplete hemoglobin values during the follow-up period.

The strengths of this study include our inclusion of all patients with CAD defined by cardiac catheterization, and patient-reported symptoms that quantified PF at baseline and during follow-up. However, there were also several limitations. We had no data on the utilization of therapies for treating anemia, such as blood transfusions, erythrocyte-stimulating agents, or iron supplementation. Such treatments may have impacted the trajectory of anemia recovery and potentially confounded the associations between anemia at discharge and subsequent outcomes.^{26,27} In addition, no objective assessment of PF was available as in some studies,¹¹ but the impact is unlikely to be significant due to the high correlation between measured and observed PF.¹¹

In summary, discharge anemia is common among patients with CAD following cardiac catheterization. Despite being associated with worse PF and survival over time, much of the associations with discharge anemia were explained by baseline characteristics. Further research to clarify the role of anemia on outcomes in this population is needed, especially to identify subpopulations that do not recover independently and who may benefit from available therapies.

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