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ORIGINAL RESEARCH

eGFRs from Asian-modified CKD-EPI and Chinese-modified CKD-EPI equations were associated better with hypertensive target organ damage in the community-dwelling elderly Chinese: the Northern Shanghai Study

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Background: With increasing age, estimated glomerular filtration rate (eGFR) decline is a frequent manifestation and is strongly associated with other preclinical target organ damage (TOD). In literature, many equations exist in assessing patients' eGFR. However, these equations were mainly derived and validated in the population from Western countries, which equation should be used for risk stratification in the Chinese population remains unclear, as well as their comparison. Considering that TOD is a good marker for risk stratification in the elderly, in this analysis, we aimed to investigate whether the recent eGFR equations derived from Asian and Chinese are better associated with preclinical TOD than the other equations in elderly Chinese.

Methods: A total of 1,599 community-dwelling elderly participants (age >65 years) in northern Shanghai were prospectively recruited from June 2014 to August 2015. Conventional cardiovascular risk factors were assessed, and hypertensive TOD including left ventricular mass index (LVMI), carotid–femoral pulse wave velocity (cf-PWV), carotid intima-media thickness (IMT), ankle–brachial index (ABI) and urine albumin to creatinine ratio (UACR) was evaluated for each participant. Participant's eGFR was calculated from the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Chinese-abbreviated MDRD (c-aMDRD), Asian-modified CKD-EPI (aCKD-EPI) equation and Chinese-modified CKD-EPI (cCKD-EPI) equation.

Results: In multivariate regression analysis, only eGFRs from aCKD-EPI were significantly and inversely associated with carotid IMT (P=0.005). In multivariate logistic models, decreased eGFR from all the equations were significantly associated with lower ABI ($P<0.001$), microalbuminuria (P=0.02 to $P<0.001$) and increased cf-PWV ($P<0.001$). Only decreased eGFRs from aCKD-EPI and cCKD-EPI equations were significantly associated with increased IMT (both crude $P<0.05$). In the receiver operator characteristic (ROC) analysis, only aCKD-EPI and cCKD-EPI equations presented significant associations with all the listed preclinical TODs (P-value from <0.05 to <0.001).

Conclusion: In community-dwelling elderly Chinese, eGFRs from aCKD-EPI and cCKD-EPI equations are better associated with preclinical TOD. aCKD-EPI and cCKD-EPI equations should be preferred when making risk assessment.

Keywords: elderly Chinese, eGFR equation, preclinical target organ damage, eGFR

Background

In terms of epidemiological transition, end-stage cardiovascular disease, including atrial fibrillation, renal disease and heart failure, is becoming more and more frequent.[1] This condition grows even worse for the aging population, as the incidence and prevalence of most known cardiovascular disorders increase with age.[2] However in China, we are lacking in evidence for the management of chronic diseases in elderly. Therefore, studies based on elderly Chinese are warranted.

Estimated glomerular filtration rate (eGFR) calculated from serum–creatinine concentration is a convenient approach to assess patients' renal function, which is strongly associated with the occurrence and development of hypertensive target organ damage (TOD).[3–6] Current hypertension guidelines including the European Society of Hypertension/European Society of Cardiology guidelines advocate the estimation of glomerular filtration rate (GFR) from serum–creatinine concentrations as an effective approach to enhancing risk prediction.[6,7] For decades, the most commonly used eGFR equations were mainly established and validated in Caucasians, such as Cockcroft–Gault, Modification of Diet in Renal Disease (MDRD) and recently emerging Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[8–10] It was reported that Cockcroft–Gault equation is less accurate than the MDRD study equation in elderly people.[11–13] However, the MDRD equation underestimated the gold standard GFR in Asian population.[14] The CKD-EPI equation is the most recent equation established for estimating GFR, and the CKD-EPI creatinine equation appears to be more accurate than the MDRD equation, as the accuracy of the CKD-EPI equation is validated in various study populations and clinical conditions.[10] Moreover, in recent years, some investigators proposed and validated some Asian- or Chinese-modified eGFR equations, which might be more appropriate for Chinese.[15,16]

