

Incidence and Predictors of Hospitalization in Patients with Atrial Fibrillation: Results from the Chinese Atrial Fibrillation Registry Study

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Abstract

Background: Patients with atrial fibrillation (AF) underwent a high risk of hospitalization, which, however, has not been paid much attention in clinic. Therefore, we aimed to assess the incidence, causes and predictors of hospitalization in AF patients.

Methods: From August 2011 to December 2017, 20,172 AF patients from the Chinese Atrial Fibrillation Registry (China-AF) Study were enrolled in this study. We described the incidence, causes of hospitalization according to age and gender categories. The Cox proportional hazards model was employed to identify predictors of first all-cause and first cause-specific hospitalization.

Results: After a mean follow-up of 37.3 ± 20.4 months, 7,512 (37.2%) AF patients experienced one or more hospitalizations. The overall incidence of all-cause hospitalization was 24.0 per 100 patient-years. Patients aged < 65 years were predominantly hospitalized for AF (42.1% of the total frequency of hospitalizations); while patients aged 65-74 and ≥ 75 years were mainly hospitalized for non-cardiovascular diseases (43.6% and 49.3%, respectively). Multivariate Cox model analysis verified the higher risk of hospitalization in patients complicated with heart failure (HF) [hazard ratio (HR) 1.15, 95% confidence interval (CI) 1.08-1.24], established coronary artery disease (CAD) (HR 1.26, 95%CI 1.19-1.34), ischemic stroke/transient ischemic attack (TIA) (HR 1.26, 95%CI 1.18-1.33), diabetes (HR 1.16, 95%CI 1.10-1.22), chronic obstructive pulmonary disease (COPD) (HR 1.41, 95%CI 1.13-1.76), gastrointestinal disorder (HR 1.39, 95%CI 1.23-1.58), and renal dysfunction (HR 1.31, 95%CI 1.16-1.48).

Conclusions: More than one-third of AF patients included in this study were hospitalized at least once during almost 3 years of follow-up. The main cause for hospitalization among elderly patients (≥ 65 years) is non-cardiovascular diseases rather than AF. Multidisciplinary management of comorbidities should be advocated as strategies to reduce hospitalization in AF patients.

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Background

Atrial fibrillation (AF), considered as a global cardiovascular pandemic, has significantly increased morbidity[1], and affects more than 3% of the population in many countries[2–4]. Due to its detrimental effect on the quality of life (QoL)[5] and higher risk of thromboembolic stroke and cardiovascular diseases (CVD)[6, 7], together with its complex interplay with clinical conditions, the hospitalization rate of AF patients for CVD or non-CVD is still considerably higher than that of patients without AF despite the advancement of medicine today[8]. The AF hospitalization-related medical resource consumption and economic cost associated are enormous and continue to be rising. A recent Australian study showed that from 1993–2013, the number of hospitalized AF patients increased by 295%, which significantly exceeds the increase of myocardial infarction (MI; increased by 73%) and heart failure (HF; increased by 39%) over the same period[9]. Furthermore, Korean National Health Insurance Service (NHIS) database

demonstrated that the overall cost of AF hospitalization-related medical care still grows exponentially (from €68.4 million in 2006 to €388.4 million in 2015; relative increase, 468%) even after the adjustment of inflation, which is equivalent to 0.78% of the Korean NHIS total expenditure[10].

According to the findings from the China National Stroke Screening and Prevention Project, the estimated overall prevalence of AF among Chinese adults aged ≥ 40 years in 2014–2015 was 2.31%[11], which is projected to increase further with the economic growth, population aging, and detection tool improvement. Considering that the increasing AF care constitutes a significant challenge for the constrained public health resources and economic cost, it is necessary to analyze the available information on hospitalization. Nevertheless, little is known about AF-related hospitalization in China. Therefore, this study was designed to analyze data from the China Atrial Fibrillation Registry (China-AF) to examine the incidence, main causes, and risk factors of hospitalization in an unselected cohort of AF patients. Such information is crucial in enabling the development of effective targeted efforts and interventions to reduce the overall medical and economic burden in this population.

Methods

Study participants

The study was based on the data from the China-AF from August 2011 to December 2017. The China-AF has been described previously[12]. In brief, it is a prospective, multicenter, and hospital-based ongoing registry study. Thirty-one tertiary and non-tertiary hospitals in Beijing providing a clinical service of AF management participated in this registry study. Eligible patients were required to age 18 years or older with diagnosed AF. For the present study, patients were excluded if they met any of these criteria as follows: (1) transient and reversible AF (e.g. caused by cardiothoracic surgery, hyperthyroidism, and binge drinking), (2) suffering from other serious diseases with a life expectancy < 1 year, (3) diagnosis of rheumatic mitral stenosis or having mitral valve prostheses, (4) HF-related score of IV by New York Heart Association (NYHA) or score of IV by European Heart Rhythm Association (EHRA) classification of AF-related symptoms requiring long-term hospitalization, (5) follow-up periods less than 6 months.

The study was approved by the Ethics Committee on Human Research of Beijing Anzhen Hospital, the Capital Medical University. All participants provided written informed consent.

