

Impact of Adverse Health Conditions on Clinical Outcomes of Older People with Atrial Fibrillation: Insights from a Prospective Cohort Study

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Objective: To evaluate the impact of adverse health conditions, including multimorbidity, frailty, malnutrition, cognitive impairment, and polypharmacy, on clinical outcomes in older people with atrial fibrillation (AF).

Patients and Methods: This prospective cohort study focused on patients aged 65 years and older with AF. They were admitted to the hospital between September 2018 and April 2019 and followed up for 1 year. We evaluated these participants for adverse health conditions including multimorbidity, frailty, malnutrition, cognitive impairment, and polypharmacy. The primary clinical outcome measured was a combination of all-cause mortality or rehospitalization.

Results: 197 older patients (≥ 65 years) with AF (mean age, 77.5 ± 7.1 years; 57.4% men) were enrolled. During 1-year follow-up, Primary endpoint events (all-cause mortality or rehospitalization) occurred in 82 patients (41.6%). Compared with the non-event group, the Charlson comorbidity index (CCI) was higher (2.5 ± 1.9 vs 1.7 ± 1.3 , $p=0.004$), more heart failure (32.9% vs 17.4%, $p=0.01$) and chronic kidney disease (17.1% vs 7.0%, $p=0.03$), with lower systolic blood pressure (125.3 ± 18.3 mmHg vs 132 ± 17.9 mmHg, $p=0.005$) in the event group. On multivariate Cox regression showed that the CCI was associated with a higher odds ratio of the composite outcome of all-cause mortality and rehospitalization (HR: 1.26; 95% CI: 1.02–1.56, $p=0.03$). Other adverse health conditions showed no significant association with the composite outcome of all-cause mortality and rehospitalization.

Conclusion: Among adverse health conditions in older people with AF, multimorbidity appears to be a significant determinant of adverse clinical outcomes.

Clinical Trial Registration: ChiCTR1800017204; date of registration: 07/18/2018.

Keywords: atrial fibrillation, older people, multimorbidity, prognosis

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and a major cause of stroke, heart failure (HF), cardiovascular morbidity, and sudden death.¹ Patients with AF are often older and overburdened with adverse health conditions (multimorbidity, frailty, malnutrition and cognitive impairment).² Previous studies revealed that adverse health conditions are associated with worse clinical outcomes in older people with AF.^{3–6} Nevertheless, the impact on clinical outcomes, which is stronger and which is weaker, remains unclear. Therefore, in the present study, we evaluated the prognostic significance of adverse health condition, including multimorbidity, frailty, malnutrition, cognitive impairment, and polypharmacy, on clinical outcomes in older people with AF.

Methods

The data from a prospective observational cohort study on frailty in China (Trial registration: ChiCTR1800017204; date of registration: 07/18/2018). The Study recruited ≥ 65 years elderly inpatients who were consecutively admitted to 3 tertiary referral hospitals in Beijing, China, from September 2018 to April 2019, which approved by the Ethics Committee of Beijing Hospital (approval no. 2018BJYYEC-121-02).

Study Population

The study population included 197 consecutive ≥ 65 years elderly inpatients with a diagnosis of current or resolved atrial fibrillation. Baseline data collection included sociodemographics, hospitalization information, medical history, comorbidities, physical examinations, laboratory tests, echocardiographic data and medications.

