Anemia is an Independent Predictor of Long-Term Adverse Outcomes in Patients Hospitalized With Heart Failure in Japan

— A Report From the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) —

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Background: Anemia is common in patients with heart failure (HF) and is associated with worse outcomes. However, the effects of anemia are unknown in an unselected group of HF patients encountered in routine clinical practice in Japan. The impact of anemia on long-term outcomes including mortality and rehospitalization among patients hospitalized with HF was thus assessed.

Methods and Results: The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) prospectively studied the characteristics and treatments in a broad sample of patients hospitalized with worsening HF and the outcomes were followed. Study cohorts (n=1,960) were classified into 4 groups by discharge hemoglobin quartiles: <10.1 g/dl (n=482), 10.1–11.9 g/dl (n=479), 12.0–13.6 g/dl (n=487), and ≥13.7 g/dl (n=512). Of the total cohort of HF patients, 57% had anemia, defined by using the World Health Organization definition. Patients with lower hemoglobin quartiles had higher rates of all-cause death, cardiac death, and rehospitalization due to worsening HF. After multivariable adjustment, the risk for all-cause death, cardiac death, and rehospitalization significantly increased with low hemoglobin concentrations.

Conclusions: Anemia was quite common especially in patients with HF encountered in routine clinical practice in Japan, and lower hemoglobin was independently associated with long-term adverse outcomes in these patients. (Circ J 2009; 73: 1901–1908)

Key Words: Anemia; Heart failure; Hemoglobin; Mortality; Prognosis

Anemia is common in patients with chronic heart failure (HF) and has been proposed as a novel therapeutic target for HF. The prevalence of anemia in patients with HF ranged 4.3–28% in clinical trials,^{1–9} however, it was present in 30–50% of patients with HF in cohort studies.^{8,10–25} Even though the variability in the prevalence of anemia is partly attributable to inconsistent definitions of anemia between studies, it might be higher in “real-world” HF patients, encountered in routine clinical practice, with advanced age and more comorbidities, who are selected far less for randomized clinical trials. In addition, a number of previous studies have assessed the association between anemia and mortality as well as morbidity in HF.^{1–25} Most studies have demonstrated higher mortality rates in HF patients with anemia.^{1–10, 12–32} In a recent systematic review and meta-analysis of HF patients (n=153,180), 37.2% were anemic and anemia was independently associated with an increased risk of mortality in both systolic and diastolic

HF.³³ However, other studies could not document an adverse effect of anemia on the outcomes in HF.^{11,34} Therefore, a better understanding of the prevalence, demographics, and clinical characteristics of anemia, and its relation to long-term adverse outcomes including mortality and hospitalization due to worsening HF is critically needed. Moreover, most previous studies on this important issue have been reported from the USA and Europe. The impact of anemia on outcomes needs to be assessed in a broad cohort of HF patients in Japan.

The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) prospectively studied the characteristics and treatments in a broad sample of patients hospitalized with HF at teaching hospitals in Japan from January 2004 to June 2005, and the outcomes including death and rehospitalization were followed through to 2007.³⁵ The JCARE-CARD program enrolled 2,675 patients admitted with HF in a web-based registry at 164 participating hospi-

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Figure 1. Distribution of discharge hemoglobin concentration among the total cohort of 1,960 patients with heart failure.

tals with an average follow up of 2.4 years.

The aim of the present study was to determine the prevalence of anemia in a broad sample of Japanese patients hospitalized with HF by using the JCARE-CARD database and to analyze the prognostic value of low hemoglobin on long-term mortality and rehospitalization due to worsening HF.

Methods

Study Patients

The details of the JCARE-CARD have been described previously.³⁵ Briefly, eligible patients were those hospitalized due to worsening HF as the primary cause of admission. For each patient, baseline data included: (1) demography; (2) causes of HF; (3) precipitating causes; (4) comorbidities; (5) complications; (6) clinical status; (7) electrocardiographic and echocardiographic findings; (8) plasma brain-type natriuretic peptide (BNP); and (9) treatments including discharge medications.

Baseline Hemoglobin Data

The JCARE-CARD enrolled a total of 2,675 patients hospitalized for HF at 164 participating hospitals. Hemoglobin concentration data were obtained in this study at the time of discharge. Seven hundred and fifteen patients were excluded from this study because of missing hemoglobin measurements, resulting in 1,960 patients included in this analysis.

Outcomes

The status of all patients was surveyed at least 1 year after discharge and the following information was obtained: (1) survival, (2) cause of death; and (3) the rehospitalization due to an exacerbation of HF that required more than continuation of their usual therapy on prior admission. Only patients who survived the initial hospitalization were included in the follow-up analysis. Follow-up data were obtained in 1,582 out of 1,960 patients (80.7%). The mean postdischarge follow up was 873 ± 258 days (2.4 ± 0.7 years).

