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Severity of Anemia Predicts Hospital Length of Stay but Not Readmission in Patients with Chronic Kidney Disease

A Retrospective Cohort Study

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Abstract: The aim of this study was to examine the relationship of severe anemia to hospital readmission and length of stay (LOS) in patients with chronic kidney disease (CKD) stage 3–5. Compared with the general population, patients with moderate CKD have a higher hospital readmission rate and LOS. Anemia in patients with moderate CKD is associated with higher morbidity and mortality. The influence of anemia on hospital outcomes in patients with moderate CKD has not been characterized.

We conducted a retrospective cohort study at Maine Medical Center, a 606-bed academic tertiary care hospital. Patients with CKD stages 3–5 and not on dialysis admitted during February 2013 to January 2014 were eligible. Patients with end stage renal disease on hemodialysis or peritoneal dialysis, kidney transplant, acute kidney injury, gastrointestinal bleeding, active malignancy, pregnancy, and surgery were excluded. The cohort was split into severe anemia (hemoglobin ≤9 g/dL) versus a comparison group (hemoglobin >9 g/dL), and examined for differences in 30-day hospital readmission and LOS.

In this study, the data of 1141 patients were included, out of which 156 (13.7%) had severe anemia (mean hemoglobin 8.1 g/dL, SD 0.8). Severe anemia was associated with increased hospital LOS (mean 6.4 (SD 6.0) days vs mean 4.5 (SD 4.0) days, $P < 0.001$). The difference was 1.7 day longer (95% CI 0.94, 2.45). There was no difference in readmission rate (mean 11.5% vs 10.2%, $P = 0.7$).

Patients with moderate CKD and severe anemia are at risk for increased hospital LOS. Interventions targeting this high-risk population, including outpatient management of anemia, may benefit patient care and save costs through improved hospital outcomes.

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Abbreviations: CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, ESRD = end stage renal disease, LOS = length of stay, MMC = Maine Medical Center.

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INTRODUCTION

Chronic kidney disease (CKD) and anemia are risk factors for poor patient and hospital outcomes. Compared with the general population, patients with CKD have a 20% higher 30-day readmission rate, 50% increase in 1-year mortality, and an average hospital length of stay (LOS) that is 3 days longer.[1] Anemia has been shown to be a predictor of a poor outcome in a number of patient populations. Several large cohort studies report anemia as a risk factor for death after discharge, increased hospital LOS, in hospital mortality, and readmission in patients with end stage renal disease (ESRD) on dialysis.[2–4] In patients with heart failure, an observational study showed that hospital mortality increased by 39% and readmission rate rose by 13% for each 1 g/dL decrease in hemoglobin.[5]

Anemia is highly prevalent in patients with CKD, reported in up to 50% of patients not on dialysis. The severity of anemia is directly correlated with the degree of CKD; the largest percentage drop in hemoglobin occurs in CKD stage 3 when estimated glomerular filtration rate (eGFR) declines <60 mL/min/1.73 m^2.[6] A recent prospective multicenter study of patients with CKD stage 3 followed for 3 years showed that patients who developed anemia had a faster progression to CKD stages 4 and 5, increased hospitalizations, increased morbidity from major cardiovascular events, and higher mortality than those patients without anemia.[7] These findings are supported by a descriptive study showing that men with moderate CKD stages 3–5 not on dialysis who had anemia were at increased risk for mortality and progression to ESRD compared with patients without anemia.[8]

Kidney Disease Improving Global Outcomes designates severe anemia as hemoglobin ≤9 g/dL because it is the level by which most patients become symptomatic with fatigue, shortness of breath, and decreased quality of life.[9] The symptoms and adverse outcomes attributed to anemia are related to the hemodynamic influences of anemia on the heart (increased cardiac output and increased left ventricular hypertrophy) to meet the required oxygen demands of end organs. The severity of anemia as measured by hemoglobin level at which hospital outcomes are influenced is not well described. Although data exist in patients with ESRD on dialysis,[2–4] the relationship between anemia and such outcomes in nondialysis patients with moderate CKD has not been characterized. An improved understanding of these relationships may influence clinician decision-making regarding the management of anemia in patients with CKD.

In this retrospective cohort study, we report the prevalence of severe anemia, defined as hemoglobin ≤9 g/dL, in hospitalized patients with CKD stages 3–5 not on dialysis, and examine its relationship to hospital readmission and LOS. We hypothesized that severe anemia would be associated with increased readmission rate and longer LOS.

