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Improved and new-onset anemia during follow-up in patients with acute decompensated heart failure

Characteristics and outcomes

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Abstract

There was no previous report on the prognostic impact of new-onset or improved anemia after discharge from acute decompensated heart failure (ADHF).

We analyzed 771 patients with ADHF and who were followed in multicenters in Japan was divided into 4 groups based on the hemoglobin values at discharge and 6-month index visit: 373 patients (48.4%) with persistent anemia, 87 patients (11.3%) with new-onset anemia, 91 patients (11.8%) with improved anemia, and 220 patients (28.5%) without anemia.

The primary outcome measure was a composite of all-cause death or HF hospitalization after index visit. The cumulative 6-month incidences of the primary outcome measure were 25.2% for persistent anemia, 18.5% for new onset anemia, 9.0% for improved anemia, and 9.2% for no anemia (log-rank $P < .001$). Compared with the no anemia group, the excess risk for the primary outcome measure remained significant in the persistent anemia group [hazard ratio (HR) 2.70, 95% confidence interval (95% CI), 1.45–5.44, $P = .001$] and in the new-onset anemia group (HR 2.73, 95% CI 1.19–6.25, $P = .02$), while it was not significant in the improved anemia group (HR 1.69, 95% CI 0.68–4.03, $P = .25$).

Persistent and new-onset anemia at 6-month visit were associated with a subsequent higher risk for all-cause death or HF hospitalization in patients with ADHF, suggesting the importance of detecting anemia during follow-up.

Abbreviations: ACE-I = angiotensin converting enzyme inhibitor, ADHF = acute decompensated heart failure, ARB = angiotensin II receptor blocker, BMI = body mass index, BNP = brain natriuretic peptide, CHF = chronic heart failure, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded arteries, HF = heart failure, KCHF = Kyoto Congestive Heart Failure, LVEF = left ventricular ejection fraction, MRA = mineralocorticoid receptor antagonist, NYHA = New York Heart Association.

Keywords: anemia, clinical outcome, heart failure, prospective

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The authors declare that there is no conflict of interest

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Anemia is a common finding in chronic heart failure (CHF), and is associated with dyspnea, impaired functional capacity, increased cardiac workload, and increased risk for hospitalizations and death.[1–12] It has also been investigated whether the amount of changes in hemoglobin levels can predict acute events in patients with CHF. Some previous studies have shown that the decrease in hemoglobin levels over time was associated with the increased morbidity and mortality in patients with CHF.[8,9] In patients with acute decompensated heart failure (ADHF), a recent study reported a decrease in hemoglobin levels during hospitalization was associated with subsequent mortality and adverse cardiovascular events regardless of left ventricular ejection fraction (LVEF).[13] In addition, new-onset anemia during hospitalization was associated with worse outcomes in patients with ADHF.[13,14] However, it is unclear whether the improved or new-onset anemia after discharge from ADHF has any prognostic associations with clinical outcomes in patients with ADHF. In daily clinical practice, we usually check the hemoglobin level in patients at a follow-up visit and compare it to that at discharge. In the present study, we aimed to assess the risk of improved anemia or new onset anemia along with persistent anemia relative to no anemia at 6-month visit for the subsequent clinical outcomes, based on the data from a large contemporary all-comer Japanese registry of patients with ADHF.

2. Methods

2.1. Study design, setting, and population

The KCHF (Kyoto Congestive Heart Failure) registry is a physician-initiated, prospective, observational, multicenter cohort study enrolling consecutive patients who were admitted to the hospital due to ADHF for the first time between October 2014 and March 2016.[15–20] In parallel with the main KCHF study, we designed a prospective, longitudinal study enrolling a subgroup of patients from the KCHF study in which the selected patients were to have a 6-month visit with an allowance of 1 month.[15] At the follow-up visit, we collected the data for physical findings, echocardiography, laboratory data and medications at 6-month after enrollment. Time zero for the clinical follow-up in the present study was the day of the 6-month follow-up visit, and considered as the index day. Clinical follow-up was censored at 210 days after the 6-month visit. Exclusion criteria for the prospective longitudinal follow-up study were as follows: no written informed consent (N=238), patient age <20 years (N=1), fever or infectious diseases at admission (N=297), acute coronary syndrome at admission (N=157), end-stage renal failure (N=218), severe comorbidity limiting the life expectancy within 1 year assessed by attending physicians at each participating center, such as end-stage cancer, severe cognitive dysfunction, and end-stage liver dysfunction (N=112), ineligible for follow up (unable to visit each participating hospital for various reasons) (N=1516). After excluding 271 patients who died during index hospitalization and 2539 patients who did not meet the pre-specified criteria of follow-up, 1246 patients were enrolled in the prospective longitudinal follow-up study. We excluded 23 patients who died within 6 months after initial hospitalization, 14 patients with lost to follow-up during 6 months after enrollment, 95 patients with lost to follow-up after 6-month visit, and 343 patients with missing hemoglobin data at discharge and/or at 6-month visit. The current study population consisted of 771 patients with available data for hemoglobin both at discharge and at 6-month visit (Fig. 1A). We used World Health Organization criteria of anemia and stratified the patients into 4 groups according to hemoglobin value at discharge and 6-month visit as follows: persistent anemia - anemia at discharge and 6-month visit, new-onset anemia - normal hemoglobin level at discharge and anemia at 6-month visit, improved anemia - anemia at discharge and normal hemoglobin level at 6-month visit, and no anemia - normal hemoglobin level at discharge and 6-month visit.

2.2. Ethics

The present investigation conforms to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the ethical committees at the Kyoto University Hospital (local identifier: E2311), as well as at each participating hospital. Written informed consent was obtained from the patients enrolled in the longitudinal prospective cohort study. We made identifiable patient data anonymous before the analysis.

