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Association of Chronic Kidney Disease and Anemia with Physical Capacity: The Heart and Soul Study

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Abstract

Chronic kidney disease (CKD) and anemia are common conditions in the outpatient setting, but their independent and additive effects on physical capacity have not been well characterized. The association of CKD and anemia with self-reported physical function was evaluated and exercise capacity was measured in patients with coronary disease. A cross-sectional study of 954 outpatients enrolled in the Heart and Soul study was performed. CKD was defined as a measured creatinine clearance <60 ml/min, and anemia was defined as a hemoglobin level of <12g/dl. Physical function was self-assessed using the physical limitation subscale of the Seattle Angina Questionnaire (0 to 100), and exercise capacity was defined as metabolic equivalent tasks achieved at peak exercise. In unadjusted analyses, CKD was associated with lower self-reported physical function (67.6 *versus* 74.9; $P < 0.001$) and lower exercise capacity (5.5 *versus* 7.9; $P < 0.001$). Similarly, anemia was associated with lower self-reported physical function (62.6 *versus* 74.3; $P < 0.001$) and exercise capacity (5.7 *versus* 7.5; $P < 0.001$). After multivariate adjustment, CKD (69.4 *versus* 74.2; $P = 0.003$) and anemia (67.5 *versus* 73.6; $P = 0.009$) each remained associated with lower mean self-reported physical function. In addition, patients with CKD (6.3 *versus* 7.7; $P < 0.001$) or anemia (6.5 *versus* 7.4; $P = 0.004$) had lower adjusted mean exercise capacities. Participants with both CKD and anemia had lower self-reported physical function and exercise capacity than those with either alone. CKD and anemia are independently associated with physical limitation and reduced exercise capacity in outpatients with coronary disease, and these effects are additive. The broad impact of these disease conditions merits further study.

Chronic kidney disease (CKD) and anemia are common conditions in the outpatient population that often are present concurrently. Both conditions have been associated with reduced physical function, but their independent effects have not been well evaluated. Understanding the relative impact of these conditions on patient physical function is complicated by their similar symptoms and their overlap with aging and other common disease conditions, such as heart failure and malnutrition.

Most previous studies that evaluated the association of renal dysfunction with physical capacity examined people with ESRD. Previous studies have found an association between CKD and reduced exercise capacity, but these studies primarily included patients with severe CKD (1–3). Although a few studies have examined the association of moderate CKD with physical function (4–6), all have used subjective measures of function that may not accurately reflect objective physical capacity. Anemia is a complication of declining renal function, and other studies have found an association between anemia and physical capacity in individuals with

severe renal disease (7–11). However, the comparative effects of kidney disease and anemia on objective physical function are not known.

We evaluated the association of two predictors, CKD and anemia, with two outcomes, self-reported physical function and objectively measured exercise capacity, in an outpatient cohort of people with coronary disease. Our goals were to compare the strength of each condition's effect on physical capacity and to determine whether they were additive. We hypothesized that CKD and anemia each would be independently associated with self-reported physical limitations and reduced exercise capacity and that the combination of CKD and anemia would have an additive effect on physical function.

Materials and Methods

Patients

The Heart and Soul Study is a prospective cohort designed to examine the influence of psychosocial factors on cardiac outcomes in participants with known coronary disease. From September 2000 to December 2002, patients were recruited from the San Francisco Veterans Affairs Medical Center; the Veterans Affairs Palo Alto Health Care System; the University of California, San Francisco Medical Center; and nine public health clinics in the Community Health Network of San Francisco. Patients were eligible to participate when they had one of the following inclusion criteria: history of myocardial infarction, angiographic evidence of >50% stenosis in one or more coronary vessels, evidence of exercise-induced ischemia by treadmill or nuclear testing, history of coronary revascularization, or documented diagnosis of coronary artery disease by an internist or cardiologist. Patients were excluded when they had had a myocardial infarction in the past 6 mo, were unable to walk one block, or were planning to move out of the area in the next 3 yr.

Among 15,438 potential patients, 1024 were enrolled. Additional descriptions of the cohort have been previously published (12,13). For this analysis, we excluded patients who did not have 24-h urine collection data or who were missing data for both outcome measurements ($n = 70$). All participants provided written informed consent, and the protocol was approved by the appropriate institutional review boards.

