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Clinical impact of red blood cell transfusion on adverse clinical events in acute heart failure patients with anemia

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ABSTRACT

Background: Anemia has been recognized as an important comorbidity in patients with acute heart failure (AHF) and is associated with adverse clinical events. However, the clinical impact of red blood cell (RBC) transfusion in such patients is unclear.
Method: This study was a retrospective single-center registry including AHF patients admitted to Kyorin University Hospital between 2007 and 2014. Anemia was defined as a hemoglobin level < 130 g/L in males or < 120 g/L in females. Those with major bleeding with a fall in hemoglobin concentration of >20 g/L were excluded. AHF readmission at 3 months and in-hospital and 2-year all-cause mortality were evaluated.
Results: Of 501 AHF patients, 38 were excluded owing to major bleeding; finally, 463 (age, 77 ± 11 years; males, 58%) were evaluated. RBC transfusion during hospitalization was performed in 112 patients (24%). Hemoglobin level on admission was 105 ± 16 g/L (transfusion, 89 ± 17 g/L; no transfusion, 110 ± 12 g/L; $p < 0.001$). AHF readmission at 3 months and in-hospital and 2-year all-cause mortality were observed in 46 (10%), 16 (3%), and 121 (26%) patients, respectively. Univariate Cox regression analysis demonstrated that RBC transfusion was not associated with AHF readmission at 3 months (hazard ratio: 0.80; 95% confidence interval: 0.39–1.66) The association did not differ at any hemoglobin concentration or left ventricular ejection fraction value. Multivariate Cox regression analysis revealed similar results. Furthermore, RBC transfusion was not correlated with in-hospital and 2-year all-cause mortality.
Conclusions: RBC transfusion was not associated with AHF readmission or all-cause mortality.

1. Introduction

Anemia has been recognized as an important comorbidity in patients with congestive heart failure; its prevalence varies from 30% to 55% [1–3]. Anemia is associated with adverse clinical events such as mortality and readmission [3–5]. Ferro therapy for heart failure patients with iron-deficiency anemia was not noted to reduce long-term mortality, but it improved the 6-min walk test and quality-of-life assessments [6]. A previous study demonstrated that ferro therapy might be associated with a reduction in the risk of hospitalization for worsening heart failure [7]. Darbepoetin alfa, an erythropoiesis-stimulating agent, was expected to improve prognosis; however, the therapy did not improve clinical outcomes in patients with systolic heart failure and mild-to-moderate anemia [8]. Rather, such agents may be associated with serious adverse effects. It is unclear whether anemia itself affects the clinical outcomes or the cause of anemia does. Indeed, the clinical implication of transfusion in acute heart failure (AHF) patients with anemia has not been investigated. AHF readmission has recently attracted attention because repeat hospitalization is related to the increased costs of health care and early readmission contributes to the subsequent worse outcomes [9,10]. Therefore, assessment of AHF readmission is important as well as mortality. The present study aimed to elucidate the clinical impact of transfusion of red blood cell (RBC) on AHF readmission and mortality in patients with AHF and anemia.

2. Material and methods

2.1. Study population

The study was a single-center, retrospective registry study. AHF patients with anemia who admitted to Kyorin University Hospital between 2007 and 2014 were included. Based on Framingham criteria, a diagnosis of AHF was defined as rapid–onset heart failure, new or worsening signs, and symptoms of heart failure requiring urgent

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therapy and hospitalization [11]. According to the definition provided by the World Health Organization, anemia was defined as a hemoglobin level < 130 g/L in males or < 120 g/L in females [12]. Patients with acute coronary syndrome were excluded owing to different pathophysiology as compared with the other etiologies. Furthermore, those with major bleeding were excluded because the comorbidity could strongly affect the prognosis and such patients usually need RBC transfusion.

2.2. Indication for RBC transfusion

Because the present study was a retrospective study, the definitive indication was not determined beforehand, but was based on each cardiologist's discretion. Many cardiologists determined the need for RBC transfusion based on the so-called 10/30 rule [13]; namely, transfusing patients with a hemoglobin level of under 100 g/L and a hematocrit value of under 30%.

