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ORIGINAL ARTICLE

Effective blood hemoglobin level to predict prognosis in heart failure with preserved left ventricular ejection fraction: results of the Japanese heart failure syndrome with preserved ejection fraction registry

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Abstract
High prevalence of anemia in heart failure with preserved left ventricular ejection fraction (HFpEF) has been reported. However, little is known about the association of anemia and gender with prognosis in HFpEF patients. In addition, effective blood hemoglobin (Hb) level for prognosis in HFpEF patients remains largely unknown. In this study, we investigated the association between anemia, gender, and prognosis in 535 HFpEF patients enrolled in Japanese heart failure syndrome with preserved ejection fraction registry. Furthermore, we assessed effective blood Hb level to predict prognosis in HFpEF patients. According to the World Health Organization criteria, the prevalence rate of anemia on admission was about 70% in both male and female HFpEF patients. Kaplan–Meier analysis for all-cause mortality demonstrated that anemic patients had poor prognosis compared with non-anemic patients in both male and female HFpEF patients. Interestingly, multivariate analysis revealed that blood Hb level at discharge was an independent predictor of all-cause mortality in both male and female HFpEF patients. According to survival classification and regression tree analysis, blood Hb level at discharge of 9.4 g/dL for male and 12.3 g/dL for female was more accurate cutoff value to predict all-cause mortality in HFpEF patients. Anemia was implicated in poor prognosis in both male and female HFpEF patients. In particular, blood Hb level at discharge was an independent predictor of all-cause mortality in both male and female HFpEF patients. Effective cutoff value of blood Hb level at discharge to predict all-cause mortality was lower in male than in female HFpEF patients.

Keywords Anemia · Hemoglobin · Heart failure with preserved left ventricular ejection fraction

Introduction

Anemia is a frequent finding in patients with heart failure (HF), regardless of whether left ventricular ejection fraction is preserved or reduced [1–3]. In addition, anemia has been reported to be associated with poor prognosis in patients with HF [4–6].

Although several factors such as hemodilution and iron deficiency are associated with anemia in HF [7, 8], the etiology of anemia in HF remains largely unknown. Renal insufficiency is one of the contributing factors of anemia in HF, and the interaction among HF, anemia, and chronic kidney disease is called as cardio-renal anemia syndrome [9].

A previous report has shown that the prevalence of anemia is higher in HF with preserved left ventricular ejection fraction (HFpEF) than in HF with reduced left ventricular

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ejection fraction [10]. However, little is known about the association between anemia, gender, and prognosis in HFpEF patients. In addition, effective blood hemoglobin (Hb) level for prognosis in HFpEF patients has been largely unknown. In this study, we investigated the association between anemia, gender, and prognosis in 535 HFpEF patients enrolled in Japanese heart failure syndrome with preserved ejection fraction (JASPER) registry [11]. Furthermore, we assessed effective blood Hb level to predict all-cause mortality in these HFpEF patients.

Methods

Study design

The JASPER registry is a multicenter, observational, prospective cohort that includes patients aged 20 and above requiring hospitalization with a diagnosis of acute HF according to the Framingham criteria [12] by at least two experienced cardiologists, with preserved left ventricular systolic function defined as left ventricular ejection fraction ≥ 50% with the modified Simpson method or left ventricular fractional shortening ≥ 25% by echocardiography. Patients with acute coronary syndrome, receiving hemodialysis, severe aortic or mitral valvular disease, or with a history of heart transplantation were excluded. The patients' demographic data including co-morbid conditions, clinical signs, laboratory, and echocardiographic data, in-hospital treatment including oral and intravenous medication, and length of hospital stay were obtained. Echocardiography and blood examination were performed on admission and at discharge. Anemia was defined according to the World Health Organization (WHO) criteria (blood Hb level < 13 g/dL in male, blood Hb level < 12 g/dL in female) [13]. Follow-up was performed at discharge, 12 months after discharge, and 24 months after discharge by direct contact with patients or their physicians at the hospital or outpatient clinic, telephone interview of patients or, if deceased, of family members, and mail, by dedicated coordinators and investigators. In this study, because patient information was anonymized and de-identified prior to analyzes, written informed consent was not obtained from each patient. However, we publicized the study by posting a summary of the protocol (with an easily understood description) on the website of the National Cerebral and Cardiovascular Center; the notice clearly informed patients of their right to refuse enrollment. These procedures for informed consent and enrolment were in accordance with the detailed regulations regarding informed consent described in the guidelines, and this study, including the procedure for enrolment, has been approved by the Institutional Review Board of each site, and registered under the Japanese UMIN Clinical Trials Registration (UMIN000010601).

