Hemoglobin and Clinical Outcomes in Hemodialysis: An Analysis of US Medicare Data From 2018 to 2020

Eric W. Young, Dongyu Wang, Alissa Kapke, Jeffrey Pearson, Marc Turenne, Bruce M. Robinson, and Edwin D. Huff

Rationale & Objective: Anemia management in patients treated with maintenance dialysis remains a challenge. We sought to update information in this area by evaluating the association between hemoglobin and various outcome and utilization measures using data-rich Medicare sources.

Study Design: Observational cohort study using data from the Consolidated Renal Operations in a Web-enabled Network and Medicare claims.

Setting & Participants: We studied 371,250 prevalent patients treated with hemodialysis, covering 3,326,072 patient-months in 2019.

Exposure: Monthly patient hemoglobin concentrations.

Outcomes: We examined several outcomes, including mortality, all-cause hospitalization, cause-specific hospitalization, and emergency department utilization in the month following the exposure measurement.

Analytical Approach: For each monthly observation period, we calculated unadjusted and adjusted (for demographics and comorbid condition) hazard ratios using Cox regression.

Results: The hemoglobin concentration was <10.5 g/dL for 40% of observations. We found an inverse association between mortality and hemoglobin measured over a range from <9 g/dL (HR, 2.53; 95% CI, 2.45-2.61; $P < 0.0001$, reference = 10.5-11 g/dL) to 11-11.5 g/dL (HR, 0.92; 95% CI, 0.89-0.96; $P < 0.0001$). Mortality risk started to increase at hemoglobin levels >11.5 g/dL. All-cause hospitalization, cause-specific hospitalization (including cardiovascular, infection, and several subcategories including coronavirus disease 2019 hospitalization), and emergency department utilization were inversely associated with hemoglobin concentration, with risk reduction stabilizing at hemoglobin levels of approximately 11.5-12 g/dL and higher.

Limitations: As with prior observational studies, the observed associations are not necessarily causal.

Conclusions: In a large US hemodialysis population, there were better clinical outcomes at higher hemoglobin concentrations over short exposure and follow-up periods, consistent with other observational studies that generally used longer exposure and follow-up times. Mortality risk increased at hemoglobin concentrations >11.5 g/dL, consistent with findings from erythropoiesis-stimulating agent clinical trials. The apparently beneficial short-term effects associated with higher hemoglobin concentrations suggest that hemoglobin measurements capture unmeasured elements of patient risk.

Visual Abstract included

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The majority of patients with advanced kidney disease have some degree of anemia. Patients with kidney failure treated by dialysis also face higher mortality and morbidity risks and lower quality of life than the general population. A widely held hypothesis holds that anemia accounts for some of the excess health risks faced by patients with kidney failure treated by dialysis and that correction of anemia could ameliorate some of the excess risk. These hypotheses have been extensively tested over the past 30 years but not fully resolved.[1,2]

The Medicare Improvements for Patients and Providers Act of 2008 directed establishment of the End-Stage Renal Disease Quality Incentive Program (ESRD QIP), including a specific provision for measurement of anemia management that reflects the labeling approved by the Food and Drug Administration.[3] The ESRD QIP has employed several measures of anemia-related performance.[4] The Centers for Medicare & Medicaid Services (CMS) requires dialysis facilities to provide anemia management data to support the ESRD QIP anemia measures. The clinical and claims data used by ESRD QIP represents a valuable research resource. We took advantage of this rich data resource to describe the association between hemoglobin concentration and important patient-relevant outcomes of mortality, hospitalization, and emergency department (ED) utilization.

METHODS

The study was conducted under a monitoring and evaluation contract with the CMS. The CMS Privacy Board approved the use of CMS data (CONT-2016-50530), and the study was granted human subjects exempt status by the Ethical and Independent Services Institutional Review Board (E&I ID#20013).

The main exposure variable was hemoglobin concentration as reported via Consolidated Renal Operations in a Web-enabled Network by dialysis facilities for all patients treated with maintenance dialysis at the end of each month. We used monthly hemoglobin levels recorded from December 2018 through November 2019. We measured outcomes in the month following each hemoglobin measurement. The analysis was restricted to hemodialysis patients covered by the traditional Medicare Part A and B fee-for-service

PLAIN-LANGUAGE SUMMARY

Anemia is characterized by a lower-than-normal concentration of hemoglobin in the blood, which compromises delivery of oxygen to body organs and tissues. Most patients with kidney disease requiring dialysis exhibit some degree of anemia. Anemia has been thought to be related to poor outcomes in this patient population. We used a large Medicare database to study the relationship between hemoglobin concentration and several important patient outcomes, including death, hospitalization, and emergency department visit rates. In general, we found that death, hospitalization, and emergency department visit rates were lower in patients with higher hemoglobin concentrations. Our findings, along with other published studies, suggest that anemia is a sensitive marker of patient risk but not necessarily the cause of poor outcomes.

program who had a 12-month claim history before the hemoglobin measurement.

