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# Evaluation of the ABC pathway in patients with atrial fibrillation: A machine learning cluster analysis

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ABSTRACT

*Background:* Atrial fibrillation Better Care (ABC) pathway is recommended by guidelines on atrial fibrillation (AF) and exerts a protective role against adverse outcomes of AF patients. But the possible differences in its effectiveness across the diverse range of patients in China have not been systematically evaluated. We aim to comprehensively evaluate multiple clinical characteristics of patients, and probe clusters of ABC criteria efficacy in patients with AF.

*Methods:* We used data from an observational cohort that included 2,016 patients with AF. We utilized 45 baseline variables for cluster analysis. We evaluated the management patterns and adverse outcomes of identified phenotypes. We assessed the effectiveness of adherence to the ABC criteria at reducing adverse outcomes of phenotypes.

*Results:* Cluster analysis identified AF patients into three distinct groups. The clusters include Cluster 1: old patients with the highest prevalence rates of atherosclerotic and/or other comorbidities (n = 964), Cluster 2: valve-comorbidities AF in young females (n = 407), and Cluster 3: low comorbidity patients with paroxysmal AF (n = 644). The clusters showed significant differences in MACNE, all-cause death, stroke, and cardiovascular death. All clusters showed that full adherence to the ABC pathway was associated with a significant reduction in the risk of MACNE (all $P < 0.05$). For three clusters, adherence to the different 'A'/'B'/'C' criterion alone showed differential clinic impact.

*Conclusion:* Our study suggested specific optimization strategies of risk stratification and integrated management for different groups of AF patients considering multiple clinical, genetic and socioeconomic factors.

## 1. Introduction

Atrial fibrillation (AF), the most common sustained arrhythmia, is associated with the increased risk of adverse clinical event [1]. Due to a variety of comorbidities and underlying pathophysiology, AF represents a highly complex group of diseases. The heterogeneity of AF poses numerous challenges to its comprehensive characterization and management strategies [2].

Recently, the Atrial Fibrillation Better Care (ABC) pathway has been recommended as an integrated care approach to AF management by the most recent guidelines [3]. The ABC pathway is based on three pivotal pillars: (A) Avoid stroke; (B) Better symptom management (rate or rhythm control); (C) Cardiovascular and comorbidity risk reduction [4]. Multiple clinical studies reported that adherence to the ABC pathway have a positive impact on outcomes [5]. However, these studies categorized AF patients based upon simple classifications (ie, sex, [6]

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comorbidity number, [7–10] comorbidity type, [11–14] or medication use [8,15]). Indeed, there is a need to evaluate adherence to the ABC pathway in the more comprehensive clinical phenotypes underrepresented in large randomized trials.

Cluster analysis, an unsupervised machine learning technique, was used to characterize the heterogeneity of AF populations [16–22]. The previous studies identified comprehensive and informative clinical phenotypes in several regions, exhibiting varied management patterns and adverse outcomes [16–21]. Compared with conventional classifications, cluster classification, providing a more comprehensive picture of clinical variations of AF population, is a better identification of patient subgroups which could benefit from fundamental therapy.

Accordingly, we aim to comprehensively evaluate multiple clinical characteristics of Chinese patients, an underrepresented population, with cluster analysis. Then, we assess the relationships between identified subgroups and clinical management or adverse outcomes. Moreover, we investigate if an approach based on the ABC pathway is associated with reduced risk of adverse clinical events in subgroups identified by cluster analysis.

## 2. Methods

### 2.1. Data source

The cohort of this analysis was from a multicenter, prospective, observational one-year follow-up AF registry study in China. The cohort recruited a total of 2,016 consecutive patients with AF, either as the primary or secondary diagnosis, who presented to emergency departments (ED) at 20 hospitals from November 2008 to October 2011 [23]. We included 2,015 AF patients with a one-year follow-up visit. One patient (0.05 %) was lost to follow-up and were excluded from our analysis. The study design and protocol obeyed the Declaration of Helsinki and were approved by the ethics committee of each institution, and all participating patients had signed consent forms.

### 2.2. ABC pathway cohort definition

Adherence to the ABC pathway, was defined according to the original definition. 'A' criterion: For patients with $CHADS_2 \geq 2$, we considered optimal control of anticoagulation therapy as greater than or equal to two-thirds of all follow-up international normalised ratio values were within the therapeutic range. Also, for patients with $CHADS_2 \geq 2$, we also considered optimal control of anticoagulation therapy when patients on other anticoagulants (novel oral anticoagulants/direct oral anticoagulants). Besides, Patients with $CHADS_2$ scores $< 2$ who did not receive anticoagulation therapy were also considered to meet the 'A' criterion. For the 'B' criterion, we defined good symptom(s) control when the patient received rate control or(and) anti arrhythmic agents. For the 'C' criterion, only cardiovascular drugs use was available from our database, and therefore we evaluated optimal pharmacologic management of the main cardiovascular comorbidities according to current European recommendations as first-line therapy. A patient qualified for the 'C' criterion when affected with $\geq 1$ of these conditions and prescribed/treated according to the best medical treatment defined according to the current clinical guidelines. Optimal medical treatment was defined as follows: (i) for hypertension, treatment with the use of one or several antihypertensive agents (angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blocker (ARB), β-blockers, calcium channel blockers and digoxin). (ii) for coronary artery disease (CAD), treatment with ACEI/ ARB, β-blockers, and lipid lowering agents; (iii) for previous stroke/TIA, treatment with lipid lowering agents; (iv) for heart failure (HF), treatment with ACEI/ ARB and β-blockers; For all the comorbidities considered, those optimally treated for all the conditions reported were defined as fulfilling the 'C' criterion