2.3. Definitions

The detailed definitions of baseline patient characteristics were previously described. Anemia was defined using the World Health Organization criteria (hemoglobin <12.0 g/dL in women and <13.0 g/dL in men).[21,22] Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. End-stage renal disease was defined as eGFR <30 mL/min/1.73 m^2 based on the chronic kidney disease grades. HF was classified according to LVEF, as HF with preserved LVEF (LVEF ≥50%), HF with mid-range LVEF (40% ≤ LVEF <50%), and HF with reduced LVEF (LVEF <40%).[23] The bleeding events in the current analysis was defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded arteries (GUSTO) bleeding events.[24] The changes (delta, Δ) for each laboratory data were calculated according to the following equation: (the value at 6-month visit) - (the value at discharge).

2.4. Outcomes

The primary outcome measure for the present analysis was a composite of all-cause death or HF hospitalization after 6-month visit. Secondary outcome measures were the individual components of the primary outcome measure such as HF hospitalization and all-cause death. HF hospitalization was defined as hospitalization due to worsening of HF requiring intravenous drug therapy.[15]

2.5. Statistical analysis

Categorical variables were presented as numbers with percentages. Continuous variables were expressed as mean with standard deviation (SD) or median with interquartile range (IQR). Comparisons among 4 groups were performed using a 1-way ANOVA or Kruskal–Wallis test for continuous variables and the Chi-square test for categorical variables.

The cumulative incidences of the clinical events after the 6-month visit were estimated using the Kaplan–Meier method with the between-groups difference assessed by the log-rank test.

Multivariable Cox proportional hazards model was developed to estimate the adjusted risk of the persistent anemia group, the new-onset anemia group, and the improved anemia group, respectively, relative to the no anemia group for the primary and secondary outcome measures. We included the following 9 clinically relevant risk-adjusting variables into the model: age ≥80 years, sex, LVEF <40% by echocardiography, eGFR <30 mL/min/1.73 m^2 at 6-month visit, albumin <3.0 g/dL at 6-month visit, and medications at 6-month visit [angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB), β-blocker, mineralocorticoid receptor antagonist (MRA), and diuretics]. We selected these variables according to their clinical relevance to the clinical outcomes and based on the previous studies.[17,18] The continuous variables were dichotomized by clinically meaningful reference values or median values. The results were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were conducted by 2 physicians (Y.S. and T.K.) and a statistician (T.M.) using JMP 14. All the reported *P* values were 2-tailed, and the level of statistical significance was set at $P < .05$.

3. Results

3.1. Baseline characteristics and medications

We categorized the patients into 4 groups according to hemoglobin value at discharge and 6-month visit: the persistent anemia group (N = 373, 48.4%), the new-onset anemia group (N = 87, 11.3%), the improved anemia group (N = 91, 11.8%), and the no anemia group (N = 220, 28.5%) (Fig. 1A and B). The distributions of hemoglobin in men and women were are presented in Supplementary Figure 1A, http://links.lww.com/MD2/A309 and 1B, http://links.lww.com/MD2/A310. The mean hemoglobin value was 12.0 ± 2.0 g/dL at 6-month visit. Patients in the persistent anemia and new-onset anemia groups were older than those in the no anemia group. Patients in the persistent anemia and improved anemia groups had a higher prevalence of myocardial infarction than those in the no anemia group (Table 1). Patients in the persistent anemia group and in the new-onset anemia group had a lower body mass index (BMI), higher brain natriuretic peptide (BNP) level, lower eGFR, higher blood urea nitrogen, and lower albumin level than those in the no anemia group. Patients in the persistent anemia group had a higher C-reactive protein (CRP) level than those in the no anemia group (Table 1).

As for medications at 6-month visit, patients in the persistent anemia and improved anemia groups received antiplatelet agents more frequently than those in the no anemia group. Patients in the persistent anemia group received diuretics more frequently and β blockers less frequently than those in the no anemia group (Table 1). Medications at discharge are presented in Supplementary Table 1, http://links.lww.com/MD2/A311. The status of edema, NYHA class III/IV, BMI at admission, discharge, and 6-month visit are presented in Supplementary Table 2, http://links.lww.com/MD2/A312. Volume status at 6-month visit indicated congestion in the persistent and new onset anemia.

3.2. Changes in BNP, BMI, albumin, eGFR, and CRP level between discharge and 6-month visit

Between discharge and 6-month visit, patients in the persistent anemia and new onset anemia groups had an increase in BNP levels, while patients in the improved anemia and no anemia groups had a decrease in BNP levels (Table 1, and Fig. 2A). Patients in the persistent anemia and new-onset anemia groups had a lesser increase in BMI between discharge and 6-month visit than patients in the improved anemia and no anemia groups (Table 1, and Fig. 2B). Patients in the new-onset anemia group had a lesser increase in albumin between discharge and 6-month visit, whereas patients in the improved anemia group had a greater increase in albumin (Table 1, and Fig. 2C). The decreases in eGFR and CRP between discharge and 6-month visit were consistently seen among the 4 groups (Table 1, and Fig. 2D and E).

3.3. Breeding events between discharge and 6-month visit and during subsequent follow-up

There was no significant difference among the 4 groups stratified by the status of anemia in terms of the bleeding events from discharge to 6-month visit (Supplementary Table 3, http://links.lww.com/MD2/A313) and the bleeding events during subsequent follow-up after 6-month visit (Supplementary Table 4, http://links.lww.com/MD2/A314).