2.3. Data collection

Data on patient background (including age, sex, body mass index, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, chronic obstructive pulmonary disease, history of heart failure and stroke, vital signs, New York Heart Association (NYHA) classification, the etiology of AHF, laboratory data, left ventricular ejection fraction [LVEF] medication, and device therapy), and outcomes (all-cause mortality and AHF readmission) were collected. The causes of anemia were surveyed in those who received RBC transfusion. The patients were classified into 3 groups according to the LVEF as follows: heart failure with reduced ejection fraction (HFrEF), defined as LVEF < 40%; heart failure with mid-range EF (HFmrEF), LVEF ≥ 40% and < 50%; and heart failure with preserved EF (HFpEF), LVEF ≥ 50% [14].

2.4. Endpoints

Readmission for AHF at 3 months was evaluated as the primary endpoint. Readmission was determined based on each cardiologist's discretion. The secondary endpoints were in-hospital and 2-year all-cause mortality.

2.5. Ethical statement

This study protocol conforms to the 1975 Declaration of Helsinki [15] and is in line with the Ethical Guidelines for Epidemiological Research established by the Japanese government. The study was approved by the ethics committee at our institution. According to the guidelines, the study satisfied the conditions to waive the requirement for informed consent from individual participants. Therefore, informed consent was waived, which was approved by the ethics committee.

2.6. Statistical analysis

Numerical data are presented as mean ± standard deviation if the data followed a normal distribution. Otherwise, data are displayed as median and interquartile range (Q1–Q3) values. Categorical variables are expressed as absolute numbers or percentages. Continuous variables were analyzed using unpaired Student's *t*-tests or Mann–Whitney *U* tests, while Fisher's exact test or the chi-squared test was used for categorical variables. In-hospital all-cause mortality was assessed using uni- and multivariate logistic regression analyses and expressed as odds ratio (OR), 95% confidence interval (CI), and *p*-value. The cumulative incidence of 3-month AHF readmission was assessed using the Kaplan-Meier estimated curve with log-rank test. The risks of 3-month AHF readmission and 2-year all-cause mortality were assessed using Cox regression analysis and expressed as hazard ratio (HR), 95% CI, and *p*-value. Variables with a *p*-value < 0.10 in univariate analysis were retained for the multivariate logistic or Cox regression analysis with least absolute shrinkage and selection operator. Statistical significance was defined as $p < 0.05$. All statistical analyses were carried out using Stata version 14 (Stata Corp; College Station,

Table 1
Patient characteristics.

