Increased mortality in patients with secondary diagnosis of atrial fibrillation: Report from Chinese AF registry

Xing-Hui Shao MD, PhD | Yan-Min Yang MD, PhD | Jun Zhu MD, PhD | Li-Tian Yu MD, PhD | Li-Sheng Liu MD, PhD

Emergency and Intensive Care Center, Fuwai Hospital, Chinese Academy Of Medical Sciences, Beijing, China

Correspondence
Yan-Min Yang, Emergency and Intensive Care Center, Fuwai Hospital, Chinese Academy Of Medical Sciences and Peking Union Medical College, No.167 Rd. Beilishi. Beijing 100037, China. Email: yymfuwai@163.com

Abstract

Background: The relationship between mortality and the primary diagnosis in AF patients is poorly recognized. The purpose of the study is to compare the differences on mortality in patients with a primary or secondary diagnosis of AF and to identify risk factors amenable to treatment.

Methods: This was a prospective cohort study using data from the Chinese AF registry. For admitted patients, a follow-up was completed to obtain the outcomes during 1 year.

Results: A total of 2015 patients with confirmed AF were included. AF was the primary diagnosis in 40.9% (n = 825) of them. 78.9% (n = 939) of the secondary AF diagnosis patients and 55.5% (n = 458) of the primary AF diagnosis patients were sustained AF. Compared with primary AF diagnosis group, the secondary AF diagnosis group was older with more comorbidities. At 1 year, the unadjusted mortality was much higher in the secondary AF diagnosis groups compared with the primary AF diagnosis groups. In Cox regression analysis with adjustment for confounding factors, patients with secondary AF diagnosis were associated with an increased mortality (relative risk 1.723; 95% CI: 1.283 to 2.315, p < .001). On multivariate analysis, age ≥ 75, LVSD, COPD, and diabetes were independent predictors of mortality in patients with primary AF diagnosis, while for the secondary AF diagnosis group, the risk factors were age ≥ 75, heart failure, and previous history of stroke.

Conclusions: Patients presenting to ED with secondary diagnosis of AF were suffering from higher mortality risks compared with primary AF diagnosis patients. Physicians should distinguish these two groups in clinical practice.

Keywords: atrial fibrillation, diagnosis, emergency medicine, heart failure, mortality

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder associated with increased morbidity and mortality (Lip, Brechin, & Lane, 2012). It is recognized as a considerable health-care burden, because of an aging population and the strong relevance between AF and its concomitant diseases such as stroke, myocardial infarction, and congestive heart failure (Airaksinen...
et al., 2013; Camm et al., 2010; Dickinson, Chen, & Francis, 2014). Data from the Framingham study demonstrated a 1.5-fold to 1.9-fold risk of mortality in patients with AF after adjustment for the preexisting cardiovascular conditions (Benjamin et al., 1998). Subsequently, numerous studies have drawn the same conclusion in various populations (Badheka et al., 2011; Jabre et al., 2011). However, there is relatively little research concerning on the relationship between mortality and the primary diagnosis of these

### TABLE 1 Overview of data from patients with sustain or non-sustain AF and an alternative primary ED diagnosis

| Demography                        | Secondary AF diagnosis (n = 1,190) | Primary AF diagnosis (n = 825) | p value |
|-----------------------------------|-----------------------------------|-------------------------------|---------|
|                                   | Sustain AF (n = 939)               | Non-sustain AF (n = 251)      |         |
| Age (years)                       | 69.83 (13.15)                     | 69.48 (13.12)                | <.001   |
|                                   | 67.58 (12.92)                     | 65.35 (13.63)                |         |
| Female gender                     | 518 (55.2)                        | 138 (55.0)                   | <.820   |
| BMI (kg/m²)                       | 23.15 (3.73)                      | 23.44 (3.30)                 | <.001   |
| Systolic BP (mmHg)                | 133.77 (24.03)                    | 134.49 (25.92)               | <.001   |
| Diastolic BP (mmHg)               | 80.74 (15.96)                     | 80.31 (15.99)                | <.019   |
| Heart rate (time/minute)          | 97.12 (26.67)                     | 98.59 (28.70)                | <.001   |
| Mean CHADS<sub>2</sub> score<sup>a</sup> | 2.16 (1.40)                      | 1.85 (1.36)                  | <.001   |
| Medical history                   |                                   |                               |         |
| Myocardial infarction             | 86 (9.2)                          | 28 (11.2)                    | <.001   |
| Coronary artery disease           | 432 (46.0)                        | 122 (48.6)                   | <.001   |
| Heart failure                     | 512 (54.5)                        | 72 (28.7)                    | <.001   |
| Hypertension                      | 513 (54.6)                        | 143 (57.0)                   | <.001   |
| LVH                               | 196 (20.9)                        | 33 (13.2)                    | <.001   |
| Stroke/TIA                        | 221 (23.5)                        | 47 (18.7)                    | <.001   |
| Sleep apnea                       | 35 (3.7)                          | 9 (3.6)                      | .538    |
| Smoke                             | 219 (23.3)                        | 45 (17.9)                    | .110    |
| LVSD                              | 259 (27.6)                        | 37 (14.7)                    | <.001   |
| Cognitive disorder                | 30 (3.2)                          | 6 (2.4)                      | .016    |
| COPD                              | 144 (15.4)                        | 32 (12.7)                    | <.001   |
| Diabetes                          | 162 (17.3)                        | 43 (17.1)                    | .079    |
| Hyperthyroidism                   | 24 (2.6)                          | 8 (3.2)                      | .110    |
| Valvular heart disease            | 215 (22.9)                        | 18 (7.2)                     | <.001   |
| Major bleeding                    | 31 (3.3)                          | 5 (2.0)                      | .083    |
| Medication                        |                                   |                               |         |
| ACE inhibitor                      | 282 (30)                          | 59 (23.5)                    | <.001   |
| ARB                               | 169 (18.0)                        | 50 (19.9)                    | .476    |
| β-blocker                         | 452 (48.1)                        | 110 (43.8)                   | <.001   |
| CCB                               | 237 (25.2)                        | 82 (32.7)                    | .004    |
| Diuretics                         | 522 (55.6)                        | 80 (31.9)                    | <.001   |
| Digoxin                           | 451 (48.0)                        | 53 (21.1)                    | <.001   |
| Lipid-lowering medication         | 242 (25.8)                        | 76 (30.3)                    | .007    |
| Aspirin or platelet inhibitor     | 592 (63)                          | 160 (63.7)                   | .953    |
| Oral anticoagulant                | 196 (20.9)                        | 42 (16.7)                    | .057    |
| Outcomes                          |                                   |                               |         |
| 1-year all-cause mortality        | 179 (19.3)                        | 34 (13.9)                    | .001    |
| Cardiovascular mortality          | 98 (54.7)                         | 18 (52.9)                    | .245    |

