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Clinical phenotypes of patients with non-valvular atrial fibrillation as defined by a cluster analysis: A report from the J-RHYTHM registry

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ABSTRACT

Background: Atrial fibrillation (AF) is a heterogeneous condition caused by various underlying disorders and comorbidities. A cluster analysis is a statistical technique that attempts to group populations by shared traits. Applied to AF, it could be useful in classifying the variables and complex presentations of AF into phenotypes of coherent, more tractable subpopulations.

Objectives: This study aimed to characterize the clinical phenotypes of AF using a national AF patient registry using a cluster analysis.

Methods: We used data of an observational cohort that included 7406 patients with non-valvular AF enrolled from 158 sites participating in a nationwide AF registry (J-RHYTHM). The endpoints analyzed were all-cause mortality, thromboembolisms, and major bleeding.

Results: The optimal number of clusters was found to be 4 based on 40 characteristics. They were those with (1) a younger age and low rate of comorbidities (n = 1876), (2) a high rate of hypertension (n = 4579), (3) high bleeding risk (n = 302), and (4) prior coronary artery disease and other atherosclerotic comorbidities (n = 649). The patients in the younger/low comorbidity cluster demonstrated the lowest risk for all 3 endpoints. The atherosclerotic comorbidity cluster had significantly higher adjusted risks of total mortality (odds ratio [OR], 3.70; 95% confidence interval [CI], 2.37–5.80) and major bleeding (OR, 5.19; 95% CI, 2.58–10.9) than the younger/low comorbidity cluster.

Conclusions: A cluster analysis identified 4 distinct groups of non-valvular AF patients with different clinical characteristics and outcomes. Awareness of these groupings may lead to a differentiated patient management for AF.

1. Introduction

Atrial fibrillation (AF) poses a significant public health burden and is caused by underlying processes and disorders leading to a very heterogeneous patient population [1]. A large variety of risk factors for non-valvular AF have been identified, including the age, male sex, hypertension, diabetes, obesity, sleep apnea, heart failure, and coronary artery disease [1]. Racial differences have also been reported to affect the incidence of AF and risk of bleeding from oral anticoagulants [2,3]. Currently, AF is classified based on the symptoms or duration of the AF episodes (e.g., paroxysmal, persistent, and permanent). Although this classification has several prognostic roles, we believe a more

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sophisticated classification of AF is highly desirable, not only to prevent strokes and bleeding events, but also to provide more individualized adjustments to rhythm- or rate-control therapy.

A cluster analysis, an unsupervised data-driven approach, has been used in the cardiovascular realm [4–9]. It successfully classifies subjects from heterogeneous populations into similar groups based on the clinical information. Recent data using heart failure with a reduced (preserved) ejection fraction has indicated that clustering techniques analyzed by standard clinical features can classify patients into several different phenotypes (clusters) that exhibit a different mortality, hospitalization rate, and response to pharmacological therapy or exercise training [4–7]. A recent cluster analysis study using a prospective registry of AF patients in the US demonstrated an improvement in the phenotypic categorization of the disease [8]. That study, though unique and useful, was lacking in having a significant Asian cohort. In this study, we set two objectives: [1] to perform the cluster analysis to identify unique clinically relevant phenotypes of AF using a prospective Japan-wide AF registry and [2] to examine the phenotype-based clinical outcomes.

2. Methods

2.1. Data source and study population

The study design and the main outcome analysis of the J-RHYTHM Registry have been reported elsewhere [10–12]. Briefly, the J-RHYTHM Registry is an observational, prospective cohort study that enrolled patients with AF between January 2009 and July 2009 at 158 sites in Japan. Eligible patients were those ≥20 years of age who had at least one episode of AF captured on a standard 12-lead electrocardiogram, who were able to provide informed consent, and who adhered to a local follow-up. This post-hoc study included 7406 patients after excluding patients with mitral stenosis or that had undergone a mechanical valve replacement (n = 410). Warfarin was used as an oral anticoagulation therapy because no direct oral anticoagulant was available when this registry was carried out. The study protocol conformed to the 1975 Declaration of Helsinki and was approved by the institutional review board of the participating institutions. All patients gave their written informed consent.

2.2. Outcomes

The primary outcome was defined as all-cause mortality, thromboembolisms, or major bleeding. Thromboembolisms included ischemic strokes, transient ischemic attacks, and systemic embolisms. Major bleeding included intracranial hemorrhages, gastrointestinal bleeding, and other causes of bleeding requiring hospitalization. We defined an ischemic stroke as a sudden neurological deficit lasting >24 h, corresponding to a vascular territory in the absence of a primary hemorrhage that was not explained by other causes such as trauma or an infection. The diagnosis of a stroke was made with computed tomography or magnetic resonance imaging. The patients were followed for 2 years, or until an endpoint, whichever occurred first. All analyses of the rates of the endpoints were based on the first event during the follow-up. A local investigator ascertained the events.