3.4. Clinical outcomes after 6-month visit

Final follow-up rate after the 6-month visit was completed in 97.5% of patients. The cumulative 6-month incidence of the primary outcome measure was 25.2% in the persistent anemia group, 18.5% in the new-onset anemia group, 9.0% in the improved anemia, and 9.2% in the no anemia group ($P < .001$) (Fig. 3A). For the primary outcome measure, the excess adjusted risk remained significant in the persistent anemia group (HR 2.70, 95% CI 1.45–5.44, $P = .001$) and in the new-onset anemia group (HR 2.73, 95% CI 1.19–6.25, $P = .02$) relative to the no anemia group, while the excess risk was not significant in the improved anemia group (HR 1.69, 95% CI 0.68–4.03, $P = .25$) (Table 2). The cumulative 6-month incidence of all-cause death was 11.7% in the persistent anemia group, 7.0% in the new-onset anemia group, 3.4% in the improved anemia group, and 3.2% in the no anemia group ($P < .001$) (Fig. 3B). For all-cause death, the excess adjusted risk remained significant in the persistent anemia group (HR 4.25, 95% CI 1.40–18.54, $P = .009$) relative to the no anemia group, while the excess risk was no longer significant in the new-onset anemia group (HR 3.41, 95% CI, 0.80–17.17, $P = .10$), and in the improved anemia group (HR 2.42, 95% CI, 0.44–13.31, $P = .29$) (Table 2). The cumulative 6-month incidence of HF hospitalization was 16.6% in the persistent anemia group, 11.8% in the new-onset anemia group, 5.7% in the improved anemia group, and 6.5% in the normal group ($P = .001$) (Fig. 3C). For HF hospitalization, the excess adjusted risk remained significant in the persistent anemia group (HR 2.32, 95% CI 1.12–5.31, $P = .02$) relative to the no anemia group, while the excess risk was no longer significant in the new-onset anemia group (HR 2.20, 95% CI 0.77–6.01, $P = .13$), and in the improved anemia group (HR 1.44, 95% CI 0.48–4.05, $P = .50$) (Table 2).

When we stratified patients by LVEF <40% and LVEF ≥40%, the trends in both strata were fully consistent with the main analysis. There was no significant interaction between the LVEF strata and the risk of the persistent anemia group, the new-onset anemia group, and the improved anemia group relative to the no anemia group for the primary outcome ($P = .90$, Supplementary Table 5, http://links.lww.com/MD2/A315).

Table 1

Baseline characteristics, laboratory findings, and medications at 6-month visit.

