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Prognostic Impact of Anemia in Patients With Chronic Heart Failure

– With Special Reference to Clinical Background: Report From the CHART-2 Study –

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Background: We aimed to elucidate the prognostic impact of anemia with special reference to the clinical background of patients with chronic heart failure (CHF).

Methods and Results: We examined 4,646 consecutive patients with Stage C/D CHF registered in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study (n=10,219). Among them, 1,627 (35%) had anemia and were characterized by higher age (74 vs. 66 years), lower estimated glomerular filtration rate (52.8 vs. 66.1 ml/min/1.73 m^2) and higher B-type natriuretic peptide levels (154.5 vs. 81.8 pg/ml) (all P<0.001) but comparable left ventricular ejection fraction (LVEF; 57.5 vs. 56.7%). Anemic patients were more frequently treated with diuretics (55.1 vs. 42.3%) but less often treated with β-blockers (45.4 vs. 51.1%) (both P<0.001). During a median follow-up of 3.8 years, 371 and 272 patients died with and without anemia, respectively (22.8 vs. 9.0%, adjusted hazard ratio 1.40; 95% confidence interval 1.15–1.71, P=0.001). Subgroup analysis revealed that the prognostic impact of anemia was comparable in terms of age, sex, renal function and double product, but differed by LVEF level and CHF etiology (both, P for interaction <0.001). In particular, a difference in the prognostic impact of LVEF level was noted in patients with ischemic heart disease.

Conclusions: These results indicate that the prognostic impact of anemia is evident in CHF patients with preserved EF and it differs by CHF etiology. (*Circ J* 2015; **79:** 1984–1993)

Key Words: Anemia; Etiology; Heart failure; Left ventricular ejection fraction; Prognosis

Anemia is characterized by reduced blood hemoglobin (Hb) levels. According to the World Health Organization (WHO) definition, it is Hb <13 g/dl in men and <12 g/dl in women.[1] Anemia is a major comorbidity in patients with chronic heart failure (CHF) and has been reported to be present in 17–43% of CHF patients.[2–5] Anemia is clinically important because it is associated with poor prognosis in CHF patients, independent of other risk factors.[4,6,7] Although the mechanisms of the development of anemia in CHF patients appear to be complicated, several factors have been postulated, including renal dysfunction with reduced erythropoiesis,[8] inflammation associated with resistance to erythropoietin,[9] bone marrow dysfunction,[10] iron deficiency,[11] and adverse effects of angiotensin-converting enzyme inhibitors.[12] Recently, Silverberg et al proposed the cardiorenal anemia syndrome, a vicious cycle formed by interactions among CHF, chronic kidney disease and anemia, where cardiac dysfunction worsens renal function and anemia through renal congestion and bone marrow dysfunction, while anemia conversely worsens cardiac and renal functions through organ ischemia.[8] Furthermore, previous studies examined the impact of anemia in relation to left ventricular ejection fraction (LVEF)[2,13,14] and

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sex.[15] Because many other factors could also affect the long-term prognosis of CHF patients, the clinical impact of anemia should be examined with special reference to the clinical background of patients with CHF.

Editorial p1893

In the present study, we thus aimed to examine the prognostic impact of anemia with special reference to a broad range of clinical backgrounds of CHF patients registered in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study (n=10,219).[16–20]

Methods

CHART-2 Study

The CHART-2 Study is a multicenter, prospective observational study with a total of 10,219 patients with CHF or those at high risk for CHF,[16–20] which was conducted according to the ethical principles described in Declaration of Helsinki. Briefly, patients aged 20 years or older with significant coronary artery disease or Stage B HF (n=5,483) and those with Stage C/D CHF (n=4,736) according to the definition of the ACCF/AHA guidelines were enrolled between October 2006 and March 2010.[16–20] All information, including medical history, laboratory data and echocardiography data, was recorded at the time of registration, and thereafter annually by trained clinical research coordinators.[16–20]

Study Design

The study flow is shown in Figure 1. Of the 4,736 consecutive patients with Stage C/D CHF, 4,646 patients were finally enrolled in the present study after excluding 63 patients on hemodialysis and 27 without sufficient laboratory data. Both male (n=3,036) and female (n=1,425) patients were divided according to the presence or absence of anemia, defined according to the WHO definition.[1] We compared clinical characteristics, treatment and long-term outcomes between patients with and without anemia, and also examined the prognostic impact of anemia with a special reference to clinical background, including age, sex, double product, renal function, etiology of CHF and LVEF. Double product was calculated by multiplying systolic blood pressure (SBP) and heart rate, as an index parameter of myocardial oxygen consumption.[21]

The diagnosis of HF was made based on the criteria of the Framingham Study[22] and the main etiology of CHF was determined in each patient. The etiology of CHF was classified as ischemic heart disease (IHD) when prior myocardial infarction or coronary artery disease was present. Those without IHD were classified as having dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM) or valvular heart disease (VHD) if they had a previous diagnosis of these conditions. In the present study, VHD was specifically defined as severe aortic or mitral valvular disease by echocardiography with the use of standard criteria.[23] CHF was attributed to hypertension (HT) when a patient did not have IHD, DCM, HCM or VHD, but had a history of HT. If a patient had atrial fibrillation (AF) in the absence of IHD, DCM, HCM, VHD or HT, the CHF etiology was classified as AF.[23] If a patient was classified as having none of IHD, DCM, HCM, VHD, HT or AF, the CHF etiology was classified as "other".[23] Finally, CHF patients were categorized into 7 etiology groups: IHD, DCM, HCM, VHD, HT, AF and others.[23]