The outcome measures were mortality, hospitalization, and ED utilization in 2019 (except as otherwise noted). We ascertained patient death based on Medicare reporting mechanisms, including enrollment records, ESRD Death Notification Form (CMS-Form 2746) and the Consolidated Renal Operations in a Web-enabled Network. We derived hospitalization and ED utilization from claims submitted on behalf of beneficiaries covered by the traditional Medicare fee-for-service program. We also evaluated cardiovascular- and infection-specific hospitalization as defined by relevant *International Classification of Diseases, Tenth Revision* diagnosis codes. Within the cardiovascular category, we evaluated hospitalizations related to congestive heart failure, acute myocardial infarction, cardiac dysrhythmia, and cardiac arrest. Within the infection category, we evaluated hospitalizations related to septicemia, dialysis access, and coronavirus disease 2019. We used hemoglobin and hospitalization data from 2020 for the coronavirus disease 2019 analysis only.

We analyzed outcomes as time-to-event using the Cox proportional hazards model, using a robust sandwich covariance matrix estimate to account for within-patient correlation. The hospitalization and ED outcomes were censored for mortality. For hospitalization and ED visits, we used the first event in the follow-up window after the hemoglobin measurement. Patients were potentially eligible for evaluation for multiple months. We used a basic set of adjustment factors including age (categorical and continuous), sex, race, ethnicity, diabetes as cause of kidney failure, and time receiving dialysis. We created a separate set of models that adjusted for 23 comorbid conditions (see Table 1)[5] in addition to basic patient characteristics. The comorbid conditions were derived from diagnosis codes in Medicare claims in the year before each monthly hemoglobin measurement. Diagnosis codes were mapped to Agency for Healthcare Research and Quality condition codes using the approach used for the All-Cause Hospital Readmission Reduction Program.[5] The statistical models expressed mortality, hospitalization, and ED risk as hazard ratios and were displayed graphically using a log-spaced scale.

RESULTS

Patient characteristics are summarized in Table 1 for 371,250 patients who accounted for 3,326,072 patient-months. The prevalence of most comorbid conditions was higher among patients with low hemoglobin levels.

Fig 1 shows the hemoglobin concentration distribution across months. The modal hemoglobin was in the 10.5-11 g/dL category, which was used as the reference group in statistical models. Hemoglobin measurements include erythropoiesis-stimulating agent (ESA) users (approximately 74% of patients) and ESA nonusers.

Fig 2 shows the association between mortality and hemoglobin concentration. The all-cause mortality risk was lower with each step increase in the hemoglobin concentration range from <9 to 11-11.5 g/dL. Above a hemoglobin concentration of 11.5 g/dL, the mortality risk was progressively higher at each hemoglobin category. The adjustment for comorbid condition attenuated a portion of the mortality risk in the lower 4 hemoglobin categories but had minimal impact on hemoglobin concentration >10 g/dL. Findings were similar when analyzed by ESA use status except the upward movement of mortality at higher hemoglobin concentrations was not found among ESA nonusers. Table S1 shows hazard ratios, confidence limits and *P* values at each hemoglobin category for mortality and the other outcome measures.

The association between hospitalization risk and hemoglobin appears in Fig 3. The all-cause hospitalization rate was progressively lower at each hemoglobin category from <9 to 11-11.5 g/dL, after which the risk was stable (left panel). As with mortality, adjustment for comorbid condition attenuated the magnitude of the association at the lower hemoglobin concentration ranges. The comorbid condition-adjusted hospitalization rates for cardiovascular and infection-related conditions showed a similar inverse association with hemoglobin, plateauing at approximately 11.5 g/dL (right panel). Unlike mortality, hospitalization risk did not increase at higher hemoglobin concentrations. The comorbid condition adjustment attenuated the cause-specific hospitalization risk as it did for all-cause risk.

Similar associations with hemoglobin concentration were found for specific categories of cardiovascular hospitalization, including congestive heart failure, acute myocardial infarction, arrhythmia, and cardiac arrest (Fig 4). Fig 5 shows the association for several categories of infection-related hospitalization, including sepsis, dialysis access,

Table 1. Patient Characteristics by Hemoglobin Category for Medicare FFS Patients

