



# Relationship between creatinine clearance and clinical outcomes in Chinese emergency patients with atrial fibrillation

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## Abstract

**Background:** Few real-world data on the relation between creatinine clearance (CrCl) and adverse clinical outcomes in Chinese emergency department (ED) patients with nonvalvular atrial fibrillation (AF).

**Methods:** In this prospective, observational, multicenter AF study, enrolled AF patients presenting to an ED at 20 hospitals in China from November 2008 to October 2011, with a follow-up of 12 month. A total of 863 AF patients with CrCl data were analyzed, and patients were categorized as  $\text{CrCl} \geq 80$ ,  $50 \leq \text{CrCl} < 80$ ,  $30 \leq \text{CrCl} < 50$ , and  $\text{CrCl} < 30$  (ml/min). Outcomes of analyses were all-cause death, cardiovascular death, thromboembolism (TE), and major bleeding.

**Results:** Among the whole patients, 126(14.6%) patients died during 12-month follow-up, 53(40.2%) among  $\text{CrCl} < 30$  ml/min group, and 48(16.2%), 22(6.5%), and 3(3.2%) among  $30 \leq \text{CrCl} < 50$ ,  $50 \leq \text{CrCl} < 80$ , and  $\text{CrCl} \geq 80$  ml/min groups, respectively ( $p < 0.001$ ). Cardiovascular death and TE rates also increased with decreasing CrCl. On multivariate analysis, patients with  $\text{CrCl} < 30$  ml/min were associated with higher risks of all-cause death ( $HR 5.567$ ; 95%CI 1.618–19.876;  $p = .007$ ) and higher cardiovascular death ( $HR 11.939$ ; 95%CI 1.439–99.031;  $p = .022$ ) as compared with  $\text{CrCl} \geq 80$  ml/min category. Nevertheless, for TE and major bleeding risk, CrCl groups showed no significant difference after adjustment for variables in CHA<sub>2</sub>DS<sub>2</sub>-VASc score and status of warfarin prescription in our cohort.

**Conclusions:** In Chinese ED nonvalvular AF patients, incidence rates of death increased with reducing CrCl across the whole range of renal function.  $\text{CrCl} < 30$  ml/min was associated with all-cause death, cardiovascular death, but not for TE and major bleeding.

## KEYWORDS

atrial fibrillation, creatinine clearance, death, emergency, major bleeding, thromboembolism

Juan Wang and Tao Zhang contributed equally to this work.

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## 1 | INTRODUCTION

Worldwide, atrial fibrillation (AF) is the most common sustained arrhythmia in adults, and the estimated prevalence of AF in adults currently ranges between 2% and 4% (Benjamin et al., 2019). AF is associated with increased morbidity and mortality (Hindricks et al., 2021). There are many risk factors for AF development, such as age, obesity, diabetes mellitus (DM), heart failure (HF), and hypertension (Hindricks et al., 2021). Moreover, renal dysfunction also plays an important role (Boriani et al., 2015). AF and renal dysfunction have a close bidirectional relationship and often coexist; renal dysfunction predisposes to incident AF and, renal dysfunction was a prothrombotic and pro-hemorrhagic condition independent of AF (Olesen et al., 2012), whereas AF is associated with an increased incidence of renal dysfunction and an increased risk of chronic kidney disease (CKD) development and progression (Potpara et al., 2018).

Nowadays, AF and CKD were increasingly prevalent worldwide, coexisting in 15–20% of CKD patients, AF was associated with increased mortality (Zimmerman et al., 2012), whereas CKD may be present in 40–50% of AF patients (Banerjee et al., 2014). Both conditions were associated with an increased risk of thromboembolism (TE), mortality, and morbidity (Lau et al., 2016). Importantly, TE and major bleeding were common clinical issues in patients with AF and CKD and should be considered in the risk-benefit analysis for anti-thrombotic treatment. Especially in the emergency department (ED), patients with AF in ED seems associated with more co-morbidity, ED plays an important role in the management of patients with AF and renal dysfunction. Therefore, a comprehensive understanding of the association between renal function and AF may be helpful for risk stratification, management, and prediction of prognosis.

Recent studies have reported that moderate to severe renal impairment was a better independent predictor of all-cause death and bleeding but not an independent predictor of TE in AF patients (Cho et al., 2017). Both creatinine clearance (CrCl) and estimated glomerular filtration rate (eGFR) were common tools for evaluating renal function. Lastly, a study showed that CrCl was superior to GFR in predicting adverse outcomes in nonvalvular AF patients (Kodani et al., 2020). Kodani et al showed worsening CrCl values were independently associated with all-cause mortality and TE, but not with major hemorrhage in Japanese AF patients (Kodani et al., 2018). Nevertheless, other Japanese AF registry studies demonstrated that patients with Lower CrCl had a high risk for death, cardiovascular events, TE, and major bleeding (Abe et al., 2017; Yuzawa et al., 2020). These different results may be considered in the condition of confounding factors such as race, co-morbidity, degree of renal impairment, and antithrombotic therapy. There are few real-world registry data on the relation between CrCl and adverse clinical outcomes in Chinese ED patients with AF. Therefore, the object of this study was to evaluate the relation between CrCl and 12-month outcomes (including all-cause death, stroke, noncentral nervous system (non-CNS) systemic embolism, and major bleeding) in Chinese ED patients with AF.

