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Prognostic factors of clinical endpoints in elderly patients with atrial fibrillation during a 2-year follow-up in China

An observational cohort study

Hao Wang, PhD[a], Hai-Jun Wang, PhD[a], Ya-Dong Chen, MM[b], Tao Tao, PhD[a], Yu-Tao Guo, PhD[a], Xiao-Ning Zhao, PhD[a], Hong-Bin Liu, PhD[a,*], Yu-Tang Wang, PhD[a,*]

Abstract

This study aimed to reveal the incidence of clinical endpoints in elderly patients with atrial fibrillation (AF) during a 2-year follow-up and evaluate the related prognostic factors of these endpoints.

In total, 200 elderly patients with AF and 400 age- and sex-matched patients without AF were enrolled in this prospective observational cohort study. The incidence of clinical endpoints, including thromboembolism, hemorrhage, and all-cause death, during the 2-year follow-up was analyzed. Other follow-up data, including disease history, laboratory examinations, medication status, and other clinical endpoints, were collected. The prognostic factors of these clinical endpoints were then evaluated by Cox-survival analysis. In addition, the predicative role of C-reactive protein (CRP) and platelet-activating factor (PAF) on these clinical endpoints was analyzed.

The incidence of clinical endpoints, including thromboembolism, hemorrhage, and all-cause death, was significantly higher in patients with AF than in those without AF (27.8% vs 9.8%, 29.4% vs 12.7%, and 28.7% vs 11.6%, respectively; all $P < .001$). Antithrombotic therapy significantly reduced the incidences of all-cause deaths ($P < .05$). Body mass index (BMI) and digoxin were prognostic risk factors of thromboembolism; age, massive hemorrhage history, and digoxin were prognostic risk factors of hemorrhage and age, renal insufficiency history, massive hemorrhage history, and digoxin were prognostic risk factors of all-cause death ($P < .05$). Further, both CRP and PAF were prognostic risk factors of thromboembolism and massive hemorrhage ($P < .05$).

Age, BMI, massive hemorrhage history, and digoxin appear to be prognostic risk factors of clinical endpoints in elderly patients with AF. Appropriate drug use during follow-up may be beneficial in preventing the occurrence of clinical endpoints in elderly patients with AF.

Trial registration number: ChiCTR-OCH-13003479.

Abbreviations: ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, AF = atrial fibrillation, BMI = body mass index, CHADS2 = congestive heart failure, hypertension, age, diabetes, prior stroke or transient ischemic attack, CRP = C-reactive protein, PAF = platelet-activating factor, VKA = vitamin K antagonists.

Keywords: all-cause death, atrial fibrillation, hemorrhage, prognostic risk factor, thromboembolism

1. Background

Atrial fibrillation (AF) is the most common type of abnormal heart rhythm that is characterized by rapid and irregular beating.[1] According to statistics, in Asia, the prevalence of hospital- and community-based AF ranges from 0.37% to 3.56% and 2.8% to 15.8%, respectively.[2] The morbidity of AF always increases with age, which can affect up to 12% of individuals aged 75 to 84 years.[3] Although the research on AF treatment has greatly progressed, AF has not been effectively controlled. The hospital admission rate of patients with AF has exceeded that of patients with heart failure and myocardial infarction, and the worldwide mortality of AF has doubled from 1990 to 2010.[4,5] Thus, the prevention and treatment of AF in elderly patients need urgent attention.

Thromboembolism is considered to be one of the most common complications in elderly patients with AF.[6] The formation and detachment of the thrombus in patients with AF can increase the risks of ischemic stroke and systemic thrombosis.[6] It has been reported that the risk of ischemic stroke in patients with AF is 6-fold higher than that in healthy individuals and approximately 23.5% of elderly patients with AF suffer from ischemic stroke at the age of 80 to 90.[7] Because high mortality and disability rates are always associated with AF-induced ischemic stroke, anticoagulation therapy for the prevention of thrombus has become an effective treatment strategy for AF.[8] However, although the administration of anticoagulants is effective in the prevention of ischemic events, it can lead to

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HW and H-JW have contributed equally to this work.

