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Jyunichi Hoshino, Daniel Muenz, Jarcy Zee, Nidhi Sukul, Elodie Speyer, et al.. Associations of Hemoglobin Levels With Health-Related Quality of Life, Physical Activity, and Clinical Outcomes in Persons With Stage 3-5 Nondialysis CKD. *Journal of Renal Nutrition*, 2020, 30 (5), pp.404-414. 10.1053/j.jrn.2019.11.003 . hal-03032365

HAL Id: hal-03032365

<https://hal.science/hal-03032365>

Submitted on 14 Dec 2020

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Associations of Hemoglobin Levels With Health-Related Quality of Life, Physical Activity, and Clinical Outcomes in Persons With Stage 3-5 Nondialysis CKD



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Objective: Conflicting findings and knowledge gaps exist regarding links between anemia, physical activity, health-related quality of life (HRQOL), chronic kidney disease (CKD) progression, and mortality in moderate-to-advanced CKD. Using the CKD Outcomes and Practice Patterns Study, we report associations of hemoglobin (Hgb) with HRQOL and physical activity, and associations of Hgb and physical activity with CKD progression and mortality in stage 3-5 nondialysis (ND)-CKD patients.

Design and Methods: Prospectively collected data were analyzed from 2,121 ND-CKD stage 3-5 patients, aged ≥ 18 years, at 43 nephrologist-run US and Brazil CKD Outcomes and Practice Patterns Study-participating clinics. Cross-sectional associations were assessed of Hgb levels with HRQOL and physical activity levels (from validated Kidney Disease Quality of Life Instrument and Rapid Assessment of Physical Activity surveys). CKD progression (first of $\geq 40\%$ estimated glomerular filtration rate [eGFR] decline, eGFR < 10 mL/min/1.73 m², or end-stage kidney disease) and all-cause mortality with Hgb and physical activity levels were also evaluated. Linear, logistic, and Cox regression analyses were adjusted for country, demographics, smoking, eGFR, serum albumin, very high proteinuria, and 13 comorbidities.

Results: HRQOL was worse, with severe anemia (Hgb < 10 g/dL), but also evident for mild/moderate anemia (Hgb 10-12 g/dL), relative to Hgb > 12 g/dL. Odds of being highly physically active were substantially greater at Hgb > 10.5 g/dL. Lower Hgb was strongly associated with greater CKD progression and mortality, even after extensive adjustment. Physical inactivity was strongly associated with greater mortality and weakly associated with CKD progression. Possible residual confounding is a limitation.

Conclusion: This multicenter international study provides real-world observational evidence for greater HRQOL, physical activity, lower CKD progression, and greater survival in ND-CKD patients with Hgb levels > 12 g/dL, exceeding current treatment guideline recommendations. These findings help inform future studies aimed at understanding the impact of new anemia therapies and physical activity regimens on improving particular dimensions of ND-CKD patient well-being and clinical outcomes.

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Introduction

ANEMIA IS A common complication of chronic kidney disease (CKD). Its prevalence increases with disease progression.¹⁻⁴ Associated symptoms include fatigue

and weakness.⁵ Persons living with nondialysis (ND)-CKD often have lower health-related quality of life (HRQOL)^{2,3,6} and physical functioning^{7,8} compared with the general population. Anemia correction has been

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Financial Disclosure/Support: See Acknowledgments on page 413.

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1051-2276

<https://doi.org/10.1053/j.jrn.2019.11.003>

shown to improve disorders such as anorexia, insomnia, depression, impaired sexual function, and cardiomegaly.^{9,10} A key question is to what extent these result from anemia.

Higher hemoglobin (Hgb) levels have been inconsistently associated with HRQOL in persons with moderate-to-advanced CKD in observational studies and randomized clinical trials (RCTs).¹¹⁻¹³ The findings of RCTs have limited generalizability, as their often restrictive inclusion criteria do not accurately represent the broad ND-CKD stage 3-5 population.¹¹⁻¹⁴ We are not certain how different HRQOL domains relate to Hgb levels, particularly as they relate to current clinical guidelines. A small number of studies have observed a more consistent association between Hgb levels and HRQOL domains of fatigue, vitality, energy, physical role, and physical component summary (PCS) scores.^{7,8} Strong associations between hemodialysis patient survival, numerous HRQOL measures, and prevalence of depression symptoms with aerobic physical activity levels, measured via the self-reported Rapid Assessment of Physical Activity (RAPA) questionnaire, were reported previously from the Dialysis Outcomes and Practice Patterns Study.¹⁵ Our understanding of the link between anemia and physical functioning among ND-CKD patients is incomplete.

In the present work, we have explored associations of Hgb and physical activity levels with patient outcomes in ND-CKD patients, using CKD Outcomes and Practice Patterns Study (CKDopps) data. These included CKD progression, mortality, and patient-reported physical activity (via the validated RAPA questionnaire) and HRQOL (via Kidney Disease Quality of Life Instrument [KDQOL-36]).^{16,17} We hypothesized that anemia is associated with reduced HRQOL and low physical activity, with anemia and low activity associated with poorer clinical outcomes of CKD progression and mortality.

Methods

Patient Sample

CKDopps is an ongoing prospective cohort study of stage 3-5 ND-CKD patients treated in nephrologist-led CKD clinics in Brazil, France, Germany, Japan, and the United States. CKDopps sites were randomly selected from CKD clinics after stratification by region. CKDopps study design details and objectives have previously been published.¹⁸ CKDopps was approved by national and/or local ethics committees, as required by local ethics regulations, with informed patient consent obtained, as required.

