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Impact of hemoglobin concentration and platelet count on outcomes of patients with non-valvular atrial fibrillation: A subanalysis of the J-RHYTHM Registry

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ABSTRACT

Background: To clarify the influence of hemoglobin concentration and platelet count on adverse outcomes of Japanese patients with non-valvular atrial fibrillation (NVAF), a post hoc analysis of the J-RHYTHM Registry was performed.
Methods: A consecutive series of outpatients with atrial fibrillation were enrolled from 158 institutions and followed up for 2 years or until an event occurred (thromboembolism, major hemorrhage, or all-cause death). Among 7406 patients with NVAF, 6536 with complete blood count data (69.8 ± 9.9 years, 71.0% men) were divided into 4 groups according to the baseline hemoglobin level (<10.0, 10.0–11.9, 12.0–13.9, and ≥14.0 g/dL) or platelet count (<10.0, 10.0–19.9, 20.0–29.9, and ≥30.0 × 10^4/μL).
Results: Incidence rates of major hemorrhage ($p = 0.004$ for trend), all-cause death ($p < 0.001$ for trend), and composite events ($p < 0.001$ for trend) increased as hemoglobin levels decreased, and composite events ($p = 0.045$ for trend) increased as platelet counts decreased. After adjusting for multiple confounders, the incidence of all-cause death and composite events was higher with hemoglobin levels <12.0 g/dL than a hemoglobin level ≥14.0 g/dL. In contrast, platelet count was not associated with any events. This was also true when multivariate analysis was performed using the stepwise forward method.
Conclusions: A low hemoglobin level (<12.0 g/dL) was an independent risk factor for all-cause death and composite events in Japanese patients with NVAF. However, platelet count did not impact outcomes.
Clinical trial registration: http://www.umin.ac.jp/ctr/ (unique identifier: UMIN000001569).

1. Introduction

Atrial fibrillation (AF) is a common arrhythmia and strong risk factor for cardiogenic thromboembolism [1,2]. Although $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and history of stroke or transient ischemic attack [TIA]) [3] and CHA_2DS_2-VASc scores (additionally, vascular disease, age 65–74 years, and female sex) [4] are widely used for risk stratification of thromboembolism in patients with non-valvular atrial fibrillation (NVAF), other clinical characteristics not included in these scores are possible risk factors for adverse outcomes such as thromboembolism, major hemorrhage, and all-cause death in patients with NVAF. Indeed, a low body weight or body mass index (BMI) [5,6] and low creatinine clearance (CrCl) value [7,8] are independent risk factors for these adverse outcomes. Moreover, baseline hemoglobin level or anemia is reportedly associated with poorer outcomes and/or higher mortality in patients with various cardiac diseases such as coronary artery diseases after percutaneous coronary intervention [9,10], chronic heart failure [11], and AF [12,13]. A lower platelet count is reportedly associated with a lower risk of stroke but a higher risk of bleeding events [14]. However, data are still limited as for impact of hemoglobin level and platelet count on outcomes among Asian patients with NVAF. Therefore, to clarify the influence of hemoglobin concentration and platelet count on adverse outcomes in Japanese patients with NVAF, a post hoc analysis was performed using data from the J-RHYTHM Registry [15].

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2. Methods

2.1. Study design of the J-RHYTHM Registry

The J-RHYTHM Registry was conducted as a prospective observational study. Its main aim was to investigate the optimal anticoagulation therapy with warfarin in Japanese patients with AF [15]. The study design and baseline patient characteristics were reported elsewhere [15,16]. Briefly, a consecutive series of outpatients with AF of any type was enrolled from 158 institutions without any exclusion criterion regarding hemoglobin levels and platelet counts. The study protocol conformed to the Declaration of Helsinki and was approved by the ethics committee of each participating institution. All participants provided written informed consent at the time of enrollment. All treatment strategies including antithrombotic drug selection were determined at the discretion of the treating cardiologists. Patients with valvular AF (mechanical prosthetic valve and rheumatic mitral stenosis) were excluded from this subanalysis. Patients were followed up for 2 years or until the occurrence of an event, whichever occurred first. Primary endpoints were defined as thromboembolism including symptomatic ischemic stroke, TIA, and systemic embolism; major hemorrhage including intracranial hemorrhage, gastrointestinal hemorrhage, and other hemorrhages requiring hospitalization; or all-cause death. The composite outcome of thromboembolism, major hemorrhage, and all-cause death, whichever occurred first in each subject, was also evaluated. The diagnostic criteria for each event have been described elsewhere [15,16]. CrCl was calculated using the Cockcroft-Gault formula [17]. Anticoagulation therapy intensity was determined using the prothrombin time international normalized ratio (PT-INR) in patients receiving warfarin, while the time in therapeutic range (TTR) was determined using the method developed by Rosendaal [18]. The target PT-INR level was set at 1.6–2.6 for elderly patients aged ≥70 years and at 2.0–3.0 for patients aged <70 years according to Japanese guidelines [19]. In this subanalysis, patients were divided into 4 groups according to baseline hemoglobin level (<10.0, 10.0–11.9, 12.0–13.9, and ≥14.0 g/dL) or platelet count (<10.0, 10.0–19.9, 20.0–29.9, and ≥30.0 × 10^4/μL).

