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Exploring the Association between Anemia and Negative Treatment Outcomes in Dialysis Patients at Medicare Facilities in the United States by County Poverty Levels

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Master of Public Health

Epidemiology

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Bachelor of Science

University of Georgia

2013

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Abstract

Exploring the Association between Anemia and Negative Treatment Outcomes in Dialysis Patients at Medicare Facilities in the United States by County Poverty Levels

By Emily Fawcett

End-stage kidney disease (ESKD), the final stage of chronic kidney disease (CKD) is a condition that affects thousands of adults annually. ESKD requires dialysis to ensure survival and has many comorbidities. Anemia is a common complication and is present in over half of all ESKD patients in the US. Anemia is also associated with an increased risk of negative health outcomes, most notably mortality and cardiovascular disease. Community-level poverty has also been shown to be associated with increased incidence and prevalence of ESKD and poorer medical care received.

This study investigated the association between anemia and the standardized ratios for mortality, hospitalization, readmission, and transfusion (SMR, SHR, SRR, and STrR) among Medicare dialysis facilities. In addition, poverty was included as an effect modifier of this relationship.

Data are from the Medicare Dialysis Facility Compare database, which collects patient data at dialysis facilities across the US. Poverty prevalence was obtained from 2010-2014 US Census data and matched to facilities based on county. Anemia was divided into high and low prevalence (facilities with less than 20% anemic patients were considered low prevalence), and poverty was divided into quintiles.

One-way ANOVAs were used to determine the relationship between anemia level and each of the four outcome variables individually. Next, multi-factor ANOVA incorporated poverty quintile as a predictor and an interaction term between anemia and poverty. Finally, two-way ANOVAs with only anemia and poverty as predictors were used for the outcome variables for which the interaction term was insignificant.

The means for SMR, SHR, SRR, and STrR all differed across anemia levels. In the multi-factor ANOVA, the interaction term was significant for the SMR and SRR models. Two-way ANOVA was run for the SHR and STrR models. Means for these two variables differed across both anemia levels and poverty quintiles.

Increased anemia prevalence had a negative impact upon SMR, SHR, SRR, and STrR. The effect of poverty was less well-defined, but means for the outcome variables varied across poverty quintiles. Trends were less coherent across poverty quintiles.

Future studies involving patient-level data rather than facility-level may improve the reliability of the results found here.

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Introduction

Disease Background

Kidney failure is the fifth and most severe stage of chronic kidney disease (CKD) and is quantified by a glomerular filtration rate of less than 15 mL/min per 1.73 m^2 (1). End-stage kidney disease (ESKD) is often used to describe patients with kidney failure, but it specifically refers to those who must be treated with either transplantation or dialysis to ensure survival (1-2). In a person with properly functioning kidneys, wastes and excess fluid are removed from the blood (3). When the kidney fails to function normally, waste products build up in the blood and increase blood pressure. In addition, excess fluids and minerals may be retained, while fewer red blood cells than required for normal function may be produced (3).

As of December 31, 2013, 661,648 people in the United States were living with ESKD. The unadjusted incidence rate of ESKD in the United States in 2013 was 363 cases per million per year (4), and adjusted incidence rates have slightly declined since a surge in the early 2000s. This is possibly due to advances in treatment and care of CKD that slow its progression to ESKD (4**)**. Despite the decline in incidence, prevalence has increased by 68% since 2000, which shows that patients diagnosed with ESKD are experiencing longer survival times (4). The annual prevalence of ESKD in 2013 was 1,901 cases per million, adjusted for age, gender, and race (4). Diabetes is the most common etiology of ESKD and is responsible for 43% of the overall incidence rate (4). Hypertension, the second most common etiology, causes 29% of the incidence rate of ESKD (4).

Apart from diabetes and hypertension, risk factors for ESKD include sex, race/ethnicity, age, and socioeconomic status (SES). Males are about 1.6 times more likely than females to be diagnosed with ESKD (4). Blacks have an incidence rate ratio of 3.0 compared to whites. The incidence rate ratio for Native Americans to Whites is 1.1, and for Asians/Pacific Islanders, it is 1.2 (4). The ratio comparing Hispanics to non-Hispanics is 1.4 (4). Older adults are more likely to develop ESKD than younger persons. The incidence rate of ESKD among those aged 75 or older was 1,646.9 cases per million, over 13 times greater than the incidence rate of the 22-44 year age group. The mean age at the start of ESKD therapy in 2013 was 62.5 (4). SES is another important factor in ESKD incidence. One study found a 41% lower odds of developing CKD among wealthy populations compared to less wealthy populations (5), and a different study found a 59% greater odds of CKD among low SES compared to high SES (6). Lower income has also been associated with increased levels of disability due to CKD (7) and a higher burden of treatment (8).

ESKD requires treatment with long-term hemodialysis, peritoneal dialysis, or a kidney transplant (3). Hemodialysis mimics the work of a healthy kidney by removing solutes and water from the bloodstream using an artificial filter. In peritoneal dialysis, capillaries in the peritoneum serve as a filter in place of the kidneys. Alternatively, patients may receive a transplant kidney from a living or a deceased donor. Among incident cases in 2013, 88.2% began treatment with hemodialysis, 9.0% started with peritoneal dialysis, and only 2.6% were initially treated with a kidney transplant (4). Just over 29% of prevalent cases of ESKD in the US received transplants in 2013, while the remainder continued to undergo dialysis (4). Of those receiving dialysis, 93% use

hemodialysis (HD) over peritoneal dialysis, and over 2.6 million people worldwide rely on hemodialysis to survive (4).

The 2013 mortality rate for ESKD was 137.8 per 1,000 patient-years at risk, adjusting for age, sex, race/ethnicity, ESKD etiology, and length of time since ESKD diagnosis (4). Mortality rates have fallen by 30% among all ESKD patients overall since 1996, but they remain higher than rates of heart failure and many cancers (4). The five-year survival rate in the United States has been increasing since 2000 and is now 42.6% (4). The five-year survival rate is 40.2% among hemodialysis patients and 50.3% among peritoneal dialysis patients (4). However, survival rates are much greater among patients who receive transplants than among those being treated with dialysis. Patients who receive transplants from deceased donors have a survival rate of 74.6%, and survival is 86.9% for living donor transplants (4). The high mortality rates may be due in part to comorbidities, such as cardiovascular disease and diabetes, which increase the mortality rate by 2 to 3 times for ESKD patients with these conditions compared to ESKD patients without them (4). In addition to high mortality rates, ESKD patients often experience a variety of complications, such as increased potassium levels, cardiovascular disease, anemia, central nervous system damage, and decreased immune response. These complications can lead to increased hospitalizations and hospital readmissions (9).

