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Anemia and Renal Insufficiency Are Independent Risk Factors for Death among Patients with Congestive Heart Failure Admitted to Community Hospitals: A Population-Based Study

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Abstract. The purpose of this retrospective cohort study was to examine the associations among chronic kidney disease, anemia, and risk of death among patients with heart failure. Retrospective cohort study. Patients with a principal diagnosis of heart failure (ICD9 codes 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, and 428.xx) were included. Chronic kidney disease (CKD) was defined as a serum creatinine >1.4 mg/dl for women and >1.5 mg/dl for men. There were 665 eligible patients in the sample with a mean (SD) age of 75.7 (10.9) yr; 60% were women, 71% were white, and 38% had CKD. On admission, a hematocrit ≥40% was found for 30.3% of the patients; 22.9% had a hematocrit between 36% and 40%, 33.2% between 30% and 35%, and 13.6% had a hematocrit of <30%. The 1-yr death rates among individuals with and without CKD were 44.9% and 31.4%, respectively (relative risk [RR], 1.43; 95% confidence interval [CI], 1.17 to 1.75). The mortality at 1 yr was 31.2% for individuals with a hematocrit ≥40%; 33.8% (RR, 1.08; 95% CI. 0.79 to 1.47) for hematocrit 36 to 39%; 36.7% (RR, 1.17; 95% CI, 0.89 to 1.54) for hematocrit between 30 and 35%; and 50.0% (RR, 1.60; 95% CI, 1.19 to 2.16) for those with a hematocrit <30% (χ^2 for trend was 7.37; $P = 0.007$). Both hematocrit and serum creatinine were independently associated with increased risk of death during follow-up after controlling for other patient risk factors. In conclusion, CKD and anemia are frequent among older patients with heart failure and are independent predictors of subsequent risk of death.

Anemia is a frequent complication of chronic kidney disease (CKD) and is primarily due to failure of erythropoietin production to respond to decreased hemoglobin concentration (1,2). The onset of anemia during the progression of CKD is variable, but it is common after serum creatinine reaches 1.5 mg/dl and increases in prevalence with decreasing creatinine clearance (3,4). At the onset of end-stage renal disease (ESRD), the mean hematocrit is <30%, despite the use of erythropoietin replacement in over a quarter of new patients (5). A recent report by al-Ahmad *et al.* (6) found that CKD and anemia are independent risk factors for mortality among patients with heart failure due to left ventricular dysfunction (*i.e.*, an ejection fraction ≤35%) enrolled in the Studies of LV Dysfunction (SOLVD) clinical trial. Increased risk of death was noted among patients with a hematocrit between 35 and 39% as well as those with more severe degrees of anemia. This report is of particular interest given that the prevalence of heart failure was 33% among new ESRD patients (5).

Although CKD has been a known risk factor for mortality among patients with heart failure, the findings of al-Ahmad *et al.* were unexpected, as a contribution of anemia to the risk of death had not been previously reported (7–16). It is possible that the association between anemia and mortality observed in this clinical trial was a consequence of selection of patients for SOLVD, and similar results might not pertain in a more general population of heart failure patients. The purpose of this study was to determine if similar associations among CKD, anemia, and risk of death exist in a population-based sample of patients discharged from community hospitals with heart failure due to either left ventricular systolic or diastolic dysfunction.

Materials an Methods

Study Design

This is a retrospective cohort study of randomly selected Medicare beneficiaries discharged from community hospitals with a primary diagnosis of heart failure.

Study Population

All Medicare beneficiaries admitted to any general hospital in a single southeastern state between July 1, 1998 and December 31,

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1998, who were alive at discharge with a principal diagnosis of heart failure (ICD9 codes 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, and 428.xx) were eligible for inclusion in the study. We excluded patients with a history of renal disease identified as a history of chronic dialysis in the medical record ($n = 9$). We also excluded patients who died before discharge ($n = 26$) and patients for whom we could find no record of their clinical status in the state Medicare status file ($n = 50$).

Patient Sample

Records for eligible patients were identified by the Medicare Medical Information System, and a random sample of eligible discharges was chosen.

Data Abstraction

Trained abstractors used a standardized form to abstract patient charts. Data abstracted for each patient included date of admission and discharge, demographic information (age, race, and gender), and degree of mobility on discharge. Abstracted comorbid conditions as recorded by the clinician included a history of stroke, ESRD (defined as chronic dialysis), myocardial infarction, heart failure, coronary artery disease, angina pectoris, diabetes mellitus, and hypertension. We used the ICD-9 diagnoses reported on the hospital discharge record to calculate a Charlson comorbidity score for each patient (17). The Charlson comorbidity score is the sum of weighted values for ICD-9 codes assigned during a hospitalization and is predictive of subsequent risk of hospitalization and death. Patients given an angiotensin-converting enzyme inhibitor (ACEI) on discharge were also identified.