Our analyses included Brazil and US patients (2014-2018). Data from Japan and Germany were unavailable at time of analysis; French sites used a different physical activity questionnaire.

From the initial sample of 2,465 enrolled patients, different subsets were included in each analysis (Figure S1). There were 2,121 (86%) patients included in

at least one analysis—1,404 from 28 US clinics; 717 from 15 Brazilian clinics.

Outcome Definitions

Baseline was defined as date of Hgb measure or RAPA response. Outcomes were according to the following:

Health-related Quality of Life

Self-reported HRQOL was assessed via the KDQOL-36 questionnaire.^{16,17} Items were summed to yield burdens and effects of disease, mental component summary (MCS), and PCS scores. Data to calculate symptoms of disease score were not available for all country cohorts. We also calculated scores for eight MCS and PCS subdomains: emotional role, emotional well-being, energy, general health, pain, physical function, physical role, and social functioning. We treated each summary score as a continuous measure, with higher scores indicating higher HRQOL across the possible range of 0-100.

Physical Activity Level

Self-reported physical activity was assessed via RAPA questionnaires, showing good correlation with direct measurement of physical activity via accelerometers.^{19,20} RAPA consists of nine binary questions (yes/no), with graphic and textual illustrations. We defined three levels of physical activity based on the first seven RAPA questions, applying the approach of Topolski et al.¹⁹: (1) never active; (2) low active (referred to in Topolski et al. as infrequently or sometimes active); or (3) highly active (also referred to as often or very active). For some analyses, we collapsed these three categories into two roughly equal sample sizes: highly active versus not (low or never active). We used physical activity as an outcome and exposure.

Progression of CKD

CKD progression was defined as a 40% decline in estimated glomerular filtration rate (eGFR) from baseline,²¹ eGFR <10 mL/min/1.73 m², or end-stage kidney disease (ESKD) requiring dialysis/transplantation, whichever occurred first.

Mortality

Fatal events from all causes during follow-up were included.

Statistical Analyses

Baseline patient characteristics and unadjusted outcome measures were assessed for all patients. The distributions of Hgb and physical activity level by country and CKD stage are shown in Figure 1. For each HRQOL outcome, linear regression was used to estimate the adjusted mean difference between categorical Hgb levels of <10, 10-12, and >12 g/dL (as the reference level). For physical activity as the outcome, logistic regression was used to estimate the adjusted odds ratio (OR) of being highly active (vs. not) by continuous Hgb level, coding Hgb as a natural cubic spline, with knots at 10, 11, 12, 13, and 14 g/dL. All models

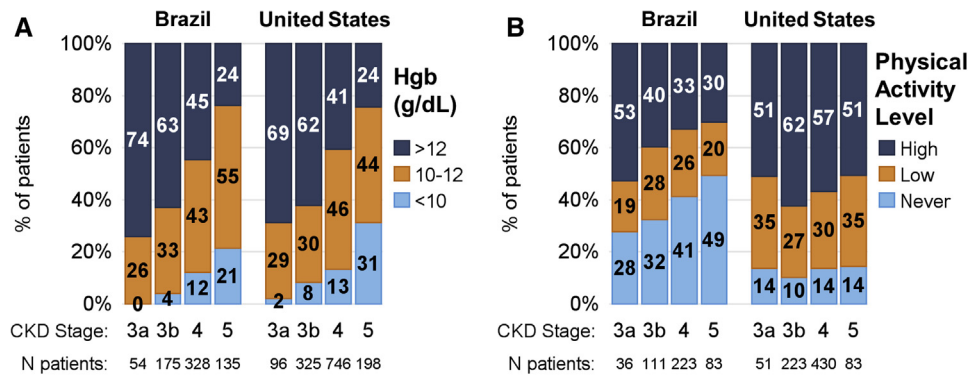


Figure 1. Distribution of (A) Hgb and (B) physical activity level, by CKD stage and country. Physical activity level was self-reported via the Rapid Assessment of Physical Activity questionnaire. CKD, chronic kidney disease; Hgb, hemoglobin.

used generalized estimating equations with exchangeable working correlation structure to account for clustering of patients within clinics. See [Figure 2](#) footnote for list of model adjustments.

Cox regression was used to estimate adjusted hazard ratios (HRs) for the outcomes of CKD progression and all-cause mortality, by baseline exposures of Hgb and physical activity. Hgb was coded separately as a three-level categorical variable (<10, 10–12, and >12 g/dL) and as a natural cubic spline, with knots at 10, 12, and 14 g/dL. Physical activity was coded as a three-level categorical variable (never, low, and highly active). Models were adjusted for other baseline characteristics ([Table 1](#)). Patient clustering within clinics was accounted for with the robust sandwich covariance estimator.²² Time at risk for all Cox models began at the baseline exposure and ended at the occurrence of an outcome or last date of study follow-up. For all-cause mortality, time at risk was censored at ESKD.

Multiple imputation, implemented by IVEware,²³ was used in all analyses to impute missing covariate values, and in the minority of cases when only some survey questions for calculating KDQOL-36 and RAPA scores were answered. Twenty complete data sets were imputed, all analyses were performed with each data set, and results were combined using Rubin's rules.²⁴

All analyses used SAS software, version 9.4 (SAS institute, Cary, NC). Confidence intervals (CIs) are reported with 95% confidence level.