Patients suffering from ESKD tend to experience high rates of hospitalization and are responsible for a large part of health care resource utilization due to the intensive treatment required for ESKD and its associated comorbidities (4). Hospitalization among ESKD patients imposes a large financial burden on the Medicare system since Medicare spends $30.9 billion on ESKD patients annually, and inpatient care accounts for 40% of

this total. ESKD patients experience an average of 1.7 admissions per patient year and 11.2 days in the hospital per patient year, but these numbers have declined in the past decade (4). Hospitalization rates are lower for kidney transplant recipients (5.4 hospital days per patient year) as compared to those receiving hemodialysis or peritoneal dialysis (11.1 and 11.7 hospital days per patient, respectively). Rehospitalizations, or hospital admissions within 30 days of discharge, are a significant drain of resources because of a lack in coordination among medical care teams and poor overall health care quality. Additionally, readmissions are correlated with increased morbidity, mortality, and decreased quality of life, especially among ESKD patients. The readmission rate for ESKD patients in 2013 was 34.8%, greater than twice that of older Medicare patients without kidney disease, and 40.5% were readmitted and/or died within 30 days of hospital discharge.

Anemia

Anemia, a well-documented consequence of kidney disease (10-11), is the reduction in the number of red blood cells (RBCs) in the blood. This lessens the amount of oxygen in the blood that can be delivered to tissues and organs in the body (12). Erythropoietin, a hormone that regulates the production of RBCs, is released in response to a decrease of RBCs in the blood. Therefore, less oxygen circulates in the bloodstream, leading to the release of erythropoietin and subsequent production of erythrocytes (12). Patients with kidney damage tend to suffer from a lack of erythrocytes, leading to lower levels of RBC production than are necessary. The kidney is the main source of endogenous erythropoietin in the body, which may explain the link between kidney

disease and anemia. In addition, CKD patients often experience blood loss due to dialysis and a shortened survival of RBCs, both of which may contribute to development of anemia.

Hemoglobin (Hgb) measurements, or the proportion of RBCs in the blood, are used to diagnose anemia since they can be measured easily, unlike RBC counts (3, 12). Definitions for anemia vary among groups, but the WHO considers males with Hgb levels below 13.0 g/dL and women with Hgb below 12.0 g/dL to be anemic (3). Anemia is a common complication of CKD and is even more common among patients suffering from ESKD, with prevalence estimates ranging from 23% to 71% worldwide (13). In the United States, 53.4% of ESKD patients have anemia compared to 7.6% of the general population (14). The average Hgb level in ESKD patients at disease onset is 9.6 g/dL (4).

Anemia in CKD patients is associated with an increased risk of adverse outcomes, such as mortality, development of left ventricular hypertrophy (a marker of adverse cardiovascular events), and proliferative retinopathy, especially among diabetics (15-18). Very anemic patients with CKD experience a fivefold increase in risk of hospitalization due to myocardial infarction (19). Anemia has also been found to be associated with lowered cognition as well as a reduced immune response (12). In addition, anemia may actually hasten the progression of CKD/ESKD (20-21) and increase all-cause mortality (22). Fortunately, treating anemia in CKD patients tends to lead to improvements in physical function, cognitive function, social activity, and other quality of life indicators (23-25) and can slow progression of CKD (26).

Treatment for anemia initially involved red blood cell transfusions, which can cause serious negative side effects. Transfusions can lead to excessive levels of iron in

the blood and can lower the likelihood of transplant acceptance if an organ transplant is required in the future (11). However, in the late 1980s, recombinant human erythropoietin became available as a treatment option. With the development of erythropoiesis-stimulating agents (ESAs), there was an alternative to transfusions as an anemia treatment. Now, transfusions are used to treat anemia only in patients at a high risk for complications from ESA therapy, such as stroke, or for patients who did not improve upon treatment with ESAs.

ESAs act to increase RBC production in a similar mechanism to erythropoietin, leading to higher Hgb levels in the blood. While ESAs seem to have a renoprotective effect, some studies have shown negative effects in other parts of the body due to excessive ESA treatment (27). Attempting to normalize Hgb levels may be too drastic for most patients. Instead, ESAs should be used to increase Hgb levels only slightly (aiming for about 10.5-11.5 g/dL instead of 13-15 g/dL). Increasing Hgb to higher levels has been associated with death, cardiovascular events, and stroke (27-28, 38).

Another option for the treatment of anemia is the use of oral or intravenous iron agents. Iron supplementation can prevent iron deficiency in CKD patients receiving ESA, lower necessary ESA doses, and increase Hgb levels by increasing erythropoiesis activity (15).

Income/Poverty

Community-level poverty may influence the care that a patient with ESKD receives. Geographic variation exists in kidney transplantation rates and has been at least partially explained by SES. Counties with a higher median household income

experienced higher rates of transplantation, which may lead to higher survival rates (29). Additionally, low-income patients with CKD suffer a 1.58 times greater hazard ratio for mortality after adjusting for patient characteristics (30).

Furthermore, patients with lower income undergo a higher treatment burden than those with higher SES due to miscommunication with their doctors and difficulty enacting lifestyle changes (8). Barriers to receiving transplants and other obstacles to proper care may exacerbate the effect of anemia upon health outcomes experienced by those living with kidney disease.

Data Measures

In 1973, the US enacted legislation that provided public funding for dialysis and kidney transplantation through Medicare for those with ESKD who could not afford proper care, sustaining life for many Americans in need. Medicare provides data to compare dialysis facilities across the US over several metrics, including standardized mortality ratio (SMR), standardized hospitalization ratio for admissions (SHR), standardized readmission ratio (SRR), and standardized transfusion ratio (STrR). Medicare also reports the percentage of Medicare patients with Hgb levels below 10 g/dL to indicate the proportion of patients at each facility suffering from anemia.

Mortality is a negative consequence of any disease, so SMR is an important outcome to study. In addition, increased hospitalization reflects higher morbidity among dialysis patients and a decreased quality of life. Therefore, hospitalization ratios are another important treatment outcome to assess. Unplanned hospital readmission ratio is another indicator of patient morbidity and quality of life due to the negative impact of

unplanned hospital stays. Since transfusion is often the last resort option to treat anemia in dialysis patients, the STrR represents either a failure in alternative anemia treatment methods or an underutilization of these alternative methods (such as ESAs and iron therapy) by the facility.

Hypothesis

We plan to investigate whether anemia (measured by percentage of patients at a facility with Hgb < 10 g/dL) is associated with poorer health outcomes (standardized mortality, hospitalization, readmission, and transfusion ratios). Additionally, we will look at how community poverty level affects the relationship between anemia and these health outcomes.