2.2. Statistical analysis

Data are presented as number of patients (%) or mean ± standard deviation. The trends among the 4 groups were tested using the Cochran-Armitage test for categorical variables or the Jonckheere-Terpstra test for continuous variables as appropriate. Association between 2 variables was assessed by the Pearson's correlation coefficient. Kaplan-Meier curves were used to compare time to events with log-rank tests. A Cox proportional hazard model was used to investigate the influence of hemoglobin level and platelet count on adverse events. The hazard ratio (HR) and 95% confidence interval (CI) of each group were calculated with a hemoglobin level ≥14.0 g/dL or a platelet count ≥30.0 × 10^4/μL as a reference. Explanatory variables for multivariate analysis were adopted from well-known risk factors and previously reported independent risk factors for outcome events, i.e., CHA_2DS_2-VASc score components [4], warfarin and antiplatelet use, AF type [20], CrCl <30 mL/min [7,8], and BMI <18.5 kg/m^2 [6]. In addition, to identify significant predictors of outcome events, the stepwise forward method of the multivariate Cox proportional hazard analysis including hemoglobin level <12.0 g/dL was performed. To confirm the impact of hemoglobin level and platelet count on outcome events determined as a categorical variable, HRs were also determined using hemoglobin level and platelet count as a continuous variable. Additionally, the predictive ability of hemoglobin level for outcome events was determined by the area under the curve (AUC) of the receiver operating characteristic (ROC) curves, and the cutoff values were also determined at the maximum Youden index (sensitivity + specificity − 1). Two-tailed p values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS software version 23.0 (IBM Corporation, Armonk, NY, USA).

3. Results

Among the 7937 patients with AF who were enrolled in the J-RHYTHM Registry, 421 (5.3%) with valvular AF were excluded and 110 (1.5%) were lost to follow-up. Of the remaining 7406 patients with NVAF, 870 patients without baseline hemoglobin level or platelet count were excluded. Consequently, a total of 6536 patients constituted the study subjects of this subanalysis.

3.1. Baseline patient characteristics and medications

Of the whole study cohort, distributions of hemoglobin levels and platelet counts are shown in Supplementary Fig. 1. Mean hemoglobin level and platelet count were 13.7 ± 1.8 g/dL and 19.7 ± 6.0 × 10^4/μL, respectively. Baseline patient characteristics and medications by group are shown in Tables 1A and 1B. Out of the study subjects, 86.8% patients received warfarin at baseline.

Among the 4 groups of hemoglobin levels, platelet counts were comparable. The prevalence of coronary artery disease, heart failure, hypertension, older age, history of stroke or TIA, and antiplatelet use gradually increased as hemoglobin level decreased ($p < 0.05$ for trend); consequently, risk scores for thromboembolism ($CHADS_2$ and CHA_2DS_2-VASc scores) were higher in the lower hemoglobin level groups ($p < 0.001$ for trend) (Table 1A). Concomitant use of warfarin plus antiplatelet was positively correlated with the coexistence of coronary artery disease ($r = 0.362$, $p < 0.001$) and a history of stroke or TIA ($r = 0.148$, $p < 0.001$). Diastolic blood pressure, BMI, and CrCl were significantly lower in the lower hemoglobin level groups ($p < 0.001$ for trend), whereas frequency of warfarin use and PT-INR were comparable among the 4 groups. TTR was lower in the hemoglobin level groups of Hb < 10.0 and ≥14.0 g/dL than in the remaining groups (Table 1A); and the association between hemoglobin level and TTR was week ($r = -0.096$).

Among the 4 platelet count groups, hemoglobin levels and BMI were comparable. Similarly to the hemoglobin level groups, the prevalence of coronary artery disease, hypertrophic cardiomyopathy, heart failure, and older age gradually increased as platelet count deceased ($p < 0.05$ for trend); and risk scores for thromboembolism were higher in the lower platelet count groups ($p < 0.001$ for trend) (Table 1B). Systolic and diastolic blood pressure and CrCl were significantly lower in the lower platelet count groups ($p < 0.001$ for trend). The frequency of warfarin use was significantly higher in the lower platelet count groups, whereas that of antiplatelet use and baseline PT-INR were comparable among the 4 groups (Table 1B).