METHODS

Study Population

A retrospective cohort study of patients admitted at Maine Medical Center (MMC), an academic tertiary care hospital with 606 beds, over 12 months (February 1, 2013–January 31, 2014) was conducted. Inclusion criteria consisted of diagnosis of CKD stages 3–5, eGFR <60 mL/min/1.73 m^2 and not on dialysis. eGFR was measured by the Modified Diet in Renal Disease equation using the creatinine value on discharge. Patients with ESRD on hemodialysis or peritoneal dialysis, kidney transplant, acute kidney injury, gastrointestinal bleeding, active malignancy, pregnancy, and surgery were excluded. Exclusion and inclusion criteria were identified on admission for the initial hospitalization using the International Classification of Disease (http://en.wikipedia.org/wiki/ICDICD) from the 9th revision and Diagnostic Related Group coding. Demographics (age, sex, and race), primary diagnosis, heart failure, and diabetes mellitus were identified on the initial admission. Race was collapsed into Caucasian and non-Caucasian categories due to low prevalence of racial minority patients in Maine.

Study Design

The study was powered to detect a 15% difference in readmission between the group with severe anemia and the comparison group. Using published studies in patients with CKD not on dialysis, we predicted a 20% readmission rate in the comparison group.[1,5] A sample size of 170 in each group had an 80% power to detect this difference using a 2-sided *t* test with a *P* value of 0.05. The cohort of patients with CKD stages 3–5 was split into severe anemia, defined as hemoglobin ≤ 9 g/dL, versus a comparison group of patients with hemoglobin >9 g/dL. The groups were examined for differences in hospital 30-day readmission and LOS. Because readmission was the primary outcome, the discharge hemoglobin value, which was the last hemoglobin value during the admission, was used in the primary analysis. A secondary analysis was conducted to assess if admission hemoglobin, rather than discharge hemoglobin, was a predictor of hospital LOS as this would have greater clinical utility. The study was granted exemption from the MMC Internal Review Board because no identifying information was used and there was no risk to the subjects. The study did not involve patient consent, and informed consent was not given. There was no funding for this study.

Statistical Analysis

The 2 groups were tested for differences in demographics, comorbidities, eGFR, and primary diagnosis using descriptive statistics with χ^2 tests for categorical variables and student *t* tests for continuous variables. Readmission rates were calculated as proportions; hospital LOS was analyzed as a categorical variable (≥ 5 days) and a continuous variable (number of days). Because the data were normally distributed, crude outcomes were compared between the severe anemia group and the comparison group using χ^2 tests for differences in proportions and *t* tests for differences in means. In the adjusted analysis, multivariable logistic regression was used for categorical variables and linear regression was conducted for continuous variables with severe anemia as the predictor of interest. Readmission rate and LOS were the dependant variables in the regression models. Covariates were selected based on their bivariate associations with readmission rate and LOS. All multivariable regression models were adjusted for the same covariates: age, sex, race, diabetes, heart failure, and eGFR. We fit 3 multivariable regression models. Two logistic regression models were constructed with readmission as the dependent variable for the first and LOS ≥ 5 days for the second. A linear regression model was also constructed with LOS as the dependent variable. A *P* value of 0.05 was designated as significant and 2-tailed tests were used. Differences were reported as odds ratios (ORs) or differences with 95% confidence intervals (CIs). No data were collected on the hospital readmission. All data were gathered using the electronic medical record; Epic. Computer software with SPSS and SAS were used.

RESULTS

Patient Characteristics

A total of 1141 patients were included in the study (Figure 1). Of these, 156 (13.7%) had severe anemia at discharge (mean hemoglobin 8.1 g/dL, SD 0.8) and were well separated from the comparison group (mean hemoglobin 11.8 g/dL, SD 1.6). The 2 groups did not differ based on sex or race. However, the severe anemia group was younger compared with the comparison group (mean 72.9 (range 23–96) years vs mean 76.7