	All	Transfusion	No transfusion	*p* value
	n = 463	n = 112	n = 351	
Age, years	77 ± 11	78 ± 11	77 ± 11	0.795
Male, n (%)	268 (58)	55 (49)	213 (61)	0.031
Body mass index, kg/m^2	21 ± 4	20 ± 3	21 ± 4	0.020
Hypertension, n (%)	332 (72)	77 (69)	255 (73)	0.400
Dyslipidemia, n (%)	165 (36)	44 (39)	121 (35)	0.375
Diabetes mellitus, n (%)	181 (39)	45 (40)	136 (39)	0.787
Atrial fibrillation, n (%)	161 (35)	34 (30)	127 (36)	0.260
Medical history of heart failure, n (%)	123 (27)	36 (32)	87 (25)	0.089
Medical history of ischemic stroke, n (%)	69 (15)	20 (18)	49 (14)	0.360
COPD, n (%)	41 (9)	6 (5)	35 (10)	0.180
Hemodialysis, n (%)	40 (9)	12 (11)	28 (8)	0.439
Ischemic heart failure, n (%)	139 (30)	32 (29)	107 (30)	0.701
NYHA classification on admission ≥ III, n (%)	412 (89)	103 (92)	309 (88)	0.300
NYHA classification at discharge ≥ III, n (%)	171 (37)	48 (43)	123 (35)	0.136
Laboratory data on admission				
Sodium, mmol/L	139 ± 4	138 ± 5	139 ± 4	0.002
Potassium, mmol/L	4.3 ± 0.7	4.3 ± 0.7	4.3 ± 0.7	0.864
Creatinine, μmol/L	106 (75–179)	124 (80–248)	105 (72–159)	0.009
eGFR, ml/min/m^2	40 (23–58)	29 (16–52)	43 (26–60)	<0.001
Hemoglobin, g/L	105 ± 16	89 ± 17	110 ± 12	<0.001
Albumin, g/L	3.5 ± 0.5	3.3 ± 0.5	3.5 ± 0.5	0.036
Laboratory data at discharge				
Sodium, mmol/L	138 ± 6	137 ± 11	138 ± 4	0.041
Potassium, mmol/L	4.4 ± 0.6	4.4 ± 0.6	4.4 ± 0.6	0.974
Creatinine, μmol/L	115 (80–194)	124 (80–256)	111 (80–177)	0.047
eGFR, ml/min/m^2	38 (22–55)	29 (16–54)	39 (25–56)	0.010
Hemoglobin, g/L	110 ± 15	104 ± 13	112 ± 15	<0.001
Albumin, g/L	3.3 ± 0.6	3.1 ± 0.5	3.3 ± 0.6	<0.001
LVEF, %	49 ± 14	51 ± 14	49 ± 14	0.164
Medication on admission				
Beta blockers, n (%)	181 (39)	33 (29)	148 (42)	0.017
RAS inhibitors, n (%)	187 (40)	46 (41)	141 (40)	0.857
MRA, n (%)	30 (6)	6 (5)	24 (7)	1.000
Furosemide, n (%)	225 (49)	56 (50)	169 (48)	0.682
Tolvaptan, n(%)	6 (1)	1 (1)	5 (1)	1.000
Antiplatelet therapy, n (%)	170 (37)	39 (35)	131 (37)	0.651
Anticoagulation, n (%)	121 (26)	29 (26)	92 (26)	0.418
Medication at discharge				
Beta blockers, n (%)	310 (67)	64 (57)	246 (70)	0.012
RAS inhibitors, n (%)	260 (56)	62 (55)	198 (56)	0.901
MRA, n (%)	127 (27)	33 (29)	94 (27)	0.540
Furosemide, n (%)	353 (76)	82 (73)	271 (77)	0.387
Tolvaptan, n(%)	16 (3)	6 (5)	10 (3)	0.230
Antiplatelet therapy, n (%)	216 (47)	46 (41)	170 (48)	0.189
Anticoagulation, n (%)	183 (40)	37 (33)	146 (42)	0.154
Devices				
PMI, n (%)	57 (12)	13 (12)	44 (13)	0.870
ICD, n (%)	12 (3)	2 (2)	10 (3)	0.739
CRT, n (%)	6 (1)	2 (2)	4 (1)	0.636

COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PMI, pacemaker implantation; RAS, renin-angiotensin system.

TX, USA) and R version 3.4.3 (R Foundation for Statistical Computing; Vienna, Austria).

3. Results

3.1. Patient characteristics

The present study included 463 patients (age, 77 ± 11 years; males, 58%). Of them, 112 (24%) received RBC transfusion. The patient characteristics are shown in Table 1. Hemoglobin level on admission was 105 ± 16 g/L (transfusion, 89 ± 17 g/L; no transfusion, 110 ± 12 g/L; $p < 0.001$). In comparison, the value at discharge was 110 ± 15 g/L (transfusion, 104 ± 13 g/L; no transfusion, 112 ± 15 g/L; $p < 0.001$).

3.2. The causes of anemia in patients with RBC transfusion

Of 112 patients who received RBC transfusion, renal anemia was observed in 29 patients; iron deficiency anemia, 18 patients; hematopoietic disorders, 15; dilution owing to congestion, 4; liver cirrhosis, 2; unknown, 44.