<sup>a</sup>A risk stratification scheme for atrial fibrillation. A score of 0–6 is derived based on the following factors: congestive heart failure (1 point); hypertension (1 point); age > 75 years (1 point); diabetes mellitus (1 point); and previous stroke or TIA (2 point).
diagnosis patients and other primary diagnosis patients in a group trial to compare the difference on mortality between primary AF were poorly recognized. Therefore, we performed a prospective and outcomes of AF patients with a different primary diagnosis were excluded in the study.

The Chinese AF registry was a multicenter, prospective, observational study enrolled patients from 20 participating hospitals between November 2008 and October 2011. Patients who presented to an emergency department (ED) with atrial fibrillation or flutter were recruited in the study. Based on their primary diagnosis, admitted patients were divided into two groups: AF/flutter or the other. For all the individuals, one-year follow-up was performed. The study was approved by the ethics committees of each institution, and informed consent was obtained from all individual participants included in the study.

All participating centers were encouraged to enroll consecutive patients to minimize selection bias. The inclusion criteria were as follows: identification of patients using electronic hospital databases recording emergency department diagnoses, review of electrocardiograms, and telemetry recordings from the emergency department and direct screening by emergency department staff. Each hospital admission is assigned one primary diagnosis and up to nine secondary diagnoses when discharged. The primary diagnosis describes the main cause of hospitalization. Baseline data collected included patient demographics, visit characteristics, medical history, medication and interventions in ED, and hospital discharge information. Follow-up was carried out at one year from time of enrollment by telephone interview. All-cause mortality and the primary reason for death were identified. We defined heart failure, stroke and pulmonary embolism, and myocardial infarction as cardiovascular mortality. All treatment decisions were left to the discretion of the treating physician.

For blood pressure and heart rate, initial data at registration were documented. Body mass index (BMI) (weight [kg]/height[m]^2) was calculated using the weight and height measured at enrollment. The definitions of AF types were in accordance with American College of Cardiology/American Heart Association/European Society of Cardiology 2006 guidelines for AF (Fuster et al., 2006). We combined persistent AF and permanent AF as sustain AF. The risk stratification scheme CHADS2 based on a scoring systemic in which 2 points are assigned for a history of stroke and transient ischemic attack and 1 point each is assigned for age more than 75 year, a history of hypertension, diabetes, or recent clinical heart failure or impaired left ventricular systolic function.

Data were collected on a standardized case report form (CRF) through searching medical record and patient interview from each center. The CRF was sent to Fuwai hospital by fax at the earliest opportunity. Using a validation plan, integrated in the data entry software, data were checked for missing or contradictory entries and values out of the normal range. Additional edit checks were performed by the staff in Fuwai hospital.

2 | MATERIALS AND METHODS

The Chinese AF registry was a multicenter, prospective, observational study enrolled patients from 20 participating hospitals between November 2008 and October 2011. Patients who presented to an emergency department (ED) with atrial fibrillation or flutter were recruited in the study. Based on their primary diagnosis, admitted patients were divided into two groups: AF/flutter or the other. For all the individuals, one-year follow-up was performed. The study was approved by the ethics committees of each institution, and informed consent was obtained from all individual participants included in the study.