Definition of Adverse Health Conditions/Clinical Complexity

Participants were followed up to assess the occurrence of adverse health conditions/clinical complexity including multimorbidity, frailty, malnutrition, cognitive impairment and polypharmacy. Multimorbidity were measured by the Charlson comorbidity index (CCI).⁷ The CCI has been validated as a reliable tool to evaluate the burden of multimorbidity, which comprised 19 diagnoses to which different weights have been assigned and summed to obtain the final calculation ([Supplementary Table 1](#)). We used the Edmonton frailty score (EFS) to assess frailty.⁸ EFS is a multidimensional frailty assessment tool that includes general health status, functional independence, social support, cognition, medication use, nutrition, continence and mood. Subjects with an EFS ≥ 8 are classified as frail ([Supplementary Table 2](#)). Malnutrition was defined according to the short form mini nutritional assessment (MNA-SF) ≤ 7 points ([Supplementary Table 3](#)).⁹ We used the mini-mental state examination (MMSE)¹⁰ and clock drawing test (CDT)¹¹ to define cognitive impairment ([Supplementary Table 4](#)): (1) below 24 points of MMSE or (2) $24 \leq \text{MMSE} \leq 26$ and incorrect CDT. Polypharmacy was defined according to the number of drugs prescribed at baseline, as the presence of ≥ 7 different drugs taken by a patient.¹²

Study End Points

The primary outcome was a composite of all-cause death or rehospitalization. All events were independently reviewed. We separately considered all-cause death or rehospitalization as independent outcomes. Clinical follow-up was routinely performed via clinical visit and/or telephone interview at 3, 6 and 12 months.

Statistical Analysis

The subjects were divided into two groups based on the occurrence of the primary endpoint. Continuous variables are presented as mean \pm SD, and independent *t* test was performed for intergroup comparison. Non-normally distributed variables were reported as median (25th-75th percentile), and Wilcoxon rank-sum test was performed for intergroup comparison. Categorical variables are expressed as count (%), and comparisons were performed by using the Fisher exact test or chi-squared test.

Univariable and multivariable Cox proportional hazards models were developed to determine independent predictors of all-cause death or rehospitalization. We took frailty as an independent variable. We determined the covariates for the multivariable analysis based on two criteria: significant differences between groups and clinical significance. CCI, cognitive impairment, malnutrition, polypharmacy, age, sex, education, living alone, smoking, drinking, body mass index (BMI), $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 5$, $\text{HAS-BLED} \geq 3$, heart failure, heart rate, hemoglobin, albumin, high-sensitivity C-reactive protein (hsCRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), D-dimer, left atrial anteroposterior diameter and left ventricular ejection fraction were analyzed as dependent variables. The Cox models were tested for the proportional hazards assumption and linearity of continuous variables. We checked using the variance inflation factor ensuring that the variance inflation factor for each variable was < 10 . Cumulative survival curves were estimated by Kaplan-Meier methods and compared between groups using the Log rank test. All statistical tests were bilateral tests, and a *P* value of < 0.05 was considered to indicate statistical significance. All the analyses were performed using SAS software, version 9.4 (SAS Institute Inc).

Results

Baseline Characteristics

Among the 197 patients included (Figure 1), the mean mean \pm SD age was years, and 57.4% were men. 52.3% of patients were paroxysmal AF. The CHADS-VASc Score was 4.4 ± 1.6 and the HAS-BLED Score was 1.9 ± 0.7 . Mean (\pm SD) CCI was 2.0 ± 1.6 . Patients with high multimorbidity (CCI ≥ 4) was 34 (17.3%). There were 55 (27.9%) patients with frailty, 9 (4.6%) patients with malnutrition, 57 (28.9%) patients with cognitive impairment and 89 (45.2%) patients with polypharmacy (Figure 2).

Clinical Outcomes

188 patients completed 1-year follow-up, with a total loss rate of 4.6%. There were 6 cases of all-cause mortality (3.0%), and 80 patients experienced rehospitalization (40.6%). The primary end point event (all-cause death or rehospitalization) occurred in 82 patients (41.6%). The cohort was divided into 2 groups on the basis of the occurrence of primary endpoint events (events group and no-events group). Baseline clinical differences between the groups are shown in Table 1. Patients with an adverse event more frequently had heart failure and chronic kidney disease (CKD), had higher CCI and lower systolic blood pressure (SBP).