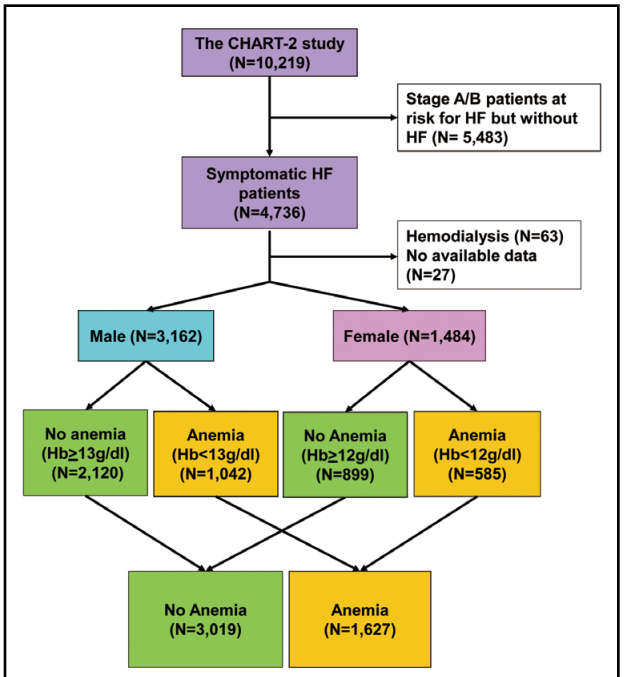


Figure 1. Study flowchart. Hb, hemoglobin; HF, heart failure.

Statistical Analysis

All continuous variables are reported as mean±standard deviation or median. All categorical variables are represented as frequency (percentage). Fisher's exact test was used to compare categorical variables. Welch's t-test was used to compare continuous variables. The Kaplan-Meier method and the log-rank test were used to estimate survival curves and HF-free survival curves. The multivariate Cox proportional hazard model was used to evaluate determinants of all-cause death. The covariates of multivariable analysis included sex, age, body mass index (BMI), history of HT, diabetes mellitus, dyslipidemia, smoking, HF admission, stroke, AF, etiology of CHF (VHD, IHD, DCM, HCM, HT, AF and others), LVEF, end-diastolic LV dimension, SBP, heart rate, double product, estimated glomerular filtration rate (eGFR), Hb, mean corpuscular volume of red blood cells, B-type natriuretic peptide (BNP) and medical treatments (β-blockers, renin-angiotensin system inhibitors, diuretics, statins and oral iron). Among these covariates, the most efficient ones were chosen by a stepwise method. Interactions between Hb and other covariates were estimated by the Cox proportional hazard model, including interaction terms using the same variables chosen by the stepwise method. To calculate the most effective cutoff value of Hb for defining anemia, we used a classification and regression tree (CART). $P<0.05$ and P-value for interaction <0.1 were considered to be statistically significant. Statistical analysis was performed using R version 3.1.1.[24]

Results

Baseline Characteristics

The distribution of Hb levels is shown in Figures 2A–C. Most common Hb level in males was 14.0–14.9 g/dl and 12.0–12.9 g/dl in females. Among the 4,646 patients with Stage C/D HF, 35% had anemia (males, 33.0% and females, 39.4%). Baseline characteristics of the patients are shown in Table 1.

