Clinical Research Report

Moderate chronic kidney disease and left atrial enlargement independently predict thromboembolic events and mortality in elderly patients with atrial fibrillation: a retrospective single-center study

Hai-jun Wang1,*, Kai-liang Li1,*, Jian Li2, Kun Lin2, Yang Shi1, Hao Wang1, Quan-jin Si1 and Yu-tang Wang1

Abstract
Objective: This study aimed to evaluate the effects of moderate chronic kidney disease (CKD) and left atrial enlargement on the risks of thromboembolic events, and all-cause and cardiovascular mortalities in elderly patients with atrial fibrillation (AF).
Methods: We retrospectively studied 751 patients (82.16% men, mean age: 79.0 ± 9.1 years) with AF who were followed up for an average of 34.5 months at a single center. Adjusted hazard ratios (HRs) of risk factors for adverse clinical events were calculated using the Cox proportional hazards model.
Results: The risks of thromboembolic events, and all-cause and cardiovascular deaths were higher in patients with moderate CKD compared with patients with normal renal function after adjusting for other traditional risk factors (HR: 1.63, 95% confidence interval (CI): 1.03–2.58; HR: 1.55, 95% CI: 1.08–2.23; HR: 3.49, 95% CI: 1.57–7.74; respectively). Left atrial volume index >28.0 mL/m² was an independent risk factor associated with thromboembolic

1Department of Cardiology, the Second Medical Center, Chinese PLA General Hospital; National Clinical Research Center for Geriatric Diseases, Beijing, China
2Department of Cardiology, the First Medical Center, Chinese PLA General Hospital, Beijing, China

*These authors contributed equally to this work.
Corresponding author:
Quan-jin Si, Department of Cardiology, the Second Medical Center, Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, China.
Emails: quanjin301@163.com

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events and all-cause and cardiovascular deaths (HR: 1.62, 95% CI: 1.21–2.33; HR: 1.56, 95% CI: 1.16–2.10; HR: 1.87, 95% CI: 1.07–3.28; respectively).

**Conclusions:** Moderate CKD and left atrial enlargement may predict thromboembolic events, and all-cause and cardiovascular mortalities in elderly patients with AF without anticoagulation therapy.

**Keywords**
Aged, atrial fibrillation, chronic kidney disease, left atrial enlargement, mortality, thromboembolic complication

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**Introduction**

Atrial fibrillation (AF) is one of the most common types of sustained arrhythmia, and is strongly associated with an increased risk of thromboembolic events (TEs), including ischemic stroke. The prevalence of AF increases with age in line with a decline in the estimated glomerular filtration rate (eGFR). Chronic kidney disease (CKD) is defined by decreased kidney function measured by the glomerular filtration rate, and kidney damage characterized by albuminuria or proteinuria. CKD and AF are both major global health concerns that commonly coexist in elderly individuals. Some studies found that approximately 7%–18% of patients with CKD had AF, while 10%–33% of patients were found to have CKD when AF was diagnosed.\(^1\) The occurrence of AF may promote the progression of CKD and increase the risk of developing end-stage renal disease.\(^2\) Importantly, comorbid AF and CKD (eGFR <60 mL/min/1.73 m\(^2\)) have been shown to be related to adverse cardiovascular events and all-cause mortality.\(^3,4\) Some studies identified atrial fibrosis and atrial cardiopathy as fundamental characteristics of the structural pathology associated with cardioembolic complications, both of which were independent risk factors for stroke, especially in elderly patients with CKD, regardless of whether or not the arrhythmia was sustained.\(^5,6\) However, this speculation remains debatable.