	Total (N = 771)	Persistent anemia (N = 373)	New-onset anemia (N = 87)	Improved anemia (N = 91)	No anemia (N = 220)	*P*	Total N
Clinical Characteristics							
Age, yr	75.8 ± 12.2	80.2 ± 8.8	76.3 ± 9.5	72.9 ± 14.0	69.2 ± 14.0	<.001	771
Age ≥80 yr*	348 (45.1)	222 (59.5)	36 (41.4)	30 (33.0)	60 (27.3)	<.001	771
Women*	332 (43.1)	167 (44.8)	38 (43.7)	40 (44.0)	87 (39.6)	.66	771
BMI, kg/m^2	22.7 ± 4.7	21.5 ± 3.6	22.4 ± 3.8	23.4 ± 5.0	24.6 ± 5.6	<.001	565
BMI ≤22 kg/m^2	278 (49.2)	166 (59.9)	27 (46.6)	29 (45.3)	56 (33.7)	<.001	565
ΔBMI	0.4 ± 2.0	0.3 ± 1.6	0.1 ± 1.6	0.8 ± 2.6	0.5 ± 2.3	.03	563
Medical history							
Atrial fibrillation or flutter	445 (57.7)	206 (55.2)	51 (58.6)	48 (52.8)	140 (63.6)	.17	771
Hypertension	582 (75.5)	286 (76.7)	62 (71.3)	75 (82.4)	159 (72.3)	.19	771
Diabetes	295 (38.3)	154 (41.3)	28 (32.2)	40 (44.0)	73 (33.2)	.09	771
Dyslipidemia	317 (41.1)	159 (42.6)	26 (29.9)	48 (52.8)	84 (38.2)	.01	771
Previous myocardial infarction	177 (23.0)	102 (27.4)	13 (14.9)	28 (30.8)	34 (15.5)	<.001	771
Previous stroke	122 (15.8)	62 (16.6)	15 (17.2)	16 (17.6)	29 (13.2)	.64	771
Chronic lung disease	102 (13.2)	45 (12.1)	12 (13.8)	19 (20.9)	26 (11.8)	.14	771
Malignant neoplasm	109 (14.1)	70 (18.8)	6 (6.9)	10 (11.0)	23 (10.5)	.004	771
Vital signs at 6-month visit							
Heart rate, bpm	74.8 ± 14.2	72.8 ± 12.9	75.4 ± 14.8	76.3 ± 13.9	77.2 ± 15.6	.006	622
Systolic BP, mm Hg	121.9 ± 21.1	122.5 ± 22.2	118.0 ± 23.7	120.3 ± 19.5	123.0 ± 18.6	.32	652
Diastolic BP, mm Hg	67.6 ± 13.6	64.3 ± 12.1	66.1 ± 13.2	67.5 ± 12.2	73.7 ± 14.4	<.001	649
Laboratory test results at 6-month visit							
LVEF, %	50.7 ± 15.6	51.3 ± 15.9	52.3 ± 14.2	51.3 ± 15.6	48.9 ± 15.8	.26	676
ΔLVEF, %	5.2 ± 12.8	2.1 ± 10.9	11.3 ± 13.5	5.1 ± 15.5	7.8 ± 12.8	<.001	670
LVEF classification						.46	
HFpEF (LVEF>50%)	385 (57.0)	192 (59.4)	48 (61.5)	45 (57.0)	100 (51.0)		676
HFmEF (LVEF40–49%)	113 (16.7)	52 (16.1)	14 (18.0)	11 (13.9)	36 (18.4)		676
HFrEF (LVEF<40%)*	178 (26.3)	79 (24.5)	16 (20.5)	23 (29.1)	60 (30.6)		676
BNP, pg/mL	184.9 (79.7–379.2)	244.0 (123.8–460.5)	185.2 (58.3–418.7)	156.4 (63.0–311.8)	114.4 (38.4–241.3)	<.001	597
ΔBNP, pg/mL	-17.2 ± 435.4	19.5 ± 530.6	46.3 ± 332.5	-116.9 ± 437.8	-61.7 ± 252.0	.03	435
NT-proBNP, pg/mL	1219.0 (568.1–2759.5)	2135.0 (882.0–4922.0)	1081.0 (335.9–2523.0)	779.4 (412.0–2675.5)	853.3 (361.7–1829.0)	<.001	297
Serum creatinine, mg/dL	1.33 ± 0.65	1.51 ± 0.75	1.25 ± 0.56	1.22 ± 0.48	1.09 ± 0.41	<.001	768
ΔSerum creatinine, mg/dL	0.09 ± 0.43	0.08 ± 0.50	0.19 ± 0.48	0.09 ± 0.35	0.06 ± 0.30	.12	768
eGFR, mL/min/1.73 m^2	44.9 ± 20.3	38.7 ± 18.9	46.5 ± 19.7	47.4 ± 19.4	53.8 ± 19.8	<.001	768
<60 mL/min/1.73 m^2	611 (79.6)	323 (87.1)	66 (75.9)	67 (73.6)	155 (70.8)	<.001	768
<30 mL/min/1.73 m^2*	195 (25.4)	136 (36.7)	20 (23.0)	20 (22.0)	19 (8.7)	<.001	768
ΔeGFR, mL/min/1.73 m^2	-2.5 ± 12.6	-1.4 ± 11.1	-4.7 ± 14.1	-3.7 ± 12.6	-2.9 ± 14.3	.09	768
Blood urea nitrogen, mg/dL	27.3 ± 14.7	31.7 ± 16.6	24.5 ± 10.9	27.4 ± 14.9	21.1 ± 8.9	<.001	765
Albumin, g/dL	3.89 ± 0.52	3.73 ± 0.48	3.86 ± 0.62	4.12 ± 0.40	4.08 ± 0.51	<.001	717
<3.0 g/dL*	25 (3.5)	14 (4.1)	5 (6.2)	0 (0)	6 (2.9)	.14	717
ΔAlbumin, g/dL	0.37 ± 0.52	0.36 ± 0.44	0.15 ± 0.63	0.62 ± 0.39	0.38 ± 0.60	<.001	654
Sodium, mEq/L	139.6 ± 3.3	139.7 ± 3.3	139.9 ± 2.6	139.4 ± 4.2	139.5 ± 3.2	.73	765
<135 mEq/L	48 (6.3)	25 (6.8)	2 (2.3)	5 (5.6)	16 (7.3)	.40	765
Hemoglobin, g/dL	12.0 ± 2.0	10.5 ± 1.3	11.6 ± 0.9	13.5 ± 0.9	14.1 ± 1.3	<.001	771
ΔHemoglobin level	-0.1 ± 1.7	0 ± 1.4	-1.8 ± 1.0	2.3 ± 1.4	-0.5 ± 1.4	<.001	771
CRP, mg/dL	0.15 (0.05–0.43)	0.20 (0.07–0.64)	0.12 (0.05–0.46)	0.15 (0.05–0.47)	0.11 (0.05–0.29)	.005	649
ΔCRP, mg/dL	-0.24 ± 1.90	-0.15 ± 2.13	-0.15 ± 2.30	-0.48 ± 1.95	-0.33 ± 1.12	.50	618
Medications at 6-month visit							
Antiplatelet agent	276 (43.6)	152 (48.9)	28 (43.1)	39 (50.7)	57 (31.7)	.001	633
Aspirin	227 (35.9)	130 (41.8)	20 (30.8)	30 (39.0)	47 (26.1)	.004	633
Thienopyridines	95 (15.0)	53 (17.0)	9 (13.9)	13 (16.9)	20 (11.1)	.33	633
Others	21 (3.3)	12 (3.9)	3 (4.6)	1 (1.3)	5 (2.8)	.62	633
DAPT	60 (9.5)	38 (12.2)	4 (6.2)	5 (6.5)	13 (7.2)	.14	633
Oral anticoagulant	332 (52.2)	148 (47.3)	34 (52.3)	45 (57.7)	105 (58.3)	.08	636
Warfarin	176 (27.7)	97 (31.0)	14 (21.5)	27 (34.6)	38 (21.1)	.03	636
DOAC	156 (24.5)	51 (16.3)	20 (30.8)	18 (23.1)	67 (37.2)	<.001	636
ACE-I/ARBs*	379 (60.1)	183 (59.0)	43 (66.2)	43 (55.1)	110 (61.8)	.54	631
β blockers*	478 (75.4)	218 (70.1)	47 (72.3)	59 (75.6)	154 (85.6)	.002	634
MRAs*	289 (45.8)	127 (40.8)	37 (56.9)	39 (50.7)	86 (48.3)	.06	631
Diuretics*	536 (84.3)	280 (88.9)	55 (84.6)	62 (80.5)	139 (77.7)	.008	636
Loop diuretics	520 (81.9)	271 (86.6)	55 (84.6)	60 (76.9)	134 (74.9)	.007	635
Tolvaptan	94 (14.9)	58 (18.7)	11 (17.2)	10 (13.0)	15 (8.5)	.02	629

Comparisons among 4 groups were performed using the Chi-square test for categorical variables, and 1-way ANOVA or Kruskal–Wallis test for continuous variables. Values are number (%), mean ± standard deviation (SD).

Delta (Δ) was calculated according to the following equation: Continuous variables = (the value at follow-up) − (the value at discharge or baseline in LVEF). Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, while end-stage renal disease was defined as estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2.

ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, BNP = brain-type natriuretic peptide, BP = blood pressure, CRP = c-reactive protein, DAPT = double antiplatelet therapy, DOAC = direct oral anticoagulants, eGFR = estimated glomerular filtration rate, HFmrEF = heart failure with mid-range ejection fraction, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, LVEF = left ventricular ejection fraction, MRA = mineralocorticoid receptor antagonist, NT-pro BNP = N-terminal-pro brain-type natriuretic peptide.

* Risk-adjusting variables selected for the Cox proportional hazard models.

4. Discussion

The main findings of the present study are as follows. The new-onset anemia was associated with an increased risk for a composite of all-cause death or HF hospitalization in patients after discharge from ADHF and the magnitude of risk of the new-onset anemia was comparable to that of persistent anemia. There were no significant differences in the risks for the primary and secondary outcome measures between the improved anemia and no anemia. BNP was increased in the persistent anemia and the new-onset anemia, whereas BNP was decreased in the improved anemia and no anemia.