Methods

Study Population and Data Source

The study population is composed of facility-level patient populations from ESKD treatment facilities in the United States included in Medicare's Dialysis Facility Compare database for the fiscal year 2014-2015 (31). Data came from quarterly Medicare claims data through the National Claims History Analytical Files as well as facility information from Consolidated Renal Operations. Data for local poverty were obtained from 2010-2014 US Census data, and facilities were matched to poverty data based on the county of the facility location (32). In all, 2,840 facilities in 1,215 counties and all 50 states plus Washington, D.C. were included in the dataset.

Measurements

Exposure: Anemia prevalence for each facility was assessed by using the percentage of patients at the facility with Hgb levels less than 10 g/dL (n=2,486). Three hundred fifty-four facilities were missing values for anemia.

Outcome: The standardized mortality, readmission, hospitalization, and transfusion ratios were calculated prior to inclusion in the Medicare Dialysis Facility Compare database. The SMR, SHR, SRR, and STrR equal the actual number of events divided by the expected total number of events. Thus, a ratio greater than 1.0 shows that more events were observed than expected, while a result less than 1.0 indicates fewer observed events than expected. These ratios serve as a comparison of each individual facility to a national average.

For the expected mortality rate, SMR used national death rates of dialysis patients with similar demographics as those in a particular facility. The expected mortality is adjusted for patient age, race, ethnicity, sex, diabetes, duration of ESKD, nursing home status, comorbidities at incidence, BMI at incidence, and calendar year. It also controlled for age-adjusted population death rates by state and race. SMR is calculated by dividing the facility's death rate by the expected mortality rate, adjusting for the above factors.

SHR compares a given facility's hospital admission rates to the expected number of hospital admissions based on the national average. The expected number of admissions is adjusted for the above confounders except race and ethnicity. Instead of time since ESKD diagnosis, SHR was adjusted for ESKD duration, which was divided into the following cut points: 6 months, 1 year, 2 years, 3 years, and 5 years. For a given patient, the time at risk is multiplied by the adjusted national admissions rate for that time interval, and this result is summed over all patients at a facility to determine the expected total admissions for that facility.

The SRR compares unplanned readmissions to the average national readmission rate. The expected number of readmissions for a facility comes from the number and characteristics of hospital discharges, adjusted for the discharging hospital and the same patient characteristics controlled for in the measures listed for SHR except for nursing home status and calendar year. The expected number is also adjusted for high-risk diagnoses at discharge as well as length of stay of index hospitalization.

STrR uses transfusions as a gauge of success in treating anemia and general patient care. It was adjusted for patient age, diabetes status, ESKD duration, nursing

home status, comorbidities at ESKD diagnosis, BMI at diagnosis, and calendar year. ESKD duration is divided into the same 6 intervals as SHR when used to adjust for STrR.

Other Variables: Facilities were matched to county poverty data from the 2014 US Census (32). Poverty was measured by using the percentage of individuals in a county whose income in the last 12 months was below the poverty line. We treated poverty as an effect modifier of anemia.

Statistical Analysis

Data were described and analyzed using SAS version 9.4 (SAS Institute, Cary NC). Data were checked for outliers and duplicate observations, but none were found. Anemia prevalence (percentage of patients at a facility with Hgb < 10 g/dL) was divided into two categories, high and low anemia prevalence, based upon the distribution, and the cut point was 20%. Facilities with anemia prevalence less than 20% were considered to have low anemia prevalence, while those with anemia levels greater than or equal to 20% had high anemia prevalence. Poverty level was divided into quintiles for data analysis. Relationships between exposure and outcome variables were viewed to assess linearity. Observations with missing values for the exposure variable of anemia prevalence were removed from the dataset.

One-way analysis of variance (ANOVA) tests were used to assess differences in the means of negative health outcomes (SMR, SHR, SRR, and STrR) across both levels of anemia prevalence. Next, multi-factor ANOVA was employed to add poverty level as an exposure variable and as an effect modifier to the model. In instances where no

evidence was found for poverty quintiles as an effect modifier, the interaction term between poverty and anemia prevalence was dropped from the model.

Confounding by many factors was controlled for in calculating the outcome variables (SMR, SHR, SRR, and STrR) as mentioned above.

Results

Descriptive Statistics

Data on anemia prevalence was found for 2,486 of the 2,840 facilities included in the Medicare Dialysis Facility Compare database. Those facilities missing data on anemia prevalence (n = 354) were removed from the data set. Among the remaining observations, 344 were missing data on SMR, 35 had missing values for SHR, 44 lacked SRR values, and 121 values were missing for STrR. Forty-six observations were missing data for county poverty level.

The mean for anemia prevalence among all facilities was 15.9% (SD = 11.9), ranging from 0 to 85% (**Table 1**). The percentage of individuals living below the poverty line by county ranged from 3.8 to 52.6% with a mean of 16.7% (SD = 6.1). Among all facilities, the mean for SMR was 1.01 (SD = 0.29), SHR was 0.98 (SD = 0.29), SRR was 0.98 (SD = 0.28), and STrR was 0.99 (SD = 0.52) (**Table 1, Figures 1-4**). Overall, SMR ranged from 0.00 to 3.35 with an IQR of 0.31 and median of 0.99, SHR varied from 0.15 to 2.38 with IQR 0.35 (median = 0.95), and SRR ranged from 0.00 to 2.45 (IQR = 0.35; median = 0.99). STrR had the widest range, from 0.00 to 4.45 with a median of 0.91, and its IQR of 0.62 was also the largest.

When divided into quintiles based upon poverty level, the mean for anemia prevalence ranged from 15.4% (SD = 11.2) to 16.4% (SD = 11.9). When poverty was divided into quintiles, SRR had the smallest range of means (0.97 to 0.99), and STrR had the largest (0.93 to 1.03) (**Figure 3, Figure 4**). SMR's mean by poverty quintile ranged from 0.99 to 1.01, and SHR varied from 0.96 to 1.00 (**Figure 1, Figure 2**).

One-way ANOVA analysis for SMR showed a significant difference in means between high and low anemia prevalence (F value = 16.08; $p < .0001$) (**Table 2**). However, the R^2 value was 0.007. Therefore, less than one percent of the variation within SMR can be explained by anemia quintile. Similar results were found for the remaining outcome variables (SHR, SRR, and STrR). The means for SHR also differed across anemia levels ($F = 45.06$; $p < .0001$) with an R^2 value of 0.018. The ANOVA test for SRR was also significant ($F = 9.72$; $p = .0018$) with an R^2 value of 0.004. Finally, STrR significantly varied across anemia levels ($F = 68.66$; $p < .0001$) with an R^2 value of 0.028.