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[a] Department of Geriatric Cardiology, Nanlou Division, Chinese PLA General Hospital, [b] Health Division of Guard Bureau, Joint Staff of the Central Military Commission, Beijing, China.

[*] Correspondence: Yu-Tang Wang, Department of Geriatric Cardiology, Nanlou Division, Chinese PLA General Hospital, 28 Fuxing Road, Haidian District, Beijing 100853, China (e-mail: wangyutang45@163.com), Hong-Bin Liu (e-mail: liuhbin301@sohu.com)

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hemorrhage.[9] As reported previously, incidences of cerebral micro-hemorrhages and brain infarcts increase with age and are associated with a greater risk of warfarin-related hemorrhages following ischemic stroke.[10] Furthermore, treatment with vitamin K antagonists (VKA) is associated with a 3-fold increase in the risk of gastrointestinal hemorrhage, and the risk is doubled by concomitant treatment with antiplatelet therapy and VKA.[11–13] In addition, several new oral anticoagulants, such as dabigatran etexilate, rivaroxaban, apixaban, and edoxaban, have been used for AF treatment, but increased gastrointestinal bleeding has also been found.[14] Thus, to prevent the risk of poor clinical endpoints such as thromboembolism, hemorrhage, and even death, it is essential to evaluate the prognostic risk factors of these clinical endpoints in patients with AF.

To date, various prognostic risk factors related to the incidence of thromboembolism during AF have been identified, such as old age, hypertension, valvular heart disease, coronary heart disease, heart failure, type 2 diabetes, chronic obstructive pulmonary disease, drinking, and smoking.[15] Based on these risk factors, various risk assessment models have been established; these include the Stroke Prevention in AF; Framingham; Congestive Heart Failure, Hypertension, Age, Diabetes, Prior Stroke, or Transient Ischemic Attack (CHADS2); and CHADS2-Vascular Disease, Age, and Sex Category schemes.[16] However, clinical research findings have shown that the diagnostic accuracy of these models is still limited in AF, which indicates that some prognostic factors associated with the risk of thromboembolism in patients with AF may not have been revealed.[17,18] In addition, hemorrhage risk stratification scores such as Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; HEMORR2HAGES and ATRIA have been developed.[19] However, because of regional and ethnic differences in patient populations, the prognostic factors of thromboembolism and hemorrhage in elderly patients with AF may differ in different places.

Therefore, the present study focused on investigating the prognostic factors and incidence of clinical endpoints, including thromboembolism, hemorrhage, and all-cause death, during a 2-year follow-up of elderly patients with AF in China. Further, the prognostic factors of these endpoints were evaluated, and the forecasting performances of inflammatory factors were also analyzed. Our findings extend our understanding of clinical endpoints in elderly patients with AF, which will be beneficial in guiding the prevention and treatment of elderly patients with AF in China.

2. Methods

2.1. Patients

As a prospective observational cohort study (clinical trial registration number: ChiCTR-OCH-13003479), 200 elderly patients (>65 years) with nonvalvular AF within 1 year of diagnosis were screened at the General Hospital of the People's Liberation Army between January 1, 2014 and December 31, 2015. AF was identified by electrocardiogram, as described previously.[20] Patients who had rheumatic heart disease, those who had serious uncontrolled infection, those who did not have episodes of AF for more than 1 year, and those who had undergone biological or mechanical valve replacement or mitral valve repair were excluded from this study. In addition, 400 age- and sex-matched elderly patients without AF were selected from the same hospital and enrolled as the control group (Table 1). This study was approved by the local Institutional Review Board, and informed consent was obtained from all the patients.