In addition, AF often results from loss of atrial systole, dilatation of the left atrium, and increased atrial pressure load in the atrium in elderly patients.\(^7\) Left atrial volume index (LAVI) has often been used as a more accurate marker than left atrial diameter for determining left atrial size. Increased LAVI has been regarded as a risk factor for the occurrence or recurrence of AF and is associated with thromboembolism, even in patients without AF.\(^8\) However, the most common thromboembolic risk score is the CHA\(_2\)DS\(_2\)-VASc risk score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, and sex category), which does not consider either CKD or LAVI as an independent risk factor for ischemic stroke in patients with AF. This study therefore investigated the roles of CKD and LAVI in predicting TEs and mortality in elderly patients with non-valvular AF who did not receive anticoagulation therapy.

**Patients and methods**

**Study subjects**

We retrospectively reviewed the data for 751 hospitalized elderly patients with
non-valvular AF who did not receive anti-coagulation therapy and who were admitted to the Chinese PLA General Hospital between July 2008 and June 2011. All patients had a permanent and personal registration number in the hospital, which allowed complete collection of information regarding their outpatient and inpatient attendance. The hospital’s electronic medical database included information on all the patients’ medical histories, therapeutic procedures, cardiovascular events, and laboratory and imaging data. Patients aged 65 years or older and those with established AF confirmed by electrocardiogram, continuous electrocardiographic monitoring, or 24-hour Holter monitoring were included, regardless of AF pattern (paroxysmal, persistent, or permanent). Patients were excluded if they were taking anticoagulants at the time of study initiation or were prescribed anticoagulants in the 3 months preceding the study, had valvular heart diseases such as critical aortic or mitral stenosis on echocardiography, received radiofrequency catheter ablation or left atrial appendage occlusion, had severe renal insufficiency (eGFR <30 mL/min/1.73 m²), laboratory or clinical findings suggestive of infectious and inflammatory diseases, or acute myocardial infarction and confirmed stroke in the 3 months preceding the study.

The content of this study was approved by the medical ethics committee of the Chinese PLA General Hospital, in accordance with the relevant requirements for a clinical retrospective single-center study. Written informed consent was obtained from the patients or their carers for participation in this retrospective study.

Clinical data collection and measurements

Patients’ general health status, age, sex, body mass index (BMI), smoking status, and history of cardiovascular diseases were recorded on admission. BMI was calculated as weight (kg)/[height (m)]². Echocardiography parameters including left ventricular ejection fraction (LVEF) and left atrial volume (LAV) were derived from the echocardiographic data. LVEF and LAV were measured separately using Simpson’s method and the area–length method. We defined a left ventricular mass index (LVMI) of >125 g/m² for men and 110 g/m² for women as cut-off values for left ventricular hypertrophy (LVH). LAV was calculated using the following formula:

\[ \text{LAV (mL)} = \frac{(\pi/6) \times D1 \times D2 \times D3}{C2} \]

where \( D1, D2, \text{ and } D3 \) are the distance from the posterior wall of the aorta to the left atrium and the two axes of the left atrium). LAVI was calculated as LAV divided by the body surface area for each patient. Partition values for LAVI were taken with a cut-off value of 28 mL/m² regardless of the sex of the patient.9,10

Serum creatinine and hemoglobin were assessed at the central laboratory of our hospital using blood samples obtained at admission. CKD stage was determined by eGFR calculated using the abbreviated equation developed using the Modification of Diet in Renal Disease study:

\[ \text{eGFR} = \frac{186 \times [\text{SCR}]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ if female}] \times 1.233}{C2} \]

where SCR is serum creatinine and 1.233 is the adjustment coefficient for Chinese individuals.11 Patients were classified into three kidney-function groups according to the eGFR values: normal renal function, eGFR ≥90 mL/min/1.73 m²; mild CKD, eGFR 60–90 mL/min/1.73 m²; and moderate CKD, eGFR 30–60 mL/min/1.73 m².