All participating centers were encouraged to enroll consecutive patients to minimize selection bias. The inclusion criteria were as follows: identification of patients using electronic hospital databases recording emergency department diagnoses, review of electrocardiograms, and telemetry recordings from the emergency department and direct screening by emergency department staff. Each hospital admission is assigned one primary diagnosis and up to nine secondary diagnoses when discharged. The primary diagnosis describes the main cause of hospitalization. Baseline data collected included patient demographics, visit characteristics, medical history, medication and interventions in ED, and hospital discharge information. Follow-up was carried out at one year from time of enrollment by telephone interview. All-cause mortality and the primary reason for death were identified. We defined heart failure, stroke and pulmonary embolism, and myocardial infarction as cardiovascular mortality. All treatment decisions were left to the discretion of the treating physician.

For blood pressure and heart rate, initial data at registration were documented. Body mass index (BMI) (weight [kg]/height[m]^2) was calculated using the weight and height measured at enrollment. The definitions of AF types were in accordance with American College of Cardiology/American Heart Association/European Society of Cardiology 2006 guidelines for AF (Fuster et al., 2006). We combined persistent AF and permanent AF as sustain AF. The risk stratification scheme CHADS2 based on a scoring systemic in which 2 points are assigned for a history of stroke and transient ischemic attack and 1 point each is assigned for age more than 75 year, a history of hypertension, diabetes, or recent clinical heart failure or impaired left ventricular systolic function.

Data were collected on a standardized case report form (CRF) through searching medical record and patient interview from each center. The CRF was sent to Fuwai hospital by fax at the earliest opportunity. Using a validation plan, integrated in the data entry software, data were checked for missing or contradictory entries and values out of the normal range. Additional edit checks were performed by the staff in Fuwai hospital.

2.1 | Statistical analysis

Categorical variables were expressed as frequencies and percentage, and the normally distributed continuous variables were presented as mean with standard deviation (SD). Different patient strata were compared by chi-squared tests for categorical variables and by the t test for continuous variables. Cox proportional hazards regression analyses were used to identify whether patients with AF as the secondary diagnosis were associated with increased 1-year mortality and the independent predictors of mortality in each group. The models included age (as a second-degree polynomial), sex, body mass index (as a second-degree polynomial), type of AF, history of myocardial infarction, coronary artery disease, heart failure, hypertension, diabetes, previous stroke/TIA, history of left ventricular systolic dysfunction, left ventricular hypertrophy, chronic obstructive pulmonary disease, valvular heart diseases, prior major bleeding, sleep apnea, hyperthyroidism, smoke and medications (including ACE inhibitors or angiotensin II receptor blockers (ARB), β-blockers, calcium channel blockers (CCB), digoxin, diuretics, anticoagulants, aspirin, or platelet inhibitors and lipid-lowering drugs). Kaplan–Meier curves were constructed for time to event and were compared by log-rank test. Stratification was performed by the type of AF and whether AF was the primary diagnosis at admission in order to meet model assumptions. The data were analyzed with SPSS 17.0, and a 2-sided p value < .05 was considered statistically significant.
3 | RESULTS

The Chinese AF registry has recruited 2016 patients with confirmed atrial fibrillation or atrial flutter. After excluded 1 patient with incomplete baseline data, a total of 2015 patients with a mean age of 68.46 ± 13.28 years were enrolled in the final analysis: of 1,190 patients in the secondary AF diagnosis group, 939 (78.9%) were sustain AF (group 1), 251 were non-sustain AF (group 2), and of 825 patients in the primary AF diagnosis group, 458 (55.5%) were sustain AF (group 3), 367 were non-sustain AF (group 4).

Patient demographics, past medical history, and medication during the ED visit of the four groups are demonstrated in Table 1. Compared with the two primary AF diagnosis groups, secondary AF diagnosis groups, on average, were much older, and more likely to have a history of myocardial infarction, coronary artery disease, heart failure, left ventricular systolic dysfunction (LVSD), previous stroke/TIA or chronic obstructive pulmonary disease (COPD), and had a similar prevalence of hypertension, diabetes, hyperthyroidism, or smoking.

At enrollment, blood pressure was higher, but heart rate was much lower in the two secondary AF diagnosis groups compared with the primary AF diagnosis groups. The mean CHADS<sub>2</sub> score was higher in the secondary AF diagnosis group than primary AF diagnosis group. As the increasing score of CHADS<sub>2</sub> marking scheme, the proportion of patients with a secondary diagnosis of AF was increasing (Figure 1). In patients with secondary diagnosis of AF, the top 7 definite primary ED diagnosis are listed in Table 2, along with the 7 most common presenting chief complaints.

During hospitalization, ACE inhibitors, diuretics, digoxin were all given significantly more often in patients with secondary diagnosis of AF, whereas they less frequently received β-blocker and CCB, especially in group 1. There was no difference between the groups with regard to ARB, lipid-lowering medication, or antithrombotic therapy (Table 1).