## 2 | METHODS

### 2.1 | Patients' selection

The design and rationale of the Chinese ED AF registry (CEAFR) study have been reported previously (Huang et al., 2014; Wang et al., 2014). In brief, CEAFR was a multicenter, observational and prospective, and registry study, which was designed to enroll patients who presented to an ED with AF from Nov 2008 to Oct 2011. Twenty sites represent different levels of medical care (academic and nonacademic, general and specialized, urban and rural) in China participated in the AF registry. The central administrative office of the study is located at the Fuwai Hospital, Beijing. The study was performed in accordance with the principle of the declaration of Helsinki and approved by the Ethics committee of Fuwai Hospital. The study was performed following the principle of the declaration of Helsinki and approved by the Ethics committee. Written informed consent was obtained from all patients.

Patients had documented (electrocardiographic evidence by ECG, Holter, rhythm strip, pacemaker electrogram) were included in this registry. AF at the time of ED visits for any reason from Nov 2008 to Oct 2011. All patients gave written consent for study participation. Patients' characteristics, co-morbidities, and medications were collected, and the diagnosis of all medical conditions was based on the patients' medical records. Patients with valvular AF (mechanical valve replacement and moderate/severe mitral stenosis) were excluded from this sub-analysis; we excluded patients without baseline CrCl data. The CrCl was estimated by the Cockcroft-Gault formula,  $\text{CrCl (ml/min)} = (140 - \text{age (years)}) \times (\text{weight (kg)}) / (72 \times \text{SCr (mg/dL)}) \times 0.85$  (if female) (Cockcroft & Gault, 1976). Patients were divided into 4 different CrCl categories,  $\text{CrCl} \geq 80$ ,  $50 \leq \text{CrCl} < 80$ ,  $30 \leq \text{CrCl} < 50$ , and  $\text{CrCl} < 30$  (ml/min). The CHA<sub>2</sub>DS<sub>2</sub>-VASc (Lip et al., 2010) (congestive heart failure, hypertension, age  $\geq 75$  years, DM, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, and sex category) scores were calculated after the first diagnosis of AF during hospital admission, as was the HAS-BLED (Pisters et al., 2010) (hypertension with SBP  $> 160$  mmHg, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) score.

### 2.2 | Follow-up and clinical outcomes

Follow-up outcomes information about death, TE (including stroke and Non-CNS systemic embolism), and major bleeding were obtained. Follow-up was completed in November 2012; the mean follow-up period was 12 month. All clinical adverse events were confirmed by reviewing the medical records. In this study, the primary outcome was all-cause death, and secondary outcomes were cardiovascular death and TE and major bleeding. Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent

with the territory of a major cerebral artery and categorized as ischemic, hemorrhagic, or unspecified. Non-CNS systemic embolism was defined as an acute vascular occlusion of an extremity or organ, documented by means of imaging, surgery, or autopsy. Major bleeding was defined as: life-threatening bleeding, and/or symptomatic bleeding in a critical area or organ, such as intra-cranial, or pericardial, or intra muscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more unites of whole blood or red cells.

### 2.3 | Statistical analysis

All data were assessed and edited by two experienced research statisticians. Data are presented as means  $\pm$  standard deviation (SD) for continuous variable and counts and proportions for categorical variables. 4 group comparisons were conducted using variance analysis for continuous variables and Pearson's Chi-squared test for categorical variables, respectively. Estimates for outcomes were made by the Kaplan–Meier method, and differences were assessed by the log-rank test. Cox's proportional hazards model with clustered standard errors was used for the analysis. Univariate analysis and multivariate regression using Cox proportional hazard model were carried out for all-cause death, cardiovascular death, TE, and major bleeding. In multivariable analyses, well-known risk factors and variables with a *p*-value of .05 were then entered into a multivariable analysis (all listed in the Tables). CrCl was as a continued and category variable in models, respectively. All tests were two-sided. A probability value of  $< 0.05$  was considered statistically significant. All statistical analysis was made using SPSS 25.0 (IBM Corporation, New York, NY, USA).

## 3 | RESULTS

### 3.1 | Baseline characteristics

A total of 2015 patients were enrolled in the CEAfr by the end of December 2011, 880 nonvalvular AF patients with baseline CrCl data, and 12-month clinical follow-up was available for 863 patients enrolled for this subgroup analysis. Of these analysis groups, 495(57.6%) were female. The average age was  $69.4 \pm 13.8$  years. The mean CrCl was  $52.9 \pm 24.5$  ml/min. The numbers of patients categorized in CrCl  $< 30$ ,  $30 \leq$  CrCl  $< 50$ ,  $50 \leq$  CrCl  $< 80$ , CrCl $\geq 80$  ml/min groups were 132(15.3%), 297(34.4%), 339(39.3%), and 95(11.0%), respectively.

Baseline characteristics among CrCl categories were shown in Table 1. Risk scores for both TE (CHA<sub>2</sub>DS<sub>2</sub>-VASc scores) and bleeding (HAS-BLED score) were the highest in the CrCl  $< 30$  ml/min group. Compared to the group with CrCl $> 80$  ml/min, groups with CrCl  $< 30$  and  $30 \leq$  CrCl  $< 50$  ml/min were older, and had more co-morbidity, like coronary artery disease (CAD), hypertension, and DM, previous stroke, or transient ischemic attack (TIA) and chronic

obstructive pulmonary disease (COPD). Patients in the CrCl  $< 30$  and  $30 \leq$  CrCl  $< 50$  ml/min categories were more likely to be on calcium channel blocker (CCB), diuretic, and lipid-lowering agents compared with  $50 \leq$  CrCl  $< 80$ , CrCl $\geq 80$  ml/min groups. The percentage of warfarin and anti-arrhythmia use was higher in  $50 \leq$  CrCl  $< 80$ , CrCl $\geq 80$  patients (Table 1).