Assessment of clinical outcomes

Information on the endpoints was obtained from medical records and questionnaires answered by the patients themselves or their relatives. The main study outcomes were TEs (including ischemic stroke and
thromboembolism), all-cause death, and cardiovascular death. Ischemic stroke was defined as sudden onset of neurological deficit lasting over 24 hours, confirmed by computed tomography or magnetic resonance imaging. Thromboembolism was defined as sudden occlusion of an artery to a visceral organ or extremity documented by imaging or pathology and not attributable to concomitant atherosclerosis or other etiologies. Cardiovascular death was death attributed to myocardial infarction, heart failure, sudden cardiac death, or stroke.

**Statistical analysis**

Continuous variables are shown as mean ± standard deviation. Univariate analysis was computed using analysis of variance for continuous variables and χ² tests for categorical variables. The cumulative incidences of TEs and mortalities were plotted as Kaplan–Meier curves among the different groups, and differences were assessed using the log rank test. Adjusted hazard ratios (HRs) of risk factors for clinical adverse events were calculated using the Cox proportional hazards model. Adjusted HRs with 95% confidence intervals (CIs) were reported separately. A P value of <0.05 was considered statistically significant.

**Results**

**Baseline characteristics of study participants**

A total of 751 patients with AF (male, 82.16%; mean age at baseline, 78.95 ± 9.11 years) were followed up for an average of 34.5 months. This cohort included 673 patients (89.61%) at high risk of thromboembolism (CHA₂DS₂-VASc risk score ≥2) and who satisfied the guideline recommendations and did not receive oral anticoagulation therapy. The reasons for not administering anticoagulants in selected elderly patients included a high risk of bleeding, history of recent cerebral hemorrhage or major bleeding, rejection by patients, poor patient compliance, and inadequate recommendation of non-cardiovascular specialists for anticoagulant therapy.

The clinical characteristics of the study population in relation to the severity of CKD are shown in Table 1. In this cohort, 334 (44.47%) patients met the eGFR criteria for mild CKD, and 140 (18.64%) patients met the eGFR criteria for moderate CKD. There were no significant differences in the duration of follow-up, sex, current smoking status, BMI, type of AF, hypertension, prior stroke, and prior TE between patients with normal renal function and those with moderate CKD (P>0.05). However, patients with moderate CKD were significantly older and had a significantly higher LVMI, LAVI, and CHA₂DS₂-VASc score (4.34 ± 1.46 and 3.36 ± 1.72, respectively) and significantly lower LVEF and hemoglobin than patients with normal renal function (P<0.05). Patients with AF and moderate CKD also had significantly higher frequencies of coronary heart disease, heart failure, chronic obstructive pulmonary disease (COPD), diabetes mellitus, peripheral arterial disease, and use of antiplatelet drugs than patients with AF and normal renal function (P<0.05).

**Clinical events**

Clinical outcomes and crude incidence rates of patients with AF according to the stage of CKD are listed in Table 2. Over a total of 2156.9 person-years of follow-up (median: 35.5 months), 200 (26.63%) patients died, 54 (7.19%) experienced cardiovascular death, and 133 (17.71%) experienced TEs. The annual all-cause mortality in patients with AF and moderate CKD was approximately 15.57 per 100 person-years, which declined stepwise to 8.82 and 7.41 per 100
person-years in patients with normal renal function and patients with mild CKD, respectively. Moreover, the annual incidences of TEs and cardiovascular death were highest in patients with moderate CKD (10.01 and 5.84 per 100 patient-years, respectively), intermediate in patients with mild CKD (5.56 and 2.34 per 100 patient-years, respectively), and
lowest in patients with normal renal function (5.19 and 1.17 per 100 patient-years, respectively). Univariate analysis revealed significant differences in the Kaplan–Meier estimates of cumulative incidences of TEs, all-cause death, and cardiovascular death according to the stage of CKD or LAVI ($P<0.01$) (Figure 1 and Figure 2).