Reports of left ventricular ejection fractions were identified and recorded. If a previous and a current ejection fraction were both present in the record, we used the lower value for the purposes of analysis. We categorized individuals with an ejection fraction of ≤40% as having left ventricular systolic dysfunction (LVSD), those with a ejection fraction >40% as having left ventricular diastolic dysfunction (LVDD), and those without a recorded value as undetermined left ventricular function (18).

The pulse rate, systolic and diastolic BP, and the presence of peripheral edema on admission were recorded. Radiographic changes of pulmonary edema or heart failure were recorded. Laboratory values for the first serum creatinine and hematocrit recorded in the chart were abstracted. We defined CKD as a serum creatinine >1.4 mg/dl for women and >1.5 mg/dl for men. We also calculated the GFR using the equation used in the Modification of Diet in Renal Disease (MDRD) study, as modified for age, gender, and race (19), and substituted the resulting rate for creatinine levels in some models. In some analyses, anemia was defined as a hematocrit of <30%.

Follow-up

Follow-up began on the date of hospital discharge for the index admission and continued until March, 1, 2001. Patients were characterized as dead if a date of death had been recorded for them in the Medicare database and as missing if neither a date of death nor a current Medicare eligibility record was found. We were unable to identify either a death date or evidence for current eligibility for 18 (2.6%) of the patients, and these patients were excluded from mortality analyses.

Statistical Analyses

We calculated descriptive statistics and the 12-mo risk of death for selected categories of key covariates. We described the crude associations between level of hematocrit and the presence of CKD with mortality by Kaplan-Meier plots. We used risk ratios and associated confidence intervals to measure the association between categorical variables and risk of death. To account for confounding and to assess the joint effects of renal insufficiency and anemia, we used Cox regression models. In most models, we used serum creatinine and hematocrit as continuous variables along with age, ejection fraction, and indicators for sex, race, comorbid history (stroke, myocardial infarction, coronary artery disease, and angina pectoris), hypertension, diabetes mellitus, a previous history of heart failure, and discharge functional status. We also treated creatinine (CKD yes/no) and hematocrit (anemia yes/no) as dichotomous in some models. Hematocrit was dichotomized at <30% and ≥30% for the purposes of these models.

We assessed the independent association between anemia and mortality for type of left ventricular function in two ways. First, we examined the association between anemia (hematocrit <30%) and mortality for the three levels of left ventricular function. Second, we included interaction terms in the multivariate model between left ventricular function and anemia.

We assessed the proportional hazards assumption using plots of log-log survival and interaction terms with time. We screened for potential collinearity using correlation coefficients. We further assessed model fit by including interaction terms between creatinine and hematocrit, with other independent variables. To determine the importance of these factors on mortality soon after hospital discharge, we repeated these survival analyses by limiting the follow-up to the first 90 d, 180 d, 270 d, and to 1 yr. All analyses were conducted using SAS Version 8.1 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

Our sample included 755 patients admitted to community hospitals with heart failure. After excluding duplicate records, patients with a history of renal disease, patients who died before discharge, and patients lost to follow-up, data from 665 patients were analyzed. Records of patients from 120 hospitals were sampled, yielding a mean (SD) of 5.5 (5.3) patients per hospital and a 25^{th} to 75^{th} intraquartile range from 2 to 7 patients. The range of patients contributed to the sample by an individual hospital was from 1 to 2.

The mean (SD) age was 75.7 (10.9) yr, with a range from 29 to 100 yr; 60% were women, and 71% were white. A history of heart failure was present for 75% of the patients. A history of stroke was reported for 20%, myocardial infarction for 26%, coronary artery disease for 51%, and angina pectoris for 15% of patients. Hypertension was reported for 66% and diabetes mellitus for 44% (Table 1).

A report describing previous or current left ventricular ejection fraction was found in 60.0% of the patient's charts. The mean (SD) ejection fraction was 38.4% (16.9), with a range from 10 to 85%. Among the 399 patients with a recorded ejection fraction, 60% had LVSD with a mean (SD) ejection fraction of 26.5% (8.1). The mean ejection fraction among individuals with LVDD was significantly higher at 56.4% (9.0%) ($P < 0.0001$).