Measurements

Predictors

Primary: CKD was defined *a priori* as a creatinine clearance <60 ml/min ($\geq$ stage 3 by the National Kidney Foundation classification) (14). Creatinine clearance was measured, on the basis of 24-h urine collection, using the following formula: urine Cr (mg/dl) $\cdot$ 24-h urine volume (dl)/serum Cr (mg/dl) $\cdot$ 1440 (min/d). At the intake appointment, patients were given a 3-L collection jug and instructed to save all urine between the end of their intake appointment and the time when a researcher recovered the urine. The patients were instructed to void before beginning the urine collection. Research personnel visited the patients' home 24 h after their intake appointments to ensure accurately timed specimens. When >1 h had passed since their last void, patients were asked to void again to complete the collection. In addition, the patients were asked whether they were able to collect all urine or some fraction had been accidentally discarded. When the sample was reported to be incomplete, patients were asked to repeat the collection, and research personnel returned 24 h later to re-collect the urine. Hemoglobin levels were measured in the hematology laboratory at the San Francisco VA Medical Center, and anemia was defined as a hemoglobin level <12g/dl (14).

Secondary: Age, gender, race, education, income, marital status, medical history, smoking status, and alcohol use were determined by self-report. We measured height and weight and

calculated body mass index. After a 12-h fast, serum samples were collected for measurement of total cholesterol, HDL, LDL, and albumin. Left ventricular ejection fraction was determined by two-dimensional resting echocardiogram. Depression was defined as a score of 10 or greater on the Patient Health Questionnaire (15).

Outcomes—Participants' self-perception of their physical function was assessed by the Seattle Angina Questionnaire (SAQ; nine-item physical limitation scale) (16), which measures how daily activities are limited by symptoms of coronary disease. Responses were scored 0 to 100, with higher scores representing better physical function. In previous studies, the physical limitation scale of the SAQ had strong and significant correlations with the physical functioning ($r = 0.63$, $P < 0.001$) and physical component ($r = 0.59$, $P < 0.001$) subscales of the Medical Outcomes Study Short-Form 36 (17). In a validation study, the physical limitation scale of the SAQ was significantly associated with exercise treadmill test duration ($r = 0.42$, $P = 0.001$) (16). A change in score of 10 points is considered a clinically important difference (16). On the basis of previous literature, physical limitation was defined as a score of <75 (18).

Objective exercise capacity was assessed on a graded exercise treadmill test using a standard Bruce protocol. Maximum exercise capacity was determined by the total number of metabolic equivalent tasks (MET) achieved; we defined low exercise capacity as a score of <5 MET (19). For reference, the MET of some common activities are as follows: sitting, 1.0 MET; dressing, 2.0 MET; house cleaning, 3.0 MET; brisk walking (4 mph), 5.0 MET; tennis, 7.0 MET; running (6 mph), 10.0 MET (20). We use the umbrella term “physical capacity” to refer to either self-reported physical function or measured exercise capacity.

Statistical Analyses

We evaluated baseline characteristics of patients by presence of CKD and anemia using a t test (or nonparametric equivalent) for continuous variables and χ^2 statistic for dichotomous variables. The unadjusted associations of physical function scores and exercise capacity with CKD and anemia were also compared using a t test. To test for a dose-dependent effect of creatinine clearance and hemoglobin levels on each outcome variable, we subcategorized creatinine clearance (<40 , 40 to <60 , 60 to <90 , and 90+ ml/min) and hemoglobin levels (<11 , 11 to <12 , 12 to <13 , 13 to <14 , and 14+ g/dl). An ANOVA test evaluated the outcome scores across the categories.

We used linear regression to determine the independent association of the primary predictors with each outcome, after adjustment for the secondary predictors listed above. Backward stepwise regression was used with a criterion of $P < 0.10$ for inclusion. Models that evaluated kidney disease as the primary predictor were adjusted for anemia, and anemia models were conversely adjusted for CKD. Adjusted mean physical function and exercise capacity scores were calculated for patients who were stratified by presence of CKD and anemia, on the basis of the parameter estimates from the linear regression models.

To evaluate further the strength of association of CKD and anemia with physical capacity, we used multivariate logistic regression with each outcome variable dichotomized as described above. Backward stepwise regression models were used, with the same candidate predictor variables and inclusion criterion as for the multivariate linear regression models.

We tested for interactions between CKD and age, gender, race, anemia, hypertension, diabetes, heart failure, and depression for predicting each outcome. We also tested for interactions of anemia with age, gender, race, heart failure, and depression for predicting each outcome. All analyses were performed using Stata 8.0 (Stata Corp., College Station, TX).