**Multivariate analysis**

We further analyzed the risk factors associated with adverse events in univariate and multivariate analyses. HRs using normal renal function as the reference during the observation period are shown in Table 3. We applied a multivariate Cox regression model including stage of CKD, age, sex, type of AF, current smoking status, coronary heart disease, hypertension, COPD, diabetes mellitus, heart failure, prior stroke, prior TE, peripheral arterial disease, left ventricular hypertrophy (LVH), anemia, and clinical medications. The crude HRs for TEs, all-cause death, and cardiovascular death during the observation period were significantly higher in patients with AF and moderate CKD compared with AF patients

![Figure 1. Kaplan–Meier estimates of cumulative incidences of (a) thromboembolic events, (b) all-cause death, and (c) cardiovascular death according to the stage of chronic kidney disease. eGFR: estimated glomerular filtration rate.](image)
with AF and normal renal function, and they remained significant after adjusting for other traditional risk factors (HR: 1.63, 95% CI: 1.03–2.58, \( P = 0.037 \); HR: 1.55, 95% CI: 1.08–2.23, \( P = 0.018 \); HR: 3.49, 95% CI: 1.57–7.74, \( P = 0.002 \), respectively). Similarly, multivariate analysis also identified LAVI >28.0 mL/m\(^2\) as an independent risk factor associated with TEs, all-cause death, and cardiovascular death after adjusting for other risk factors (HR: 1.62, 95% CI: 1.21–2.33, \( P = 0.010 \); HR: 1.56, 95% CI: 1.16–2.10, \( P = 0.003 \); HR: 1.87, 95% CI: 1.07–3.28, \( P = 0.029 \), respectively). Additionally, age \( \geq 75 \) years, current smoking, and prior stroke were independent risk factors for TEs after adjusting for other risk factors (\( P < 0.05 \)). Moreover, age \( \geq 75 \) years, heart failure, and prior stroke significantly increased the risk of all-cause death (all \( P < 0.05 \)), and heart failure, prior stroke, and LVH increased the risk of cardiovascular death (all \( P < 0.05 \)) (Table 3).

**Discussion**

We simultaneously investigated the impacts of renal insufficiency (eGFR \( \geq 30 \) or...

![Figure 2. Kaplan–Meier estimates of cumulative incidences of (a) thromboembolic events, (b) all-cause death and (c) cardiovascular death according to left atrial volume index.](image-url)
(60 mL/min/1.73 m²) and left atrial enlargement (LAVI >28 mL/m²) on TEs, mortality, and cardiovascular death in a cohort of elderly patients with AF who did not receive anticoagulation therapy. Notably, we showed that both moderate CKD and LAVI were significant prognostic factors for TEs, all-cause death, and cardiovascular death.

A total of 44.47% patients with AF in the current study had mild CKD and 18.64% had moderate CKD, according to the current criteria. CKD was often combined and associated with AF in elderly patients. Recent studies have often, but not always, considered CKD as a well-established risk factor for stroke and thromboembolism in patients with AF. Nevertheless, conflicting results have been reported regarding the ability of CKD to improve the predictive value of TEs and mortality risk stratifications. The annual all-cause mortality and incidences of TEs and cardiovascular deaths in patients with AF and moderate CKD in the current study were comparable with findings from previous studies. We also observed a higher mortality and higher incidence of TEs and cardiovascular death in patients with moderate CKD than in patients with normal renal function, which supported and extended the results of previous studies. The occurrence of death was mostly related to cardiovascular causes. With regard to the prognostic significance of moderate CKD, several studies have shown that moderate CKD is associated with not only mortality, but also with TEs and cardiovascular death.