Statistical analysis

Continuous variables were presented as mean ± standard deviation when normally distributed, and as median and interquartile range (IQR) when non-normally distributed. Continuous variables were compared using an unpaired *t* test. Categorical variables were made by Chi-squared test or Fisher's exact test for dichotomous variables, when appropriate. The correlations of blood Hb level with estimated glomerular filtration rate (eGFR) were assessed by Pearson correlation analysis. The cumulative incidence of the composite of all-cause mortality and HF rehospitalization was estimated using Kaplan–Meier analysis. The associations of parameters with all-cause mortality and HF rehospitalization were assessed by Cox proportional hazards regression analysis. Multivariate analysis was performed using covariates which were related to all-cause mortality and HF rehospitalization. Particularly, to investigate the impacts of cardio-renal anemia syndrome on the prognosis, covariates which were closely related to cardio-renal anemia syndrome (age, past hospitalization of HF, blood Hb level, and eGFR) were chosen in this study. Moreover, to evaluate the most effective cutoff value of blood Hb level at discharge, we used a survival classification and regression tree (CART) analysis. All tests were two-tailed, and a value of $p < 0.05$ was considered statistically significant. All analyzes were performed with R version 3.3.2.

Results

Patient characteristics

The baseline characteristics on admission are described in Table 1. According to the WHO criteria, 72% patients have anemia in all HFpEF patients. The prevalence rate of anemia was 74% in male patients and 70% in female patients (Fig. 1).

As shown in Table 1, patients with anemia were older (79.3 versus 74.0 years, $p < 0.001$), with lower systolic blood pressure (148 versus 159 mmHg, $p < 0.001$), and lower heart rate (80 versus 99 beats/min, $p < 0.001$) compared to patients without anemia. Anemic patients had higher prevalence of hypertension (80.3% versus 70.3%, $p = 0.013$), diabetes mellitus (42.2% versus 27.9%, $p = 0.002$), old myocardial infarction (15.0% versus 5.5%, $p = 0.002$), and past hospitalization of HF (42.0% versus 26.0%, $p = 0.001$) compared with non-anemic patients. There was no difference in gender, New York Heart Association (NYHA) functional class, Body Mass

Table 1 Baseline characteristics of study patients on admission

	Anemia (−) ($n=149$)	Anemia (+) ($n=386$)	p value
Age (years)	74.0 ± 11.8	79.3 ± 9.7	< 0.001
Male, *n* (%)	69 (46.3)	199 (51.6)	0.277
Systolic BP (mmHg)	159 ± 42	148 ± 33	< 0.001
Heart rate (beats/min)	99 ± 32	80 ± 25	< 0.001
NYHA functional class, I/II/III/IV, *n*	1/38/45/60	3/72/167/127	0.922
Body Mass Index	24.3 ± 4.5	23.7 ± 4.7	0.252
Hypertension, *n* (%)	104 (70.3)	309 (80.3)	0.013
Diabetes mellitus, *n* (%)	41 (27.9)	163 (42.2)	0.002
Atrial fibrillation, *n* (%)	91 (61.5)	238 (62.5)	0.835
OMI, *n* (%)	8 (5.5)	58 (15.0)	0.002
Aortic regurgitation, I/II/III/IV, *n*	31/12/3/0	103/26/12/0	0.271
Mitral regurgitation, I/II/III/IV, *n*	61/24/8/0	122/91/28/0	0.131
Past hospitalization for HF, *n* (%)	38 (26.0)	156 (42.0)	0.001
eGFR (mL/min/1.73m^2)	63.9 ± 27.6	44.1 ± 22.8	< 0.001
Hemoglobin (g/dL)	13.9 ± 1.3	10.2 ± 1.5	< 0.001
Albumin (g/dL)	3.8 ± 0.5	3.6 ± 0.4	< 0.001
HbA1c (%)	6.2 ± 1.1	6.1 ± 1.0	0.370
Median BNP (IQR) (pg/mL)	366 (212–573)	431 (235–697)	0.097
LV posterior wall thickness (mm)	11 ± 2.2	10 ± 2.0	0.020
LV end-diastolic dimension (mm)	45 ± 7.1	47 ± 6.5	< 0.001
LAD (mm)	44 ± 8.1	46 ± 9.6	0.015
TRPG (mmHg)	33 ± 11	38 ± 13	< 0.001
E/*e*′	18 ± 9.2	20 ± 9.4	0.091
LV ejection fraction (%)	59 ± 8.4	60 ± 8.0	0.272
β-Blockers, *n* (%)	53 (35.6)	179 (46.4)	0.025
ACE inhibitors, *n* (%)	16 (10.7)	79 (20.5)	0.008
ARBs, *n* (%)	57 (38.3)	168 (43.5)	0.269
Ca antagonists, *n* (%)	67 (45.0)	207 (53.6)	0.072
Loop diuretics, *n* (%)	51 (34.2)	226 (58.5)	< 0.001
Vitamin K antagonists, *n* (%)	41 (27.5)	169 (43.8)	0.001
NOACs, *n* (%)	13 (8.7)	22 (5.7)	0.205