Peripheral edema was noted on admission in 70% of patients, and a chest x-ray with findings of either pulmonary edema or heart failure was present for 76%. There was no

Table 1. Characteristics of patients and proportion with CKD and corresponding 12-mo mortality rates[a]

Characteristic	*n*	CKD (%)	12-mo Mortality Rate (%)	RR (95% CI)
Age				
≤70 yr	169	31.3	31.4	1
71 to 75 yr	114	37.3	32.5	1.03 (0.73 to 1.46)
76 to 80 yr	129	38.1	35.7	1.14 (0.82 to 1.57)
>80 yr	253	42.6	43.1	1.37 (1.05 to 1.79)
Gender				
female	402	32.9	35.1	1
male	263	45.5	39.5	1.13 (0.92 to 1.38)
Race				
black	186	39.6	32.8	1
white	462	37.8	39.0	1.19 (0.94 to 1.50)
Previous CHF	502	41.5	39.8	1.44 (1.1 to 1.89)
Comorbidity				
stroke	132	43.4	38.6	1.06 (0.83 to 1.35)
MI	176	41.4	39.2	1.09 (0.88 to 1.36)
CAD	342	43.9	36.0	0.95 (0.78 to 1.16)
AP	103	37.4	33.0	0.88 (0.65 to 1.18)
HBP	442	42.4	35.3	0.88 (0.72 to 1.09)
diabetes	293	43.2	37.9	1.05 (0.86 to 1.28)
Functional status				
normal	285	41.4	39.0	1
mild impairment	207	29.8	27.1	0.69 (0.53 to 0.91)
moderate impairment	153	45.6	43.8	1.12 (0.89 to 1.42)
severe impairment	20	11.1	55.0	1.41 (0.93 to 2.15)
Left ventricular function				
diastolic dysfunction	158	36.6	26.0	1
systolic dysfunction	241	39.7	37.8	1.46 (1.07 to 1.98)
undetermined	266	37.2	45.2	1.64 (1.21 to 2.2)

[a] CHF, chronic heart failure; MI, myocardial infarction; CAD, coronary artery disease; AP, angina pectoris; HBP, high BP.

difference in either the proportion of patients with peripheral edema ($P = 0.082$) or positive findings on chest x-ray ($P = 0.54$) among those individuals with undetermined left ventricular function, LVSD and LVDD. An ACEI was prescribed at discharge for 54% of the cohort. ACEI use was less common among individuals with CKD (49%) compared with those without CKD (58%) ($P = 0.018$).

Prevalence of CKD

A serum creatinine value was reported on admission for 646 members (97%) of the cohort. The mean (SD) value was 1.46 (0.78) mg/dl, with a range from 0.5 to 7.5 mg/dl and a 25th to 75th intraquartile range from 1.0 to 1.7 mg/dl. CKD, defined by a serum creatinine of ≥1.4 mg/dl for women and ≥1.5 mg/dl for men, was present in 38% of the cohort. Men (46%) were more likely than were women (33%) to have CKD, (odds ratio [OR], 1.70; 95% confidence interval [CI], 1.23 to 2.36). The mean (SD) serum creatinine among individuals with CKD was 2.16 (0.86) mg/dl; among those without CKD, it was 1.02 (0.21) mg/dl ($P < 0.0001$).

Prevalence of Anemia

A hematocrit was recorded for 633 members (95%) of the cohort. The mean (SD) hematocrit was 36.6% (6.3), with a 25th to 75th intraquartile range from 32.6% to 40.9%. The proportion of patients with a hematocrit ≥40% was 30.3%; 22.9% had a hematocrit between 36% and 39%, 33.2% between 30% and 35%, and 13.6% had a hematocrit of <30%.

The proportion of patients with CKD increased with increasing anemia (Table 2). A third (33%) of individuals with a serum creatinine between 2 and 3 mg/dl and half (50%) with a creatinine >3 mg/dl had a hematocrit <30%. Of note was that 25.1% of nonanemic CHF patients had CKD, and 40.0% of severely anemic patients had normal serum creatinine (Table 2). The mean (SD) serum creatinine was 1.26 (0.56) mg/dl among patients with no anemia, 1.35 mg/dl (0.55) in patients with mild anemia, 1.48 mg/dl (0.75) for moderate anemia, and 2.01 mg/dl (1.23) for severe anemia ($P < 0.0001$).

Mortality

Mortality rates were high; 59% of the cohort ($n = 393$) died during follow-up, and mortality at 1 yr was 36.8%. The pres-

Table 2. Characteristics of patients according to hematocrit (Hct) level

	Hematocrit			
	≥40%	36 to 39%	30 to 35%	<30%
n (%)	192 (30%)	145 (23%)	210 (33%)	86 (14%)
Mean (SD) Hct[a]	43.8% (3.2)	37.9% (1.1)	33.2% (1.6)	26.4% (3.3)
CKD (%)[a]	25%	35%	44%	60%
Mean (SD) serum creatinine[b] mg/dL	1.26 (0.56)	1.35 (0.55)	1.48 (0.75)	2.01 (1.23)
% discharged with ACEI[c]	59%	59%	51%	42%
Mortality				
total[d]	52.1%	54.5%	61.9%	70.9%
1-yr[e]	31.3%	33.8%	36.7%	50.0%

[a] $P < 0.0001$; [b] $P = 0.0352$; [c] $P = 0.0231$; [d] $P = 0.016$; [e] $P = 0.007$.

ence of CKD was associated with an increased risk of death (Figure 1); 67% of patients with and 54% of those without CKD died during follow-up (relative risk [RR], 1.26; 95% CI, 1.11 to 1.42). One-year mortality rates among individuals with and without CKD were 44.9% and 31.4% respectively (RR, 1.43; [95% CI, 1.17 to 1.75).

