ORIGINAL RESEARCH

$R_{2(GFR)}$CHADS$_2$ and $R_{2(GFR)}$CHA$_2$DS$_2$VASc schemes improved the performance of CHADS$_2$ and CHA$_2$DS$_2$VASc scores in death risk stratification of Chinese older patients with atrial fibrillation

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Background: This analysis was carried out to refine the CHADS$_2$ and CHA$_2$DS$_2$VASc scores by combining creatinine clearance (CrCl) and glomerular filtration rate (GFR) and evaluate the performance of CrCl-based and GFR-based schemes in death risk stratification of Chinese older patients with atrial fibrillation (AF).

Methods: There were 219 older patients with AF, and all-cause mortality was assessed during the follow-up of 1.11 years. Renal function was evaluated using the CrCl formula and different GFR (Modification of Diet in Renal Disease [MDRD], Chinese MDRD [CMDRD], Mayo Clinic Quadratic [Mayo] and Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) formulas, and five kinds of R$_2$CHADS$_2$ and R$_2$CHA$_2$DS$_2$VASc schemes were generated by combining CrCl and GFR with CHADS$_2$ and CHA$_2$DS$_2$VASc scores.

Results: In Cox regression multivariate analysis, CrCl <60 mL/min was moderately associated with death risk (P=0.122 and P=0.144). When MDRD, CMDRD, CKD-EPI and Mayo formulas were used to ascertain the GFR, GFR <60 mL/min/1.73 m^2 was significantly associated with death risk (P<0.001 for all). In the models with CHADS$_2$ and CHA$_2$DS$_2$VASc scores as the linear covariates, CrCl and GFR as the continuous variables were significantly associated with death risk (P<0.05 for all). C-statistics of CrCl-based schemes – $R_{2(CrCl)}$CHADS$_2$ and $R_{2(CrCl)}$CHA$_2$DS$_2$VASc – moderately exceeded that of CHADS$_2$ and CHA$_2$DS$_2$VASc scores (P=0.081 and 0.082). C-statistics of GFR-based schemes – $R_{2(GFR)}$CHADS$_2$ and $R_{2(GFR)}$CHA$_2$DS$_2$VASc – significantly exceeded that of CHADS$_2$ and CHA$_2$DS$_2$VASc scores (P<0.05 for all).

Conclusion: Chinese older patients with AF with lower levels of GFR and GFR <60 mL/min/ 1.73 m^2 had a significantly high death risk, and those with lower levels of CrCl or CrCl <60 mL/min had a significantly or modestly high death risk. There was significantly better performance of GFR-based schemes and moderately better performance of CrCl-based schemes in death risk stratification compared with CHADS$_2$ and CHA$_2$DS$_2$VASc scores.

Keywords: atrial fibrillation, CHADS$_2$, CHA$_2$DS$_2$VASc, older patients, creatinine clearance, glomerular filtration rate

Background

As the most common arrhythmia, atrial fibrillation (AF) has a clear increase in prevalence with an increasing age and is obviously associated with death risk.[1–3] A key step in reducing the death risk for patients with AF is an effective stratification of death risk. Various clinical features have been identified to stratify the death risk. However, there is no mature and practical scheme developed for stratifying the

death risk in patients with AF, and some researchers like Nakagawa et al have successfully applied the CHADS$_2$ score, commonly used for assessing the thromboembolic events, to effective stratification of death risk in patients with AF.[4] Although this transition has an important value for clinical practice, the currently available schemes, such as CHADS$_2$ and CHA$_2$DS$_2$VASc scores, are largely derived from dated populations and have a limited discriminatory ability.[5,6] Renal function has emerged as a risk factor for mortality in patients with AF, and thus, Piccini et al has made attempts to combine creatinine clearance (CrCl) with the CHADS$_2$ score. However, as a standard index of renal function, glomerular filtration rate (GFR) has not been systematically analyzed in the clinical studies, and nobody knows if it is appropriate or even better to combine GFR with these schemes, including CHADS$_2$ and CHA$_2$DS$_2$VASc scores.[7] Moreover, ongoing validations of these schemes in other populations with AF from different ethnic and age groups will confirm their true value. The objectives of this analysis were to refine the CHADS$_2$ and CHA$_2$DS$_2$VASc scores by combining not only CrCl but also GFR and evaluate the performance of new CrCl-based and GFR-based schemes in death risk stratification of Chinese older patients with AF.