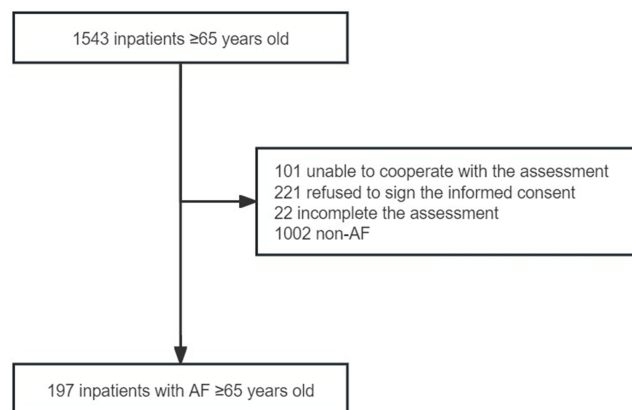


Figure 1 Selection of the study population.

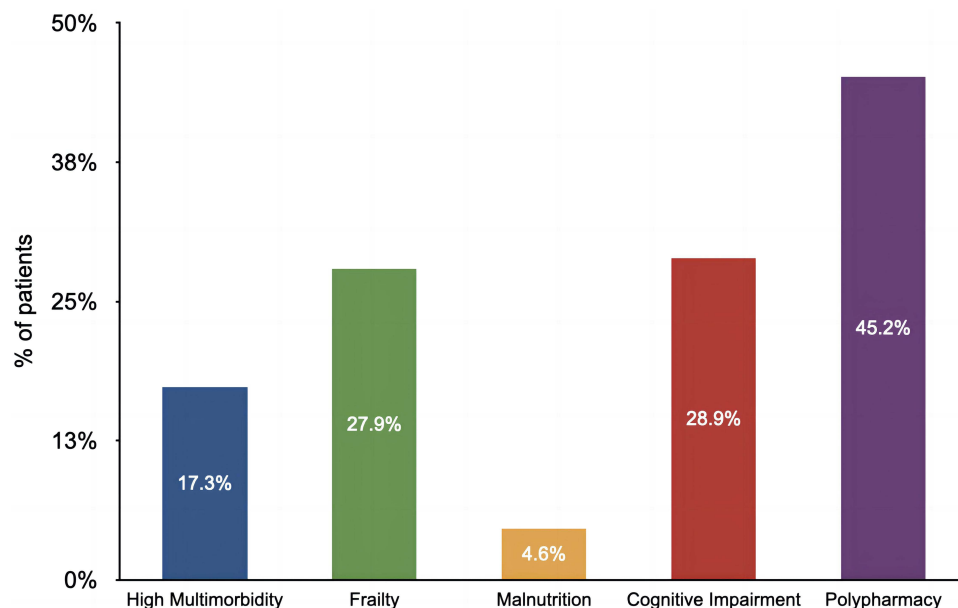


Figure 2 Prevalence of adverse health conditions (multimorbidity, frailty, malnutrition, cognitive impairment, and polypharmacy). High multimorbidity = CCI ≥ 4 .

Abbreviation: CCI, Charlson comorbidity Index.