2.3. Definitions

The components of the CHA_2DS_2-VASc score [13] was defined by congestive heart failure, hypertension, age ≥ 75 (2 points), diabetes, strokes (2 points), vascular disease, an age 65–74, and the sex category (female). With regard to the CHA_2DS_2-VASc score, we modified the "V" criterion to include coronary artery disease only, because no data were available regarding peripheral artery disease or aortic plaque. The components of the HAS-BLED bleeding risk score for major bleeding [14] were defined by hypertension, abnormal renal/liver function (1 point each), strokes, a bleeding history or predisposition, a labile international normalized ratio (INR) (therapeutic time in a range [TTR] < 60%), elderly (>65 years), and the use of drugs (antiplatelet agents and nonsteroidal anti-inflammatory drugs) or alcohol > 8 U/week (1 point each). Abnormal renal function was defined as the presence of chronic dialysis, renal transplantation, or serum creatinine > 200 mmol/L was classified as abnormal kidney function. Abnormal liver function was defined as biochemical evidence of significant hepatic derangement (eg, bilirubin > 2x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase > 3x upper limit normal). The time in a therapeutic range (TTR) was determined by the method of Rosendaal et al. [15]. For this determination, the target INR level was set at 1.6–2.6 for patients aged 70 years or older and at 2.0–3.0 for patients aged younger than 70 years, according to the Japanese guidelines [16].

2.4. Statistical analysis

The baseline variables of the patients are presented as the number and frequency or mean ± standard deviation (SD) values. There were several variables with missing data including the height (13.8%), body weight (13.1%), hemoglobin (11.5%), platelets (11.6%), creatinine (11.1%), creatinine clearance (11.1%), aspartate aminotransferase (11.1%), and alanine aminotransferase (11.1%). These numerical missing data were imputed with a sequential regression multivariate imputation [17]. In this study we used a hierarchical cluster analysis (Ward's method) using 40 data items recorded for each patient in the J-RHYTHM Registry shown in the Supplementary file (Appendix S1). We show dendrogram, cubic clustering criterion and constellation tree diagram to estimate the number of likely clusters within our population (Supplementary file, Figs. S1–S3). Between-cluster comparisons were performed using analysis of variance or χ^2 test. To compare the outcomes between the clusters, Kaplan-Meier estimates with log-rank testing were applied to assess the equality of the survival distributions for each endpoint. A logistic regression model was used to test the association between clusters and outcomes, and whether the type of AF (paroxysmal vs. non-paroxysmal [persistent or permanent]) was associated with outcomes for each cluster and all patients. The models were adjusted by the age and sex for all-cause death, by the CHA_2DS_2-VASc score for thromboembolisms, and by the HAS-BLED scores for major bleeding. The odds ratios (ORs) for each cluster are presented with 95% confidence intervals (CIs). We used JMP 15 software (SAS Institute, USA) and R-project (R foundation, Vienna, Austria) for the analyses, including the cluster analysis. A two-tailed p-value of <0.05 was considered significant.

3. Results

3.1. Clinical characteristics of the identified phenotypes

In the overall study population at baseline (n = 7406), the mean age was 70 ± 10 years, with 29.2% women and 100% Asian participants. A total of 6382 (86.1%) patients were taking warfarin, the mean CHA_2DS_2-VASc score was 2.8 ± 1.6, and the mean HAS-BLED score was 2.7 ± 1.2. The cluster analysis identified 4 clinical phenotypes, and Table 1 shows the clinical characteristics across them.

3.2. Younger/low comorbidity cluster

This cluster (n = 1876) was composed of younger patients (mean age 67 ± 10 years) with a relatively lower body weight (mean 59 ± 13 kg) and higher rates of paroxysmal AF (45%). They had considerably lower rates of risk factors and comorbidities, including the lowest rates of heart failure (14%), hypertension (12%), diabetes (13%), a prior stroke or transient ischemic attack (TIA) (13%), coronary artery disease (1%), cardiomyopathy (4%), and malignancy (7%). The key characteristic of this cluster was highest rate of alcohol use > 8U/week. Notably, they

Table 1
Baseline characteristics of patients stratified by defined atrial fibrillation clusters.