BP blood pressure, *NYHA* New York Heart Association, *OMI* old myocardial infarction, *HF* heart failure, *eGFR* estimated glomerular filtration rate, *Hemoglobin* blood hemoglobin level, *Albumin* serum albumin level, *BNP* plasma B-type natriuretic peptide level, *IQR* interquartile range, *LV* left ventricular, *LAD* left atrial dimension, *TRPG* tricuspid regurgitation peak gradient, *E*/*e*′ early diastolic mitral inflow velocity/early diastolic mitral annular velocity, *ACE* angiotensin-converting-enzyme, *ARBs* angiotensin II receptor blockers, *NOACs* novel oral anticoagulants

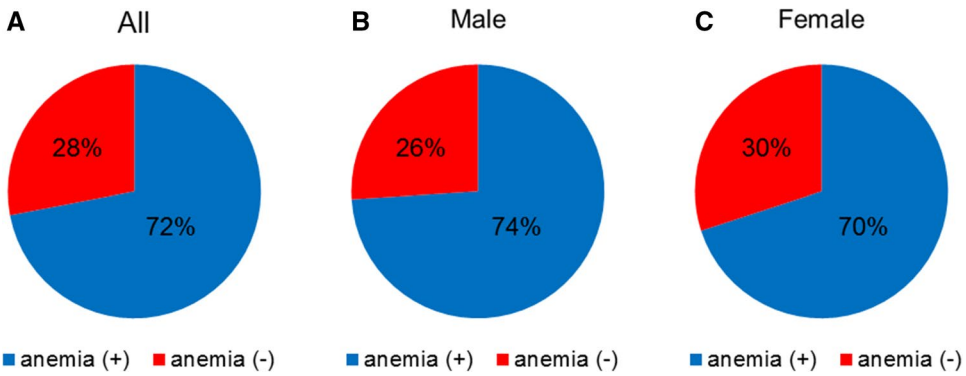

Fig. 1 Prevalence rate of anemia in HFpEF patients. Prevalence rate of anemia in **a** all ($n=535$), **b** male ($n=268$), and **c** female ($n=267$) patients with HFpEF

Index, and prevalence of atrial fibrillation between anemic and non-anemic patients. eGFR and serum albumin level were lower in anemic patients (44.1 versus 63.9 mL/min/1.73m^2, 3.6 versus 3.8 g/dL, respectively; $p < 0.001$) than in non-anemic patients. Of interest, blood Hb level was positively correlated with eGFR in anemic patients but not in non-anemic patients (Fig. 2).

Left ventricular posterior wall thickness was shorter, and left ventricular end-diastolic dimension and left atrial dimension were longer in anemic patients than in non-anemic patients. Tricuspid regurgitation peak gradient was higher and early diastolic mitral inflow velocity/early diastolic mitral annular velocity tended to be higher in anemic patients than in non-anemic patients. On the other hand, plasma b-type natriuretic peptide (BNP) level and left ventricular ejection fraction were similar in anemic and non-anemic patients.

With respect to medications, anemic patients were more frequently treated with β-blockers (46.4% versus 35.6%, $p = 0.025$), angiotensin-converting-enzyme (ACE) inhibitors (20.5% versus 10.7%, $p = 0.008$), loop diuretics (58.5% versus 34.2%, $p < 0.001$), and vitamin K antagonists (43.8% versus 27.5%, $p = 0.001$) compared with non-anemic patients.

Outcomes

During a median follow-up of 23.2 months, 81 patients died. Cardiovascular death occurred in 37 patients, while non-cardiovascular death occurred in 44 patients. Then, we investigated the relation between anemia and prognosis in all HFpEF patients. As shown in Fig. 3, Kaplan–Meier analysis for all-cause mortality and HF rehospitalization showed that anemic patients had worse prognosis compared with non-anemic patients (44.4% versus 31.8%, $p < 0.001$). We then investigated the prognostic impacts of anemia on all-cause mortality and HF rehospitalization by gender.

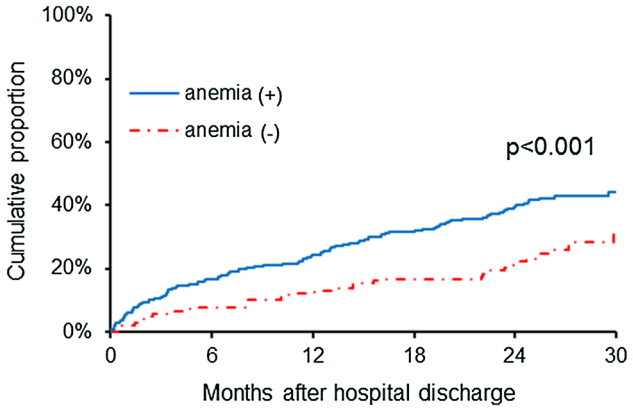

Fig. 3 Survival curves for all-cause mortality and heart failure rehospitalization by anemia status in HFpEF patients. Kaplan–Meier analysis for all-cause mortality and heart failure rehospitalization in anemic patients ($n = 373$) and non-anemic ($n = 146$) patients with HFpEF