Table I Baseline Patients Characteristics

	Event-free n=115 (58.4%)	Event n=82 (41.6%)	p value
Age, y	77.2±7.1	77.8±7.0	0.55
Male	62 (53.9)	51 (62.2)	0.25
University or higher	45 (39.1)	33 (40.2)	0.98
Living alone	9 (7.8)	6 (7.3)	0.89
HR, bpm	76.4±19.9	77.8±18.2	0.63
SBP, mmHg	132.6±17.9	125.3±18.3	0.81
DBP, mmHg	74.5±11.2	74.1±11.3	0.14
BMI, kg/m ²	25.1±3.4	24.4±3.7	0.16
Paroxysmal AF	60 (52.2)	43 (52.4)	0.97
CHA ₂ DS ₂ -VASc score			0.08
≤4	68 (59.1)	38 (46.3)	
≥5	47 (40.9)	44 (53.7)	
HAS-BLED score			0.54
≤2	96 (83.5)	65 (79.3)	
≥3	19 (16.5)	17 (20.7)	
Frailty	45 (39.1)	35 (42.7)	0.62
CCI	1.7±1.3	2.5±1.9	0.004
Cognitive impairment	32 (27.8)	25 (30.5)	0.68
Malnutrition	5 (4.3)	4 (4.9)	0.86
Polypharmacy	50 (43.5)	39 (47.6)	0.47
HTN	85 (73.9)	64 (78.0)	0.51
CAD	52 (45.2)	44 (53.7)	0.24
MI	8 (7.0)	12 (14.6)	0.08
HF	20 (17.4)	27 (32.9)	0.01
PVD	18 (15.7)	16 (19.5)	0.48
Diabetes	30 (26.1)	28 (34.1)	0.22
Stroke/TIA	25 (21.7)	21 (25.6)	0.53
CKD	8 (7.0)	14 (17.1)	0.03
Hb, g/l	130.8±17.7	126.3±23.0	0.14
Alb, g/l	39.4±2.9	38.7±3.6	0.1
D-dimer, ng/mL	141.0 (88.0, 250.0)	166.5 (97.0, 335.0)	0.44
hsCRP, mg/dl	1.0 (0.7, 1.8)	1.2 (0.8, 2.6)	0.98
NT-proBNP, pg/mL	672.2 (180.4–1526.0)	993.1 (204.6–1759.0)	0.24
LVEF, %	59.6±7.9	57.3±9.6	0.08
LAD, mm	41.4±7.7	42.9±7.8	0.18
OAC	57 (49.6)	32 (40.2)	0.27
Intervention/surgery	53 (46.3)	29 (35.4)	0.13

Notes: Values are presented as mean±SD or median (interquartile range: 25th to 75th percentiles) or number (percentage).

Abbreviations: AF, atrial fibrillation; Alb, albumin; BMI, body mass index; CAD, coronary artery disease; CCI, Charlson comorbidity Index; CKD, chronic kidney disease; DBP, diastolic blood pressure; Hb, hemoglobin; HF, heart failure; HR, heart rate; hs-CRP, high-sensitive C-reactive protein; HTN, hypertension; LAD, left atrial anteroposterior diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OAC, oral anticoagulants; PVD, peripheral vascular disease; SBP, systolic blood pressure; TIA, transient ischemic attack.

Association Between Adverse Health Conditions and Clinical Outcomes

Cox univariable regression analysis (Table 2) showed that CCI was associated with a significantly higher risk of all-cause death or rehospitalization events (HR: 1.29; 95% CI: 1.13 to 1.47, $p<0.001$), and other risk factors associated with all-cause death or rehospitalization events included heart failure (HR: 1.84; 95% CI: 1.17 to 1.81, $p=0.009$), Log Hb (OR: 0.30; 95% CI: 0.13 to 0.69, $p=0.04$) and LVEF (HR: 0.98; 95% CI: 0.95 to 1.00, $p=0.04$). On multivariate Cox regression

Table 2 Univariate and Multivariate Cox Regression Analyses for the Primary Outcome of All-Cause Death or Rehospitalization