Data collection

Each patient's demographic data such as age, gender, education level, and health insurance status were collected. Components of AF history included AF type, duration, the severity of symptoms, and prior treatment. The cardiovascular risk factors were smoking, drinking, and obesity. Current or preexisting comorbid conditions consisted of hypertension (HTN), coronary artery disease (CAD, any history of MI, percutaneous coronary intervention or coronary artery bypass grafting), HF, cardiomyopathy, ischemic stroke/transient ischemic attack (TIA), bleeding, chronic obstructive pulmonary disease (COPD), gastrointestinal disorder, renal dysfunction, hyperthyroidism/hypothyroidism, diabetes mellitus (DM), and

hyperlipidemia. The vital signs, laboratory tests, imaging examinations of patients were recorded. Medications were composed of rhythm control agents, rate control agents, antithrombotic drugs, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs), and cholesterol-lowering agents.

Outcomes

The primary outcome was all-cause hospitalization during the follow-up of patient cohort in this study. The secondary outcome was cause-specific hospitalization. Enrolled patients were followed up every 6 months by outpatient clinic visit or telephone interview. The main cause for hospitalization was determined by the site investigators according to the discharge diagnosis, which was broadly classified into AF, other CVD (CVD excluding AF), and non-CVD. Incidence rates for all-cause and cause-specific hospitalization were calculated as the ratio of hospitalization times to follow-up time per 100 person-years. Patients who participated within China-AF study during hospitalization were not accounted for this calculation.

Statistical analysis

Patients enrolled in this study were stratified by age (< 65 years; 65-74 years; \geq 75 years). Continuous variables were presented as mean (standard deviation, SD) and categorical variables were shown as counts (proportions). The comparison of variables of patients in different age groups was analyzed using one-way analysis of variance (ANOVA) (for continuous variables), and chi-square tests (for categorical variables). Hospitalization rate (per 100 patient-years) was expressed by age and gender. Kaplan-Meier curve was used to describe the number of patients at risk and the survival free of hospitalization to interpret the endpoints of the first all-cause and first cause-specific hospitalization time. Univariate and multivariate Cox proportional hazard regression analyses variables were conducted with (a) the first all-cause hospitalization, (b) the first AF hospitalization, and (c) the first other CVD hospitalization as the dependent variable to identify factors that are significantly associated with all-cause and cause-specific hospitalizations. The predictors that satisfied $P \leq 0.1$ in the univariate model were input into the multivariate stepwise Cox proportional analysis. Age and gender were mandatory in multivariate analyses. Hazard ratios (HRs) [95% confidence interval (CI)] and P-values were presented. P-value <0.05 was considered statistically significant. All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient baseline characteristics

A total of 23,108 patients from 31 separate sites from August 2011 to December 2017 were collected in the China-AF study, and after excluding, 20,172 AF patients were enrolled in this study (a mean age of 64.1 ± 12.0 years; 38.2% female). Their baseline characteristics stratified by age are presented in Table 1. The majority of patients (95.3%) were fully or partially covered by health insurance. More than 1/3 of

patients in each group have at least earned high school diplomas. Patients aged ≥ 75 years showed a higher proportion of female patients and persistent AF patients, more patients with EHRA score of ≥ 3 (AF-related symptoms), a higher prevalence of current or preexisting comorbid conditions, including CVD, DM, COPD, and renal dysfunction, as well as a more frequent use of ventricular rate control drugs, antiplatelet agents, ACEIs/ARBs and statins than patients in other age groups (all $P < 0.01$). Patients aged < 65 years tended to have more proneness to paroxysmal AF, more cardiovascular risk factors (47.7% overweight, 24.6% obese, 23.2% smoking and 28.3% drinking), and a higher prevalence of performing the radiofrequency catheter ablation (RFCA), together with a more frequent use of antiarrhythmic drugs and direct oral anticoagulants (DOACs) ($P < 0.01$). There was no significant difference in the proportion of patients with AF duration ≥ 1 year in each group.

Table 1
Baseline characteristics of the patients stratified by age.

Characteristics	Total (N = 20172)	< 65 (N = 9977)	65–74 (N = 5875)	≥ 75 (N = 4320)	P value
Female, n (%)	7707 (38.2)	2866 (28.7)	2740 (46.6)	2101 (48.6)	< 0.01
High school or above, n (%)	6137 (34.1)	3266 (36.4)	1643 (31.2)	1228 (33.0)	< 0.01
Health insurance, n (%)					
No insurance reimbursement	917 (4.7)	550 (5.8)	256 (4.5)	111 (2.6)	< 0.01
Partial insurance reimbursement	16670 (85.6)	8505 (89.1)	4875 (85.9)	3290 (77.3)	< 0.01
Full insurance reimbursement	1886 (9.7)	487 (5.1)	546 (9.6)	853 (20.1)	< 0.01
BMI, n (%)					
Normal (< 24 kg/m ²)	6310 (33.2)	2646 (27.7)	1918 (34.5)	1746 (44.7)	< 0.01
Overweight (24–28 kg/m ²)	8668 (45.6)	4559 (47.7)	2509 (45.1)	1600 (41.0)	< 0.01
Obese (BMI ≥ 28 kg/m ²)	4036 (21.2)	2344 (24.6)	1131 (20.4)	561 (14.4)	< 0.01
Smoking, n (%)	3170 (15.7)	2317 (23.2)	601 (10.2)	252 (5.8)	< 0.01
Drinking, n (%)	3881 (19.2)	2819 (28.3)	734 (12.5)	328 (7.6)	< 0.01
AF type, n (%)					
Newly diagnosed	1205 (6.0)	473 (4.8)	332 (5.7)	400 (9.3)	< 0.01
Paroxysmal AF	11692 (58.1)	6038 (60.7)	3465 (59.1)	2189 (50.8)	< 0.01