Nevertheless, which eGFR equation should be used for risk prediction in elderly Chinese is still under debate.[17] We have documented in the protocol that TOD, as an intermediate state between conventional risk factors (age, smoking, diabetes mellitus [DM]) and clinical events, may be a good marker for risk stratification in the elderly.[18,19] It might better represent exposure to risk factors than the risk factor itself.[20] To make risk assessment in an elderly participant, examining the associations between eGFR and preclinical TOD is essential, as well as dictating which equation to choose. A unique eGFR equation is essential to make the risk prediction and risk score calculation.

To date, there are no studies comparing the eGFR equations in their associations with preclinical TOD in elderly Chinese.[13] Therefore, based on the existing eGFR equations, we used data from the Northern Shanghai Study to investigate: whether eGFR calculated from newly established eGFR equations associates more strongly with the preclinical hypertensive TOD in a Chinese community-based elderly cohort.

Methods

Study design and participants

This analysis was nested in the Northern Shanghai Study (ClinicalTrials.gov Identifier: NCT02368938) under the registered name "Prognosis Factors of Mortality and Cardiovascular Diseases in the Elderly Chinese: the Northern Shanghai Study", which was a prospective, ongoing and multistage community-based study.[19] This study was approved by the Shanghai Tenth People's Hospital Institutional Review Board.

The study design was described in the protocol already.[19] Between June 2014 and August 2015, 1,721 subjects were invited, of whom 1,599 (92.9%) were enrolled. In 1,599 participants, 1,586 participants' serum creatinine concentrations were measured. Among these 1,586 participants, 1,579 (99%) had intima-media thickness (IMT), 1,553 (98%) had ankle–brachial index (ABI), 1,577 (99%) had left ventricular mass index (LVMI), 1,537 (97%) had urine albumin to creatinine ratio (UACR) and 1,533 (97%) had pulse wave velocity. All these 1,586 participants had basic anthropometric data, including body weight, body height and office blood pressure. Thus, the final sample size in our analysis was 1,586.

Social, anthropometric and biological parameters

As it was described already, information including sex, age, weight, and height, smoking habits, history of DM, hypertension, cardio- or cerebrovascular diseases and usage of medications was obtained from the questionnaire.[19] The venous blood and the urine sample were obtained in a fasting state in the morning. Blood creatinine was measured by enzymatic method.

Estimation of GFR

To estimate GFR, the MDRD study equation, the derived Chinese-abbreviated MDRD (c-aMDRD) equation, the CKD-EPI equation, the Asian-modified CKD-EPI (aCKD-EPI) equation and the Chinese-modified CKD-EPI (cCKD-EPI) equation were used.[8,10,13,15–17,21]

Measurements of hypertensive TOD

As previously described, carotid artery IMT was measured using the MyLab 30 Gold Cardiovascular System (Esaote SpA, Genoa, Italy) with a 7.5 MHz transducer.[19,22,23] Four-limb blood pressure of participants was measured with VP-1000 (Omron Healthcare, Kyoto, Japan). Carotid–femoral pulse wave velocity (cf-PWV), as a golden standard of arterial stiffness, was performed with applanation tonometry (SphygmoCor, AtCor Medical, Sydney, Australia) according to the European Expert Consensus on Arterial Stiffness.[24–26] The urine microalbumin to creatinine ratio was calculated from the urine sample test.