2.2. Clinical data collection

The baseline data of enrolled patients included name, gender, age, body mass index (BMI), systolic pressure, diastolic pressure, heart rate, smoking and drinking histories, disease history (such as ischemic stroke, hypertension, and peripheral vascular disease), as well as medication status, including the use of digoxin, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker (ACEI/ARB), or statins. Follow-up data, including medication status, laboratory examinations, and clinical endpoints, were collected each year by a specially trained attending physician in the Department of Cardiology through medical records, telephonic interviews, and questionnaires. Anticoagulation therapy included oral warfarin or rivaroxaban; antiplatelet therapy included oral aspirin or clopidogrel; and nonantithrombotic therapy included neither anticoagulants nor antiplatelet agents. For clinical endpoints, the incidences of thromboembolism (ischemic stroke, acute coronary syndrome, or

Table 1

Baseline characteristics in patients with and without atrial fibrillation.

Characteristics	Atrial fibrillation (n = 200)	Nonatrial fibrillation (n = 400)	*P*
Age, y, mean ± SD	86.60 ± 8.41	85.93 ± 11.13	.145
Male, n (%)	192 (96%)	380 (95%)	.5841
Systolic pressure, mm Hg, mean ± SD	133.82 ± 13.65	131.35 ± 17.64	.165
Diastolic pressure, mm Hg, mean ± SD	69.91 ± 10.62	67.55 ± 9.43	.243
Body mass index, kg/m^2, mean ± SD	23.98 ± 5.07	22.13 ± 6.35	.124
Heart rate, beat/min, mean ± SD	71.13 ± 12.28	73.71 ± 11.30	.058
Smoking history, n (%)	90 (45%)	150 (37.5%)	.077
Drinking history, n (%)	90 (45%)	113 (28.35%)	<.001
Ischemic stroke history, n (%)	88 (44%)	67 (16.75%)	<.001
Peripheral vascular disease, n (%)	102 (51%)	73 (18.25%)	<.001
Hypertension, n (%)	144 (72%)	254 (63.5%)	.0378
Type II diabetes, n (%)	67 (33.5%)	117 (29.25%)	.2872
The use of digoxin, n (%)	12 (6%)	1 (0.25%)	<.001
The use of ACEI/ARB, n (%)	74 (37%)	169 (42.25%)	.2169
The use of statin, n (%)	116 (58%)	132 (33%)	<.001

ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, SD = standard deviation.

Table 2

Clinical endpoints of elderly patients with or without atrial fibrillation during follow-up.

Clinical endpoints	Atrial fibrillation (n = 194)	Nonatrial fibrillation (n = 387)	*P*
Thromboembolism	54 (27.8%)	38 (9.8%)	<.001
Ischemic stroke	11 (5.7%)	9 (2.3%)	.0370
Acute coronary syndrome	31 (16.0%)	26 (6.7%)	.0004
Other system thrombosis	24 (12.4%)	7 (1.8%)	<.001
Hemorrhage	57 (29.4%)	49 (12.7%)	<.001
Massive hemorrhage	28 (14.4%)	9 (2.3%)	<.001
Micro-hemorrhage	40 (20.6%)	43 (11.1%)	.002
All-cause death	56 (28.7%)	45 (11.6%)	<.001

other systemic thrombosis [thromboembolism, except for deep vein thrombosis of the lower extremities]), hemorrhage (massive and micro-hemorrhage), and all-cause death were particularly noted during follow-up. Massive hemorrhage was defined as fatal bleeding and/or symptomatic bleeding in a key organ or area such as the brain, pericardium, or liver as well as a 20 g/L reduction in the hemoglobin level.[21] Micro-hemorrhage was defined as bleeding in several areas such as the alimentary canal, respiratory tract, urinary tract, or oral cavity, which was sufficient to be noted in medical records but which did not fulfill the criteria of massive hemorrhage. Finally, there were 194 patients with AF and 387 patients without AF for whom the data collection was completed, and the other patients were lost to follow-up.

2.3. Statistical analyses

Statistical analysis was performed using SPSS version 19.0 (SPSS Inc., Chicago, IL). Measurement data were expressed as the mean ± standard deviation. Qualitative data were expressed as number (percentage), and comparisons among the anticoagulation, antiplatelet, and nonantithrombosis groups were made using the chi-squared test in 3×2 contingency tables. Survival analysis based on the Cox model was used to evaluate the prognostic factors of clinical endpoints in elderly patients with AF during follow-up. A P value $< .05$ was considered significantly different.