Methods
Study participants
The current analysis was made up of 219 patients older than 60 years with AF. All of them had the medical history, clinical symptoms and electrocardiograph records showing AF. The Chinese People's Liberation Army General Hospital was their designated hospital and had their integrated long-term medical and final death records, which made it easier for us to follow up these patients effectively and judge the end point accurately. The study protocol was approved by ethics committee of the Chinese People's Liberation Army General Hospital (Beijing, China). Each participant provided written informed consent to be included in the study.

Risk stratification schemes
CHADS$_2$ score awards 1 point each for the presence of congestive heart failure, hypertension, age $\geq$75 years and diabetes mellitus and 2 points for prior stroke or transient ischemic attack (TIA). CHA$_2$DS$_2$VASc score awards 1 point each for the presence of congestive heart failure, hypertension, vascular diseases, diabetes mellitus and female sex; 2 points for prior stroke or TIA and 0, 1 or 2 points depending on age. For each patient, the current analysis obtained the additional risk schemes by combining the CHADS$_2$ and CHA$_2$DS$_2$VASc scores with an additional 2 points for

CrCl $<$60 mL/min and GFR $<$60 mL/min/1.73 m^2 and designated them as R$_2$CHADS$_2$ and R$_2$CHA$_2$DS$_2$VASc schemes.

Risk factor definition
Patients with mean systolic blood pressure $\geq$140 mmHg, mean diastolic blood pressure $\geq$90 mmHg or medications for the treatment of hypertension were defined as having hypertension. Mean systolic and diastolic blood pressures were taken as the average of five separate measurements. Patients with fasting glucose concentration $\geq$7.0 mmol/L or treatment with oral hypoglycemic agents/insulins were defined as having diabetes mellitus. Standard echocardiogram was performed, and left ventricular ejection fraction was measured by the Simpson's method.[8] Stroke was defined as the new, sudden focal neurological deficit resulting from a presumed cerebrovascular cause that persisted $>$24 hours rather than other identifiable causes such as tumor or seizure. Events that involved the symptoms that lasted $<$24 hours were considered as TIA. Myocardial infarction and peripheral artery disease were combined as a single variable termed vascular diseases. Serum creatinine concentration was measured using an enzymatic method, and the calibration formula of Jaffe's kinetic method was as follows:[9]

Jaffe's kinetic method of serum creatinine (mg/dL) = 0.795 $\times$ [enzymatic method of serum creatinine (mg/dL)] + 0.29.

The enzymatic method of serum creatinine was used in the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, and the Jaffe's kinetic method of serum creatinine was used in the other four formulas. CrCl and GFR of all participants were evaluated with different formulas as follows:

- Cockcroft–Gault formula:[10]

$$CrCl = [140 - age\ (years)] \times weight\ (kg) \times 0.85\ (if\ female)/72 \times\ Scr\ (mg/dL)$$

- Modification of Diet in Renal Disease (MDRD) formula:[11]

$$MDRD = 186 \times Scr\ (mg/dL)^{-1.154} \times age\ (years)^{-0.203} \times 0.742\ (if\ female)$$

- Chinese MDRD (CMDRD) formula:[12]

$$CMDRD = 175 \times Scr\ (mg/dL)^{-1.234} \times age\ (years)^{-0.179} \times 0.79\ (if\ female)$$

- Mayo Clinic Quadratic (Mayo) formula:[13]

$$Mayo = Exp\ [1.911 + 5.249/Scr\ (mg/dL) - 2.114/Scr\ (mg/dL)^2 - 0.00686 \times age\ (years) - 0.205\ (if\ female)]$$

- CKD-EPI formula:[14]

    If female and if Scr ≤ 0.7 mg/dL:

    $$CKD\text{-}EPI = 144 \times Scr\ (mg/dL)/0.7^{-0.329} \times 0.993^{age\ (years)}$$

    If female and if Scr > 0.7 mg/dL:

    $$CKD\text{-}EPI = 144 \times Scr\ (mg/dL)/0.7^{-1.209} \times 0.993^{age\ (years)}$$