Variables	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.12	0.83–1.51	0.45	0.83	0.55–1.25	0.36
Male	1.24	0.80–1.93	0.34	1.80	0.85–3.84	0.13
University or higher	0.90	0.49–1.65	0.74	0.91	0.36–2.31	0.84
Living alone	1.02	0.42–2.49	0.96	1.37	0.56–3.37	0.49
Smoking	1.10	0.70–1.74	0.68	0.81	0.41–1.61	0.56
Drinking	1.08	0.67–1.73	0.76	1.27	0.62–2.61	0.51
BMI	0.96	0.90–1.02	0.16	0.98	0.91–1.06	0.64
CHA ₂ DS ₂ -VASc score ≥ 5	1.52	0.99–2.33	0.06	1.20	0.63–2.31	0.58
HAS-BLED score ≥ 3	1.24	0.75–2.07	0.41	0.90	0.44–1.84	0.76
Frailty	1.22	0.79–1.88	0.37	1.05	0.57–1.95	0.87
CCI	1.29	1.13–1.47	<0.001	1.26	1.02–1.56	0.03
Cognitive impairment	1.13	0.71–1.81	0.61	1.17	0.55–2.48	0.68
Malnutrition	1.19	0.36–3.92	0.78	0.59	0.17–1.98	0.39
Polypharmacy	1.06	0.69–1.62	0.79	0.62	0.34–1.14	0.12
HF	1.84	1.17–2.92	0.009	1.14	0.58–2.27	0.70
HR	1.00	0.99–1.02	0.37	1.01	0.99–1.02	0.31
Log Hb	0.30	0.13–0.69	0.004	0.31	0.08–1.24	0.10
Log Alb	0.06	0.00–1.09	0.06	0.10	0.00–4.56	0.24
Log hsCRP	1.09	0.93–1.29	0.29	0.94	0.76–1.16	0.56
Log D-dimer	1.19	0.96–1.47	0.11	0.98	0.72–1.33	0.89
Log NT-proBNP	1.13	0.97–1.32	0.12	1.07	0.87–1.32	0.52
LAD	1.03	1.00–1.06	0.09	1.02	0.98–1.06	0.30
LVEF	0.98	0.95–1.00	0.04	1.01	0.98–1.04	0.73

Notes: Adjusted for age, sex, education, living alone, smoking, drinking, BMI, CHA₂DS₂-VASc ≥ 5 , HAS-BLED ≥ 3 , Frailty, CCI, HF, Cognitive impairment, Malnutrition, HR, Log Hb, Log Alb, Log hsCRP, Log NT-proBNP, LAD, LVEF, ≥ 7 medications.

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity Index; CI, confidence interval; HF, heart failure; HR, heart rate; HR, hazard ratio; LAD, left atrial anteroposterior diameter; Log Alb, Logarithm albumin; Log D-dimer, Logarithm D-dimer; Log Hb, Logarithm hemoglobin; Log hsCRP, Logarithm high-sensitive C-reactive protein; Log NT-proBNP, Logarithm N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction.

(Table 2) showed that the CCI was associated with a higher odds ratio of the composite outcome of all-cause mortality and rehospitalization (HR: 1.26; 95% CI: 1.02–1.56, $p=0.03$). Kaplan-Meier survival curve showed that the presence of high multimorbidity (CCI ≥ 4) had significantly lower all-cause mortality or rehospitalization survival rate (log-rank $P < 0.01$) within 1 year (Figure 3).

Discussion

In the prospective cohort study, our principal findings are as follows: (1) The adverse health conditions (multimorbidity, frailty, malnutrition, cognitive impairment and polypharmacy) are common among the older people with AF; (2) Patients with all-cause death or rehospitalization present a higher burden of multimorbidity, heart failure and CKD, and lower SBP; (3) Feature of multimorbidity is associated with a higher risk of all-cause mortality and rehospitalization, even after adjustment for main domains of adverse health conditions.

The prevalence of AF is increasing due to the aging population and epidemiological trends, posing challenges to clinical and public health systems. Older people with AF often have comorbidities such as multimorbidity, frailty, malnutrition, cognitive impairment, and polypharmacy.² These conditions are known as adverse health conditions or geriatric syndromes.¹³ In recent years, there has been significant focus on the impact of adverse health conditions or geriatric syndromes in patients with AF, as they greatly influence clinical management and the risk of adverse outcomes.