### 3.2 | Endpoints analysis and CrCl

Outcomes at 12-month for all pre-defined endpoints in CrCl categories are shown in Figure 1. A total of 126 deaths and 59 cardiovascular deaths occurred over the 12-month follow-up. The 12-month all-cause mortality was 14.6% among the whole analysis patients, mortality was the highest in CrCl  $< 30$  ml/min group and declined stepwise to 16.2, 6.5, and 3.2 with increasing CrCl (categories  $30 \leq$  CrCl  $< 50$ ,  $50 \leq$  CrCl  $< 80$ , CrCl $\geq 80$  ml/min respectively;  $p < 0.001$ ). The cardiovascular mortality among the subgroup patients was 6.8%, among CrCl $\geq 80$ ,  $50 \leq$  CrCl  $< 80$ ,  $30 \leq$  CrCl  $< 50$ , and CrCl  $< 30$  ml/min categories were 1.1%, 2.7%, 8.1% and 18.9%, respectively ( $p < .001$ ). There were 87(10.1%) TE events occurred in the study population over 12-month follow-up, and the TE events showed similar patterns, patients with CrCl  $< 30$  ml/min categories had the worst outcomes, and CrCl $\geq 80$  patients had the lowest events rates ( $p < .001$ ): 23(17.5%) events occurred in the CrCl  $< 30$  ml/min category, 31(10.4%) in the  $30 \leq$  CrCl  $< 50$  ml/min category, 29(8.6%) in the  $50 \leq$  CrCl  $< 80$  ml/min category, and 4(4.2%) in the CrCl $\geq 80$  ml/min category (Figure 1). Eleven(1.3%) Major bleeding events occurred during 12-month follow-up, and there were no significant differences among the 4 categories.

Survival curves for endpoints of CrCl groups are shown in Figure 2. All-cause death risk (unadjusted) was the highest in CrCl  $< 30$  ml/min group (HR: 16.187, 95%CI: 5.057–51.813,  $p < .001$ ) compared with patients with CrCl  $\geq 80$  ml/min (reference group). Cardiovascular death risk (unadjusted) was highest in CrCl  $< 30$  ml/min group (HR: 19.829, 95%CI: 2.68–146.35,  $p = .003$ ) compared with CrCl  $\geq 80$  ml/min. Table 2 shows the final multivariate Cox proportional models of predictors for all-cause death and cardiovascular death based on stepwise selection. After adjustment for multiple relevant co-variables (details in Table 2), as a continuous variable, decreased CrCl was a risk factor for all-cause death (HR: 0.96, 95%CI: 0.95–0.98;  $p < .001$ ) and cardiovascular death (HR: 0.96, 95%CI: 0.94–0.98;  $p = .001$ ); as a category variable, group with CrCl  $< 30$  ml/min was significantly associated with a higher risk of all-cause death (HR: 4.936, 95%CI: 1.371–17.766,  $p = .015$ ) and cardiovascular death (HR: 8.821, 95%CI 1.020–76.305,  $p = .048$ ) compared to CrCl  $\geq 80$  ml/min group.

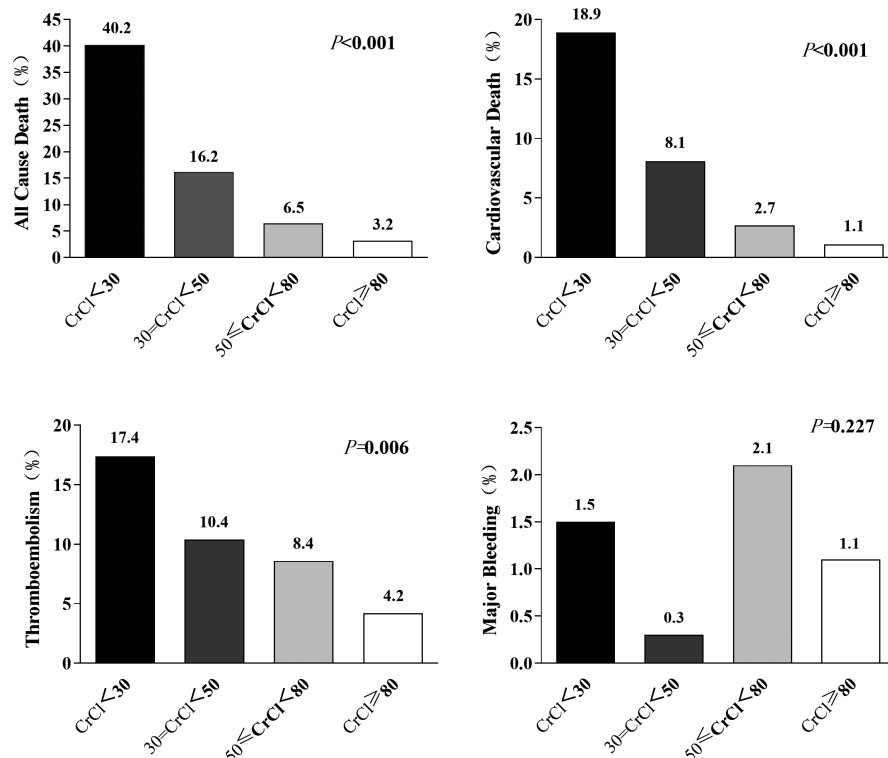
Kaplan–Meier curves for the incidence of TE and major bleeding among 4 CrCl categories were shown in Figure 2, and those of patients treated with or without warfarin were shown in Figure 3. TE risk (unadjusted) was the highest in CrCl  $< 30$  ml/min group in the whole cohort and patients without warfarin but not in those with warfarin. After adjustment for variables in CHA<sub>2</sub>DS<sub>2</sub>-VASc score and