Results

At baseline, participants had an overall mean eGFR of 26 mL/min/1.73 m²; 32% had stage 3 ND-CKD, 52% stage 4, and 16% stage 5. Sixty-six percent of patients were from the United States; 34% from Brazil. Mean age was 68 ± 13 years; 48% were female; 23% were of black race; mean body mass index was 30.4 ± 6.9 kg/m²; 55%, 17%, and 11% had a history of diabetes mellitus, congestive heart failure, and lung disease ([Table 1](#)). Patients had a median (interquartile range [IQR]) of 2.0 (1.0 to 3.0) of 10 other comorbidities ([Table 1](#) footnote). Thirteen percent of patients had an Hgb level of <10 g/dL, 41% of 10–

12 g/dL, and 46% of >12 g/dL. Of these, 881 patients presented Hgb higher than 12 g/dL, 636 presented Hgb 12–14 g/dL, and 245 presented above 14 g/dL (including only one patient treated with an erythropoiesis-stimulating agent [ESA]). For self-reported physical activity, 23%, 28%, and 49% of patients were categorized as never, low, and highly active.

Missingness was <4% for all covariates except serum albumin (29%), albuminuria (27%), and body mass index (18%). For KDQOL-36, all included patients answered at least six questions, of whom 90% answered at least 30 of 36 questions. For RAPA, all included patients answered at least one of 9 questions, of whom 87% answered at least eight. The median time between closest Hgb measurement and KDQOL-36 questionnaire completion was 12 days (IQR: 1–49 days, maximum 1 year).

The prevalence of some factors differed considerably by Hgb and physical activity levels. Patients with more severe anemia were more likely to be female, of black race, have more advanced CKD, and have diabetes. ESA use ranged from 4% among patients with Hgb >12 g/dL to 35% with Hgb <10 g/dL, and from 9% among highly active patients to 18% among never-active patients. Intravenous (IV) and oral iron use were also higher at lower Hgb levels and at lower physical activity levels, with 41% and 11% prescribed oral and IV iron, respectively, among patients with Hgb <10 g/dL. A transferrin saturation <20% was of slightly higher prevalence at Hgb <10 g/dL (36%) than at Hgb >12 g/dL (32%), and with any physical activity; ferritin <100 ng/mL was more common with higher Hgb and with any physical activity. Mean serum albumin levels were slightly lower for patients with Hgb <10 g/dL versus ≥10 g/dL, whereas nutritional supplement use was 2% overall, with little variation by Hgb or physical activity level. Patients who reported being never active were more likely to be female or of black race.

Anemia was more prevalent in higher CKD stages and was somewhat more prevalent in the United States than Brazil ([Figure 1](#)). Brazilian patients reported being less physically active than U.S. patients. In Brazil, patients in higher CKD stages reported being less active, whereas there