Statistical analysis

Baseline demographic and clinical characteristics were presented as mean ± standard deviation (SD) or median (interquartile range) for continuous variables and count (percentage) for categorical variables. Relations between eGFR and hypertensive TOD indicators were performed using multivariate regression analysis. Logistic regression analysis was performed to determine the independent relations between different equation-derived eGFRs and the hypertensive TOD. The SD of eGFR values was calculated respectively (Table S1). To adjust confounders, systolic blood pressure, smoking, body mass index (BMI), DM, low-density lipoprotein cholesterol (LDL-c), urinary albumin, serum calcium, serum phosphorus and hypertension duration were forced into the model. On the other hand, use of age and sex as adjustors for relations between eGFR and TOD, in which eGFR is also calculated from age and sex, would have resulted in adjustments for age and sex effects twice. Thus, we exclude age and sex from the confounders to avoid excessive computation. Maximum likelihood parameter estimates of odds ratios with 95% Wald confidence intervals were calculated. C-statistics were used to assess the discrimination abilities of adjusted logistic models (Table S2). Akaike information criterion was used to compare the goodness-of-fit among the different models (Table S3). The area under the curve (AUC) of the receiver operator characteristic (ROC) curves was used to indicate the detection value of eGFR equations. *Z*-test was used to compare the AUCs. Statistical analyses were performed using the SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA). The two-sided significant level of 5% was considered as the level of statistical significance.

Ethics approval

This study was approved by the Shanghai Tenth People's Hospital Institutional Review Board. All participants signed a consent form.

Results

Characteristics of the participants and investigated eGFR equations

Basic anthropometric data and associated disease conditions were available in 1,586 participants (Table 1), including conventional cardiovascular risk factors, asymptomatic hypertensive TOD, eGFR, diseases and treatment. The present elderly population had an average age of 72.7±6.0 years. Among these community-dwelling elderly, 44.58% (n=707) were male and 22.8% (n=362) were smokers, with an average BMI of 23.9±3.5 kg/m² and an average blood pressure of 134±18/79±9 mmHg (Table 1). Following the population sample condition, the overall hypertensive TOD conditions are listed (Table 1). The preliminary values of eGFRs (n=1,586) are listed in Table 1, and a different profile of eGFRs is also listed. A large proportions of participants with

Table 1 Characteristics of the community-based participants

Sample number (male), n (%)	1,586 (44.58)
Age (years)	72.7±6.0
BMI (kg/m²)	23.9±3.5
Brachial SBP/DBP (mmHg)	134±18/79±9
Smoking, n (%)	362 (22.8)
TODs	
LVMI (g/m²)	89.96±28.55
LVH %	27.5
Aortic PWV (m/s)	9.41±2.31
Increased aortic PWV %	32.4
IMT (mm)	0.61±0.15
Increased IMT %	4.1
LABI	1.04±0.13
Low ABI %	18.9
UACR (mg/g)	54.9±181.9
Microalbuminuria %	38.7
eGFR, n=1,586	
MDRD	84.02±20.56
c-aMDRD	92.45±24.49
CKD-EPI	78.18±14.26
aCKD-EPI	93.04±18.03
cCKD-EPI	76.31±14.92
Diseases and treatments, n=1,586	
DM, n (%)	310 (19.6)
Hypertensive patients, n (%)	834 (52.6)
Antihypertensive treatment, n (%)	791 (49.9)
Stage 2 CKD, n (%)	904 (57.0)
Stage 3 or more CKD, n (%)	134 (8.5)

Notes: Continuous variables are shown as mean ± SD or median (interquartile range) as appropriate. Stage 2 CKD: eGFR 60–89 mL/min/1.73 m² (MDRD) and stage 3 or more CKD: eGFR <60 mL/min/1.73 m² (MDRD).
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TOD, target organ damage; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; PWV, pulse wave velocity; IMT, intima–media thickness; LABI, left ankle brachial index; ABI, ankle–brachial index; UACR, urine albumin to creatinine ratio; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; c-aMDRD, Chinese-abbreviated MDRD; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; aCKD-EPI, Asian-modified CKD-EPI; cCKD-EPI, Chinese-modified CKD-EPI; DM, diabetes mellitus; SD, standard deviation; CKD, chronic kidney disease.

hypertension (52.6%, n=834) and stage 2 CKD (57%, n=904) are also described (Table 1). The original studies from which the eGFR equation was derived are listed in Table S4.