3. Results

3.1. Clinical endpoints in elderly patients with AF during follow-up

As shown in Table 1, no significant differences were found in patient characteristics, including BMI, systolic pressure, diastolic pressure, heart rate, smoking history, hypertension, type II diabetes, and the use of ACEI/ARB, between patients with AF and those without AF. Significant differences were found in drinking history; ischemic stroke history; peripheral vascular disease; and the use of digoxin, ACEI/ARB, and statins between patients with AF and those without AF ($P < .01$). The incidence of clinical endpoints in elderly patients with AF was initially analyzed during follow-up. The incidences of thromboembolism (ischemic stroke, acute coronary syndrome, or other systemic thrombosis), hemorrhage (massive and micro-hemorrhage), and all-cause death were all significantly higher in patients with AF than in those without AF ($P < .05$, Table 2). Because different antithrombotic therapies were administered to patients with AF, the related clinical endpoints were also evaluated. As shown in Table 3, no significant differences were found in thromboembolism (ischemic stroke, acute coronary syndrome, or other systemic thrombosis) and hemorrhage (massive and micro-hemorrhage) among the anticoagulation, antiplatelet, and nonantithrombotic therapy groups. However, all-cause death was significantly increased by nonantithrombotic therapies ($P < .05$).

3.2. Prognostic factors of clinical endpoints in elderly patients with AF during follow-up

Based on demographic data, disease history and treatments of patients with AF during the 2-year follow-up, the prognostic factors of clinical endpoints (thromboembolism, hemorrhage, and all-cause death) were evaluated. BMI and the use of digoxin were found to be prognostic risk factors associated with the incidence of thromboembolism, whereas the use of statins was found to be a favorable prognostic factor of thromboembolism ($P < .05$). For common types of thrombosis, the prognostic risk factors of ischemic stroke were ischemic stroke history and peripheral vascular disease, whereas that of acute coronary syndrome was the use of digoxin ($P < .05$ for both). However, other systemic thrombosis exhibited no significant prognostic risk factors (Table 4).

Hemorrhage was another important clinical endpoint identified during follow-up of elderly patients with AF. As shown in Table 5, age, massive hemorrhage history, and the use of digoxin were all found to be prognostic risk factors of hemorrhage, whereas the use of β-blockers and nondihydropyridine calcium antagonists were found to be favorable prognostic factors of hemorrhage in elderly patients with AF ($P < .05$). Meanwhile, the prognostic risk factors of massive and micro-hemorrhage were found to be heart failure history and massive hemorrhage history, respectively ($P < .05$). Moreover, a favorable prognostic factor of massive hemorrhage was found to be the use of calcium antagonists ($P < .01$) (Table 5).

Table 3

Clinical endpoints of elderly patients with atrial fibrillation underwent different antithrombotic therapies during follow-up.

Clinical endpoints	Anticoagulation (n = 37)	Antiplatelet (n = 125)	Nonantithrombosis (n = 32)	*P*
Thromboembolism	10 (27.0%)	35 (28%)	9 (28.1%)	.9925
Ischemic stroke	1 (2.7%)	8 (6.4%)	2 (6.3%)	.6860
Acute coronary syndrome	7 (18.9%)	20 (16%)	4 (12.5%)	.7685
Other systemic thrombosis	4 (12.4%)	14 (11.2%)	6 (18.8%)	.4862
Hemorrhage	11 (29.7%)	39 (31.2%)	7 (21.9%)	.5855
Massive hemorrhage	5 (13.5%)	19 (15.2%)	4 (12.5%)	.9132
Micro-hemorrhage	7 (18.9%)	29 (23.2%)	4 (12.5%)	.3940
All-cause death	6 (16.2%)	35 (28%)	15 (46.9%)	.0185

Anticoagulation: warfarin or rivaroxaban; antiplatelet: aspirin or clopidogrel.

Table 4

Prognostic factors of thromboembolism in elderly patients with atrial fibrillation during follow-up.