Statistical Analysis

Patient characteristics and treatments were compared using the Pearson chi-squared test for categorical variables and one-way ANOVA for continuous variables. The relationship between hemoglobin concentration and outcomes was evaluated among patients with multivariable adjustment. Baseline clinical variables, treatment factors, and data about the severity of HF at discharge were used in developing the postdischarge Cox proportional hazard models. A P value of <0.05 was used as a criteria for variables to stay in the model. SPSS version 16.0 J for Windows was used for all statistical analyses.

Results

Patient Characteristics

Figure 1 shows the distribution of the discharge hemoglobin among the total cohort of study patients ($n=1,960$). The mean discharge hemoglobin was 12.0 ± 2.5 g/dl, ranging from 3.0 to 19.4 g/dl. Those patients with anemia (1,111 patients; 56.7%) were defined as having a hemoglobin level of <13.0 g/dl in men and <12.0 g/dl in women, according to the criteria defined by the World Health Organization.

Table 1 provides a comparison of clinical characteristics for the total cohort of patients ($n=1,960$) and those classified into 4 groups according to discharge hemoglobin quartiles: <10.1 g/dl ($n=482$), 10.1 – 11.9 g/dl ($n=479$), 12.0 – 13.6 g/dl ($n=487$), and ≥ 13.7 g/dl ($n=512$). The mean age was 71.5 years and 58.1% were men. The etiology of HF was ischemic in 32.8%, valvular heart disease in 28.9%, hypertensive in 26.8%, and dilated cardiomyopathic in 16.1% of patients. The mean left ventricular ejection fraction (LVEF) was $42.8 \pm 17.6\%$ on admission and $45.1 \pm 16.5\%$ at discharge.

Patients with low hemoglobin quartiles were older, more often women, and had a smaller body mass index. They had more valvular heart disease as causes of HF, but less dilated cardiomyopathy. They had more extensive comorbidities including hyperuricemia and stroke, but less chronic atrial fibrillation. Serum creatinine levels, New York Heart Association (NYHA) functional classes, and plasma BNP levels were higher in patients with lower

Table 1. Baseline Patient Characteristics According to the Discharge Hemoglobin

	Total (n=1,960)	Discharge hemoglobin (g/dl)				P value
		<10.1 (n=482)	10.1–11.9 (n=479)	12.0–13.6 (n=487)	≥13.7 (n=512)	
Demographic						
Age, years (mean±SD)	71.5±13.0	76.0±11.3	74.6±12.0	71.6±11.6	64.4±13.6	<0.001
Male, %	58.1	47.3	48.2	54.4	81.1	<0.001
BMI, kg/m ²	22.2±4.1	21.1±3.5	21.2±3.7	22.3±4.2	23.9±4.4	<0.001
Causes of heart failure, %						
Ischemic	32.8	36.7	34.0	31.2	29.3	0.069
Valvular heart disease	28.9	38.2	33.2	27.9	17.2	<0.001
Hypertensive	26.8	29.9	28.4	22.4	26.8	0.051
Dilated cardiomyopathy	16.1	6.2	10.9	20.5	26.0	<0.001
Medical history, %						
Hypertension	53.4	57.7	53.9	50.4	51.7	0.119
Diabetes mellitus	30.9	34.2	29.5	28.8	31.1	0.279
Hyperlipidemia	24.8	23.2	23.8	24.8	27.4	0.423
Hyperuricemia	50.1	54.2	49.8	41.6	54.7	<0.001
Stroke	15.3	18.7	16.4	15.1	11.2	0.009
COPD	6.6	6.8	7.2	5.8	6.8	0.848
Smoking	37.2	29.6	30.5	35.7	51.6	<0.001
Atrial fibrillation	34.2	29.4	32.2	34.0	40.9	0.001
Sustained VT/VF	6.4	6.2	7.3	6.6	5.7	0.769
Procedures, %						
PCI	18.5	21.8	18.8	17.1	16.3	0.128
CABG	8.9	10.5	10.4	9.4	5.7	0.027
Valvular surgery	7.2	8.6	9.5	5.8	4.9	0.016
Vital signs at discharge						
Heart rate, beats/min	70.5±12.3	70.4±12.1	70.5±12.2	70.7±12.2	70.5±12.7	0.987
SBP, mmHg	117.6±19.1	122.4±21.2	117.1±18.6	116.2±18.9	115.1±17.2	<0.001
DBP, mmHg	66.0±11.8	64.6±12.3	64.3±12.0	66.3±11.3	68.7±11.1	<0.001
Renal function						
Serum creatinine, mg/dl	1.37±1.25	2.04±1.71	1.3±1.00	1.12±0.85	1.11±1.08	<0.001
eGFR, ml·min ⁻¹ ·1.73 m ⁻²	51.3±25.3	37.2±25.2	50.3±26.2	55.9±22.6	59.9±21.4	<0.001
NYHA functional class						
Admission	3.32±0.69	3.38±0.67	3.32±0.69	3.30±0.70	3.29±0.71	0.150
Discharge	1.77±0.73	1.96±0.86	1.73±0.67	1.72±0.69	1.69±0.65	<0.001
Plasma BNP, pg/ml						
Admission	894±1,019	1,112±1,183	955±1,179	823±960	724±675	<0.001
Discharge	405±544	560±715	472±658	339±373	271±299	<0.001
Echocardiographic parameters on admission						
LV EDD, mm	55.9±10.5	53.3±9.2	55.0±10.4	55.9±10.7	59.1±10.8	<0.001
LV ESD, mm	43.8±12.4	39.6±10.9	42.7±16.8	44.3±12.3	48.2±12.7	<0.001
LVEF, %	42.8±17.6	48.8±17.2	44.6±17.7	41.7±16.8	37.1±16.9	<0.001
MR positive, %	85.6	89.1	84.6	86.4	82.6	0.046
MR ≥3°, %	28.2	29.1	30.4	27.7	25.8	0.125
Echocardiographic parameters at discharge						
LV EDD, mm	55.2±10.4	51.5±9.4	55.1±10.2	55.4±10.9	57.7±10.0	<0.001
LV ESD, mm	42.5±12.4	37.2±11.3	42.5±12.3	43.1±12.6	45.8±12.0	<0.001
LVEF, %	45.1±16.5	50.8±16.5	46.3±17.1	43.1±15.3	41.7±15.8	<0.001
MR positive, %	79.3	79.5	82.5	77.1	78.1	0.539
MR ≥3°, %	16.6	17.9	18.0	17.1	14.0	0.705