	Younger/low comorbidity cluster (n = 1876)	Hypertensive cluster (n = 4579)	High bleeding risk cluster (n = 302)	Atherosclerotic comorbid cluster (n = 649)	P-value
Age, years	67 ± 10	70 ± 9	71 ± 9	73 ± 8	<0.001
Male, n (%)	1366 (73)	3096 (68)	236 (78)	542 (84)	<0.001
Height (m)	163 ± 9	161 ± 9	162 ± 9	161 ± 8	<0.001
Body weight (kg)	59 ± 13	61 ± 13	61 ± 13	61 ± 12	<0.01
Heart rate (beat per min)	73 ± 13	73 ± 14	72 ± 12	70 ± 11	<0.001
Systolic blood pressure (mmHg)	123 ± 15	127 ± 17	126 ± 16	125 ± 15	<0.001
Diastolic blood pressure (mmHg)	73 ± 10	74 ± 11	73 ± 11	71 ± 11	<0.001
Type of AF, n (%)					<0.001
Paroxysmal	844 (45)	1655 (36)	100 (33)	237 (36)	
Persistent	303 (16)	677 (15)	33 (11)	68 (11)	
Permanent	729 (39)	2247 (49)	169 (56)	344 (53)	
Comorbidities, n (%)					
Congestive heart failure	268 (14)	1400 (31)	95 (32)	291 (45)	<0.001
Hypertension	224 (12)	3616 (79)	202 (67)	437 (67)	<0.001
Age ≥ 75 years	520 (28)	1606 (35)	133 (44)	307 (47)	<0.001
Diabetes	242 (13)	824 (18)	59 (20)	232 (36)	<0.001
Previous stroke or TIA	235 (13)	604 (13)	66 (22)	111 (17)	<0.001
Coronary artery disease	25 (1.3)	67 (1.5)	44 (15)	644 (99)	<0.001
COPD	27 (1.4)	78 (1.7)	10 (3.3)	16 (2.5)	0.100
Cardiomyopathy	69 (3.7)	503 (11)	34 (11)	28 (4.3)	<0.001
Malignancy	130 (6.9)	333 (7.3)	44 (15)	54 (8.3)	<0.001
Hepatitis	68 (3.6)	180 (3.9)	29 (9.6)	30 (4.6)	<0.001
Abnormal renal function[1)]	13 (0.7)	71 (1.6)	16 (5.3)	31 (4.8)	<0.001
Abnormal liver function[2)]	28 (1.5)	53 (1.2)	15 (5.0)	4 (0.6)	<0.001
Alcohol >8U/week	625 (33)	1369 (30)	67 (22)	201 (31)	<0.001
Congenital heart disease	29 (2)	60 (1)	3 (1)	4 (<1)	0.250
Hyperthyroidism	27 (1)	98 (2)	3 (<1)	3 (<1)	0.002
Previous bleeding, n (%)	20 (1)	3 (<1)	302 (100)	2 (<1)	<0.001
Intracranial	5 (<1)	2 (<1)	74 (25)	0 (0)	<0.001
Gastrointestinal	10 (<1)	0 (0)	158 (52)	2 (<1)	<0.001
Other sites	5 (<1)	1 (<1)	70 (23)	0 (0)	<0.001
Laboratory data					<0.001
Hemoglobin (g/dL)	14 ± 1.5	14 ± 1.7	13 ± 2.0	13 ± 1.8	<0.001
Platelet ($x10^4$/uL)	22 ± 17	24 ± 28	22 ± 21	24 ± 33	0.02
Creatinine (mg/dL)	0.9 ± 0.4	1.0 ± 0.6	1.1 ± 0.9	1.1 ± 0.7	<0.001
CCr (mL/min)	67 ± 32	63 ± 31	60 ± 30	55 ± 27	<0.001
Total cholesterol (mg/dL)	193 ± 30	189 ± 29	183 ± 31	177 ± 28	<0.001
Total bilirubin (mg/dL)	0.8 ± 0.4	0.8 ± 0.3	0.8 ± 0.3	0.7 ± 0.3	<0.001
AST (mg/dL)	26 ± 9.9	26 ± 11	27 ± 16	26 ± 11	0.233
ALT (mg/dL)	23 ± 13	23 ± 13	21 ± 14	22 ± 13	0.115
TTR, % (n)	62 ± 25 (n = 1292)	64 ± 25 (n = 3546)	68 ± 24 (n = 233)	66 ± 22 (n = 509)	<0.001
Risk scores, points					
CHA_2DS_2-VASc	1.8 ± 1.4	2.9 ± 1.5	3.1 ± 1.6	4.3 ± 1.5	<0.001
HAS-BLED	2.2 ± 1.1	2.8 ± 1.2	3.6 ± 1.1	3.2 ± 1.2	<0.001
Medications, n (%)					
Class I antiarrhythmic drug	408 (22)	713 (16)	46 (15)	81 (13)	<0.001
Class III antiarrhythmic drug	34 (2)	137 (3)	8 (3)	44 (7)	<0.001
Beta-blocker	107 (6)	534 (12)	37 (12)	75 (12)	<0.001
Calcium channel blocker	75 (4)	153 (3)	16 (5)	26 (4)	0.240
Digitalis	153 (8)	398 (8)	22 (7)	49 (8)	0.620
ACE-I/ARB	12 (<1)	3344 (73)	177 (59)	399 (62)	<0.001
Statin	297 (16)	1118 (24)	63 (21)	316 (49)	<0.001
Warfarin	1508 (81)	4028 (88)	273 (90)	573 (88)	<0.001
Antiplatelet agent	364 (19)	1044 (23)	74 (25)	454 (70)	<0.001