### 2.3. Patient outcomes

Blinded independent clinical events committees reviewed and adjudicated all of the events according to standardized principles. The primary endpoint for our analyses was a composite of the major adverse cardiac events or neurological events (MACNE), including all-cause death, stroke, and non-CNS (central nervous system) systemic embolism. The secondary endpoint included major bleeding, cardiovascular death, hospital readmission for AF complications, HF and MI. Major bleeding was defined by the International Society of Thrombosis and Hemostasis criteria (Supplementary Appendix 1) [24].

### 2.4. Clustering

The process of characterizing clusters of the AF population comprised several steps. First, we utilized 45 baseline variables of AF patients (Supplementary Appendix 2), which were maximally parallel with those used in previous studies. Continuous variables were normalized and categorical variables were encoded using the one-hot vector encoding for subsequent analysis. The k-prototypes algorithm is used to cluster data with mixed numeric and categorical values, which is applicable to identify patient clusters. The distance between each patient and prototype was calculated as a weighted sum of hamming distance on categorical variables and Euclidean distance on continuous variables. The distance between two mixed-type objects $X$ and $Y$, which were described by variables $V_1^r, V_2^r, \cdots, V_m^r, V_{m+1}^c, \cdots, V_n^c$, where the first m variables were numerical values while the others were categorical values, was measured by $d(X,Y) = \sum_{j=1}^{m}\left(x_j - y_j\right)^2 + \gamma\sum_{j=m+1}^{n}\delta\left(x_j, y_j\right)$, where the first term was the squared Euclidean distance measure on the numerical variables and the second term was the hamming distance measure on the categorical variables. The weight $\gamma$ was used to balance the contribution of two types of variables [25,26].

The k-prototypes algorithm iteratively clustered patients by repeating (1) selecting initial prototypes from data, (2) assigning each patient to the nearest prototype as clusters by calculating distances with prototypes, and (3) reallocating prototypes within each cluster, until the prototypes stayed consistent. The highest frequency of categorical variables and the mean values of continuous variables were utilized to reallocate prototypes in each cluster. On account of the number of k needed to be pre-determined in the k-prototypes method, silhouette coefficient analysis, which validated homogeneity within clusters and heterogeneity among clusters, was performed to choose the optimal number. The silhouette coefficients changed along with the clustering number k in the k-prototypes method (Fig. S1). Seeing that the higher silhouette coefficient indicated clearer clustering patterns, the 3-cluster k-prototypes model was chosen in this study.

### 2.5. Characteristics and outcome Comparisons among clusters

Baseline characteristics were compared among three clusters using the one-way ANOVA test for continuous variables, which presented as medians with interquartile ranges or means with standard deviations (SDs), and the chi-square test for categorical variables, which presented as counts and percentages.

For MACNE, all-cause death, stroke, non-CNS systemic embolism, cardiovascular death, and major bleeding, unadjusted and adjusted hazard ratios (HR and aHR) with their 95 % confidence interval (CI) were calculated using Cox proportional hazards models. The adjustments of them included $CHADS_2$ score, specialists for AF management, and medications (Supplementary Appendix 3). Kaplan-Meier survival curves were derived from baseline to the time of each outcome, compared with using the Log-Rank test. To assess the impact of adherence to the ABC pathway on MACNE, HR and aHR with their 95 % CI were calculated using the Cox regression model for ABC (A, B, C) vs. non-ABC (A, B, C).

## 3. Results

### 3.1. Baseline characteristics in three clusters

Demographics and clinical variables in the three identified clusters are shown in Table 1. The radar chart demonstrates the distribution of the main characteristics within each cluster (Fig. S2). We summarize the principal characteristics of each cluster in the following.

### 3.2. Cluster 1: Old patients with Atherosclerotic-Comorbidities

This cluster (n = 964) was the largest among the three. It represents the oldest (median age, 75 years; interquartile range [IQR], 69–80 years) persistent/permanent AF population. The main characteristics of this cluster were the highest prevalence rates of previous atherosclerotic and/or other comorbidities, which included CAD (67.5 %), MI (12.0 %), hypertension (72.0 %), diabetes mellitus (DM, 20.9 %), left ventricular hypertrophy (LVH, 20.7 %), stroke/TIA (transient ischemic attack, 24.6 %), dementia or cognitive defects (3.6 %) and emphysema/ chronic obstructive pulmonary disease (COPD, 16.6 %). Corresponding to the highest degree of comorbidities, they had the highest mean (SD) $CHADS_2$ score (2.3 [1.4]).