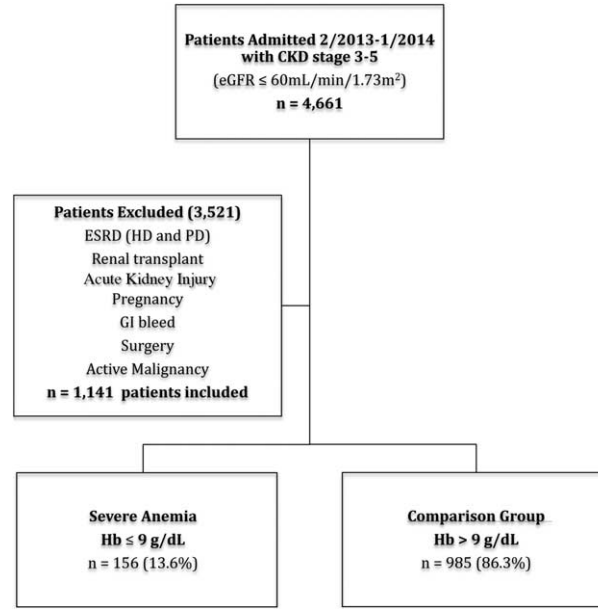

FIGURE 1. Study population diagram. Retrospective study of a cohort of patients admitted at Maine Medical Center during February 2013 to January 2014. Inclusion criteria consisted of CKD stages 3–5, determined by the eGFR as measured by the Modified Diet in Renal Disease equation using the creatinine value on discharge, ICD from the 9th revision, and DRG coding. Patients with ESRD on HD or PD, kidney transplant, acute kidney injury, pregnancy, GIB, surgery, and active malignancy were excluded. Exclusion criteria were identified on admission for the initial hospitalization using ICD of Disease and Diagnostic Related Group coding. Patients could have more than 1 reason to be excluded, thus the exact number for each exclusion criterion are not reported. The cohort was split into severe (Hb ≤ 9 g/dL) and a comparison group (Hb >9 g/dL). CKD = chronic kidney disease, DRG = Diagnostic Related Group, eGFR = estimated glomerular filtration rate, ESRD = end stage renal disease, GIB = gastrointestinal bleeding, Hb = hemoglobin, HD = hemodialysis, ICD = International Classification of Disease, PD = peritoneal dialysis.

TABLE 1. Characteristics of Patients with Chronic Kidney Disease Admitted February 2013 to January 2014 According to Severity of Anemia*

Characteristic	Severe Anemia (Hb ≤ 9.0 g/dL) n = 156		Comparison (Hb >9.0 g/dL) n = 985		*P*
	n	Mean (SD)	n	Mean (SD)	
Age, y; mean (SD)	156	72.9 (14.3)	985	76.7 (13.2)	0.001*
Female (%)	91 (58.3%)		566 (57.5%)		0.91
Caucasian (%)	148 (94.9%)		949 (97.4%)		0.12
Diabetes (%)	82 (52.6%)		636 (64.6%)		0.005*
Heart failure (%)	59 (37.8%)		376 (38.2%)		1.00
Discharge Hb; mean (SD)	156	8.1 (0.8)	985	11.8 (1.6)	<0.001*
eGFR, mL/min/1.73 m^2; mean (SD)	156	32.7 (16.7)	985	43.9 (13.3)	<0.001*
eGFR ≤45 mL/min/1.73 m^2 (%)	111 (71.2%)		443 (45.0%)		<0.001*
Primary diagnoses (%)					<0.001*
Acute coronary syndrome	6 (3.9%)		74 (7.6%)		
Arrhythmia	7 (4.6%)		72 (7.4%)		
Congestive heart failure	21 (13.7%)		118 (12.2%)		
Endocrine abnormality	3 (2.0%)		21 (2.2%)		
Gastrointestinal illness	11 (7.2%)		31 (3.2%)		
Infection	40 (26.1%)		185 (19.1%)		
Musculoskeletal	7 (4.6%)		47 (4.8%)		
Neurological disease	8 (5.2%)		108 (11.1%)		
Psychiatric illness	2 (1.3%)		39 (4.0%)		
Respiratory distress	6 (3.9%)		79 (8.1%)		
Stroke	13 (8.5%)		117 (12.1%)		
Other	29 (19.0%)		79 (8.1%)		

eGFR was calculated with the Modified Diet in Renal Disease equation using creatinine value on discharge. eGFR = estimated glomerular filtration rate, Hb = hemoglobin. There were 11 patients in the comparison group whose race was unknown.
* International Classification of Disease codes from the 9th revision and Diagnostic Related Group coding was used.