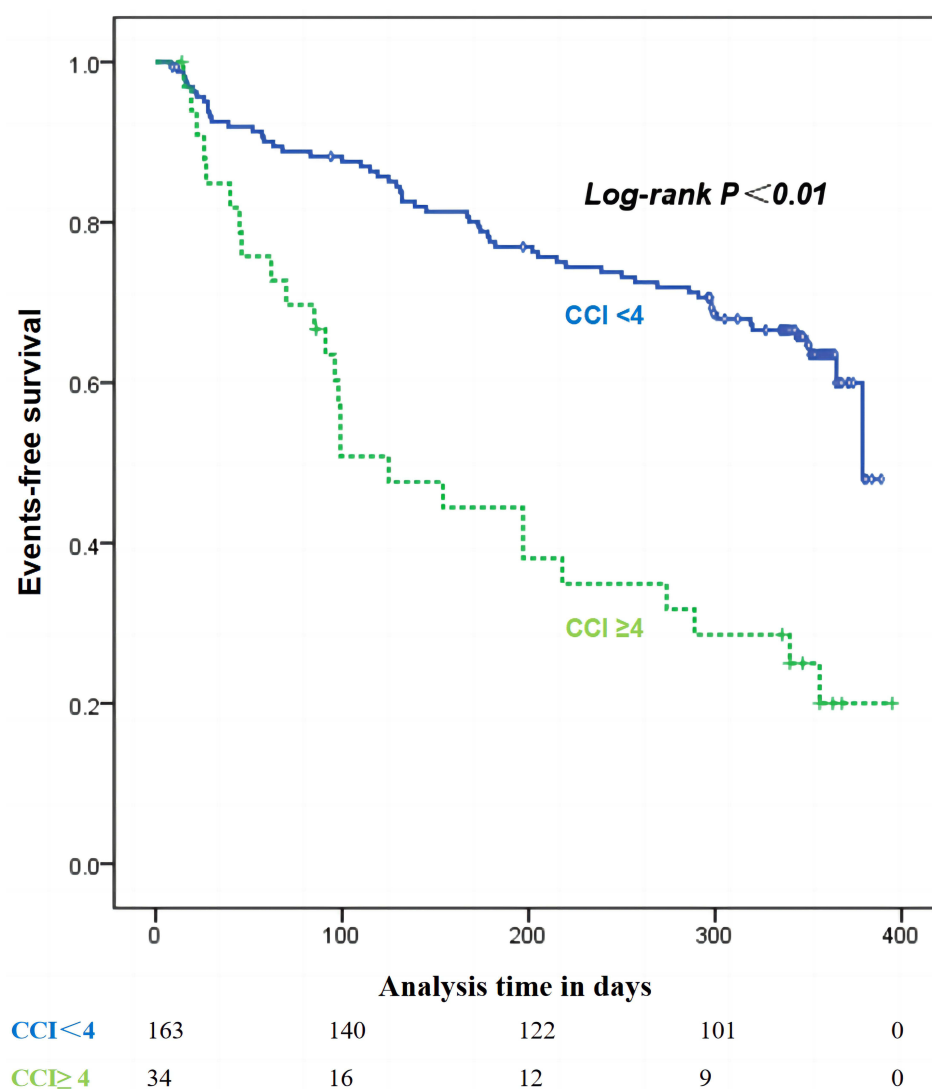


Figure 3 Kaplan-Meier Analysis of all-cause mortality or rehospitalization Events According to the presence of High Multimorbidity in patients with AF. High multimorbidity = CCI ≥ 4 . **Abbreviation:** CCI, Charlson comorbidity Index.