AF = atrial fibrillation, TIA = transient ischemic attack, COPD = chronic obstructive pulmonary disease, CCr = creatinine clearance, AST = aspartate aminotransferase, ALT = alanine aminotransferase, TTR = time in therapeutic range of international normalized ratio of prothrombin time, ACE-I = angiotensin converting enzyme inhibitor, ARB = angiotensin II type 1 receptor blocker. Please see the definition of CHA_2DS_2-VASc and HAS-BLED scores in the supplementary file. 1) Abnormal renal function was defined as the presence of chronic dialysis, renal transplantation, or serum creatinine > 200 mmol/L was classified as abnormal kidney function. 2) Abnormal liver function was defined as biochemical evidence of significant hepatic derangement (eg, bilirubin > 2x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase >3x upper limit normal). Data represent number, frequency or means ± SD.

had a relatively preserved renal function (mean creatinine clearance 67 ± 32 ml/min) and the highest total cholesterol level (193 ± 30 mg/dL). The rate of class I antiarrhythmic drug use (22%) was the highest, but antiplatelet agent (19%) and statin (16%) use was lowest. Reflecting the younger age of the patients in this cluster, they had the lowest CHA_2DS_2-VASc score (1.8 ± 1.4) and HAS-BLED score (2.2 ± 1.1).

3.3. Hypertensive cluster

This was the largest cluster (n = 4579). The distinguishing characteristic of this cluster was that it had the highest proportion of hypertension (79%) and angiotensin converting enzyme inhibitor or angiotensin II type 1 receptor blocker use (73%). However, the mean value of the office systolic blood pressure (127 ± 17 mmHg), though statistically higher than that of the other clusters, was only 4 mmHg greater than the mean value of the lowest cluster. This cluster had the

highest percentage of females (32%). It had the second lowest rates of diabetes, coronary artery disease, and chronic obstructive pulmonary disease after the younger/ low comorbidity cluster. It also had the second lowest CHA_2DS_2-VASc and HAS-BLED scores.

3.4. High bleeding risk cluster

This was the smallest cluster (n = 302) and exhibited an intermediate age (mean age 71 ± 9 years). The key characteristic of this cluster was that 100% of the patients had a history of some bleeding compared to 1 % or less for the other 3 clusters. Reflecting the presence of a bleeding history, they had the highest HAS-BLED score (3.6 ± 1.1). Ninety percent of the patients were on warfarin and had the highest TTR. Of the four clusters, this cluster had the highest percentage of permanent AF (56%), a history of a stroke or TIA (22%), malignancy (15%), hepatitis (10%), abnormal renal function (5.3%) and abnormal liver function (5.0%).

3.5. Atherosclerotic comorbid cluster

This cluster (n = 649) had the oldest patients (mean age 73 ± 8 years) and highest proportion of male patients (84%). A major feature of this cluster was that 99.2% of the patients had coronary artery disease as compared to less than 2% for the younger/low comorbidity and hypertensive clusters and 15% for the high bleeding risk cluster. They also had the highest rates of congestive heart failure (45%) and diabetes (36%), and lowest creatinine clearance (55 ± 27 ml/min). They had the highest rate of antiplatelet agent (70%) and statin (49%) use. Reflecting the presence of multiple comorbidities, this cluster demonstrated the highest CHA_2DS_2-VASc score (4.3 ± 1.5).

3.6. Association with conventional grouping

We examined the relationship between the four clusters and conventional AF classifications including the AF subtype, CHA_2DS_2-VASc score, and HAS-BLED score (Supplementary files, Figure S4. The differences in the distribution of the AF subtype, CHA_2DS_2-VASc score, and HAS-BLED score varied significantly across the clusters. These results suggest that the cluster analysis included and integrated information on the AF subtype, CHA_2DS_2-VASc score, and HAS-BLED score.

3.7. Prognostic relationship between AF clusters and the outcomes

The Kaplan-Meier curves of 3 outcomes across the 4 clusters are shown in Fig. 1. For all-cause death (Panel A) and thromboembolisms (Panel B), the patients in the younger/low comorbidity cluster had the lowest risk, followed by the hypertensive cluster, high bleeding risk cluster, and atherosclerotic comorbid cluster in that order. For major bleeding (Panel C), the pattern was the same except that the order of the high bleeding risk cluster and atherosclerotic comorbid cluster were flipped. To reiterate, the patients in the younger/low comorbidity cluster demonstrated the lowest risk followed by the hypertensive cluster for all 3 endpoints. A logistic regression analyses showed the difference in outcomes across the clusters after an adjustment for the covariates (Fig. 2). Compared to the younger/low comorbidity cluster, the adjusted risk of all-cause mortality was significantly higher in the atherosclerotic comorbid cluster (OR, 3.70; 95% CI, 2.37–5.80). While there was no significant difference in the risk of thromboembolisms among the 4 clusters, the risk of major bleeding was significantly higher in the 3 other clusters as compared to the younger/low comorbidity cluster: hypertensive cluster (OR, 2.79; 95% CI, 1.58–5.40), high bleeding risk cluster (OR, 14.6; 95% CI, 7.45–30.3), and atherosclerotic