TABLE 1 Baseline characteristics of 4 CrCl categories

	CrCl < 30 ml/min N = 132	30 ≤ CrCl < 50 ml/min N = 297	50 ≤ CrCl < 80 ml/min N = 339	CrCl ≥ 80 ml/min N = 95	p-value
Age in years Mean ± SD	77.08 ± 10.88	75.51 ± 9.77	55.53 ± 11.24	49.81 ± 14.47	<.001
Female (%)	81 (61.4)	171 (57.6)	196 (57.8)	47 (49.5)	.346
Body Weight (Kg) Mean ± SD	59.94 ± 10.10	62.59 ± 10.59	66.04 ± 10.66	72.24 ± 12.84	<.001
SBP (mmHg) Mean ± SD	137.08 ± 25.25	134.11 ± 24.52	129.91 ± 22.94	122.98 ± 19.27	<.001
DBP (mmHg) Mean ± SD	78.87 ± 14.98	79.28 ± 15.81	80.11 ± 15.43	79.21 ± 13.06	.837
HR (bpm)	104.83 ± 30.98	101.46 ± 30.17	105.73 ± 29.76	103.91 ± 33.87	.359
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	4.58 ± 1.94	4.51 ± 1.78	3.22 ± 1.86	1.74 ± 1.67	<.001
HAS-BLED score	2.36 ± 0.94	2.04 ± 0.89	1.63 ± 0.97	0.86 ± 0.81	<.001
Current Smoking (%)	22 (16.7)	45 (15.2)	62 (18.3)	21 (22.1)	.432
Current Drinking (%)	9 (6.8)	7 (2.4)	22 (6.5)	15 (15.8)	<.001
Type of AF (%)					<.001
Paroxysmal	27 (20.5)	88 (29.6)	138 (40.7)	42 (44.2)	
Persistent	36 (27.3)	57 (19.2)	68 (20.1)	23 (24.2)	
Permanent	69 (52.3)	152 (51.2)	133 (39.2)	30 (31.6)	
Co-morbidities (%)					
Heart Failure	48 (36.4)	94 (31.6)	107 (31.6)	20 (21.1)	.100
Hypertension	93 (70.5)	209 (69.4)	184 (54.3)	30 (31.6)	<.001
Diabetes mellitus	26 (19.7)	72 (24.2)	54 (15.9)	7 (7.4)	.01
Previous Stroke or TIA	39 (29.5)	90 (30.3)	69 (20.4)	11 (11.6)	<.001
Previous major bleeding	5 (3.8)	2 (0.7)	111 (3.2)	1 (1.1)	.070
Coronary artery disease	71 (53.8)	162 (54.5)	120 (35.4)	23 (24.2)	<.001
Prior Myocardial Infarction	15 (11.4)	33 (11.1)	28 (8.3)	5 (5.3)	.256
Left Ventricular Hypertrophy	17 (12.9)	19 (6.4)	40 (11.8)	7 (7.4)	.056
Congenital heart disease	3 (2.3)	4 (1.3)	9 (2.7)	4 (4.2)	.405
COPD	21 (15.9)	52 (17.5)	34 (10.0)	7 (7.4)	.010
Sleep apnea	3 (2.3)	7 (2.4)	11 (3.2)	5 (5.3)	.495
Hyperthyroidism	4 (3.0)	10 (3.4)	8 (2.4)	5 (5.3)	.542
Medications (%)					
Warfarin	20 (15.2)	54 (18.2)	71 (20.9)	31 (32.6)	.008
INR	1.77 ± 0.41	1.97 ± 0.46	1.97 ± 0.49	1.85 ± 0.39	.513
Anti-platelet	81 (61.4)	195 (65.7)	234 (69.0)	52 (54.7)	.054
Beta-Blocker	69 (52.3)	162 (54.5)	189 (55.8)	54 (56.8)	.890
Diuretic	60 (45.5)	114 (38.4)	1119 (35.1)	24 (25.3)	.015
Digoxin	38 (28.8)	76 (25.6)	100 (29.5)	27 (28.4)	.733
CCB	47 (35.6)	117 (39.4)	107 (31.6)	14 (14.7)	<.001
Anti-arrhythmia	11 (8.3)	26 (8.8)	61 (18.0)	14 (14.7)	.002

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CCB, calcium channel blockers; CHA<sub>2</sub>DS<sub>2</sub>-VASc=congestive heart failure, hypertension, age≥75years, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, and sex category; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; DBP, diastolic blood pressure; HAS-BLED=hypertension with SBP>160 mmHg, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; HR, heart rate; INR, international normalized ratio; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischemic attack.