The crude results indicated that all-cause mortality was significantly higher in secondary AF diagnosis group than in the primary AF diagnosis group at 1 year, while the cardiovascular mortality was no significant difference between these groups (Table 1). The unadjusted absolute risk augment of death within 1 year was 14.3% in group 1 compared with group 4; Kaplan–Meier

---

### TABLE 2 Presenting Primary ED Diagnoses and Chief Complaint of 1,190 Patients with Atrial Fibrillation and an Alternative Primary ED Diagnosis

| Characteristic | N (%) | 95% CI |
|---------------|-------|-------|
| **Definite primary ED diagnosis (n = 756)** | | |
| Heart failure | 366 | 48.4 | 44.8–52.0 |
| Stroke | 80 | 10.6 | 8.4–12.8 |
| Pneumonia | 44 | 5.8 | 4.1–7.5 |
| Infection | 39 | 5.2 | 3.6–6.8 |
| Acute coronary syndrome | 34 | 4.5 | 3.0–6.0 |
| Hypertension | 28 | 3.7 | 2.4–5.0 |
| Coronary heart disease | 27 | 3.6 | 2.3–4.9 |
| **Chief complaint of indefinite ED diagnosis (n = 434)** | | |
| Palpitation | 89 | 20.5 | 16.7–24.3 |
| Fever | 83 | 19.1 | 15.4–22.8 |
| Dyspnea | 80 | 18.4 | 14.8–22.0 |
| Dizzy | 68 | 15.7 | 12.3–19.1 |
| Chest distress | 45 | 10.4 | 7.5–13.3 |
| Abdominal pain/ Chest pain | 22 | 5.1 | 3.0–7.2 |
| Weakness/Fatigue | 10 | 2.3 | 0.9–3.7 |

---

### FIGURE 2 Kaplan–Meier estimates of cumulative survival of endpoint in each group (a: all-cause mortality, b: cardiovascular mortality)
cumulative hazard curves are shown in Figure 2. After adjustment for the confounders, 1-year mortality was still significantly increased in secondary AF diagnosis group, with a relative risk of 1.72 (95% CI 1.28–2.32; \( p < .001 \)) compared with primary AF diagnosis group. The all-cause mortality risk showed no heterogeneity for a large number of subgroups analyzed, except for patients with a history of COPD, among whom there was a tendency toward decreased risk in secondary AF diagnosis group. In regard

### TABLE 3 Adjusted relative risk of 1-year mortality in patients on secondary AF diagnosis versus primary AF diagnosis

|                | Proportion (%) | All-cause mortality | Cardiovascular mortality |
|----------------|----------------|---------------------|-------------------------|
|                |                | Relative risk | 95% CI     | Relative risk | 95% CI     |
| All            | 100%           | 1.723        | 1.283–2.315 | 1.384        | 0.927–2.065 |
| Male           | 45.2           | 2.308        | 1.463–3.641 | 2.331        | 1.111–4.889 |
| Female         | 54.8           | 1.367        | 0.924–2.022 | 0.988        | 0.606–1.609 |
| <75            | 66.0           | 1.740        | 1.070–2.829 | 1.448        | 0.794–2.639 |
| ≥75            | 34.0           | 1.611        | 1.112–2.336 | 1.286        | 0.754–2.193 |
| Non-sustain AF | 30.7           | 1.824        | 0.982–3.386 | 2.277        | 0.868–5.976 |
| Sustain AF     | 69.3           | 1.669        | 1.196–2.328 | 1.243        | 0.804–1.921 |
| No History of MI| 92.7           | 1.626        | 1.203–2.198 | 1.222        | 0.811–1.844 |
| History of MI  | 7.3            | 6.747        | 0.816–55.807| 1.456        | 0.842–2.516 |
| No History of CAD| 58.2          | 1.735        | 1.144–2.631 | 1.126        | 0.621–2.042 |
| History of CAD | 41.8           | 1.544        | 1.013–2.354 | 0.943        | 0.528–1.685 |
| No History of HF| 62.6           | 1.483        | 1.025–2.146 | 2.027        | 1.092–3.762 |
| History of HF  | 37.4           | 2.302        | 1.349–3.929 | 1.286        | 0.754–2.193 |
| NO history of HTN| 44.5           | 1.847        | 1.125–3.031 | 1.254        | 0.654–2.403 |
| History of HTN | 55.5           | 1.593        | 1.097–2.314 | 1.352        | 0.802–2.281 |
| No history of LVH| 83.7           | 1.767        | 1.283–2.433 | 1.483        | 0.943–2.334 |
| History of LVH | 16.3           | 1.435        | 0.660–3.120 | 1.194        | 0.489–2.919 |
| No diabetes    | 84.5           | 1.788        | 1.285–2.488 | 1.474        | 0.945–2.301 |
| Diabetes       | 15.5           | 1.173        | 0.576–2.388 | 1.105        | 0.407–2.998 |
| No history of stroke/TIA| 81.2   | 1.534        | 1.097–2.146 | 1.313        | 0.845–2.041 |
| history of stroke/TIA| 18.8  | 2.145        | 1.128–4.081 | 1.849        | 0.687–4.972 |
| NO history of LVSD| 80.9          | 1.845        | 1.320–2.579 | 1.547        | 0.944–2.535 |
| history of LVSD| 19.1           | 1.289        | 0.684–2.432 | 1.123        | 0.560–2.252 |
| No history of COPD| 88.3          | 2.025        | 1.445–2.836 | 1.556        | 0.993–2.438 |
| history of COPD| 11.7           | 0.822        | 0.440–1.536 | 0.599        | 0.238–1.509 |
| No Valvular heart disease| 83.3  | 1.720        | 1.251–2.366 | 1.435        | 0.905–2.276 |
| Valvular heart disease| 16.7  | 1.729        | 0.774–3.862 | 1.242        | 0.538–2.866 |
| No history of Bleeding| 97.6  | 1.730        | 1.284–2.331 | 1.378        | 0.922–2.059 |
| History of bleeding| 2.4           | 1.806        | 1.285–2.538 | 1.396        | 0.856–2.274 |
| No ACE inhibitor| 73.5          | 1.806        | 1.285–2.538 | 1.396        | 0.856–2.274 |
| ACE inhibitor  | 26.5           | 1.375        | 0.755–2.504 | 1.303        | 0.635–2.676 |
| No \( \beta \)-blocker| 49.6          | 1.857        | 1.218–2.830 | 1.677        | 0.906–3.104 |
| \( \beta \)-blocker| 50.4          | 1.583        | 1.042–2.403 | 1.236        | 0.723–2.114 |
| No diuretics   | 57.5           | 1.567        | 1.060–2.315 | 1.294        | 0.688–2.433 |
| diuretics      | 42.5           | 1.814        | 1.144–2.877 | 1.489        | 0.882–2.515 |
| No digoxin     | 64.4           | 2.043        | 1.388–3.009 | 1.794        | 0.981–3.279 |
| Digoxin        | 35.6           | 1.228        | 0.781–1.931 | 1.101        | 0.652–1.859 |