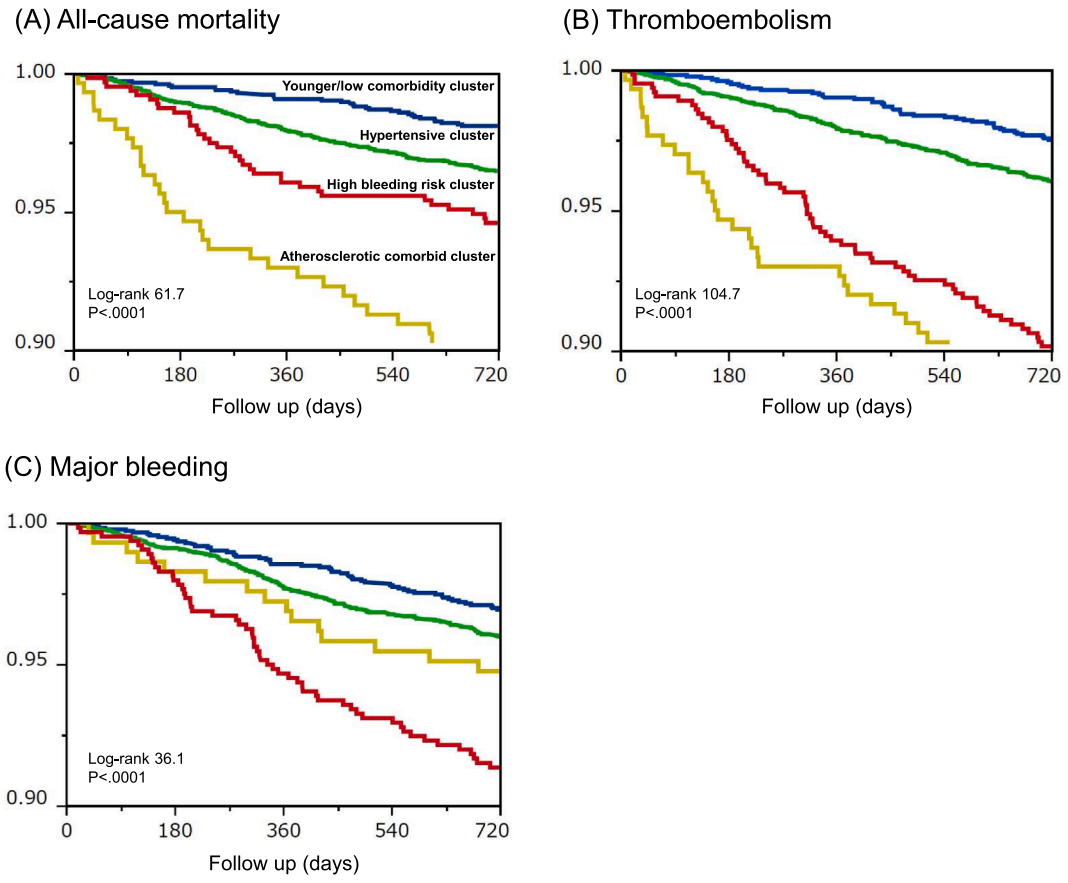

Fig. 1. Kaplan-Meier curves for the endpoint stratified by the 4 clusters. (A) All-cause death, (B) Thromboembolisms, and (C) Major bleeding. Patients in the younger/low comorbidity cluster consistently demonstrated the lowest risk for all outcomes.