3.2. Event rates and hemoglobin level or platelet count

Two-year event rates of the hemoglobin level and platelet count groups are shown in Supplementary Table 1. Hemoglobin levels showed significant trends for major hemorrhage ($p = 0.004$ for trend), all-cause death ($p < 0.001$ for trend), and composite events ($p < 0.001$ for trend) (Supplementary Table 1A). However, platelet counts showed a significant trend only for composite events ($p = 0.045$ for trend) (Supplementary Table 1B). The Kaplan-Meier curves of outcome events are shown in Supplementary Figs. 2 and 3. Significant differences in the event-free rates of major hemorrhage ($p = 0.013$), all-cause death ($p < 0.001$), and composite events ($p < 0.001$) among the hemoglobin level groups were revealed by the log-rank test (Supplementary Fig. 2). Differences were also seen in all-cause death ($p < 0.001$) and composite events ($p < 0.001$) among the platelet count groups (Supplementary Fig. 3).

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Table 1A
Baseline characteristics and medications in the 4 hemoglobin level groups.

	Hemoglobin level (g/dL)				p for trend
	<10.0 (n = 167)	10.0–11.9 (n = 848)	12.0–13.9 (n = 2469)	≥14.0 (n = 3052)	
Age, years	76.5 ± 10.0	75.8 ± 8.2	71.3 ± 9.2	66.5 ± 9.7	<0.001
Sex, female	69 (41.3)	449 (52.9)	1021 (41.4)	357 (11.7)	<0.001
Type of atrial fibrillation					
Paroxysmal	66 (39.5)	339 (40.0)	1046 (42.4)	1038 (34.0)	0.001
Persistent	14 (8.4)	95 (11.2)	312 (12.6)	482 (15.8)	
Permanent	87 (52.1)	414 (48.8)	1111 (45.0)	1532 (50.2)	
Comorbidities					
Coronary artery disease	34 (20.4)	122 (14.4)	262 (10.6)	296 (9.7)	<0.001
Cardiomyopathy	9 (5.4)	65 (7.7)	208 (8.4)	297 (9.7)	0.007
Hypertrophic	3 (1.8)	28 (3.3)	90 (3.6)	126 (4.1)	0.078
Dilated	6 (3.6)	37 (4.4)	118 (4.8)	171 (5.6)	0.053
Congenital heart disease	2 (1.2)	17 (2.0)	32 (1.3)	39 (1.3)	0.295
COPD	6 (3.6)	26 (3.1)	47 (1.9)	45 (1.5)	0.001
Hyperthyroidism	2 (1.2)	16 (1.9)	61 (2.5)	39 (1.3)	0.081
Risk factors for stroke					
Heart failure	90 (53.9)	362 (42.7)	695 (28.1)	704 (23.1)	<0.001
Hypertension	110 (65.9)	536 (63.2)	1509 (61.1)	1819 (59.6)	0.017
Age (≥75 years)	109 (65.3)	515 (60.7)	998 (40.4)	633 (20.7)	<0.001
Diabetes mellitus	41 (24.6)	164 (19.3)	458 (18.6)	543 (17.8)	0.051
Stroke/TIA	33 (19.8)	142 (16.7)	329 (13.3)	397 (13.0)	0.002
$CHADS_2$ score	2.5 ± 1.3	2.2 ± 1.2	1.7 ± 1.2	1.5 ± 1.1	<0.001
CHA_2DS_2-VASc score	4.0 ± 1.5	3.8 ± 1.4	3.0 ± 1.5	2.3 ± 1.5	<0.001
Clinical parameters					
Hemoglobin, g/dL	9.1 ± 0.8	11.2 ± 0.6	13.0 ± 0.6	15.2 ± 0.9	<0.001
Platelet count, $\times 10^4/\mu L$	18.7 ± 8.5	19.8 ± 6.8	19.9 ± 8.2	19.6 ± 5.3	0.321
Body mass index, kg/m^2	22.0 ± 3.6	22.1 ± 3.6	23.3 ± 4.6	24.4 ± 3.4	<0.001
Heart rate, /min	73.5 ± 14.1	71.8 ± 12.9	71.8 ± 13.2	73.0 ± 13.2	<0.001
Systolic BP, mm Hg	124.8 ± 19.6	125.5 ± 18.1	125.9 ± 16.4	126.2 ± 15.5	0.106
Diastolic BP, mm Hg	66.7 ± 12.7	70.6 ± 30.5	72.3 ± 10.8	75.5 ± 17.1	<0.001
Creatinine clearance, mL/min	39.8 ± 27.3	48.9 ± 22.4	65.3 ± 25.8	77.6 ± 26.3	<0.001
Medications					
Warfarin	139 (83.2)	752 (88.7)	2147 (87.0)	2633 (86.3)	0.364
Dosage, mg/day	2.4 ± 1.1	2.6 ± 1.0	2.8 ± 1.1	3.0 ± 1.2	<0.001
PT-INR	1.90 ± 0.62	1.92 ± 0.52	1.90 ± 0.50	1.91 ± 0.48	0.430
TTR[a], %	56.2 ± 30.4	64.8 ± 27.6	61.4 ± 28.6	56.2 ± 29.5	<0.001
Antiplatelet	57 (34.1)	261 (30.8)	647 (26.2)	763 (25.0)	<0.001
Aspirin	45 (26.9)	219 (25.8)	564 (22.8)	682 (22.3)	0.027
Others	16 (9.6)	70 (8.3)	147 (5.9)	141 (4.6)	<0.001
Warfarin + antiplatelet	43 (25.7)	197 (23.2)	473 (19.2)	507 (16.6)	<0.001

