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New-onset anemia and its association with ventricular arrhythmias and sudden cardiac death in patients with heart failure with preserved ejection fraction

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ABSTRACT

Background: Anemia is a common comorbidity associated with adverse outcomes in patients with heart failure with preserved ejection fraction (HFpEF). However, the clinical relevance of new-onset anemia to sudden cardiac death (SCD) in patients with HFpEF remains unclear. This study investigated the association between new-onset anemia with ventricular arrhythmias (VAs) and SCD.

Methods: Anemia was defined as a hemoglobin (Hb) level of <13 g/dL in men and <12 g/dL in women. Patients with Hb levels above these thresholds were categorized as without anemia. We analyzed data of 686 patients with symptomatic HFpEF (ejection fraction ≥ 50 %, New York Heart Association class II–IV) without anemia at baseline from a multicenter prospective observational CHART-2 study. The primary endpoint was a composite of ventricular tachycardia, ventricular fibrillation, and SCD.

Results: At the 1-year follow-up, 109 patients developed new-onset anemia (median Hb, 11.9 g/dL), whereas 577 remained without anemia (median Hb, 14.0 g/dL). Over a median follow-up of 9.2 years, patients with new-onset anemia had a significantly higher incidence of composite outcomes (12.8 % vs. 5.2 %, P = 0.008). After adjusting for potential confounders, new-onset anemia was associated with an elevated risk of the composite outcome (adjusted hazard ratio 2.20, 95 % confidence interval 1.10–4.42, P = 0.027). The association between new-onset anemia and lethal arrhythmias was independent of heart failure hospitalization or myocardial infarction occurring before the primary endpoint.

Conclusions: New-onset anemia was significantly associated with an increased risk of VAs and SCD in patients with HFpEF, underscoring the importance of monitoring Hb levels for risk stratification.

Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00418041.

1. Introduction

The number of patients with heart failure (HF) with preserved ejection fraction (HFpEF) continues to increase with the increasing prevalence of HF [1,2]. Sudden cardiac death (SCD) is one of the most critical adverse outcomes of HFpEF, accounting for 25 % of cardiovascular deaths [3,4]. However, the potential risks and mechanisms that contribute to SCD in patients with HFpEF remain unclear.

Anemia is a common comorbidity in patients with HF and has been associated with worse clinical outcomes, including exacerbation of HF symptoms and increased cardiovascular mortality [5–7]. In patients with heart failure with reduced ejection fraction (HFrEF), anemia has

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also been linked to an increased risk of SCD and ventricular arrhythmias [8]. Although the prevalence of anemia is comparable between patients with HFrEF and those with HFpEF, it is known to increase with age, and new-onset anemia is more frequently observed in those with HFpEF [9,10]. The development of new-onset anemia has emerged as an important risk factor, potentially reflecting worsening clinical status, such as deterioration in renal function or impairment in nutritional condition, both of which can occur in HFpEF [11,12]. Despite the likelihood of new-onset anemia in HFpEF, its prognostic impact on ventricular arrhythmic events, including SCD, has not been fully elucidated. Therefore, we aimed to investigate the clinical significance of new-onset anemia in patients with HFpEF, with a particular focus on its association with lethal ventricular arrhythmias and SCD. Because interim HF hospitalization and acute MI are established risk factors for ventricular arrhythmia in patients with HFpEF and HF with mildly reduced EF [13], these events were considered as potential confounders when assessing the association between anemia and arrhythmic events.

This multicenter, longitudinal observational study aimed to investigate the prognostic significance of new-onset anemia on the risk of lethal arrhythmic events, including ventricular tachycardia, ventricular fibrillation, and SCD, using the data from the Chronic Heart Failure Analysis and Registry in Tohoku District-2 (CHART-2, NCT00418041) [14]. We further examined the time course between ventricular arrhythmia (VA) and the duration after new-onset anemia to evaluate whether the risk increased shortly after anemia development or over time.

2. Methods

2.1. Study design

The CHART-2 study was a multicenter, prospective, observational study that enrolled 10,219 patients with chronic HF between October 2006 and March 2010. Detailed information regarding this study has been previously described [14,15]. The study protocol prespecified annual data collection.