BMI, body mass index; AF, atrial fibrillation; CAD, coronary artery disease; TIA, transient ischemic attack; DOAC, direct oral anticoagulants; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; RFCA, radiofrequency catheter ablation; LAD, left atrial diameter; LVEF, left ventricular ejection fraction. $eGFR (ml/min \cdot 1.73 m^2) = 186 \times Scr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times 1.233$ (if Chinese). Renal dysfunction was defined as $eGFR < 60 ml/min \cdot 1.73 m^2$. According to the proportion of medical insurance company payment, health insurance was divided into three levels: full, partial, and no insurance reimbursement.

Characteristics	Total (N = 20172)	< 65 (N = 9977)	65–74 (N = 5875)	≥ 75 (N = 4320)	P value
Persistent AF	7229 (35.9)	3434 (34.5)	2071 (35.3)	1724 (40.0)	< 0.01
AF duration ≥ one year, n (%)	12236 (60.7)	6015 (60.3)	3626 (61.7)	2595 (60.1)	0.14
EHRA score, n (%)					
I	1655 (9.3)	796 (8.9)	478 (9.2)	381 (10.0)	< 0.01
II	11520 (64.4)	5952 (66.9)	3265 (63.2)	2303 (60.4)	< 0.01
III	4705 (26.3)	2154 (24.2)	1423 (27.6)	1128 (29.6)	< 0.01
Hypertension, n (%)	13393 (66.4)	5587 (56.0)	4365 (74.3)	3441 (79.7)	< 0.01
Heart failure, n (%)					
NYHA I	3946 (53.8)	1945 (67.4)	1208 (53.9)	793 (36.0)	< 0.01
NYHA II	2431 (33.2)	735 (25.5)	767 (34.2)	929 (42.1)	< 0.01
NYHA III	957 (13.1)	206 (7.1)	267 (11.9)	484 (21.9)	< 0.01
Established CAD, n (%)	3020 (15.0)	937 (9.4)	1050 (17.9)	1033 (24.0)	< 0.01
Cardiomyopathy, n (%)	365 (1.8)	233 (2.3)	88 (1.5)	44 (1.0)	< 0.01
Ischemic stroke/TIA, n (%)	2884 (14.3)	914 (9.2)	982 (16.7)	988 (22.9)	< 0.01
Haemorrhagic stroke, n (%)	225 (1.1)	91 (0.9)	60 (1.0)	74 (1.7)	< 0.01
Diabetes mellitus, n (%)	4702 (23.3)	1909 (19.1)	1539 (26.2)	1254 (29.0)	< 0.01

BMI, body mass index; AF, atrial fibrillation; CAD, coronary artery disease; TIA, transient ischemic attack; DOAC, direct oral anticoagulants; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; RFCA, radiofrequency catheter ablation; LAD, left atrial diameter; LVEF, left ventricular ejection fraction. $eGFR (ml/min \cdot 1.73 m^2) = 186 \times Scr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times 1.233$ (if Chinese). Renal dysfunction was defined as $eGFR < 60 ml/min \cdot 1.73 m^2$. According to the proportion of medical insurance company payment, health insurance was divided into three levels: full, partial, and no insurance reimbursement.

Characteristics	Total (N = 20172)	< 65 (N = 9977)	65–74 (N = 5875)	≥ 75 (N = 4320)	P value
Hyperlipidemia, n (%)	9785 (48.5)	5110 (51.2)	2816 (47.9)	1859 (43.0)	< 0.01
Chronic obstructive pulmonary disease, n (%)	169 (0.8)	35 (0.4)	54 (0.9)	80 (1.9)	< 0.01
Gastrointestinal disorder, n (%)	633 (3.1)	299 (3.0)	189 (3.2)	145 (3.4)	0.48
Hyperthyroidism/Hypothyroidism, n (%)	994 (4.9)	448 (4.5)	323 (5.5)	223 (5.2)	0.01
Renal dysfunction, n (%)	566 (3.5)	85 (1.1)	137 (3.0)	344 (10.2)	< 0.01
CHA2DS2-VASc score ≥ 2, n (%)	13424 (75.4)	3790 (49.8)	5314 (90.5)	4320 (100.0)	< 0.01
Antiarrhythmic drugs, n (%)	7330 (36.3)	4454 (44.6)	1969 (33.5)	907 (21.0)	< 0.01
Ventricular rate control, n (%)	9575 (47.5)	4096 (41.1)	2951 (50.2)	2528 (58.5)	< 0.01
Warfarin, n (%)	9449 (46.8)	4762 (47.7)	2941 (50.1)	1746 (40.4)	< 0.01
DOACs, n (%)	3268 (16.2)	1975 (19.8)	867 (14.8)	426 (9.9)	< 0.01
Aspirin/ Clopidogrel, n (%)	4894 (24.3)	1879 (18.8)	1478 (25.2)	1537 (35.6)	< 0.01
ACEIs/ARBs, n (%)	6828 (33.9)	2690 (27.0)	2265 (38.6)	1873 (43.4)	< 0.01
Statin, n (%)	7461 (37.0)	2987 (29.9)	2522 (42.9)	1952 (45.2)	< 0.01
History of RFCA, n (%)	8801 (43.6)	5595 (56.1)	2355 (40.1)	851 (19.7)	< 0.01
LAD, mm, (SD)	40.4 ± 6.5	39.8 ± 6.3	40.5 ± 6.4	41.7 ± 7.0	< 0.01