In male patients, Kaplan–Meier analysis for all-cause mortality demonstrated that anemic patients had worse prognosis compared with non-anemic patients (26.8% versus 11.2%, $p = 0.03$; Fig. 4a). In male patients, cardiovascular death occurred in 20 patients, while non-cardiovascular death occurred in 24 patients. However, HF rehospitalization rate was not statistically different between anemic and non-anemic patients (27.5% versus 21.9%, $p = 0.169$; Fig. 4b). Interestingly, these prognostic impacts of anemia on all-cause mortality and HF rehospitalization were observed similarly in female patients (22.5% versus 5.8%, $p = 0.006$ for all-cause mortality; Fig. 4c, 34.3% versus 32.7%, $p = 0.102$ for HF rehospitalization rate; Fig. 4d). In female patients, cardiovascular death occurred in 17 patients, while non-cardiovascular death occurred in 20 patients.

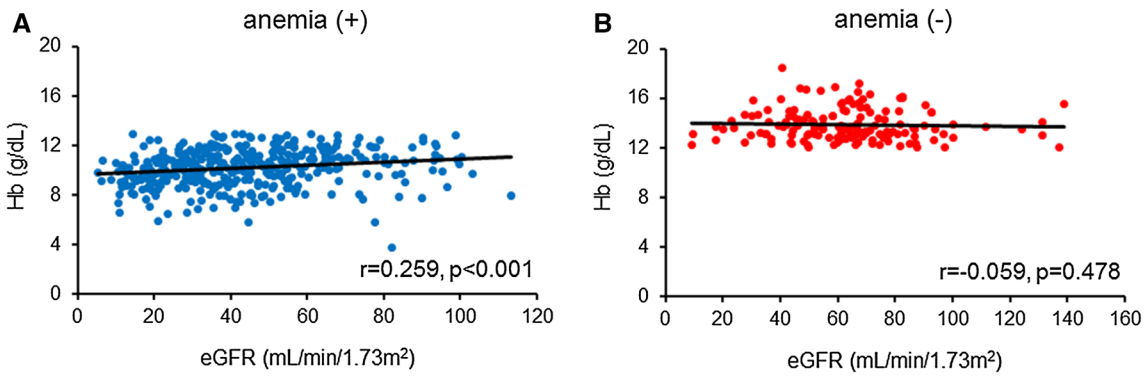

Fig. 2 Correlation between blood hemoglobin level and estimated glomerular filtration rate in HFpEF patients. Correlation between blood hemoglobin level and estimated glomerular filtration rate in **a** anemic ($n = 386$) and **b** non-anemic ($n = 149$) patients with HFpEF. *Hb* blood hemoglobin level, *eGFR* estimated glomerular filtration rate

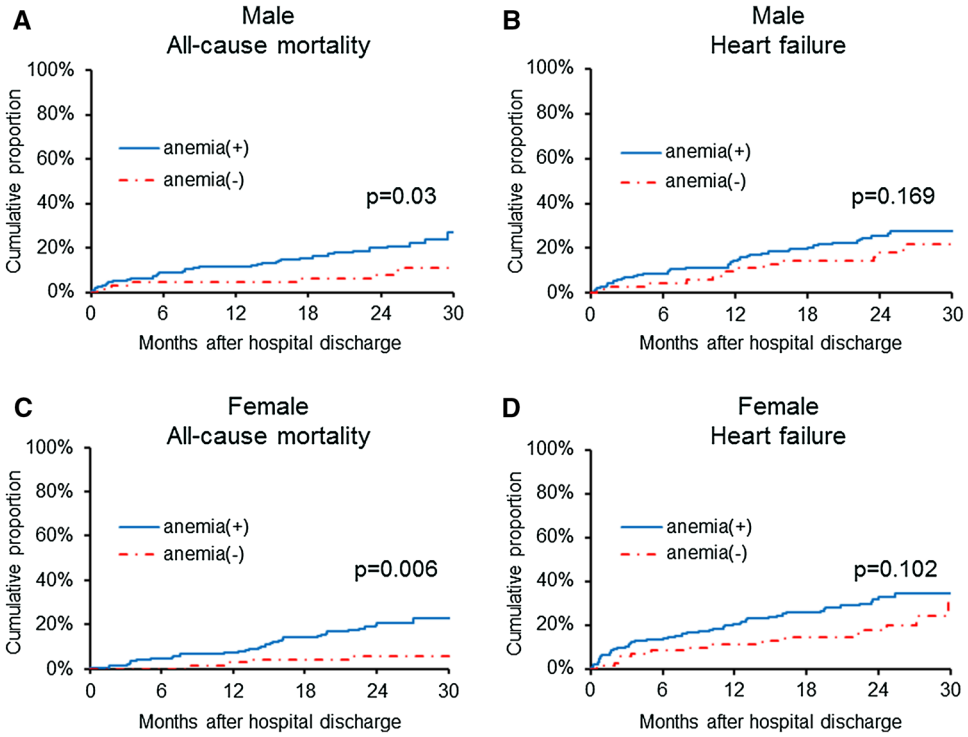

Fig. 4 Survival curves for all-cause mortality and heart failure rehospitalization by anemia status in male and female HFpEF patients. Kaplan–Meier analysis for **a** all-cause mortality and **b** heart failure rehospitalization in male anemic ($n=188$) and non-anemic ($n=69$) patients with HFpEF. Kaplan–Meier analysis for **c** all-cause mortality and **d** heart failure rehospitalization in female anemic ($n=185$) and non-anemic ($n=77$) patients with HFpEF