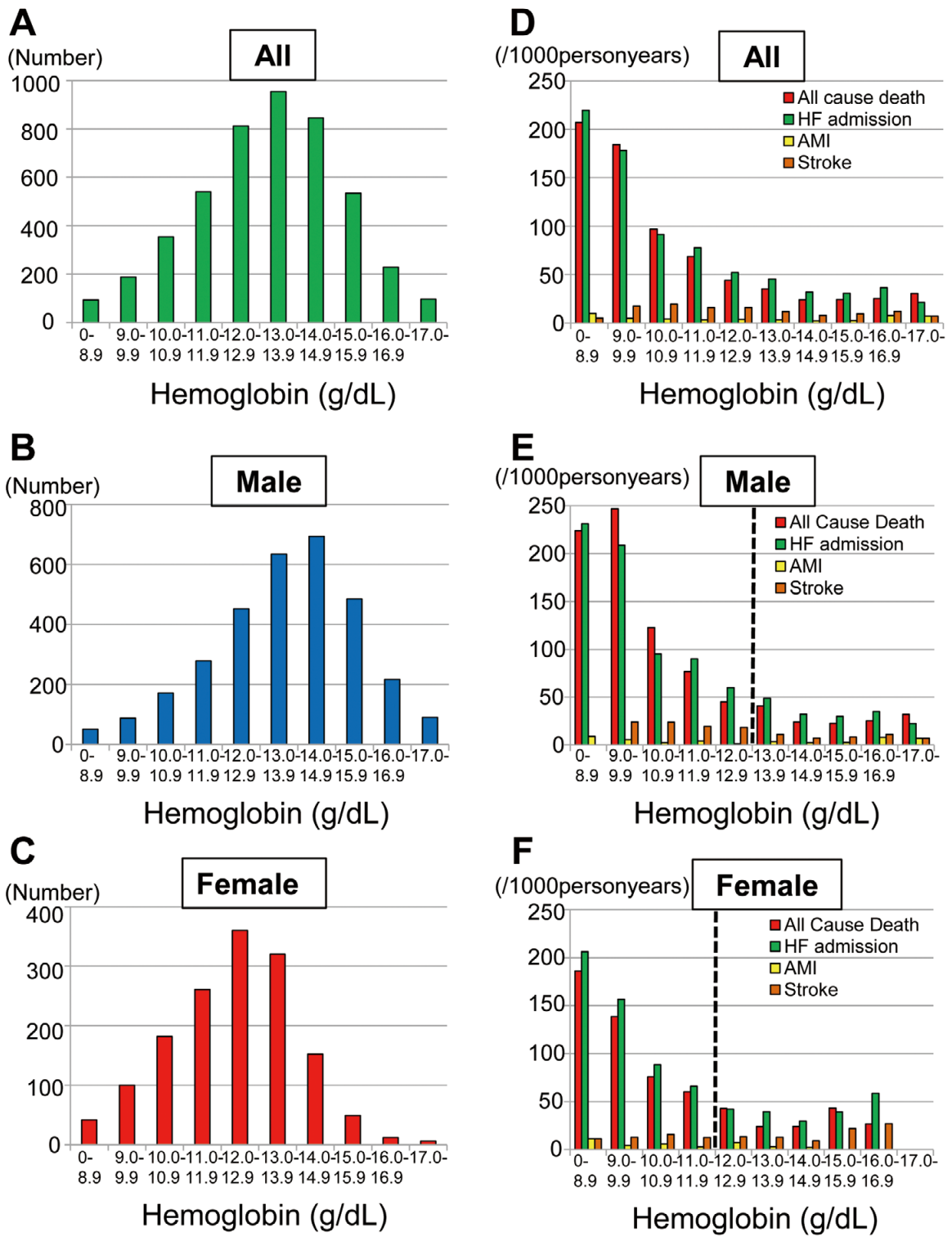


Figure 2. Distribution of hemoglobin (Hb) levels and incidence of cardiovascular events according to baseline Hb levels. (**A**) Overall study group, and (**B**) male, and (**C**) female patients. Incidences of all-cause death, HF admission, acute myocardial infarction, and stroke (per 1,000 person-years) for (**D**) overall, (**E**) male, and (**F**) female patients. Dashed lines in (**E**) and (**F**) depict the threshold of the WHO definition of anemia. AMI, acute myocardial infarction; HF, heart failure.

Table 1. Baseline Characteristics of Study Patients With CHF

	All (n=4,646)	Anemia (n=1,627)	No anemia (n=3,019)	P value
Age, (years)	68.9±12.4	73.8±10.4	66.3±12.5	<0.001
Female sex (n, %)	1,484 (31.9)	585 (36.0)	899 (29.9)	<0.001
BMI (kg/m²)	23.4±4.9	22.1±5.0	24.0±4.8	<0.001
NYHA class (n, %)				<0.001
I	1,075 (23.2)	300 (18.5)	775 (25.8)	
II	3,032 (65.5)	1,040 (64.3)	1,992 (66.2)	
III	481 (10.4)	251 (15.5)	230 (7.7)	
IV	38 (0.8)	27 (1.7)	11 (0.4)	
Etiology of CHF (n, %)				
IHD	2,176 (46.8)	779 (47.9)	1,397 (46.3)	0.309
DCM	646 (13.9)	149 (9.2)	497 (16.5)	<0.001
VHD	466 (10.0)	223 (13.7)	243 (8.1)	<0.001
HCM	157 (3.38)	41 (2.52)	116 (3.84)	0.017
HT	1,139 (24.5)	417 (25.6)	722 (23.9)	0.198
Risk factors (n, %)				
Hypertension	3,600 (77.5)	1,271 (78.2)	2,329 (77.1)	0.439
Diabetes mellitus	1,222 (26.3)	457 (28.1)	765 (25.3)	0.043
Dyslipidemia	3,372 (72.6)	1,104 (67.9)	2,268 (75.1)	<0.001
Smoking	2,016 (46.2)	643 (42.3)	1,373 (48.3)	<0.001
Previous history (n, %)				
Myocardial infarction	1,568 (33.8)	540 (33.2)	1,028 (34.1)	0.558
Atrial fibrillation	1,547 (33.6)	533 (33.0)	1,014 (33.9)	0.601
Cerebral infarction	829 (17.9)	343 (21.1)	486 (16.1)	<0.001
Malignant disease	544 (11.7)	290 (17.8)	254 (8.4)	<0.001
Hemodynamics and LV function				
Systolic BP (mmHg)	126.2±18.2	125.8±20.7	126.4±18.2	0.289
Diastolic BP (mmHg)	72.3±12.0	69.7±12.2	73.6±11.6	<0.001
Heart rate (beats/min)	72.3±14.9	72.4±14.7	72.3±15.0	0.892
Double product	9,123.5±35.0	9,084.1±58.6	9,144.6±43.5	0.407
LVDd (mm)	52.1±9.3	51.7±9.0	52.3±9.4	0.053
LVEF (%)	57.0±15.3	57.5±15.3	56.7±15.5	0.088
Laboratory findings				
Hemoglobin (g/dl)	13.2±2.2	11.1±1.2	14.3±1.6	<0.001
eGFR (ml/min/1.73 m²)	61.4±23.2	52.8±22.7	66.1±22.1	<0.001
Albumin (mg/dl)	4.1±0.5	3.8±0.5	4.2±0.4	<0.001
LDL-C (mg/dl)	105.2±30.7	98.7±30.1	108.7±30.5	<0.001
BNP (pg/ml)	101.7	154.5	81.8	<0.001
Medications (n, %)				
β-blockers	2,281 (49.1)	738 (45.4)	1,543 (51.1)	<0.001
RAS inhibitors	3,369 (72.5)	1,220 (75.0)	2,149 (71.2)	0.006
Diuretics	2,173 (46.8)	896 (55.1)	1,277 (42.3)	<0.001
Aldosterone antagonists	1,155 (24.9)	433 (26.6)	722 (23.9)	0.046
Calcium channel blockers	1,803 (38.8)	667 (41.0)	1,136 (37.6)	0.025
Statins	1,780 (38.3)	553 (34.0)	1,227 (40.6)	<0.001
Oral iron	182 (3.9)	146 (9.0)	36 (1.2)	<0.001

BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HT, hypertension; IHD, ischemic heart disease; LDL-C, low-density lipoprotein cholesterol; LVDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VHD, valvular heart disease.

Patients with anemia, as compared with those without it, were characterized by older age (73.8 vs. 66.3 years, P<0.001), higher prevalence of female sex (36.0% vs. 29.9%, P<0.001), lower BMI (22.1 vs. 24.0 kg/m², P<0.001) and eGFR (52.8 vs. 66.1 ml/min/1.73 m², P<0.001), higher prevalence of diabetes mellitus (28.1% vs. 25.3%, P=0.043), lower prevalence of dyslipidemia (67.9% vs. 75.1%, P<0.001), and higher prevalence of prior cerebral infarction (21.1% vs. 16.1%, P<0.001), and malignant diseases (17.8% vs. 8.4%, P<0.001). Anemic patients had lower prevalence of cardiomyopathy (13.6% vs. 22.7%, P<0.001) and were more frequently treated with diuretics (55.1% vs. 42.3%, P<0.001) and less frequently

Table 2. Multivariate Cox Regression for All-Cause Death in All Patients With Stage C/D CHF

Clinical characteristic	HR	95% CI	P value
Age	1.041	1.030–1.052	<0.001
Female sex	0.854	0.707–1.032	0.102
BMI	0.957	0.940–0.974	<0.001
NYHA	1.593	1.362–1.862	<0.001
DCM	0.806	0.610–1.065	0.129
HT	0.817	0.662–1.009	0.060
Cerebral infarction	1.209	0.981–1.491	0.075
Malignant disease	1.583	1.275–1.967	<0.001
Double product	1.045	1.008–1.085	0.017
eGFR	0.991	0.987–0.996	0.001
BNP	1.101	1.083–1.120	<0.001
MCV	1.013	0.999–1.027	0.076
Loop diuretics	1.389	1.143–1.687	0.001
Statins	0.753	0.615–0.923	0.006
Anemia	1.408	1.156–1.715	0.001

CHF, chronic heart failure; CI, confidence interval; HR, hazard ratio; MCV, mean corpuscular volume. Other abbreviations as in Table 1.

treated with statins (34.0% vs. 40.6%, P<0.001) and β-blockers (45.4% vs. 51.1%, P<0.001). Finally, anemic patients, as compared with non-anemic patients, had higher NYHA class and increased BNP levels (154.5 vs. 81.8 pg/ml, P<0.001), but had comparable LVEF (57.5% vs. 56.7%), SBP (126 mmHg vs. 126 mmHg), and double product (9,144.6 vs. 9,084.1). Table 2 shows the prognostic factors of CHF patients identified by the stepwise method. Anemia was identified as one of the prognostic predictors of CHF patients in addition to other factors such as age, renal dysfunction, cardiac dysfunction, DCM and medications (Table 2).

Anemia and Incidence of Cardiac Events

There were 643 deaths during the median follow-up of 3.8 years. Among them, 318 (49.5%) and 278 (43.2%) had cardiovascular and non-cardiovascular causes, respectively, and the remaining 47 deaths (7.3%) were of unknown cause. The incidences of all-cause death, HF admission, acute myocardial infarction and cerebral infarction according to Hb levels are shown in Figures 2D–F. The incidence of all-cause death and HF admission, but not that of myocardial infarction or cerebral infarction, gradually increased as the Hb level fell below 13.0 g/dl in males and 12.0 g/dl in females (Figures 2D–F). The incidence of HF death, sudden death, other cardiovascular death and non-cardiovascular death gradually increased as the Hb level fell below 13.0 g/dl in males and 12.0 g/dl in females, respectively (Figure 3). The CART analysis indicated that the discriminating value of Hb level to discern the risk for all-cause mortality was 11.75 g/dl for men and 9.75 g/dl for women (hazard ratio [HR] 1.90, 95% confidence interval [CI] 1.55–2.33, P<0.001 for patients with Hb <11.75 g/dl for men and 9.75 g/dl for women, when patients with Hb >11.75 g/dl for men and >9.75 g/dl for women those without them served as reference).