BMI, body mass index; AF, atrial fibrillation; CAD, coronary artery disease; TIA, transient ischemic attack; DOAC, direct oral anticoagulants; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; RFCA, radiofrequency catheter ablation; LAD, left atrial diameter; LVEF, left ventricular ejection fraction. $eGFR (ml/min \cdot 1.73 m^2) = 186 \times Scr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times 1.233$ (if Chinese). Renal dysfunction was defined as $eGFR < 60 ml/min \cdot 1.73 m^2$. According to the proportion of medical insurance company payment, health insurance was divided into three levels: full, partial, and no insurance reimbursement.

Characteristics	Total (N = 20172)	< 65 (N = 9977)	65–74 (N = 5875)	≥ 75 (N = 4320)	P value
LVEF, (SD)	62.9 ± 8.3	62.7 ± 8.2	63.5 ± 8.2	62.6 ± 8.9	< 0.01
BMI, body mass index; AF, atrial fibrillation; CAD, coronary artery disease; TIA, transient ischemic attack; DOAC, direct oral anticoagulants; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; RFCA, radiofrequency catheter ablation; LAD, left atrial diameter; LVEF, left ventricular ejection fraction. $eGFR (ml/min \cdot 1.73 m^2) = 186 \times Scr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times 1.233$ (if Chinese). Renal dysfunction was defined as $eGFR < 60 ml/min \cdot 1.73 m^2$. According to the proportion of medical insurance company payment, health insurance was divided into three levels: full, partial, and no insurance reimbursement.					

Rate and Causes of hospitalization

Over a mean follow-up of 37.3 ± 20.4 months, a total of 14,828 hospitalizations were identified, 7,512 patients (37.2%) had at least one hospitalization. The overall incidence of all-cause hospitalization was 24.0 per 100 patient-years. Hospitalization incidence rates and causes of AF patients of different ages and genders were shown in Fig. 1. Hospitalization rates of patients aged < 65, 65–74, and ≥ 75 years were 18.3 per 100 patient-years, 26.0 per 100 patient-years, and 33.5 per 100 patient-years, respectively. Hospitalizations occurred most frequently in female patients aged ≥ 75 years and were more common among females of all age groups. Among patients aged < 65 years, hospitalizations attributed to AF accounted for the largest proportion, reaching 42.1% of the total frequency of hospitalizations. While, patients aged 65–74 and ≥ 75 years were predominantly hospitalized for non-CVD (43.6% and 49.3% respectively). Kaplan-Meier curves of the first hospitalization for all-cause, AF, other CVD, or non-CVD causes were displayed in Fig. 2.

Factors associated with first all-cause hospitalization

The multivariate analysis identified several risk factors of first all-cause hospitalizations in AF patients (Table 2). Elderly patients were more likely to have all-cause hospitalization, as indicated by our results, compared with patients in the < 65 age group, patients in the 65–74 age group (HR 1.18, 95% CI 1.12–1.25, $P < 0.01$) and in the ≥ 75 age group (HR 1.38, 95% CI 1.29–1.47, $P < 0.01$) were more likely to experience hospitalization. EHRA ≥ 2 (HR 1.13, 95% CI 1.04–1.23, $P < 0.01$) and EHRA ≥ 3 (HR 1.18, 95% CI 1.08–1.30, $P < 0.01$) showed a significantly predictive role for all-cause hospitalization. Paroxysmal AF, AF duration ≥ 1 year, and left atrial enlargement were highly associated with risks of all-cause hospitalization. In addition, HTN (HR 1.09, 95% CI 1.03–1.15), HF (HR 1.15, 95% CI 1.08–1.30), CAD (HR 1.26, 95% CI 1.19–1.34), and ischemic stroke/TIA (HR 1.26, 95% CI 1.18–1.33) also contributed to the increased risk of all-cause hospitalization. Furthermore, non-cardiovascular comorbidities including DM (HR 1.16, 95% CI 1.10–1.22), COPD (HR 1.41, 95% CI 1.13–1.76), gastrointestinal disorder (HR 1.39, 95% CI 1.23–1.58), hyperthyroidism/hypothyroidism (HR 1.26, 95% CI 1.13–1.40), and renal dysfunction (HR

1.31, 95% CI 1.16–1.48) were tightly linked to a higher all-cause hospitalization rate during follow-up. Of note, the use of ACEIs/ARB was identified as a protective factor of all-cause hospitalization.