HFpEF was defined according to the European Society of Cardiology Guidelines as follows: (i) symptomatic HF with left ventricular ejection fraction (LVEF) $\geq$ 50 %, (ii) B-type natriuretic peptide (BNP) >35 pg/mL or N-terminal pro-brain natriuretic peptide >125 pg/mL, and (iii) relevant structural heart disease (LV mass index >95 g/m^2 in women and >115 g/m^2 in men or left atrial dilation >40 mm) and/or diastolic abnormality (E/A ratio <0.75 or >1.5, or deceleration time of E-wave <140 ms) [16]. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2. Anemia was defined according to the World Health Organization criteria as hemoglobin (Hb) <13 g/dL in men and <12 g/dL in women [17]. Patients with Hb levels above these thresholds were categorized as without anemia.

Of the 10,219 patients enrolled in the CHART-2 study, we identified 898 with HFpEF who had New York Heart Association (NYHA) class II–IV symptoms and no anemia at baseline. Patients without sufficient data at the prespecified 1-year follow-up, those with an implantable cardioverter defibrillator, or those on hemodialysis were excluded. The final analysis included a total of 686 patients. The included patients were divided into two groups based on their Hb levels at the 1-year follow-up as follows: 109 patients with new-onset anemia and 577 patients without anemia (Supplementary Fig. 1).

2.2. Clinical outcomes

Clinical outcomes were assessed from the 1-year follow-up. The outcomes included VAs, HF hospitalization, acute myocardial infarction (AMI), and mode of death. The primary outcome was a composite of the first occurrence of VAs or SCD. VAs included ventricular tachycardia and ventricular fibrillation. Ventricular tachycardia was defined as tachycardia lasting >30 s or hemodynamically unstable tachycardia, whereas ventricular fibrillation was defined as a polymorphic VA with an RR interval <200 ms. SCD was defined as instantaneous, unexpected death or death within an hour of symptom onset not related to circulatory failure [18]. All clinical outcomes were reviewed and adjudicated by an independent data-monitoring committee.

2.3. Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQRs). Categorical data are presented as frequencies (percentages). Groups were compared using Student's *t*-test or Mann-Whitney *U* test for continuous variables and Fisher's exact test for categorical variables, as appropriate.

In the primary analysis, the cumulative incidence rate of the composite outcome (VAs and SCD) was assessed. Kaplan–Meier estimates were plotted to assess clinical outcomes. Cox proportional hazards models were used to evaluate the association between new-onset anemia and the baseline characteristics of the composite event. In the multivariable analysis, covariates that showed significant differences in baseline characteristics (Table 1) were adjusted for, including age (per 1-year increase), body mass index (per 1 kg/m^2 increase), NYHA class, history of HF hospitalization, CONUT score (controlling nutritional status score), CKD (chronic kidney disease [eGFR <60 ml/min/1.73]), and log-transformed BNP (per 1-unit increase). The association between changes in Hb levels from baseline to 1-year follow-up, treated as a continuous variable, and the risk of VAs and SCD was evaluated using a cubic spline model. The Cox proportional hazard model was adjusted for age, sex, atrial fibrillation, and CKD.

In the secondary analysis, the same model was constructed as in the primary analysis with the addition of interim HF hospitalization and AMI as time-updated covariates to account for their potential impact on arrhythmia risk [19].

All statistical analyses were performed using the R software (version 4.4.0). Statistical significance was set at $P < 0.05$.

3. Results

3.1. Clinical characteristics

Among the 686 symptomatic (NYHA class II–IV) patients with HFpEF, median age was 71 (IQR, 64–77) years, and 39.8 % were women. Approximately half of them had a history of HF hospitalization, 60.2 % for atrial fibrillation, and 45.3 % for CKD (Table 1). The baseline median Hb level at registration was 13.7 (IQR, 12.8–14.8) g/dL, showing a standard distribution (Supplementary Fig. 2).

At 1-year follow-up, 109 (15.9 %) patients developed new-onset anemia, with a median Hb level of 11.9 (IQR, 10.9–12.4) g/dL, whereas 577 patients remained non-anemic, with a median Hb level of 14.0 (IQR, 13.3–15.0) g/dL. The relationship between baseline Hb level and Hb at 1 year is shown as a scatter plot graph (Supplementary Fig. 3). Compared with patients without new-onset anemia, those with new-onset anemia were older; had lower body mass index, baseline Hb levels, RBC counts, hematocrit, and mean corpuscular hemoglobin concentration; had higher rates of HF hospitalization; exhibited more advanced NYHA class symptoms; had a higher prevalence of malignant diseases and chronic kidney disease; and higher CONUT score; and presented with higher BNP levels. All patients with new-onset anemia showed low hematocrit (<45 % in men, <40 % in women), normal mean corpuscular hemoglobin concentration (30–35 %). Among them, only 8 (7.3 %) had low MCV (<80 fL), whereas 88 had normal MCV (80–100 fL) and 13 had high MCV (>100 fL).