Prognostic Impact of Anemia in CHF Patients

Kaplan-Meier estimates for all-cause death and HF admission revealed that anemic patients had significantly poorer prognosis compared with non-anemic patients (Figures 4A,B). Interestingly, the impact of anemia was comparable for both sexes (Figures 4C–F). Figure 5 shows the results of the univariate and multivariate Cox regression analyses for all-cause death according to the subgroups. In the univariate analysis, anemia was associated with increased mortality regardless of age, sex, eGFR, double product, etiology of HF or LVEF level (Figure 5A). After adjustment for clinical variables, anemia still remained a strong predictor for all-cause death (HR 1.41, 95% CI 1.16–1.72, P=0.001) (Figure 5B). However, the multivariate analysis revealed a significant interaction between the prognostic impact of anemia and LVEF; the prognostic impact of anemia disappeared in patients with LVEF ≤40% (HR 0.73, 95% CI 0.48–1.09, P=0.124), but it remained significant in those with LVEF ≥50% (HR 1.59, 95% CI 1.25–2.02, P<0.001), suggesting different prognostic impact of anemia at different LVEF levels (P value for interaction <0.001) (Figure 5B). Similarly, the multivariate Cox regression analysis revealed that anemia was not an independent predictor for all-cause mortality in CHF patients with IHD, DCM, VHD, HCM or AF, but was significantly associated with all-cause death in those with HT or other etiologies (P value for interaction=0.001) (Figure 5B). The prognostic impact of anemia did not differ by age or sex in the multivariate Cox regression analysis (Figure 5B).

Interactions of Anemia With LVEF and Etiology

To further evaluate the possible interactions among anemia, LVEF and HF etiology, we performed a multivariate Cox regression analysis for subgroups divided by LVEF level in patients with IHD and DCM. As shown in Figure 6, there was a significant interaction between anemia and LVEF in patients with IHD (P for interaction <0.001), but not in those with DCM (P for interaction=0.61). Because of the small number of patients with LVEF ≤40%, we were unable to perform this analysis in CHF patients with VHD, HCM, HT, AF or other etiologies.

Discussion

The novel findings from the present large-scale CHF cohort were that (a) more than one-third of the CHF patients had anemia that was associated with increased mortality, (b) anemia was associated with poor progress in patients with CHF

regardless of age, sex, eGFR or double product, and (c) the prognostic impact of anemia was evident in CHF patients with preserved EF and also differed by CHF etiology. To the best of our knowledge, this is the first study demonstrating the importance of comprehensive consideration of clinical background in the management of anemia in CHF patients.

Prevalence of Anemia in CHF Patients

In the present study, anemia was present in 35% of the CHF patients (33.0% in males, 39.4% in females), which is higher than reported for the Japanese general population (12.3% in males, 13.3% in females >65 years old),[25] and is comparable with or slightly higher than that reported in other CHF cohorts (17–42%).[2–5] In the present study, anemic patients were characterized by older age, lower BMI, higher prevalence of VHD, previous cerebral infarction and malignant disease, lower prevalence of DCM, diabetes mellitus and dyslipidemia, and lower levels of serum albumin, all of which are common characteristics of elderly patients. In addition, anemic patients, as compared with non-anemic patients, not only had lower eGFR but also higher NYHA class and increased BNP levels despite comparable LVEF levels. However, it remains to be clarified whether the coexistence of renal dysfunction, advanced CHF and anemia in the present study reflects one aspect of the cardiorenal anemia syndrome[8] or is simply a result of the higher prevalence of anemic elderly patients.

Cardiovascular Events in Anemic Patients With CHF

The present study revealed that anemia was associated with poorer prognosis. Lower Hb levels were associated with higher incidence of all-cause death and hospitalization for HF, but not with the incidence of myocardial infarction or cerebral infarction, suggesting that anemia has a different impact on disease progression among death, HF and atherosclerotic disease. Interestingly, the incidence of all-cause death and HF hospitalization gradually increased as Hb levels fell below 13.0 g/dl in males and 12.0 g/dl in females, suggesting that the definition of anemia in the WHO criteria[1] has useful clinical value for discerning the mortality risk of CHF patients of both sexes. However, the CART analysis demonstrated that Hb of 11.75 g/dl for men and 9.75 g/dl for women more accurately discerned the risk for all-cause mortality, suggesting that the prognostic threshold of anemia should be considered as much lower than that indicated by the WHO definition.[1]

Prognostic Impact of Anemia According to LVEF and CHF Etiology

In the present univariate analysis, anemia had an increased risk for all-cause mortality regardless of subgroups divided by age, sex, double product, HF etiology or LVEF level, suggesting a significant and broad impact of anemia in real-world practice. However, the multivariate analysis revealed that age, sex, eGFR and double product had no significant influence on the prognostic impact of anemia in patients with HF. In contrast, the multivariate subgroup analysis revealed that the impact of anemia differed by HF etiology; the prognostic impact of anemia was noted in patients with HT but not in those with IHD, DCM or VHD. Similarly, the prognostic impact of anemia was noted in patients with preserved LVEF but not in those with reduced LVEF. Although it is difficult to further elucidate the mechanism of the differences in prognostic impact of anemia among the subgroups, the present finding that anemia has a significant impact on mortality in both patients with preserved LVEF and those with HT is of clinical interest. It is now recognized that the number of CHF patients with preserved LVEF is rapidly increasing worldwide, for which HT may play an important role.[26] Thus, the present findings suggest that treatment for anemia is beneficial in CHF patients with preserved LVEF and those with HT, although neither erythropoietin nor oral iron has necessarily been shown to improve the survival of CHF patients.[27–29] In order to confirm this notion, randomized controlled trials addressing the clinical background of anemic CHF patients are warranted.