	Hemoglobin Category (g/dL)								
	<9	**9-<9.5**	**9.5-<10**	**10-<10.5**	**10.5-<11**	**11-<11.5**	**11.5-<12**	**12-<13**	**≥13**
Unique Patients	*41,812*	*26,952*	*37,770*	*57,120*	*65,138*	*56,611*	*36,117*	*32,574*	*17,156*
Patient-Months	*276,479*	*203,623*	*318,150*	*523,946*	*631,444*	*552,019*	*345,841*	*307,939*	*166,631*
Age, y									
Mean (SD)	64.4 (14.3)	64.4 (14.1)	64.2 (14.1)	64.1 (13.9)	64.3 (13.8)	64.2 (13.7)	63.7 (13.8)	62.5 (13.9)	59.2 (13.3)
18-44	4,373 (10.5%)	2,590 (9.6%)	3,680 (9.7%)	5,356 (9.4%)	5,865 (9.0%)	5,068 (9.0%)	3,418 (9.5%)	3,508 (10.8%)	2,405 (14.0%)
45-64	13,986 (33.5%)	9,423 (35.0%)	13,785 (36.5%)	21,577 (37.8%)	24,637 (37.8%)	21,649 (38.2%)	14,183 (39.3%)	13,578 (41.7%)	8,491 (49.5%)
65-74	12,816 (30.7%)	8,166 (30.3%)	11,048 (29.3%)	16,411 (28.7%)	18,888 (29.0%)	16,442 (29.0%)	10,299 (28.5%)	8,900 (27.3%)	4,022 (23.4%)
75+	10,637 (25.4%)	6,773 (25.1%)	9,257 (24.5%)	13,776 (24.1%)	15,748 (24.2%)	13,452 (23.8%)	8,217 (22.8%)	6,588 (20.2%)	2,238 (13.0%)
Sex: F	19,439 (46.5%)	12,567 (46.6%)	17,681 (46.8%)	26,411 (46.2%)	29,411 (45.2%)	24,485 (43.3%)	14,995 (41.5%)	11,953 (36.7%)	4,312 (25.1%)
Race									
White	23,923 (57.2%)	16,106 (59.8%)	22,529 (59.7%)	33,697 (59%)	38,363 (58.9%)	33,716 (59.6%)	21,841 (60.5%)	19,888 (61.1%)	10,713 (62.4%)
Black	15,302 (36.6%)	9,092 (33.7%)	12,641 (33.5%)	19,385 (33.9%)	22,009 (33.8%)	18,891 (33.4%)	11,902 (33%)	10,550 (32.4%)	5,394 (31.4%)
Asian	1,575 (3.8%)	1,128 (4.2%)	1,615 (4.3%)	2,370 (4.2%)	2,776 (4.3%)	2,342 (4.1%)	1,366 (3.8%)	1,126 (3.5%)	491 (2.9%)
Pacific Islander	456 (1.1%)	292 (1.1%)	450 (1.2%)	750 (1.3%)	930 (1.4%)	805 (1.4%)	422 (1.2%)	459 (1.4%)	252 (1.5%)
American Indian and Alaska Native	419 (1%)	289 (1.1%)	447 (1.2%)	773 (1.4%)	871 (1.3%)	691 (1.2%)	510 (1.4%)	447 (1.4%)	262 (1.5%)
Other/unknown/ multiple	137 (0.3%)	45 (0.2%)	88 (0.2%)	145 (0.3%)	189 (0.3%)	166 (0.3%)	76 (0.2%)	104 (0.3%)	44 (0.3%)
Ethnicity: Hispanic	5,028 (12%)	3,569 (13.2%)	5,398 (14.3%)	8,753 (15.3%)	10,085 (15.5%)	8,659 (15.3%)	5,462 (15.1%)	4,871 (15%)	2,631 (15.3%)
Diabetes as cause of kidney failure	18,799 (45.0%)	12,762 (47.4%)	18,069 (47.8%)	27,400 (48.0%)	31,188 (48.0%)	26,831 (47.4%)	16,763 (46.4%)	14,388 (44.2%)	6,689 (39.0%)
Time with kidney failure									
<1 y	16,085 (38.5%)	7,779 (28.9%)	8,514 (22.5%)	10,180 (17.8%)	9,888 (15.2%)	8,803 (15.6%)	5,840 (16.2%)	5,243 (16.1%)	1,943 (11.3%)
1-2 y	8,510 (20.4%)	6,301 (23.4%)	9,776 (25.9%)	16,101 (28.2%)	19,287 (29.6%)	16,931 (29.9%)	10,798 (29.9%)	9,483 (29.1%)	4,197 (24.5%)
3-4 y	6,188 (14.8%)	4,699 (17.4%)	7,087 (18.8%)	11,407 (20%)	13,283 (20.4%)	11,262 (19.9%)	6,918 (19.2%)	5,979 (18.4%)	3,148 (18.4%)
4+ y	11,029 (26.4%)	8,173 (30.3%)	12,393 (32.8%)	19,432 (34%)	22,680 (34.8%)	19,615 (34.7%)	12,561 (34.8%)	11,869 (36.4%)	7,868 (45.9%)
Comorbid conditions									
Arrhythmia	21,748 (52%)	12,923 (48%)	16,924 (44.8%)	24,212 (42.4%)	27,026 (41.5%)	23,404 (41.3%)	15,037 (41.6%)	13,369 (41%)	6,524 (38%)
Arthritis	4,404 (10.5%)	2,625 (9.7%)	3,311 (8.8%)	4,665 (8.2%)	5,098 (7.8%)	4,202 (7.4%)	2,698 (7.5%)	2,421 (7.4%)	1,081 (6.3%)
CHF	26,755 (64%)	16,285 (60.4%)	21,473 (56.9%)	30,771 (53.9%)	34,026 (52.2%)	29,110 (51.4%)	18,459 (51.1%)	16,179 (49.7%)	7,682 (44.8%)
COPD	13,178 (31.5%)	7,770 (28.8%)	9,870 (26.1%)	13,641 (23.9%)	15,040 (23.1%)	12,975 (22.9%)	8,352 (23.1%)	7,545 (23.2%)	3,535 (20.6%)
Coronary, cerebral, peripheral atherosclerosis	34,820 (83.3%)	22,000 (81.6%)	30,263 (80.1%)	44,864 (78.5%)	50,845 (78.1%)	44,244 (78.2%)	28,148 (77.9%)	25,187 (77.3%)	12,916 (75.3%)
Liver cirrhosis	3,556 (8.5%)	1,718 (6.4%)	2,154 (5.7%)	2,895 (5.1%)	3,006 (4.6%)	2,502 (4.4%)	1,526 (4.2%)	1,425 (4.4%)	650 (3.8%)
Coagulation defect	12,233 (29.3%)	6,650 (24.7%)	8,475 (22.4%)	11,570 (20.3%)	12,369 (19%)	10,603 (18.7%)	6,668 (18.5%)	6,018 (18.5%)	3,291 (19.2%)
Drug/alcohol	3,120 (7.5%)	1,590 (5.9%)	2,021 (5.4%)	2,678 (4.7%)	2,803 (4.3%)	2,411 (4.3%)	1,542 (4.3%)	1,560 (4.8%)	790 (4.6%)