Table 2
Factors associated with all-cause hospitalization

Characteristics	Multivariate analysis	
	HR (95%CI)	P value
Age (years)		
< 65	Ref	-
65–74	1.18 (1.12,1.25)	< 0.01
≥ 75	1.38 (1.29,1.47)	< 0.01
Health insurance		
No insurance reimbursement	Ref	-
Partial insurance reimbursement	1.13 (1.01,1.27)	0.03
Full insurance reimbursement	1.05 (0.92,1.19)	0.49
AF type		
Newly diagnosed	Ref	-
Paroxysmal AF	1.17 (1.06,1.30)	< 0.01
Persistent AF	1.11 (1.00,1.24)	0.05
AF duration ≥ 1 year	1.11 (1.06,1.17)	< 0.01
EHRA score		
0	Ref	-
1	1.13 (1.04,1.23)	< 0.01
2	1.18 (1.08,1.30)	< 0.01
Hypertension	1.09 (1.03,1.15)	< 0.01
Heart failure	1.15 (1.08,1.24)	< 0.01
Established CAD	1.26 (1.19,1.34)	< 0.01
Ischemic stroke/TIA	1.26 (1.18,1.33)	< 0.01
Diabetes mellitus	1.16 (1.10,1.22)	< 0.01
Chronic obstructive pulmonary disease	1.41 (1.13,1.76)	< 0.01
Gastrointestinal disorder	1.39 (1.23,1.58)	< 0.01
AF, atrial fibrillation; CAD, coronary artery disease; TIA, transient ischemic attack; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; LAD, left atrial diameter; HR, hazard ratio; 95% CI, 95% confidence interval.		

Characteristics	Multivariate analysis	
Hyperthyroidism/Hypothyroidism	1.26 (1.13,1.40)	< 0.01
Renal dysfunction	1.31 (1.16,1.48)	< 0.01
Ventricular rate control	1.05 (1.00,1.11)	0.04
ACEIs/ARBs	0.94 (0.89,0.99)	0.02
LAD, (per 1 mm increase)	1.01 (1.00,1.01)	< 0.01
AF, atrial fibrillation; CAD, coronary artery disease; TIA, transient ischemic attack; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; LAD, left atrial diameter; HR, hazard ratio; 95% CI, 95% confidence interval.		

Factors associated with first cause-specific hospitalization

We also modeled predictors of first AF and other CVD hospitalization. We found that the major predictors of AF hospitalization were severe symptoms (EHRA \geq 3, HR 1.28, 95% CI 1.09–1.49, $P < 0.01$; EHRA \geq 4, HR 1.28, 95% CI 1.08–1.51, $P < 0.01$) and antiarrhythmic drugs (HR 1.36, 95% CI 1.25–1.48, $P < 0.01$) (Table 3). For other CVD hospitalization, the potent predictor was complicating CVD (Table 4). Additionally, we observed that RFAC was associated with a decrease of AF-related hospitalization (12%) (HR 0.88, 95% CI 0.79–0.97, $P = 0.01$) and subsequent CVD hospitalization (14%) (HR 0.86, 95% CI 0.78–0.96, $P = 0.01$).

Table 3
Factors associated with AF hospitalization

Characteristics	Multivariate analysis	
	HR (95%CI)	P value
Age (years)		
< 65	Ref	-
65–74	0.84 (0.77,0.92)	< 0.01
≥ 75	0.68 (0.61,0.76)	< 0.01
Female	1.17 (1.08,1.26)	< 0.01
High school or above	1.09 (1.00,1.19)	0.047
AF duration ≥ 1 year	1.29 (1.19,1.40)	< 0.01
EHRA score		
□	Ref	-
□	1.28 (1.09,1.49)	< 0.01
□	1.28 (1.08,1.51)	< 0.01
Established CAD	1.24 (1.12,1.37)	< 0.01
Antiarrhythmic drugs	1.36 (1.25,1.48)	< 0.01
History of RFCA	0.88 (0.79,0.97)	0.01
AF, atrial fibrillation; CAD, coronary artery disease; RFCA, radiofrequency catheter ablation; HR, hazard ratio; 95% CI, 95% confidence interval.		

Table 4
Factors associated with other CVD hospitalization

Characteristics	Multivariate analysis	
	HR (95%CI)	P value
Age (years)		
< 65	Ref	-
65–74	1.41 (1.27,1.55)	< 0.01
≥ 75	1.70 (1.53,1.90)	< 0.01
High school or above	0.89 (0.81,0.98)	0.02
Hypertension	1.21 (1.10,1.33)	< 0.01
Heart failure	1.49 (1.34,1.65)	< 0.01
Established CAD	1.45 (1.32,1.59)	< 0.01
Cardiomyopathy	1.31 (1.03,1.67)	0.03
Ischemic stroke/TIA	1.37 (1.25,1.50)	< 0.01
Diabetes mellitus	1.21 (1.11,1.31)	< 0.01
Gastrointestinal disorder	1.44(1.17,1.78)	< 0.01
Hyperthyroidism/Hypothyroidism	1.25 (1.04,1.50)	0.02
Renal dysfunction	1.35 (1.14,1.59)	< 0.01
Statin	1.15 (1.05,1.25)	< 0.01
History of RFCA	0.86 (0.78,0.96)	0.01
LAD, (per 1 mm increase)	1.01 (1.01,1.02)	< 0.01
CAD, coronary artery disease; TIA, transient ischemic attack; RFCA, radiofrequency catheter ablation; LAD, left atrial diameter; HR, hazard ratio; 95% CI, 95% confidence interval.		