    If male and if Scr ≤ 0.9 mg/dL:

    $$CKD\text{-}EPI = 141 \times Scr\ (mg/dL)/0.9^{-0.411} \times 0.993^{age\ (years)}$$

    If male and if Scr > 0.9 mg/dL:

    $$CKD\text{-}EPI = 141 \times Scr\ (mg/dL)/0.9^{-1.209} \times 0.993^{age\ (years)}$$

End point ascertainment

Given the priority of all-cause mortality in the outcome studies, as well as the high prevalence of multiple organ failure in the elderly, the primary end point in the current analysis was all-cause mortality. The current analysis performed the follow-up to assess the all-cause mortality during the mean time of 1.11 years (406 days; median: 313 days; interquartile range: 199–532 days) and had the survival status for all these patients. Death was determined from death records, a legal document including time, site and other information.

Statistical analysis

Baseline characteristics were summarized as frequencies for categorical variables and median values with interquartile range for continuous variables. Cox regression model was used to explore whether renal function is a significant factor associated with death risk after adjusting for $CHADS_2$ and CHA_2DS_2VASc scores or their components during the follow-up. C-statistic was calculated to assess the discriminatory ability of these schemes for primary outcome. Two-sided P-value < 0.05 was considered significant. Statistics analysis was performed using Statistical Package for the Social Sciences version 17 (SPSS Inc., Chicago, IL, USA) and MedCalc 11.6 for Windows (MedCalc Software bvba, Mariakerke, Belgium).

Results

For all patients, median age was 86 years, median $CHADS_2$ score was 3.0 and median CHA_2DS_2VASc score was 4.0; 14.6% of patients were female. Over the median follow-up of 1.11 years, 24.2% of patients died. Baseline characteristics of all patients according to death occurrence are shown in Table 1.

In Cox regression univariate analysis (Table 2), not only lower levels of CrCl, MDRD-GFR, CMDRD-GFR, EPI-GFR and Mayo-GFR but also CrCl < 60 mL/min, MDRD-GFR < 60 mL/min/1.73 m², CMDRD-GFR < 60 mL/min/1.73 m², EPI-GFR < 60 mL/min/1.73 m² and Mayo-GFR < 60 mL/min/1.73 m² were significantly associated with death risk ($P < 0.05$ for all). After accounting for all the factors that constituted the $CHADS_2$ and CHA_2DS_2VASc scores in the Cox regression multivariate analysis, CrCl < 60 mL/min was modestly associated with death risk ($P=0.122$ and $P=0.144$). When MDRD, CMDRD, CKD-EPI and Mayo formulas were used to ascertain the GFR, GFR < 60 mL/min/1.73 m² was significantly associated with death risk after adjusting for the components of $CHADS_2$ and CHA_2DS_2VASc scores ($P < 0.001$ for all). In the models developed with $CHADS_2$ and CHA_2DS_2VASc scores used as the linear covariates, CrCl, MDRD-GFR, CMDRD-GFR, EPI-GFR and Mayo-GFR as the continuous variables were significantly associated with death risk ($P < 0.05$ for all).

As provided in Table 3, C-statistics of $R_{2(CrCl)}CHADS_2$ and $R_{2(CrCl)}CHA_2DS_2VASc$ schemes moderately exceeded that of $CHADS_2$ and CHA_2DS_2VASc scores ($P=0.081$ and $P=0.082$). C-statistics of $R_{2(MDRD\text{-}GFR)}CHADS_2$, $R_{2(CMDRD\text{-}GFR)}CHADS_2$, $R_{2(EPI\text{-}GFR)}CHADS_2$ and $R_{2(Mayo\text{-}GFR)}CHADS_2$ and $R_{2(MDRD\text{-}GFR)}CHA_2DS_2VASc$, $R_{2(CMDRD\text{-}GFR)}CHA_2DS_2VASc$, $R_{2(EPI\text{-}GFR)}CHA_2DS_2VASc$ and $R_{2(Mayo\text{-}GFR)}CHA_2DS_2VASc$ schemes significantly exceeded that of $CHADS_2$ and CHA_2DS_2VASc scores ($P < 0.05$ for all). There were no differences in C-statistics between $R_{2(MDRD\text{-}GFR)}CHADS_2$, $R_{2(CMDRD\text{-}GFR)}CHADS_2$, $R_{2(EPI\text{-}GFR)}CHADS_2$ and $R_{2(Mayo\text{-}GFR)}CHADS_2$ and between $R_{2(MDRD\text{-}GFR)}CHA_2DS_2VASc$, $R_{2(CMDRD\text{-}GFR)}CHA_2DS_2VASc$, $R_{2(EPI\text{-}GFR)}CHA_2DS_2VASc$ and $R_{2(Mayo\text{-}GFR)}CHA_2DS_2VASc$.