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; HTN, hypertension; LVH, left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; TIA, transient ischemic attack.

\( a \)Relative risk (95% CI) of history of bleeding was too small to demonstrate.
to the cardiovascular mortality, patients with a history of COPD and without a history of HF were associated with decreased risk in secondary AF diagnosis group (Table 3). Heart failure, infection or stroke and pulmonary embolus were the most common causes of death among both of the two groups (Figure 3).

In the multivariable Cox analysis, advanced age (HR: 3.104, 95% CI: 2.291–4.205), history of heart failure (HR: 1.877, 95% CI: 1.361–2.588), and previous stroke/TIA (HR: 1.388, 95% CI: 1.021–1.888) were the independent predictors of all-cause mortality in the secondary AF diagnosis group. In contrast, risk factors of all-cause mortality for the primary AF diagnosis group were advanced age (HR: 3.710, 95% CI: 2.137–6.441), left ventricular systolic dysfunction (HR: 2.754, 95% CI: 1.202–6.306), history of COPD (HR: 3.115, 95% CI: 1.676–5.788), and diabetes (HR: 2.135, 95% CI: 1.092–4.172). For cardiovascular mortality, advanced age (HR: 2.737, 95% CI: 1.802–4.160), a history of heart failure (HR: 3.235, 95% CI: 1.980–5.285) were independent predictors in the secondary AF diagnosis group, while advanced age (HR: 3.460, 95% CI: 1.647–7.267), female gender (HR: 2.597, 95% CI: 1.029–6.558), LVSD (HR: 4.438, 95% CI: 1.658–11.883), history of COPD (HR: 2.482, 95% CI: 1.011–6.092) were risk factors in primary AF diagnosis group (Table 4).

4 | DISCUSSION

This analysis from the Chinese AF registry shows that ED patient with a secondary diagnosis of AF had remarkably high mortality rate compared with those with a primary diagnosis of AF. The all-cause mortality risk was increased by 72% in secondary AF diagnosis patients compared with primary AF diagnosis patients after adjustment for the confounders.

To the best of our knowledge, this is the first large outcome study to explore the impact of primary diagnosis on mortality in AF patients. In a pilot study, Atzema et al. (Atzema, Lam, Young, & Kester-Greene, 2013) described the characteristics and outcomes in a small group of AF patients and found that the crude mortality was three times higher in secondary AF diagnosis patients than in those with a primary diagnosis of AF. Nevertheless, due to the limitation of this single-center, retrospective study with a portion of incomplete data, the authors emphasized that the conclusions might be inconclusive and further study was warranted. Here we performed a well-designed, multicenter, prospective work to demonstrate a more convincible result as expected and to further explore the potential risks of mortality in each group.