### 3.3. Cluster 2: Young female with Valve-Comorbidities

Patients (n = 407) in Cluster 2 were the youngest (median age, 58 years; IQR, 52–68) and more likely to be female (67.6 %). Typical characteristics of this cluster were the highest rates of VHD (64.9 %), RHD (63.4 %), and previous valve surgery/percutaneous valvuloplasty (21.6 %). They also had the highest prevalence of HF (74.9 %) and LVSD (left ventricular systolic dysfunction, 31.4 %). Notably, this cluster had the lowest rates of CAD (9.6 %), MI (2.5 %), hypertension (15.2 %), DM (8.4 %), stroke/TIA (13.3 %), and emphysema/COPD (6.1 %).

### 3.4. Cluster 3: Paroxysmal AF patients with low comorbidities

Cluster 3 (n = 644) was a middle-aged (median age, 69 years; IQR, 56–76) paroxysmal AF patient cluster. These patients were more likely to be new-onset AF (21.6 %) and had the highest BMI (median BMI, 24.0 $kg/m^2$; IQR, 22.1–26.4). Compared with Cluster 1, Cluster 3 had lower rates of comorbidities including HF (10.7 %), LVH (9.8 %), LVSD (6.2 %), CAD (23.8 %), MI (3.4 %), hypertension (56.2 %), DM (11.8 %), stroke/TIA (13.7 %), dementia or cognitive defects (0.8 %) and emphysema/COPD (7.9 %).

### 3.5. Management patterns by clusters

The differences in management patterns across clusters were summarized in Table 2. Compared with patients in other clusters (Cluster 3: 60.2 % vs. Cluster 2: 36.6 % vs. Cluster 1: 29.9 %; P < 0.001), patients in Cluster 3 were more likely to meet the 'A' criterion, primarily due to their lower $CHADS_2$ scores, which indicated a reduced need for anticoagulant therapy in accordance with guideline recommendations. Among 3 clusters, most patients satisfied the adequate rate or rhythm control requirement of 'B' criterion (Cluster 1: 85.4 % vs. Cluster 2: 83.0 % vs. Cluster 1: 73.9 %; $P < 0.001$). Moreover, 417 of 644 (64.8 %) patients in Cluster 3 satisfied the comorbidity management requirements of 'C' criterion, followed by Cluster 2 and Cluster 1 (35.9 %, 31.3 % respectively; $P < 0.001$). Overall, 82 patients in Cluster 1 (8.5 %), 44 patients in Cluster 2 (10.8 %), 193 patients in Cluster 3 (30.0 %) were managed in accordance with the ABC pathway (P < 0.001).

### 3.6. Association with clinical outcomes

The clinical outcomes of each cluster were markedly different. Occurrences of MACNE varied significantly among clusters (Table S1).

**Table 1**
Characteristics of the 2,015 AF patients according to the three identified clusters [a].

| Characteristic | Cluster 1 n = 964 (47.8 %) | Cluster 2 n = 407 (20.2 %) | Cluster 3 n = 644 (32.0 %) | P Value |
|---|---|---|---|---|
| Demographics | | | | |
| Age, median (IQR), y | 75 (69–80) | 58 (52–68) | 69 (56–76) | 0<.001 |
| Female, No. (%) | 549 (57.0 %) | 275 (67.6 %) | 280 (43.5 %) | 0<.001 |
| Body mass index, median (IQR), $kg/m^2$ | 23.4 (21.3–25.6) | 22.2 (19.7–24.5) | 24.0 (22.1–26.4) | 0<.001 |
| Systolic blood pressure, median (IQR), mm Hg | 139 (120–150) | 120 (107–130) | 128 (116–142) | 0<.001 |
| Diastolic blood pressure, median (IQR), mm Hg | 80 (70–90) | 75 (68–80) | 80 (70–88) | 0<.001 |
| Initial Heart Rate, median (IQR), beats/min | 92 (78–115) | 93 (76–113) | 109 (87–135) | 0<.001 |
| ED visit | | | | |
| Prior diagnosis of AF before this ED visit | | | | |
| New-onset AF | 83 (8.6 %) | 20 (4.9 %) | 139 (21.6 %) | 0<.001 |
| ED visit cause of AF | 261 (27.1 %) | 102 (25.1 %) | 462 (71.7 %) | 0<.001 |
| Patient in AF when leaving ED | 873 (90.6 %) | 387 (95.1 %) | 288 (44.7 %) | 0<.001 |
| Patient outcome from ED visit | | | | |
| Admitted | 771 (80.0 %) | 150 (36.9 %) | 127 (19.7 %) | 0<.001 |
| Discharged | 191 (19.8 %) | 256 (62.9 %) | 516 (80.1 %) | 0<.001 |
| Referred to specialist for management of AF | 577 (59.9 %) | 269 (66.1 %) | 269 (41.8 %) | 0<.001 |
| Medical history, No. (%) | | | | |
| MI | 116 (12.0 %) | 10 (2.5 %) | 22 (3.4 %) | 0<.001 |
| CAD | 651 (67.5 %) | 39 (9.6 %) | 153 (23.8 %) | 0<.001 |
| CHD | 15 (1.6 %) | 19 (4.7 %) | 9 (1.4 %) | 0<.001 |
| HF | 380 (39.4 %) | 305 (74.9 %) | 69 (10.7 %) | 0<.001 |
| RHD | 40 (4.1 %) | 258 (63.4 %) | 20 (3.1 %) | 0<.001 |
| LVH by electrocardiogram or echo | 200 (20.7 %) | 67 (16.5 %) | 63 (9.8 %) | 0<.001 |
| Permanent pacemaker | 41 (4.3 %) | 9 (2.2 %) | 14 (2.2 %) | 0.031 |
| Cardiac surgery < 30 days ago | 1 (0.1 %) | 5 (1.2 %) | 2 (0.3 %) | 0.009 |
| Hypertension | 694 (72.0 %) | 62 (15.2 %) | 362 (56.2 %) | 0<.001 |
| Stroke/TIA | 237 (24.6 %) | 54 (13.3 %) | 88 (13.7 %) | 0<.001 |
| Sleep apnea | 28 (2.9 %) | 14 (3.4 %) | 28 (4.3 %) | 0.301 |
| LVSD | 217 (22.5 %) | 128 (31.4 %) | 40 (6.2 %) | 0<.001 |
| Dementia or cognitive defects | 35 (3.6 %) | 4 (1.0 %) | 5 (0.8 %) | 0<.001 |
| Pericarditis | 1 (0.1 %) | 6 (1.5 %) | 1 (0.2 %) | 0<.001 |
| Emphysema/COPD | 160 (16.6 %) | 25 (6.1 %) | 51 (7.9 %) | 0<.001 |
| DM | 201 (20.9 %) | 34 (8.4 %) | 76 (11.8 %) | 0<.001 |
| Hyperthyroidism | 30 (3.1 %) | 11 (2.7 %) | 25 (3.9 %) | 0.535 |