Relations between equation-derived eGFRs and preclinical hypertensive TOD

As shown in Table 2, eGFRs calculated from all the equations were inversely associated with cf-PWV and positively associated with ABI after adjusting confounders ($P<0.001$). eGFRs from CKD-EPI, aCKD-EPI and cCKD-EPI equations were inversely associated with LVMI ($P<0.05$). eGFRs from the CKD-EPI equation were significantly associated with UACR (β=−0.06, P=0.01). As for IMT, after adjustment, only eGFRs calculated from the aCKD-EPI equation were significantly associated with IMT (β=−0.07, P=0.005; Table 2). Crude linear regression results were consistent with it and are shown in Table S5 (β=−0.10, $P<0.001$ and β=−0.08, P=0.002 for aCKD-EPI and cCKD-EPI, respectively).

eGFRs and occurrence of carotid hypertrophy

For carotid hypertrophy (IMT $\geq$0.9 mm), decreased eGFRs from all the equations failed to show an independent association with carotid hypertrophy (all $P>0.05$; Table 3). However, eGFRs calculated from aCKD-EPI and cCKD-EPI equations showed a good performance in associations with increased IMT (both $P<0.05$ versus AUC =0.5, Figure 1Ai). Especially for the eGFR from cCKD-EPI, it had a better performance than the other equations (except for aCKD-EPI) in distinguishing carotid hypertrophy ($P<0.05$ versus AUC of other equations except for aCKD-EPI; Figure 1Ai and Aii).

eGFRs and occurrence of lower limb atherosclerosis

For lower limb atherosclerosis, which was characterized with a lower ABI ($\leq$0.9), decreased eGFRs calculated from

all the equations were independently associated with lower limb atherosclerosis (all $P<0.001$; Table 3). Moreover, eGFR from all the equations showed a good performance in associations with lower limb atherosclerosis ($P<0.05$ to $P<0.001$ versus AUC =0.5; Figure 1Bi). Especially, the eGFR from cCKD-EPI showed a better association with lower limb atherosclerosis than eGFRs from other equations except for aCKD-EPI ($P<0.05$ versus AUC of other equations except for aCKD-EPI; Figure 1Bi and Bii).

eGFRs and occurrence of cardiac hypertrophy

For left ventricular hypertrophy, the increased eGFRs from aCKD-EPI and cCKD-EPI equations were independently associated with cardiac hypertrophy (P=0.016 and P=0.045 for aCKD-EPI and cCKD-EPI, respectively). Moreover, only eGFRs from aCKD-EPI and cCKD-EPI equations showed a good performance for the detection of LVH (both P=0.002 versus AUC =0.05; Figure 1Ci and Cii).

eGFRs and occurrence of microalbuminuria

For microalbuminuria, which was defined as an increased UACR ($>$30 mg/g), decrease in eGFRs calculated from all the equations was independently associated with the occurrence of microalbuminuria after confounders were adjusted (P=0.02 to $P<0.001$; Table 3). The eGFRs from all the equations showed a good performance in distinguishing the occurrence of microalbuminuria ($P<0.001$ versus AUC =0.5; Figure 1Di). However, no significant differences in detection value were found within these equations (Figure 1Di and Dii).

eGFRs and occurrence of arterial stiffening

For the arterial stiffening, which was defined as pulse wave velocity (PWV) $>$10 m/s, decrease in eGFRs calculated