Anemia on admission to the hospital was associated with an increased risk of death (Table 2 and Figure 2). Compared with individuals with a hematocrit ≥40%, the RR (95% CI) for death for individuals with a hematocrit between 36 and 39% was 1.05 (0.86 to 1.28); 1.19 (1.00 to 1.41) for a hematocrit between 30 and 35%; and 1.36 (1.12 to 1.65) for a hematocrit <30% (χ^2 for trend 10.0, 1 df; $P = 0.016$). Corresponding 1-yr RR were 1.08 (0.79 to 1.47); 1.17 (0.89 to 1.54); and 1.60 (1.19 to 2.16); χ^2 for trend was 7.37; $P = 0.007$.

Individuals with left ventricular diastolic and systolic dysfunction, as well as those with undetermined ventricular function, had comparable increased risk of death during the first year. Compared with individuals with a hematocrit ≥30%, the RR (95% CI) for death within 1 yr for anemic patients with left ventricular diastolic dysfunction was 1.74 (0.7 to 4.33); left ventricular systolic dysfunction, 1.56 (0.65 to 3.23); and undetermined left ventricular function, 2.03 (1.27 to 3.23). The estimates of RR did not differ significantly from one another by the Breslow-Day test for homogeneity ($P = 0.61$).

Multivariate Analysis

Both hematocrit and serum creatinine were independently associated with increased mortality during follow-up (Table 3) after controlling for age, gender, race, comorbidity, hypertension, and diabetes mellitus, a previous history of heart failure, lowest ejection fraction, discharge functional status, Charlson comorbidity index, and status of ACEI use at discharge. For each 1% increase in hematocrit, the mortality rate declined 1.6% ($P = 0.09$); for each one mg/dl increase in serum creatinine, the rate increased 16% ($P = 0.025$).

During the first year of follow-up, there was a 2.4% decrease in the hazard ratio associated with a 1% increase in hematocrit ($P = 0.046$) and a 15% increase in the hazard ratio associated with a one mg/dl increase in serum creatinine ($P = 0.08$) (Table 3). After controlling for all other risk factors, the hazard ratio associated with either the presence of anemia, 1.07 (0.59 to 1.9), or CKD, 1.24 (0.93 to 1.7), alone at 1 yr were comparable. The hazard ratio associated with the presence of both conditions was 2.17 (1.4 to 3.3), somewhat more than would be expected under a multiplicative model, but interaction terms in the statistical analysis were NS. The interaction terms for anemia-left ventricular function were NS.

We also examined the hazard ratio for both serum creatinine and hematocrit at 90 d, 180 d, and 270 d to determine the relative importance of the two measures immediately after hospital discharge. We retained the same covariates in these models that were used in the all-years mortality and 1-yr mortality analyses. The association between the hematocrit and risk of death was stable during the first year of follow-up and became significant at 270 d. The RR (95% CI) for a 1% increase in hematocrit at 90 d was 0.98 (0.95 to 1.02); at 180 d, 0.98 (0.95 to 1.01); and at 270 d, 0.97 (0.95 to 0.999).

The RR (95% CI) for a 1 mg/dl increase in serum creatinine was slightly less pronounced during the first year of follow-up than it was for all years combined. During the first 90 d of follow-up, the RR of death for each 1 mg/dl increase in serum creatinine was 1.05 (0.81 to 1.35); at 180 d, 1.07 (0.88 to 1.31); and at 270 d, 1.07 (0.9 to 1.27).

We treated both CKD and anemia as dichotomous exposures by grouping hematocrit as <30% (severe anemia) and those with a hematocrit ≥≥30%. When we retained the same covariates in the Cox models, the mortality rate during 1 yr of follow-up associated with severe anemia was 1.48 (1.04 to 2.12) ($P = 0.029$) and the mortality rate at 1 yr associated with CKD was 1.43 (1.06 to 1.92) ($P = 0.0182$).