	Thromboembolism		Ischemic stroke		Acute coronary syndrome		Other systemic thrombosis	
Risk factors	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
BMI (increased 1 kg/m^2 each)	1.086 (1.034–1.141)	.001	—	.325	—	.105	—	.058
Ischemic stroke history	—	.619	1.544 (1.010–2.184)	.036	—	.667	—	.848
Peripheral vascular disease	—	.052	4.236 (0.915–5.620)	.045	—	.118	—	.269
The use of digoxin	1.952 (1.056–3.607)	.033	—	.944	2.268 (1.038–4.955)	.040	—	.174
The use of ACEI/ARB	—	.174	—	.221	—	.404	—	.606
The use of statin	0.580 (0.471–1.302)	.028	—	.365	—	.955	—	.681

ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, BMI = body mass index, CI = confidence interval, HR = hazards ratio.

Table 5

Prognostic factors of hemorrhage in elderly patients with atrial fibrillation during follow-up.

	Hemorrhage		Massive hemorrhage		Micro-hemorrhage	
Risk factors	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age (increased each year)	1.066 (1.016–1.118)	.009	—	.433	—	.079
Massive hemorrhage history	2.573 (1.475–4.235)	.025	—	.487	2.984 (1.590–5.602)	.010
Heart failure history	—	.079	4.452 (2.054–9.650)	.001	—	.074
The use of digoxin	1.925 (1.058–3.503)	.032	—	.094	—	.090
The use of β-blockers	0.402 (0.233–0.693)	.001	—	.083	—	.057
The use of nondihydropyridine calcium antagonists calcium antagonist	0.413 (0.219–0.737)	.001	0.228 (0.081–0.641)	.005	—	.241

CI = confidence interval, HR = hazard ratio.

Table 6

Prognostic factors of all-cause death in elderly patients with atrial fibrillation during follow-up.

Risk factors	**HR (95% CI)**	***P***
Age (increased each year)	1.061 (1.014–1.110)	.01
Renal insufficiency history	2.44 (1.41–4.221)	.003
Massive hemorrhage history	2.546 (1.403–4.620)	.002
The use of digoxin	2.155 (1.188–3.906)	.011
The use of ACEI/ARB	0.503 (0.267–0.945)	.033
The use of nondihydropyridine calcium antagonists calcium antagonist	0.507 (0.281–0.915)	.024
The use of statin	0.411 (0.237–0.714)	.002

ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, CI = confidence interval, HR = hazard ratio.

Finally, various prognostic risk factors of all-cause death in elderly patients with AF were obtained during follow-up, including age, renal insufficiency history, massive hemorrhage history, and the use of digoxin ($P < .05$). Conversely, the favorable prognostic factors of all-cause death were found to be the use of ACEI/ARB, nondihydropyridine calcium antagonists, and statins ($P < .05$) (Table 6).

3.3. Risks of clinical endpoints correlated with CRP and PAF in elderly patients with AF

The relationship between inflammatory factors and clinical endpoints of AF was further analyzed by risk analysis. As a result, during follow-up, both C-reactive protein (CRP) and platelet-activating factor (PAF) were found to be prognostic risk factors of thromboembolism and massive hemorrhage in elderly patients with AF ($P < .05$). Only CRP was found to be a prognostic risk factor of hemorrhage ($P < .05$). However, there were no significant correlations between CRP and PAF levels and all-cause death (Table 7).

4. Discussion

It is well-established that AF is accompanied by severe clinical endpoints. The reported incidence of thromboembolism in

Table 7

Predicative roles of CRP and PAF on clinical endpoints in elderly patients with atrial fibrillation during follow-up.