(Continued)

Table 1 (Cont'd). Patient Characteristics by Hemoglobin Category for Medicare FFS Patients

	Hemoglobin Category (g/dL)								
	<9	9-<9.5	9.5-<10	10-<10.5	10.5-<11	11-<11.5	11.5-<12	12-<13	≥13
Gastrointestinal	14,690 (35.1%)	7,845 (29.1%)	9,485 (25.1%)	12,668 (22.2%)	13,657 (21%)	11,532 (20.4%)	7,373 (20.4%)	6,631 (20.4%)	3,117 (18.2%)
Hip fracture	1,389 (3.3%)	779 (2.9%)	967 (2.6%)	1,353 (2.4%)	1,432 (2.2%)	1,232 (2.2%)	792 (2.2%)	662 (2%)	274 (1.6%)
Lung disease	2,829 (6.8%)	1,611 (6%)	1,924 (5.1%)	2,617 (4.6%)	2,767 (4.3%)	2,483 (4.4%)	1,611 (4.5%)	1,349 (4.1%)	642 (3.7%)
Malnutrition	9,689 (23.2%)	5,103 (18.9%)	6,548 (17.3%)	9,341 (16.4%)	10,316 (15.8%)	8,811 (15.6%)	5,962 (16.5%)	5,171 (15.9%)	2,390 (13.9%)
Metastatic cancer	1,484 (3.6%)	674 (2.5%)	649 (1.7%)	833 (1.5%)	870 (1.3%)	721 (1.3%)	409 (1.1%)	335 (1%)	154 (0.9%)
Other cancers	9,732 (23.3%)	5,565 (20.7%)	7,083 (18.8%)	10,051 (17.6%)	11,085 (17%)	9,432 (16.7%)	5,983 (16.6%)	5,198 (16%)	2,468 (14.4%)
Other infectious disease	27,452 (65.7%)	16,375 (60.8%)	21,829 (57.8%)	31,124 (54.5%)	34,416 (52.8%)	29,706 (52.5%)	18,743 (51.9%)	16,461 (50.5%)	7,898 (46%)
Paralysis	9,484 (22.7%)	5,403 (20.1%)	7,058 (18.7%)	9,851 (17.3%)	10,907 (16.7%)	9,449 (16.7%)	6,189 (17.1%)	5,435 (16.7%)	2,685 (15.7%)
Psychiatric	18,701 (44.7%)	11,190 (41.5%)	14,808 (39.2%)	20,799 (36.4%)	22,685 (34.8%)	19,527 (34.5%)	12,584 (34.8%)	11,274 (34.6%)	5,556 (32.4%)
Respiratory failure	2,026 (4.9%)	869 (3.2%)	977 (2.6%)	1,150 (2%)	1,207 (1.9%)	983 (1.7%)	609 (1.7%)	571 (1.8%)	250 (1.5%)
Seizure disorder	4,933 (11.8%)	2,635 (9.8%)	3,399 (9%)	4,715 (8.3%)	4,947 (7.6%)	4,184 (7.4%)	2,600 (7.2%)	2,296 (7.1%)	1,177 (6.9%)
Sepsis	12,109 (29%)	6,354 (23.6%)	7,599 (20.1%)	9,977 (17.5%)	10,912 (16.8%)	9,380 (16.6%)	6,100 (16.9%)	5,526 (17%)	2,647 (15.4%)
Severe cancer	3,312 (7.9%)	1,591 (5.9%)	1,876 (5%)	2,459 (4.3%)	2,581 (4%)	2,121 (3.8%)	1,296 (3.6%)	1,108 (3.4%)	475 (2.8%)
Shock	17,437 (41.7%)	9,514 (35.3%)	11,826 (31.3%)	15,844 (27.7%)	16,991 (26.1%)	14,547 (25.7%)	9,240 (25.6%)	7,943 (24.4%)	3,602 (21%)
Skin ulcer	10,872 (26%)	6,024 (22.4%)	7,718 (20.4%)	10,839 (19%)	11,696 (18%)	10,203 (18%)	6,489 (18%)	5,943 (18.2%)	3,037 (17.7%)