We assessed the eGFR by using the revised equations for estimating GFR in Japan.⁵²

BMI, body mass index; COPD, chronic obstructive pulmonary disease; VT/VF, ventricular tachycardia/fibrillation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; BNP, B-type natriuretic peptide; LV, left ventricular; EDD, end-diastolic diameter; ESD, end-systolic diameter; EF, ejection fraction; MR, mitral regurgitation.

Values are percent or means±SD.

hemoglobin quartiles. However, they had smaller LV end-diastolic diameter and higher LVEF. Patients with low hemoglobin quartiles were less frequently prescribed angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -blockers, digitalis, antiarrhythmic agents, and warfarin at discharge (**Table 2**). In contrast, they were prescribed more Ca channel blockers, α -blockers, and nitrates.

Outcomes

During the 2.4 year follow up after hospital discharge, the rates of adverse outcomes were as follows: all-cause death

21.7%, cardiac death 14.4%, rehospitalization due to the worsening HF 35.8%, and all-cause death or rehospitalization 43.6%. All-cause death or rehospitalization increased with reduced hemoglobin levels: 23.6% for hemoglobin ≥ 13.7 g/dl, 35.1% for 12.0–13.6 g/dl, 40.7% for 10.1–11.9 g/dl, and 41.9% for <10.1 g/dl ($P<0.001$, **Table 3; Figure 2**).

On multivariate analysis, patients with a hemoglobin level of <10.1 g/dl had a significantly elevated risk for all-cause death or rehospitalization (adjusted hazard ratio (HR) 1.834, 95% confidence interval (CI) 1.387–2.424,

Table 2. Medication Use at Hospital Discharge According to the Discharge Hemoglobin

	Total (n=1,960)	Discharge hemoglobin (g/dl)				P value
		<10.1 (n=482)	10.1–11.9 (n=479)	12.0–13.6 (n=487)	≥13.7 (n=512)	
ACE inhibitor, %	36.2	28.6	37.8	35.7	41.9	<0.001
ARB, %	46.0	41.4	44.1	46.7	50.9	0.026
β -blocker, %	46.4	37.7	42.6	46.3	57.7	<0.001
Diuretics, %	87.6	87.0	89.1	86.4	87.8	0.637
Digitalis, %	30.8	22.3	30.6	33.5	35.7	<0.001
Ca channel blocker, %	25.8	34.4	26.9	21.2	21.8	<0.001
α -blocker, %	3.8	7.2	4.1	1.9	2.4	<0.001
Nitrates, %	24.2	32.6	28.2	20.2	17.0	<0.001
Antiarrhythmic, %	16.3	10.5	15.1	20.6	18.4	<0.001
Aspirin, %	48.6	50.7	49.8	46.9	47.3	0.597
Warfarin, %	39.1	26.5	36.9	42.0	49.3	<0.001
Statin, %	20.4	18.4	20.1	22.5	20.4	0.493