No significant differences in sex, prevalence of etiologies, or LVEF were observed between the two groups.

Table 1
Clinical characteristics stratified by new-onset anemia.

	All (n = 686)	New-onset anemia (n = 109)	Without anemia (n = 577)	P-value
Age (years)	71 (64–77)	74 (68–80)	71 (64–76)	0.004
Women, n (%)	273 (39.8)	45 (41.3)	228 (39.5)	0.81
BMI (kg/m^2)	24.1 (21.8–26.7)	22.9 (20.7–25.1)	24.4 (22.1–26.9)	<0.001
Heart rate (/min)	69 (60–79)	69 (60–78)	69 (60–79)	0.69
Systolic BP (mmHg)	127 (117–139)	128 (115–139)	126 (117–139)	0.34
NYHA class, n (%)				0.002
II	629 (91.7)	92 (84.4)	537 (93.1)	
III	56 (8.2)	16 (14.7)	40 (6.9)	
IV	1 (0.1)	1 (0.9)	0 (0)	
Prior cardiovascular history, n (%)				
Myocardial infarction	14 (2.0)	5 (4.6)	9 (1.6)	0.09
HF hospitalization	362 (52.8)	73 (67.0)	289 (50.1)	0.002
Stroke or TIA	122 (17.8)	23 (21.1)	99 (17.2)	0.40
Echocardiogram				
LVEF (%)	63 (55–70)	64 (55–73)	63 (55–70)	0.25
LVDd (mm)	49 (44–55)	51 (45–56)	49 (44–54)	0.06
LVDs (mm)	32 (27–37)	32 (27–40)	32 (27–37)	0.46
LVH[b], n (%)	437 (69.1)	74 (74.0)	363 (68.2)	0.30
LA diameter (mm)	44 (39 – 50)	47 (41–54)	44 (39–50)	0.008
Comorbidities, n (%)				
Hypertension	655 (95.5)	107 (98.2)	548 (95.0)	0.22
Diabetes mellitus	272 (39.7)	37 (33.9)	235 (40.7)	0.22
Dyslipidemia	583 (85.0)	89 (81.7)	494 (85.6)	0.36
COPD	38 (5.5)	8 (7.3)	30 (5.2)	0.50
Malignant disease	93 (13.6)	24 (22.0)	69 (12.0)	0.008
History of atrial fibrillation	413 (60.2)	74 (67.9)	339 (58.8)	0.09
History of ventricular arrhythmia	20 (2.9)	3 (2.7)	17 (2.9)	0.98
Etiologies, n (%)				
Ischemic heart disease,	286 (41.7)	46 (42.2)	240 (41.6)	0.99
Hypertrophic cardiomyopathy	6 (0.9)	1 (0.9)	5 (0.9)	1
Valvular heart disease	117 (17.1)	23 (21.1)	94 (16.3)	0.28
Laboratory findings				
Hb (g/dl)	13.7 (12.8–14.8)	11.9 (10.9–12.4)	14.0 (13.3–15.0)	
Red blood cell (10^4/μL)	441 (407–476)	380 (356–404)	449 (422–482)	<0.001
Hematocrit (%)	41.0 (38.4–44.0)	35.6 (33.4–37.0)	41.8 (39.6–44.7)	<0.001
Mean corpuscular volume (fL)	93.6 (90.4–96.7)	93.4 (90.1–97.3)	93.6 (90.5–96.5)	0.95
Mean corpuscular Hb (pg)	31.5 (30.1–32.5)	31.1 (29.6–32.4)	31.5 (30.2–32.5)	0.061
Mean corpuscular Hb concentration (%)	33.5 (32.9–34.2)	33.2 (32.4–34.0)	33.6 (33.0–34.2)	<0.001
Reticulocyte (%)	1.2 (0.9–1.5)	1.2 (0.9–1.5)	1.2 (0.9–1.5)	0.95
Iron (μg/dL)	91 (70–115)	67 (47–88)	95 (74–118)	<0.001
eGFR (mL/min/1.73 m^2)	62 (51–74)	54 (40–70)	62 (52–74)	<0.001
eGFR <60 mL/min/1.73 m^2	311 (45.3)	64 (58.7)	247 (42.8)	0.003
BNP (pg/mL)	109 (63–208)	176 (89–276)	103 (59–183)	<0.001
Albumin (g/dL)	4.2 (3.9–4.4)	4.0 (3.7–4.2)	4.2 (4.0–4.5)	<0.001
CONUT score	1 (0–2)	2 (1–3)	1 (0–2)	<0.001
Sodium (mEq/L)	142 (140–143)	142 (140–143)	142 (140–143)	0.84
Potassium (mEq/L)	4.3 (4.1–4.6)	4.3 (4.1–4.6)	4.3 (4.1–4.6)	0.96
Treatments, n (%)				
Beta-blocker	372 (54.2)	60 (55.0)	312 (54.1)	0.93
RASI	506 (73.8)	83 (76.1)	423 (73.3)	0.62
Loop diuretic	356 (51.9)	66 (67.0)	290 (56.3)	0.06
Anti-arrhythmic drug	20 (2.9)	7 (6.4)	13 (2.3)	0.04
Furosemide-equivalent dose (mg)	20 (0–20)	20 (0–40)	10 (0–20)	0.03
Antiplatelet	391 (57.0)	65 (59.6)	326 (56.5)	0.62
Warfarin or DOAC	364 (53.1)	60 (55.0)	304 (52.7)	0.73
Pacemaker	13 (1.9)	5(4.6)	8 (1.4)	0.06