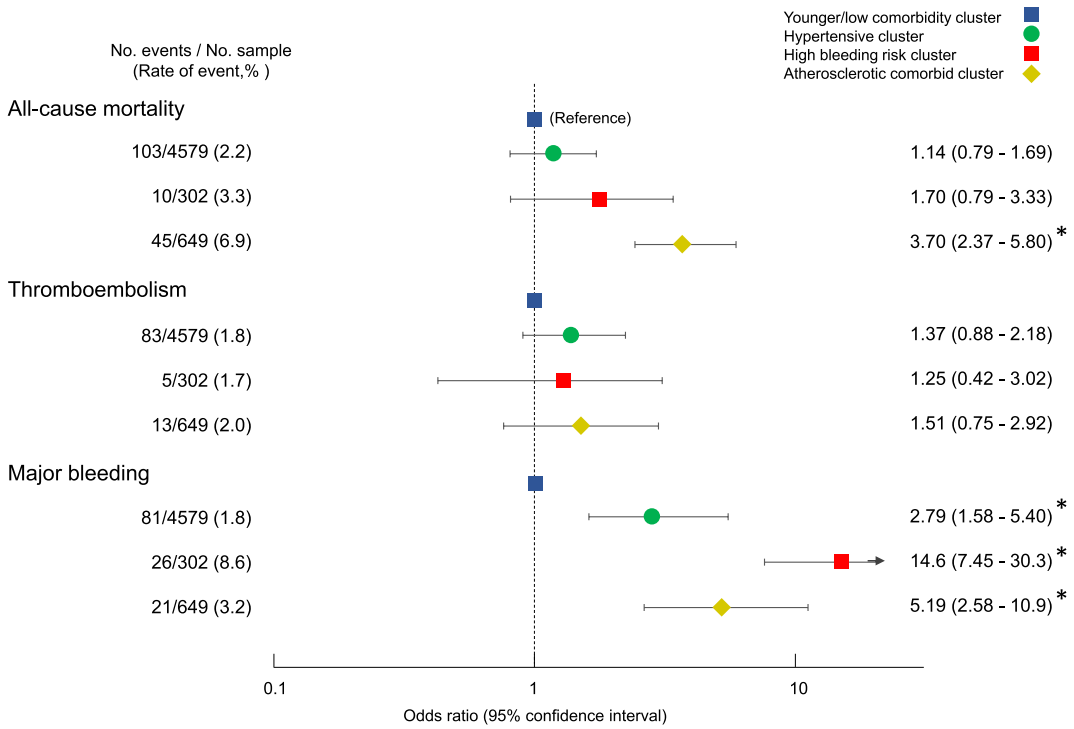

Fig. 2. Four clusters and adjusted odds ratio for the endpoints. The logistic models were adjusted by the age and sex for all-cause death, thromboembolisms were adjusted for the CHA_2DS_2-VASc score, and major bleeding risk was adjusted for the HAS-BLED scores. The younger/low comorbidity cluster was used as a reference. The odds ratios (ORs) for each cluster are presented with 95% confidence intervals (CIs). *: $p < 0.05$.

cluster (OR, 5.19; 95% CI, 2.58–10.9). A comparison of the C-indices among the models are shown in the Supplementary file (Table S1). The combination of the existing risk scores and cluster analysis improved the prediction accuracy of the three endpoints.

3.8. Prognostic relationship between AF types and the outcomes

We further examined whether the type of AF has an impact on outcomes in all patients and each cluster (Fig. 3). A multivariate logistic