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

Table 3. HRs for Outcomes According to the Discharge Hemoglobin Levels

Outcome	Discharge hemoglobin (g/dl)				P value
	<10.1 (n=355)	10.1–11.9 (n=401)	12.0–13.6 (n=404)	≥13.7 (n=422)	
All-cause death (%)	130 (36.6)	97 (24.2)	70 (17.3)	46 (10.9)	<0.001
Unadjusted HR	4.016	2.454	1.692	1.0	
(95%CI)	(2.869–5.622)	(1.727–3.485)	(1.166–2.455)		
Adjusted HR	1.963	1.606	1.315		
(95%CI)	(1.300–2.963)	(1.067–2.417)	(0.858–2.016)		
Cardiac death (%)	86 (24.2)	66 (16.5)	46 (11.4)	30 (7.1)	<0.001
Unadjusted HR	4.078	2.566	1.709	1.0	
(95%CI)	(2.690–6.180)	(1.667–3.952)	(1.079–2.707)		
Adjusted HR	2.155	1.706	1.39		
(95%CI)	(1.308–3.548)	(1.039–2.800)	(0.832–2.324)		
Rehospitalization (%)	153 (43.1)	162 (40.4)	146 (36.1)	104 (24.6)	<0.001
Unadjusted HR	2.295	2.022	1.701	1.0	
(95%CI)	(1.788–2.945)	(1.581–2.588)	(1.323–2.188)		
Adjusted HR	1.748	1.685	1.440		
(95%CI)	(1.290–2.368)	(1.265–2.242)	(1.081–1.919)		
All-cause death or rehospitalization (%)	202 (56.9)	195 (48.6)	171 (42.3)	121 (28.7)	<0.001
Unadjusted HR	2.605	2.093	1.712	1.0	
(95%CI)	(2.079–3.264)	(1.668–2.626)	(1.356–2.161)		
Adjusted HR	1.834	1.720	1.479		
(95%CI)	(1.387–2.424)	(1.319–2.242)	(1.132–1.933)		

The Cox regression model used in the analysis was adjusted for the following covariates; demographic (age, sex, BMI), causes of heart failure (ischemic, hypertensive, valvular heart disease, dilated cardiomyopathy), medical history (hyperuricemia, stroke, smoking, chronic arterial fibrillation or flutter), serum creatinine, NYHA functional class at discharge, BNP at discharge, LVEF at discharge, and medication use (ACE inhibitor, ARB, β -blocker, digitalis, Ca channel blocker, α -blocker, nitrates, antiarrhythmic, warfarin). Patients with a discharge hemoglobin level of ≥ 13.7 g/dl were treated as a reference group. BNP and LVEF at discharge were entered into the model as the categorical variables; that is, BNP at discharge ≥ 240 pg/ml or <240 pg/ml or unknown and LVEF at discharge $<40\%$ or $\geq 40\%$ or unknown.

HR, hazard ratio; CI, confidence interval. See Tables 1 and 2 for abbreviation definitions.

$P<0.001$), as did those with hemoglobin levels of 10.1–11.9 g/dl (adjusted HR 1.720, 95%CI 1.319–2.242, $P<0.001$) and 12.0–13.6 g/dl (adjusted HR 1.479, 95%CI 1.132–1.933, $P=0.004$; **Table 3**). Therefore, long-term adverse outcomes were significantly associated with the discharge hemoglobin level, even after adjustment for other covariates.

The independent predictors associated with death or rehospitalization among those entered into the Cox proportional hazard analysis were: serum creatinine, discharge hemoglobin, age, NYHA functional class at discharge, hyperuricemia, smoking, and BNP level at discharge (**Table 4**). There was 8.9% increase in all-cause death or

rehospitalization for each 1-g/dl decrease in discharge hemoglobin concentration ($P<0.001$).

In the subgroup analysis for all-cause death or rehospitalization, which was limited to patients who were ≥ 65 years, rates increased with reduced hemoglobin levels (**Table 5**).

Discussion

The present study demonstrated by using the JCARE-CARD database that anemia was seen in as high as 57% of the patients hospitalized with HF. More importantly, low hemoglobin was independently associated with adverse

Figure 2. Kaplan–Meier, event-free curves free from all-cause death (A), cardiac death (B), rehospitalization due to worsening heart failure (C), and all-cause death or rehospitalization (D) according to discharge hemoglobin quartiles; <10.1 g/dl (n=355), 10.1–11.9 g/dl (n=401), 12.0–13.6 g/dl (n=404), and ≥13.7 g/dl (n=422).