Finally, we examined both hematocrit and creatinine clearance using the equation for calculating GFR as mentioned earlier. The creatinine clearance variable replaced creatinine, and all other covariates were retained. In examining total mortality, for each 1% increase in hematocrit, the mortality rate declined 1.6% ($P = 0.087$); for each 1 ml/min increase in creatinine clearance, the rate decreased 0.6% ($P = 0.011$). For

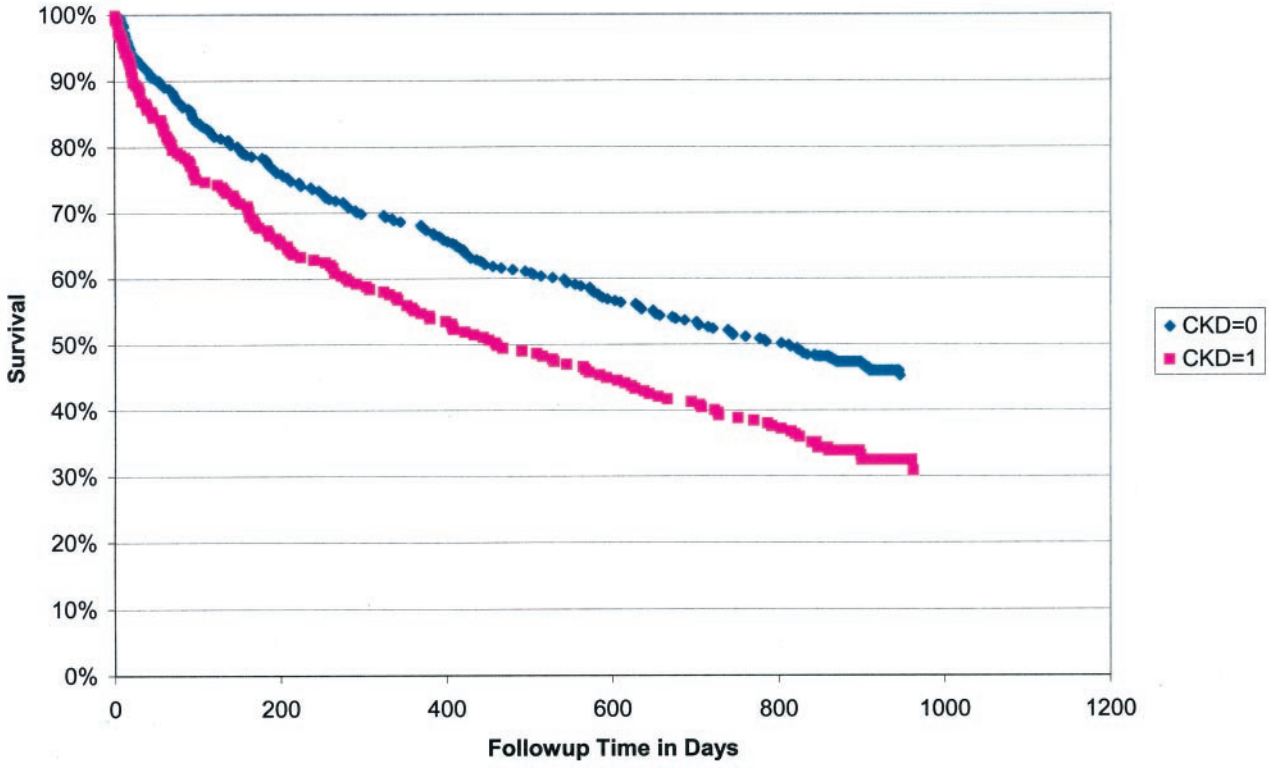

Figure 1. Survival among heart failure patients with and without CKD adjusted for anemia, age, sex, race, stroke, heart attack, coronary artery disease, angina pectoris, hypertension and diabetes mellitus status, a previous history of heart failure, ejection fraction and discharge functional status.