Patient with a secondary diagnosis of AF was much older and had a worse condition with more concomitant disease compared with primary AF diagnosis patients. This was consistent with the former study (Andersson et al., 2013; Atzema et al., 2013). As we all know, AF is particularly common in elderly people, and any condition that predisposes to left atrial enlargement will associate a rising incidence of AF (Schoonderwoerd, Smit, Pen, & Van Gelder, 2008). Apparently, a number of classical factors, such as heart failure, hypertension, valvular disease, diabetes mellitus, cardiomyopathy, obesity, or thyroid disease, are powerful stimulus for the initiation and development of AF, and this is quite familiar in the clinical practice. In our study, beta-blockers were less often used in patients with a secondary diagnosis of AF, which may relate to the higher age and more comorbidities. Treatment with digoxin was more frequent among secondary AF diagnosis group and that may reflect the lower heart rates on admission. Due to its narrow therapeutic index and a potential to contribute to life-threatening arrhythmia, the use of digoxin for rate control in AF patients remains controversial (Hallberg et al., 2007). Especially, two recent post hoc analysis of the AFFIRM data got opposite conclusions on digoxin use and all-cause mortality (Gheorghide et al., 2013; Whitbeck et al., 2013). In the present study, digoxin was not associated with mortality neither in primary AF diagnosis group nor in secondary AF diagnosis group in multivariable Cox analysis, and we expect further study to investigate the role of digoxin in the contemporary management of AF patients. There was no significant difference between these two groups on antithrombotic therapy. However,
it was worth noting that the oral anticoagulants prescription in our population was much lower than reported from previous study (Nieuwlaat et al., 2005). Under-treatment with anticoagulation agents is a great challenge, especially in secondary AF diagnosis group which was at high risk of thrombosis.

After adjustment for confounders, the all-cause mortality risk for patients with a secondary diagnosis of AF remained significantly higher than those with primary AF diagnosis, indicating that secondary AF diagnosis was an independent risk of mortality. The observed difference between patients with AF as a primary diagnosis and as a secondary diagnosis indicated the great influence of concomitant diseases on mortality risk. In our analysis, the top one reason for admission in secondary AF diagnosis patients and the major cause of death for the total study population was heart failure. Atrial fibrillation and heart failure are two of the most prevalent cardiovascular disease conditions. They often coexist and lead to significant morbidity and mortality. Many patients with advanced heart failure develop AF as the severity of heart failure increases. The SOLVD trial (Dries et al., 1998) suggested that the presence of AF tends to worsen the prognosis of patients with asymptomatic and symptomatic left ventricular systolic dysfunction. Analysis from the CHARM program demonstrated that AF is associated with an increased risk of cardiovascular outcomes in patients with heart failure, both in reduced and preserved left ventricular ejection fraction (Olsson

### TABLE 4 Risk factors of Death for primary or secondary AF diagnosis patients (A: all-cause mortality, B: cardiovascular mortality)

|                        | Secondary AF diagnosis | Primary AF diagnosis |
|------------------------|------------------------|----------------------|
|                        | Hazard Ratio  | 95% CI  | Hazard Ratio  | 95% CI  |
| **(A)**                |             |        |             |        |
| Female gender          | 0.756       | 0.563-1.014 | 1.110       | 0.628-1.962 |
| Aged ≥ 75              | 3.104       | 2.291-4.205 | 3.710       | 2.137-6.441 |
| Sustain AF             | 1.217       | 0.836-1.771 | 1.587       | 0.898-2.805 |
| MI                     | 1.032       | 0.654-1.628 | 0.308       | 0.041-2.323 |
| CAD                    | 0.742       | 0.542-1.018 | 1.145       | 0.651-2.015 |
| HF                     | 1.887       | 1.361-2.588 | 0.699       | 0.342-1.428 |
| HTN                    | 0.925       | 0.692-1.264 | 0.953       | 0.528-1.719 |
| Stroke/TIA             | 1.388       | 1.021-1.888 | 0.950       | 0.478-1.886 |
| Smoke                  | 0.925       | 0.650-1.316 | 0.823       | 0.393-1.726 |
| LVSD                   | 1.062       | 0.752-1.501 | 2.754       | 1.202-6.306 |
| COPD                   | 1.226       | 0.873-1.722 | 3.115       | 1.676-5.788 |
| Diabetes               | 1.224       | 0.869-1.723 | 2.135       | 1.092-4.172 |
| Valvular disease       | 0.976       | 0.658-1.447 | 1.528       | 0.648-3.605 |
| Major bleeding         | 0.633       | 0.277-1.445 | 1.343       | 0.182-9.907 |
| OAC prescription       | 0.870       | 0.594-1.274 | 0.570       | 0.239-1.359 |
| **(B)**                |             |        |             |        |
| Female gender          | 0.892       | 0.587-1.357 | 2.597       | 1.029-6.558 |
| Aged ≥ 75              | 2.737       | 1.802-4.160 | 3.460       | 1.647-7.267 |
| Sustain AF             | 1.035       | 0.608-1.760 | 2.241       | 0.944-5.320 |
| MI                     | 1.742       | 0.949-3.198 | 2.241       | 0.944-5.320 |
| CAD                    | 0.481       | 0.298-0.775 | 1.128       | 0.522-2.438 |
| HF                     | 3.235       | 1.980-5.285 | 0.733       | 0.303-1.773 |
| HTN                    | 1.234       | 0.805-1.891 | 0.825       | 0.372-1.829 |
| Stroke/TIA             | 1.151       | 0.728-1.819 | 1.000       | 0.388-2.575 |
| Smoke                  | 1.051       | 0.649-1.700 | 1.713       | 0.609-4.824 |
| LVSD                   | 1.347       | 0.875-2.074 | 4.438       | 1.658-11.883 |
| COPD                   | 1.115       | 0.677-1.838 | 2.482       | 1.011-6.092 |
| Diabetes               | 1.230       | 0.755-2.002 | 2.317       | 0.912-5.887 |
| Valvular disease       | 1.174       | 0.713-1.933 | 2.081       | 0.783-5.526 |
| Major bleeding         | 0.417       | 0.101-1.720 | 0.862       | 0.315-2.359 |
| OAC prescription       | 0.961       | 0.591-1.562 | 0.862       | 0.315-2.359 |

Note: The acronym was the same as Table 3.