Results

Patient Characteristics

Of the 954 eligible Heart and Soul Study Participants, 228 (24%) had CKD and 90 (9%) had anemia. Compared with participants who had normal renal function, those with CKD were older and were more likely to have anemia, hypertension, heart failure, ischemia, previous myocardial infarction, previous stroke, poor nutrition, lower body mass index, and lower left ventricular ejection fraction (Table 1). Compared with participants who were not anemic, those with anemia were more likely to be female and to have CKD, diabetes, heart failure, peripheral vascular disease, and lower serum albumin. Participants with anemia were less likely to smoke and use alcohol and had lower total cholesterol and triglyceride levels (Table 2).

Self-Assessed Physical Function

In unadjusted analyses, both CKD (67.6 ± 24.2 versus 74.9 ± 22.9 ; $P < 0.001$) and anemia (62.6 ± 22.7 versus 74.3 ± 23.2 ; $P < 0.001$) were associated with lower self-reported physical function. Mean physical function score was lowest in participants with creatinine clearance <40 ml/min and seemed to increase with higher measured creatinine clearances (Figure 1A). We observed a comparable relationship between hemoglobin levels and self-reported physical function (Figure 1B), whereby mean scores seemed to be reduced in participants with hemoglobin ≤ 12 g/dl. After multivariate adjustment, CKD and anemia each remained associated with lower self-reported physical function (Table 3). In addition, the adjusted mean physical function score was lower in participants with both comorbidities than in those with either alone.

Exercise Capacity

In unadjusted analyses, participants with CKD (5.5 ± 2.8 versus 7.9 ± 3.3 ; $P < 0.001$) or anemia (5.7 ± 2.3 versus 7.5 ± 3.4 ; $P < 0.001$) had a significantly lower exercise capacity. We observed a nearly linear relationship between measured creatinine clearances and exercise capacity, although exercise capacity was similar among <40 and 40 to <60 ml/min (Figure 1C). Exercise capacity also seemed to be associated with hemoglobin levels, as participants with hemoglobin levels <13 g/dl demonstrated lower MET achieved (Figure 1D). After multivariate adjustment, CKD and anemia remained associated with low exercise capacity, and people with both conditions had lower MET achieved than those with either condition alone (Table 3).

Using dichotomized outcomes, we compared adjusted associations of renal function and hemoglobin levels with self-assessed physical limitation (SAQ <75) and measured low exercise capacity (<5 MET). Participants with creatinine clearance <60 ml/min ($\geq$ stage 3 CKD) or hemoglobin <12 g/dl were at greater risk for self-reported physical limitation. We observed no associations of creatinine clearance 60 to 90 ml/min (stage 2 CKD) or hemoglobin levels 12 to 14 g/dl with self-assessed physical limitation (Table 4). In contrast, we observed increased odds for low measured exercise capacity in participants with even mildly reduced creatinine clearances (>60 to 90 ml/min). Of note, patients with $\geq$ stage 3 CKD had a sixfold odds for low exercise capacity compared with patients with creatinine clearance >90 ml/min.

Test for Interactions

We found no significant interactions between CKD and age, gender, race, anemia, hypertension, diabetes, and heart failure in any of the regression models for predicting the outcomes. There were also no significant interactions between anemia and age, gender, race, heart failure, and depression as predictors of the outcomes in this study. We found a single interaction of CKD and depression for predicting self-assessed physical function. In adjusted analysis, CKD was associated with a 13.7-point reduction in depressed patients but only a 2.2-

point reduction in patients without depression ($P = 0.05$ for interaction). In contrast, we observed no interaction of CKD and depression for predicting exercise capacity.

Discussion

In the Heart and Soul study, we found that both CKD and anemia were independently associated with reduced self-assessed physical function and exercise capacity on a treadmill test, and the presence of both conditions was associated with an additive reduction in self-assessed or objectively measured physical function compared with either condition alone. We also found that measured impairments in exercise capacity were present at milder renal dysfunction, compared with self-assessed physical limitation. These findings highlight the importance of both CKD and anemia as determinants of physical capacity and suggest that patient report of physical limitation may be an insensitive marker for actual physical impairment in patients with kidney disease.

Our findings are consistent with other cross-sectional studies that have demonstrated an association between CKD and impaired subjective physical function (4–6,21,22). For example, in the African American Study of Kidney Disease and Hypertension trial, the participants, all of whom had CKD, scored significantly lower on the Physical Component Scores of the Short Form-36 than the general population (4). Investigators in the Modification of Diet in Renal Disease Study also found a significant positive correlation between Quality of Well-Being index and GFR measurements within a sample of people with CKD (5). Other studies have included patients with a broader range of renal function but could use only creatinine-based estimations of renal function (6,21,22). Each of these studies found associations between estimated GFR and self-reported physical function.