**FIGURE 1** Event rates of outcome variables in patients with AF in CrCl categories



status of warfarin prescription, however, patients with 4 CrCl groups showed no significant difference (Table 2). Major bleeding risk was not statistically significant in the 4 CrCl groups in the whole cohort, both in patients with warfarin and without warfarin subgroup (Figures 2, 3 and Table 2), and remained no significantly different after adjustment for variables in HAS-BLED score (Table 2).

## 4 | DISCUSSION

In this study, we demonstrated severe renal impairment was a poor prognostic factor of 12-month clinical outcomes in Chinese ED AF patients. The most important findings of our study were as follows. First, patients with renal impairment were characterized as high risk for both all-cause death and cardiovascular death. Second, there were significant trends of incidence of TE among the four CrCl groups, and event rates increased along with a decrease in CrCl values; these trends remained significantly different in patients without warfarin treatment, but not statistics differently in patients with warfarin treatment. Third, renal impairment was not an independent risk predictor for major bleeding; no matter with or without warfarin treatment in Chinese ED AF patients.

### 4.1 | Renal impairment and death

Our study showed that AF patients in ED with severe renal impairment (CrCl < 30 ml/min vs. CrCl ≥ 80 ml/min) were significantly associated with a higher risk of all-cause death (HR 4.936) and cardiovascular death (HR 8.821). Our results were consistent with some other AF

registry studies; Boriani et al. (2016) assessed 1-year outcomes in patients with AF enrolled in the EurObservational Research Programme AF General Pilot Registry, they enrolled 2398 AF patients and found that renal function was a major determinant of adverse outcomes at 1 year, and even mild or moderate renal impairments were associated with an increased risk of all-cause death (OR 3.64 for estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m<sup>2</sup>, OR 3.30 for 30–49 ml/min/1.73 m<sup>2</sup>, and OR 2.09 for 50–79 ml/min/1.73 m<sup>2</sup> vs. eGFR ≥ 80 ml/min/1.73 m<sup>2</sup>). Proietti et al (Proietti et al., 2018) performed on the data of the Antithrombotic Agents Atrial Fibrillation study and showed that impaired eGFR (< 60 ml/min/1.73 m<sup>2</sup>) heralds a higher risk for cardiovascular morbidity and all-cause mortality among patients with AF. In the Fushimi AF Registry study (Abe et al., 2017), AF Patients with CrCl < 30 ml/min had the greatest risk of all-cause death, stroke, major bleeding, and hospitalization for myocardial infarction and HF. A Japanese AF registry, the J-Rhythm Registry study (Kodani et al., 2018), also showed similar results, which reported that even a moderate renal impairment (CrCl 30–49.9 ml/min) carries an increased risk for all-cause and cardiovascular mortality in patients with AF. Most recently, a prospective Garfield-AF Registry (Goto et al., 2019) including 35 countries and over 33,000 patients showed moderate-to-severe CKD was independently associated with mortality in newly diagnosed AF, and this effect is even greater in patients from Asia than the rest of the world. Another Japanese registry study (Yuzawa et al., 2020) also showed that an impaired renal function was significantly associated with all adverse events in AF patients (CrCl < 50 ml/min vs. CrCl ≥ 80 ml/min, adjusted HRs: 2.53 for death, 2.53 for cardiovascular events).

As we know, AF and renal dysfunction presenting a growing global burden of disease, both impairments of renal function and