Variables are presented as medians (interquartile ranges), or total numbers (percentages).
BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CKD, chronic kidney disease; CONUT score, controlling nutritional status score; COPD, chronic pulmonary obstructive disease; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HF, heart failure; LA, left atrial; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; RASI, renin–angiotensin system inhibitor.
[h]hemoglobin level < 13 g/dL in men and <12 g/dL in women.
[b] Left ventricular mass index >115 g/m^2 in men and >95 g/m^2 in women.

3.2. Impact of newly developed anemia on VAs and SCD

During a median follow-up period of 9.2 years (IQR, 5.0–11.2), 73 (67.0 %) patients with new-onset anemia and 235 (40.7 %) patients without anemia died. Composite outcome of VAs and SCD was observed in 44 (6.4 %) of the 686 patients. The new-onset anemia group showed a significantly higher incidence of the composite outcome (n = 14, 12.8 %) than those without anemia (n = 30, 5.2 %), with a hazard ratio (HR) of 2.51 (95 % confidence interval [CI]: 1.34–4.71, P = 0.004) (Fig. 1). The median duration until the first occurrence of a composite of VAs or SCD was 3.9 years in the new-onset anemia group. VAs occurred in 8 (7.3 %) patients with new-onset anemia and in 18 (3.1 %) without anemia (P = 0.043). SCD was observed in 6 (5.5 %) patients with new-onset anemia and in 12 (2.1 %) without anemia (P = 0.052). New-onset anemia was significantly associated with an increased risk of the composite outcome of VAs and SCD (adjusted HR [aHR] 2.20, 95 % CI, 1.10–4.42, P = 0.027) after adjusting for age, body mass index, NYHA class, history of HF hospitalization, malignant disease, CONUT score, CKD, and BNP (Table 2). However, baseline Hb was not associated with arrhythmia event (per 1 g/dL decrease; HR 1.03, 95 % CI, 0.82–1.30, P = 0.78) in this non-anemic population.

The median change in Hb levels from baseline to 1-year follow-up was −1.4 g/dL (IQR, −2.2 to −0.7) in patients with new-onset anemia, compared to 0 g/dL (IQR, −0.5 to 0.5) in those without. A 1 g/dL decrease in Hb level was significantly associated with a higher risk of VAs and SCD (HR, 1.33, 95 % CI, 1.04–1.70; P = 0.023), even after adjusting for age, sex, atrial fibrillation, and CKD (aHR, 1.31, 95 % CI, 1.02–1.68; P = 0.032). A cubic spline model showed a progressive increase in the composite outcome risk with declining Hb levels (Supplementary Fig. 4).

3.3. Association of interim HF hospitalization or MI and subsequent VAs and SCD

After the 1-year follow-up, the number of HF hospitalizations significantly increased in patients with new-onset anemia (n = 37, 33.9 %) compared to those without anemia (n = 144, 25.0 %, P = 0.049, Fig. 2A). Patients with new-onset anemia also had a higher incidence of AMI events (n = 5, 4.6 %) than those without it (n = 9, 1.6 %, P = 0.053) (Fig. 2B). Among those who experienced composite outcomes of VAs and SCD (n = 44), interim HF hospitalization was observed in 12 (27.3 %), whereas interim AMI occurred in 2 (4.5 %).