Note: Cells show patient count and percent in parentheses unless otherwise indicated.
Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; FFS, fee-for-service.

and coronavirus disease 2019. The risk profile was similar for the infection-related categories.

The association between ED utilization risk and hemoglobin appears in Fig 6. Risk was lower at progressively higher hemoglobin concentrations (left panel). The comorbid condition adjustment attenuated the risk at lower hemoglobin concentrations. Similar patterns were seen for ED episodes associated with hospitalization and those not associated with hospitalization (right panel).

DISCUSSION

We found a strong, consistent association between hemoglobin concentration and the 1-month risk of multiple patient outcome and utilization measures, including mortality, all-cause hospitalization, multiple cause-specific hospitalizations, and ED utilization. These findings add to the body of observational studies with similar findings.[6-14] Compared with most prior reports, this study captures a more recent era of anemia management characterized by bundled payments for anemia medications, refinements to clinical practice guidelines,[15] and the Food and Drug Administration-approved drug label for ESAs.[16] Furthermore, the proportion of patients receiving dialysis maintained with a hemoglobin concentration <10 g/dL has increased dramatically since 2006.[17] In addition, our data source included a large number of patients and observation periods relative to most prior studies. The large sample size allows estimates of risk magnitude over a wide range of hemoglobin concentrations. We were also able to include a wide variety of outcome and utilization measures. Also, we used relatively short exposure and follow-up periods (1 month) in alignment with the original data collection process. Our findings contribute to the ongoing discussion about hemoglobin targets and the differing findings from observational studies compared with clinical trials.

The study outcomes of mortality, hospitalization, and ED utilization were affected by the comorbid condition adjustment (Figs 2, 3, and 6). In all cases, the risk profile was attenuated but not eliminated at the lower hemoglobin concentrations, generally <10 g/dL. The comorbid condition adjustment did not alter the risk profile at higher hemoglobin concentrations. The findings suggest that patients who present with lower hemoglobin concentrations have poorer health status, independent of the hemoglobin concentration. A low hemoglobin concentration is a marker of

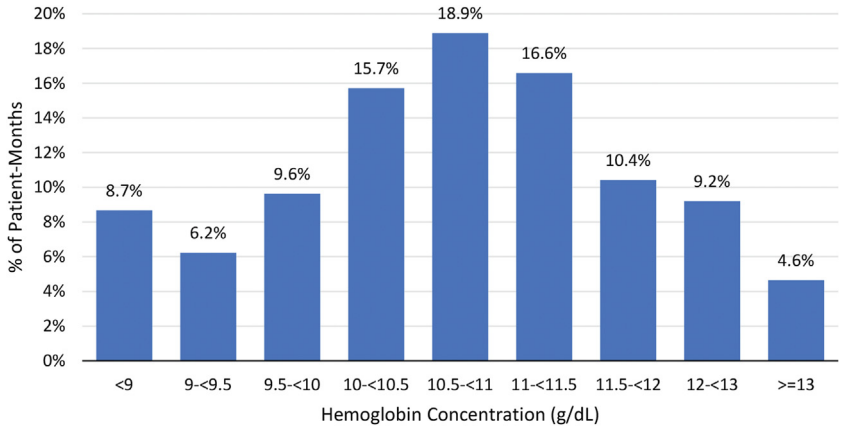

Figure 1. Distribution of monthly hemoglobin levels.

compromised health status as well as a potential mediator. The finding that multiple outcome measures demonstrate a similar inverse association with hemoglobin suggests an important role for patient health status at lower hemoglobin concentrations. Comorbid conditions were more prevalent for the lower hemoglobin categories (Table 1). Our comorbid condition adjustment derives from claims-based diagnosis and does not necessarily capture all aspects of patient risk, including severity of illness. We cannot exclude the possibility that more complete or accurate comorbid condition adjustment would further attenuate the observed associations. The effect of hemoglobin on human health is generally considered to be a chronic effect manifest over years of exposure and follow-up. The finding of strong associations between hemoglobin and various clinical outcomes over short exposure and follow-up periods suggests that hemoglobin may be capturing unmeasured markers of patient risk.