Our study is unique as it compared both subjective and objective measures of physical capacity in patients with and without CKD, and it distinguished the independent effects of measured creatinine clearance and hemoglobin levels. In addition, we examined physical function in patients with mild renal dysfunction, a group commonly overlooked. In the setting of ESRD, Johansen *et al.* (23) found that self-assessed physical function was a valid approximation for physical capacity; however, we are aware of no comparable study in patients with CKD. Self-assessed health status may not be sensitive enough to detect small changes in physical function and thus may underestimate the effects of CKD. We found patients with creatinine clearance 60 to 90 ml/min (stage 2 CKD) to have an increased risk for low exercise capacity; however, their subjective physical limitation scores on the SAQ were not different compared with patients who had normal creatinine clearance. In addition, patients with moderate kidney disease (<60 ml/min [$\geq$ stage 3 CKD]) had a greater odds for low exercise capacity compared with subjective physical limitation. Thus, it seems that measured exercise capacity detects changes in physical capacity at earlier stages of renal dysfunction, compared with self-assessed questionnaire.

The mechanisms by which physical capacity is reduced in people with CKD are unclear. Previous studies have found an association between nutritional status and physical function in patients with kidney dysfunction (24–26). However, we found the association between CKD and physical limitation to persist, even after adjustment for albumin and hemoglobin levels. Inflammatory markers are elevated in kidney disease (27) and could mediate the association. Similar mechanisms have been proposed to explain the association of reduced kidney function with increased risk for cardiovascular outcomes (28,29). In addition, there may be factors that were unmeasured in this study that could affect the associations of kidney disease and anemia with physical limitation.

There is evidence that anemia is associated with reduced physical capacity in the setting of ESRD and that erythropoietin therapy may improve exercise capacity (7–9). However, these studies were limited by small sample sizes and were in patients with ESRD. Correction of anemia has also been associated with improvements in health-related quality of life in ESRD and CKD patients (10,11). Revicki *et al.* (11) examined the effect of correction of anemia on quality of life in 83 patients with predialysis CKD. Patients had a mean GFR of 10.1 ml/min, and correction of anemia (hematocrit >36%) was achieved in 34 of 43 patients who were on erythropoietin therapy. The treatment group had significant increases in energy and self-assessed physical function ($P < 0.05$). Our study found both CKD and anemia to be strongly associated with physical function and exercise capacity, despite adjustment for each other. Although anemia is an important contributing factor to physical limitations in many people with CKD, correction of anemia does not restore physical function completely to normal. Studies have found that adding exercise therapy to erythropoietin may optimize the effects of the increased hematocrit (30). Further research is needed to determine whether there are other modifiable determinants of functional decline in the setting of CKD.

Although anemia is a well-described risk factor for reduced physical capacity, many studies have focused on severe levels of anemia. We found that even moderate decrements in hemoglobin (<12 g/dl) were associated with decreased measured exercise capacity and decreased self-reported physical function in these participants with coronary disease. Moreover, the observed association of anemia with poor physical function was independent of renal insufficiency. These findings are noteworthy in the context of typical clinical practice, which would treat anemia in patients with coronary disease only if the hemoglobin were <10 g/dl or the hematocrit were <30%.

One strength of this study was the direct measure of renal function by 24-h urine collection. Many studies rely on serum creatinine levels as a measure of renal function, but creatinine levels are influenced by body mass, race, age, and gender, which limits their ability to assess accurately renal function. Although imperfect compared with GFR, these rigorously collected 24-h urine samples likely provided an accurate reflection of renal function. Our study also had limitations that should be considered when interpreting the results. This was a cross-sectional analysis, which limits our ability to determine causation. Medical history was determined by participant self-report, and some patients may have misreported the presence of a comorbid condition. Although lack of regular exercise may affect physical capacity, we did not adjust for self-reported routine physical activity because of its similarity with our outcome measurements. In addition, we cannot exclude the possibility that the associations of kidney disease and anemia with physical limitation were confounded by unmeasured factors. Finally, the Heart and Soul Study was a cohort of predominantly male patients with coronary artery disease; therefore, our results may not be applicable to women or to the general population.