Data are number of patients (%) or mean ± SD.
COPD, chronic obstructive pulmonary disease; $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and history of stroke or TIA; CHA_2DS_2-VASc, $CHADS_2$ components plus vascular disease (coronary artery disease), age 65–74 years, and female sex; TIA, transient ischemic attack; BP, blood pressure; PT-INR, prothrombin time international normalized ratio; TTR, time in therapeutic range.
[a] Target PT-INR was 2.0–3.0 (<70 years) or 1.6–2.6 (≥70 years).

3.3. Univariate analysis of impact of hemoglobin level and platelet count on events

In the univariate analysis, major hemorrhage, all-cause death, and the composite events were more frequently associated with low hemoglobin levels than a hemoglobin level ≥14.0 g/dL (Table 2A). When used as a continuous variable, hemoglobin level was also significantly associated with incidence rates of these outcome events (Supplementary Table 2). Regarding the platelet count, only the group with the lowest count displayed a significant association with major hemorrhage, all-cause death, and the composite events in the univariate analysis (Table 2B). When used as a continuous variable, platelet count was significantly associated with incidence rates of all-cause death and composite events (Supplementary Table 2).

3.4. Multivariate analysis of impact of hemoglobin level and platelet count on events

After adjusting for possible confounding factors, hemoglobin levels of <10.0 and 10.0–11.9 g/dL were associated with higher risks of all-cause death and composite events than a hemoglobin level ≥14.0 g/dL (Table 3A). When hemoglobin level was used as a continuous variable, risk of all-cause death (HR, 1.24; 95% CI, 1.13–1.36; $p < 0.001$) and composite events (HR, 1.13; 95% CI 1.07–1.21, $p < 0.001$) increased significantly for every 1-g/dL decrease in hemoglobin level after adjusting confounding factors (Supplementary Table 2). In contrast, platelet count was not associated with outcome events when used as a categorical (Table 3B) or a continuous variable (Supplementary Table 2).

Based on the abovementioned results, a stepwise forward multivariate Cox hazard analysis was employed to determine independent predictors of all-cause death and composite events. A hemoglobin level <12.0 g/dL emerged as an independent predictor of all-cause death (HR, 2.09; 95% CI, 1.52–3.17; $p < 0.001$) and composite events (HR, 1.61; 95% CI, 1.52–3.17; $p < 0.001$). However, a lower platelet count ($<10.0 \times 10^4/\mu L$) did not (Table 4). Several clinical variables including lower CrCl values <30 mL/min also emerged as independent predictors of all-cause death or composite events (Table 4).

3.5. Predictive ability of hemoglobin levels for outcome events

Predictive ability of hemoglobin level determined by the AUC of ROC curves for all-cause death and composite events were 0.70 (95% CI,

Table 1B
Baseline characteristics and medications in the 4 platelet count groups.