Mortality risk was inversely associated with hemoglobin from the lowest observed level (<9 g/dL) through levels of 11-11.5 g/dL (Fig 2). At hemoglobin levels above 11.5 g/dL, we observed a directional change in the association toward higher mortality that was statistically significant above 12 g/dL. This finding is consistent with several clinical trials of ESAs that compared outcomes in control patients with average hemoglobin concentrations of 10.3-11.6 g/dL with intervention patients treated with average hemoglobin concentrations of 12.5-13 g/dL.[18-21] The high hemoglobin intervention groups did not realize the expected improvements in survival or quality of life and, rather, experienced excess adverse outcomes, including mortality and stroke. The finding is also consistent with the Kidney Disease: Improving Global Outcomes (KDIGO) anemia management guideline, which recommends that ESAs not be used to maintain hemoglobin concentration >11.5 g/dL in adult patients.[15] Our finding also aligns with the Food and Drug Administration-directed drug label for use of ESAs in adult patients receiving dialysis, which advises dose reduction or interruption as the hemoglobin level approaches or exceeds 11 g/dL.[16]

In the territory of hemoglobin concentrations <11.5 g/dL, our analysis is supportive of current clinical practice. The clinical trials conducted in support of agents that stimulate erythropoiesis demonstrated hematologic efficacy but did not examine mortality and other clinical outcomes in this hemoglobin range.[22] In the absence of ESA treatment, most patients receiving dialysis have a hemoglobin concentration <9 g/dL. The KDIGO anemia guideline asserts that treatment of hemoglobin concentrations <9 g/dL is associated with improved quality of life and transfusion avoidance.[15] However, uncertainty remains in the hemoglobin range of approximately 9-11 g/dL. The distribution of actual hemoglobin measurements shows that approximately 40% of patients have hemoglobin concentrations <10.5 g/dL and >31% of patients have a hemoglobin concentration between 9 and 10.5 g/dL (Fig 2). In the absence of clinical trial results that focus on hemoglobin levels below approximately 11 g/dL, the available clinical practice guidelines offer a decision framework. The Food and Drug Administration-approved drug label states that ESA treatment should be initiated in adult patients receiving dialysis when the hemoglobin level is <10 g/dL.[16] The drug label does not specify a lower-range

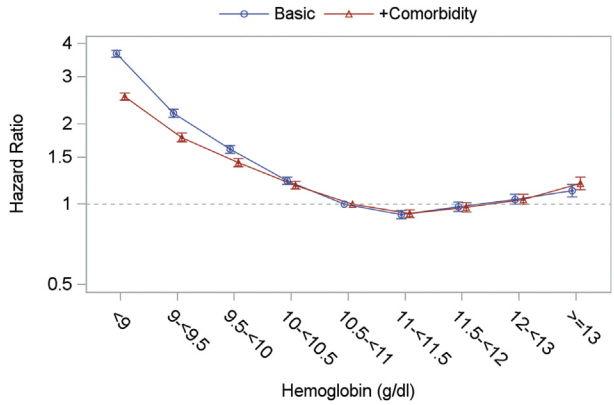

Figure 2. Mortality risk vs hemoglobin adjusted for basic patient characteristics and, additionally, for comorbid conditions. Reference hemoglobin, 10.5-11 g/dL.

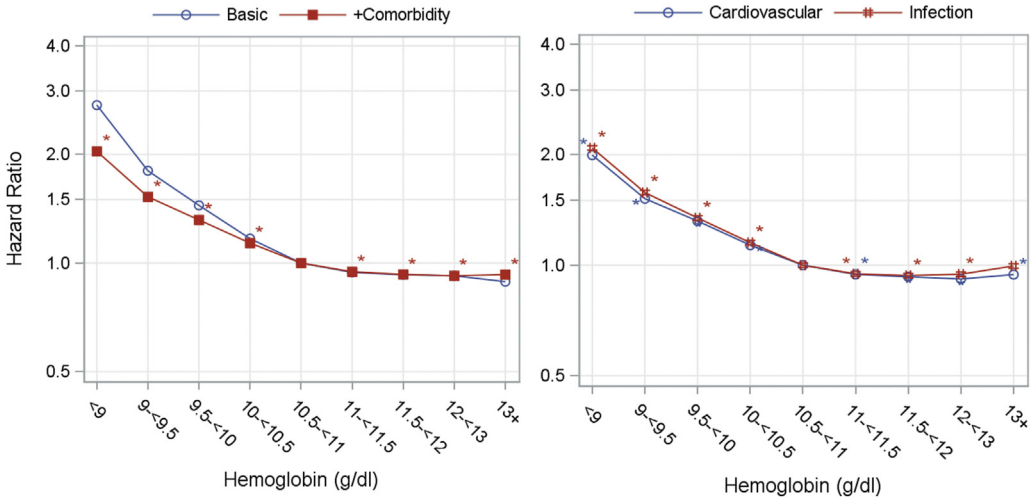

Figure 3. Hospitalization risk vs hemoglobin adjusted for basic patient characteristics and, additionally, for comorbid conditions (left panel). Cardiovascular and infectious hospitalization risk vs hemoglobin adjusted for basic patient characteristics and comorbid conditions (right panel). Reference hemoglobin, 10.5-11 g/dL.

hemoglobin target. The KDIGO anemia guideline for adult patients receiving dialysis recommends starting ESA therapy when the hemoglobin is between 9.0 and 10.0 g/dL to avoid having the hemoglobin concentration are <9.0 g/dL.[15] Most of the patients in the observed hemoglobin distribution (Fig 1) are within the hemoglobin targets set in the KDIGO anemia management guidelines.