A multi-factor ANOVA analysis using anemia levels, poverty quintiles, and an interaction term between the two were used to investigate the effect of these variables on outcomes. The interaction term used to assess effect modification was removed from models in which it was found to be insignificant. Therefore, we conducted two-way ANOVA using only anemia levels and poverty quintiles as the predictor variables in the models for SHR and STrR.

The models for SMR and SRR found both anemia levels ($F = 24.33$, $p < .0001$; $F = 11.58$, $p = .0007$) and the interaction term to be significant ($F = 3.00$, $p = 0.0177$; $F = 3.51$, $p = 0.0073$), but not the poverty quintile ($F = 1.93$, $p = 0.1025$; $F = 0.55$, $p = 0.7000$) (**Table 3**). The model for SMR had an R^2 value of 0.018, and the R^2 for the SRR model was 0.012.

For SHR, both anemia levels ($F = 47.74$, $p < .0001$) and poverty quintiles ($F = 3.27$, $p = 0.0110$) were found to be significant at the significance level of 0.05, but the interaction term was insignificant ($F = 0.71$, $p = 0.5842$) (**Table 3**). The R^2 value was

0.026. Since the interaction term was insignificant, it was dropped from the model. In the reduced model, both anemia levels ($F = 47.76$, $p < .0001$) and poverty quintiles ($F = 3.27$, $p = 0.0110$) remained significant, and the R^2 value was 0.025 (**Table 5**). Both anemia levels ($F = 73.25$, $p < .0001$) and poverty quintiles ($F = 3.27$, $p = 0.0111$) were significant in the model for STrR, which had an R^2 value of 0.036 (**Table 3**). However, the interaction term was not significant ($F = 0.00$, $p = 1.0000$). Thus, we removed the interaction term and found that the reduced model retained an R^2 value of 0.036, and both anemia level ($F = 73.38$, $p < .0001$) and poverty quintile were significant predictors ($F = 3.27$, $p = 0.0110$) (**Table 5**).

The one-way ANOVA tests for significant differences in means for each of the four outcome variables were significant, but they all had relatively low R^2 values (ranging from 0.004 to 0.028), indicating that little of the variation in the outcome variables (from 0.4 to 2.8%) can be explained by anemia prevalence. Anemia prevalence was statistically significant but did not explain much of the variation in the outcomes.

After the one-way ANOVA tests, we performed multi-factor ANOVA to determine the significance of poverty quintile as an effect modifier on anemia level. Poverty quintile was not statistically significant as an effect modifier in two of the four models and therefore was removed from the models for SHR and STrR. For SMR, anemia quintile was found to be significant ($F = 24.33$, $p < .0001$), but poverty quintile was not ($F = 1.93$, $p = 0.103$). The interaction term, however, was significant ($F = 3.00$, $p = 0.0177$) The R^2 value was 0.018, with 1.8% of the variation in SMR explained by anemia level, poverty quintile, and an interaction term between the two. Anemia level was significant for SRR ($F = 11.58$, $p = .0007$), but poverty level was not ($F = 0.55$, $p =$

0.7000). The interaction term was significant ($F = 3.51$, $p = 0.0073$). The R^2 value was 0.012.

Two-way ANOVA using only anemia level and poverty quintile as predictor variables was then performed for the outcomes of SHR and STrR. Both anemia level and poverty quintile were significant in the model tested for SHR ($F = 47.76$, $p < .0001$; $F = 3.27$, $p = 0.0110$) with an R^2 value of 0.025. Finally, both anemia level and poverty quintile were significant in the STrR model ($F = 73.38$, $p < .0001$; $F = 3.27$, $p = 0.0110$), and the R^2 value was 0.036. Thus, the model for STrR based on anemia prevalence and poverty level has the highest R^2, and it explains the most variation within the outcome variable compared to the other three models.

Discussion

The primary aim of this study was to assess the relationship between facility anemia prevalence and the negative health outcomes of SMR, SHR, SRR, and STrR. In addition, we considered the independent and joint effect of county poverty level and anemia prevalence as predictors in our models. ANOVA tests were used to determine whether the means of the outcome variable (SMR, SHR, SRR, or STrR) differed across anemia levels.

This study found statistically significant relationships between anemia prevalence and the study outcomes (SMR, SHR, SRR, and STrR), but these relationships all produced small R^2 values (ranging from 0.004 to 0.028). In addition to anemia levels, poverty levels were also significant for SHR and STrR, but poverty was not significant in the SMR and SRR models. However, the interaction term was significant in the SMR and SRR models but was not significant in the SHR and STrR models. The multi-factor ANOVA models also produced fairly low R^2 values (ranging from 0.012 to 0.036).

Thus, anemia is a predictor of the negative health outcomes of SMR, SHR, SRR, and STrR because higher anemia levels were associated with higher levels of SMR, SHR, SRR, and STrR. Poverty, however, does not show a clear linear relationship across its quintiles for any of the outcomes studied. SMR means increased from the first to fourth poverty quintiles but decreased slightly at the fifth quintile. SHR means remained fairly constant across poverty quintiles with a surge at the third quintile. Patterns for SRR means were fairly erratic among the high anemia prevalence facilities, with a decrease from the first (0.98) to second (0.95) quintile, a sharp spike to the third quintile (1.05), and a gradual decrease to the fifth quintile (1.03). Among low anemia prevalence

facilities, SRR levels remained fairly consistent. Finally, STrR means were also steady across poverty quintiles among both low and high anemia prevalence facilities.

Many confounders, such as patient age, race, sex, comorbidities, BMI, duration of disease, diabetes status, and nursing home status, were previously controlled for in the calculation of the outcome variables used (SMR, SHR, SRR, STrR), so there was no need to control for them again in our analysis.

Since this study was observational in nature, it is unable to establish causality on its own. However, using the Bradford Hill criteria for establishing association, a strong case may be made for causality. These criteria include temporal relationship, strength, dose-response, consistency, plausibility, coherence, experiment, specificity, and analogy. First, the relationship between the exposure (anemia) and each of the outcomes (SMR, SHR, SRR, and STrR) is temporal because anemia always precedes the outcome of mortality, hospitalization, rehospitalization, or transfusion. Next, although the association between outcomes and anemia were statistically very strong in our ANOVA tests, with p-values ranging from <.0001 to 0.0018, the size of the effect varied. In comparing the high versus low anemia groups, facilities with high anemia had a 5.0% greater SMR than facilities with low anemia. There was a 9.0% difference for SHR, a 4.1% difference for SRR, and a 21.3% difference for STrR. The change in effect for SMR and SRR are fairly low, that of SHR is moderate, and STrR is somewhat stronger. Thus, the strength of association criterion is likely met for the STrR outcome, possibly satisfied for SHR, and might be viable for SMR and SRR.