Discussion

Hospitalization is common in AF patients. In our assessment, we observed a hospitalization rate of 24.0 per 100 patient-years, and women aged ≥ 75 years possess the highest hospitalization rate. With the increase of age, elderly AF patients (≥ 65 years) were more frequently hospitalized for non-CVD. Age, AF type and symptoms, as well as several comorbidities were independent predictors for first all-cause hospitalization.

In China, there was few data focusing on the hospitalization rate in AF patients. The present study is the first study that analyzed the total frequency of hospitalizations to evaluate the incidence rate of

hospitalization in AF patients based on real-world data in China. In 2014, the ORBIT-AF study revealed that the rate of all-cause hospitalization in AF patients was as high as 38.8 per 100 patient-years[13]. Furthermore, data from the EORP-AF Pilot registry in European Society of Cardiology nine-member countries, showed that the annual hospitalization rate in AF patients was up to 39.3 per 100 patient-years[14]. According to our study, the all-cause hospitalization rate in AF patients was 24.0 per 100 patient-years. Although the hospitalization rate of AF patients in China may not as high as that in western countries, we still can safely come to the conclusion that China is facing the same economic and health burden of hospitalization in AF patients as western countries.

To date, the main causes for hospitalization in AF patients are still highly controversial. The present study demonstrated that non-CVD were most responsible for hospitalizations in AF patients, which is similar to numerous previous researches[8, 15, 16]. However, some studies such as ROCKET AF study[17], ORBIT-AF [13] and [18] registry[13, 18] support opposite views to our results, showing that AF patients are hospitalized mainly for CVD. In patients aged < 65 years, due to few complicating diseases and high requirements for QoL, most young people may be hospitalized for improving AF-caused symptoms or seeking catheter ablation for maintaining sinus rhythm. The combined effects of the triggering or exacerbation of other diseases caused by pathophysiological alterations[19–21], old age, and the adverse events in the application of drugs during the treatment of AF[22–24], put older and multi-morbid patients at a greater risk of adverse outcomes across multiple organ systems than AF or cardiac events. Some of the conflicting findings in these studies about the main cause for hospitalization in AF patients may be attributable to different clinical setting and patient population in each study. Therefore, different therapeutic strategies are required for problems presented in different age groups. Symptoms improvements and treatment focusing on AF alone may be more effective in young AF patients, while the concomitant diseases should be paid more attention in elderly AF patients.

To improve our identification of predictors of hospitalization and focus areas for preventive efforts and intervention, we examined the association between patient baseline characteristics and hospitalization rate in AF patients. The risk of hospitalization increased substantially with the increase of age, suggesting that the burden of hospitalization for AF patients is anticipated to increase dramatically with the aging population. Of note, in the multivariate model, gender differences exhibited no or a weak effect on all-cause hospitalizations, but there was a significant difference in the trend of gender-related hospitalization rates. Among all age groups, the all-cause hospitalization rate of female AF patients was higher than that of male AF patients. A previous study has pointed out that women with AF tend to be more symptomatic and experience worse QoL than men[25]. However, a meta-analysis of 17 articles provides an equivocal conclusion on gender differences in hospitalizations[26]. Therefore, more researches should be done to evaluate these gender differences in AF hospitalization.

Consistent with numerous studies[27, 28], patients with worse symptoms by ERHA score were harbored a higher risk of hospitalization. When we modeled predictors of hospitalization for AF, symptom status was a major driving factor. Similarly, patients requiring antiarrhythmic drugs were also more likely to experience hospitalization for AF. These results suggested the need to manage patients with

symptomatic and/or uncontrolled AF, so as to reduce the incidence of hospitalization. Although catheter ablation, a new treatment approach for AF, showed no significant association with all-cause hospitalization in our study, it does improve symptoms[29] and reduce subsequent cardiovascular events[30].

Moreover, as indicated by our data, the combination of CVD (such as stroke, HF and CAD) in AF patients could significantly predict subsequent hospitalization, especially non-AF CVD hospitalizations. It is generally known that stroke, HF, and CAD are frequent comorbidities among AF patients. Given the common underlying pathophysiology and similar management concerns[31–33], AF patients are prone to a spectrum of cardiometabolic comorbidities, particularly HF and stroke, and the combination of AF with CVD also synergistically increases the risk of AF morbidity. Chamberlain et al.[15] found that AF patients complicated with HF experienced an increased risk of hospitalization by up to about 70%, and those complicated with CAD and stroke also had an over 20% increased risk of hospitalization. Furthermore, these CVD themselves alone represent a significant burden of hospitalization. Accordingly, improving the integrated management of CVD and reducing the frequency of recurrent hospitalizations in AF patients complicated with CVD are in an urgent need.

In our cohort, it is worth noting that COPD patients had the highest risk of all-cause hospitalization, showing an increase of about 41%. Even so, COPD did not contribute to the increases risk of AF hospitalization and other CVD hospitalization, which may be due to that it exerted effects mainly on non-CVD such as lung diseases. In addition to increasing the risk of all-cause hospitalization by more than 30%, renal dysfunction and gastrointestinal disorder also elevated the risk of non-AF CVD hospitalization by more than 30%. As has been suggested by a previous study, renal diseases not only induce and aggravate CVD such as hypertension, HF and CAD[34], but also increase the risk of stroke, systemic thromboembolism and bleeding[35, 36]. Gastrointestinal disorders such as gastroesophageal reflux and gastroenteritis may also elevate the risk of bleeding or cardiovascular events due to inflammation, metabolic disorders or treatment[37, 38]. Moreover, renal dysfunction and gastrointestinal disorder could lead to the reduction of the drug compliance of AF patients[39, 40]. Therefore, when managing AF patients complicated with non-CVD, cardiology experts still have the opportunity to enhance the quality and value of AF care when their attention and insights extend to the careful appraisal, management and follow-up care of preexisting non-CVD.