Table 4. Multivariate Predictors of All-Cause Death or Rehospitalization by the Cox Proportional Hazard Model

	HR	95%CI	P value
Hypertension	0.692	0.560–0.854	0.001
Serum creatinine (per 1-mg/dl increase)	1.075	1.023–1.129	0.004
Discharge hemoglobin (per 1-g/dl decrease)	1.089	1.047–1.133	<0.001
Age (per 10-years increase)	1.206	1.116–1.304	<0.001
NHYA functional class at discharge (per 1 increase)	1.218	1.053–1.408	0.008
Hyperuricemia	1.268	1.065–1.508	0.008
Smoking	1.293	1.078–1.552	0.006
BNP ≥240 pg/ml at discharge	1.774	1.376–2.285	<0.001

HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association; BNP, B-type natriuretic peptide.

Table 5. Subgroup Analysis for All-Cause Death or Rehospitalization Limited in Patients Aged ≥65 Years

Outcome	Discharge hemoglobin (g/dl)				P value
	<10.1 (n=295)	10.1–11.9 (n=329)	12.0–13.6 (n=298)	≥13.7 (n=214)	
All-cause death or rehospitalization (%)	173 (58.6)	163 (49.5)	137 (46.0)	66 (30.8)	<0.001
Unadjusted HR	2.485	1.956	1.737	1.0	
(95%CI)	(1.871–3.301)	(1.470–2.605)	(1.295–2.330)		
Adjusted HR	2.243	1.937	1.783		
(95%CI)	(1.610–3.126)	(1.400–2.679)	(1.279–2.487)		

HR, hazard ratio; CI, confidence interval.

outcomes including all-cause death, cardiac death, and rehospitalization due to worsening HF during the long-term follow up of up to 2.4 years.

The prevalence of anemia in this study (57%) was higher than the values reported in previous randomized and clinical trials; 26% in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM),³ 15.6% in the Carvedilol or Metoprolol European Trial (COMET),⁴ and 23% in the Valsartan Heart Failure Trial (Val-HeFT).⁸ In contrast, it is similar to that (51.2%) reported in the Organized Program to Initiate Lifesaving Treatment in Patients with HF (OPTIMIZE-HF).¹³ These discrepancies are attributable to the differences in study patients between studies. The study patients in the present study were more elderly and had more comorbidities such as hypertension and diabetes than those in previous studies because the JCARE-CARD registered an unselected group of HF patients and did not exclude patients with renal dysfunction who often had anemia. It would thus be well expected that our study patients and those in the OPTIMIZE-HF study had a higher prevalence of anemia, which might reflect the “real world” patients encountered in current routine clinical practice.

The present study demonstrated that anemia was associated with adverse long-term outcomes in patients hospitalized with HF, which extended the previous results of randomized clinical trials conducted in selected patients, such as in the COMET,⁴ CHARM,³ Val-HeFT,⁸ and the Evaluation of Losartan In The Elderly (ELITE II)⁵ studies to include a diverse cohort of HF patients. Although evidence from these trials shows significant adverse outcomes for anemia in patients with HF, they are recognized as unrepresentative of the general HF population in routine clinical practice. Therefore, uncertainty pertaining to the applicability of these findings to the population of patients with HF at large persists. It is of critical importance to analyze the registry data of HF patients without any exclusion criteria. Therefore, the results from the JCARE-CARD study confirmed the previous findings that anemia was associated with long-term adverse outcomes in the “real world” HF patients.

The present study also extended the findings of the OPTIMIZE-HF database, in which anemia was associated with higher in-hospital mortality and more rehospitalization by 90 days.¹³ However, the OPTIMIZE-HF limited its follow up to 60–90 days after discharge and follow-up data were obtained in only 5,791 (11.9%) out of 48,612 patients. Therefore, the present study provided the first demonstration that anemia was independently associated with the adverse outcomes during long-term follow up. The event-free curves diverged within the early period and these differences remained statistically significant during the follow up, up to 2.4 years (**Figure 2**). Both the OPTIMIZE-HF and the JCARE-CARD studies clearly demonstrated a high prevalence of anemia and its prognostic implications in patients hospitalized with HF during chronic as well as acute phases. These findings should reassure physicians that earlier evaluation and management of anemia is critically important to prevent adverse outcomes for these patients and provides an opportunity to significantly improve outcomes. However, there is little specific guidance regarding how to adequately treat anemia in this situation. Smaller previous studies suggested that erythropoiesis-stimulating proteins (ESP) could improve exercise capacity.^{36–38} Recent larger studies demonstrated that darbepoetin significantly