(continued on next page)

**Table 1** (*continued*)

| Characteristic | Cluster 1 n = 964 (47.8 %) | Cluster 2 n = 407 (20.2 %) | Cluster 3 n = 644 (32.0 %) | P Value |
|---|---|---|---|---|
| VHD | 55 (5.7 %) | 264 (64.9 %) | 17 (2.6 %) | 0<.001 |
| Valve Surgery /Percutaneous valvuloplasty | 9 (0.9 %) | 88 (21.6 %) | 6 (0.9 %) | 0<.001 |
| Major bleeding | 34 (3.5 %) | 13 (3.2 %) | 12 (1.9 %) | 0.143 |
| Falls | 81 (8.4 %) | 23 (5.7 %) | 31 (4.8 %) | 0.012 |
| AF type, No. (%) | | | | |
| Paroxysmal AF | 148 (15.4 %) | 38 (9.3 %) | 432 (67.1 %) | 0<.001 |
| Persistent AF | 215 (22.3 %) | 75 (18.4 %) | 159 (24.7 %) | 0.059 |
| Permanent AF | 601 (62.3 %) | 294 (72.2 %) | 53 (8.2 %) | 0<.001 |
| Other risk factors, No. (%) | | | | |
| Tobacco use | 210 (21.8 %) | 69 (17.0 %) | 154 (23.9 %) | 0.027 |
| Alcohol use | 46 (4.8 %) | 11 (2.7 %) | 54 (8.4 %) | 0<.001 |
| $CHADS_2$, mean (SD) | 2.3 ± 1.4 | 1.4 ± 1.1 | 1.3 ± 1.2 | 0<.001 |

Abbreviations: IQR, interquartile range; ED, emergency department; AF, atrial fibrillation; MI, myocardial infarction; CAD, coronary artery disease; CHD, congenital heart disease; HF, heart failure; RHD, rheumatic heart disease; LVH, left ventricular hypertrophy; TIA, transient ischemic attack; LVSD, left ventricular systolic dysfunction; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; VHD, valvular heart disease.

[a] Continuous variables are presented as median (IQR) or mean (SD) and categorical variables are expressed as counts and percentages.

Cluster 1 had the highest risk of MACNE, followed by Cluster 2 and Cluster 3 (3.20, 1.83, and 1.13 events per 10 patient-years, respectively; $P < 0.001$, Fig. 1A, Table S1). Kaplan-Meier curves for all-cause death and cardiovascular death showed a similar trend. Fig. 1 exhibits significant differences in stroke ($P < 0.001$, Fig. 1B, Fig. 1C, and Fig. 1D, respectively), and major bleeding ($P = 0.010$, Fig. 1E) across the three clusters. However, no significant difference was presented in terms of non-CNS systemic embolism (Table S1).

In addition, after adjustment for the $CHADS_2$ score, specialists, and medications, the differences in MACNE, all-cause death, cardiovascular death, and stroke were still significant among clusters (Fig. 2). Compared with Cluster 3, the adjusted risks of MACNE were significantly higher in the other two clusters (Cluster 1: aHR, 2.436, 95 % CI, 1.837–3.231, $P < 0.001$; and Cluster 2: aHR, 1.878, 95 % CI, 1.325–2.662, $P < 0.001$).