Discussion

As a frequent arrhythmia in clinical practice, AF increases in prevalence with age and accounts for an increased death risk.[1–3] Nakagawa et al have manifested that impaired renal function was related to an increased mortality among 387 Japanese patients with AF.[4] The current analysis validated that GFR as the continuous variable and GFR < 60 mL/min/1.73 m² were significantly and independently associated with death risk, whereas the CrCl as the continuous variable or CrCl < 60 mL/min was significantly or modestly associated with death risk during the follow-up of older patients with AF. Meanwhile, the current analysis evaluated the renal function with not only the CrCl formula but also different GFR formulas and refined five different kinds of R_2CHADS_2 and $R_2CHA_2DS_2VASc$ schemes by combining CrCl and GFR with $CHADS_2$ and CHA_2DS_2VASc scores. Moreover, the addition of GFR to $CHADS_2$ and CHA_2DS_2VASc scores fared significantly better than that to $CHADS_2$ and

Table 1 Baseline characteristics of all patients stratified by the death occurrence

Characteristics	Total (n=219)	Survivor (n=166)	Dead (n=53)	P-value
Age, years	86.0 (82.0–90.0)	85.0 (81.8–89.0)	88.0 (84.5–91.0)	0.006
≤64	2 (0.9)	2 (1.2)	0 (0)	0.243
65–74	14 (6.4)	13 (7.8)	1 (1.9)	
≥75	203 (92.7)	151 (91.0)	52 (98.1)	
Female sex	32 (14.6)	25 (15.1)	7 (13.2)	0.740
Congestive heart failure/left ventricular function <40%	102 (46.6)	67 (40.4)	35 (66.0)	0.001
Hypertension	170 (77.6)	126 (75.9)	44 (83.0)	0.279
Diabetes mellitus	78 (35.6)	51 (30.7)	27 (50.9)	0.007
Stroke/TIA	20 (9.1)	16 (9.6)	4 (7.5)	0.645
Vascular diseases	51 (23.3)	37 (22.3)	14 (26.4)	0.536
$CHADS_2$	3 (2, 3)	3 (2, 3)	3 (2, 4)	0.001
CHA_2DS_2VASc	4 (3, 5)	4 (3, 5)	5 (4, 5)	0.003
CrCl, mL/min	45.2 (34.1–56.4)	47.8 (37.9–58.0)	34.4 (21.7–46.2)	<0.001
CrCl <60 mL/min	181 (82.7)	132 (79.5)	49 (92.5)	0.022
$R_{2(CrCl)}CHADS_2$	5 (4, 5)	4 (3, 5)	5 (4, 6)	<0.001
$R_{2(CrCl)}CHA_2DS_2VASc$	6 (5, 7)	6 (5, 6)	7 (6, 7)	<0.001
MDRD-GFR, mL/min/1.73 m²	63.3 (51.5–74.4)	66.0 (55.6–75.1)	49.5 (31.6–63.6)	<0.001
MDRD-GFR <60 mL/min/1.73 m²	96 (43.8)	59 (35.5)	37 (69.8)	<0.001
$R_{2(MDRD-GFR)}CHADS_2$	4 (2, 5)	3 (2, 4)	5 (4, 6)	<0.001
$R_{2(MDRD-GFR)}CHA_2DS_2VASc$	5 (4, 6)	4 (3, 6)	6 (5, 7)	<0.001
CMDRD-GFR, mL/min/1.73 m²	65.8 (52.6–78.6)	68.7 (57.9–79.3)	51.0 (31.3–65.8)	<0.001
CMDRD-GFR <60 mL/min/1.73 m²	88 (40.2)	52 (31.3)	36 (67.9)	<0.001
$R_{2(CMDRD-GFR)}CHADS_2$	3 (2, 5)	3 (2, 5)	5 (4, 6)	<0.001
$R_{2(CMDRD-GFR)}CHA_2DS_2VASc$	5 (4, 6)	5 (4, 6)	6 (5, 7)	<0.001
EPI-GFR, mL/min/1.73 m²	60.6 (46.5–78.1)	65.9 (52.0–79.2)	44.3 (23.4–61.0)	<0.001
EPI-GFR <60 mL/min/1.73 m²	107 (48.9)	67 (40.4)	40 (75.5)	<0.001
$R_{2(EPI-GFR)}CHADS_2$	4 (2, 5)	3 (2, 4)	5 (4, 6)	<0.001
$R_{2(EPI-GFR)}CHA_2DS_2VASc$	5 (4, 6)	4 (3, 6)	6 (5, 7)	<0.001
Mayo-GFR, mL/min/1.73 m²	71.3 (55.9–84.4)	75.2 (62.3–85.9)	52.7 (26.5–72.0)	<0.001
Mayo-GFR <60 mL/min/1.73 m²	68 (31.1)	36 (21.7)	32 (60.4)	<0.001
$R_{2(Mayo-GFR)}CHADS_2$	3 (2, 4)	3 (2, 4)	5 (3, 6)	<0.001
$R_{2(Mayo-GFR)}CHA_2DS_2VASc$	4 (3, 6)	4 (3, 5)	6 (5, 7)	<0.001