The presence of these chronic comorbidities is referred to as “clinical complexity”.¹⁴ A large cohort study of European AF patients demonstrated that the presence of clinical complexity features like multimorbidity, frailty, and polypharmacy is associated with lower use of oral anticoagulants (OAC), lower quality of life, and higher use of healthcare resources. Clinical complexity features are linked to a higher risk of adverse outcomes, particularly in those with a higher burden of complexity features.¹⁵

Of the five adverse health conditions in our study, multimorbidity had the strongest association with all-cause mortality and rehospitalization in older people with AF. To the best of our knowledge, our study is the first to evaluate the prognostic impact of adverse health conditions on clinical outcomes in elderly patients with AF. Interestingly, a whole population study also showed that multimorbidity had the strongest association with mortality among the three adverse health conditions (multimorbidity, frailty, and disability).¹³ Multimorbidity is typically defined as the presence of two or more long-term conditions, although there is no clear consensus on the specific number or nature of diseases.¹⁶ It is associated with a higher risk of mortality, reduced functional status, increased healthcare expenditure and resource utilization, and adverse outcomes in elderly patients with AF.^{6,17–19} For example, a study by B.D. Jani et al found that AF participants with ≥ 4 comorbidities had a six-fold higher risk of mortality compared to participants without any comorbid

long-term health conditions.¹⁸ Proietti et al evaluated the relationship between the CCI and AF patients, showing that CCI is independently associated with an increased risk of stroke, major bleeding, and all-cause death.¹⁹ The ChiOTEAF study in elderly Chinese patients with AF confirmed that multimorbidity was an independent predictor of adverse clinical outcomes.⁶ Furthermore, multimorbidity also influences therapeutic decision-making for AF patients. Previous studies have shown that multimorbidity is inversely associated with the prescription of OAC.^{20,21} However, it has been demonstrated that the use of non-vitamin K antagonist oral anticoagulants (NOACs) is safe and significantly improves survival in AF patients with multimorbidity.^{22,23} Rhythm control therapy, including antiarrhythmic drug therapy or AF ablation, is primarily recommended to improve the quality of life in symptomatic AF patients. Similarly, multimorbidity affects the decision to pursue rhythm control therapy. It is commonly assumed that the risk of rhythm control therapy will also be higher in patients with multiple comorbidities. However, newer evidence suggests that early rhythm control therapy reduces the risk of cardiovascular death, stroke, or hospitalization for heart failure or acute coronary syndrome in patients with recently diagnosed AF and a high comorbidity burden.²⁴ Another aspect that needs attention is the relationship between the type of multimorbidity and AF, which is usually divided into cardiometabolic comorbidity and non-cardiometabolic comorbidity. Cardiovascular diseases and cardiovascular risk factors were used to define cardiometabolic conditions and included heart failure, coronary artery disease, stroke, hypertension, hyperlipidemia, and diabetes mellitus. Non-cardiometabolic conditions included arthritis, asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disease, dementia, depression, and osteoporosis. Many studies, including ours, have found that the proportion of cardiometabolic comorbidity is higher in elderly AF.^{25,26} J'Neka S. Claxton et al further found that cardiometabolic comorbidities are more strongly associated with stroke, heart failure, and major bleeding than non-cardiometabolic comorbidities.²⁵

In recent years, interest in the management of AF patients affected by multimorbidity has substantially increased. There is a growing trend towards an integrated or holistic approach to managing AF patients, with the Atrial Fibrillation Better Care (ABC) pathway being the most representative.²⁷ The ABC pathway consists of three main pillars: "A" for Avoid stroke (with Anticoagulants), "B" for Better symptom management (rate or rhythm control), and "C" for Cardiovascular and Comorbidity risk optimization. Several studies have examined the impact of adherence/non-adherence to the ABC pathway. The first two post hoc analyses, based on clinical trials, showed that adhering to the ABC pathway is associated with a lower risk of adverse outcomes such as mortality, stroke/major bleeding/cardiovascular death, and hospitalization.^{28,29} The Mobile Atrial Fibrillation Application (mAFA)-II clinical trial, a prospective cluster randomized trial conducted in China, demonstrated a significant reduction in the primary outcome when using the ABC pathway intervention through a mHealth App compared to usual care.³⁰ A review of twelve studies on the ABC pathway consistently showed a statistically significant reduction in the risk of stroke, myocardial infarction, and mortality among patients who adhered to the pathway.³¹ Another meta-analysis also found that patients treated according to the ABC pathway showed a lower risk of all-cause death, cardiovascular death, stroke and major bleeding, with moderate heterogeneity.³² Additionally, an analysis of the ESC-EHRA EURObservational Research Programme (EORP) Atrial Fibrillation General Long-Term Registry data demonstrated that an ABC-adherent approach reduced the risk of major outcomes in clinically complex AF patients.¹⁴ In addition, as an important part of the ABC pathway, the integrated care of AF patients has received more and more attention in recent years. The integrated care intervention consisted of (1) quarterly AF check-ups by trained nurses in primary care, also focusing on possibly interfering comorbidities, (2) monitoring of anticoagulation therapy in primary care, and finally (3) easy-access availability of consultations from cardiologists and anticoagulation clinics. Clinical study has confirmed that integrated care can reduce the risk of all-cause death, cardiovascular death, etc.³³ Moreover, the higher the risk and the more complications the patient has, the greater the benefit from comprehensive care.^{34,35}