Third is the dose-response or biological gradient criterion. This trend holds true for the relationship between SMR and anemia only because higher anemia prevalence is

associated with higher SMR, both at the aggregated level and upon dividing into poverty quintiles (**Table 2, Figure 1**). However, this description of the relationship is not entirely accurate when poverty quintiles are added to the model. Among facilities with low anemia prevalence, SMR increases for the first four quintiles of poverty but decreases for the fifth quintile (**Figure 1**). Among high-anemia facilities, SMR starts at 1.10 for the first quintile of poverty but sharply decreases to 1.01 at the second quintile. Then, it gradually increases and levels off at the fifth quintile.

The means for SHR were higher among facilities with high levels of anemia compared to those with low anemia in aggregated form and at each poverty quintile (**Table 2, Figure 2**). However, graphing the data does not reveal a dose-response across poverty level. Among low-anemia facilities, the means for SHR remain fairly constant for the first four quintiles and drop at the last quintile (**Figure 2**). For high-anemia facilities, the means for SHR are fairly constant across quintiles except for a slight peak in the third quintile.

Overall, the mean for SRR was higher among the high-anemia facilities than in the low-anemia ones (**Table 2**). However, of the four outcome variables examined, SRR was the only one in which the outcome was greater in the low-anemia facilities than in the high-anemia ones after dividing into poverty quintiles (**Figure 3**). In the second quintile of poverty, low-anemia facilities actually have a higher SRR (0.99) than high-anemia facilities do (0.95). Here, there is no logical dose-response mechanism among either low-anemia or high-anemia facilities. In low-anemia facilities, the second quintile has the highest SRR (0.99), the fifth has the lowest (0.95), and the other three are fairly similar. Among high-anemia facilities, the mean SRR starts at 0.98 for the first quintile of

poverty, decreases to 0.95 for the second, and jumps to 1.05 for the third quintile, from which it gradually decreases to 1.03 in the fifth poverty quintile.

Finally, the means for STrR among high-anemia facilities are higher than those of low-anemia facilities at the aggregated level and when the data is divided into poverty quintiles (**Table 2, Figure 4**). The trend across poverty quintiles, however, is nonexistent among both classes of anemia (**Figure 4**). Both groups appear to exhibit no visible trend across poverty quintiles.

Consistency is another component of the Bradford Hill criteria for causality, and many studies have found similar results to ours using different methods. Other studies have investigated the impact of anemia on mortality in patients with kidney disease and have found that increased levels of anemia are associated with increased mortality. Locatelli et al. found a strong association between hemoglobin levels and mortality among hemodialysis patients (33), and Collins et al. detected up to a 40% increase in mortality and hospitalizations among dialysis patients with hemoglobin levels below 11.0 g/dL (34). A prospective study by Portolés et al. found increasing hospital admission rates with decreasing hemoglobin levels (35), and another study based on insurance claims found a fivefold greater risk of hospitalization among patients with severe anemia compared to patients with normal hemoglobin levels (19). Hospital readmissions, another important indicator of patient health and quality of care received, have also been investigated in conjunction with anemia levels. A retrospective cohort study by Luthi et al. found increased odds of rehospitalization for patients with anemia compared to those with normal hemoglobin levels (OR = 1.60; 95% CI 1.00-2.58) after controlling for other potential risk factors (36). Finally, other studies have delineated the relationship between

low hemoglobin levels and high transfusion rates. A retrospective cohort study by Collins et al. looked into the association between dialysis facility hemoglobin levels and patients' transfusion risk and found that patients at facilities with the highest anemia prevalence had a relative risk of 1.28 (95% CI 1.22-1.34) for receiving red blood cell transfusions within a three-month period (37).

Next, the results we have found seem to be plausible based on biological mechanisms and the ill effects of anemia on the population as a whole as well as specific negative effects on persons with CKD, such as mortality, cardiovascular disease, increased hospitalization, and accelerating progression of CKD (12, 15-19, 20-22). Higher levels of anemia will increase the SMR, SHR, and SRR (19, 33-36). However, STrR rates should remain high only if anemia in patients at a particular facility is not well-controlled.

The associations between anemia and SMR, SHR, SRR, and STrR also meet the Bradford Hill criteria of coherence, meaning that current knowledge of anemia, CKD, and these outcomes logically support this association. For example, patients with severe anemia may require a blood transfusion, which directly increases the STrR. This in turn increases the SHR because hospitalization is required in order to receive a transfusion. Finally, increased hospitalizations increase the potential for more rehospitalizations. Additionally, a patient who requires one transfusion will likely need another, which increases the SRR (4). However, due to the nature of the dataset used in this study, we are unable to determine the percentage of readmissions that are due to transfusions and ultimately caused by anemia.

The experiment criterion is satisfied because studies have shown improvements in disease outcome when anemia has been adequately treated and controlled (23-26). Specifically studies have found that ESA therapy can slow the progression of CKD (26), reduce the number of hospitalizations (24) and improve quality of life (23, 25).

However, caution should be used when utilizing ESA therapy because raising hemoglobin levels too high may have detrimental cardiovascular effects. The TREAT study, conducted among type 2 diabetics with CKD, was a double-blinded placebo controlled study that found a hazard ratio of 1.92 (95% CI 1.38-2.68) for stroke for the experimental group (mean Hgb = 12.5 g/dL) compared to the control group (mean Hgb = 10.6 g/dL) (38). In addition, an earlier study on cardiac outcomes based on erythropoietin treatment was cut short because of the high mortality in the experimental group (39). Thus, normalization of hemoglobin levels is not necessary and potentially dangerous for adequate anemia treatment among dialysis patients.

A few of the Bradford Hill criteria may or may not be met in terms of the association between anemia and the negative treatment outcomes studied here. The specificity criterion may not be met because many factors lead to changes in mortality, hospitalization, readmission, and transfusion rates. Anemia could very well be responsible for these changes, but uninvestigated confounders, such as general quality of care could be part of the cause. Finally the analogy component is difficult to assess due to the uniqueness of anemia and its effects on the body and subsequent effects upon SMR, SHR, SRR, and STrR.