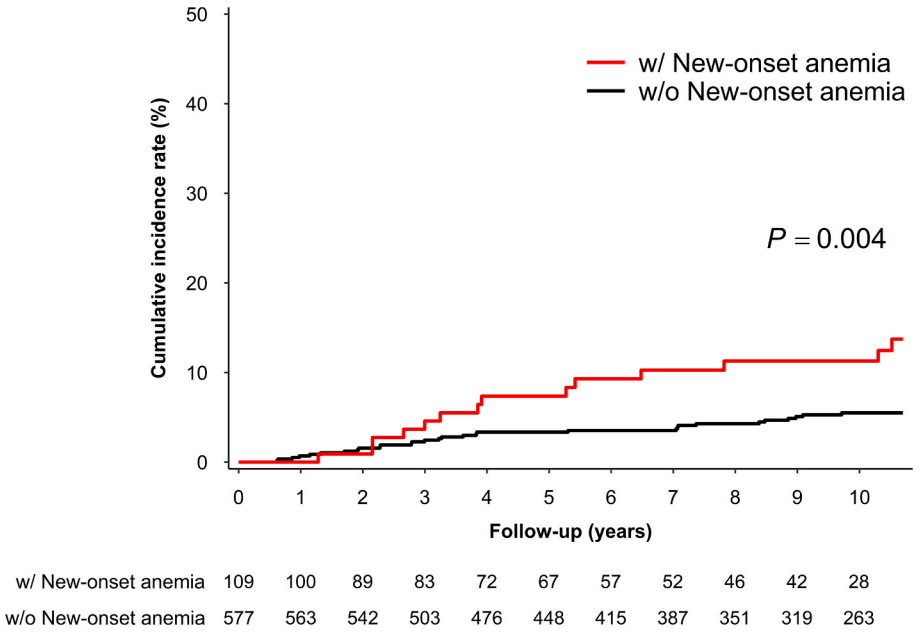

Fig. 1. Kaplan–Meier survival curves comparing cumulative incidence of composite of VAs and SCD between patients with new-onset anemia and those without anemia. The incidence rates were compared using Gray's test, considering all-cause mortality as a competing risk. VAs, ventricular arrhythmias; SCD, sudden cardiac death.

Table 2
Results of the multivariable Cox hazard model for the composite of VAs and SCD.

	Model 1		Model 2 (including interim HF hospitalization)		Model 3 (including interim AMI)	
Variables	HR (95 % CI)	P-value	HR (95 % CI)	P-value	HR (95 % CI)	P-value
New-onset anemia	2.20 (1.10–4.42)	0.027	2.17 (1.12–4.20)	0.022	2.19 (1.11–4.30)	0.024
Age (per 1 year increase)	1.01 (0.97–1.04)	0.70	1.00 (0.97–1.04)	0.82	1.01 (0.97–1.04)	0.72
BMI (per 1 kg/m^2 increase)	0.95 (0.87–1.03)	0.30	0.95 (0.89–1.02)	0.17	0.95 (0.88–1.03)	0.17
NYHA class	1.19 (0.41–3.49)	0.74	1.20 (0.53–2.72)	0.63	1.18 (0.42–3.29)	0.75
Prior HF hospitalization	1.87 (0.91–3.87)	0.06	1.74 (0.68–3.53)	0.09	1.86 (0.65–3.65)	0.11
Malignant disease	1.47 (0.66–3.29)	0.34	1.42 (0.68–2.96)	0.36	1.45 (0.69–3.04)	0.33
CONUT score	0.91 (0.66–1.25)	0.54	0.90 (0.67–1.21)	0.40	0.91 (0.68–1.21)	0.45
eGFR <60 mL/min/1.73 m^2	1.24 (0.69–2.43)	0.54	1.26 (0.64–2.48)	0.50	1.24 (0.62–2.47)	0.542
BNP*	2.01 (1.31–3.08)	0.001	1.97 (1.18–3.30)	0.01	2.01 (1.26–3.20)	0.006
Interim HF hospitalization			2.88 (1.51–5.51)	0.001		
Interim AMI					2.94 (0.55–15.55)	0.21

Interim HF hospitalization and interim AMI were defined as events that occurred before the primary endpoint of the composite of VAs and SCD. These were included in the multivariate analysis separately as time-updated covariables, along with covariables, as shown in Model 1.
Model 2 included interim HF hospitalization, and model 3 included interim MI.
CI, confidence interval; CONUT score, controlling nutritional status score; BMI, body mass index; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; NYHA, New York Heart Association; SCD, sudden cardiac death; VA, ventricular tachyarrhythmia. *BNP level was log-transformed into a model.