	Platelet count ($\times 10^4$/μL)				p for trend
	<10.0 (n = 130)	10.0–19.9 (n = 3635)	20.0–29.9 (n = 2456)	≥30.0 (n = 313)	
Age, years	74.7 ± 9.6	70.7 ± 9.5	68.2 ± 10.2	68.5 ± 11.2	<0.001
Sex, female	35 (26.9)	918 (25.3)	821 (33.4)	122 (39.0)	<0.001
Type of atrial fibrillation					
Paroxysmal	25 (19.2)	1251 (34.4)	1079 (43.9)	134 (42.8)	<0.001
Persistent	13 (10.0)	485 (13.3)	353 (14.4)	52 (16.6)	
Permanent	92 (70.8)	1899 (52.2)	1026 (41.7)	127 (40.6)	
Comorbidities					
Coronary artery disease	20 (15.4)	428 (11.8)	229 (9.3)	37 (11.8)	0.011
Cardiomyopathy	14 (10.8)	329 (9.1)	210 (8.5)	26 (8.3)	0.336
Hypertrophic	9 (6.9)	147 (4.0)	84 (3.4)	7 (2.2)	0.018
Dilated	5 (3.8)	182 (5.0)	126 (5.1)	191 (6.1)	0.415
Congenital heart disease	7 (5.4)	50 (1.4)	26 (1.1)	7 (2.2)	0.188
COPD	3 (2.3)	60 (1.7)	57 (2.3)	4 (1.3)	0.383
Hyperthyroidism	2 (1.5)	57 (1.6)	49 (2.0)	10 (3.2)	0.040
Risk factors for stroke					
Heart failure	69 (53.1)	1065 (29.3)	614 (25.0)	103 (32.9)	<0.001
Hypertension	68 (52.3)	2180 (60.0)	1550 (63.1)	176 (56.2)	0.121
Age (≥75 years)	73 (56.2)	1355 (37.3)	723 (29.4)	104 (33.2)	<0.001
Diabetes mellitus	28 (21.5)	699 (19.2)	413 (16.8)	66 (21.1)	0.148
Stroke/TIA	21 (16.2)	518 (14.3)	312 (12.7)	50 (16.0)	0.347
$CHADS_2$ score	2.2 ± 1.4	1.7 ± 1.2	1.6 ± 1.2	1.8 ± 1.3	<0.001
CHA_2DS_2-VASc score	3.4 ± 1.6	2.9 ± 1.6	2.7 ± 1.6	2.9 ± 1.7	<0.001
Clinical parameters					
Hemoglobin, g/dL	12.7 ± 2.4	13.7 ± 1.7	13.7 ± 1.7	13.0 ± 1.9	0.418
Platelet count, $\times 10^4$/μL	8.5 ± 1.5	16.2 ± 2.5	23.4 ± 2.6	35.7 ± 7.9	<0.001
Body mass index, kg/m^2	22.6 ± 3.7	23.7 ± 4.3	23.7 ± 3.5	23.2 ± 3.6	0.908
Heart rate, /min	71.6 ± 12.7	72.3 ± 12.9	72.3 ± 13.6	74.5 ± 13.7	0.542
Systolic BP, mm Hg	121.0 ± 17.2	125.7 ± 16.4	126.6 ± 16.1	125.3 ± 16.4	0.006
Diastolic BP, mm Hg	69.8 ± 12.4	73.0 ± 16.6	74.4 ± 19.8	72.8 ± 10.8	<0.001
Creatinine clearance, mL/min	53.7 ± 26.4	66.7 ± 26.9	71.5 ± 28.4	68.6 ± 29.3	<0.001
Medications					
Warfarin	115 (88.5)	3205 (88.2)	2094 (85.2)	257 (82.1)	<0.001
Dosage, mg/day	2.3 ± 1.1	2.9 ± 1.2	2.9 ± 1.2	2.8 ± 1.0	0.035
PT-INR	1.92 ± 0.57	1.90 ± 0.49	1.90 ± 0.51	1.94 ± 0.52	0.572
TTR[a], %	59.3 ± 31.6	60.4 ± 29.0	57.8 ± 29.2	57.7 ± 27.4	0.001
Antiplatelet	27 (20.8)	983 (27.0)	638 (26.0)	80 (25.6)	0.651
Aspirin	19 (14.6)	859 (23.6)	566 (23.0)	66 (21.1)	0.870
Others	9 (6.9)	213 (5.9)	129 (5.2)	23 (7.3)	0.791
Warfarin + antiplatelet	20 (15.4)	716 (19.7)	429 (17.5)	55 (17.6)	0.097

Data are number of patients (%) or mean ± SD.
COPD, chronic obstructive pulmonary disease; $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and history of stroke or TIA; CHA_2DS_2-VASc, $CHADS_2$ components plus vascular disease (coronary artery disease), age 65–74 years, and female sex; TIA, transient ischemic attack; BP, blood pressure; PT-INR, prothrombin time international normalized ratio; TTR, time in therapeutic range.
[a] Target PT-INR was 2.0–3.0 (<70 years) or 1.6–2.6 (≥70 years).