(range 21–102) years, $P = 0.001$), and there were fewer patients with diabetes in the severe anemia group versus the comparison group (52.6% vs. 64.6%, $P = 0.005$). As expected, the estimated renal function was worse in the severely anemic group versus the comparison group (mean eGFR 43.9, SD 13.3 mL/min/1.73 m^2 vs mean 32.7, SD 16.7 mL/min/1.73 m^2, $P = <0.001$) (Table 1).

Outcomes

Readmission rates did not differ between the groups, 11.5% in the severe anemia group versus 10.2% in the comparison group ($P = 0.7$), adjusted OR 1.01 (95% CI 0.58,1.76; Table 2). Severe anemia was associated with increased hospital LOS (mean 6.4 (SD 6.0) days vs mean 4.5 (SD 4.0) days, $P < 0.001$): adjusted difference 1.70 days (95% CI 0.94, 2.45). The proportion of patients with LOS ≥5 days in the severely anemic group was greater than that in the comparison group (48.1% vs. 33.1%, $P < 0.001$): adjusted OR 1.72 (95% CI 1.20, 2.47) (Table 2). This relationship held true when examining hemoglobin on admission in the secondary analysis. The severe anemia group had an increased hospital LOS compared with the comparison group (mean 6.1 (SD 5.1) days

TABLE 2. Analysis of Severe Anemia as a Predictor for Hospital Length of Stay and Readmission*

Characteristic	Severe Anemia (Hb ≤9.0 g/dL) n = 156	Comparison (Hb >9.0 g/dL) n = 985	*P*	Crude	Adjusted
				Odds Ratio (95% CI)	
Readmission, n (%)	18 (11.5)	100 (10.2)	0.70	1.15 (0.68, 1.97)	1.01 (0.58, 1.76)
LOS ≥5 d, n (%)	75 (48.1)	326 (33.1)	<0.001	1.87 (1.33, 2.63)	1.72 (1.20, 2.47)
				Difference (95% CI)	
LOS, mean (SD)	6.4 (6.0)	4.5 (4.0)	<0.001	1.92 (1.19, 2.64)	1.70 (0.94, 2.45)

CI = confidence interval, Hb = hemoglobin, LOS = length of stay.
* Adjusted for age, sex, race, diabetes, heart failure, and eGFR.

TABLE 3. Secondary Analysis of Severe Anemia as a Predictor for Hospital Length of Stay Using Admission Hemoglobin*

Characteristic	Severe Anemia (Hb ≤ 9.0 g/dL) n = 107	Comparison (Hb >9.0 g/dL) n = 1032	*P*	Crude	Adjusted
				Odds Ratio (95% CI)	
LOS ≥5 d, n (%)	52 (48.6)	349 (33.8)	0.003	1.85 (1.24, 2.76)	1.68 (1.11, 2.55)
				Difference (95% CI)	
LOS, mean days (SD) range	6.1 (5.1) 1–24	4.6 (4.2) 1–38	0.002	1.52 (0.66, 2.38)	1.24 (0.36, 2.13)

CI = confidence interval, Hb = hemoglobin, LOS = length of stay.
* Adjusted for age, sex, race, diabetes, heart failure, and eGFR.

vs. mean 4.6 (SD 4.2) days, $P = 0.002$): adjusted difference in LOS 1.24 days (95% CI 0.36, 2.13). The proportion of severe anemia patients with hospital LOS ≥5 days was statistically greater than the comparison group (48.6% vs 33.8%, $P = 0.003$): OR 1.68 (95% CI 1.11, 2.55) (Table 3).

DISCUSSION

In this study, severe anemia defined as hemoglobin ≤9.0 g/dL, whether measured at admission or at discharge, was a strong predictor of increased hospital LOS in patients with CKD stages 3–5. This effect held true when accounting for diabetes, heart failure, and eGFR. Although this relationship is well characterized in patients with ESRD on dialysis[2–4] and in patients hospitalized with heart failure,[5] this is the first study to describe this relationship in patients with moderate stage CKD controlling for heart failure.