The data for our study came from the Medicare Dialysis Facility Compare website, a data source that informs patients as well as providers about the quality of care

at all Medicare dialysis facilities in the United States. Data for each facility use a variety of measures that are compared against a national average in order to show how each facility ranks compared to the rest of the nation. This study has shown the negative impacts of anemia upon mortality, hospitalization, rehospitalization, and the need for transfusion, so anemia management is crucial for the health of dialysis patients and the quality of dialysis facilities. Due to the results of the studies mentioned above (38-39), the discrepancy in health benefits of anemia treatment and detrimental effects of cardiac events caused by increasing hemoglobin levels caused difficulties in determining a set guideline for target hemoglobin levels in renal disease patients with anemia. Because of this, the Centers for Medicare and Medicaid Services have not set a specific guideline for proper hemoglobin levels. Instead, they collect data only on the percentage of patients at a facility with hemoglobin levels less than 10 g/dL and those with hemoglobin greater than 12 g/dL.

When selecting a facility for dialysis, patients may want to keep this information in mind to ensure they choose a facility that prioritizes anemia treatment. In addition, providers should increase their focus upon anemia management to improve the health and wellness of their patients as well as to increase the ratings of their facility.

In addition to anemia, poverty also has an effect on some negative treatment outcomes. SES has been shown to be associated with not only the incidence and prevalence of ESKD, but also with treatment (40). It is unknown exactly how SES is responsible for this effect, but one possibility is due to lack of healthcare access. Additionally, low-SES patients are less likely to receive a kidney transplant, which may strongly decrease an ESKD patient's health and quality of life.

Limitations

One of our study's limitations was the use of standardized ratios and aggregated patient data for each facility. This may not provide an accurate reflection of each individual patient suffering from ESKD. Therefore, the conclusions drawn from this study might be subject to the ecological fallacy because we draw conclusions about individual risks from aggregated data. Another limitation is the use of ANOVA as the main test of association. ANOVAs test whether the means of one or more groups differ, but it does not show trends across groups. Because of this, our results can tell us that the means for SMR and the other outcomes differ across quintiles of poverty, but we cannot conclude that SMR increases with increasing poverty quintile or vice versa.

Conclusions

ESKD is a significant health problem in the United States that affects over 600,000 persons. It regularly drains health care resources, in part due to high rates of hospitalization, costing Medicare $30.9 billion annually. ESKD is associated with high mortality rates and a variety of complications, including anemia, which may worsen treatment outcomes. CKD patients with anemia experience increased mortality and other adverse health outcomes (16-18) and may progress to ESKD more quickly (20-21). Anemia treatment can reduce the risk of these negative outcomes (23-25) and even slow the progression of CKD (26). In addition to anemia's negative effect upon those suffering from CKD and ESKD, poverty has also been shown to influence CKD outcomes. Low-income patients with CKD experience a 1.58 times greater hazard ratio for mortality (30), and they undergo a higher treatment burden than high-income individuals with the

disease. Low-SES individuals are also less likely to receive a kidney transplant, which further reduces their likelihood of survival (29).

Future Directions

Further studies may investigate similar data using observations from individual patients in order to prevent the ecological fallacy. In addition, other potential predictors should be included in the model instead of anemia and poverty alone. Many confounders were already controlled for in calculation of the outcome variables, but more previously uninvestigated confounders may exist.

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Tables

Table 1. Facility Characteristics.

	All Facilities		Characteristics of Facilities by Poverty Level									
			Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
Characteristic	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
% Anemic	2486	15.9 (11.4)	477	16.4 (11.9)	469	15.4 (11.2)	489	16.1 (11.2)	559	15.7 (11.4)	446	16.4 (11.6)
SMR	2142	1.01 (0.29)	462	0.99 (0.30)	448	0.99 (0.26)	478	1.00 (0.24)	543	1.03 (0.31)	436	1.01 (0.28)
SHR	2451	0.98 (0.29)	469	0.96 (0.28)	457	0.99 (0.31)	487	1.00 (0.27)	553	0.99 (0.29)	441	0.94 (0.30)
SRR	2442	0.98 (0.28)	466	0.97 (0.30)	453	0.98 (0.27)	486	0.99 (0.28)	552	0.99 (0.28)	440	0.97 (0.27)
STrR	2365	0.99 (0.52)	450	0.93 (0.51)	434	1.03 (0.59)	471	0.96 (0.28)	534	1.03 (0.53)	433	0.99 (0.48)
Poverty	2440	16.7 (6.1)	477	8.86 (1.84)	469	13.26 (0.97)	489	16.49 (0.88)	559	18.89 (0.81)	446	25.98 (4.90)

Table 2. Results of one-way ANOVA testing with means by levels of anemia prevalence (high vs. low) for each outcome variable.

	Low Anemia Prevalence		High Anemia Prevalence				
	n	**Mean (SD)**	**n**	**Mean (SD)**	**F Value**	**p-value**	**R^2**
SMR	1775	1.00 (0.26)	637	1.05 (0.34)	16.08	**<.0001**	0.007
SHR	1799	0.95 (0.28)	652	1.04 (0.30)	45.06	**<.0001**	0.018
SRR	1789	0.97 (0.28)	653	1.01 (0.26)	9.72	**0.0018**	0.004
STrR	1741	0.94 (0.48)	624	1.14 (0.60)	68.66	**<.0001**	0.028

Table 3. Means of outcome variables by levels of anemia and poverty quintiles.

Poverty Quintile	**1**		**2**		**3**		**4**		**5**	
Anemia Level	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**
SMR Means	0.95 (0.24)	1.10 (0.41)	0.98 (0.23)	1.01 (0.32)	0.99 (0.23)	1.03 (0.29)	1.02 (0.27)	1.06 (0.39)	1.00 (0.28)	1.05 (0.26)
SHR Means	0.94 (0.27)	1.03 (0.29)	0.97 (0.30)	1.03 (0.31)	0.97 (0.26)	1.09 (0.28)	0.97 (0.27)	1.05 (0.33)	0.91 (0.29)	1.03 (0.29)
SRR Means	0.96 (0.31)	0.98 (0.29)	0.99 (0.27)	0.95 (0.26)	0.97 (0.28)	1.05 (0.27)	0.97 (0.28)	1.04 (0.26)	0.95 (0.28)	1.03 (0.22)
STrR Means	0.88 (0.45)	1.08 (0.63)	0.97 (0.56)	1.19 (0.65)	0.90 (0.43)	1.13 (0.59)	0.97 (0.47)	1.18 (0.62)	0.94 (0.47)	1.11 (0.51)

Table 4. Statistical significance of results of multi-way ANOVA testing for anemia levels, poverty quintiles, and the interaction term for the models for each of the four outcomes. The p-values for the interaction term were significant for the SMR and SRR models and insignificant for the SHR and STrR models.