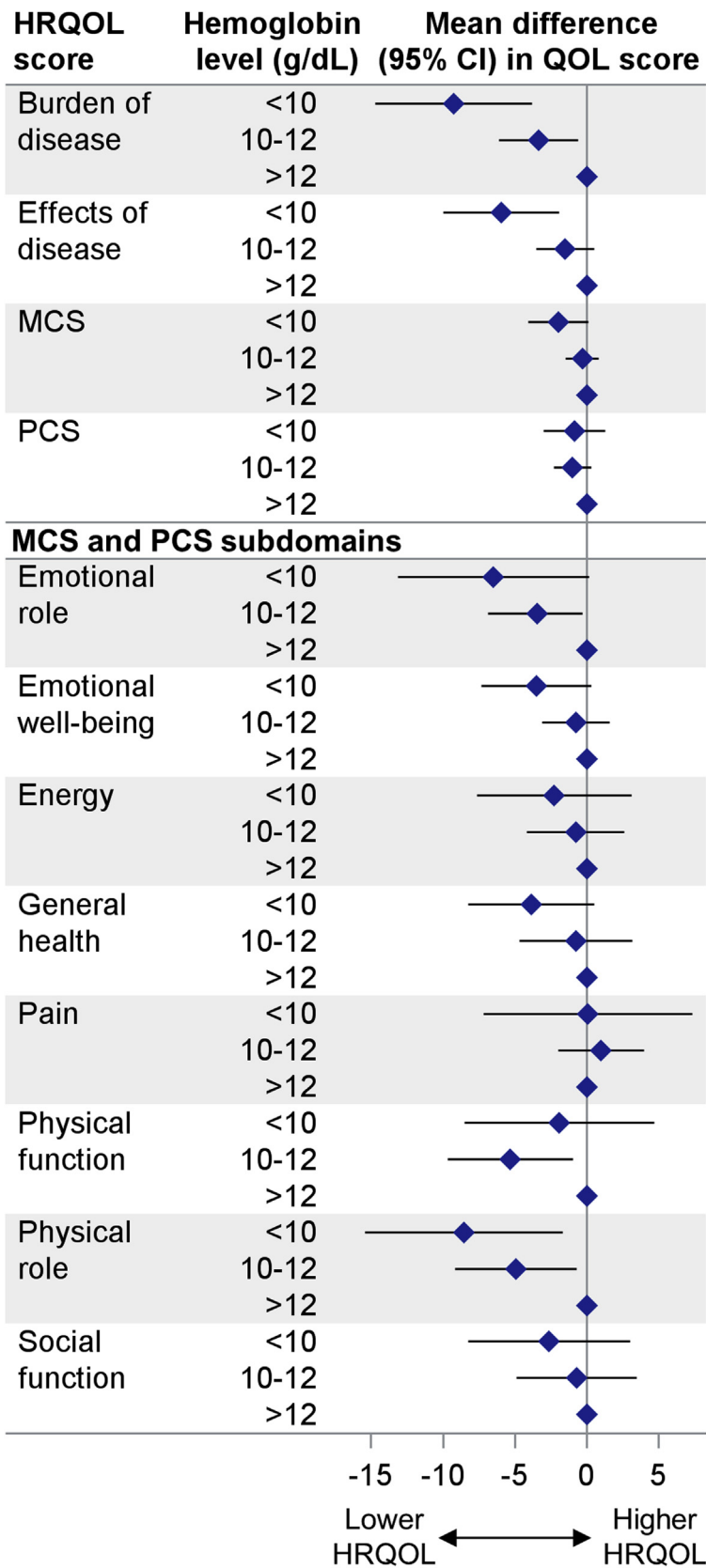


Figure 2. Mean differences (95% CI) of HRQOL scores by Hgb categories, relative to Hgb >12 g/dL. Among 1,306 ND-CKD patients. For each HRQOL score, derived from the KDQOL-36, linear regression was used to estimate the adjusted mean difference in the score by Hgb categories. Model adjustments were age, sex, black race, country, current smoking status, eGFR, BMI, serum albumin, very high proteinuria, diabetes, lung disease, congestive heart failure, and a comorbidity score (see Table 1 footnote for definition). BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; Hgb, hemoglobin; HRQOL, health-related quality of life; KDQOL-36, Kidney Disease Quality of Life 36; MCS, mental component summary; ND, nondialysis; PCS, physical component summary.

Table 1. Baseline Patient Characteristics by Hgb and Physical Activity Levels

Characteristics	All Patients (n = 2,121)	Hgb, g/dL			Physical Activity		
		<10 (n = 267)	10-12 (n = 843)	>12 (n = 947)	Never (n = 281)	Low (n = 348)	High (n = 615)
Demographics							
Age*, y	68 ± 13	68 ± 15	69 ± 14	68 ± 13	68 ± 15	68 ± 13	67 ± 13
Male*, %	52	42	43	63	43	47	58
Black race*, %	23	36	25	17	35	19	18
Current smoker*, %	8	7	7	10	10	10	6
Body mass index†, kg/m ²	30.4 ± 6.9	30.1 ± 6.9	30.3 ± 7.3	30.5 ± 6.4	29.8 ± 7.0	30.9 ± 7.2	30.1 ± 6.6
Laboratory parameters							
eGFR*, mL/min/1.73 m ²	26 ± 11	20 ± 9	24 ± 10	30 ± 11	25 ± 11	26 ± 11	27 ± 11
Serum albumin‡, g/dL	3.8 ± 0.5	3.6 ± 0.6	3.8 ± 0.5	3.9 ± 0.5	3.8 ± 0.6	3.9 ± 0.4	3.9 ± 0.5
Hgb*, g/dL	12.0 ± 1.8	9.1 ± 0.7	11.1 ± 0.6	13.5 ± 1.2	11.8 ± 1.9	11.8 ± 1.8	12.3 ± 1.8
Very high proteinuria‡, %	40	53	41	36	36	40	40
TSAT < 20%§, %	34	36	34	32	30	39	37
Ferritin < 100 ng/mL§, %	35	24	37	40	29	42	37
Medications, %							
ESA use	12	35	14	4	18	10	9
IV iron use	4	11	4	1	6	4	3
Oral iron use‡	24	41	31	14	29	27	19
ESA and IV iron use	2	5	2	0	3	1	2
ESA and any iron use	5	17	6	1	8	6	4
Nutritional supplement use	2	3	2	3	2	2	1
Comorbidities							
Diabetes*, %	55	66	60	49	55	57	53
Heart failure*, %	17	26	16	15	22	16	14
Lung disease*, %	11	15	10	11	14	12	10
Comorbidity score*, out of 10	2 [1,3]	2 [1,3]	2 [1,3]	2 [1,3]	2 [1,3]	2 [1,3]	2 [1,3]

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; Hgb, hemoglobin; IV, intravenous; IQR, interquartile range; TSAT, transferrin saturation.

Characteristics reported as mean ± standard deviation, median [IQR], or %. Laboratory parameters were measured within ±1 year of the Hgb or physical activity measurement. Medication usage was ascertained in the 6 months before and including the month of the Hgb or physical activity measurement. ESA and IV iron usage is reported both in combination and overall. ESA and any iron use refers to usage of ESA with either IV or oral iron, requiring that data on at least one of the two forms of iron is not missing. Very high proteinuria was defined as albumin-to-creatinine ratio ≥300 mg/g or albumin ≥300 mg/day. The comorbidity score was calculated per patient as the number of comorbidities out of the following 10: coronary heart disease, hypertension, other cardiovascular disease, cerebrovascular disease, peripheral vascular disease, recurrent cellulitis/gangrene, neurologic disease, psychiatric disorder, gastrointestinal bleeding, and cancer.

*0%-4% missing.

†18% missing.

‡27%-34% missing.

§62%-69% missing.

||10%-11% missing.

was little apparent association between CKD stage and physical activity in the United States.

Given the potential for selection bias in which patients responded to the KDQOL-36 and RAPA questionnaires, we assessed whether those included in the analysis (n = 1,306) differed from the 1,159 CKDopps patients who were excluded for missing questionnaire data. Baseline demographics, labs, medications, and comorbidities did not differ substantially between these groups, except the study sample had a slightly higher proportion of stage 3 CKD patients. Longitudinally, excluded patients had a slightly higher mortality rate and slightly lower CKD progression rate (Table S1).