improved clinical states, but not in exercise tolerance.³⁹ However, on the contrary, several studies showed a potentially harmful effect of ESP treatment in terms of kidney diseases.^{40,41} Therefore, large-scale prospective randomized clinical trials are critically needed to determine the impact of anemia association with outcomes caused by HF. Currently, the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) study is being conducted to answer this question. Several explanations have been postulated for the increased mortality risk of HF patients with anemia. First, anemia leads to an increased load to the heart, resulting from an increased heart rate and systemic volume overload.⁴² The increased hemodynamic overload causes LV remodeling and failure, with an increased mortality risk. Second, anemia can be a comorbidity of renal dysfunction, both of which often coexist together. HF can cause renal dysfunction due to decreased cardiac output and reduced renal perfusion. Subsequent renal dysfunction might lead to the decreased production of endogenous erythropoietin and might ultimately induce anemia, resulting in an increased cardiac hemodynamic load completing the vicious circle called the “cardio-renal-anemia syndrome”.⁴³ Moreover, renal dysfunction has been consistently demonstrated to be an independent risk for adverse outcomes in patients with HF.^{21,44–51} Furthermore, there was a higher proportion of elderly patients in the lower hemoglobin group (**Table 1**). Aging is a strong determinant of prognosis, and the prevalence of other systemic diseases such as malignancy increase with age. However, even in the subgroup of the patients aged ≥ 65 years, anemia was independently associated with poor outcomes, similar to that found in primary analysis (**Table 5**). Moreover, in the present study, the significant effect of anemia on outcomes was observed even after adjustment for various other risk factors including renal dysfunction and age. In addition, in the lower hemoglobin group, LVEF was higher and there was less frequent use of HF medications such as ACE inhibitors and β -blockers (**Table 1**). Higher LVEF in the lower hemoglobin group might be due to the greater prevalence of valvular and hypertensive causes and the lower prevalence of dilated cardiomyopathy. The LV systolic dysfunction was associated with adverse outcomes and HF medications could improve outcomes in patients with HF. However, even in the presence of LVEF and the use of HF medications at discharge, which were entered into the Cox regression model as covariates, the lower hemoglobin was independently associated with a poorer prognosis and it was not an independent predictor associated with death or rehospitalization (**Tables 3, 4**).

Study Limitations

Several limitations inherent in the design of the JCARE-CARD study should be considered. First, documentation of hemoglobin concentration at hospital discharge might not accurately reflect the level of hemoglobin after discharge or changes of hemoglobin over time. A previous study demonstrated that changes in hemoglobin over 12 months were inversely associated with a subsequent risk of mortality and morbidity, independently of the effects of baseline anemia and other important predictors.² Second, the present study did not collect the data of the hemoglobin value on admission. Previous cohort studies such as the OPTIMIZE-HF study used the value of hemoglobin or hematocrit on admission.^{10,13,17,18,20,26,31} However, the effects of hemodilution on hemoglobin values could not be excluded, especially in

the patient population hospitalized with congestion. And hemoglobin values might change during the course of treatment. Therefore, the discharge hemoglobin level might be suitable for the analysis of post-discharge long-term risk, as in the present study. Third, the JCARE-CARD study is not a prospective randomized trial and, despite covariate adjustment, other measured and unmeasured factors might have influenced outcomes. We thus could not completely exclude or ignore the fact other unmeasured factors that might also have affected the outcomes. Fourth, in the JCARE-CARD database, the information about the treatment of anemia and endogenous erythropoietin levels were not obtained. Finally, data were dependent on the accuracy of documentation and abstraction by individual medical centers that participated in the program. However, it was not the objective of this survey to restrict enrolment to the narrowly defined population of HF usually included in clinical trials but it was rather to include a broad range of patients reflecting the current reality of clinical practice rather than trials.

Conclusions

The present study demonstrated a higher prevalence of anemia in “real world” patients with HF than those enrolled in randomized clinical trials. Lower hemoglobin was associated with adverse long-term outcomes in these patients.