0.66–0.74; p < 0.001) and 0.61 (95% CI, 0.58–0.65; p < 0.001), respectively. Cutoff hemoglobin levels for all-cause death and composite events were determined to be 12.5 g/dL (with a sensitivity of 55.0% and a specificity of 76.5%) and 12.7 g/dL for composite events (with a sensitivity of 44.4% and a specificity of 73.4%).

4. Discussion

The major findings of the present study were as follows. First, in the unadjusted analysis, lower hemoglobin levels and lower platelet counts were associated with a higher incidence of major hemorrhage, all-cause

Table 2
Univariate analysis for hemoglobin level and platelet count on adverse events.

	Thromboembolism		Major hemorrhage		All-cause death		Composite events[a]	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
A. Hemoglobin level (g/dL)								
<10.0	1.68 (0.61–4.66)	0.320	2.87 (1.30–6.35)	0.009	10.23 (6.05–17.31)	<0.001	4.66 (3.17–6.85)	<0.001
10.0–11.9	1.28 (0.73–2.26)	0.396	1.80 (1.10–2.97)	0.020	4.91 (3.27–7.83)	<0.001	2.56 (1.96–3.33)	<0.001
12.0–13.9	1.25 (0.83–1.87)	0.284	1.22 (0.82–1.83)	0.330	1.71 (1.14–2.56)	0.009	1.38 (1.09–1.74)	0.007
≥14.0	Reference	–	Reference	–	Reference	–	Reference	–
B. Platelet count ($\times 10^4$/μL)								
<10.0	1.75 (0.49–6.19)	0.387	4.35 (1.04–18.22)	0.044	3.67 (1.48–9.13)	0.005	3.11 (1.63–5.93)	0.001
10.0–19.9	0.92 (0.40–2.12)	0.844	2.04 (0.64–6.48)	0.226	0.98 (0.48–2.02)	0.958	1.15 (0.70–1.88)	0.587
20.0–29.9	0.84 (0.36–1.99)	0.699	1.95 (0.61–6.25)	0.264	0.96 (0.46–2.02)	0.923	1.10 (0.66–1.81)	0.723
≥30.0	Reference	–	Reference	–	Reference	–	Reference	–

HR, hazard ratio; CI, confidence interval.
[a] Thromboembolism, major hemorrhage, and all-cause death.

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Table 3
Multivariate analysis for hemoglobin level and platelet count on adverse events.

	Thromboembolism		Major hemorrhage		All-cause death		Composite events[a]	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
A. Hemoglobin level (g/dL)								
<10.0	1.53 (0.52–4.49)	0.442	2.17 (0.91–5.15)	0.079	3.61 (1.93–6.78)	<0.001	2.57 (1.65–4.01)	<0.001
10.0–11.9	1.20 (0.63–2.27)	0.583	1.42 (0.79–2.54)	0.243	2.42 (1.48–3.95)	<0.001	1.70 (1.24–2.33)	0.001
12.0–13.9	1.21 (0.77–1.89)	0.413	1.24 (0.79–1.93)	0.347	1.36 (0.87–2.12)	0.181	1.26 (0.98–1.63)	0.075
≥14.0	Reference	–	Reference	–	Reference	–	Reference	–
B. Platelet count (×10⁴/μL)								
<10.0	0.94 (0.23–3.83)	0.935	4.55 (0.87–23.82)	0.073	2.04 (0.77–5.37)	0.149	2.92 (0.97–3.82)	0.063
10.0–19.9	0.85 (0.36–1.99)	0.702	2.91 (0.71–11.92)	0.138	1.08 (0.49–2.37)	0.846	1.23 (0.72–2.09)	0.447
20.0–29.9	0.95 (0.40–2.28)	0.916	3.00 (0.72–12.44)	0.131	1.63 (0.73–3.62)	0.232	1.50 (0.88–2.57)	0.140
≥30.0	Reference	–	Reference	–	Reference	–	Reference	–

Hazard ratios were adjusted for congestive heart failure, hypertension, age (≥75 and 65–74 years), diabetes mellitus, history of stroke or TIA, vascular disease (coronary artery disease), female sex, warfarin and antiplatelet use, atrial fibrillation type, creatinine clearance <30 mL/min, and body mass index <18.5 kg/m^2.
HR, hazard ratio; CI, confidence interval.
[a] Thromboembolism, major hemorrhage, and all-cause death.

death, and composite events. Second, after the adjustment for possible confounders, lower hemoglobin levels (<12.0 g/dL) were associated with all-cause death and composite events, whereas platelet counts were not.