Abbreviation: OAC, oral anticoagulation.
et al., 2006). Moreover, incident heart failure has an adverse impact on prognosis in AF independently of other cardiovascular diagnoses and risk factor. AF, particularly when the heart rate is poorly controlled, can lead to the development of dilated cardiomyopathy and heart failure (Suzuki et al., 2012). Clearly, atrial fibrillation is a complex condition and frequently associated with admissions for hypertension, stroke, heart failure, acute coronary syndrome, or infection. Physicians could not ignore the interaction about AF and its concomitant disease. Therefore, we emphasize the importance of focusing on patients as an entirety rather than a single disease entity.

We also analyzed risk factors of mortality in the study population. After adjustment for comorbidities, the independent predictors for all-cause mortality were advanced age, heart failure, and previous stroke in secondary AF diagnosis group, whereas for primary AF diagnosis patients, advanced age, diabetes, history of left ventricular systolic dysfunction, and chronic obstructive pulmonary disease portended a worse prognosis. Similar conclusions have been drawn on the independent predictors for both groups on cardiovascular mortality. Based on these findings, we propose that clinician should distinguish the primary diagnosis of patients with AF presenting to ED and consider a more powerful therapy in those with above risks. What’s more, it is obvious that cardiac function has a strong association with all-cause mortality in AF patients regardless of the primary diagnosis (Badheka et al., 2011). Thus, we recommended that the echocardiogram was necessary for ED visiting patients with AF.

5 | LIMITATIONS

We used a large administrative database from the Chinese AF registry for analysis, of which 2.7% were patients with atrial flutter. Typical atrial flutter has a well-defined macro-reentrant circuit in the right atrium as its major mechanism and therefore can be relatively easily cured by ablation. Nevertheless, AF and atrial flutter usually coexist and patients with atrial flutter develop AF even subsequently to successful ablation (Perez et al., 2009). Moreover, response to therapy and management approaches for atrial flutter in improvement of survival and reduction of cardiovascular complication is similar to those of AF. So they can be treated as one entity in trials designed to investigate the outcomes. In addition, the anticoagulation rate in the present study was much lower than reported from previous literature (Casciano, Singer, Kwong, Fox, & Martin, 2012). Due to the nature of an observational study that management decisions were made by individual physicians, the snapshot of anticoagulation could just reflect the current status and we underline that an appropriate management of anticoagulation therapy in AF patients was warranted.

6 | CONCLUSIONS

Patients with secondary diagnosis of AF were associated with an increased 1-year mortality compared with those with primary AF diagnosis. Physicians should distinguish these two groups and pay attention to their risk factors on treatment.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Dr Shao contributed to statistical analyses, data interpretation, and drafting and revisions of the manuscript. Dr Yang: contributed to study design and hypothesis, data interpretation, and drafting of the manuscript. Dr Zhu, Dr Yu, and Dr Liu: contributed to drafting and revision of the manuscript.

ETHICAL APPROVAL

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

ORCID

Xing-Hui Shao https://orcid.org/0000-0001-9914-0692

REFERENCES

Airaksinen, K. E., Gronberg, T., Nuotio, I., Nikkinnen, M., Ylitalo, A., Biancari, F., & Hartikainen, J. E. (2013). Thromboembolic complications after cardioversion of acute atrial fibrillation: The FinCV (Finnish Cardioversion) study. Journal of the American College of Cardiology, 62(13), 1187–1192. https://doi.org/10.1016/j.jacc.2013.04.089

Andersson, T., Magnusson, A., Bryngelsson, I. L., Frobert, O., Henrikkson, K. M., Edvardsson, N., & Poci, D. (2013). All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995–2008: A Swedish nationwide long-term case-control study. European Heart Journal, 34(14), 1061–1067. https://doi.org/10.1093/eurheartj/ ehs469

Atzema, C. L., Lam, K., Young, C., & Kester-Greene, N. (2013). Patients with atrial fibrillation and an alternative primary diagnosis in the emergency department: A description of their characteristics and outcomes. Academic Emergency Medicine, 20(2), 193–199. https://doi.org/10.1111/acem.12078

Badheka, A. O., Rathod, A., Kizilbash, M. A., Bhardwaj, A., Ali, O., Afonso, L., & Jacob, S. (2011). Comparison of mortality and morbidity in patients with atrial fibrillation and heart failure with preserved versus decreased left ventricular ejection fraction. American Journal of Cardiology, 108(9), 1283–1288. https://doi.org/10.1016/j.amjcard.2011.06.045

Benjamin, E. J., Wolf, P. A., D’Agostino, R. B., Silbershatz, H., Kannel, W. B., & Levy, D. (1998). Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. Circulation, 98(10), 946–952. https://doi.org/10.1161/01.CIR.98.10.946