In summary, we found CKD and anemia to be independently associated with reduced physical capacity measured both by questionnaire and objective treadmill test in patients with coronary artery disease. Even mild kidney disease and anemia may be associated with diminished functional status. Further studies are needed to determine the cause of the reduced physical function and to determine whether there are viable interventions for people with kidney disease.

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Figure 1.

Unadjusted association of creatinine clearance and hemoglobin level with self-reported physical function scores and objective treadmill exercise capacity ($P < 0.001$ for all).

Table 1Baseline characteristics of Heart and Soul study participants with and without renal insufficiency^a

	CKD (N = 228; Mean ± SD or n [%])	No CKD (N = 726; Mean ± SD or n [%])	P Value
Demographic			
age (yr)	71 ± 11	65 ± 10	<0.001
male	195 (86)	599 (83)	0.31
white	145 (64)	434 (60)	0.31
married	97 (43)	310 (43)	0.97
Comorbidities and laboratory measures			
creatinine clearance (ml/min)	46 ± 11	92 ± 22	<0.001
creatinine (mg/dl)	1.5 ± 0.7	1.0 ± 0.2	<0.001
hemoglobin (g/dl)	13.3 ± 1.5	14.1 ± 1.3	<0.001
anemia (<12 g/dl)	45 (20)	45 (6)	<0.001
hypertension	178 (78)	494 (68)	0.003
diabetes	66 (29)	173 (24)	0.12
heart failure	54 (24)	108 (15)	0.002
angina	139 (61)	439 (60)	0.85
ischemia	75 (33)	144 (20)	<0.001
peripheral vascular disease	19 (8)	60 (8)	0.95
previous MI	144 (63)	369 (51)	0.002
previous stroke	49 (21)	85 (12)	<0.001
previous CABG	92 (40)	255 (35)	0.16
previous angioplasty	103 (45)	276 (38)	0.06
depression (≥10 on PHQ)	38 (17)	139 (19)	0.40
hypoalbuminuria (albumin <3.6 g/dl)	45 (20)	60 (8)	<0.001
smoking (current)	47 (21)	139 (19)	0.64
alcohol (regular use)	59 (26)	214 (29)	0.30
total cholesterol (mg/dl)	175 ± 46	178 ± 41	0.39
HDL cholesterol (mg/dl)	46 ± 16	46 ± 14	0.71
LDL cholesterol (mg/dl)	103 ± 37	104 ± 32	0.53
triglycerides (mg/dl)	130 ± 90	144 ± 139	0.16
BMI (kg/m ²)	27 ± 5	29 ± 5	0.002
left ventricular ejection fraction (%)	59 ± 10	63 ± 9	<0.001

^aBMI, body mass index; CABG, coronary artery bypass graft; MI, myocardial infarction; PHQ, Patient Health Questionnaire.

Table 2

Baseline characteristics of Heart and Soul study participants with and without anemia

	Anemia (N = 90; Mean ± SD or n [%])	No Anemia (N = 864; Mean ± SD or n [%])	P Value
Demographic			
age (yr)	69 ± 12	67 ± 11	0.06
male	62 (69)	732 (85)	<0.001
white	43 (48)	536 (62)	0.008
married	33 (37)	374 (43)	0.23
Comorbidities and laboratory measures			
creatinine clearance (ml/min)	61 ± 24	83 ± 28	<0.001
creatinine (mg/dl)	1.4 ± 0.7	1.1 ± 0.4	<0.001
hemoglobin (g/dl)	11.2 ± 0.6	14.2 ± 1.1	<0.001
kidney disease (≤60 ml/min)	45 (50)	183 (21)	<0.001
hypertension	67 (74)	605 (70)	0.40
diabetes	36 (40)	203 (23)	0.001
heart failure	23 (26)	139 (16)	0.02
angina	49 (54)	529 (61)	0.20
ischemia	23 (26)	196 (23)	0.54
peripheral vascular disease	15 (17)	65 (8)	0.002
previous MI	50 (56)	463 (54)	0.67
previous stroke	13 (14)	121 (14)	0.92
previous CABG	29 (32)	318 (37)	0.41
previous angioplasty	34 (38)	345 (40)	0.74
depression (≥10 on PHQ)	18 (20)	159 (18)	0.71
hypoalbuminuria (albumin <3.6 g/dl)	25 (28)	80 (9)	<0.001
smoking (current)	10 (11)	176 (20)	0.03
alcohol (regular use)	17 (19)	256 (30)	0.04
total cholesterol (mg/dl)	168 ± 35	178 ± 53	0.02
HDL cholesterol (mg/dl)	47 ± 14	46 ± 14	0.60
LDL cholesterol (mg/dl)	99 ± 30	104 ± 34	0.13
triglycerides (mg/dl)	108 ± 95	144 ± 134	0.01
BMI (kg/m ²)	28 ± 6	28 ± 5	0.88
left ventricular ejection fraction (%)	62 ± 10	62 ± 10	0.65