Notes: $CHADS_2$: risk stratification system that awards 1 point each for the presence of congestive heart failure, hypertension, age ≥75 years and diabetes mellitus and 2 points for prior stroke or TIA; CHA_2DS_2VASc: risk stratification system that awards 1 point each for the presence of congestive heart failure, hypertension, vascular diseases, diabetes mellitus and female sex, 2 points for prior stroke or TIA and 0, 1 or 2 points depending on age; R_2CHADS_2: $CHADS_2$ +2 points if CrCl <60 mL/min and GFR <60 mL/min/1.73 m²; $R_2CHA_2DS_2VASc$: CHA_2DS_2VASc +2 points if CrCl <60 mL/min and GFR <60 mL/min/1.73 m². Results are given as median values (interquartile range) and frequencies (%).
Abbreviations: TIA, transient ischemic attack; CMDRD, Chinese MDRD; CrCl, creatinine clearance; MDRD, Modification of Diet in Renal Disease; GFR, glomerular filtration rate; EPI, epidemiology; Mayo, Mayo Clinic Quadratic.

Table 2 Effects of renal function indices on death risk in Cox regression analyses

Renal function indices	HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
CrCl	0.949 (0.931–0.967)[a]	<0.001	0.952 (0.934–0.970)[b]	<0.001	0.952 (0.934–0.970)[c]	<0.001
CrCl <60 mL/min	1.794 (1.013–3.176)[a]	0.045	1.579 (0.884–2.818)[d]	0.122	1.546 (0.862–2.772)[e]	0.144
MDRD-GFR	0.967 (0.954–0.979)[a]	<0.001	0.970 (0.957–0.983)[b]	<0.001	0.969 (0.956–0.983)[c]	<0.001
MDRD-GFR <60 mL/min/1.73 m²	1.865 (1.390–2.502)[a]	<0.001	1.767 (1.310–2.383)[d]	<0.001	1.793 (1.328–2.421)[e]	<0.001
CMDRD-GFR	0.969 (0.957–0.980)[a]	<0.001	0.972 (0.960–0.984)[b]	<0.001	0.971 (0.959–0.984)[c]	<0.001
CMDRD-GFR <60 mL/min/1.73 m²	1.964 (1.471–2.623)[a]	<0.001	1.853 (1.377–2.493)[d]	<0.001	1.915 (1.416–2.588)[e]	<0.001
EPI-GFR	0.966 (0.955–0.978)[a]	<0.001	0.969 (0.957–0.981)[b]	<0.001	0.968 (0.956–0.981)[c]	<0.001
EPI-GFR <60 mL/min/1.73 m²	1.961 (1.433–2.682)[a]	<0.001	1.859 (1.351–2.560)[d]	<0.001	1.868 (1.356–2.573)[e]	<0.001
Mayo-GFR	0.970 (0.960–0.980)[a]	<0.001	0.973 (0.962–0.983)[b]	<0.001	0.972 (0.961–0.983)[c]	<0.001
Mayo-GFR <60 mL/min/1.73 m²	2.097 (1.589–2.768)[a]	<0.001	1.922 (1.438–2.569)[d]	<0.001	1.963 (1.462–2.637)[e]	<0.001