However, implementing the ABC pathway in clinical practice poses challenges. A European study found that fewer than one-third of AF patients demonstrated complete adherence to the ABC pathway.¹⁴ Barriers to referring AF patients to specialist services for comorbidities include a lack of integrated care models, organizational/institutional issues, and patient adherence problems.³⁶ To address these challenges, it is necessary to establish clinical workshops where cardiologists and nurses can collaborate with other specialists to achieve patient-centered multidisciplinary management.

It is also important to involve empowered patients, families, and caregivers. In line with this approach, the Horizon 2020 research program launched EHRA-PATHS,³⁷ “Addressing multimorbidity in elderly atrial fibrillation patients through interdisciplinary, tailored, patient-centered care pathways”, to implement and validate this approach. Meanwhile, the “Atrial fibrillation integrated approach in frail, multimorbid, and polymedicated older people” (AFFIRMO) Programme has been funded by the European Union through the Horizon 2020 research programme.³⁸ The AFFIRMO Programme will offer novel evidence on specific care models for the general multimorbid AF population. This will aid in improving clinical management and reducing the risks of major clinical adverse outcomes in a rapidly growing and significant patient group.

Our study has some limitations. Firstly, while being a multicenter study, the sample size is relatively small, and the participants are limited to inpatients in tertiary hospitals. Secondly, While we used a multivariate Cox regression model to adjust for potential confounders, residual or unknown confounding factors might still be present. For instance, re-hospitalizations probably constituted a significant portion of the events. If these rehospitalizations are weighed similarly to other events, the results could be skewed due to their higher frequency. Additionally, the lack of association for other health conditions, such as frailty, could be attributed to limited statistical power to detect differences. It is also important to note that frailty and multimorbidity often coexist, which could further complicate the analysis. Thirdly, the follow-up period for this study was only one year, and further studies with larger sample sizes and longer follow-up periods are necessary.

Conclusion

Among adverse health conditions in older adults with atrial fibrillation (AF), multimorbidity appears to be a significant determinant of adverse clinical outcomes. Evidence suggests that multimorbidity may be an independent predictor of such outcomes. Therefore, it is advisable to consider an integrated approach that emphasizes the holistic management of comorbidities in older adults with AF.

Abbreviations

AF, Atrial fibrillation; BMI, Body mass index; CCI, Charlson comorbidity index; CDT, Clock drawing test; CGA-FI, Comprehensive geriatric assessment-frailty index; hsCRP, High sensitivity C-reactive protein; LAD, Left atrial diameter; LVEF, Left ventricular ejection fraction; MMSE, Mini-mental state examination; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Data Sharing Statement

Raw data are available upon reasonable request with the corresponding author.

Ethics Approval and Consent to Participate

The trial was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, and the research protocol was approved by the Ethics Committee of Beijing Hospital (ID number: 2018BJYYEC-121-02). Written informed consent was obtained from the patients or their legal representatives.

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An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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