4.1. Hemoglobin level or anemia and adverse outcomes

Previous reports demonstrated that anemia was associated with increased mortality and morbidity rates in patients with various diseases such as heart failure [21], angina pectoris [22], acute coronary syndrome [23], cancer [24], and human immunodeficiency virus infection [25]. In patients with AF, anemia was an independent predictor of 1-year survival and rehospitalization [12]. In the Fushimi AF Registry, a community-based survey of AF patients in Kyoto Prefecture in Japan [26], anemia defined as a hemoglobin level <13.0 g/dL for men and <12.0 g/dL for women was significantly associated with the incidence of composite events of stroke, systemic embolism, and death (adjusted HR, 2.41; 95% CI, 1.78–3.28; $p < 0.01$) in non-anticoagulated patients [13]. This was mainly due to the increased incidence rate of all-cause death.

In the present study, baseline hemoglobin levels of <10.0, 10.0–11.9, 12.0–13.9, and ≥14.0 g/dL were adopted to categorize the patients as in a previous report [10], since these values are more familiar to physicians in clinical settings than other cutoff values, e.g., those for quartiles. As shown in Table 1A, patients in the lower hemoglobin level groups were at high risk for thromboembolic events. Since the hemoglobin levels are generally affected by multiple confounding factors, it seems likely that the lower hemoglobin levels were associated with outcome events in the unadjusted model (Table 2A). However, even after the adjustment for multiple possible confounding factors, hemoglobin levels <12.0 g/dL (<10.0 and 10.0–11.9 g/dL) were associated with all-cause death and composite events (Table 3A). This was also true when hemoglobin level was used as a continuous variable. This finding is in line with that of the Fushimi AF Registry [13], and suggests that lower hemoglobin level itself independently affects all-cause death or some unmeasured confounders affect all-cause death in our NVAF patients.

Although the HR for major hemorrhage of the lowest hemoglobin level group (<10.0 g/dL) showed marginal significance ($p = 0.079$) (Table 3A), importantly, no independent association was demonstrated between hemoglobin level and the incidence of thromboembolism or major hemorrhage in the present study.

When anemia was defined as a hemoglobin level <12.0 g/dL, it was an independent predictor of all-cause death and composite events along with heart failure, age ≥75 years, history of stroke or TIA, coronary artery disease, low BMI (<18.5 kg/m^2), and low CrCl values (<30 mL/min) (Table 4). Warfarin use and female sex were associated with a lower risk of all-cause death and composite events. Age (65–74 years) and permanent AF were associated with a higher risk of the incidence of only composite events (Table 4). These results were consistent with those of previous studies [12,13] and suggest that general management of anemia, emaciation, renal dysfunction, malnutrition and/or frailty would be mandatory to lower mortality in patients with NVAF, in

Table 4
Independent predictors of all-cause death and composite events.

	All-cause death		Composite events[a]	
	HR (95% CI)	p value	HR (95% CI)	p value
Hemoglobin level <12 g/dL	2.19 (1.52–3.17)	<0.001	1.61 (1.25–2.07)	<0.001
Age 65–74 years[b]	–	–	1.44 (1.02–2.04)	0.037
Age ≥75 years[b]	2.68 (1.85–3.89)	<0.001	2.77 (1.99–3.84)	<0.001
Female sex	0.45 (0.30–0.67)	<0.001	0.58 (0.45–0.74)	<0.001
Heart failure	3.02 (2.12–4.29)	<0.001	1.64 (1.32–2.05)	<0.001
Stroke/transient ischemic attack	1.65 (1.13–2.41)	0.010	1.61 (1.27–2.06)	<0.001
Coronary artery disease	1.87 (1.29–2.71)	0.001	1.51 (1.16–1.95)	0.002
Warfarin use	0.52 (0.34–0.81)	0.004	0.64 (0.48–0.86)	0.003
Permanent atrial fibrillation[c]	–	–	1.49 (1.17–1.91)	0.001
Body mass index <18.5 kg/m^2	2.40 (1.58–3.64)	<0.001	1.86 (1.37–2.52)	<0.001
Creatinine clearance <30 mL/min	1.79 (1.18–2.72)	0.006	1.42 (1.03–1.94)	0.031

Multivariate Cox proportional hazard analysis using the stepwise forward method including variables of hemoglobin level <12 g/dL, platelet count <10 × 10^4/μL, congestive heart failure, hypertension, age (≥75 and 65–74 years), diabetes mellitus, history of stroke or transient ischemic attack, vascular disease (coronary artery disease), female sex, warfarin and antiplatelet use, atrial fibrillation type, creatinine clearance <30 mL/min, and body mass index <18.5 kg/m^2. Significant variables are shown.
HR, hazard ratio; CI, confidence interval.
[a] Thromboembolism, major hemorrhage, and all-cause death.
[b] Versus <65 years.
[c] Versus paroxysmal atrial fibrillation.