### 3.7. Adherence to ABC pathway and outcomes by clusters (Table 3)

Overall, all clusters showed that full adherence to the ABC pathway was associated with a significant reduction in the risk of MACNE. (Cluster 1: aHR, 0.488,95 % CI, 0.247–0.964, $P = 0.039$ and Cluster 2: aHR, 0.135, 95 % CI, 0.019–0.977, $P = 0.047$; Cluster 3: aHR, 0.487, 95 % CI, 0.239–0.990, $P = 0.047$). For all clusters, adherence to the 'A' criterion was critical, which significantly reduced the risk of MACNE. (Cluster 1: aHR, 0.628, 95 % CI, 0.431–0.916, $P = 0.016$; Cluster 2: aHR, 0.529, 95 % CI, 0.299–0.936, $P = 0.029$; and Cluster 3: aHR, 0.520, 95 % CI, 0.279–0.966, $P = 0.039$). In Cluster 1 and Cluster 3, adherence to the 'B' criterion was also found to be associated with a lower risk for MACNE. (Cluster 1: aHR, 0.628,95 % CI, 0.431–0.916, $P = 0.016$, and Cluster 3: aHR, 0.525, 95 % CI, 0.317–0.869, $P = 0.012$). Besides, adherence to the 'C' criterion reduced the risk of MACNE by 49.7 % in Cluster 2.

**Table 2**
Treatment patterns of the 2,015 AF patients according to the three identified clusters.

| Characteristic | Cluster 1 Atherosclerotic-Comorbid Cluster n = 964 | Cluster 2 Valve-Comorbid Cluster n = 407 | Cluster 3 Low Comorbidity Cluster n = 644 | P Value |
|---|---|---|---|---|
| Medication management strategy, No. (%) | | | | |
| ABC pathway adherence | 82 (8.5 %) | 44 (10.8 %) | 193 (30.0 %) | 0<.001 |
| Adherence to the 'A' criterion | 288 (29.9 %) | 149 (36.6 %) | 388 (60.2 %) | 0<.001 |
| Adherence to the 'B' criterion | 823 (85.4 %) | 338 (83.0 %) | 476 (73.9 %) | 0<.001 |
| Adherence to the 'C' criterion | 302 (31.3 %) | 146 (35.9 %) | 417 (64.8 %) | 0<.001 |
| Antihypertensive and rate control agents, No. (%) | 796 (82.6 %) | 336 (82.6 %) | 441 (68.5 %) | 0<.001 |
| Diuretic | 397 (41.2 %) | 267 (65.6 %) | 111 (17.2 %) | 0<.001 |
| Calcium channel blockers | 255 (26.5 %) | 34 (8.4 %) | 174 (27.0 %) | 0<.001 |
| β-blockers | 430 (44.6 %) | 167 (41.0 %) | 286 (44.4 %) | 0.445 |
| Angiotensin receptor blocker | 200 (20.7 %) | 24 (5.9 %) | 95 (14.8 %) | 0<.001 |
| Angiotensin-converting enzyme inhibitor | 265 (27.5 %) | 104 (25.6 %) | 93 (14.4 %) | 0<.001 |
| Digoxin | 292 (30.3 %) | 254 (62.4 %) | 72 (11.2 %) | 0<.001 |
| Lipid lowering agents, No. (%) | 345 (35.8 %) | 24 (5.9 %) | 113 (17.5 %) | 0<.001 |
| Statins | 344 (35.7 %) | 23 (5.7 %) | 110 (17.1 %) | 0<.001 |
| Other lipid lowering agents | 1 (0.1 %) | 1 (0.2 %) | 4 (0.6 %) | 0.171 |
| Oral anticoagulants, No. (%) | 174 (18.0 %) | 181 (44.5 %) | 96 (14.9 %) | 0<.001 |
| Warfarin | 108 (11.2 %) | 152 (37.3 %) | 82 (12.7 %) | 0<.001 |
| Other anticoagulant | 74 (7.7 %) | 33 (8.1 %) | 23 (3.6 %) | 0.001 |
| Anti-arrhythmic agents, No. (%) | 125 (13.0 %) | 30 (7.4 %) | 134 (20.8 %) | 0<.001 |
| Amiodarone | 100 (10.4 %) | 13 (3.2 %) | 80 (12.4 %) | 0<.001 |
| Flecainide | 0 (0.0 %) | 0 (0.0 %) | 1 (0.2 %) | 0.345 |
| Propafenone | 12 (1.2 %) | 4 (1.0 %) | 38 (5.9 %) | 0<.001 |
| Sotalol | 4 (0.4 %) | 0 (0.0 %) | 3 (0.5 %) | 0.405 |
| Other anti-arrhythmic agent | 16 (1.7 %) | 13 (3.2 %) | 18 (2.8 %) | 0.146 |

Abbreviations: AF, atrial fibrillation; ICD, implantable cardioverter-defibrillator.

## 4. Discussion

This study specifically focused on evaluating the ABC pathway in the comprehensive clinical profiles of AF which were identified by cluster analysis. Our principal findings were as follows: (1) we identified three clinically relevant clusters and found significant differences across the clusters in baseline characteristics, patient management, and adverse outcomes; (2) we newly identified a cluster dominated by VHD and RHD comorbidities and generalized atherosclerotic-comorbid and low-comorbidity cluster to broader populations, refining the overall understanding of AF heterogeneity; (4) adherence to the ABC pathway was independently associated with a lower risk of the MACNE in all clusters; For different clusters, adherence the 'A' /'B' /'C' criterion alone showed differential impact; (5) corresponding to the different comprehensive clinical profiles, we should pay more attention to the different ABC criterion, which may optimize strategies for individualized