At discharge, the prevalence rate of anemia was 72% in all patients, 73% in male patients, and 71% in female patients, which was almost similar to that on admission. A positive correlation was also observed between blood Hb level and eGFR in anemic patients at discharge ($r=0.324$, $p<0.001$). Then, to further investigate the prognostic impacts of anemia on all-cause mortality and HF rehospitalization after discharge, we performed univariate and multivariate Cox regression analyzes for all-cause mortality and HF rehospitalization in male and female patients using clinical data at discharge. According to multivariate analysis, past hospitalization of HF [hazard ratio (HR) 2.06; 95% confidence interval (CI) 1.05–4.05; $p=0.036$] and blood Hb level at discharge (HR 0.80; 95% CI 0.66–0.98; $p=0.010$) were independent predictors of all-cause mortality in male patients (Table 2). On the other hand, blood Hb level at discharge (HR 0.62; 95% CI 0.47–to 0.81; $p<0.001$) was an independent predictor of all-cause mortality in female patients (Table 2). With respect to HF rehospitalization, multivariate analysis showed that past hospitalization of HF was an independent predictor of HF rehospitalization in male patients (HR 2.69; 95% CI 1.53–4.73; $p<0.001$) and female patients (HR 1.69; 95% CI 1.02–2.78; $p<0.041$) (Table 3).

Although multivariate analysis showed that blood Hb level at discharge was an independent predictor of all-cause mortality in both male and female patients, effective blood Hb level for prognosis in HFpEF patients remains largely unknown. Therefore, to assess the most effective cutoff value of blood Hb level at discharge to predict all-cause mortality, we finally performed survival CART analysis in these male and female HFpEF patients. The survival CART analysis demonstrated that blood Hb level of 9.4 g/dL for male patients was a more accurate cutoff value predicting all-cause mortality (Fig. 5a). On the other hand, blood Hb level of 12.3 g/dL for female patients was an optimal cutoff value predicting all-cause mortality (Fig. 5b).

Discussion

This study showed that anemia was associated with poor prognosis in both male and female HFpEF patients. In addition, blood Hb level at discharge was an independent predictor of all-cause mortality in both male and female HFpEF patients. Of interest, effective cutoff value of blood Hb level at discharge to predict all-cause mortality was different between male and female HFpEF patients. Blood Hb level of 9.4 g/dL for male and 12.3 g/dL for female was a more accurate cutoff value predicting all-cause mortality in HFpEF patients.

Anemia is common in HF patients with preserved or reduced left ventricular ejection fraction [1–3]. According to the WHO criteria, the prevalence rate of anemia was about 70% in HFpEF patients in this study. The prevalence of anemia has been reported to be higher in HFpEF than in HF with reduced left ventricular ejection fraction [10]; thus, this prevalence rate might reflect the characteristics of HFpEF patients. However, several previous studies

Table 2 Univariate and multivariate Cox regression analysis for all-cause mortality in male and female patients at discharge