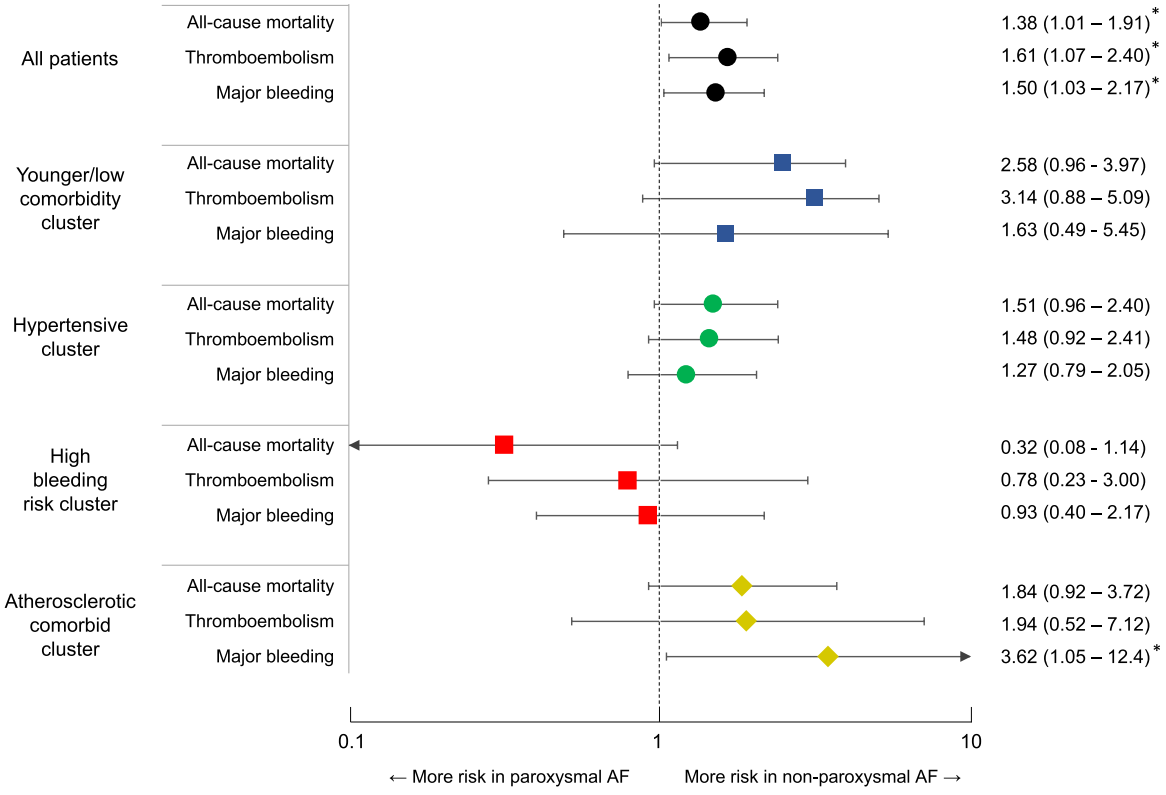

Fig. 3. Association of the AF type and outcomes in all patients and 4 clusters. The reference group is patients with paroxysmal AF. The odds ratios (ORs) and 95% confidence intervals (CIs) were shown. *: $p < 0.05$.

regression analyses showed that patients with non-paroxysmal AF had a worse prognosis than paroxysmal AF regarding the risks of all-cause mortality (OR, 1.38; 95 %CI, 1.01–1.91), thromboembolism (OR, 1.61; 95 %CI 1.07–2.40), and major bleeding (OR 1.50; 95 %CI, 1.03–2.17) in all patients. The non-paroxysmal AF was prognostic for major bleeding in atherosclerotic comorbid cluster (OR, 3.62; 95 %CI 1.05–12.4).

4. Discussion

4.1. Major findings

We performed a cluster analysis on a nationwide cohort of AF patients. The major findings were as follows: a cluster analysis identified four clinically distinct phenotypes and those four clusters were associated with a significantly different risk for the outcomes.

Physicians tracking large numbers of AF patients have long been accustomed to discrepancies between the type of AF, presence or absence of heart failure, and patient outcomes. This is due to the current crude phenotype of a highly heterogeneous disease as AF and the effects of comorbidities. A cluster analysis has been used to define the specific subtypes of various diseases with homogeneous clinical characteristics. In a recent study, Inohara et al. reported a cluster analysis of 9749 AF patients enrolled in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry [8]. They identified 4 clinically distinct AF phenotypes, each of which was significantly associated with the clinical outcome. In their study, the largest cluster, which they named the low comorbidity cluster (n = 4673), had a considerably lower burden of risk factors and comorbidities than the other three clusters, and experienced the lowest mortality. Second, the younger/ behavioral disorder cluster (n = 963) included the youngest AF patients (median 69 years), and they were most likely to be male. The distinguishing behavioral features included a higher prevalence of liver disease, alcohol abuse, drug abuse, and current smoking. They exhibited the second lowest rates of mortality. Third, the device implantation cluster (n = 1651) included patients receiving cardiac electrical devices due to sinus node dysfunction or atrioventricular node ablation. They had the highest median age (77 years) and a considerably higher burden of risk factors and comorbidities. Fourth, the atherosclerotic comorbid cluster (n = 2462) was the second largest group and included predominantly elderly men with ischemic cardiomyopathy. They also had multiple risk factors and comorbidities that resulted in the highest mortality rate. Another cluster analysis using the Japanese AF cohort identified 3 AF phenotypes, each of which was significantly associated with the adverse events including all-cause death, myocardial infarction, and stroke. The 3 AF phenotypes were younger/ paroxysmal AF (n = 1190), persistent/permanent AF with light atrium enlargement (n = 1143), and atherosclerotic comorbid AF in elderly patients (n = 125). They found that conventional risk factors, such as those included in the CHA_2DS_2-Vasc score, contribute to cluster formation, whereas AF type or left atrial size, rather than behavioral risk factors, contribute to cluster formation.

In our study, we identified 4 specific clusters, namely, the younger/ low comorbidity cluster, hypertensive cluster, high bleeding risk cluster, and atherosclerotic comorbidity cluster. The younger/low comorbidity cluster was equivalent to parts of the low comorbidity cluster and younger/ behavioral disorder cluster in the ORBIT-AF registry [8]. The younger/low comorbidity cluster had a considerably lower burden of risk factors but had a higher alcohol consumption. A previous meta-analysis showed that alcohol was associated with a dose-related increased risk of incident AF [18], and a recent randomized study confirmed that abstinence from alcohol reduced AF burden [19]. This cluster was likely to receive rhythm control therapy as was shown in the ORBIT-AF registry. This may be because physicians believe younger patients are more likely to benefit from maintaining sinus rhythm using class I or class III antiarrhythmic therapies. Accumulating evidence suggests that a lifestyle modification (weight loss and sleep apnea treatment) has a significant role in mitigating the AF burden and maintenance of sinus rhythm after catheter ablation [20,21].