3.3. Clinical impact of RBC transfusion on 3-month heart failure readmission

The median follow-up was 719 (190–1082) days. AHF readmission at 3 months occurred in 46 (10%) (transfusion, 9 (8%); no transfusion, 37 (11%)). RBC transfusion was not associated with 3-month AHF readmission (unadjusted HR, 0.80; 95% CI, 0.39–1.66; $p = 0.546$). The Kaplan-Meier curve is shown in Fig. 1. The result was similar among those with HFrEF, HFmrEF, and HFpEF (HFrEF [n = 119]: unadjusted HR, 0.66; 95% CI, 0.15–2.85; $p = 0.574$; HFmrEF [n = 97]: unadjusted HR, 3.10; 95% CI, 0.77–12.40; $p = 0.110$; HFpEF [n = 247]: unadjusted HR, 0.50; 95% CI, 0.15–1.69; $p = 0.262$) as well as even in patients with a hemoglobin level of <100 g/L on admission (unadjusted HR, 0.61; 95% CI, 0.22–1.69; $p = 0.342$) or with a hemoglobin level of <100 g/L at discharge (unadjusted HR, 1.01; 95% CI, 0.33–3.10; $p = 0.981$). These results persisted after adjustment.

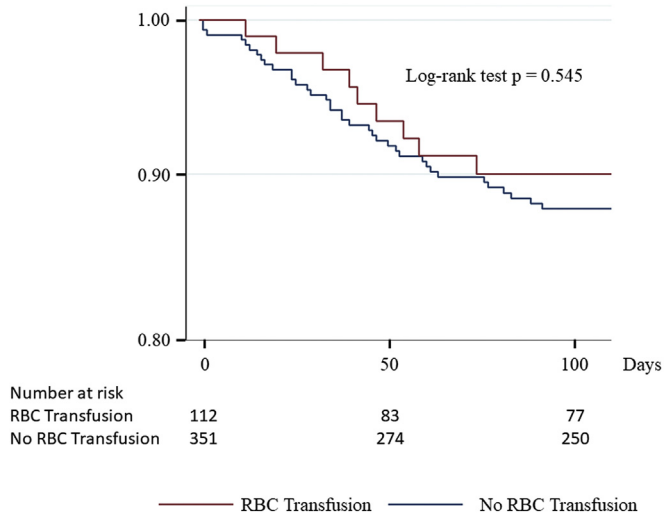

Fig. 1. Kaplan-Meier estimated survival curve. The survival curve demonstrated no association of RBC transfusion with 3-month acute heart failure readmission. RBC, red blood cell. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.4. Predictors for 3-month AHF readmission

The results of uni- and multivariate Cox regression analyses are shown in Table 2. Multivariate Cox regression analysis demonstrated that hemoglobin level and LVEF were related to AHF-related readmission (hemoglobin level: adjusted HR in an increase of 10 g/L, 0.80; 95% CI, 0.64–0.99; $p = 0.038$; LVEF: adjusted HR in an increase of 10%, 0.80; 95% CI, 0.65–0.98; $p = 0.033$), while RAS inhibitors and furosemide tended to be associated with the adverse event (RAS inhibitors: adjusted HR 0.58; 95% CI, 0.32–1.04; $p = 0.065$; furosemide: adjusted HR, 2.51; 95% CI, 0.98–6.41: $p = 0.054$).

3.5. In-hospital and 2-year all-cause mortality

In-hospital and 2-year all-cause mortality occurred in 16 (3%) (transfusion, 7 (6%); no transfusion, 9 (3%)) and 121 (26%) (transfusion, 27 (26%); no transfusion, 94 (27%)) patients. Notably, 110 patients (91% of all-cause mortality) had a non-cardiac death. RBC transfusion was related to neither in-hospital mortality (OR, 2.53; 95% CI, 0.92–6.97;

Table 2
Cox regression analysis for heart failure readmission.