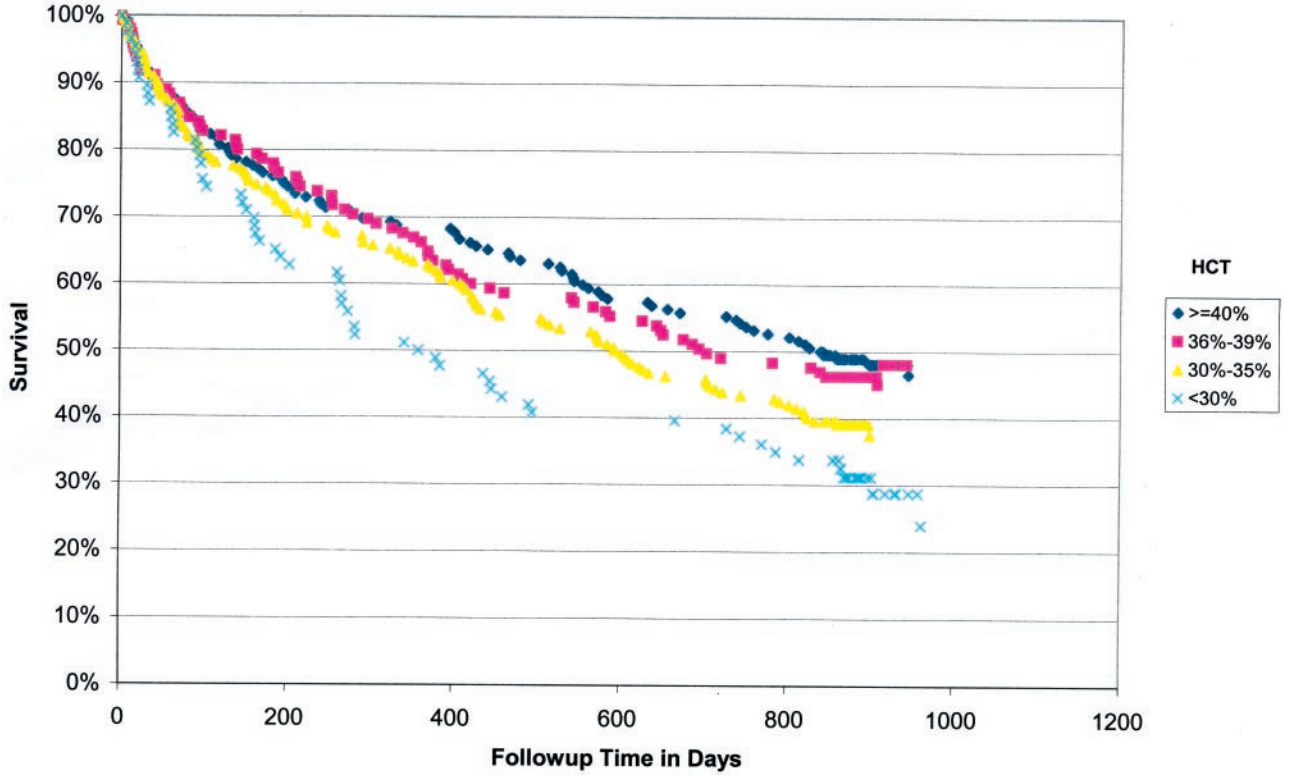

Figure 2. Survival among heart failure patients with varying degrees of anemia adjusted for renal function, age, sex, race, stroke, heart attack, coronary artery disease, angina pectoris, hypertension and diabetes mellitus status, a previous history of heart failure, ejection fraction and discharge functional status.

Table 3. Results of Cox proportional hazard models

Risk Factor	All-Years Mortality		First-Year Mortality	
	Parameter	Hazard Ratio (95% CI)	Parameter	Hazard Ratio (95% CI)
Hematocrit	−0.0163	0.98 (0.96 to 1.003)	−0.02429	0.98 (0.95 to 1.00)[a]
Serum creatinine	0.14476	1.16 (1.02 to 1.31)[a]	0.13649	1.15 (0.98 to 1.33)
Age	0.01413	1.014 (1.01 to 1.03)[a]	0.01206	1.012 (0.998 to 1.026)
Male gender	0.2806	1.32 (1.04 to 1.68)[a]	0.30344	1.36 (1.01 to 1.82)[a]
White race	0.20949	1.23 (0.95 to 1.60)	0.17694	1.19 (0.86 to 1.66)
Comorbid conditions				
stroke	0.14791	1.14 (0.84 to 1.54)	0.13118	1.14 (0.82 to 1.56)
MI	0.13016	1.14 (0.82 to 1.54)	0.27195	1.31 (0.90 to 1.91)
CAD	−0.22844	0.80 (0.60 to 1.05)	−0.21219	0.81 (0.56 to 1.16)
AP	−0.08425	0.92 (0.67 to 1.26)	−0.27309	0.76 (0.50 to 1.15)
Hypertension	−0.06985	0.93 (0.74 to 1.18)	−0.12434	0.89 (0.66 to 1.19)
Diabetes	0.02392	1.02 (0.82 to 1.28)	0.09278	1.10 (0.83 to 1.45)
Previous CHF	0.39644	1.49 (1.14 to 1.94)[a]	0.47894	1.61 (1.14 to 2.29)[a]
Left ventricular dysfunction				
diastolic		1		1
systolic	0.2853	1.33 (0.98 to 1.80)	0.48455	1.62 (1.085 to 2.43)[a]
not determined	0.23108	1.26 (0.95 to 1.67)	0.40546	1.50 (1.03 to 2.19)[a]
Functional status at discharge				
normal		1		1
mild impairment	−0.09942	0.905 (0.69 to 1.19)	−0.13932	0.87 (0.61 to 1.24)
moderate impairment	0.11977	1.13 (0.86 to 1.48)[a]	0.19697	1.22 (0.88 to 1.69)
severe impairment	0.90428	2.47 (1.39 to 4.38)[a]	0.92479	2.52 (1.27 to 4.99)[a]
Charlson score	0.03206	1.03 (1.01 to 1.06)[a]	0.01985	1.02 (0.99 to 1.05)
ACEI at discharge	−0.15569	0.86 (0.68 to 1.07)	−0.086	0.91 (0.69 to 1.22)