The hypertensive cluster was the largest cluster and was characterized by a higher prevalence of female patients and both systolic and diastolic hypertension. Much previous research has identified hypertension as a highly prevalent and modifiable risk factor for AF patients [22]. A previous randomized controlled study showed that new-onset AF occurred less in the patients assigned to a target systolic blood pressure of less than 130 mm Hg than less than 140 mm Hg [23]. Further, a recent meta-analysis suggests that blood pressure lowering treatment reduces the risk of major cardiovascular events similarly in individuals with and without AF [24].

We identified a high bleeding cluster that was not defined in the previous AF cluster studies [8,9]. The distinguishing feature of this cluster was that all patients had a history of bleeding and had the highest rate of major bleeding events during the follow-up despite a relatively well-controlled TTR. A history of previous bleeding is a well validated risk factor considered in many bleeding scores [25,26]. Further, the higher prevalence of renal or liver dysfunction, hepatitis and malignancy have been shown to be associated with this cluster. Assessment of bleeding history and minimizing modifiable risk factors, together with correct dose of anticoagulants based on a patient's characteristics and concomitant medications help reduce the risk of bleeding and mortality.

We identified an atherosclerotic comorbid cluster that had the highest mortality rate. This cluster was also identified in the previous studies [8,9], which were characterized by older male patients and high rates of comorbidities including hypertension, diabetes, reduced renal function, and heart failure. The atherosclerotic comorbid cluster seemed to be a high-risk group across several AF registries, including different races. Given that the atherosclerotic comorbid cluster had the highest mortality rate despite appropriate use of antithrombotic drugs and statin, an interdisciplinary team approach would be an optimal clinical approach.

The relationship between AF types and outcomes has shown conflicting results regarding its impact on outcomes [27–29]. Therefore, the current risk scoring schemes do not include the type of AF and current practice guidelines provide the same recommendations for anticoagulant therapy, regardless of the type of AF. We showed that patients with non-paroxysmal AF were at higher risk of three outcomes than paroxysmal AF, and this could be explained by older age and comorbidities. The type of AF, however, was no longer prognostic for outcomes in 4 clusters except for a significantly increased risk of major bleeding in patients with non-paroxysmal AF in the atherosclerotic comorbid cluster compared to patients with paroxysmal AF. In recent subgroup analyses of the ENSURE-AF cardioversion trial [30] and ENTRUST-AF PCI trial [31], Goette et al. showed that patients with paroxysmal AF had a higher incidence of myocardial infarction than those with non-paroxysmal AF. Future research is required to test whether type of AF or cluster analysis can improve risk assessment in various clinical setting and provide optimal treatment for patients with AF.

4.2. Study limitations

This study was a prospective cohort study in warfarin era and may represent a selected population within the larger group of AF patients. This study was conducted with patients of Asian origin only, and therefore our results are less generalizable to the overall population. We did not collect any data on the symptoms, physical activity, caffein intake, biomarkers, echocardiography, device implantations, catheter ablation, sleep apnea, or genetic information. We used the data imputed by sequential regression multivariate substitution. The distinctive phenotypes identified in this study need further validation in an external AF cohort. The selection of the 4 clusters and 40 variables used for the cluster analysis were somewhat arbitrary.

5. Conclusions

Our study highlighted a significant heterogeneity present in AF patients in Japan and the need to improve the identification of the phenotypes of this disorder. A cluster analysis can be used to take advantage of the various clinical variables in the AF cohort to find relevant patterns that enable new groupings of AF patients. Given the heterogeneity of risk factors and outcomes in patients with AF, future trials should focus on different interventions in the distinct phenotypes of patients with AF.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Dr. Watanabe** received a lecture fee from Daiichi-Sankyo; **Dr. Inoue** reports receiving research funds from Boehringer Ingelheim and Daiichi-Sankyo and remuneration from Daiichi-Sankyo, Bayer Healthcare and Boehringer Ingelheim; **Dr. Atarashi**, receiving lecture fees from Daiichi-Sankyo; **Dr. Okumura**, receiving research funds from Boehringer Ingelheim and Daiichi -Sankyo and remuneration from Boehringer Ingelheim, Bayer Healthcare, Daiichi-Sankyo, and Pfizer; **Dr. Yamashita**, receiving research funds from Daiichi-Sankyo, Bayer Healthcare and Bristol-Myers Squibb, and remuneration from Boehringer Ingelheim, Daiichi -Sankyo, Bayer Healthcare, Pfizer, Bristol-Myers Squibb, Ono Pharmaceutical and Toa Eiyo; **Dr. Kodani** received a lecture fee from Daiichi-Sankyo and Ono Pharmaceutical; and **Dr. Origasa**, receiving lecture fees from Daiichi -Sankyo.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100885.

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