Model	Variable	F Value	p-value	R^2
SMR	Anemia	24.33	**<.0001**	0.018
	Poverty	1.93	0.1025	
	Anemia*Poverty	3	**0.0177**	
SHR	Anemia	47.74	**<.0001**	0.026
	Poverty	3.27	**0.0110**	
	Anemia*Poverty	0.71	0.5842	
SRR	Anemia	11.58	**0.0007**	0.012
	Poverty	0.55	0.7000	
	Anemia*Poverty	3.51	**0.0073**	
STrR	Anemia	73.25	**<.0001**	0.036
	Poverty	3.27	**0.0111**	
	Anemia*Poverty	0.00	1.0000	

Table 5. Results of two-way ANOVA testing for SHR and STrR. Models dropped the interaction term that was included in the multi-way model.

		Anemia Level/Poverty Quintile												
		Low/1		**High/2**		**3**		**4**		**5**		**F value**	**p-value**	**R^2**
		n	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**			
SHR Means	**Anemia Level**	1758	0.95 (0.28)	649	1.04 (0.30)							47.76	**<.0001**	0.025
	Poverty Quintile	469	0.96 (0.28)	457	0.99 (0.31)	487	1.00 (0.27)	553	0.99 (0.29)	441	0.94 (0.30)	3.27	**0.011**	
STrR Means	**Anemia Level**	1701	0.93 (0.48)	621	1.14 (0.60)							73.38	**<.0001**	0.036
	Poverty Quintile	450	0.93 (0.51)	434	1.03 (0.59)	471	0.96 (0.49)	534	1.03 (0.53)	433	0.99 (0.48)	3.27	**0.011**	

Figures

Figure 1. SMR means by anemia levels within poverty quintiles

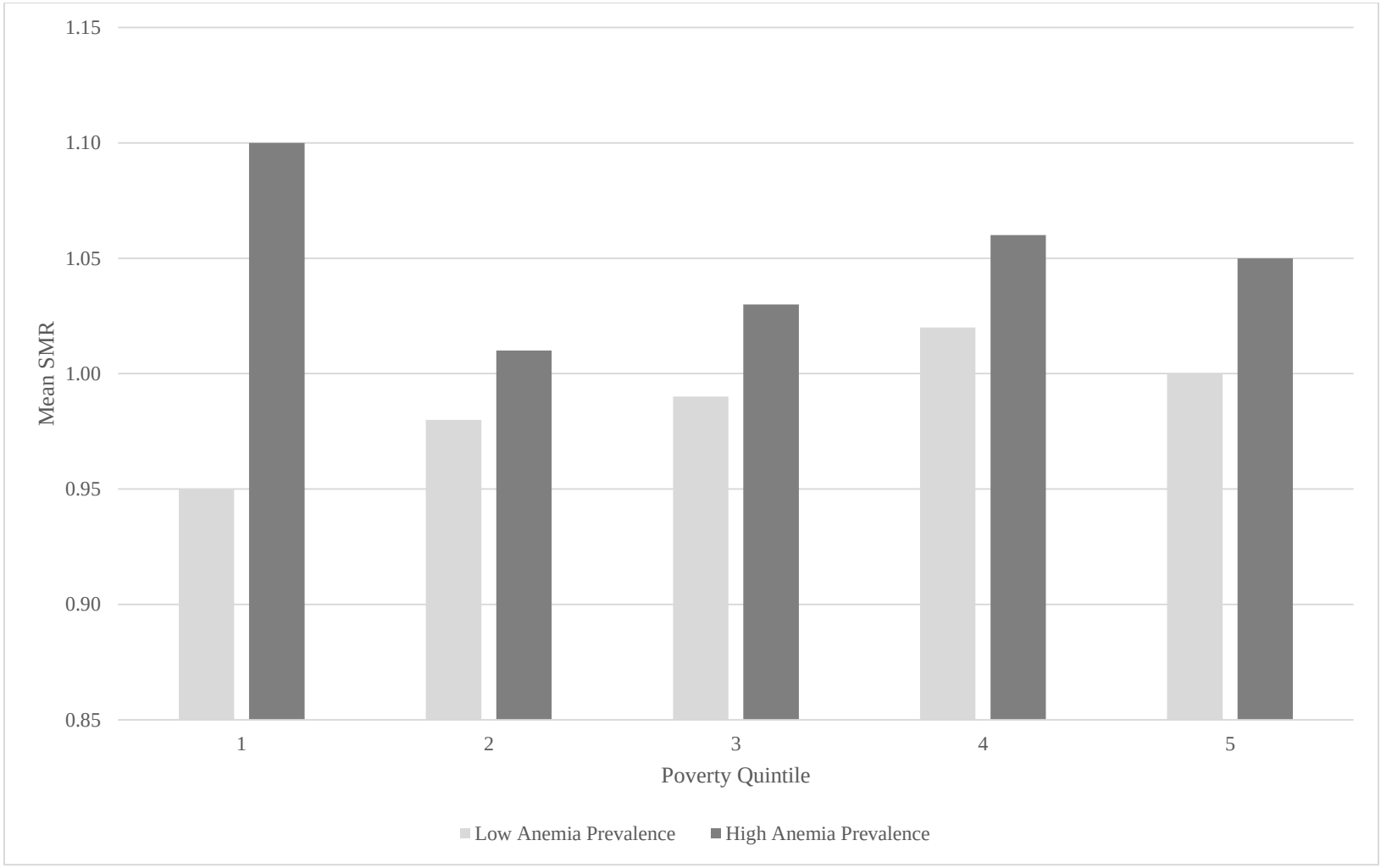

Figure 2. SHR means by anemia quintiles and poverty quintiles.