	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Age (an increase of 1 year)	1.00	0.98–1.03	0.755	NA		
Male	0.95	0.53–1.71	0.866	NA		
BMI (an increase of 1 kg/m^2)	0.92	0.84–1.00	0.048	NA		
Hypertension	0.65	0.35–1.17	0.151	NA		
Dyslipidemia	0.69	0.36–1.32	0.263	NA		
Diabetes mellitus	1.17	0.66–2.10	0.590	NA		
Atrial fibrillation	1.28	0.71–2.32	0.413	NA		
Medical history of heart failure	1.23	0.64–2.35	0.532	NA		
Medical history of ischemic stroke	0.92	0.39–2.17	0.852	NA		
COPD	0.45	0.11–1.86	0.272	NA		
Hemodialysis	0.25	0.04–1.85	0.176	NA		
Ischemic heart failure	0.91	0.48–1.74	0.785	NA		
NYHA classification at discharge ≥III	1.41	0.78–2.56	0.251	NA		
Transfusion	0.80	0.39–1.66	0.546	NA		
Laboratory data at discharge						
Creatinine (an increase of 20 μmol/L)	0.97	0.93–1.01	0.161	NA		
eGFR (an increase of 10 mL/min/m^2)	1.05	0.94–1.16	0.405	NA		
Hemoglobin (an increase of 10 g/L)	0.82	0.67–1.01	0.065	0.80	0.64–0.99	0.038
Albumin (an increase of 10 g/L)	1.44	0.87–2.36	0.154	NA		
LVEF (an absolute increase of 10%)	0.83	0.68–1.02	0.079	0.80	0.65–0.98	0.033
Medication at discharge						
Beta blockers	1.46	0.74–2.87	0.274	NA		
RAS inhibitors	0.58	0.33–1.04	0.066	0.58	0.32–1.04	0.065
MRA	0.77	0.39–1.53	0.461	NA		
Furosemide	2.23	0.88–5.63	0.091	2.51	0.98–6.41	0.054
Tolvaptan	2.21	0.69–7.13	0.184	NA		
Antiplatelet therapy	1.12	0.63–2.00	0.694	NA		
Anticoagulation	1.13	0.63–2.02	0.678	NA		
Devices						
PMI	1.34	0.62–2.87	0.455	NA		
ICD	0.81	0.11–5.90	0.838	NA		
CRT	1.39	0.19–10.05	0.747	NA		

CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, not applicable; NYHA, New York Heart Association; PMI, pacemaker implantation; RAS, renin-angiotensin system.

$p = 0.072$) nor 2-year mortality (HR, 1.05; 95% CI, 0.68–1.61; $p = 0.832$). These results were similar after multivariate analyses.

3.6. Predictors for all-cause mortality

Each predictor is shown in Table 3. Multivariate logistic regression analysis disclosed that age, body mass index, and hemodialysis were related to in-hospital mortality. Multivariate Cox regression analysis demonstrated that age, NYHA classification at discharge, albumin level, and left ventricular ejection fraction were related to two-year mortality.

4. Discussion

To the best of our knowledge, the present study is the first to state that RBC transfusion is associated with neither reduction of AHF readmission nor all-cause mortality. It is noteworthy that the treatment for anemia is not correlated with such outcomes while the anemia itself is associated with adverse events [3–5]. Etiologies of anemia vary; it may occur along with worsened general condition in some cases. The conditions that induce anemia, not the reduction in the hemoglobin level, may contribute to clinical adverse events.

4.1. Is anemia a cause of clinical adverse events or a surrogate marker?

The elderly population generally demonstrates various causes of anemia, including nutrition deficiencies, chronic kidney disease, chronic inflammation, and hematologic diseases such as myelodysplastic syndrome [16], all of which can induce AHF. In AHF patients, inflammatory cytokines such as tumor necrosis factor-α and interleukin-6 are released, which can lead to anemia [17,18]. Namely, both AHF itself and its potential causative factors may contribute to anemia. Notably, the prevalence of iron deficiency was lower than the one in previous studies. [19] This finding might be observed because most patients were not obesity, which contributes to iron deficiency through inflammation. [20] Further, relatively low BMI might reflect wasting diseases and cardiac cachexia related to anemia. Indeed, nearly half of the patients who underwent RBC transfusion had renal anemia or hematopoietic disorders in our study.

Table 3
Analysis for in-hospital and 2-year all-cause mortality.