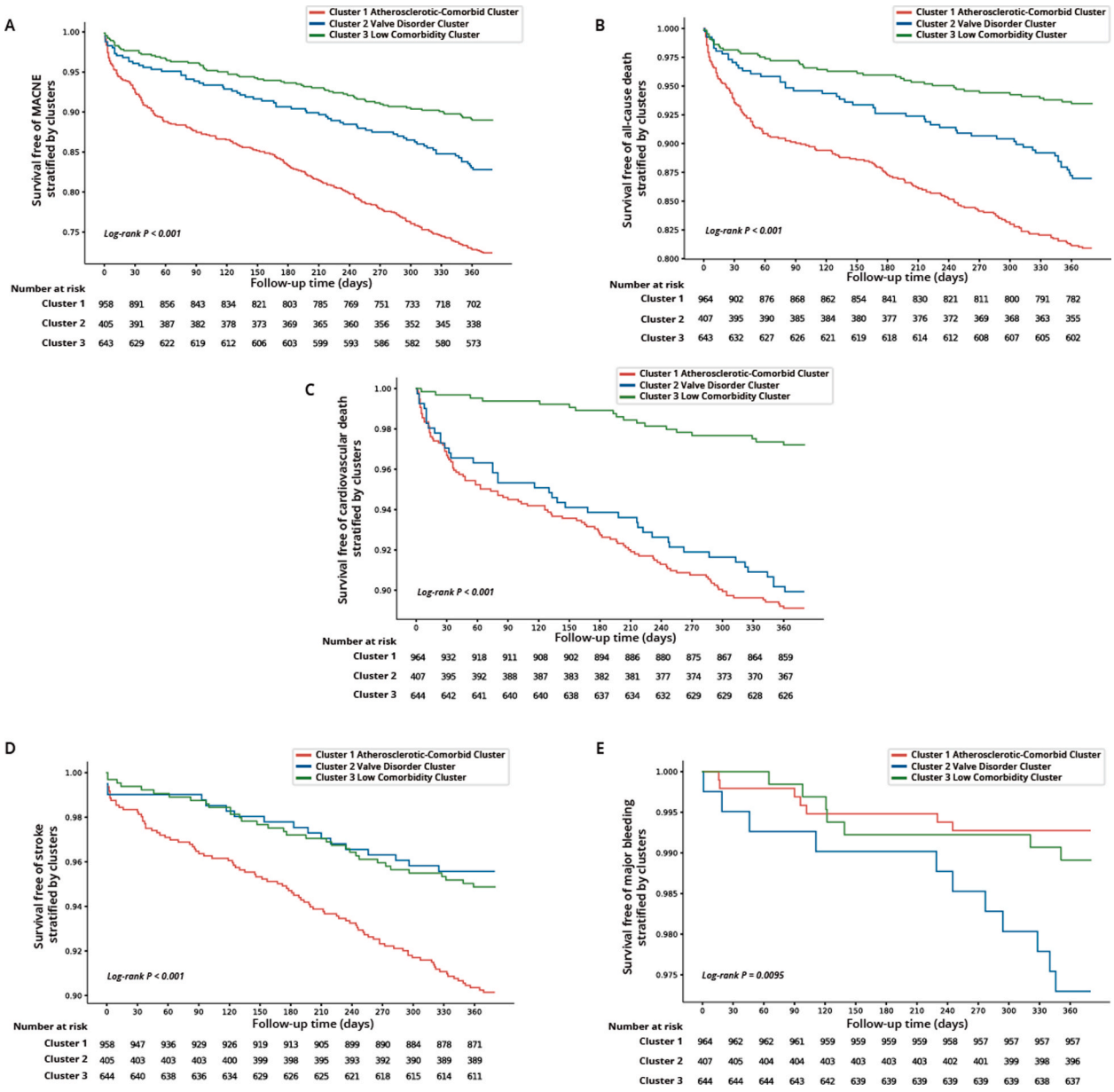


**Fig. 1.** Survival free of MACNE, all-cause death, cardiovascular death, stroke, major bleeding stratified by clusters. Kaplan-Meier curves for MACNE (A), all-cause death (B), cardiovascular death (C), stroke (D), major bleeding (E) stratified by clusters. Abbreviations: MACNE, major cardiovascular or neurological adverse outcomes.

management.

Cluster analysis, a data-driven approach, has been increasingly applied in cardiovascular diseases which allows us to improve clinical phenotype identification and optimize strategies for individualized management [16–22,27,28]. For example, Karwath et al. utilized a clustering technique to distinguish the prognostic response from β-blockers in HF patients with sinus rhythm and AF [27]. Romiti et al., Proietti et al., and Krittayaphong et al. performed cluster analysis based on cohorts of AF patients and assessed the impact of the ABC pathway on the outcomes according to clusters [20,29,30].

China has over 8 million AF patients [31,32]. The risk factors, the prevalence of RHD and VHD, concomitant diseases, and the management of AF patients in China are significantly different from the previous cohorts [33]. Using a large AF cohort in China, we can reveal the heterogeneity spectrum of AF in China, to fill in a key gap in the profiling of worldwide AF patient populations. Our results showed both similarities and differences with previous studies. Our study corroborated the previously reported groups (atherosclerotic-comorbid and low comorbidity cluster) and the differentiation ability of comorbidities/risk factors on clustering and outcomes [16–22,27,28]. Notably, our study found the new valve-comorbid cluster which was mainly differentiated by VHD and RHD. The reason that valve-comorbid cluster was not observed in previous studies may be because of the substantial prevalence difference of comorbidities. For example, the prevalence of RHD was quite lower in North America, Western and Eastern Europe than in China (2.2 %, 1.5 %, 3.8 % vs 15.7 %) [33]. Thus, resulting in insufficient numbers to differentiate clusters.