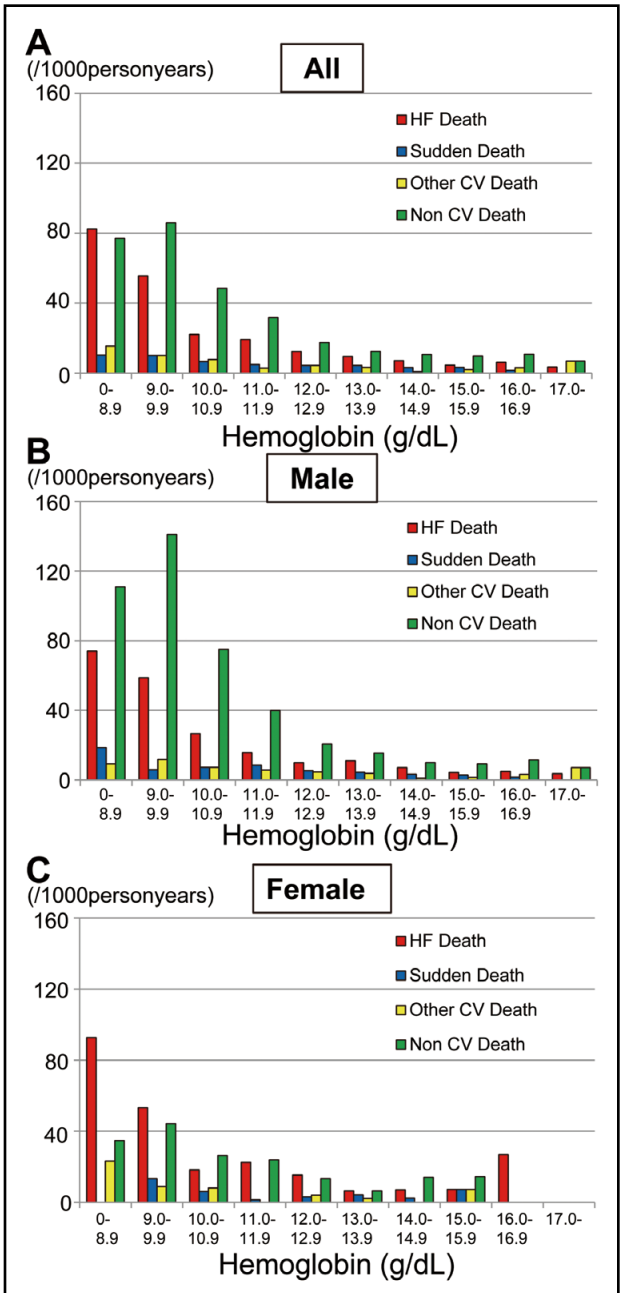
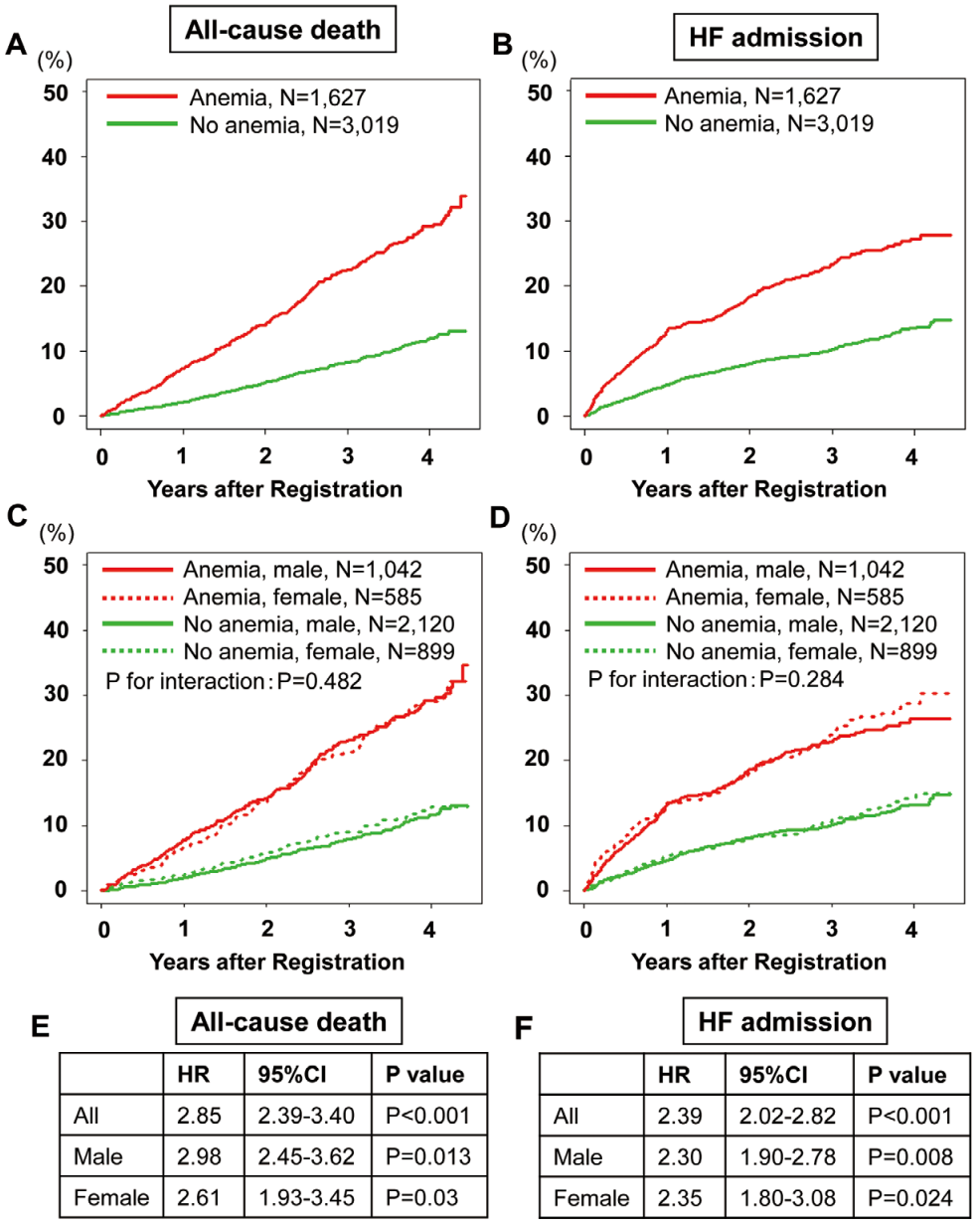