Table 2 shows KDQOL-36 primary and component summary scores by Hgb level. Compared with patients having Hgb levels >12 g/dL, HRQOL was worse with more severe anemia (Hgb <10 g/dL) and slightly lower with

even mild/moderate anemia (Hgb 10-12 g/dL). More severe anemia was most strongly related to poorer scores for the HRQOL domains of general health, physical role, emotional role, and the burden and effects of kidney disease. A higher percentage of patients were highly physically active at Hgb >12 g/dL (56%) than at Hgb <10 g/dL (41%). CKD progression and mortality were considerably lower at higher Hgb levels, with crude rates of 37, 17, and 9 events per 100 person-years for CKD progression at Hgb <10, 10-12, and >12 g/dL; mortality rates of 23, 10, and 6 deaths per 100 person-years were seen at Hgb <10, 10-12, and >12 g/dL. The relationship of physical activity with clinical outcomes was weaker. Crude rates for CKD progression were 19, 14, and 14 events per 100 person-years for never, low, and highly active patients; and 12, 7, and 7 deaths per 100 person-years for mortality.

Table 2. Unadjusted Outcomes With Hgb and Physical Activity Levels, as Exposures

Outcome Type	Unadjusted Outcome			
	Among All Patients	Hgb (g/dL) Level		
		<10	10-12	>12
With Hgb as exposure				
HRQOL scores, mean \pm SD (<i>higher score is better; range: 0-100</i>)				
Burden of disease	69 \pm 29	58 \pm 31	67 \pm 29	74 \pm 27
Effects of disease	81 \pm 21	73 \pm 24	80 \pm 21	84 \pm 18
MCS	48 \pm 12	46 \pm 12	48 \pm 13	49 \pm 12
PCS	39 \pm 12	37 \pm 11	38 \pm 12	40 \pm 12
Subdomain: Emotional role	66 \pm 37	60 \pm 37	65 \pm 37	69 \pm 37
Subdomain: Emotional well-being	70 \pm 23	67 \pm 22	69 \pm 23	71 \pm 22
Subdomain: Energy	46 \pm 29	42 \pm 30	45 \pm 29	48 \pm 29
Subdomain: General health	44 \pm 26	39 \pm 26	44 \pm 25	47 \pm 27
Subdomain: Pain	64 \pm 32	61 \pm 32	64 \pm 32	65 \pm 32
Subdomain: Physical function	52 \pm 36	49 \pm 37	49 \pm 36	57 \pm 35
Subdomain: Physical role	51 \pm 38	41 \pm 39	49 \pm 37	56 \pm 39
Subdomain: Social function	69 \pm 32	66 \pm 32	68 \pm 32	71 \pm 32
Physical activity level, %				
Never active	23	26	27	18
Low active	29	33	30	26
Highly active	49	41	43	56
Clinical events, per 100 person-years				
CKD progression	15	37	17	9
Death	9	23	10	6

Outcome Type	Unadjusted Outcome			
	Among All Patients	Physical Activity Level		
		Never	Low	High
With physical activity as exposure				
Clinical events, per 100 person-years				
CKD progression	15	19	14	14
Death	8	12	7	7

CKD, chronic kidney disease; Hgb, hemoglobin; HRQOL, health-related quality of life; KDQOL-36, Kidney Disease Quality of Life 36; MCS, mental component summary; PCS, physical component summary; RAPA, Rapid Assessment of Physical Activity; SD, standard deviation.

HRQOL scores come from the KDQOL-36, and physical activity comes from the RAPA. The eight subdomains of KDQOL-36 are the components of the MCS and PCS scores. CKD progression was the first occurrence of reaching ESKD, a 40% decline from baseline in eGFR, or the occurrence of eGFR <10 mL/min/1.73 m².

In adjusted analyses, more severe anemia was most strongly associated with poorer HRQOL summary scores for the burden and effects of kidney disease (Figure 2). MCS was slightly lower for patients with Hgb <10 g/dL versus >12 g/dL, whereas PCS differences were minimal. Among MCS and PCS subdomains, more severe anemia was most strongly associated with emotional and physical roles; weakly associated with emotional well-being, energy, general health, physical function, and social function and showed no association with pain.

As shown by spline regression analysis, the adjusted odds of being highly active (vs. not) declined substantially at lower Hgb levels over the Hgb range from 13 to 10.5 g/dL (Figure 3A), to reach an adjusted OR of 0.63 (95% CI: 0.42-0.94) at Hgb 10.5 g/dL relative to 12 g/dL. The adjusted ORs for being highly active were similar among patients at different Hgb levels below 10.5 g/dL, and only

small differences were seen above 13 g/dL. In a separate confirmatory analysis with categorical Hgb, the adjusted OR of being highly active was 0.59 (95% CI: 0.42-0.84) for patients having Hgb 10-11 g/dL versus 11.5-12.5 g/dL. In sensitivity analyses restricted to patients with reported Hgb values within 90 days of the RAPA questionnaire completion, the associations of physical activity and HRQOL scores with Hgb were similar to those in our main analysis (data not shown).