Camm, A. J., Kirchhof, P., Lip, G. Y. H., Schotten, U., Savelieva, I., Ernst, S., ... Zupan, I. (2010). Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace, 12(10), 1360–1420. https://doi.org/10.1093/europace/eup350

Casciano, J. P., Singer, D. E., Kwong, W. J., Fox, E. S., & Martin, B. C. (2012). Anticoagulation therapy for patients with non-valvular atrial fibrillation: Comparison of decision analytic model recommendations and real-world warfarin prescription use. Am J Cardiovac Drugs, 12(5), 313–323. https://doi.org/10.2165/11634150-000000000-00000

Dickinson, O., Chen, L. Y., & Francis, G. S. (2014). Atrial fibrillation and heart failure: Intersecting populations, morbidities, and mortality.
Heart Failure Reviews, 19(3), 285–293. https://doi.org/10.1007/s10741-013-9409-4

Dries, D. L., Exner, D. V., Gersh, B. J., Domanski, M. J., Waclawiw, M. A., & Stevenson, L. W. (1998). Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: A retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. Journal of the American College of Cardiology, 32(3), 695–703. https://doi.org/10.1016/S0735-1097(98)00297-6

Fuster, V., Ryden, L. E., Cannon, D. S., Crijns, H. J., Curtis, A. B., Ellenbogen, K. A., ... Zamorano, J. L. (2006). ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: Full text: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Europace, 8(9), 651–745. https://doi.org/10.1093/europace/eul097

Gheorghiade, M., Fonarow, G. C., van Veldhuisen, D. J., Cleland, J. G. F., Butler, J., Epstein, A. E., ... Ahmed, A. (2013). Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: Findings from post hoc propensity-matched analysis of the AFFIRM trial. European Heart Journal, 34(20), 1489–1497. https://doi.org/10.1093/eurheartj/eht120

Hallberg, P., Lindback, J., Lindahl, B., Stenestrand, U., Melhus, H., & Group, R.-H. (2007). Digoxin and mortality in atrial fibrillation: A prospective cohort study. European Journal of Clinical Pharmacology, 63(10), 959–971. https://doi.org/10.1007/s00228-007-0346-9

Jabre, P., Roger, V. L., Murad, M. H., Chamberlain, A. M., Prokop, L., Adnet, F., & Jouven, X. (2011). Mortality associated with atrial fibrillation in patients with myocardial infarction: A systematic review and meta-analysis. Circulation, 123(15), 1587–1593. https://doi.org/10.1161/CIRCULATIONAHA.110.986661

Lip, G. Y. H., Brechin, C. M., & Lane, D. A. (2012). The global burden of atrial fibrillation and stroke: A systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. Chest, 142(6), 1489–1498. https://doi.org/10.1378/chest.11-2888

Nieuwlaat, R., Capucci, A., Camm, A. J., Olsson, S. B., Andresen, D., Davies, D. W., ... Crijns, H. J. G. M. (2005). Atrial fibrillation management: A prospective survey in ESC member countries: The Euro Heart Survey on Atrial Fibrillation. European Heart Journal, 26(22), 2422–2434. https://doi.org/10.1093/eurheartj/ehi505

Olsson, L. G., Swedberg, K., Ducharme, A., Granger, C. B., Michelson, E. L., McMurray, J. J. V., ... Pfeffer, M. A. (2006). Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: Results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. Journal of the American College of Cardiology, 47(10), 1997–2004. https://doi.org/10.1016/j.jacc.2006.01.060

Perez, F. J., Schubert, C. M., Parvez, B., Pathak, V., Ellenbogen, K. A., & Wood, M. A. (2009). Long-term outcomes after catheter ablation of cavo-tricuspid isthmus dependent atrial flutter: A meta-analysis. Circ Arrhythm Electrophysiol, 2(4), 393–401. https://doi.org/10.1161/CIRCEP.109.871665

Schoonderwoerd, B. A., Smit, D. D., Pen, L., & Van Gelder, I. C. (2008). New risk factors for atrial fibrillation: Causes of ‘not-so-lone atrial fibrillation’. Europace, 10(6), 668–673. https://doi.org/10.1093/europace/eun124

Suzuki, S., Sagara, K., Otsuka, T., Matsuno, S., Funada, R., Uejima, T., ... Yamashita, T. (2012). A new scoring system for evaluating the risk of heart failure events in Japanese patients with atrial fibrillation. American Journal of Cardiology, 110(5), 678–682. https://doi.org/10.1016/j.amjcard.2012.04.049

Whitbeck, M. G., Charnigo, R. J., Khairy, P., Ziada, K., Bailey, A. L., Zegarra, M. M., ... Elayi, C. S. (2013). Increased mortality among patients taking digoxin–analysis from the AFFIRM study. European Heart Journal, 34(20), 1481–1488. https://doi.org/10.1093/eurheartj/ehs348

How to cite this article: Shao X-H, Yang Y-M, Zhu J, Yu L-T, Liu L-S. Increased mortality in patients with secondary diagnosis of atrial fibrillation: Report from Chinese AF registry. Ann Noninvasive Electrocardiol. 2020;25:e12774. https://doi.org/10.1111/anec.12774