Figure 3. Incidence of death from heart failure, sudden death or other cardiovascular (CV) cause, and non-cardiovascular death according to baseline hemoglobin (Hb) levels. Distribution of Hb levels for (**A**) overall, (**B**) male, and (**C**) female patients.



E All-cause death

	HR	95%CI	P value
All	2.85	2.39-3.40	P<0.001
Male	2.98	2.45-3.62	P=0.013
Female	2.61	1.93-3.45	P=0.03

F HF admission

	HR	95%CI	P value
All	2.39	2.02-2.82	P<0.001
Male	2.30	1.90-2.78	P=0.008
Female	2.35	1.80-3.08	P=0.024

Figure 4. Estimates for all-cause death and heart failure (HF) admission. Kaplan-Meier curves for (**A**) all-cause death and (**B**) HF admission in all patients and those for (**C**) all-cause death and (**D**) HF admission according to sex. Hazard ratios (HR) and 95% confidence intervals (CI) for (**E**) all-cause death and (**F**) HF admission.

Different Influence of LVEF on the Prognostic Impact of Anemia in IHD and DCM Patients

In the present study, we demonstrated an interaction of anemia with LVEF in CHF patients. However, the interaction was noted only in patients with IHD, not in those with DCM. Thus, the effects of the cardiorenal anemia syndrome on the prognostic impact of anemia may differ between IHD and DCM. Because IHD patients, as compared with DCM patients, are characterized by higher age and higher prevalence of atherosclerotic risk factors, including HT, diabetes and dyslipidemia, they are more likely to have advanced systemic atherosclerosis than DCM patients, which might have caused more adverse cardiorenal anemia interactions through hypoperfusion of bone marrow and other organs. However, it is unclear how and why the prognostic impact of anemia differed among the LVEF categories in IHD patients. Indeed, in previous reports, the relationship between LVEF and the prognostic impact of anemia has been controversial.[27,28] Thus, further studies are needed to answer this question. This discrepancy in the prognostic impact of anemia between IHD and DCM patients may be clinically important because it could explain why interventions with erythropoietin failed to show effectiveness in the