Table 2 Relations between equation-eGFR and cardiovascular TOD indicators

Equations	IMT (n=1,579)		ABI (n=1,553)		LVMI (n=1,577)		UACR (n=1,537)		Aortic PWV (n=1,533)	
	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
MDRD	0.001	0.95	0.12	<0.001	−0.05	0.07	−0.04	0.09	−0.14	<0.001
CKD-EPI	−0.02	0.42	0.16	<0.001	−0.06	0.01	−0.06	0.01	−0.20	<0.001
aCKD-EPI	−0.07	0.005	0.12	<0.001	−0.06	0.02	−0.03	0.30	−0.17	<0.001
cCKD-EPI	−0.05	0.07	0.11	<0.001	−0.06	0.02	−0.03	0.28	−0.16	<0.001
c-aMDRD	−0.01	0.78	0.11	<0.001	−0.05	0.06	−0.03	0.17	−0.13	<0.001

Note: Adjusted confounders: SBP, smoking, BMI, DM, LDL-c, urinary albumin, serum calcium, serum phosphorus and hypertension duration.
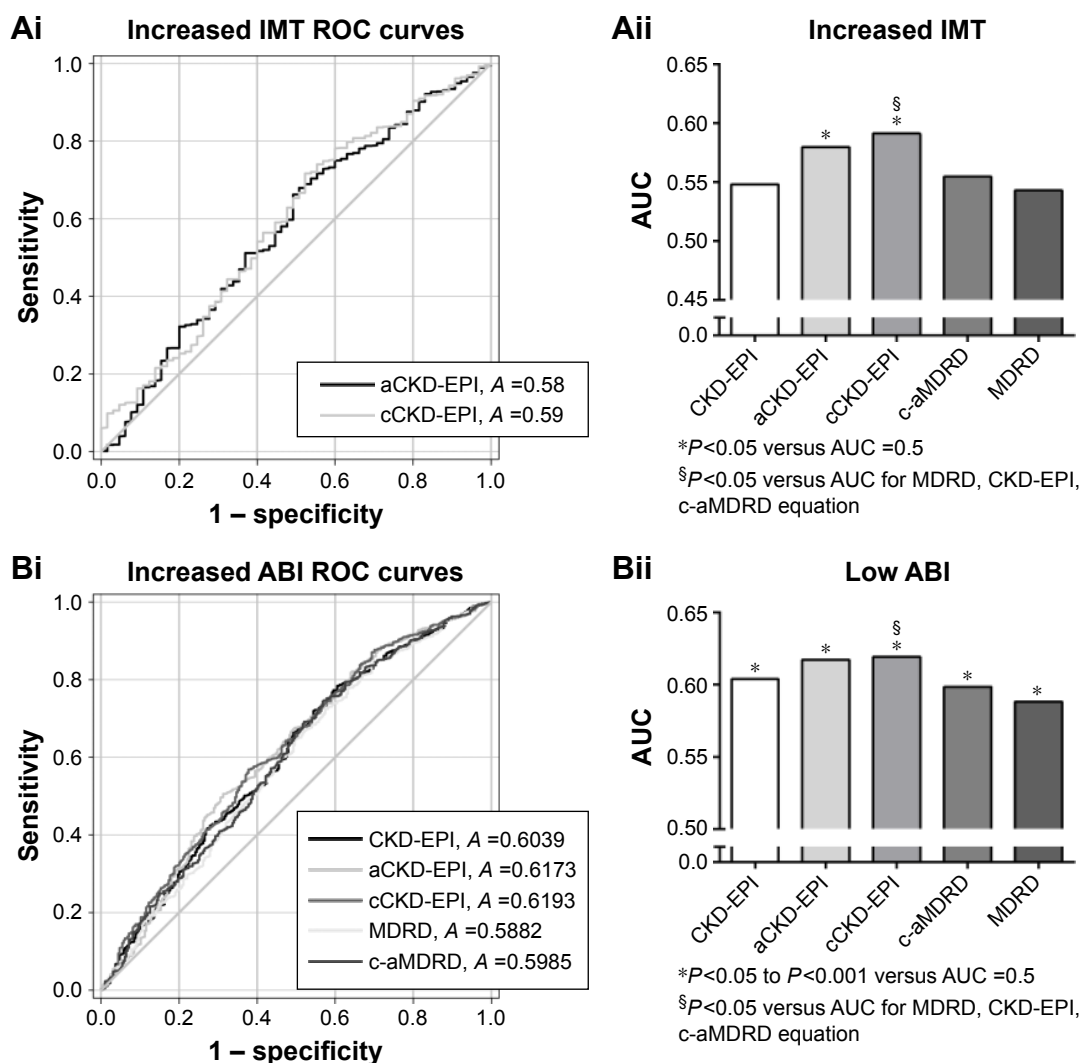**Abbreviations:** eGFR, estimated glomerular filtration rate; TOD, target organ damage; IMT, intima–media thickness; ABI, ankle–brachial index; LVMI, left ventricular mass index; UACR, urine albumin to creatinine ratio; PWV, pulse wave velocity; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; aCKD-EPI, Asian-modified CKD-EPI; cCKD-EPI, Chinese-modified CKD-EPI; c-aMDRD, Chinese-abbreviated MDRD; SBP, systolic blood pressure; BMI, body mass index; DM, diabetes mellitus; LDL-c, low-density lipoprotein cholesterol.