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References

1. Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001; **38**: 955–962.
2. Anand IS, Kuskowski MA, Rector TS, Florea VG, Glazer RD, Hester A, et al. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: Results from Val-HeFT. *Circulation* 2005; **112**: 1121–1127.
3. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Lang CC, Roger SD, et al. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: Results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. *Circulation* 2006; **113**: 986–994.
4. Komajda M, Anker SD, Charlesworth A, Okonko D, Metra M, Di Lenarda A, et al. The impact of new onset anaemia on morbidity and mortality in chronic heart failure: Results from COMET. *Eur Heart J* 2006; **27**: 1440–1446.
5. Sharma R, Francis DP, Pitt B, Poole-Wilson PA, Coats AJ, Anker SD. Haemoglobin predicts survival in patients with chronic heart failure: A substudy of the ELITE II trial. *Eur Heart J* 2004; **25**: 1021–1028.
6. Mozaffarian D, Nye R, Levy WC. Anemia predicts mortality in severe heart failure: The prospective randomized amlodipine survival evaluation (PRAISE). *J Am Coll Cardiol* 2003; **41**: 1933–1939.
7. Anand I, McMurray JJ, Whitmore J, Warren M, Pham A, McCamish MA, et al. Anemia and its relationship to clinical outcome in heart failure. *Circulation* 2004; **110**: 149–154.
8. Maggioni AP, Opasich C, Anand I, Barlera S, Carbonieri E, Gonzini L, et al. Anemia in patients with heart failure: Prevalence and prognostic role in a controlled trial and in clinical practice. *J Card Fail* 2005; **11**: 91–98.
9. Terrovitis JV, Anastasiou-Nana MI, Alexopoulos GP, Tsolakis EJ, Margari ZJ, Drakos SG, et al. Prevalence and prognostic significance of anemia in patients with congestive heart failure treated with standard vs high doses of enalapril. *J Heart Lung Transplant* 2006; **25**: 333–338.
10. McClellan WM, Flanders WD, Langston RD, Jurkovic C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: A population-based study. *J Am Soc Nephrol* 2002; **13**: 1928–1936.
11. Tanner H, Moschovitis G, Kuster GM, Hullin R, Pfiiffner D, Hess OM, et al. The prevalence of anemia in chronic heart failure. *Int J Cardiol* 2002; **86**: 115–121.
12. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. *J Am Coll Cardiol* 2002; **39**: 1780–1786.
13. Young JB, Abraham WT, Albert NM, Gattis Stough W, Gheorghiade M, Greenberg BH, et al. Relation of low hemoglobin and anemia to morbidity and mortality in patients hospitalized with heart failure (insight from the OPTIMIZE-HF registry). *Am J Cardiol* 2008; **101**: 223–230.
14. Szachniewicz J, Petruk-Kowalczyk J, Majda J, Kaczmarek A, Reczuch K, Kalra PR, et al. Anaemia is an independent predictor of poor outcome in patients with chronic heart failure. *Int J Cardiol* 2003; **90**: 303–308.
15. van der Meer P, Voors AA, Lipsic E, Smilde TD, van Gilst WH, van Veldhuisen DJ. Prognostic value of plasma erythropoietin on mortality in patients with chronic heart failure. *J Am Coll Cardiol* 2004; **44**: 63–67.
16. Ezekowitz JA, McAlister FA, Armstrong PW. The interaction among sex, hemoglobin and outcomes in a specialty heart failure clinic. *Can J Cardiol* 2005; **21**: 165–171.
17. Grigorian Shamagian L, Varela Roman A, Garcia-Acuna JM, Mazon Ramos P, Virgos Lamela A, Gonzalez-Juanatey JR. Anaemia is associated with higher mortality among patients with heart failure with preserved systolic function. *Heart* 2006; **92**: 780–784.
18. Kosiborod M, Curtis JP, Wang Y, Smith GL, Masoudi FA, Foody JM, et al. Anemia and outcomes in patients with heart failure: A study from the National Heart Care Project. *Arch Intern Med* 2005; **165**: 2237–2244.
19. Ralli S, Horwich TB, Fonarow GC. Relationship between anemia, cardiac troponin I, and B-type natriuretic peptide levels and mortality in patients with advanced heart failure. *Am Heart J* 2005; **150**: 1220–1227.
20. Formiga F, Chivite D, Castaner O, Manito N, Ramon JM, Pujol R. Anemia in new-onset congestive heart failure inpatients admitted for acute decompensation. *Eur J Intern Med* 2006; **17**: 179–184.
21. Go AS, Yang J, Ackerson LM, Lepper K, Robbins S, Massie BM, et al. Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure: The Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study. *Circulation* 2006; **113**: 2713–2723.
22. Elabbassi W, Fraser M, Williams K, Cassan D, Haddad H. Prevalence and clinical implications of anemia in congestive heart failure patients followed at a specialized heart function clinic. *Congest Heart Fail* 2006; **12**: 258–264.
23. Schou M, Gustafsson F, Kistorp CN, Corell P, Kjaer A, Hildebrandt PR. Prognostic usefulness of anemia and N-terminal pro-brain natriuretic peptide in outpatients with systolic heart failure. *Am J Cardiol* 2007; **100**: 1571–1576.
24. Kawashiro N, Kasanuki H, Ogawa H, Matsuda N, Hagiwara N. Clinical characteristics and outcome of hospitalized patients with congestive heart failure: Results of the HIJC-HF registry. *Circ J* 2008; **72**: 2015–2020.
25. Shiba N, Nochioka K, Kohno H, Matsuki M, Takahashi J, Tada T, et al. Emerging problems of heart failure practice in Japanese women: Lessons from the CHART study. *Circ J* 2008; **72**: 2009–2014.
26. Kosiborod M, Smith GL, Radford MJ, Foody JM, Krumholz HM. The prognostic importance of anemia in patients with heart failure. *Am J Med* 2003; **114**: 112–119.
27. Varadarajan P, Gandhi S, Sharma S, Umakanthan B, Pai RG. Prognostic significance of hemoglobin level in patients with congestive heart failure and normal ejection fraction. *Clin Cardiol* 2006; **29**: 444–449.
28. Maraldi C, Volpato S, Cesari M, Onder G, Pedone C, Woodman RC, et al. Anemia, physical disability, and survival in older patients with heart failure. *J Card Fail* 2006; **12**: 533–539.
29. de Silva R, Rigby AS, Witte KK, Nikitin NP, Tin L, Goode K, et al. Anemia, renal dysfunction, and their interaction in patients with chronic heart failure. *Am J Cardiol* 2006; **98**: 391–398.