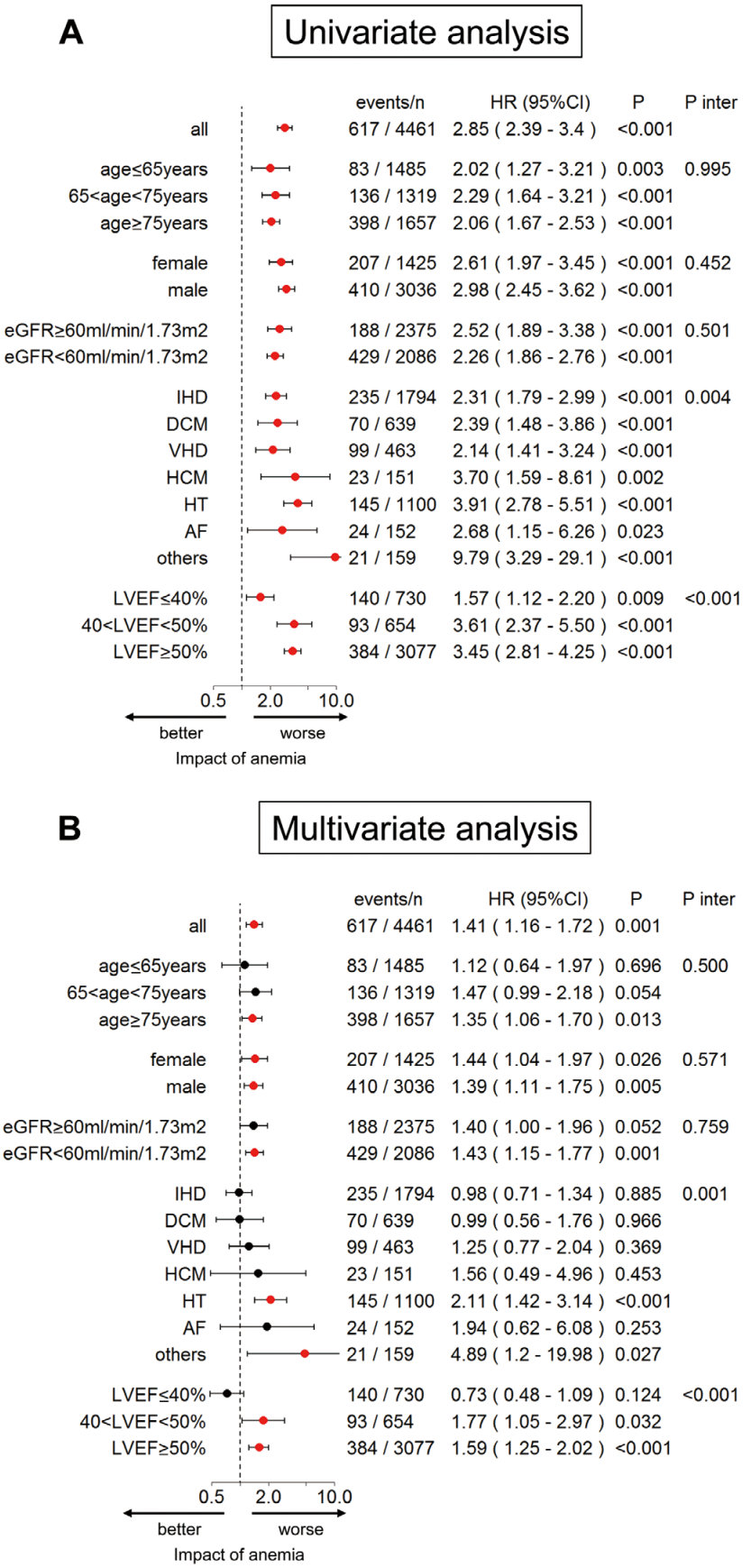


Figure 5. Cox proportional regression analysis for all-cause death. Forrest plots for (**A**) univariate and (**B**) multivariate Cox proportional regression analyses for all-cause death. Hazard ratios (HR) and 95% confidence intervals (CI) of anemia for all-cause death in subgroups divided according to age, sex, LVEF levels and HF etiology. AF, atrial fibrillation; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HT, hypertension; IHD, ischemic heart disease; HF, heart failure; LVEF, left ventricular ejection fraction; VHD, valvular heart disease.

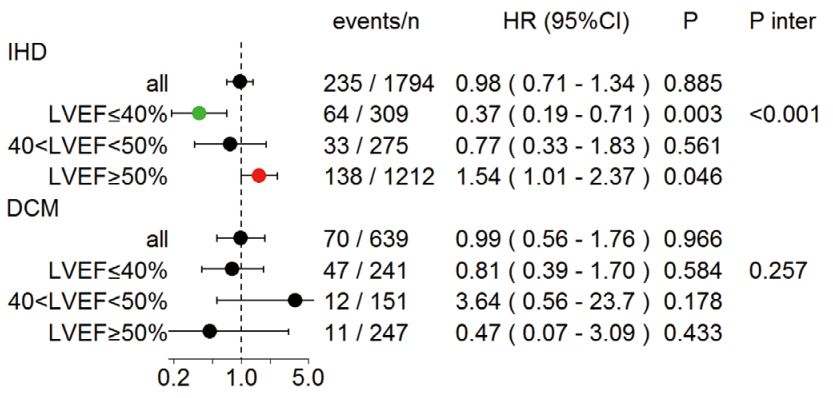


Figure 6. Cox proportional regression analysis according to etiologies and LVEF. Forrest plots for the multivariate Cox proportional regression analysis according to etiology and LVEF. CI, confidence interval; DCM, dilated cardiomyopathy; HR, hazard ratio; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction.

previous studies that mainly enrolled anemic patients with IHD.[27,28] Thus, without additional management of the confounding factors of anemia, including cardiac and renal dysfunction, simple treatment to increase the Hb level may not be sufficient for HF patients, especially those with IHD.

Study Limitations

First, in the present study, we only analyzed the clinical background data obtained at entry in the CHART-2 Study and we did not take into consideration possible changes in Hb levels during the follow-up period. This point remains to be addressed in future studies. Second, the subtype of anemia was unknown in the present study because data on erythropoietin, ferritin or folic acid were not available. Because different types of anemia may have different prognostic impacts, this issue also remains to be examined in future studies. Finally, because CHART-2 is a prospective observational study with Japanese CHF patients, caution should be taken when generalizing the present findings to other populations.

Conclusions

We were able to demonstrate that the prognostic impact of anemia in CHF patients with preserved LVEF may differ by CHF etiology. Thus, overall management considering the patient's clinical background is warranted when treating anemic CHF patients in clinical practice.

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Conflict of Interest

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Supplementary Files

Supplementary File 1

Appendix S1. CHART-2 Study Investigators

Please find supplementary file(s);
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