Table 3 The performance (adjusted logistic regression) of different eGFRs to detect the cardiovascular TODs with a specific number of each assessment

Total (n=1,586)	Carotid hypertrophy (n=1,579)		Lower limb atherosclerosis (n=1,553)		Cardiac hypertrophy (n=1,577)		Macro-albuminuria (n=1,537)		Arterial stiffening (n=1,533)	
Equations	OR*	P-value	OR*	P-value	OR*	P-value	OR*	P-value	OR*	P-value
MDRD	1.15 (0.86–1.55)	0.35	1.52 (1.30–1.78)	<0.001	1.09 (0.96–1.24)	0.19	1.83 (1.26–2.67)	0.002	1.49 (1.30–1.71)	<0.001
CKD-EPI	1.12 (0.87–1.43)	0.38	1.51 (1.33–1.71)	<0.001	1.07 (0.95–1.20)	0.27	1.71 (1.29–2.27)	<0.001	1.55 (1.38–1.75)	<0.001
aCKD-EPI	1.19 (0.91–1.55)	0.20	1.52 (1.32–1.74)	<0.001	1.17 (1.03–1.32)	0.016	1.59 (1.18–2.16)	0.003	1.48 (1.30–1.68)	<0.001
cCKD-EPI	1.26 (0.94–1.69)	0.13	1.56 (1.34–1.82)	<0.001	1.13 (1.00–1.28)	0.045	1.53 (1.07–2.19)	0.02	1.52 (1.34–1.73)	<0.001
c-aMDRD	1.17 (0.87–1.59)	0.30	1.56 (1.32–1.83)	<0.001	1.02 (0.90–1.16)	0.74	1.77 (1.21–2.60)	0.003	1.47 (1.28–1.69)	<0.001

Notes: Odds ratio is presented as OR (95%CI). *Indicating per 1 SD decrease in eGFR. Adjusted confounders: systolic blood pressure, smoking, BMI, DM, LDL-c, urinary albumin, serum calcium, serum phosphorus and hypertension duration. Considering an increased IMT (IMT ≥0.9 mm) as carotid hypertrophy, a lower ABI (≤0.9) as lower limb atherosclerosis, left ventricular hypertrophy (>115 g/m² for male and >95 g/m² for female) as cardiac hypertrophy, an increased UACR (>30 mg/g) as micro-albuminuria and an increased PWV (>10 m/s) as arterial stiffening.
Abbreviations: BMI, body mass index; TOD, target organ damage; PWV, pulse wave velocity; IMT, intima–media thickness; ABI, ankle–brachial index; UACR, urine albumin to creatinine ratio; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; c-aMDRD, Chinese-abbreviated MDRD; aCKD-EPI, Asian-modified CKD-EPI; cCKD-EPI, Chinese-modified CKD-EPI; DM, diabetes mellitus; SD, standard deviation; LDL-c, low-density lipoprotein cholesterol.