For the first time, we discovered a valve-comorbid cluster, which could complement the existing understanding of clinical profiles and suggest new optimizations in clinical practices. Patients, predominantly younger members, were more likely to be assigned to the Cluster 2 if they were female and had VHD or RHD. We found that the clinical profile as expressed by our cluster characteristics or $CHADS_2$ score was more likely related to stroke risks, irrespective of the presence of VHD

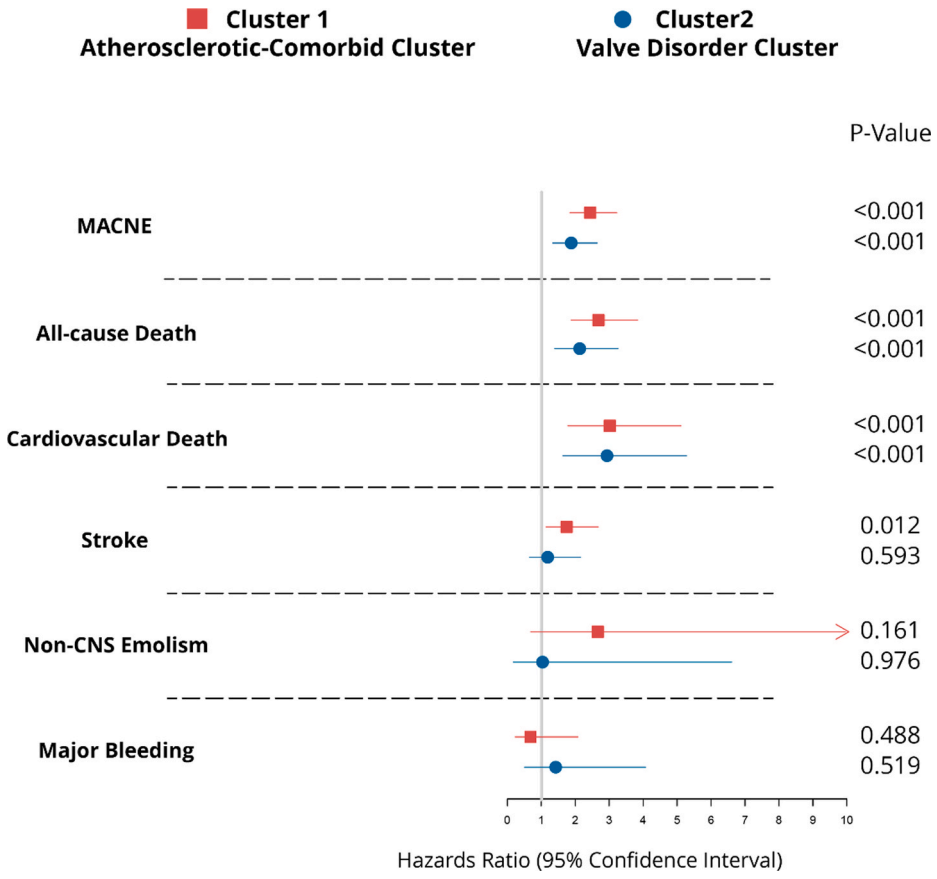


**Fig. 2.** Identified clusters and adjusted risk of clinical events (Cluster 3: low comorbidity burden AF as a reference [the lowest risk]). Abbreviations: MACNE, major cardiovascular or neurological adverse outcomes; CNS, central nervous system.

**Table 3**
Adherence to ABC pathway and MACNE by clusters.

| | MACNE | |
|---|---|---|
| | aHR (95 % CI) | P |
| Cluster 1 | | |
| ABC vs Non-ABC | 0.488 (0.247–0.964) | 0.039 |
| A vs Non-A | 0.628 (0.431–0.916) | 0.016 |
| B vs Non-B | 0.666 (0.482–0.922) | 0.014 |
| C vs Non-C | 1.115 (0.848–1.466) | 0.434 |
| Cluster 2 | | |
| ABC vs Non-ABC | 0.135 (0.019–0.977) | 0.047 |
| A vs Non-A | 0.529 (0.299–0.936) | 0.029 |
| B vs Non-B | 0.621 (0.343–1.126) | 0.117 |
| C vs Non-C | 0.503 (0.273–0.928) | 0.028 |
| Cluster 3 | | |
| ABC vs Non-ABC | 0.487 (0.239–0.990) | 0.047 |
| A vs Non-A | 0.520 (0.279–0.966) | 0.039 |
| B vs Non-B | 0.525 (0.317–0.869) | 0.012 |
| C vs Non-C | 0.720 (0.417–1.243) | 0.238 |

Abbreviations: MACNE, major adverse cardiovascular or neurological event; aHR, adjusted hazard ratio; CI confidence interval; ABC, Atrial fibrillation Better Care; A, avoid stroke; B, better symptom management; C, cardiovascular and comorbidity risk reduction [3].
[a]: Adjusted for $CHADS_2$ score, specialists for AF management and medications.