	CRP, mg/dL		PAF, μg/L	
Clinical endpoints	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Thromboembolism	1.254 (1.124–1.356)	.041	1.025 (1.012–1.204)	.026
Ischemic stroke	—	.063	—	.157
Acute coronary syndrome	—	.098	—	.253
Other systemic thrombosis	—	.142	—	.216
Hemorrhage	1.148 (1.019–1.293)	.023	—	.054
Massive hemorrhage	1.238 (1.082–1.416)	.002	1.194 (1.025–1.345)	.014
Micro-hemorrhage	—	.231	—	.379
All-cause death	—	.071	—	.103

CI = confidence interval, CRP = C-reactive protein, HR = hazard ratio, PAF = platelet activating factor.

patients with AF is approximately 5% per year, which is 2- to 7-fold higher than that in patients without AF, whereas the incidence of stroke is 4.3% per year with aspirin and 4.6% per year with warfarin in elderly patients with AF.[22] Further, there is a 4-fold higher risk of ischemic stroke and a 2-fold higher risk of all-cause death in patients with AF than in those without AF.[23] In the present study, significantly higher rates of thromboembolism (27.8% vs 9.8%), hemorrhage (29.4% vs 12.7%), and all-cause death (28.7% vs 11.6%) were found in patients with AF than in those without AF. Meanwhile, the incidence rates of clinical endpoints in the present study were found to be a little higher than those in previous studies, which indicate that the clinical endpoints of AF are more likely to occur in elderly patients. Genetic factors, living habits, and economic levels in different regions may also influence the incidence of clinical endpoints in patients with AF.[24,25] Interestingly, no significant differences were found in thromboembolism and hemorrhage among patients with AF treated by either antithrombotic (anticoagulation and antiplatelet) or nonantithrombotic therapy. This may be due to the sample size of the nonantithrombotic therapy group being smaller than that of the antithrombotic therapy group, which may lead to a bias in the results. It was also found that almost half of the patients with AF without antithrombotic therapy died within the 2-year follow-up period. Previous research has demonstrated that antithrombotic therapy with warfarin can reduce the incidences of stroke and mortality in patients with AF.[26] In addition, although the European Society of Cardiology guidelines from 2010 preferred oral anticoagulation over antiplatelet therapy in patients with AF with a high risk of stroke,[15] both anticoagulation therapy and antiplatelet therapy were able to decrease the risk of stroke in patients with AF.[27] Because thromboembolism has been the main cause of death and disability in patients with AF[28] and old age may also be a cause of high mortality because of high incidences of complications, the rational use of antithrombotic drugs could significantly reduce the incidence of all-cause death.

In the present study, during follow-up, various prognostic risk factors of clinical endpoints in elderly patients with AF were revealed. A massive hemorrhage history was found to be a prognostic risk factor of both hemorrhage and all-cause death. This result was consistent with that of a previous study in that massive hemorrhage history could lead to a 1.5-fold increase in adverse clinical endpoints.[29] Because massive hemorrhage history has always been combined with massive cardiovascular risk factors, it may directly contribute to the increased incidences of hemorrhage and all-cause death.[30] In addition, renal insufficiency history was found to be a prognostic risk factor of all-cause death in patients with AF in the present study. It has been reported that the risk of AF is 3-fold higher in patients with renal insufficiency at stage 3 to 4 than in those without renal insufficiency.[31,32] AF is a risk factor of renal insufficiency, and approximately 10% to 33% of patients with AF have been found to exhibit renal insufficiency.[33] Our findings further illustrate an obvious relationship between AF and renal insufficiency. Further, digoxin has been a commonly used drug in the treatment of heart failure with AF; however, it has been known to lead to high mortality.[34] A retrospective study of a large sample has shown that the administration of digoxin to patients with AF could significantly increase the risk of death.[35] Consistent with previous findings, our findings showed that the use of digoxin was a prognostic risk factor of all-cause death in patients with AF. Furthermore, our study also revealed that the use of digoxin was associated with thromboembolism and hemorrhage. Similarly, previous studies have suggested that increased endogenous digoxin promotes the incidence of thrombotic vascular disease.[36,37] Digoxin has also been reported to increase the risk of hemorrhage stroke.[38] These results further indicate that thrombosis or hemorrhage may increase mortality and that digoxin should be carefully used in the control of the ventricular rate in elderly patients with AF.