Ai Increased IMT ROC curves

aCKD-EPI, *A* =0.58
cCKD-EPI, *A* =0.59

Aii Increased IMT

*P<0.05 versus AUC =0.5
§P<0.05 versus AUC for MDRD, CKD-EPI, c-aMDRD equation

Bi Increased ABI ROC curves

CKD-EPI, *A* =0.6039
aCKD-EPI, *A* =0.6173
cCKD-EPI, *A* =0.6193
MDRD, *A* =0.5882
c-aMDRD, *A* =0.5985

Bii Low ABI

*P<0.05 to P<0.001 versus AUC =0.5
§P<0.05 versus AUC for MDRD, CKD-EPI, c-aMDRD equation
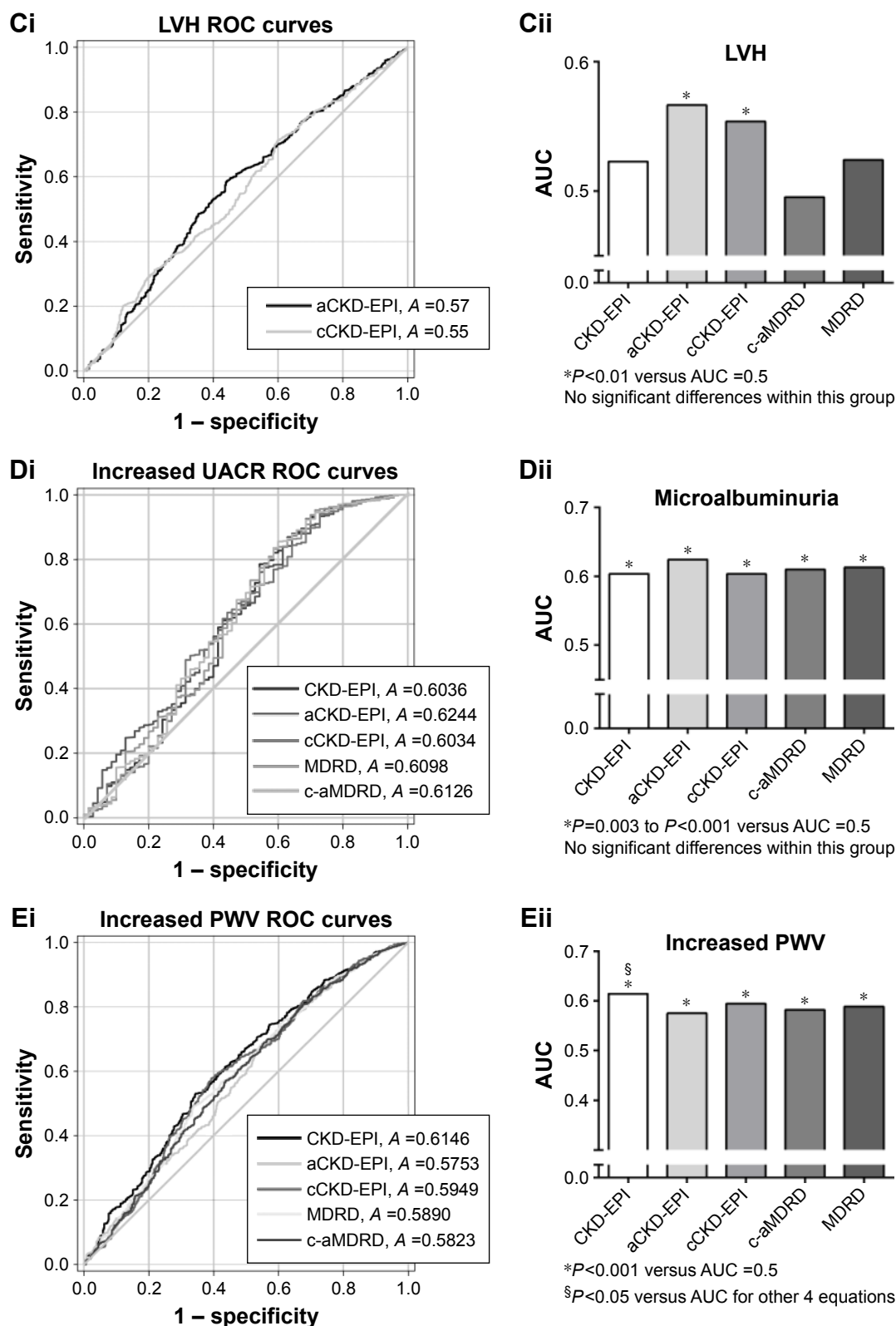
Figure 1 (*Continued*)