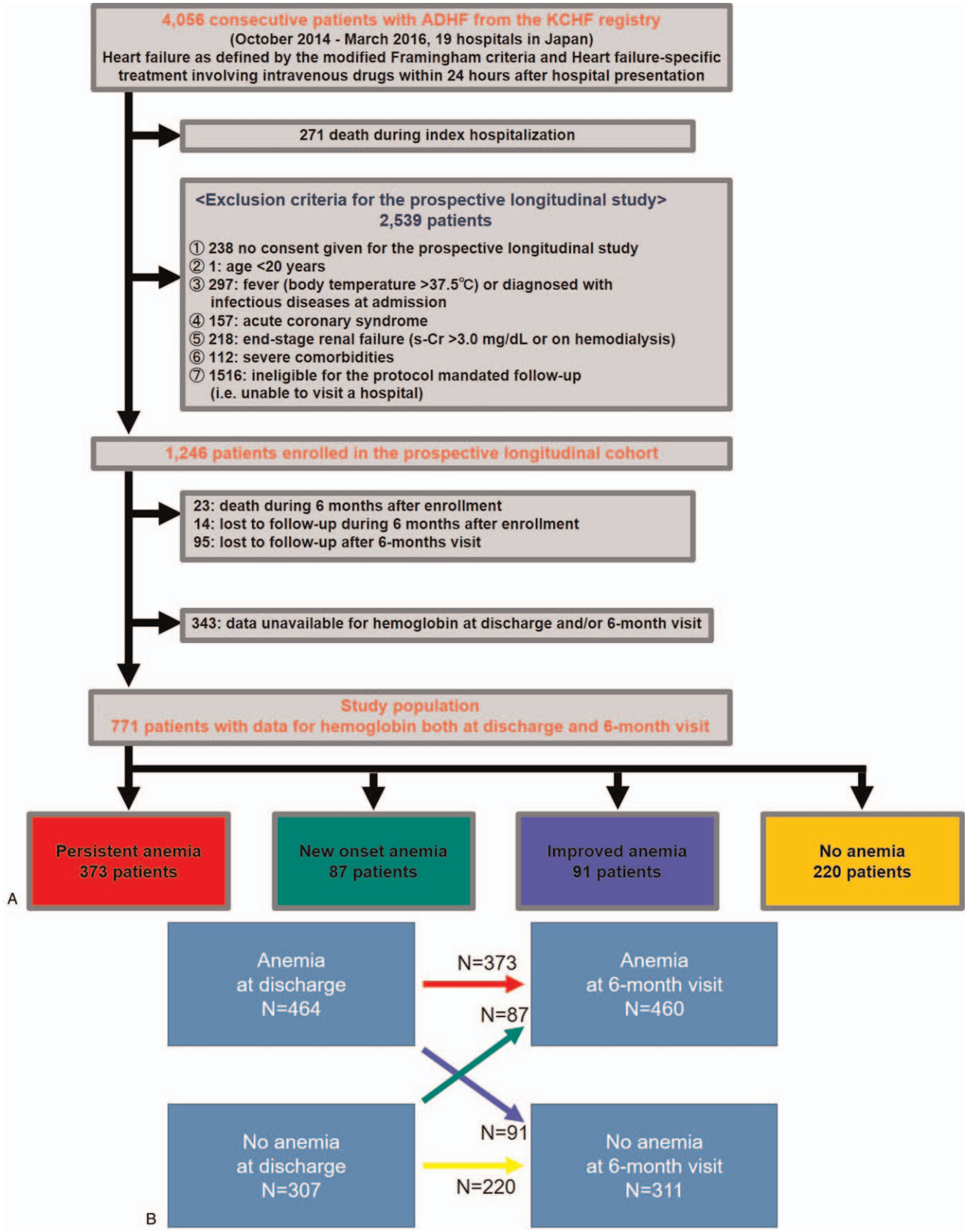


Figure 1. Study patients flow. (A) Study patients flow, and (B) The status of anemia at discharge and at 6-month visit. ADHF = acute decompensated heart failure, KCHF = Kyoto Congestive Heart Failure, s-Cr = serum creatinine.