	In-hospital mortality						2-year all-cause mortality					
	Univariate			Multivariate			Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (an increase of 1 year)	1.07	1.00–1.14	0.052	1.09	1.01–1.18	0.023	1.04	1.01–1.06	0.001	1.04	1.01–1.06	0.001
Male	1.63	0.56–4.76	0.375	NA			1.27	0.87–1.86	0.208	NA		
BMI (an increase of 1 kg/m^2)	0.81	0.68–0.95	0.012	0.82	0.68–0.99	0.042	0.96	0.91–1.00	0.075	NA		
Hypertension	0.64	0.23–1.80	0.400	NA			1.01	0.68–1.49	0.971	NA		
Dyslipidemia	1.20	0.42–3.44	0.730	NA			0.84	0.57–1.23	0.363	NA		
Diabetes mellitus	0.93	0.33–2.61	0.894	NA			0.72	0.49–1.04	0.082	NA		
Atrial fibrillation	1.13	0.40–3.17	0.816	NA			1.27	0.88–1.83	0.208	NA		
Medical history of heart failure	4.69	1.67–13.20	0.003	NA			0.77	0.50–1.19	0.243	NA		
Medical history of ischemic stroke	1.33	0.37–4.80	0.661	NA			1.12	0.69–1.81	0.645	NA		
COPD	2.47	0.67–9.06	0.172	NA			1.89	1.06–3.37	0.032	NA		
Hemodialysis	5.35	1.76–16.27	0.003	10.27	2.72–38.78	0.001	1.23	0.64–2.35	0.539	NA		
Ischemic heart failure	1.42	0.50–3.98	0.508	NA			0.96	0.64–1.42	0.823	NA		
NYHA classification at discharge ≥ III	NA*			NA			1.72	1.19–2.50	0.004	1.46	1.00–2.16	0.057
Transfusion	2.53	0.92–7.00	0.072	NA			1.05	0.68–1.61	0.832	NA		
Laboratory data at discharge												
Creatinine (an increase of 20 μmol/L)	1.04	1.01–1.08	0.015	NA			1.01	0.99–1.03	0.328	NA		
eGFR (an increase of 10 ml/min/m^2)	0.72	0.56–0.94	0.015	NA			0.93	0.86–1.00	0.058	NA		
Hemoglobin (an increase of 10 g/L)	1.03	0.75–1.41	0.871	NA			0.96	0.85–1.09	0.536	NA		
Albumin (an increase of 10 g/L)	0.16	0.04–0.69	0.014	NA			0.47	0.33–0.67	<0.001	0.49	0.34–0.71	<0.001
LVEF (an absolute increase of 10%)	1.04	0.68–1.58	0.866	NA			0.88	0.78–0.99	0.047	0.84	0.74–0.96	0.012
Medication on admission												
Beta blockers	0.67	0.23–1.97	0.467	NA			NA			NA		
RAS inhibitors	0.84	0.30–2.36	0.743	NA			NA			NA		
MRA	NA			NA			NA			NA		
Furosemide	1.72	0.61–4.82	0.301	NA			NA			NA		
Tolvaptan	NA*			NA			NA			NA		
Antiplatelet therapy	1.30	0.48–3.56	0.607	NA			NA			NA		
Anticoagulation	0.80	0.23–2.78	0.721	NA			NA			NA		
Medication at discharge												
Beta blockers	NA			NA			1.31	0.87–1.97	0.197	NA		
RAS inhibitors	NA			NA			0.71	0.50–1.02	0.065	NA		
MRA	NA			NA			0.91	0.61–1.37	0.659	NA		
Furosemide	NA			NA			1.10	0.70–1.73	0.688	NA		
Tolvaptan	NA			NA			1.55	0.57–4.21	0.392	NA		
Antiplatelet therapy	NA			NA			0.84	0.59–1.20	0.335	NA		
Anticoagulation	NA			NA			1.32	0.92–1.90	0.127	NA		
Devices												
PMI	0.50	0.06–3.87	0.506	NA			1.04	0.63–1.71	0.887	NA		
ICD	10.50	1.94–56.7	0.006	NA			1.63	0.72–3.71	0.245	NA		
CRT	NA*			NA			0.96	0.24–3.88	0.952	NA		

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, not applicable; NYHA, New York Heart Association; OR, odds ratio; PMI, pacemaker implantation; RAS, renin-angiotensin system.