[a] $P < 0.05$.

one-year mortality, for each 1% increase in hematocrit the mortality rate declined 2.5% ($P = 0.038$); for each 1 ml/min increase in creatinine clearance, the rate decreased 0.6% ($P = 0.083$).

Discussion

The main observation of our study is that CKD and anemia are highly prevalent among heart failure patients discharged from community hospitals and are independently associated with increased mortality after discharge. The high prevalence of anemia among patients with heart failure and the association between anemia and mortality in heart failure patients have not been previously reported in a population-based study. Furthermore, we observe that the increased risk of death associated with anemia was found both among patients with left ventricular systolic and diastolic dysfunction.

The high prevalence of anemia in a representative sample of Medicare patients discharged from community hospitals with heart failure deserves comment. Heart failure is the most common cause of hospitalization among Medicare beneficiaries; it accounted for over 600,000 hospital admissions, 6.5% of all admissions, during 1995 (20). In our study, nearly half (45%) of a representative sample of older patients discharged from the hospital with heart failure had an admission hematocrit <36%, and 13% had a hematocrit of <30%.

The anemia we observed among individuals with heart failure is likely multifactorial in cause. In many, there is the contribution of diminished renal function. However, 40% of the patients in our study with a hematocrit <30% did not meet our definition of CKD. This may reflect the imprecision of using serum creatinine rather than the creatinine clearance or GFR to define CKD and it is possible that those patients with low creatinine levels would have been classified as having CKD if weight measurements had been available to perform the appropriate calculations (21). However, when we used the modified MDRD equation to estimate GFR, our results were unchanged. The modified MDRD equation has not been validated in patients like ours; we therefore present these only as supporting observations. Furthermore, we cannot exclude other causes of anemia, including the presence of iron, folate and vitamin B12 deficiencies, dilutional anemia, and the anemia of chronic disease, as explanations for the anemia observed in this elderly population.

The association between increased risk of death and anemia after hospitalization for heart failure could reflect several factors. First, adaptation to chronic anemia involves increases in

heart rate, cardiac index, and stroke work as well as expansion of plasma volume (22–23). These hemodynamic compensations stress characteristics of left ventricular function associated with increased risk of death, including reduced stroke work index and reduced cardiac index (24–26). It should be noted, however, that the hemodynamic effects of chronic and acute anemia have been observed with hemoglobin in the range of 7 g/dl for patients without hemoglobinopathy and below 10 g/dl for patients with sickle cell anemia (22). It is not clear from these studies that heart failure patients with mild anemia would experience similar hemodynamic changes.

Anemia is associated with changes in left ventricular anatomy among patients with CKD, and it is possible that these changes could contribute to worsening left ventricular diastolic and/or systolic dysfunction and consequent increased risk of death. For example, Tucker *et al.* (27) found an independent association between hemoglobin level and left ventricular mass index in 118 nondiabetic patients with CKD, whereas Levin *et al.* (28) noted that patients with CKD had a 32% increase of left ventricular mass index (LVMI) for each half-gram decrease in hemoglobin. It is not unreasonable to suggest that similar increases in LVMI might be observed among individuals with chronic anemia in the absence of CKD, increasing the risk of decompensated heart failure and death.

It is also possible that other factors associated with increased risk of death among patients with heart failure contributed to the differences in survival we noted among anemic patients. This would be a factor in the present analysis if a particular risk factor was associated both with the degree of anemia present in a patient and the risk of death. We partially controlled for this possibility by including many previously identified risk factors associated with increased risk of death among heart failure patients, including age, race, gender, functional status, and ACEI use. We accounted for the presence of both specific comorbid conditions, including hypertension, diabetes, and previous cardiovascular disease, and for overall severity of illness with the Charlson comorbidity index.

In contrast, we were unable to control for cause of heart failure, and it is possible that ischemic heart disease, which has been reported in some studies to have a higher mortality rate compared with other causes of heart failure, may have influenced our results (24–26). Atrial and ventricular arrhythmias are other explicit risk factors for mortality among patients with heart failure that were not controlled for in our analyses (27–28). If either cause of heart failure or the presence arrhythmias are more frequent among anemic patients or those with CKD, then the associations we noted may reflect the presence of these factors. It is also possible that physicians perceive heart failure patients with CKD and/or anemia as more severely ill, and this may influence subsequent treatment. For example, we found that increasing degree of anemia was associated with decreasing use of an ACEI, a medication associated with decreased risk of death among heart failure patients with LVSD (18).