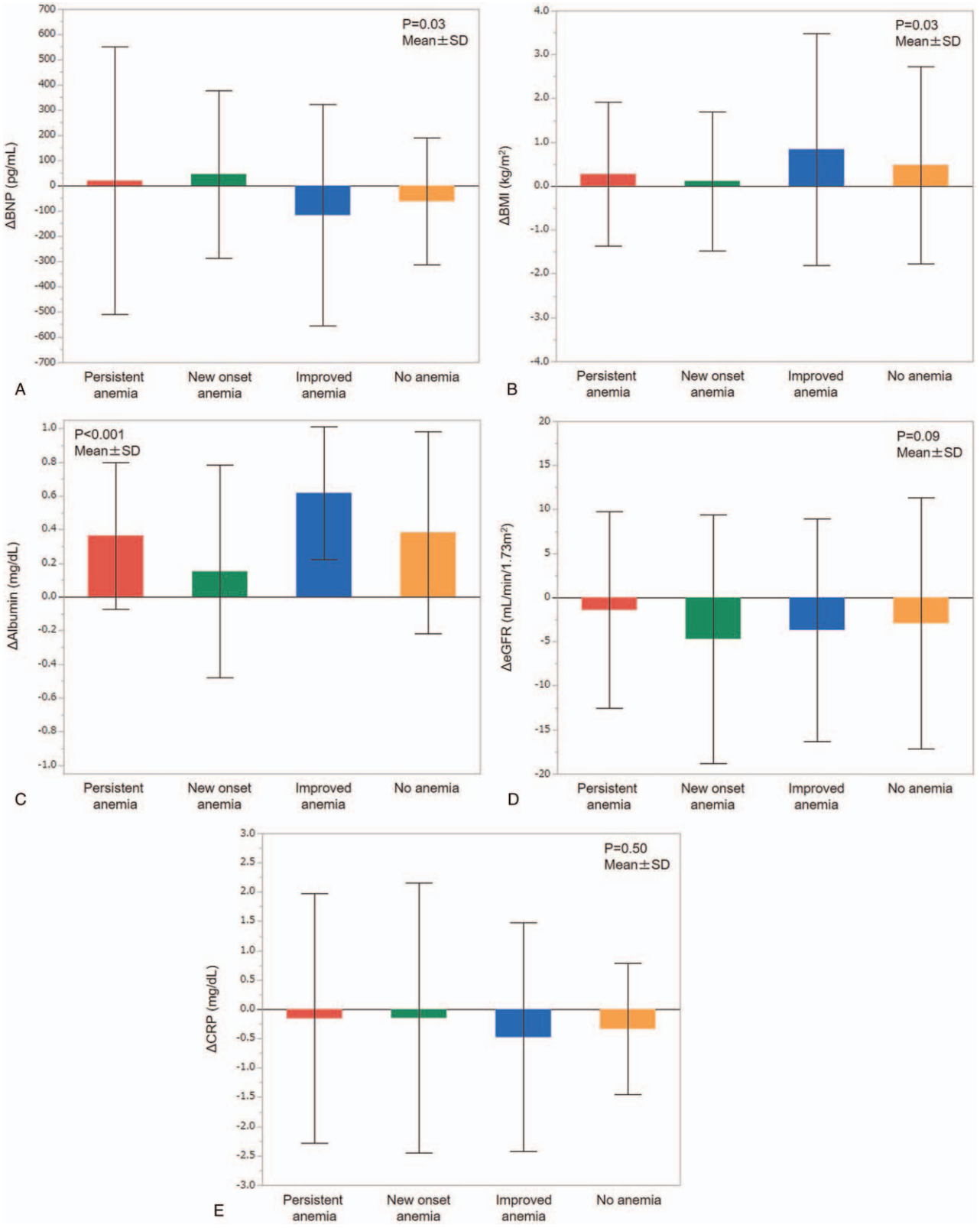
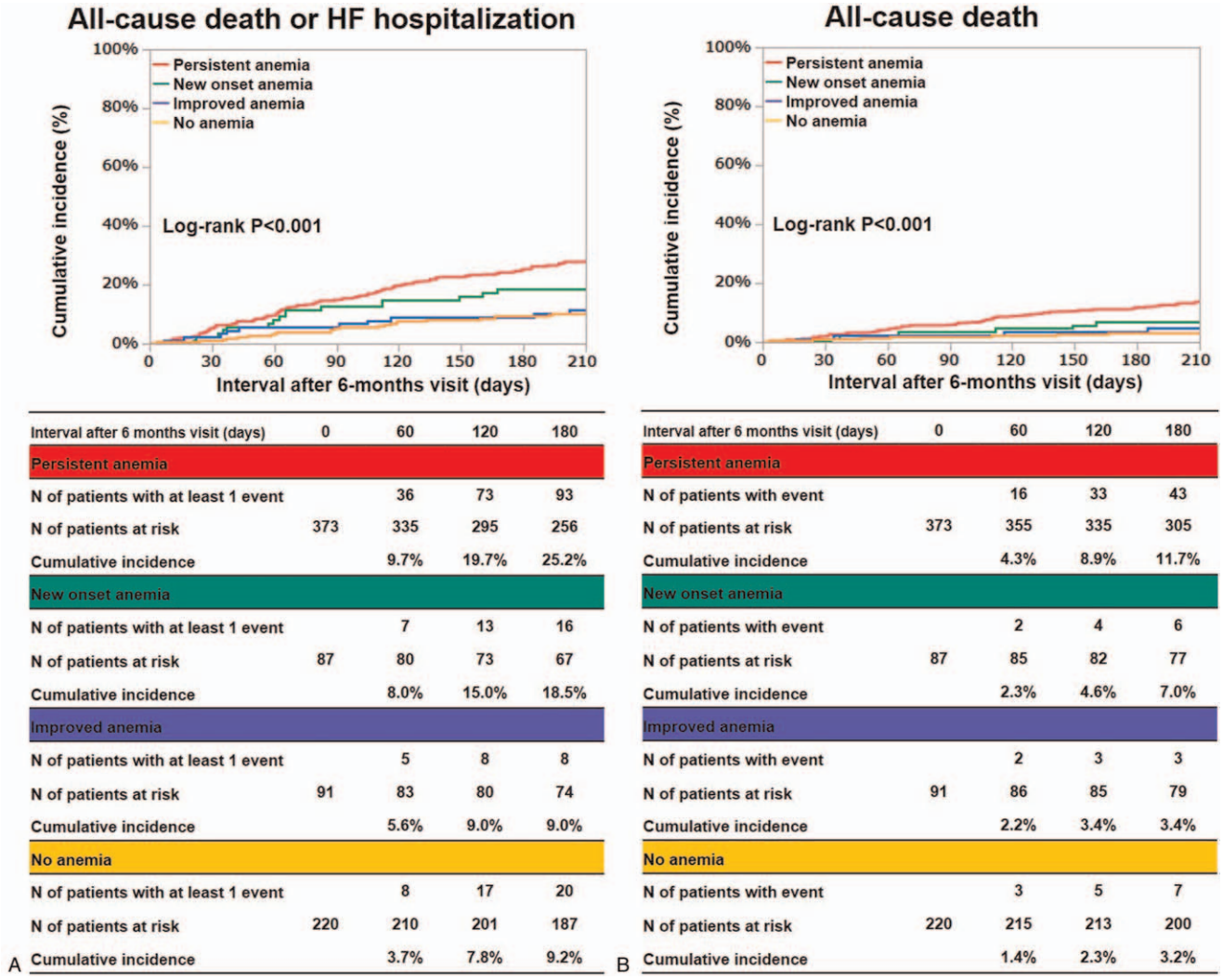


Figure 2. Changes in BMI, albumin, BNP, eGFR, and CRP in each group according to the status of anemia. (A) Δ BNP, (B) Δ BMI, (C) Δ Albumin, (D) Δ eGFR, (E) Δ CRP. BMI = body mass index, BNP = brain natriuretic peptide, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, SD = standard deviation.