Collectively, the majority of comorbidities (CVD/non-CVD) predicted a high prevalence of hospitalization, the care oriented to single disease treatment rather than targeting broad and interconnected care may make interventions and outcomes unsatisfying. Multidisciplinary management of AF and comorbidities is an inexorable trend of medical advances.

Limitations

Firstly, in this study, AF patients were recruited mainly from the urban and suburban areas, which principally mirrors the circumstance of AF patients in relatively developed regions in China, and may be

insufficient to represent the whole AF population in China, especially in rural areas. Additional studies should be undertaken to determine whether these observations are generalizable to all AF patients. Secondly, the analysis data were derived from the China-AF study. The causes for the hospitalization proposed by the researchers were relatively broad. The non-AF CVD and non-CVD were not explicitly classified. Therefore, the most important specific diseases that lead to the hospitalization of AF patients are unavailable and need further research. Lastly, this study did not collect detailed information about the length of stay and hospitalization cost and could not further analyze the economic burden of hospitalization.

Conclusions

During follow-up, about one-third of AF patients have had more than one hospitalization in this study. Hospitalizations mainly due to non-CVD events in patients aged ≥ 65 years and AF burden in the patients aged < 65 years. Age, worse AF symptoms and several comorbidities (e.g. HF and COPD) are significant predictors for hospitalization. Throughout AF patients' entire treatment and follow-up, efforts are needed to reduce hospitalizations, particularly in focusing on symptoms, as well as strengthening the multidisciplinary management of comorbidities.

List Of Abbreviations

AF	Atrial Fibrillation
ACEIs	Angiotensin-Converting Enzyme Inhibitors
ARBs	Angiotensin II Receptor Blockers
BMI	Body Mass Index
CAD	Coronary Artery Disease
CHA ₂ DS ₂ -VASc	Congestive heart failure, Hypertension, Age \geq 75years, Diabetes, Stroke, Vascular diseases, Age65-74years, Sex category
China-AF	Chinese Atrial Fibrillation Registry
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular Diseases
DM	Diabetes Mellitus
DOACs	Direct Oral Anticoagulants
EHRA	European Heart Rhythm Association
HF	Heart Failure
HR	Hazard Ratio
HTN	Hypertension
LAD	Left Atrial Diameter
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
NHIS	National Health Insurance Service
NYHA	New York Heart Association
QoL	Quality of Life
RFCA	Radiofrequency Catheter Ablation
TIA	Transient Ischemic Attack

Declarations

Ethics approval and consent to participate:

The study was approved by the Ethics Committee on Human Research of Beijing Anzhen Hospital, the Capital Medical University. All participants provided written informed consent. Name of the ethics

committee: Ethics Committee of Beijing Anzhen Hospital. Reference number: D11110700300000

Consent for publication:

Not applicable

Availability of data and materials:

The datasets generated and/or analysed during the current study are not publicly available due to the protection of patients' privacy, but are available from the corresponding author on reasonable request.

Competing interests:

Chang-sheng Ma has received honoraria from Bristol-Myers Squibb, Pfizer, Johnson & Johnson, Boehringer-Ingelheim, and Bayer for giving lectures. Jian-zeng Dong has received honoraria from Johnson & Johnson for giving lectures. The rest of the authors have declared no conflict of interest

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Authors' contributions:

X-D, CS-M and ZJ-D have designed the study. ZJ-D analyzed and interpreted the results of patients' statistic data and was a major contributor in writing the manuscript. L-H performed data statistic analysis. SX-L, C-J, SJ-X, X-S, ZX-J, DY-L, CH-S, RB-T, N-L, R-B, RH-Y, JZ-D contributed to refining the ideas and edited the manuscript. All authors read and approved the final manuscript.