30. Berry C, Norrie J, Hogg K, Brett M, Stevenson K, McMurray JJ. The prevalence, nature, and importance of hematologic abnormalities in heart failure. *Am Heart J* 2006; **151**: 1313–1321.
31. Newton JD, Squire IB. Glucose and haemoglobin in the assessment of prognosis after first hospitalisation for heart failure. *Heart* 2006; **92**: 1441–1446.
32. Felker GM, Shaw LK, Stough WG, O'Connor CM. Anemia in patients with heart failure and preserved systolic function. *Am Heart J* 2006; **151**: 457–462.
33. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, et al. Anemia and mortality in heart failure patients a systematic review and meta-analysis. *J Am Coll Cardiol* 2008; **52**: 818–827.
34. Gardner RS, Chong KS, Morton JJ, McDonagh TA. N-terminal brain natriuretic peptide, but not anemia, is a powerful predictor of mortality in advanced heart failure. *J Card Fail* 2005; **11**: S47–S53.
35. Tsutsui H, Tsuchihashi-Makaya M, Kinugawa S, Goto D, Takeshita A. Clinical characteristics and outcome of hospitalized patients with heart failure in Japan: Rationale and Design of Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2006; **70**: 1617–1623.
36. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 2000; **35**: 1737–1744.
37. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation* 2003; **107**: 294–299.
38. Ponikowski P, Anker SD, Szachniewicz J, Okonko D, Ledwidge M, Zymliński R, et al. Effect of darbepoetin alfa on exercise tolerance in anemic patients with symptomatic chronic heart failure: A randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2007; **49**: 753–762.
39. Ghali JK, Anand IS, Abraham WT, Fonarow GC, Greenberg B, Krum H, et al. Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. *Circulation* 2008; **117**: 526–535.
40. Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; **355**: 2071–2084.
41. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; **355**: 2085–2098.
42. Varat MA, Adolph RJ, Fowler NO. Cardiovascular effects of anemia. *Am Heart J* 1972; **83**: 415–426.
43. Silverberg DS, Wexler D, Iaina A. The importance of anemia and its correction in the management of severe congestive heart failure. *Eur J Heart Fail* 2002; **4**: 681–686.
44. Tokmakova MP, Skali H, Kenchaiah S, Braunwald E, Rouleau JL, Packer M, et al. Chronic kidney disease, cardiovascular risk, and response to angiotensin-converting enzyme inhibition after myocardial infarction: The Survival And Ventricular Enlargement (SAVE) study. *Circulation* 2004; **110**: 3667–3673.
45. Shlipak MG, Smith GL, Rathore SS, Massie BM, Krumholz HM. Renal function, digoxin therapy, and heart failure outcomes: Evidence from the digoxin intervention group trial. *J Am Soc Nephrol* 2004; **15**: 2195–2203.
46. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, et al. Renal impairment and outcomes in heart failure: Systematic review and meta-analysis. *J Am Coll Cardiol* 2006; **47**: 1987–1996.
47. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: Prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004; **109**: 1004–1009.
48. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006; **113**: 671–678.
49. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: A report from the ADHERE database. *J Card Fail* 2007; **13**: 422–430.
50. Komukai K, Ogawa T, Yagi H, Date T, Sakamoto H, Kanzaki Y, et al. Decreased renal function as an independent predictor of re-hospitalization for congestive heart failure. *Circ J* 2008; **72**: 1152–1157.
51. Shiba N, Matsuki M, Takahashi J, Tada T, Watanabe J, Shimokawa H. Prognostic importance of chronic kidney disease in Japanese patients with chronic heart failure. *Circ J* 2008; **72**: 173–178.
52. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al; Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53**: 982–992.