Table 3Adjusted mean physical function score and exercise capacity in patients with CKD, anemia, or both^a

	Self-Reported Physical Function (Adjusted Mean [95% CI])	P Value	Objective Exercise Capacity (Adjusted Mean MET [95% CI])	P Value
No CKD (<i>n</i> = 228)	74.2 (72.7–75.8) ^c		7.7 (7.5–7.8) ^e	
CKD (<i>n</i> = 726)	69.4 (66.6–72.1) ^c	0.003	6.3 (6.0–6.7) ^e	<0.001
No anemia (<i>n</i> = 864)	73.6 (72.3–75.0) ^c		7.4 (7.2–7.6) ^e	
Anemia (<i>n</i> = 90)	67.5 (63.1–71.9) ^c	0.009	6.5 (5.9–7.1) ^e	0.004
No anemia or CKD (<i>n</i> = 681)	74.9 (73.3–76.4) ^d		7.7 (7.5–7.9) ^f	
Anemia and CKD (<i>n</i> = 45)	64.7 (58.7–70.8) ^d	0.002	5.7 (4.9–6.4) ^f	<0.001

^aCKD, chronic kidney disease; MET, metabolic equivalent task.^b*P* < 0.05.^cModel included CKD^b, anemia^b, age^b, gender^b, race^b, hypertension^b, heart failure^b, angina^b, peripheral vascular disease^b, previous stroke^b, previous angioplasty, depression^b, smoking^b, alcohol^b, and BMI^b.^dModel included CKD^b, anemia^b, age^b, gender^b, race^b, hypertension^b, heart failure^b, angina^b, peripheral vascular disease^b, previous stroke^b, previous angioplasty, depression^b, smoking^b, alcohol^b, and BMI^b.^eModel included CKD^b, anemia^b, age^b, gender^b, marital status^b, hypertension^b, diabetes^b, heart failure^b, ischemia^b, peripheral vascular disease, previous stroke^b, previous angioplasty, depression^b, smoking^b, alcohol^b, BMI^b, and left ventricular ejection fraction^b.^fModel included CKD^b, anemia^b, age^b, gender^b, marital status^b, hypertension^b, diabetes^b, heart failure^b, ischemia, peripheral vascular disease, previous stroke^b, previous angioplasty, depression^b, smoking^b, BMI^b, and left ventricular ejection fraction^b.

Table 4

Adjusted association of CKD and anemia with physical capacity outcomes

	Self-Reported Physical Limitation (SAQ <75)		Measured Low Exercise Capacity (<5 MET)	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Renal function				
>90 ml/min (n = 345)	1.0		1.0	
60–90 ml/min (n = 381)	1.0 (0.7–1.5) ^b	0.87	2.3 (1.4–3.8) ^c	0.002
<60 ml/min (n = 228)	2.0 (1.3–3.1) ^b	0.003	6.7 (3.8–11.8) ^d	<0.001
Hemoglobin				
>14 g/dl (n = 476)	1.0		1.0	
12–14 g/dl (n = 388)	0.9 (0.6–1.3) ^c	0.57	1.2 (0.8–1.8) ^e	0.34
<12 g/dl (n = 90)	1.8 (1.0–3.2) ^c	0.04	1.7 (0.9–3.2) ^e	0.10

^a $P < 0.05$.^b Model included anemia^a, age^a, gender^a, hypertension^a, heart failure^a, angina^a, peripheral vascular disease^a, previous stroke^a, previous angioplasty^a, depression^a, smoking^a, and BMI^a.^c Model included CKD^a, age^a, gender^a, hypertension^a, heart failure^a, angina^a, peripheral vascular disease^a, previous stroke^a, previous angioplasty^a, depression^a, smoking^a, and BMI^a.^d Model included anemia^a, age^a, marital status^a, heart failure^a, peripheral vascular disease^a, previous stroke^a, previous angioplasty^a, depression^a, smoking^a, and BMI^a.^e Model included CKD^a, age^a, marital status^a, heart failure^a, peripheral vascular disease^a, previous stroke^a, previous angioplasty^a, depression^a, smoking^a, and BMI^a.