* Owing to no event in either group.

The results of our study imply that the underlying diseases may lead to poor outcomes rather than anemia itself in AHF patients with anemia. Treatment for anemia would improve the oxygen/supply mismatch and may improve hemodynamic, neurohormonal system, and renal alterations [21]. However, such positive effects on the circulatory system may not have contributed to the prognosis in our study, because most patients died due to non-cardiac diseases. Furthermore, anemia may be a result of AHF in some cases; RBC transfusions may be ineffective in such cases. In other clinical settings, such as perioperative anemia in patients undergoing cardiac surgery, RBC transfusions have been associated with higher mortality [22,23]. These results might reflect the fact that the patients' background that made the RBC transfusion necessary was actually a negative predictor, or might demonstrate that the disadvantages of the treatment surpassed its advantages.

4.2. Predictors for short-term heart failure readmission

Higher hemoglobin level and LVEF were significantly associated with a lower incidence of AHF readmission at 3 months. The results in our study regarding hemoglobin level were consistent with those of previous studies [3,4]; the possible reasons have been already described. The association of LVEF with AHF readmission may differ depending on each population, probably owing to its complicated pathophysiology. In patients with and without diabetes mellitus, LVEF was not found to be related to the adverse event. [24] On the other hand, a previous study demonstrated that patients with HFpEF underwent cardiovascular death or rehospitalization more frequently than those with HFrEF [25]; however, other studies disclosed that AHF readmission was less common among those with HFpEF compared to those with HFrEF [26,27].

4.3. Future perspectives

To determine the clinical significance of RBC transfusions, a randomized control study is necessary. Moreover, such studies should be conducted in those with specific causes of anemia and/or a hemoglobin level of <70 g/L. The treatment effects of RBC transfusions would vary in accordance with the etiologies of anemia and the hemoglobin level. The American Association of Blood Banks (AABB) recently recommends a restrictive RBC transfusion threshold in which the transfusion is not indicated until the hemoglobin level is 70 g/L for hospitalized adult patients who are hemodynamically stable [28]. Indeed, the hemoglobin level was >70 g/L in approximately 85% of the RBC transfusion group in the present study. The AABB recommendation would be appropriate in AHF patients with a hemoglobin level of >70 g/L. Until the clinical benefit of the treatment is confirmed, physicians should decide the indications carefully to avoid adverse effects and waste.

4.4. Limitations

We should be careful when interpreting the current results because the study had some limitations. First, retrospective study generally indicates only an association between dependent and independent variables, but does not show causal relationship. The patients who received RBC transfusion might be selected because they appeared to be in a worse state than those without the treatment. Second, the etiologies of anemia were not sufficiently investigated. The prognosis would be different among patients with potential poor predictors such as hematopoietic disease and chronic kidney disease and those with simple conditions such as iron deficiency. Third, the severity of anemia in many patients was not severe. The association of the treatment with prognosis has remained unclear in AHF patients with severe anemia. Finally, we did not evaluate the quality of life or use patient-oriented symptom scales. Similar to ferro therapy for AHF patients with iron-deficiency anemia, RBC transfusion may relieve their symptoms. However, even in this situation, transfusion would be inappropriate with respect to its cost and potential side effects.

5. Conclusions

RBC transfusion was not associated with short-term AHF readmission or with short- and long-term all-cause mortality. The present study might include AHF patients with various etiologies of anemia. Therefore, further studies classified according to specific causes of the morbidity are necessary to confirm the significance of RBC transfusion.

Author statement

Satoshi Higuchi designed the study, analyzed and interpreted data, and drafted manuscript. Noritaka Hata analyzed and interpreted data, revised the manuscript critically for important intellectual content. Shigeki Shibata, Kazukuri Hirabuki, Tomoya Suda, Kazuna Honda, Hiroshi Hasegawa, and Takeaki Matsuda contributed to acquisition of data, and revised the manuscript critically for important intellectual content. Final approval of the manuscript submitted was done by all the authors.

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Declaration of Competing Interest

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