Median follow-up time was 1.4 years (IQR: 0.7-2.5) for CKD progression and 1.5 years (IQR: 0.6-2.6) for all-cause mortality. Lower Hgb was strongly associated with higher risks of both outcomes, even after extensive adjustment (Table 3 and Figure 3B). Comparing patients with Hgb <10 versus Hgb >12 g/dL, the adjusted HRs for progression and death were 1.78 (95% CI: 1.29-2.47) and 3.13 (95% CI: 2.11-4.65). Comparing patients with Hgb 10-12

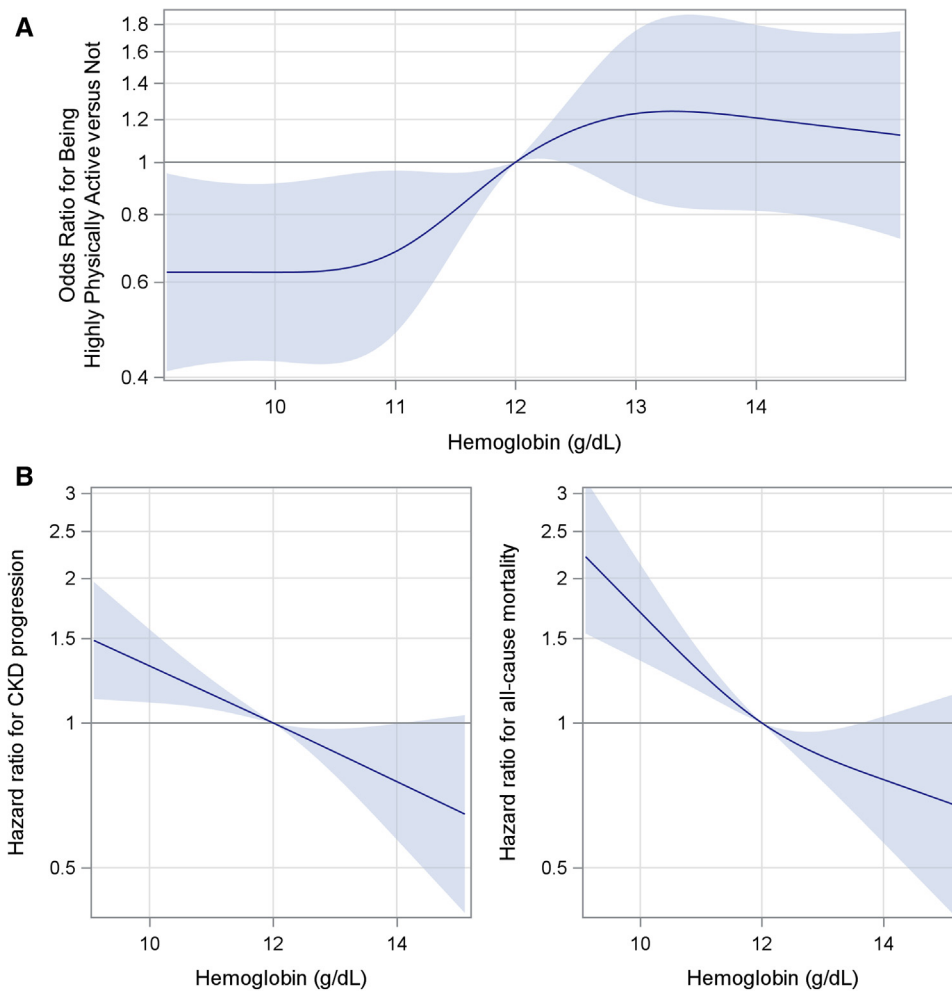


Figure 3. (A) ORs (95% CI) of being highly physically active by continuous Hgb, relative to Hgb of 12 g/dL; (B) adjusted HRs (95% CI) for CKD progression and all-cause mortality by continuous Hgb, relative to Hgb of 12 g/dL. Logistic regression was used to estimate ORs of being highly physically active (vs. not), coding the Hgb exposure as a natural cubic spline with knots at 10, 11, 12, 13, and 14 g/dL. Activity level was defined using the Rapid Assessment of Physical Activity questionnaire. Cox regression was used to estimate HRs of CKD progression and all-cause mortality, coding the Hgb exposure as a natural cubic spline with knots at 10, 12, and 14 g/dL. Adjustments for all models were the same as listed in Figure 2 footnote. CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Hgb, hemoglobin; HR, hazard ratio; OR, odds ratio.

versus Hgb >12 g/dL, the adjusted HRs for progression and death were 1.26 (95% CI: 0.98–1.63) and 1.40 (95% CI: 1.02–1.92). Physical inactivity (never active) was associated with greater risk of CKD progression and death compared with being highly active, with adjusted HRs of 1.17 (95% CI: 0.78–1.75) and 1.62 (95% CI: 1.06–2.49), respectively.

Discussion

A clear understanding of the relationships between Hgb and clinical outcomes is essential for establishing treatment goals for patients with CKD anemia. Currently, the effect of higher Hgb levels on these outcomes is difficult to assess because of restrictive clinical trial inclusion criteria and the perceived safety concerns of achieving higher Hgb levels. Therefore, new information is not likely to come from interventional studies using current therapeutic options,

namely ESAs and iron replacement. Advancing our understanding of the effects and interactions of Hgb levels with HRQOL, physical activity, and patient outcomes must alternatively rely on large, representative observational studies. Our work achieves this by featuring numerous adjustments for patient characteristics and using analytic approaches to reduce confounding, while exploring the relationships at Hgb levels beyond those that would be ethically and safely acceptable in interventional trials.