By contrast, various favorable prognostic factors of clinical endpoints in elderly patients with AF were also revealed in this study. As a type of lipid-lowering agent, statin was revealed to be a favorable prognostic factor of thrombosis and all-cause death in patients with AF. As reported previously, the long-term administration of statins in patients with persistent AF could significantly reduce the recurrence of AF.[39] Therefore, appropriate statin treatment may be considered to be an effective strategy for the improvement of poor prognosis in patients with AF. It is well known that hypertension can increase the risk of intracranial hemorrhage.[40] The present study revealed that the use of β-blockers was a favorable prognostic factor of hemorrhage in patients with AF. β-blockers are commonly used for the treatment of hypertension,[41] indicating a protective role against hemorrhage in patients with AF. Calcium antagonists are also common antihypertensive drugs[42] as well as effective drugs in the treatment of AF, as indicated in the Guidelines for the Management of AF in Canada.[43] In the present study, nondihydropyridine calcium antagonists were found to be a favorable prognostic factor of hemorrhage and all-cause death in patients with AF. This phenomenon may be explained by the effective control of heart rate by nondihydropyridine calcium antagonists that could not only reduce the risk of thrombosis but also prevent the occurrence of rapid cardiomyopathy and cardiac dysfunction. In addition, as a first-line therapy drug for hypertension, ACEI/ARB was also considered to be a favorable prognostic factor of all-cause death in patients with AF. ACEI/ARB has been reported to be able to improve the prognosis of patients with hypertension,[44] reduce the mortality of patients with chronic heart failure,[45] and inhibit the occurrence and recurrence of AF.[46] The prognosis of AF could be obviously improved using ACEI/ARB by reducing blood pressure, improving atrial fibrosis, and reducing cardiac remodeling.[29,45]

It is well known that inflammatory factors and oxidative stress are involved in the pathogenesis of AF.[47] Xie et al[48] have demonstrated that oxidative stress could promote AF development by regulating type 2 ryanodine receptors and reactive oxygen species. Meanwhile, inflammation can be induced by oxidative stress, and a reduced inflammatory response can improve AF.[49] As an inflammatory marker, CRP can mediate chronic inflammation of the body through cellular defense responses. The relationship between CRP and AF has been confirmed by a large number of studies. As reported previously, CRP levels show an increasing trend in patients with isolated AF[50] and CRP levels can predict not only the occurrence and recurrence of AF but also the incidence of clinical endpoints such as thromboembolism and death.[51] CRP is also associated with the presence of AF and could predict patients at an increased risk of future development of AF.[52] PAF is also an important inflammatory response factor. In clinical settings, PAF has been reported to be associated with the outcomes of atherosclerosis and ischemic cerebrovascular disease.[53] Further, PAF can promote the deformation and aggregation of platelets, thereby inducing thrombosis.[54] However, the role of PAF in elderly patients with AF has not been reported. In the present study, survival analysis showed that both PAF and CRP were prognostic

risk factors of thromboembolism and massive hemorrhage in patients with AF, which further illustrates that inflammation is closely related to AF. Meanwhile, the predictive role of PAF and CRP on the prognosis of AF may provide a new diagnostic strategy for clinical endpoints of AF.

However, the present study has several limitations. First, this study was limited by an insufficient number of patients, which could not reflect the status of clinical endpoints completely. Second, almost all the patients with AF who were included were male (96%), which is not representative of a typical AF cohort and may lead to a bias in the results. Third, not all potential factors that may influence clinical endpoints were included in this prospective observational study. Thus, further research on elderly patients with AF with a rational gender proportion and a more comprehensive range of potential prognostic factors in a large population is still needed.

5. Conclusions

In conclusion, more clinical endpoints, including thromboembolism, hemorrhage, and all-cause death, were exhibited in elderly patients with AF than in those without AF, and the incidence of all-cause death could be significantly reduced by antithrombotic therapy. Older age, increased BMI, massive hemorrhage history, renal insufficiency history, and the use of digoxin appear to be prognostic risk factors of thromboembolism, hemorrhage, and all-cause death. Meanwhile, the administration of statins, calcium antagonists, and ACEI/ARB seems to be a favorable prognostic factor associated with these clinical endpoints.

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