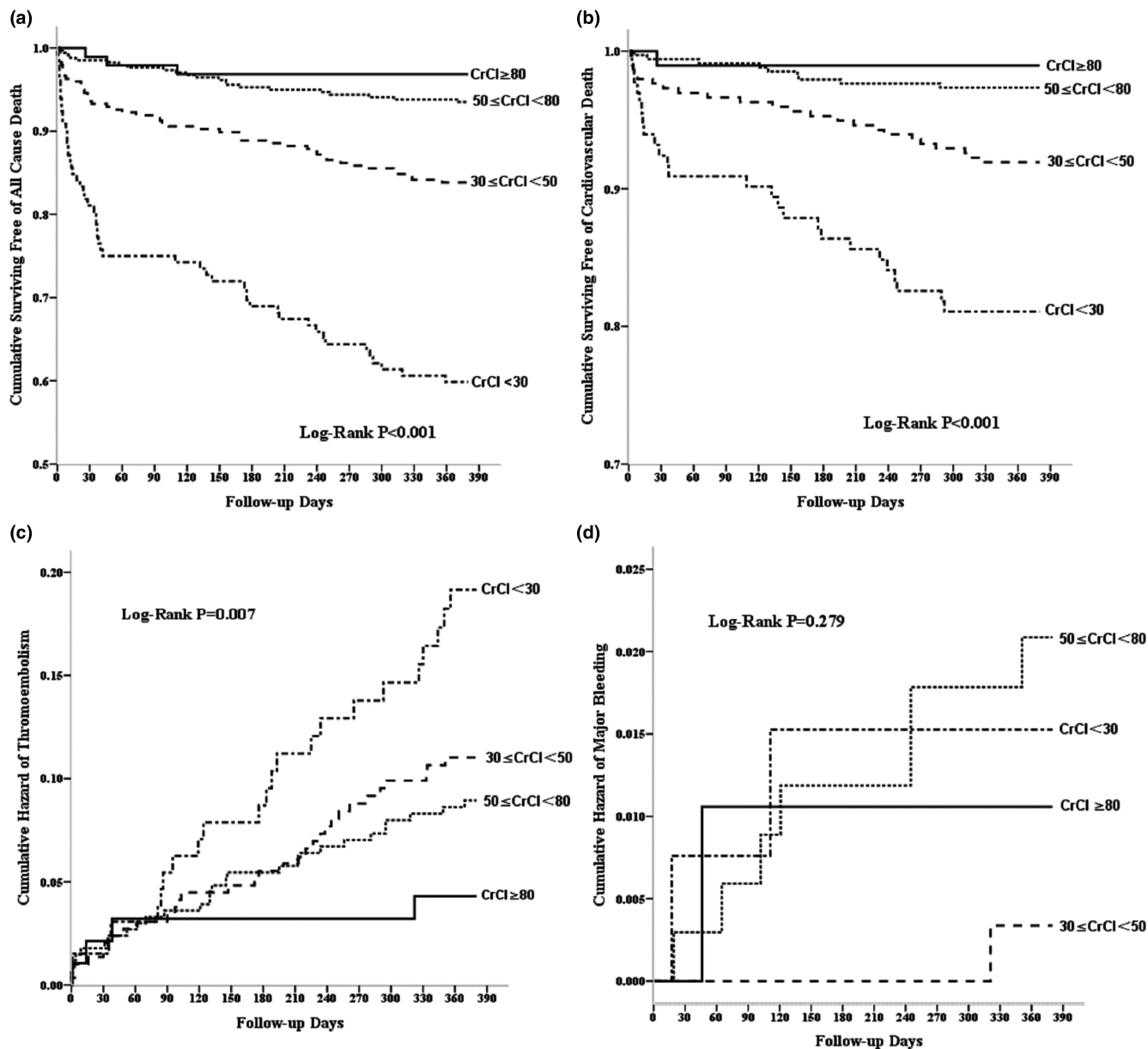


FIGURE 2 The Kaplan-Meier survival curves and event rates for (a) all-cause death, (b) cardiovascular death, (c) thromboembolism, and (d) major bleeding in patients with AF according to the different CrCl categories

AF were independently associated with poor cardiovascular outcomes and all-cause mortality, our study and all the above studies conformed that impaired renal function was a strong risk factor for prognosis in AF patients. These findings also suggested that when examining AF patients, we should understand that the characteristics of possible adverse events vary with the status of the renal function, and patients with AF and an impaired renal function should be more aware of deaths and cardiovascular events.

#### 4.2 | Renal impairment and TE

Our analysis detected a significantly higher incidence of TE events in Chinese nonvalvular AF patients with impaired renal function,

which remained statistically significant in patients without warfarin treatment. This finding aligns with recent evidence that suggests impaired renal function as a potential predictor of TE events. Go et al first evaluated the renal function and TE in the sub-study of the anticoagulation and risk factors in atrial fibrillation (ATRIA) study, and showed that AF patients with renal dysfunction had a higher rate of TE than those with normal renal function (Go et al., 2009). The Fushimi AF Registry study (Abe et al., 2017) also showed patients with  $CrCl < 30$  ml/min had the greatest risks of stroke/systemic embolism. Banerjee et al first showed that incidence rates of TE increased with reducing eGFR in nonvalvular AF patients (Banerjee et al., 2014). Nevertheless, after multivariate Cox analysis, the CrCl in our study did not show significant difference. Kodani et al (2018) also showed that  $CrCl < 30$  ml/min was

TABLE 2 Multivariable analysis for 4 CrCl categories associated with clinical outcomes in 12-month follow-up

	All-cause Death		Cardiovascular Death		Thromboembolism <sup>a</sup>		Major Bleeding <sup>b</sup>	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
CrCl≥80	1		1		1		1	
50 ≤ CrCl<80	1.040 (0.302–3.580)	.951	1.670 (0.203–13.741)	.633	1.012 (0.333–3.072)	.983	4.456 (0.500–39.704)	.181
30 ≤ CrCl<50	1.709 (0.494–5.911)	.397	4.816 (0.591–39.264)	.142	0.757 (0.238–2.407)	.637	1.542 (0.080–29.755)	.774
CrCl<30	5.567 (1.618–19.876)	.007	11.939 (1.439–99.031)	.022	1.233 (0.378–4.024)	.729	4.966 (0.363–67.940)	.230
Age (per year)	1.055 (1.031–1.080)	<.001	1.029 (0.998–1.062)	.066				
Age, ≥75years old					4.363 (1.882–10.117)	.001		
Age, 65–74years old					1.974 (0.823–4.738)	.128		
Age, >65years old							0.232 (0.048–1.132)	.071
Female	0.805 (0.556–1.166)	.251	1.103 (0.643–1.890)	.722	1.396 (0.894–2.178)	.142		
AF type								
Persistent	1		1					
Paroxysmal	1.051 (0.612–1.805)	.857	0.919 (0.420–2.014)	.833				
Permanent	1.277 (0.788–2.068)	.321	0.939 (0.477–1.848)	.856				
Co-morbidities								
Heart Failure	1.142 (0.740–1.762)	.550	1.835 (1.008–3.338)	.047	0.970 (0.598–1.574)	.903		
Hypertension	0.709 (0.440–1.141)	.156	0.848 (0.427–1.685)	.639	1.739 (1.004–3.009)	.048		
With SBP>160 mmHg							2.946 (0.339–25.577)	.327
Diabetes mellitus	1.214 (0.771–1.912)	.402	0.932 (0.454–1.913)	.849	0.841 (0.494–1.432)	.523		
Previous Stroke or TIA	1.196 (0.790–1.809)	.397	1.016 (0.544–1.898)	.961	1.186 (0.741–1.899)	.477	2.081 (0.511–8.463)	.306
Previous major bleeding	0.472 (0.112–1.983)	.305	-				11.315 (2.255–56.767)	.003
Coronary artery disease	0.715 (0.468–1.090)	.119	0.621 (0.331–1.166)	.138	1.008 (0.637–1.596)	.972		
COPD	2.143 (1.418–3.239)	<.001	1.656 (0.857–3.200)	.133				
Medications								
Warfarin	1.675 (0.967–2.904)	.066	2.420 (1.146–5.111)	.02	1.006 (0.532–1.900)	.986	23.419 (2.331–235.297)	.007
Labile INR							0.334 (0.093–1.201)	.093
Anti-platelet	1.116 (0.724–1.722)	.619	1.759 (0.915–3.381)	.090				
Beta-Blocker	1.082 (0.746–1.570)	.678	1.200 (0.688–2.095)	.520				
CCB	1.120 (0.739–1.697)	.592	0.951 (0.504–1.793)	.877				
Digoxin	0.683 (0.422–1.107)	.122	0.746 (0.379–1.472)	.339				