Our findings showed that levels of Hgb >12 g/dL were associated with better HRQOL, higher odds of being physically active, lower progression of CKD, and greater survival. This suggests that Hgb levels greater than the current recommendations of 10.0–11.5 g/dL may benefit patients with ND-CKD. Except for one study patient, none of the study patients having Hgb >12 g/dL were treated with iron or

Table 3. Adjusted HRs for CKD Progression and Death by Hgb and Physical Activity Levels

Exposure	CKD Progression		Death	
	N Events/Patients	HR (95% CI)	N Events/Patients	HR (95% CI)
Hgb, g/dL				
<10	84/221	1.78 (1.29, 2.47)	58/208	3.13 (2.11, 4.65)
10-12	195/714	1.26 (0.98, 1.63)	99/619	1.40 (1.02, 1.92)
>12 (ref)	132/809	1 (ref)	72/719	1 (ref)
Physical activity level				
Never active	72/262	1.17 (0.78, 1.75)	38/200	1.62 (1.06, 2.49)
Low active	75/314	0.94 (0.69, 1.29)	38/283	1.03 (0.70, 1.52)
Highly active (ref)	128/559	1 (ref)	66/528	1 (ref)

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Hgb, hemoglobin; HR, hazard ratio.

Cox regression was used to estimate HRs of CKD progression and death by Hgb and physical activity categories. All models were adjusted for baseline age, sex, black race, country, smoking status, eGFR, BMI, serum albumin, macroalbuminuria, diabetes, lung disease, congestive heart failure, and a comorbidity score (see Table 1 footnote for definition). With physical activity as the exposure, models were additionally adjusted for Hgb.

ESA. Therefore, our results largely represent the effect of spontaneously higher Hgb levels on outcomes and not the impact of therapies targeting these higher Hgb levels.

Findings regarding the association between anemia and HRQOL are variable and inconsistent in published trials. Among the RCTs targeting higher Hgb levels via ESA treatments—Correction of Hemoglobin and Outcomes in Renal (CHOIR),¹¹ Time to Reconsider Evidence for Anemia Treatment (TREAT),¹³ and Cardiovascular Reduction Early Anemia Treatment Epoetin β^{12} —TREAT was the only double-blind, placebo-controlled trial. Inclusion in TREAT was restricted to diabetic ND-CKD patients with baseline Hgb ≤ 11 g/dL. Investigators found a significant improvement in the Functional Assessment of Cancer Therapy fatigue score over 25 weeks for patients targeted to a higher Hgb of 13 g/dL but no improvement in the Short Form-36 energy or physical function HRQOL domains. CHOIR, restricted to ND-CKD patients having baseline Hgb < 11 g/dL, failed to see improvements in HRQOL domains for patients targeted to Hgb 13.0–13.5 g/dL versus 10.5–11.0 g/dL. The open-label Cardiovascular Reduction Early Anemia Treatment Epoetin β trial, restricted to CKD patients having Hgb 11.0–12.5 g/dL, found significant HRQOL improvements at 1 year for those targeted to Hgb 13–15.0 g/dL versus 10.5–11.5 g/dL. Improvement was initially seen in general and mental health, physical function and role, vitality, and social function. At 2 years after randomized treatment initiation, significant HRQOL improvements remained only for general health and vitality.

Unfortunately, these restricted RCT participants represented less than half of the entire ND-CKD patient population, thereby limiting generalizability of findings to clinical practice. Meta-analyses of these and other similar RCTs have further reinforced the overall lack of consistency and strong positive associations between Hgb improvements and changes in HRQOL measures.^{14,25}

In the present study, we found consistent associations between Hgb and the HRQOL domains of burden and effects of kidney disease, and with multiple subdomains of the MCS and PCS, even after accounting for numerous patient characteristics. When compared with patients having Hgb > 12 g/dL, HRQOL scores were lowest in patients with Hgb levels < 10 g/dL; poorer HRQOL was also evident for some measures even at Hgb 10–12 g/dL.

Our study patients had stage 3–5 ND-CKD and treated in nephrologist-run clinics, with 46% having Hgb > 12 g/dL, of which only 4% were prescribed an ESA and 1% prescribed IV iron. None would have been eligible for TREAT or CHOIR trials. Thus, our real-world findings indicating strong associations of particular HRQOL domains with higher Hgb levels may be more representative of the broader ND-CKD patient population. In addition, our analyses extended beyond purely physical- and energy-related domains. Some of the strongest associations were with emotional role and the burden and effects of kidney disease. Findings of prior observational studies of stage 3–5 ND-CKD patients have varied from reporting no or weak associations between Hgb levels and various HRQOL domains,²⁶ to reporting strong associations between Hgb levels with some of the same HRQOL domains observed in this study.^{6,10,27–32}

Very limited information exists regarding the connection between anemia and physical functioning in ND-CKD patients.^{7,8,33} In response, we collected data on patient-reported physical activity levels via the RAPA instrument. RAPA responses have shown good correlation and diagnostic accuracy when compared with direct measurement of physical activity via accelerometer and with the long-form Community Healthy Activities Model Program for Seniors survey in adults > 50 without CKD; 90% of our study population was aged > 50 years.^{19,20,34,35} In our study, patients had significantly higher odds of being highly active (vs. not) at higher Hgb levels, with self-reported

physical activity declining proportionally at lower Hgb levels between Hgb of 13.0 g/dL and 10.5 g/dL; we observed no further decline in physical activity at Hgb levels <10.5 g/dL. To the best of our knowledge, our work is the first description of the association between anemia and physical activity using a validated instrument in a large, population-based stage 3–5 ND-CKD patient cohort.

We also found an association of greater anemia with poorer clinical outcomes of mortality and progression of kidney disease. Compared with patients having Hgb >12 g/dL, the HR of death was over 3-fold higher for patients having Hgb <10 g/dL and 1.4-fold higher for patients with 10–12 g/dL. Similarly for CKD progression, compared with patients having Hgb >12 g/dL, the HR of progression was 1.8-fold higher at Hgb <10 g/dL and 1.3-fold higher at 10–12 g/dL.