[34]. Our findings were in agreement with the current guidelines for AF management which recommended using the $CHA_2DS_2$-VASc score to assess stroke risk for AF patients without moderate-to-severe mitral stenosis/mechanical heart valve defects [35–38]. Interestingly, cardiovascular mortality of patients in cluster 2 surprisingly high which could be due to the poorest cardiac function of these patients. Also, we found that adherence to the ABC pathway was associated with statistically lower rates of MACNE in patients with in cluster 2, which was mainly influenced by adherence to the 'A' and 'C' criterion. Thus, we should focus not only on the management of AF (anticoagulant therapy) but also on how to treat varied underlying cardiovascular disease (especially HF and VHD) in those patients. Moreover, considering the rate of RHD is high in economically disadvantaged populations, low-cost interventions such as early education, and primary/secondary prophylaxis should be taken to prevent RHD and the development of AF [39].

The major features of Cluster 1 were the highest rates of comorbidities, the highest risks of important adverse outcomes, and the highest value of $CHA_2DS_2$-VASc/$CHADS_2$. For patients with atherosclerotic comorbidities, our study underscored the effectiveness of full adherence to the ABC pathway and found a significant proportion of them were on anticoagulation therapy ('A' criterion) and rate or rhythm control ('B' criterion) which provided evidence to support the suggestion of recent guidelines [37,38]. Besides, our results showing that adherence to the C criterion was not associated with a risk reduction in MACNE for Cluster 1 were somewhat surprising and, to a certain extent, disappointing. However, several potential reasons may explain this finding. Based on data from a multicenter, prospective, observational study in China, our results reflect real-world healthcare disparities. In regions with limited medical infrastructure or insufficient awareness of comprehensive comorbidity management, patients in Cluster 1 may encounter challenges in accessing optimal treatments for their comorbidities, particularly during acute care in emergency settings. This may contribute to the observed lower adherence to the 'C' criterion. Furthermore, patients in Cluster 1 had significantly higher rates of comorbidities. Even with adherence to the C criterion, the residual risk of adverse outcomes may

remain substantial, potentially diminishing the observable protective effects of comorbidity management. These findings highlight the challenges of implementing comprehensive comorbidity management in elderly patients with multiple conditions, emphasizing the need for personalized interventions and equitable access to healthcare resources.

Alongside generalized treatment protocol for high-risk patients, cluster analysis could also help develop management strategies specifically for low-risk populations (Cluster 3). Patients in Cluster 3 had comparatively lower comorbidity frequencies and better heart functions. The majority of those patients diagnosed with paroxysmal AF are likely to receive anti-arrhythmic therapy. Low comorbidity patients showed the lowest value of $CHADS_2$ and the most favorable prognosis for all outcomes. The data suggest that even in low-risk cluster, adherence to the ABC pathway, especially 'A' criterion and 'B' criterion, exerted a notable protective role. We indicated that appropriate management of anticoagulation and symptom was necessary for low comorbidity patients. Besides, considering that a relatively large proportion of low comorbidity patients had a history of alcohol taking, smoking, and the highest relative BMI, it's important to produce relevant health education, prompt intervention, and lifestyle modification for better outcomes.

It is important to underline that patients were collected consecutively from different grades of hospitals and with a minimal set of inclusion/exclusion criteria. Even though the cohort is not population based, its recruitment of patients with AF from EDs avoids some potential biases of other studies that enrolled patients from cardiology specialty clinics. Also, we included all variables in our clustering analysis as close as possible from a real clinical situation.

## 5. Limitations

First, although this study included a large sample size from a prospective multicenter cohort, expanding the dataset to incorporate more diverse sources would be beneficial. Second, due to data limitations, the variables used in the clustering analysis did not include echocardiographic parameters or several concomitant diseases, such as vascular events, which might have enhanced the precision of cluster classifications and phenotypic descriptions. Third, the study did not comprehensively evaluate comorbidities and risk factor management, such as diabetes control, or lifestyle modifications, including alcohol consumption and physical activity, in AF patients. Consequently, the role of the 'C' criterion may have been underestimated. Fourth, the dataset was collected over a decade ago. Given the advancements in AF management (catheter ablation) in recent years, the findings of this study should be interpreted with caution. Fifth, the lack of external validation limits the extrapolation of these findings to broader patient populations. Therefore, prospective and external validations are further needed in the future.

## 6. Conclusion

We identified three distinct clinical AF clusters of phenotype patterns with different underlying pathophysiology and differential risks of adverse outcomes through a cluster analysis in a large multicenter cohort in China. The results refined existing stratification of AF and may optimize personalized and integrative management strategies of AF according to comprehensive clinical profiles.

## CRediT authorship contribution statement

**Jingyang Wang:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Haiyang Bian:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Jiangshan Tan:** Writing – review & editing, Methodology, Conceptualization. **Jun Zhu:** Writing – review & editing, Supervision, Data curation. **Lulu Wang:** Writing – review & editing, Data curation. **Wei Xu:** Writing – review & editing, Methodology. **Lei Wei:** Writing – review & editing, Methodology. **Xuegong Zhang:** Writing – review & editing, Supervision, Methodology, Funding acquisition. **Yanmin Yang:** Writing – review & editing, Supervision, Investigation, Data curation, Conceptualization.

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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.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2025.101621.

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