### Table 3. Cox regression risk analyses of thromboembolic events, all-cause death, and cardiovascular death.

| Entire cohort | Univariate model* | Multivariate model † |
|---------------|-------------------|---------------------|
| **Thromboembolic events** | | |
| Moderate CKD | 2.149 1.368–3.375 0.001 | 1.630 1.029–2.583 0.037 |
| Age ≥75 years | 2.462 1.496–4.049 <0.001 | 1.892 1.130–3.167 0.015 |
| Current smoking | 1.902 1.256–2.879 0.002 | 2.130 1.391–3.262 0.001 |
| Prior stroke | 2.188 1.553–3.082 <0.001 | 2.037 1.429–2.903 <0.001 |
| LAVI >28 mL/m² | 1.809 1.265–2.588 0.001 | 1.616 1.121–2.328 0.010 |
| **All-cause death** | | |
| Moderate CKD | 1.738 1.220–2.476 0.002 | 1.551 1.077–2.233 0.018 |
| Age ≥75 years | 5.358 3.053–9.402 <0.001 | 4.306 2.436–7.611 <0.001 |
| Heart failure | 2.125 1.520–2.970 <0.001 | 1.992 1.416–2.802 <0.001 |
| Prior stroke | 1.502 1.126–2.004 0.006 | 1.378 1.028–1.847 0.032 |
| LAVI >28 mL/m² | 1.736 1.298–2.322 <0.001 | 1.560 1.162–2.096 0.003 |
| **Cardiovascular death** | | |
| Moderate CKD | 4.970 2.276–10.853 <0.001 | 3.489 1.572–7.743 0.002 |
| Heart failure | 4.848 2.803–8.386 <0.001 | 4.036 2.320–7.019 <0.001 |
| Prior stroke | 2.426 1.422–4.140 0.001 | 2.336 1.364–4.000 0.002 |
| Left ventricular hypertrophy | 2.545 1.479–4.381 0.001 | 1.795 1.013–3.181 0.045 |
| LAVI >28 mL/m² | 2.414 1.407–4.414 0.001 | 1.870 1.065–3.284 0.029 |

HR: hazard ratio; CI: confidence interval, CKD: chronic kidney disease, LAVI: left atrial volume index.

*Univariate analysis of adverse events using a Cox proportional hazards model.
†Cox proportional hazards model adjusted for stage of chronic kidney disease, age, sex, type of atrial fibrillation, current smoking status, coronary heart disease, hypertension, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, prior stroke, prior thromboembolism, peripheral arterial disease, left ventricular hypertrophy, anemia, and clinical medications.
in patients with AF.\textsuperscript{12,14} For example, analysis of the RE-LY trial found that the incidences of stroke, thromboembolism, and mortality were all associated with decreased renal function.\textsuperscript{15} A meta-analysis involving 538,479 patients with non-valvular AF found that impaired renal function (eGFR <60 mL/min/1.73 m\textsuperscript{2}) was an independent predictor of stroke and TEs and could slightly improve the stroke-risk stratification, such as the CHADS\textsubscript{2} score.\textsuperscript{6} Furthermore, some studies found that the addition of renal impairment (eGFR <60 mL/min/1.73 m\textsuperscript{2}) to the CHADS\textsubscript{2} or CHA\textsubscript{2}DS\textsubscript{2}-VASc risk score had high discriminative performance for the prediction of TEs in patients after catheter ablation of AF, even in patients with AF and advanced renal failure (eGFR <30 mL/min/1.73 m\textsuperscript{2}).\textsuperscript{16,17} The mechanisms underlying the higher risks of TEs and mortality among patients with moderate CKD may be partly attributed to unmeasured comorbidities not accounted for in the CHA\textsubscript{2}DS\textsubscript{2}-VASc risk score. Patients with CKD are associated with a ‘pro-thrombotic status’, which indicates a higher presence of thrombotic cofactors such as endothelial dysfunction, subclinical inflammation, elevated levels of plasminogen activator inhibitor-1, and abnormal coagulation factor activities. CKD often causes various pathophysiological changes, including activation of the renin-angiotensin-aldosterone system (RAAS), oxidative and anti-oxidative imbalance, and excessive sympathetic nerve excitation, which can in turn accelerate the processes of atherosclerosis and atrial remodeling, and increase the risks of TEs and cardiovascular death.\textsuperscript{18} Additionally, oxidative stress is involved in the pathogenesis of AF and could represent a link between CKD and AF.\textsuperscript{19}