When considering interim events (HF hospitalization or AMI) that occurred before the composite outcome of VAs and SCD or all-cause mortality, we used time-updated covariates for each (Table 2). New-onset anemia as was identified as an independent risk factor for VAs and SCD when considering interim HF hospitalization in Model 2 (aHR, 2.17; 95 % CI, 1.12–4.20; P = 0.022), after adjusting for the same covariates as in Model 1. New-onset anemia also remained significant when considering interim AMI in Model 3 (aHR, 2.19; 95 % CI, 1.11–4.30; P = 0.024), after adjusting for the same covariates. New-onset anemia was associated with an increased risk of lethal VAs, independent of interim HF hospitalization or interim AMI occurring after the development of anemia.

4. Discussion

In the present study where we examined the prognostic impact of new-onset anemia on lethal arrhythmic events in patients with HFpEF, we had three novel findings. First, new-onset anemia was associated with a more than two-fold increase in the rate of VAs and SCD in patients with HFpEF. Second, HF hospitalization was more frequent in patients with new-onset anemia than in those without anemia. Third, the detrimental effect of new-onset anemia on the primary outcome was independent of interim HF hospitalization or AMI.

4.1. Prognostic impact of anemia on lethal VAs in patients with HFpEF

To the best of our knowledge, the present study is the first to reveal the independent effects of new-onset anemia on VAs and SCD in patients with HFpEF. A previous study demonstrated the prognostic effect of baseline anemia on VAs in patients with reduced LVEF. Goldenberg et al. reported that baseline anemia in patients who received implantable cardioverter-defibrillator (ICD) therapy for primary prevention was