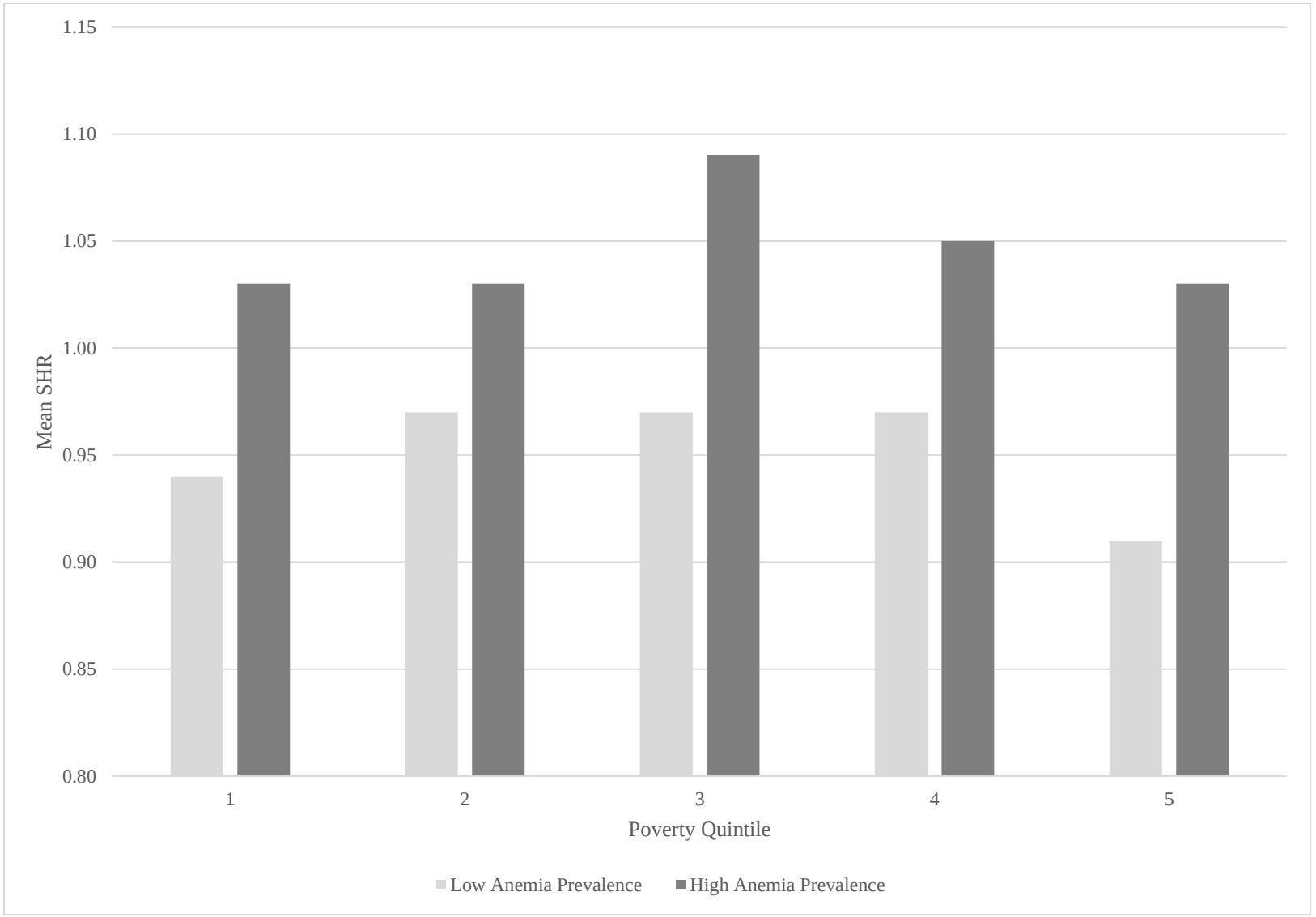

Figure 3. SRR means by anemia quintiles and poverty quintiles.

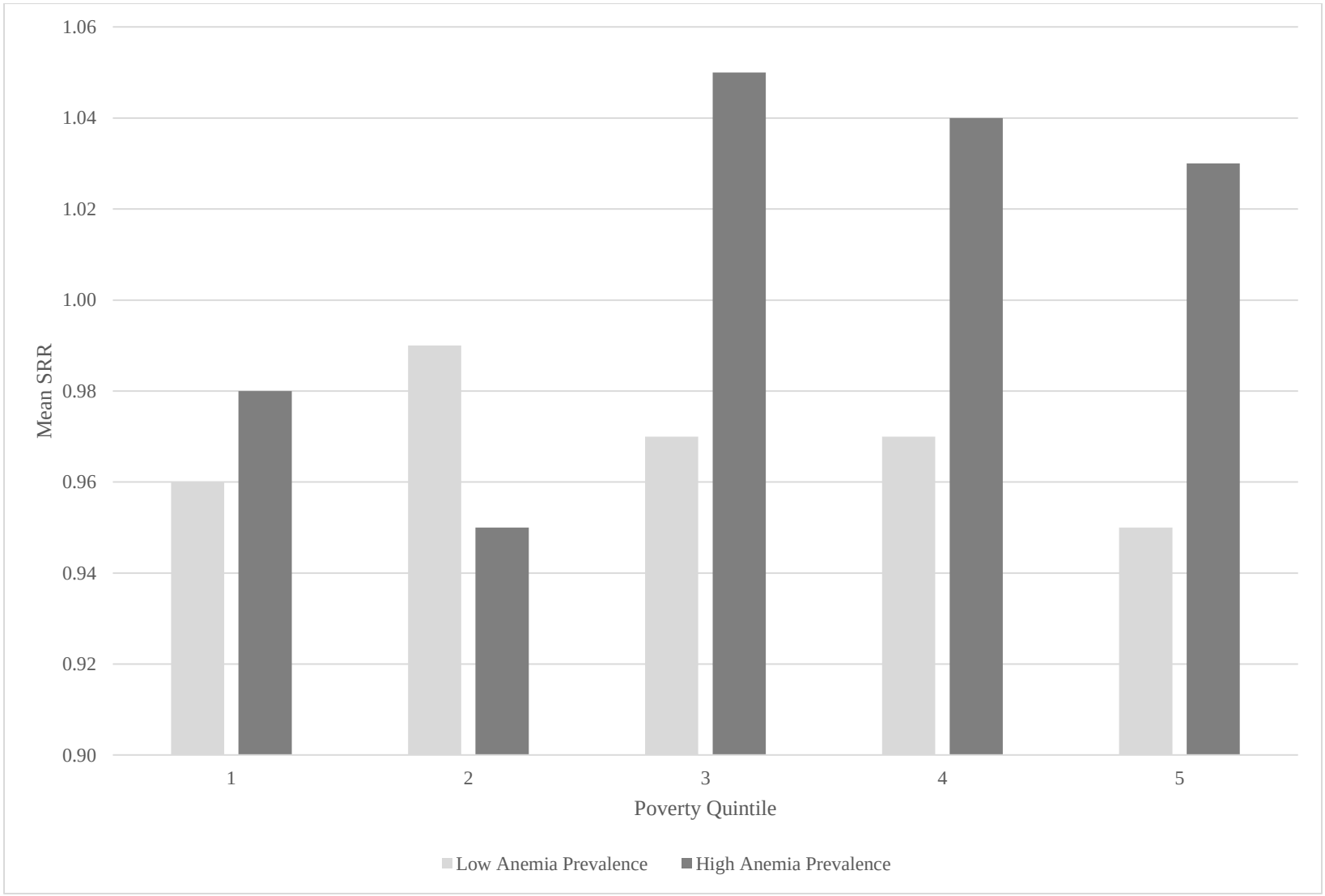

Figure 4. STrR means by anemia quintiles and poverty quintiles.