Notes: $CHADS_2$: risk stratification system that awards 1 point each for the presence of congestive heart failure, hypertension, age ≥75 years and diabetes mellitus and 2 points for prior stroke or TIA; CHA_2DS_2VASc: risk stratification system that awards 1 point each for the presence of congestive heart failure, hypertension, vascular diseases, diabetes mellitus and female sex, 2 points for prior stroke or TIA and 0, 1 or 2 points depending on age. [a]Not adjusted. [b]After adjusting for the $CHADS_2$ score as the linear covariate. [c]After adjusting for the CHA_2DS_2VASc score as the linear covariate. [d]After adjusting for the components of the $CHADS_2$ score. [e]After adjusting for the components of CHA_2DS_2VASc score.
Abbreviations: HR, hazard ratio; CrCl, creatinine clearance; MDRD, Modification of Diet in Renal Disease; GFR, glomerular filtration rate; CMDRD, Chinese MDRD; EPI, epidemiology; Mayo, Mayo Clinic Quadratic; TIA, transient ischemic attack.

Table 3 Comparison of abilities in death risk stratification between different models

Risk stratification models	C-statistics (95% CI)	P-value			
		Compared with CHADS$_2$ and CHA$_2$DS$_2$VASc	Compared with R$_{2(MDRD-GFR)}$CHADS$_2$ and R$_{2(MDRD-GFR)}$ CHA$_2$DS$_2$VASc	Compared with R$_{2(CMDRD-GFR)}$CHADS$_2$ and R$_{2(CMDRD-GFR)}$ CHA$_2$DS$_2$VASc	Compared with R$_{2(EPI-GFR)}$CHADS$_2$ and R$_{2(EPI-GFR)}$ CHA$_2$DS$_2$VASc
CHADS$_2$	0.639 (0.552–0.726)				
CHA$_2$DS$_2$VASc	0.633 (0.546–0.720)	0.784			
R$_{2(CrCl)}$CHADS$_2$	0.674 (0.591–0.757)	0.081			
R$_{2(CrCl)}$CHA$_2$DS$_2$VASc	0.665 (0.581–0.748)	0.082			
R$_{2(MDRD-GFR)}$CHADS$_2$	0.732 (0.657–0.807)	0.007			
R$_{2(MDRD-GFR)}$CHA$_2$DS$_2$VASc	0.718 (0.641–0.795)	0.005			
R$_{2(CMDRD-GFR)}$CHADS$_2$	0.737 (0.662–0.813)	0.003	0.635		
R$_{2(CMDRD-GFR)}$CHA$_2$DS$_2$VASc	0.721 (0.643–0.799)	0.003	0.761		
R$_{2(EPI-GFR)}$CHADS$_2$	0.731 (0.659–0.802)	0.009	0.898	0.666	
R$_{2(EPI-GFR)}$CHA$_2$DS$_2$VASc	0.717 (0.642–0.792)	0.007	0.925	0.778	
R$_{2(Mayo-GFR)}$CHADS$_2$	0.739 (0.662–0.817)	0.001	0.728	0.897	0.702
R$_{2(Mayo-GFR)}$CHA$_2$DS$_2$VASc	0.723 (0.642–0.803)	0.001	0.792	0.898	0.773

Notes: CHADS$_2$: risk stratification system that awards 1 point each for the presence of congestive heart failure, hypertension, age ≥75 years and diabetes mellitus and 2 points for prior stroke or TIA; CHA$_2$DS$_2$VASc: risk stratification system that awards 1 point each for the presence of congestive heart failure, hypertension, vascular diseases, diabetes mellitus and female sex, 2 points for prior stroke or TIA and 0, 1 or 2 points depending on age; R$_2$CHADS$_2$: CHADS$_2$ +2 points if CrCl <60 mL/min and GFR <60 mL/min/1.73 m^2; R$_2$CHA$_2$DS$_2$VASc: CHA$_2$DS$_2$VASc +2 points if CrCl <60 mL/min and GFR <60 mL/min/1.73 m^2.
Abbreviations: CrCl, creatinine clearance; MDRD, Modification of Diet in Renal Disease; GFR, glomerular filtration rate; CMDRD, Chinese MDRD; EPI, epidemiology; Mayo, Mayo Clinic Quadratic.