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addition to the specific treatment for comorbidities such as heart failure and coronary artery disease.

The impact of concomitant use of warfarin and antiplatelet drugs on outcome events deserves comment. The group of hemoglobin level <10.0 g/dL had higher prevalence of concomitant use of warfarin and antiplatelet drugs than the other groups (Table 1A); however this group showed numerically higher incidence rate of thromboembolic events (Table 2). This could be due, at least in part, to higher thromboembolic risk score and lower CrCl level [7,8] in this group (Table 1A).

4.2. Platelet count and adverse outcome

Platelets play an important role in primary aggregation. Therefore, platelet activity is related with the incidence of both thrombosis and hemorrhagic events. Platelet size measured by mean platelet volume (MPV) is reportedly associated with the incidence of stroke [27,28] or coronary artery disease [29]. Platelet count, which indicates platelet production from the bone marrow, is also associated with the development of stroke or bleeding events [27,28]. In patients with AF, MPV was an independent predictor for stroke [30] and left atrial thrombus [31]; lower platelet counts were associated with a lower risk of stroke and a higher risk of bleeding events [14].

In the present study, the lower platelet counts ($<10.0 \times 10^4/\mu L$) were significantly associated with a higher incidence of major hemorrhage, all-cause death, and composite events in the unadjusted model (Table 2B). However, the independent association between platelet counts and outcome events was not observed in the multivariate analysis. The association between lowest platelet count ($<10.0 \times 10^4/\mu L$) and major hemorrhage showed marginal significance ($p = 0.073$, Table 3B). This was also true when platelet count was used as a continuous variable. In addition, a platelet count ($<10.0 \times 10^4/\mu L$) was not an independent predictor of any event based on the stepwise forward method on the multivariate analysis. This finding indicates that a low platelet count is a weaker risk factor for adverse events than a low hemoglobin level in our cohort of Japanese NVAF patients. The discrepancy between a previous report [14] and the present result may be explained by the higher rate of warfarin use, and the lower cumulative stroke and bleeding event rates in our cohort than in the previous study [14].

5. Limitation

The present study had several limitations. First, this study was a post hoc analysis of an observational study and was therefore hypothesis-generating in nature. Reverse-causality phenomenon could not be completely eliminated even after adjusting for possible confounding covariates in the multivariate model. The precise mechanisms underlying the increased event rates among patients with lower hemoglobin levels could not be determined. Second, the participants were recruited from only 158 institutions in Japan. Most of the participating physicians specialized in cardiology and in the management of cardiac arrhythmias. More than 80% of patients were given warfarin at baseline. Therefore, these results cannot be extrapolated to the general Japanese population of patients with NVAF. Third, owing to missing complete blood count data, 870 (11.7%) patients were excluded from the present analysis. In addition, hematocrit, which is reportedly associate with mortality and hospitalization in patients with AF [12], was not collected; and MPV as a marker of platelet activity, which was an independent predictor for stroke [30], was not determined in the present study. Anemia type and the serial changes in hemoglobin level and platelet count over the follow-up period were also undetermined.

6. Conclusions

A lower hemoglobin level (<12.0 g/dL) was an independent risk factor for all-cause death and composite events in Japanese patients with NVAF. However, platelet count was not independently associated with outcome events.

Declaration of competing interest

Dr. Kodani received remuneration from Daiichi-Sankyo, Bristol-Myers Squibb, and Ono Pharmaceutical; Dr. Inoue received remuneration from Daiichi-Sankyo, Bayer Healthcare, Boehringer Ingelheim, and Bristol-Myers Squibb; Dr. Atarashi received remuneration from Daiichi-Sankyo; Dr. Okumura received research funding from Boehringer Ingelheim and Daiichi-Sankyo and remuneration from Boehringer Ingelheim, Bayer Healthcare, Daiichi-Sankyo, and Pfizer; Dr. Yamashita received research funding from Daiichi-Sankyo, Bayer Healthcare, and Bristol-Meyers Squibb and remuneration from Daiichi-Sankyo, Pfizer, Bayer Healthcare, Bristol-Myers Squibb, Toa Eiyo, and Ono Pharmaceutical; and Dr. Origasa received remuneration from Daiichi-Sankyo and Bayer Healthcare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.11.127.

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