The present study also found that left atrial enlargement (LAVI >28 mL/m\textsuperscript{2}) was an independent risk factor for TEs, all-cause death, and cardiovascular death. LAVI has been proven to be a more accurate measure of left atrial remodeling than left atrial diameter, and has often been used as a useful predictor of the incidence or recurrence of AF, including silent AF.\textsuperscript{10} In the present study, patients with LAVI >28 mL/m\textsuperscript{2} showed higher adjusted risks of all-cause death, TEs, and cardiovascular death. These results were partly in accordance with those of other studies in patients with AF. For example, Chung et al.\textsuperscript{9} reported that an enlarged left atrium (LAVI >28 mL/m\textsuperscript{2}) predicted an increased risk of stroke recurrence in patients with non-sustained atrial tachycardia, while another study reported that increased LAVI was associated with poorer initial neurologic deficits in patients with stroke and non-valvular AF.\textsuperscript{20} Additionally, left atrium mechanics, including left atrial longitudinal strain, LAVI, and emptying fraction, were associated with the CHA\textsubscript{2}DS\textsubscript{2}-VASc risk score, suggesting that left atrial remodeling might represent a useful method for identifying patients at high risk of TEs and cardiovascular mortality.\textsuperscript{21} In our current study, both moderate CKD and left atrial enlargement were independent risk factors for TEs, all-cause death, and cardiovascular death after adjusting for other traditional risk factors in the CHA\textsubscript{2}DS\textsubscript{2}-VASc risk score. Several potential mechanisms may contribute to the higher risks of recurrence of AF and TEs among patients with AF and left atrial enlargement.\textsuperscript{22,23} Left atrial enlargement may be associated with disorder or degradation of suture junction and structural proteins, decreased atrial conduction velocity, and increased atrial dispersion. This could promote the progression of atrial remodeling and interstitial fibrosis, leading to the development of AF. Increased LAVI may increase the atrial filling pressure and blood vortex in the atrium, leading to atrial thrombosis. In addition, CKD is associated with activation of the RAAS and excessive sympathetic excitation, which can further promote atrial remodeling in patients with AF. Some recent studies demonstrated that the autonomic
nervous system might play an important role in determining heterogeneous electrophysiological changes in atrial cardiomyocytes, causing atrial fibrillation episodes.\(^{24,25}\) Furthermore, changes in autonomic activity might trigger different signaling pathways, including proinflammatory cytokines, epicardial adipose tissue, the RAAS, and oxidative stress, which could in turn determine atrial derangement and promote atrial cardiopathy.\(^{24}\) These mechanisms could account for the significantly increased risks of mortality, cardiovascular death, and TEs in elderly patients with AF and renal insufficiency and/or left atrial enlargement.

The current study had several limitations. First, the observational retrospective nature of the study and the relatively small sample size from a single institution might have led to selection bias. Second, CKD is also associated with a higher risk of ventricular arrhythmia, which can also cause cardiovascular death, and this was not considered in our study. Third, we did not consider changes in eGFR during follow-up, and might therefore have misclassified the stages of CKD. Fourth, we did not use different cut-offs of LAVI for the different sexes, which might have resulted in sex bias. Finally, elderly patients with AF who were prescribed anticoagulants were excluded from the present study, which might have affected the applicability of the conclusions to the general Chinese population. The potential effects of including patients who received anticoagulants and/or had none of the CHA\(_2\)DS\(_2\)-VASc risk factors were unclear. In addition, the cut-off of LAVI did not vary according to sex, and the sex differences need to be confirmed in larger-scale studies.

**Conclusion**

The results of the current study demonstrate that both moderate CKD and left atrial enlargement predict TEs and all-cause and cardiovascular mortalities in elderly patients with AF who do not receive anticoagulation therapy.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

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**ORCID iD**

Hai-jun Wang  [ID](https://orcid.org/0000-0001-9814-0041)

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