CHA$_2$DS$_2$VASc scores, whereas the addition of CrCl to CHADS$_2$ and CHA$_2$DS$_2$VASc scores fared marginally better than that to CHADS$_2$ and CHA$_2$DS$_2$VASc scores.

How to implement the effective stratification of death risk and accordingly decrease the death risk in patients with AF are of great concern. Various clinical factors have the ability to predict the death risk. However, there was no reliable schema developed for stratifying the death risk in patients with AF, and some researchers like Nakagawa et al have successfully applied the CHADS$_2$ score, generally used for appraising the thromboembolic likelihood, to stratifying the death risk in patients with AF.[4] This transition had an important value for clinical practice, but the current schemes including the CHADS$_2$ and CHA$_2$DS$_2$VASc scores have a limited discriminatory ability.[5,6] Renal function is a powerful risk factor for mortality in patients with AF, and thus, Piccini et al have made attempts to combine CrCl with the CHADS$_2$ score. However, as a standard index of renal function, GFR has not been adequately assessed, and nobody knows if it is appropriate or even better to combine GFR with these scoring systems (CHADS$_2$ and CHA$_2$DS$_2$VASc scores).[7] The current analysis certified that GFR-based schemes – R$_{2(GFR)}$CHADS$_2$ and R$_{2(GFR)}$CHA$_2$DS$_2$VASc – refined by four different formula-calculated GFR provided a significant improvement of predictive ability for death risk in older patients with AF, but with the addition of CrCl to CHADS$_2$ and CHA$_2$DS$_2$VASc scores – R$_{2(CrCl)}$CHADS$_2$ and R$_{2(CrCl)}$CHA$_2$DS$_2$VASc, there was only a modest improvement in death risk stratification.

We are unaware of other published studies that have used GFR to refine the CHADS$_2$ and CHA$_2$DS$_2$VASc scores and verified that GFR-based schemes performed better than original versions in death risk stratification of Chinese older patients with AF.

The current analysis has some limitations. First, as the current analysis was made up of 219 Chinese older patients with AF, to validate the current conclusion in a larger study population will be more valuable and very necessary. Second, due to the priority of all-cause mortality in the outcome studies, as well as the high prevalence of multiple organ failure in the elderly, all-cause mortality rather than cardiovascular/stroke-related mortality was considered in the current analysis.

Conclusion

The current analysis confirmed that Chinese older patients with AF with lower levels of GFR and GFR <60 mL/min/1.73 m^2 had a significantly high death risk and those with lower levels of CrCl or CrCl <60 mL/min had a significantly or modestly high death risk. To aid the death risk scoring, the current analysis evaluated the renal function using not only CrCl formula but also different GFR formulas and then generated five different kinds of R$_2$CHADS$_2$ and R$_2$CHA$_2$DS$_2$VASc schemes by combining CrCl and GFR with CHADS$_2$ and CHA$_2$DS$_2$VASc scores. Meanwhile, the current analysis provided evidence for the significantly better performance of GFR-based schemes – R$_{2(GFR)}$CHADS$_2$

and $R_{2(GFR)}CHA_2DS_2VASc$ – and the moderately better performance of CrCl-based schemes – $R_{2(CrCl)}CHADS_2$ and $R_{2(CrCl)}CHA_2DS_2VASc$ – in death risk stratification compared with other published schemes without considering renal function ($CHADS_2$ and CHA_2DS_2VASc scores). To our knowledge, it is the first time that GFR was applied to refine the $CHADS_2$ and CHA_2DS_2VASc scores, and GFR-based schemes – $R_{2(GFR)}CHADS_2$ and $R_{2(GFR)}CHA_2DS_2VASc$ – were testified to be superior to original versions in the risk stratification of Chinese older patients with AF.

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Disclosure

The authors report no conflicts of interest in this work.

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