In summary, we used the national Medicare data set to produce a detailed analysis of the association between hemoglobin and several outcomes, including mortality, hospitalization, and ED visits among patients receiving dialysis. We found that mortality risk declined with increasing hemoglobin levels up to 11.5 g/dL, above which mortality started to increase. We found that hospitalization and ED utilization risk declined with increasing hemoglobin levels up to approximately 12 g/dL, above which risk stabilized. The observed risks were reduced after adjustment for measured patient comorbid condition based on claims diagnoses. Adjustment for case-mix severity could further attenuate the risk profile, and the lack of severity information constitutes a study limitation. These findings generally support current guidelines and clinical practice related to anemia management.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Patient Outcomes by Hemoglobin Category.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Eric W. Young, MD, MS, Dongyu Wang, MS, Alissa Kapke, MS, Jeffrey Pearson, MS,

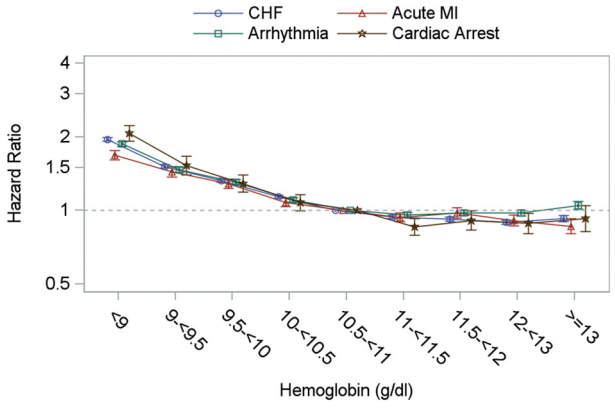

Figure 4. Specific causes of cardiovascular hospitalization risk vs hemoglobin adjusted for basic patient characteristics and comorbid conditions. Symbols: * $P < 0.0001$; † $P < 0.001$; ‡ $P < 0.05$ compared with reference hemoglobin of 10.5-11 g/dL. CHF, congestive heart failure, MI, myocardial infarction.

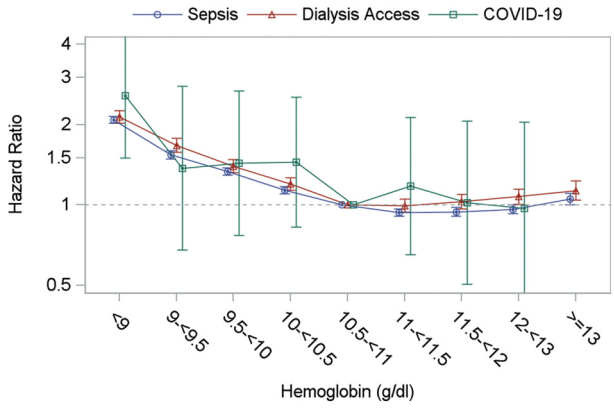

Figure 5. Specific causes of infection-related hospitalization risk vs hemoglobin adjusted for basic patient characteristics and comorbid conditions. Reference hemoglobin, 10.5-11 g/dL. COVID-19, coronavirus disease 2019.

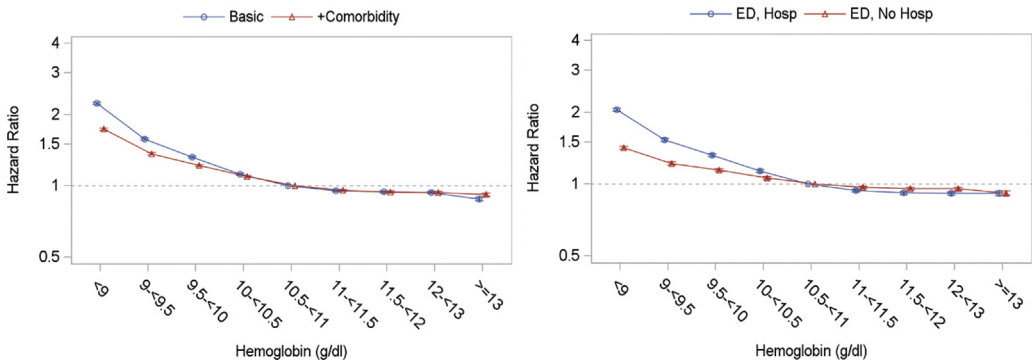

Figure 6. ED utilization risk vs hemoglobin adjusted for basic patient characteristics and, additionally, for comorbid conditions (left panel). ED utilization risk with and without subsequent hospitalization vs hemoglobin adjusted for basic patient characteristics and comorbid conditions (right panel). Reference hemoglobin, 10.5-11 g/dL. ED, emergency department.