Previous studies suggest that anemia increases the risk of readmission in patients with ESRD on dialysis,[2–4] heart failure,[5] and stage 3 CKD.[7] The finding that hospital readmission in patients with CKD was not influenced by severe anemia in our study was unexpected. This may be related to the overall low readmission rate in both groups: 11.5% in the severely anemic group and 10.2% in the comparison group. Previous studies in patients with CKD not on dialysis found that 30-day hospital readmission rate was approximately 20%.[1,5] The national average readmission rate for all adult hospitalized patients at academic tertiary centers was 18%[10] and was 14% at MMC during the study time period. In recent years, MMC has instituted multiple interventions to reduce readmissions, including tighter linkages to primary care practices, discharge summary completion within 24 hours, placement of geriatricians in skilled nursing facilities, and adoption of the Care Transition Intervention (CTI). CTI employs a registered nurse who acts as the patient's coach as they transition to the ambulatory setting after their hospitalization, separate from home health aids or visiting nurses. They assist the patients with follow-up appointments, understanding red flag symptoms or warning signs, and medication reconciliation. These interventions may have decreased the effect of anemia on readmission rate.

Our results that higher hemoglobin on admission predicted a shorter hospital LOS suggest that the outpatient management of anemia in patients with moderate CKD may have an impact on hospital outcomes. However, the outpatient management of anemia in patients with CKD stages 3–5 before dialysis is complex and the management strategies are actively evolving. A study in patients with moderate CKD before initiating dialysis conducted from 1995 to 2010 showed the use of Erythropoiesis Stimulating Agents (ESAs) increased from 3.2% to 35.0% and intravenous iron increased from 1.2% to 12.3%.[11] The increased utilization of ESA and intravenous iron was, in part, justified by a therapeutic goal to decrease use of blood transfusions, thereby reducing the risk of transfusion reactions and allosensitization. However, this has not been without harmful consequences. In the ESRD population on dialysis, intravenous iron, at least, has been shown to increase the risk of infection[12] and cardiovascular disease.[13,14] Furthermore, deposition of iron in the liver and pancreas has lead to cirrhosis and insulin resistance, respectively, approaching the levels of hemosiderosis and hemochromatosis.[15–17] In several large randomized controlled trials in patients with CKD not on dialysis, ESA therapy was complicated by the risk of ischemic strokes, hypertension, thrombosis, and cardiovascular disease.[18–20] As more information about the risks of intensive ESA and intravenous iron use has appeared, practice patterns in the outpatient management of anemia in CKD have shifted. These studies have prompted reevaluation of the target hemoglobin level for patients with CKD. Some aspects of anemia management are protocol driven, especially for patients with ESRD on dialysis. However, increased understanding of the risks, benefits, and long-term outcomes highlights the importance of shared decision-making and individualized management of anemia.

The strengths of this study include a simple design addressing an important question in the context of increasing consciousness of healthcare utilization and costs. Our CKD cohort was identified using creatinine on discharge to calculate eGFR, as opposed to admission. This is more likely to represent baseline renal function and less likely to represent changes in kidney function associated with acute illness. Rigorous exclusion criteria allowed for identification of a homogenous sample population of patients with anemia of CKD. Furthermore, we focused on severe anemia that is likely to cause symptoms impacting patients' quality of life. Adjusting for important confounding comorbidities such as diabetes, heart failure, and CKD in the multivariable analysis provides added confidence to our findings.

Our study population represents the demographics of Maine, which is majority Caucasian, with a high prevalence of comorbidites such as diabetes and heart failure in patients with CKD. Limitations include our inability to generalize the findings to more racially diverse patient populations. The lower than expected readmission rates in both groups may have led to a weaker conclusion regarding anemia and readmission. Given the low proportion of patients readmitted, the study sample size required to detect a significant effect of anemia on readmission may have been larger than predicted by the power analysis,

thereby leading to a type II error. Because this was a retrospective cohort study, the association we found between anemia and LOS may not be due to anemia, but an unmeasured factor associated with both anemia and LOS.

In this study, severe anemia is associated with increased hospital LOS in patients with CKD stages 3–5. These findings support the role of outpatient anemia management from both nephrologists and primary care physicians for patients with moderate CKD who are not on dialysis. The ideal target hemoglobin in patients with CKD is still not fully understood and there is no simple therapeutic algorithm that fits all patients. New therapies for anemia are being developed including alternative forms of iron and biosimilar epoietin that may have reduced toxicity and side effects. This study raises our clinical awareness of patients with moderate CKD and severe anemia as a high-risk population for which focused strategies and increased resources may improve hospital outcomes.

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