Our mortality and CKD progression findings based on this broader patient population differ considerably from those seen in previous RCTs that failed to demonstrate a substantial benefit for patient survival or for delaying kidney disease progression for patients targeted to higher versus lower Hgb levels with ESAs.^{11–13,36} However, post hoc analyses suggest ESA hyporesponsiveness may have contributed to the lack of benefit seen for patients targeted to higher Hgb levels.^{37–39} Our study sample appears to differ considerably from patients included in these RCTs, in that nearly half of our participants had a baseline Hgb >12 g/dL without ESA treatment. It is conceivable that, although ND-CKD patients have a similar eGFR at one point in time, their subsequent eGFR trajectories differ for those having high versus lower Hgb levels. The potential impact of higher than currently recommended Hgb levels on improved clinical outcomes (including patient-centered outcomes) will benefit from future investigation.

We also examined the association of self-reported physical activity levels with the longitudinal outcomes of mortality and kidney disease progression. With median follow-up of 1.4–1.5 years for 1,000+ patients, there was significantly higher mortality (HR = 1.62) and a trend toward more rapid CKD progression (HR = 1.17) among those not physically active (vs. highly active). This mortality association is of similar magnitude to that seen by Lopes et al.¹⁵ among 5,763 hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study, in which patients who were very active and often active had an HR (95% CI) of mortality of 0.60 (0.47, 0.77) and 0.81 (0.68, 0.96), when compared with patients who were never or rarely physically active.

A limitation of observational design is that we cannot conclude causality for these associations. For the cross-sectional analyses, we also cannot conclude the predictor/outcome directionality for associations of Hgb with physical activity and HRQOL domains. Although we adjusted for numerous patient characteristics, residual confounding, such as lack of information regarding comorbidity severity,

could remain. Incomplete response to the instruments may have introduced bias in estimating physical activity or HRQOL levels if participation was associated with level of physical activity, HRQOL, patient characteristics like comorbidities, or outcome status. However, the very similar distribution of patient characteristics, comorbidities, and mortality for patients included versus excluded from the HRQOL analyses suggests that any such potential bias is small. Despite these limitations, this study is unique, as it is based on an international and relatively large sample of CKD patients. The careful sampling process used to recruit clinics captured populations that were representative of the real-world setting in those countries. In addition, the present study reports a combination of traditional and patient-reported outcomes, such as self-reported physical activity, at a range of Hgb levels that are not usually described in interventional clinical trials.

Negative outcomes from RCTs understandably lead clinicians to refrain from treating with ESAs to higher Hgb levels. Our findings provide encouragement by indicating that maintaining Hgb levels higher than the current recommendations may lead to improved HRQOL and greater physical activity levels, as well as lower risk of CKD progression. The individual contribution of the greater physical activity associated with higher Hgb on improved outcomes in CKD deserves further investigation.

Our findings help inform the design of future studies aimed at understanding the effects of anemia therapies in CKD patients and how anemia correction may impact improvements in well-being and clinical outcomes. Moreover, our work helps further inform individualized patient-centered care, as recommended by Kidney Disease: Improving Global Outcomes (KDIGO)⁴⁰ and Klinger et al,⁴¹ whereby anemia treatment in CKD should focus on the particular patient-perceived outcomes that are most important to an individual and may be modifiable by correction of anemia.

Practical Application

Hgb levels, as an indicator of anemia, have been inconsistently associated with HRQOL and physical activity in persons with moderate-to-advanced CKD in observational studies and RCTs. In the present study, we analyzed data from 2,121 persons having stage 3–5 CKD (not on dialysis) being treated at 28 U.S. and 15 Brazilian nephrologist-run CKD clinics. Our findings showed that Hgb levels >12 g/dL were associated with slower progression of CKD, greater survival, higher odds of being physically active, and better HRQOL (for HRQOL domains of general health, emotional role, physical role, and burden/effects of kidney disease). However, additionally, an important finding of this work is that even moderate anemia (Hgb levels from 10 to 12 g/dL) was associated with poorer HRQOL, rate of CKD progression, and mortality.

Acknowledgments

Janet Leslie, medical technical writer, with Arbor Research Collaborative for Health, assisted in revising the presentation of the researchers' results and finalizing the manuscript. Heather Van Doren, senior medical editor with Arbor Research Collaborative for Health, provided editorial assistance on this manuscript.

Financial Disclosure: Coauthors Heleen van Haalen and Glen James are employees of AstraZeneca. The authors declare that they have no relevant financial interests.

Support: This work, produced by CKDopps as part of the Dialysis Outcomes and Practice Patterns Study (DOPPS) Program, has been supported by specific funding from AstraZeneca. To see all funding for the DOPPS Program, please visit dopps.org. All support is provided without restrictions on publications.

Authors' contributions: J.H., H.v.H., G.J., R.P-H., B.M.R., and R.L.P. contributed to research idea and study design; J.H., A.A.L., K.A., R.P-F, B.M.R., and R.L.P. contributed to data acquisition; J.H., D.M., J.Z., N.S., E.S., M.G., A.A.L., K.A., H.v.H., G.J., R.P-F, B.B., B.M.R., and R.L.P. contributed to data analysis/interpretation; D.M., J.Z., and B.B. contributed to statistical analysis; R.P-F, B.B., B.M.R., and R.L.P. were responsible for supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1053/j.jrn.2019.11.003>.

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