Although we controlled for ACEI use in our analyses, it is possible that other treatment limitations, perhaps for nonrelated comorbidities, may have been more likely to occur among heart failure patients with CKD or anemia, contributing to an increased risk of death. Consistent with this observation is the recent study by Beattie *et al.* (29). They reported that following physicians were less likely to use mortality-reducing therapy after myocardial infarction in patients with advanced CKD and suggested that this may reflect a therapeutic nihilism among the clinicians caring for these individuals with advanced chronic disease.

Our observations extend the report of Al-Ahmad *et al.* (6) in several ways. First, we found that risk was increased among individuals with left ventricular diastolic dysfunction as well as systolic dysfunction. Furthermore, our population differed substantially from the SOLVD study beyond inclusion of patients with both diastolic and systolic left ventricular dysfunction. It was also 15 yr older in average age, and the patients were four times more likely to be women and 20% less likely to be white.

Despite these differences, both studies report that independent associations between both CKD and anemia were found with increased risk of mortality. The risk of increased mortality associated with a 1% reduction in hemoglobin in the SOLVD study was 2.7% and was comparable to the 2.0% increased risk we observed (6). Furthermore, the risk of increased mortality associated with a 10 ml/min reduction in estimated GFR in the SOLVD study was 6.4% and was comparable to the 6.0% increased risk we observed. These observations suggest that anemia, perhaps through mechanisms similar to those described above, is a clinically important risk factor for death among heart failure patients with and without CKD that clinicians encounter in day-to-day practice.

What are the clinical implications of these findings for patients with heart failure? Failure to correct severe anemia among patients with CKD confers a preventable burden of reduced quality of life, exercise capacity and cognitive function, while clinical trials have demonstrated that correction of anemia improves these measures (30). CKD patients in whom heart failure is present should be carefully evaluated for anemia and, if present, treated according to current clinical practice guidelines (30). At present, nearly half of incident ESRD patients have a hematocrit of $\leq$30% at the initiation of dialysis, and there has been only slight improvement in this rate during the last 5 yr (31). Although the prevalence of severe anemia among incident ESRD patients with a diagnosis of heart failure has not been reported, it is likely that rates similar to that for the entire ESRD population prevail in this high-risk group.

Furthermore, there is evidence that treatment of anemia in heart failure may be beneficial. Portoles *et al.* (32) reported that partial correction of the hematocrit from 26.3% to 34.7% among individuals with severe CKD was associated in a 17.3% reduction in LVMI, and Hayashi *et al.* (33) reported that increasing the hematocrit from 23.6% to 47.2% was associated with a 21% reduction over baseline LVMI. Silverberg *et al.* (34) recently reported that 56% of patients in a heart failure clinic with New York Heart Association (NYHA) class IV heart failure had hemoglobin of $<$12 g/dl, which was associated with increased hospitalization and impaired functional status. In a randomized trial of 32 of these patients with NYHA class III and IV heart failure and a hemoglobin $<$12 g/dl, these

investigators found that correction of anemia was associated with improved functional status and decreased hospitalization (35).

Although it is tempting to speculate about the benefit of anemia treatment on risk of mortality among CKD patients with heart failure, there is no evidence that correction of anemia among these patients will reduce the risk of death. Furthermore, in the absence of definitive clinical trials, the role of anemia correction among patients with heart failure in the absence of CKD is problematic. Clinicians caring for these patients should identify and treat reversible causes of anemia and should be aware of a recent report that unrecognized iron deficiency may be an important factor in the pathogenesis of anemia in these patients (35). It seems reasonable to suggest that anemic heart failure patients without CKD who have no treatable causes for their anemia should be considered for a trial of erythropoietin therapy.

There are several limitations to our results. By using the admission, rather than final hematocrit, it is possible that a portion of the decreased hematocrit we observed was due to volume expansion that resolved with therapy. Although this possibility does not change the importance of a low admission hematocrit as a mortality risk factor, it does emphasize the importance of further study of this association using final as well as initial hematocrit. It is unlikely that our results are a consequence of selection bias, as the study population was randomly selected from all Medicare patients hospitalized in community hospitals. However, the patterns of anemia and CKD that we observed may not prevail among other populations or among younger patients with heart failure.

In conclusion, we observed that the presence of either CKD or anemia increased the risk of death at 1 yr among patients hospitalized with heart failure. The association persisted after controlling for other factors associated with increased risk of death in these patients. These observations suggest that additional studies are warranted to confirm our observations and to establish the impact of correction of anemia on risk of death in this patient population.

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