Predictors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Male				
Age	1.04 (1.01–1.08)	0.019	1.02 (0.99–1.06)	0.241
Systolic BP	0.99 (0.97–1.01)	0.189		
Heart rate	1.02 (0.99–1.04)	0.232		
NYHA, III or IV	3.73 (1.45–9.55)	0.006		
BMI	0.91 (0.83–1.00)	0.054		
Hypertension	0.69 (0.37–1.30)	0.254		
DM	1.00 (0.57–1.79)	0.987		
AF	1.08 (0.59–1.98)	0.794		
OMI	1.24 (0.58–2.66)	0.578		
HF	2.88 (1.55–5.37)	< 0.001	2.06 (1.05–4.05)	0.036
eGFR	0.99 (0.97–1.00)	0.131	1.00 (0.99–1.02)	0.612
Hb	0.77 (0.65–0.91)	0.002	0.80 (0.66–0.98)	0.010
Albumin	0.42 (0.21–0.81)	0.010		
Log BNP	3.21 (1.39–7.37)	0.006		
LV posterior wall thickness		0.971		
LV end-diastolic dimension	1.02 (0.97–1.08)	0.470		
LAD	1.02 (0.97–1.06)	0.462		
TRPG	1.03 (1.00–1.06)	0.046		
E/*e*′	1.07 (1.02–1.12)	0.004		
LVEF	1.01 (0.96–1.05)	0.998		
β-Blockers	1.03 (0.57–1.87)	0.920		
ACE inhibitors	1.19 (0.66–2.17)	0.559		
ARBs	0.66 (0.36–1.21)	0.181		
Ca antagonists	0.50 (0.27–0.90)	0.021		
Loop diuretics	1.08 (0.56–2.08)	0.819		
Vitamin K antagonists	1.03 (0.58–1.82)	0.928		
NOACs	1.35 (0.53–3.41)	0.528		
Female				
Age	1.06 (1.02–1.10)	0.006	1.04 (0.98–1.08)	0.095
Systolic BP	1.00 (0.99–1.03)	0.661		
Heart rate	1.01 (0.99–1.04)	0.343		
NYHA, III or IV	4.06 (1.65–9.99)	0.002		
BMI	0.84 (0.76–0.92)	< 0.001		
Hypertension	0.83 (0.39–1.76)	0.626		
DM	0.64 (0.30–1.35)	0.240		
AF	1.37 (0.67–2.80)	0.385		
OMI	0.74 (0.23–2.42)	0.618		
HF	1.07 (0.55–2.10)	0.836	0.79 (0.39–1.60)	0.518
eGFR	0.97 (0.96–0.99)	0.007	0.99 (0.97–1.01)	0.438
Hb	0.57 (0.45–0.73)	< 0.001	0.62 (0.47–0.81)	< 0.001
Albumin	0.18 (0.09–0.34)	< 0.001		
Log BNP	2.97 (1.38–6.38)	0.005		
LV posterior wall thickness	1.10 (0.91–1.33)	0.314		
LV end-diastolic dimension	0.99 (0.94–1.05)	0.781		
LAD	0.96 (0.91–1.01)	0.104		
TRPG	1.02 (0.98–1.07)	0.236		
E/*e*′	1.02 (0.99–1.05)	0.235		
LVEF	1.02 (0.97–1.06)	0.446		

Table 2 (continued)

Predictors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
β-Blockers	0.96 (0.49–1.88)	0.904		
ACE inhibitors	0.58 (0.26–1.27)	0.171		
ARBs	1.18 (0.62–2.25)	0.621		
Ca blockers	0.90 (0.47–1.71)	0.738		
Loop diuretics	2.16 (0.84–5.54)	0.109		
Vit K antagonists	0.66 (0.34–1.28)	0.218		
NOACs	0.72 (0.22–2.35)	0.588		

BP blood pressure, *BMI* Body Mass Index, *DM* diabetes mellitus, *AF* atrial fibrillation, *OMI* old myocardial infarction, *HF* past hospitalization for heart failure, *eGFR* estimated glomerular filtration rate, *Hb* blood hemoglobin level, *Albumin* serum albumin level, *Log BNP* log-transformed plasma B-type natriuretic peptide level, *LV* left ventricular, *LAD* left atrial dimension, *TRPG* tricuspid regurgitation peak gradient, *E/e'* early diastolic mitral inflow velocity/early diastolic mitral annular velocity, *LVEF* left ventricular ejection fraction, *ACE* angiotensin-converting-enzyme, *ARBs* angiotensin II receptor blockers, *Vit K antagonists* vitamin K antagonists, *NOACs* novel oral anticoagulants

have reported that the prevalence rate of anemia in HFpEF patients was 27–58% [1–3], which is lower than that of our study. This prevalence rate of anemia might express real-world data in Japanese HFpEF patients.

Several factors are associated with anemia in HF; however, the etiology of anemia in HF remains largely unknown. Renal insufficiency is one of the contributing factors of anemia in HF, and the interaction among HF, anemia, and chronic kidney disease is called as cardio-renal anemia syndrome [9]. In this study, eGFR was lower in anemic patients than in non-anemic patients, indicating an association between renal insufficiency and anemia in HF. In fact, blood Hb level was positively correlated with eGFR in anemic patients but not in non-anemic patients.

In this study, anemic patients had higher prevalence of hypertension, diabetes mellitus, and past hospitalization of HF. In addition, cardiac echo parameters of diastolic function such as left atrial dimension and tricuspid regurgitation peak gradient were worse in anemic patients than in non-anemic patients. Therefore, anemic patients might be in more advanced stage in HF compared with non-anemic patients. However, there were no significant differences on plasma BNP level or HF rehospitalization rate between anemic and non-anemic patients. Anemic patients were more frequently treated with β-blockers, ACE inhibitors, and loop diuretics compared with non-anemic patients. Thus, the symptom of HF might have been well controlled by these medications in anemic patients.

With respect to medications and anemia, ACE inhibitors are reported to be associated with a reduction in blood Hb level in patients with renal failure [14]. Since anemic patients were more frequently treated with ACE inhibitors compared with non-anemic patients, this medication may be partly implicated in anemia of this population.