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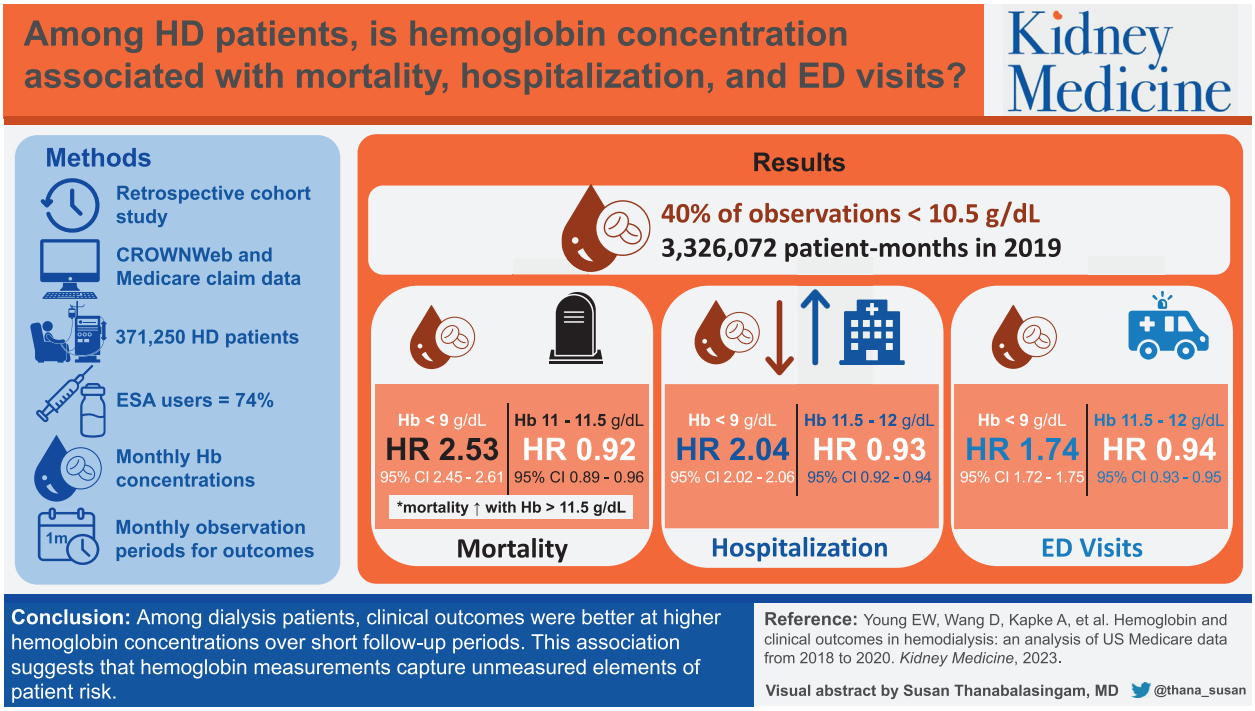
Among HD patients, is hemoglobin concentration associated with mortality, hospitalization, and ED visits?
Kidney Medicine
Methods
Retrospective cohort study
CROWNWeb and Medicare claim data
371,250 HD patients
ESA users = 74%
Monthly Hb concentrations
Monthly observation periods for outcomes
1m
Results
40% of observations < 10.5 g/dL
3,326,072 patient-months in 2019
Hb < 9 g/dL
HR 2.53
95% CI 2.45 - 2.61
Hb 11 - 11.5 g/dL
HR 0.92
95% CI 0.89 - 0.96
*mortality ↑ with Hb > 11.5 g/dL
Mortality
Hb < 9 g/dL
HR 2.04
95% CI 2.02 - 2.06
Hb 11.5 - 12 g/dL
HR 0.93
95% CI 0.92 - 0.94
Hospitalization
Hb < 9 g/dL
HR 1.74
95% CI 1.72 - 1.75
Hb 11.5 - 12 g/dL
HR 0.94
95% CI 0.93 - 0.95
ED Visits
Conclusion: Among dialysis patients, clinical outcomes were better at higher hemoglobin concentrations over short follow-up periods. This association suggests that hemoglobin measurements capture unmeasured elements of patient risk.
Reference: Young EW, Wang D, Kapke A, et al. Hemoglobin and clinical outcomes in hemodialysis: an analysis of US Medicare data from 2018 to 2020. Kidney Medicine, 2023.
Visual abstract by Susan Thanabalasingam, MD @thana_susan