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Figures

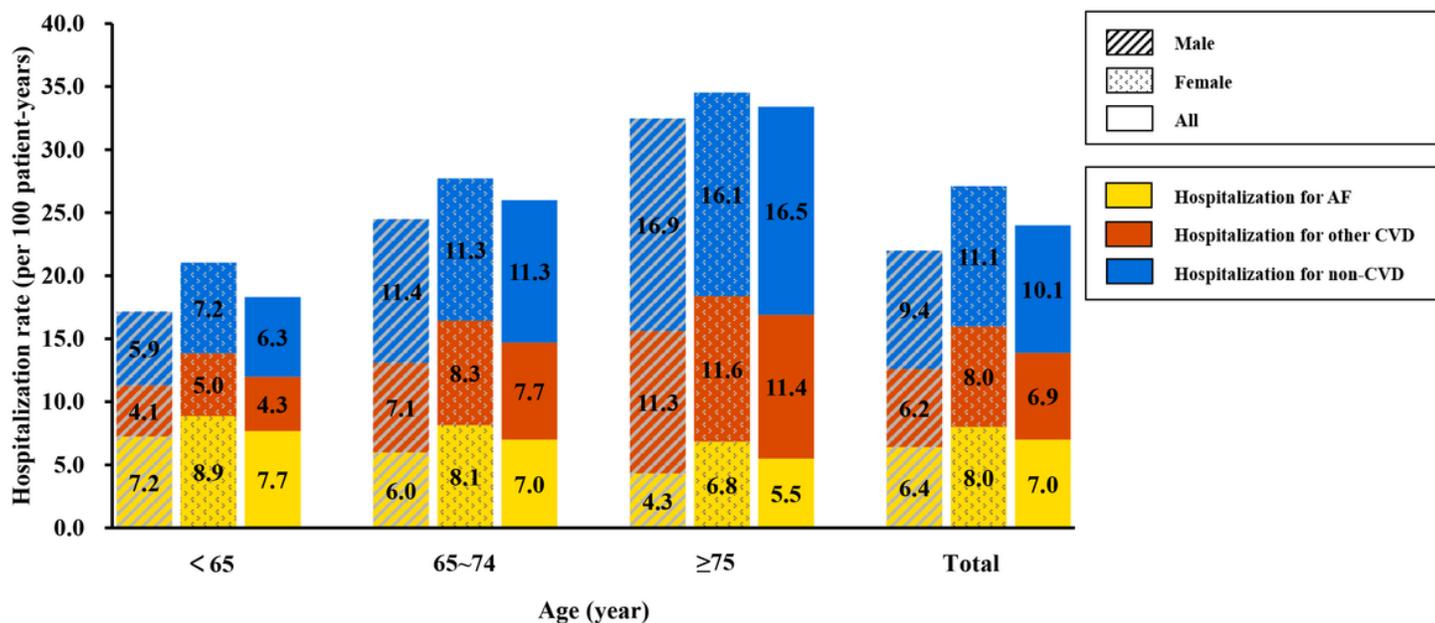


Figure 1

Hospitalization rate (per 100 patient-years) for different causes across age and gender groups. AF, atrial fibrillation; CVD, cardiovascular diseases

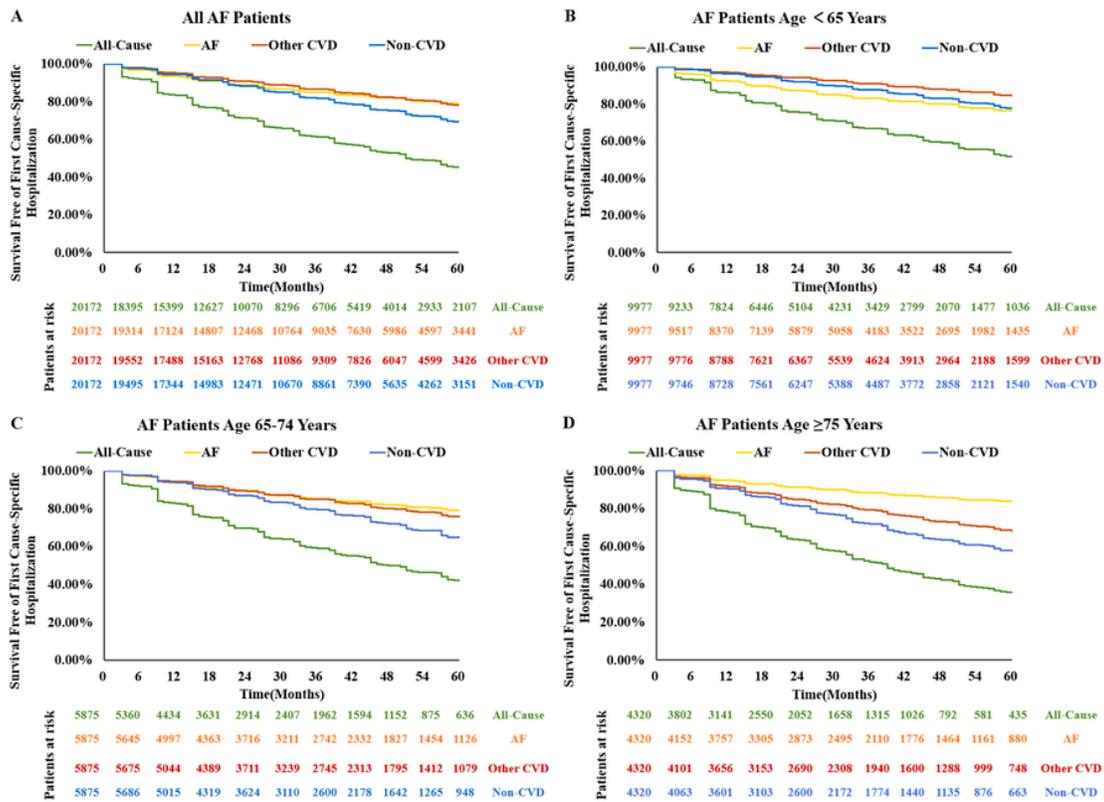


Figure 2

Survival free of first all-cause and first specific-cause hospitalization in different age groups. (A) the entire cohort; (B) patients age <65 years; (C) patients age 65-74 years; (D) patients age ≥75years. AF, atrial fibrillation; other CVD, cardiovascular diseases excluding AF; non-CVD, non-cardiovascular diseases.

Supplementary Files

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