Anemic patients had worse prognosis compared with non-anemic patients in this study. Of note, anemia was associated with all-cause mortality in both male and female HFpEF patients, while anemia was not related to HF rehospitalization in either male or female HFpEF patients. In fact, multivariate analysis showed that blood Hb level at discharge was not an independent predictor of HF rehospitalization in both male and female HFpEF patients. These results suggest that anemia was not mainly associated with HF rehospitalization in HFpEF patients.

On the other hand, Kaplan–Meier analysis for all-cause mortality demonstrated that anemic patients had worse prognosis compared with non-anemic patients in both male and female HFpEF patients. In addition, blood Hb level at discharge was an independent predictor for all-cause mortality in both male and female HFpEF patients. Therefore, anemia is considered to be an important factor for all-cause mortality in HFpEF patients. To reduce all-cause mortality in HFpEF patients, anemia might have to be intervened. However, effective blood Hb level at discharge to predict all-cause mortality in HFpEF patients has been completely unknown. To the best of our knowledge, this study demonstrated, for the first time, most effective blood Hb level at discharge to predict all-cause mortality in male and female HFpEF patients by survival CART analysis. The survival CART analysis revealed that effective cutoff value of blood Hb level at discharge to predict all-cause mortality was different between male and female HFpEF patients. This difference of effective cutoff value may depend on gender difference in the oxygen affinity of Hb [15]. Blood Hb level is higher in male than in female. This may be partly due to the influence of testosterone [16]. In addition, male has more stored iron in the body than female. That is, male is less likely to become anemic

Table 3 Univariate and multivariate Cox regression analysis for heart failure rehospitalization in male and female patients at discharge

Predictors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Male				
Age	0.99 (0.97–1.03)	0.936	0.99 (0.96–1.01)	0.290
Systolic BP	0.99 (0.97–1.01)	0.189		
Heart rate	1.02 (0.99–1.04)	0.232		
NYHA, III or IV	3.73 (1.45–9.55)	0.006		
BMI	0.91 (0.83–1.00)	0.054		
Hypertension	1.01 (0.55–1.85)	0.977		
DM	1.31 (0.78–2.20)	0.303		
AF	0.97 (0.57–1.66)	0.912		
OMI	1.42 (0.74–2.74)	0.293		
HF	2.92 (1.72–4.98)	0.001	2.69 (1.53–4.73)	< 0.001
eGFR	0.98 (0.97–0.99)	0.014	0.99 (0.97–1.01)	0.156
Hb	0.89 (0.77–1.02)	0.083	0.93 (0.80–1.08)	0.323
Albumin	0.71 (0.37–1.36)	0.297		
Log BNP	2.87 (1.33–6.16)	0.007		
LV posterior wall thickness	1.18 (1.00–1.40)	0.044		
LV end-diastolic dimension	0.97 (0.92–1.02)	0.217		
LAD	1.01 (0.98–1.05)	0.546		
TRPG	1.01 (0.98–1.04)	0.441		
E/*e*′	1.04 (0.99–1.09)	0.059		
LVEF	0.99 (0.95–1.03)	0.684		
B-Blockers	1.15 (0.67–1.98)	0.610		
ACE inhibitors	1.02 (0.59–1.77)	0.940		
ARBs	0.73 (0.42–1.25)	0.254		
Ca blockers	0.67 (0.40–1.14)	0.138		
Loop diuretics	2.18 (1.07–4.44)	0.032		
Vit K antagonists	1.78 (1.04–3.04)	0.035		
NOACs	0.38 (0.09–1.55)	0.177		
Female				
Age	1.02 (0.99–1.05)	0.062	1.02 (0.99–1.04)	0.239
Systolic BP	0.99 (0.98–1.01)	0.540		
Heart rate	1.01 (0.99–1.03)	0.202		
NYHA, III or IV	1.07 (0.39–2.96)	0.891		
BMI	0.97 (0.92–1.02)	0.225		
Hypertension	1.37 (0.73–2.56)	0.323		
DM	1.03 (0.62–1.71)	0.901		
AF	1.74 (1.02–2.97)	0.042		
OMI	1.54 (0.78–3.01)	0.211		
HF	1.89 (1.17–3.04)	0.009	1.69 (1.02–2.78)	0.041
eGFR	0.99 (0.98–1.00)	0.052	0.99 (0.98–1.01)	0.422
Hb	0.90 (0.78–1.04)	0.164	0.97 (0.83–1.13)	0.674
Albumin	0.92 (0.52–1.63)	0.778		
Log BNP	2.28 (1.27–4.10)	0.006		
LV posterior wall thickness	0.98 (0.84–1.15)	0.815		
LV end-diastolic dimension	0.98 (0.94–1.03)	0.474		
LAD	1.01 (0.99–1.04)	0.373		
TRPG	1.03 (1.00–1.06)	0.024		
E/*e*′	1.03 (1.01–1.05)	0.013		
LVEF	0.99 (0.96–1.02)	0.541		