A	Interval after 6 months visit (days)	0	60	120	180
	Persistent anemia				
	N of patients with at least 1 event		36	73	93
	N of patients at risk	373	335	295	256
	Cumulative incidence		9.7%	19.7%	25.2%
	New onset anemia				
	N of patients with at least 1 event		7	13	16
	N of patients at risk	87	80	73	67
	Cumulative incidence		8.0%	15.0%	18.5%
	Improved anemia				
	N of patients with at least 1 event		5	8	8
	N of patients at risk	91	83	80	74
	Cumulative incidence		5.6%	9.0%	9.0%
	No anemia				
	N of patients with at least 1 event		8	17	20
	N of patients at risk	220	210	201	187
	Cumulative incidence		3.7%	7.8%	9.2%

B	Interval after 6 months visit (days)	0	60	120	180
	Persistent anemia				
	N of patients with event		16	33	43
	N of patients at risk	373	355	335	305
	Cumulative incidence		4.3%	8.9%	11.7%
	New onset anemia				
	N of patients with event		2	4	6
	N of patients at risk	87	85	82	77
	Cumulative incidence		2.3%	4.6%	7.0%
	Improved anemia				
	N of patients with event		2	3	3
	N of patients at risk	91	86	85	79
	Cumulative incidence		2.2%	3.4%	3.4%
	No anemia				
	N of patients with event		3	5	7
	N of patients at risk	220	215	213	200
	Cumulative incidence		1.4%	2.3%	3.2%

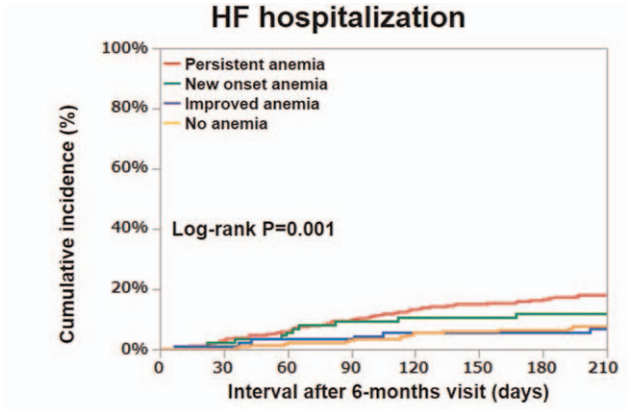
Figure 3. Kaplan–Meier curves for the primary outcome measure, and its individual components. (A) The primary outcome measure: a composite of all-cause death or HF hospitalization, (B) All-cause death, and (C) HF hospitalization. CI = confidence interval, HF = heart failure, HR = hazard ratio.

4.1. Change in hemoglobin levels over time in patients with ADHF

One of the novel findings of our study was that the new-onset anemia after discharge from ADHF was associated with a subsequent increased risk of mortality or HF hospitalization. Our data are in line with previous studies on the decrease in hemoglobin in the stable patients with chronic HF [The Valsartan Heart Failure Trial (Val-HeFT) and the Carvedilol or Metoprolol European Trial (COMET) sub studies].[8,9] Nevertheless, it should be noted in the present study that the magnitude of risk of new-onset anemia was comparable to that of persistent anemia in patients with ADHF regardless of LVEF. In addition, Kajimoto et al[13] reported that in patients hospitalized for ADHF, the anemia status at admission and discharge was associated with subsequent clinical outcomes. The outcomes were different based on the LVEF. In patients with LVEF ≥40%, anemia at discharge was associated with a higher risk, whereas in patients with LVEF <40%, anemia at admission and/or discharge was associated a higher risk for adverse events.[13] The proposed reason for the differences based on LVEF was that the ideal hemoglobin level to target and the prognostic value of hemoglobin might differ between patients with a preserved or a reduced ejection fraction.[13] In the present analyses comparing the anemia at discharge and 6-month visit, the new-onset anemia was associated with a higher risk for adverse events, but the improved anemia was not. Changes in hemoglobin during hospitalization may reflect the responses of the treatment for fluid retention. In contrast, as most patients were discharged in a condition with relatively improved clinical congestion, we can observe the changes in hemoglobin from the condition under control for HF in the present study and investigate the association of new-onset or improved anemia with the prognosis.

4.2. Mechanism underlying anemia

Our study also revealed the possible mechanism of anemia after discharge in patients with ADHF hospitalization. Previous studies reported that the mechanistic links to the progression of anemia might include erythropoietin production, erythropoietin resistance, hematinic deficiency, fluid overload and hemodilution, kidney dysfunction, change in nutrition status, change in



Interval after 6 months visit (days)	0	60	120	180
Persistent anemia				
N of patients with at least 1 event		21	47	58
N of patients at risk	373	335	295	256
Cumulative incidence		5.8%	13.2%	16.6%
New onset anemia				
N of patients with at least 1 event		5	9	10
N of patients at risk	87	80	73	67
Cumulative incidence		5.8%	10.6%	11.8%
Improved anemia				
N of patients with at least 1 event		3	5	5
N of patients at risk	91	83	80	74
Cumulative incidence		3.4%	5.7%	5.7%
No anemia				
N of patients with at least 1 event		5	12	14
N of patients at risk	220	210	201	187
C Cumulative incidence		2.3%	5.6%	6.5%