(Continues)

TABLE 2 (Continued)

	All-cause Death		Cardiovascular Death		Thromboembolism <sup>a</sup>		Major Bleeding <sup>b</sup>	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Diuretic	1.221 (0.792–1.883)	.365	1.396 (0.744–2.617)	.298				
Anti-arrhythmia	1.126 (0.608–2.084)	.706	1.102 (0.462–2.629)	.827				
ARB/ACEI	0.522 (0.336–0.810)	.004	0.828 (0.449–1.527)	.545				
Lipid Lowering Agents	1.132 (0.709–1.808)	.604	0.675 (0.325–1.401)	.291				

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CCB, calcium channel blockers; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; HR, hazard ratio; INR, international normalized ratio; SBP, systolic blood pressure; TIA, transient ischemic attack.

<sup>a</sup>Adjusted for variables in CHA<sub>2</sub>DS<sub>2</sub>-VASc score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, and sex category) and warfarin treatment.

<sup>b</sup>Adjusted for variables in HAS-BLED score (hypertension with SBP > 160 mmHg, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly).

not associated with the highest HR for TE. In our cohort, patients with renal dysfunction had more risk factors for TE, like older age and hypertension, statistics significant in multivariate analysis. So renal dysfunction increased risk for TE may be caused by combined factors. This study showed that the decreased CrCl was not a risk factor for TE in warfarin treatment group. Previous studies already showed that warfarin effectively reduced TE rates in patients with AF and CKD (Carrero et al., 2014). This suggested that although decreasing CrCl increased the risk of TE, warfarin treatment is still effective.

### 4.3 | Renal impairment and Major Bleeding

HAS-BLED scores provided a practical tool to assess the individual bleeding risk of real-world patients with AF (Pisters et al., 2010), and renal dysfunction was included. The presence of renal dysfunction in AF patients was associated with a substantial increase in TE incidence and an increased risk of bleeding events (Potpara et al., 2018). Previous studies already demonstrated that moderate to severe renal impairment increased the risk of bleeding in AF patients (Abe et al., 2017; Banerjee et al., 2014; Cho et al., 2017; Yuzawa et al., 2020), but some other studies showed different results, renal impairment was not a risk factor for bleeding (Boriani et al., 2016; Kodani et al., 2018). This study showed renal dysfunction was not an independent predictor for major bleeding. This difference may be contributing to patient characteristics, and the proportion of receiving warfarin was lower than other studies. Major Bleeding could have been strongly associated with other confounding factors such as a history of bleeding, Labile INR in our cohort.

There were multiple possible explanations for whether and how renal impairment and AF interact to increase the risk of adverse outcomes. Patients with renal dysfunction were more likely to develop hypertension, and to have control of blood pressure and volume, and resulting extracellular fluid expansion might lead to left ventricular hypertrophy, poor ventricular compliance (Bansal et al., 2013), increased left ventricular after-load in systole and reduced coronary perfusion in diastole lead to hypertrophy, ischemia, and dilatation of the left atrium and left ventricle, thus aggravating AF-related blood flow abnormalities. In our cohort, the proportional of hypertension increased along with decreasing CrCl, up to 70.5% in the CrCl < 30 ml/ml group. Previous study showed that left ventricular EF decreased and left atrial size increased in the eGFR < 60 ml/min group (Cho et al., 2017). And our study showed higher proportion of DM, CAD, and previous stroke, which may affect the outcome. But for TE and major bleeding, our cohort result was not consistent with previous study. Whether renal dysfunction would increase the risk of TE or major bleeding is still controversial, and more large-scale studies are needed for further evaluation. For the clinical management of patients with AF, the evaluation of renal function is necessary. Choosing the appropriate anticoagulation therapy is particularly critical for the improvement of the patient's prognosis.