Table 3 (continued)

Predictors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
β-Blockers	1.65 (0.95–2.85)	0.076		
ACE inhibitors	0.91 (0.54–1.53)	0.717		
ARBs	1.09 (0.67–1.75)	0.734		
Ca blockers	1.05 (0.65–1.69)	0.847		
Loop diuretics	1.19 (0.67–2.11)	0.549		
Vit K antagonists	1.48 (0.92–2.39)	0.109		
NOACs	1.01 (0.46–2.21)	0.980		

BP blood pressure, *BMI* Body Mass Index, *DM* diabetes mellitus, *AF* atrial fibrillation, *OMI* old myocardial infarction, *HF* past hospitalization for heart failure, *eGFR* estimated glomerular filtration rate, *Hb* blood hemoglobin level, *Albumin* serum albumin level, *Log BNP* log-transformed plasma B-type natriuretic peptide level, *LV* left ventricular, *LAD* left atrial dimension, *TRPG* tricuspid regurgitation peak gradient, *E/e'* early diastolic mitral inflow velocity/early diastolic mitral annular velocity, *LVEF* left ventricular ejection fraction, *ACE* angiotensin-converting-enzyme, *ARBs* angiotensin II receptor blockers, *Vit K antagonists* vitamin K antagonists, *NOACs* novel oral anticoagulants

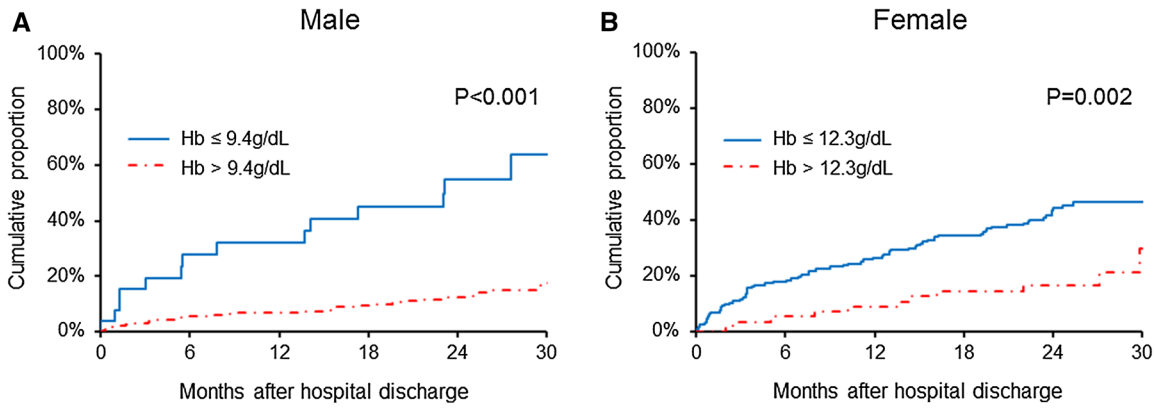

Fig. 5 Survival classification and regression tree analysis for all-cause mortality in HFpEF patients. Survival classification and regression tree analysis for all-cause mortality in **a** male ($n=259$) and **b** female ($n=262$) patients with HFpEF

than female. Conversely, blood Hb level in female is less than that of male and tends to be anemic. These differences also may affect gender difference of effective cutoff value of blood Hb level predicting all-cause mortality in HFpEF patients.

The survival CART analysis showed that blood Hb level of 12.3 g/dL at discharge was the most effective cutoff value predicting all-cause mortality in female HFpEF patients. On the other hand, according to the WHO criteria (blood Hb level < 12 g/dL in female), the prevalence rate of anemia was 71% in female patients at discharge. Taken together, these results suggest that female HFpEF patients are at high risk of all-cause mortality and it is necessary to pay more attention to the progression of anemia in female HFpEF patients. The prognostic factors of HFpEF patients have yet to be known as we do not have effective strategy to improve their survival. Anemia is one of the possible factors which we can intervene. Because HFpEF patients have few proven therapeutic options, treatment of anemia may lead to improve the prognosis in HFpEF patients.

Our study has limitations. First, this study was an observational cohort study and was not designed to assess the mechanism of anemia and in-hospital management with anemia. In addition, the details of anemia were unknown, because we had no data on serum iron and ferritin levels, and history of cancer. Second, since covariates which were closely related to cardiorenal anemia syndrome were chosen in multivariate analysis, a few covariates that showed p value < 0.05 on univariate analysis were not subjected to multivariate analysis.

Conclusions

Anemia was implicated in poor prognosis in HFpEF patients. In particular, blood Hb level at discharge was an independent predictor of all-cause mortality in both male and female

HFpEF patients. Effective cutoff value of blood Hb level at discharge to predict all-cause mortality was lower in male than in female HFpEF patients. Blood Hb level of 9.4 g/dL for male and 12.3 g/dL for female was a more accurate cutoff value predicting all-cause mortality in HFpEF patients.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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