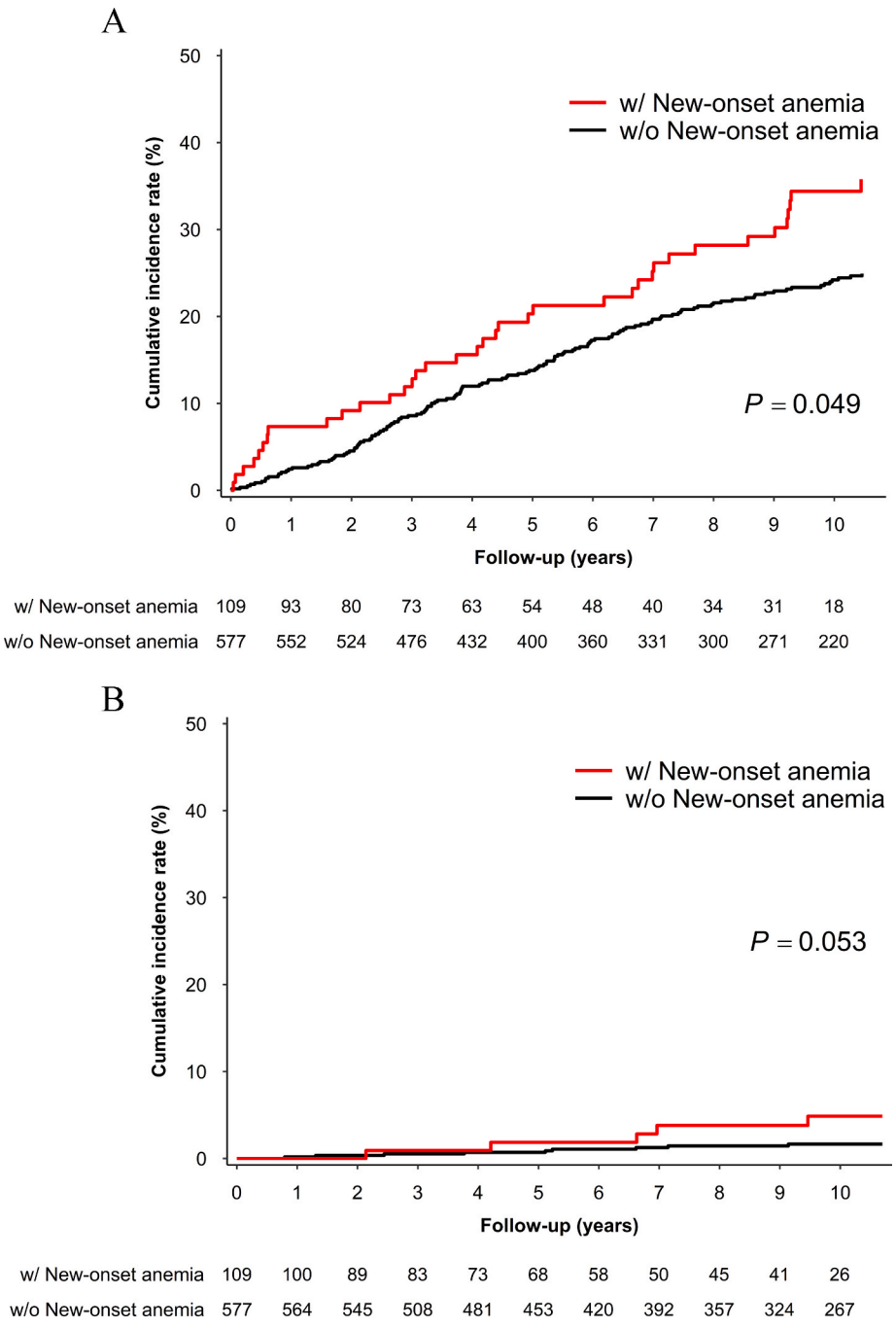

Fig. 2. Cumulative incidence of HF hospitalization and acute myocardial infarction between the two groups with and without new-onset anemia. The incidence rates were compared using Gray's test, considering all-cause mortality as a competing risk. (**A**) HF hospitalization. (**B**) Acute myocardial infarction. HF, heart failure.

associated with an increased risk of appropriate ICD therapy for VAs, HF hospitalization, and long-term mortality [8]. Moreover, an increased rate of arrhythmic events associated with baseline anemia has been reported in patients resuscitated from VAs [20]. These studies suggest a detrimental impact of baseline anemia on VAs, even in patients already considered at a high risk for such events. However, the prognostic impact of anemia in patients with HF without an ICD or prior VA events, particularly those with HFpEF, requires further investigation. The TOPCAT trial showed that baseline anemia was associated with all-cause mortality, cardiovascular mortality, and HF hospitalization among HF patients with LVEF $\geq$ 45 % [5]. Among the causes of cardiovascular mortality, SCD and aborted cardiac arrest increased significantly in patients with baseline anemia, suggesting a potential link between anemia and SCD, even in those with a relatively preserved LVEF [5]. However, the effect of new-onset anemia on SCD remains unclear. A prospective study of acute decompensated HF reported that new-onset anemia at 6-month follow-up after discharge was associated with an increased risk of all-cause death or HF hospitalization, with a risk magnitude comparable to that of persistent anemia [10]. Given that new-onset anemia may indicate worsening clinical status, such as declining renal function and impaired nutrition [11,21], its role in VAs warrants further investigation. The present study provides new insights into the relationship between anemia and VAs in patients with HFpEF.

4.2. Mechanisms of arrhythmia and clinical significance of new-onset anemia

Activation of the sympathetic nervous system has been identified as one of the mechanisms contributing to ventricular arrhythmias [22]. In HF, elevated sympathetic activity is well established. A recent study further demonstrated that, in patients with HFpEF, those with anemia had higher serum norepinephrine levels, even when the Hb reduction was mild (median Hb 11.9 g/dL) [23]. These findings suggest that, in HFpEF with anemia, ventricular arrhythmias may be mediated by alterations in sympathetic nervous system activity. Given the gradually increasing trend of VAs and SCD after new-onset anemia (Fig. 1), we speculate that the development of anemia may play a role in VAs, not only as a trigger but also as an influencing factor of the underlying cardiac conditions. The true mechanisms and roles of anemia in creating electrical instability need to be elucidated.

Since anemia can arise from multiple causes, the influence of underlying conditions on SCD risk should be considered. In our study, anemic patients were older and had a higher prevalence of CKD. Although the effect of anemia on SCD was adjusted for CKD, defined by eGFR decline, in the multivariable analysis, a potential pathological link between anemia and renal dysfunction cannot be entirely excluded. Possible mechanisms include activation of the sympathetic nervous system and ventricular dysfunction, which may contribute to elevated cardiovascular mortality, particularly from SCD [24–26]. Detailed analyses of renal function were not performed in this study, and further research is warranted to explore its association with anemia and SCD.