Figure 3. Continued

inflammatory status, and change in medications including anticoagulants, antiplatelet agents, ARBs, and β blockers in patients with CHF.[8,9,25–27] Regarding the data at discharge, patients in the persistent anemia and new-onset anemia groups had a numerically lower BMI, higher BNP level, and a lower albumin and eGFR level. Patients in the persistent anemia group had a numerically higher CRP level. Low albumin reflects hemodilution[28] and might be an early manifestation of the development of a cachexia state with lower BMI and higher CRP.[28–30] Our results might suggest that hemodilution, malnutrition with an inflammation, and renal dysfunction may all lead to the anemia in patients with HF. In addition, we found BNP was decreased in groups with relatively good prognosis, such as the improved anemia and no anemia groups. Albumin was numerically less increased in the new-onset anemia group and numerically more increased in the improved anemia group than the no anemia group. Consequently, the improvement anemia including the maintenance of normal hemoglobin reflects good clinical course from discharge to the 6-month visit and this good clinical course is associated with subsequent favorable outcomes. The use of β blockers and ARBs were reported to be associated with decrease in hemoglobin.[8,9] However, we could not find the adverse impact of β blockers and ARBs on anemia, because their prescription rates were not high in patients with anemia at either discharge or 6-month visit in our study. In addition, β blockers are less likely to be given in patients in the persistent anemia group. Diuretics were more likely to be given patients in the persistent anemia and new-onset anemia groups. This finding was consistent with previous studies in chronic HF with reduced LVEF.[8,9] However, there are many variables that are hard to address all in the etiology of anemia. Anemia in HF is multifactorial and the association with adverse outcomes post hospital discharge could be an indirect relationship.

Antiplatelet agents may cause anemia with iron loss due to visible or concealed breeding,[31] which were more likely to be given in patients in the persistent anemia and the improved anemia groups. On the contrary, patients in the persistent anemia group were less likely to be given oral anticoagulants at discharge, despite of the presence of atrial fibrillation. Oral anticoagulants might have been avoided in patients with anemia in our study, as the patients have a higher risk of bleeding, such as a lower BMI and a higher prevalence of renal dysfunction.[32,33]

4.3. Treatment of anemia in HF

Previous randomized controlled studies showed that treatment of anemia with iron[34] and hematopoietic agents such as erythropoietin[35,36] and darbepoetin alfa[37,38] improve cardiac function, a decrease in diuretic dose and exercise tolerance, but did not improve clinical outcomes in patients with CHF. Moreover, other studies reported that increases in hemoglobin might elevate systemic vascular resistance.[39,40] Thus, targeting the hemoglobin levels for the treatment of heart failure is not adopted in the current guidelines.[23,41,42] However, avoiding severe anemia is commonly recommended in the current guidelines.[23,41,42] In the present study, we showed the outcomes in patients with improvement of anemia during 6-month were comparable with normal group. This may be the consequence of the successful treatment during 6-month. Thus, assessing the direction of the change in hemoglobin levels is useful for assessing the quality of the treatment in a given patient. Further studies are required to understand the basis of the remarkable association of anemia in patients with HF and clinical outcomes, to assess the potential benefit of improved anemia, and to evaluate the ideal hemoglobin value in each patient.

4.4. Limitations

This study had several limitations. First, laboratory test at 6-month visit was not available in a substantial proportion of patients. Very advanced age of the longitudinal follow-up study population might be one of the reasons for the low rate of laboratory test at 6 months. In addition, data on the post-discharge drugs were also not available in a substantial proportion of patients, because of the lack of detailed information from the general practitioners who were in charge of the patients. Second, the observational study design is subject to selection bias and residual confounding. The KCHF registry had comprehensive data on patient characteristics. By adjusting for 9 variables, we accounted for most conceivable confounders. Nevertheless, residual unmeasured confounding could affect the results. Third, this study excluded some population groups (acute coronary syndrome, end-stage renal failure such as serum creatinine >3.0 or end-stage renal disease). It may cause selection

Table 2

Crude and adjusted clinical outcomes.

	Persistent anemia N of patients with event/N of patients at risk (Cumulative 6-month incidence [%])	New onset anemia N of patients with event/N of patients at risk (Cumulative 6-month incidence [%])	Improved anemia N of patients with event/N of patients at risk (Cumulative 6-month incidence [%])	No anemia N of patients with event/N of patients at risk (Cumulative 6-month incidence [%])		Unadjusted		Adjusted	
					Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
Primary outcome measure									
A composite of all-cause death or HF hospitalization	93/373 (25.2)	16/87 (18.5)	8/91 (9.0)	20/220 (9.2)	Persistent anemia	3.05 (1.96–4.95)	<.001	2.70 (1.45–5.44)	.001
					New-onset anemia	1.95 (1.01–3.69)	.048	2.73 (1.19–6.25)	.02
					Improved anemia	1.14 (0.52–2.35)	.73	1.69 (0.68–4.03)	.25
					No anemia	1 (reference)		1 (reference)	
Secondary outcome measures									
All-cause death	43/373 (11.7)	6/87 (7.0)	3/91 (3.4)	7/220 (3.2)	Persistent anemia	4.46 (2.17–10.80)	<.001	4.25 (1.40–18.54)	.009
					New-onset anemia	2.20 (0.71–6.63)	.17	3.41 (0.80–17.17)	.10
					Improved anemia	1.42 (0.37–4.71)	.58	2.42 (0.44–13.31)	.29
					No anemia	1 (reference)		1 (reference)	
HF hospitalization	58/373 (16.6)	10/87 (11.8)	5/91 (5.7)	14/220 (6.5)	Persistent anemia	2.54 (1.50–4.55)	<.001	2.32 (1.12–5.31)	.02
					New-onset anemia	1.68 (0.73–3.64)	.21	2.20 (0.77–6.01)	.13
					Improved anemia	0.94 (0.34–2.29)	.90	1.44 (0.48–4.05)	.50
					No anemia	1 (reference)		1 (reference)	

CI = confidence interval, HF = heart failure, HR = hazard ratio.

bias and may hamper the validity and generalizability of the study. Fourth, follow-up laboratory test period in this study was set at 6 months after discharge, but our study did not provide the data regarding the optimal time interval for follow-up. Fifth, we did not have information about the etiology of anemia, the urine output, and the complete set of the volume status. Sixth, it is unknown whether anemia has progressed after 6-month visit.

5. Conclusion

Persistent and new-onset anemia were associated with a higher risk for all-cause death or HF hospitalization in patients after discharge from ADHF, suggesting the importance of assessing hemoglobin at discharge and during follow-up.

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