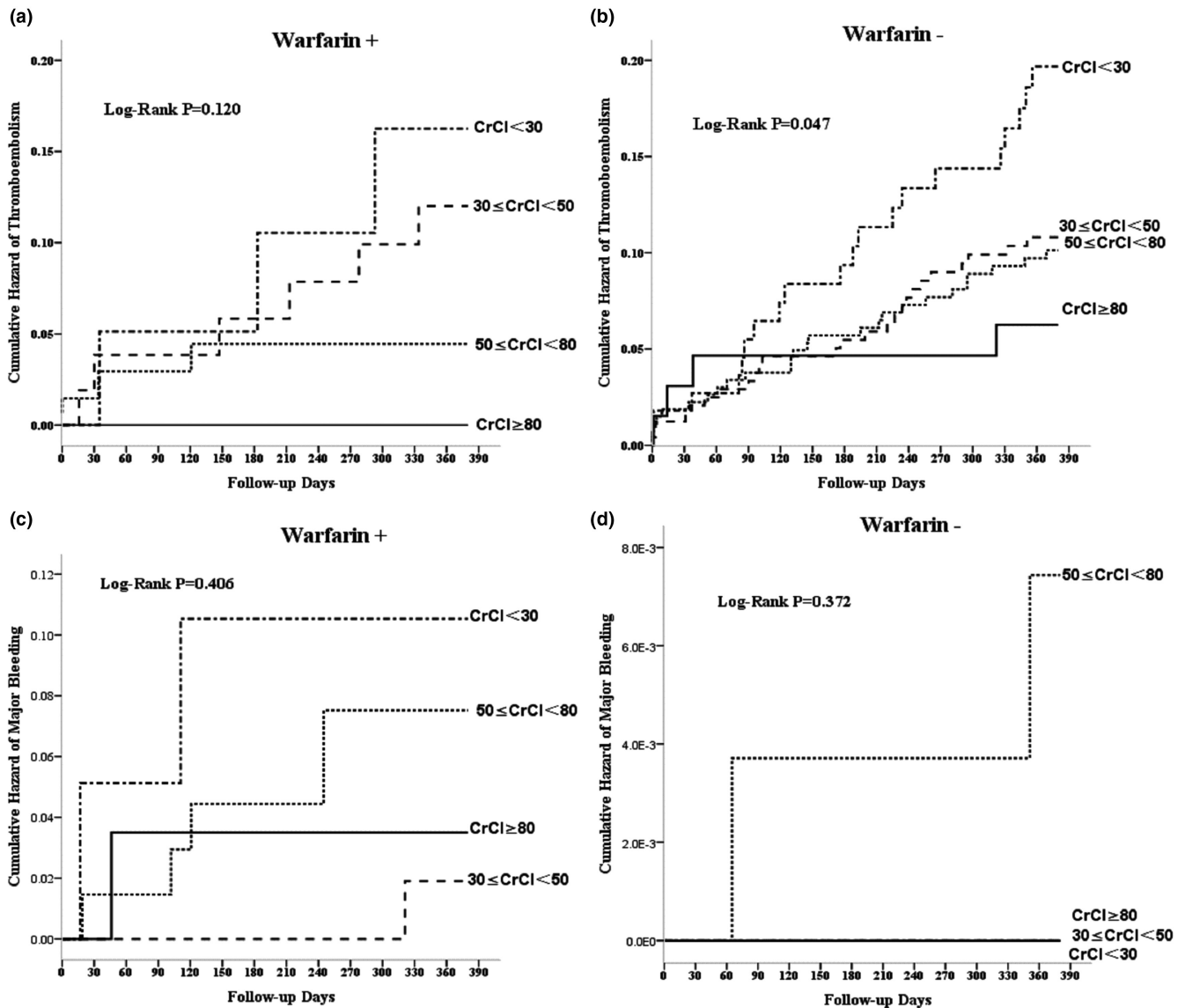


FIGURE 3 The Kaplan–Meier curves for thromboembolism event in patients treated with warfarin (a) and without warfarin (b); and for major bleeding events in patients treated with warfarin (c) and without warfarin (d) according to the 4 CrCl categories

#### 4.4 | Limitations

This study has several limitations to consider. First, the present study was conducted as a retrospective analysis of prospectively collected data, and its pity not collects all patients renal function data, however, we believe that the present real-world registry data reflects the status of ED AF treatment in China, and has a clinical implication for the clinical management of ED AF patients with renal dysfunction. Second, this study was in a contemporary real-world population, whereas the AF cohort stopped recruiting in 2011 and novel oral anticoagulants (NOACs) were not approved for clinical use in China. Therefore, the effects of NOACs on the relationship between renal function and adverse clinical events were not clarified in the present analysis. Third, only selected institutions within a limited geographical area in China participated in the CEAFR, and

the patients in our study were associated with more co-morbidity, which may also affect the renal function, and it would be difficult to assume that these findings can be generalized to the general AF patients in China. Large-scale prospective studies were needed.

#### 5 | CONCLUSION

In this 12-month follow-up analysis of a registry of “real world” ED patients with AF, renal function was a major determinant of adverse outcomes, incidence rates of all-cause death and cardiovascular death increased with reducing CrCl across the whole range of renal function. Renal impairment was an independent predictor of death, but not for TE and major bleeding in Chinese ED patients with non-valvular AF.

## CONFLICT OF INTERESTS

All authors report no conflict of interest.

## AUTHOR CONTRIBUTIONS

J. Wang and T. Zhang participated in literature search, study design, data collection, data analysis, data interpretation, and wrote the manuscript. H Zhang and XH. Shao carried out the data collection and analysis and provided the critical revision. Y. Yang and J. Zhu conceived the study, participated in its design and coordination, and provided the critical revision. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was performed in accordance with the principle of the declaration of Helsinki and approved by the Ethics committee of Fuwai Hospital. Written informed consent was obtained from all patients or their legal guardians.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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