Furthermore, anemia is associated with worsening HF, leading to increased myocardial oxygen demand and hemodynamic stress [27], which may further predispose patients to malignant arrhythmias. Previous studies also suggested a link between anemia and a recurrent ischemic event in patients with coronary artery disease [28]. These cardiovascular events may increase the risk of lethal VAs [13]. Thus, new-onset anemia itself, rather than interim HF hospitalization or AMI, may be an independent risk factor for the development of lethal VAs.

4.3. Importance of preventing anemia to reduce the risk of VAs

Regular screening for anemia is recommended in the latest HF management guidelines because detecting anemia should prompt further evaluation to identify the underlying cause and initiate early management [1]. Our key finding suggests that anemia may contribute to VAs, underscoring the importance of early recognition of anemia. Accordingly, insights derived from the annual follow-up framework and long-term prognosis of the CHART-2 study may provide valuable guidance for formulating future clinical screening strategies to improve prognosis. Regular follow-up assessments to monitor Hb levels and identify anemia may be important for mitigating this risk. Although our study lacked detailed information on the specific causes of anemia, such as hemorrhagic anemia, iron deficiency, and folic acid deficiency, identifying the cause is essential because some forms of anemia may be treatable once recognized [29]. Although specific intervention is not feasible when anemia is mild, careful monitoring of Hb trajectories and addressing modifiable factors in the presence of a downward trend are important. Further studies are required to determine whether treating anemia reduces the risk of VAs. Implementing appropriate screening strategies and initiating timely interventions may help reduce the adverse effects of anemia on cardiovascular outcomes, particularly in patients with HFpEF.

In the present study, patients with new-onset anemia had a higher prevalence of previous myocardial infarction or atrial fibrillation, whereas the use of antiplatelet or anticoagulant agents at enrolment was similar between the two groups. Antithrombotic agents are known to cause anemia through iron loss due to clinically significant or minor bleeding [30]. Importantly, anemia in patients with coronary artery disease has been associated with worse clinical outcomes, including higher risks of mortality and cardiovascular events [31,32]. Despite adjustments for bleeding risk, anemia still developed, highlighting the need for careful evaluation of antithrombotic strategies [33,34].

5. Study limitations

The present study has some limitations. First, detailed information on the cause of anemia was not collected, limiting our ability to assess its prognostic impact based on specific etiologies. Reproducibility of Hb measurements within individual patients could not be verified, and inter-measurement variability may exist. Second, echocardiographic data were insufficient to evaluate key parameters, such as ventricular diastolic dysfunction (e.g., E/e′) and right ventricular function. Third, the dataset was collected before sodium-glucose cotransporter-2 inhibitors became available in our country, preventing the evaluation of their potential effects. Finally, because all the participants were Japanese, caution is required when generalizing the present findings to other populations.

5.1. Conclusions

New-onset anemia was associated with an increased risk of VAs and SCD in patients with HFpEF, independent of interim HF hospitalization or AMI. These findings underscore the importance of early anemia detection and management to reduce arrhythmic risk. Further studies are needed to determine whether anemia treatment can improve outcomes in this population.

CRediT authorship contribution statement

Tomohiro Ito: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Kotaro Nochioka:** Writing – review & editing, Project administration, Investigation, Data curation. **Takashi Noda:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Takashi Shiroto:** Writing – review & editing. **Shinichi Yamanaka:** Writing – review & editing. **Nobuhiko Yamamoto:** Writing – review & editing. **Hiroyuki Sato:** Writing – review & editing. **Takahiko Chiba:** Writing – review & editing. **Makoto Nakano:** Writing – review & editing. **Takumi Inoue:** Writing – review & editing. **Kai Susukita:** Writing – review & editing. **Hiroyuki Takahama:** Writing – review & editing. **Jun Takahashi:** Writing – review & editing. **Satoshi Miyata:** Writing – review & editing. **Hiroaki Shimokawa:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Satoshi Yasuda:** Writing – review & editing, Supervision, Resources, Funding acquisition.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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IRB information

This study was approved by the Ethics Committee of Tohoku University Graduate School of Medicine (2021-1-634).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2025.101812.

Data availability

The CHART-2 Study data are available upon reasonable request to the corresponding author.

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