Figure 1 The performance (AUC of the ROC curve) of different eGFRs to detect specific cardiovascular TOD.

Notes: Only $P<0.05$ versus AUC =0.5 of the eGFR equations are shown in the ROC curves. On the left panel (**Ai, Bi, Ci, Di, Ei**), only eGFR equations with $P<0.05$ versus AUC =0.5 are presented in the ROC curves. On the right panel (**Aii, Bii, Cii, Dii, Eii**), AUCs of different eGFR equations are presented as histograms of different gray levels. The abbreviation for each equation is under the *x*-axis. The significance is presented at bottom.

Abbreviations: AUC, area under the curve; ROC, receiver operator characteristic; eGFR, estimated glomerular filtration rate; TOD, target organ damage; IMT, intima-media thickness; aCKD-EPI, Asian-modified CKD-EPI; cCKD-EPI, Chinese-modified CKD-EPI; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; c-aMDRD, Chinese-abbreviated MDRD; MDRD, Modification of Diet in Renal Disease; ABI, ankle–brachial index; LVH, left ventricular hypertrophy; UACR, urine albumin to creatinine ratio; PWV, pulse wave velocity.

from all the equations was independently associated with arterial stiffening ($P<0.001$; Table 3). The eGFRs from all the equations had a good performance in detecting increased PWV ($P<0.001$ versus AUC =0.5; Figure 1Ei), especially eGFRs from the CKD-EPI equation ($P<0.05$ versus AUC of other four equations; Figure 1Ei and Eii).

Performances of the model from a specific eGFR equation to detect different TODs

The discriminatory properties of the adjusted logistic model depended on the choice of TOD and the equation to calculate eGFR (Table S2). To detect the listed cardiovascular TOD, all the logistic models in which the eGFRs were calculated from different equations showed moderate predictive ability for the discrimination of TOD (C-statistics from 0.613 [95% CI, 0.536–0.690] to 0.747 [95% CI, 0.667–0.828]). There is a trend that the model had a better performance in detecting microalbuminuria and arterial stiffening (C statistics from 0.707 [95% CI, 0.680–0.734] to 0.747 [95% CI, 0.667–0.828]). Under most conditions, the goodness-of-fit among the different models showed no significant differences. In particular, eGFRs from the CKD-EPI equation showed the best goodness-of-fit among the different models compared with eGFRs from other equations (Table S3).

Figure 2 shows a preliminary performance summary of eGFRs to detect TOD, classified by a specific equation. The eGFRs from aCKD-EPI and cCKD-EPI equations have a good performance for the detection of all the listed hypertensive TOD (Figure 2D and E). The eGFRs from other three equations failed to distinguish cardiac hypertrophy and carotid hypertrophy (Figure 2A–C).

Discussion
Summary of findings

The Northern Shanghai Study is one of the largest ongoing prospective population study in 1,599 community-dwelling elderly Chinese, and it was authorized and municipal funded with prior registration. In the present analysis, we identified that eGFRs from aCKD-EPI and cCKD-EPI have a better linear dependence with IMT. By ROC analysis, the aCKD-EPI and cCKD-EPI showed a better performance for the detection of the listed hypertensive TOD. Therefore, eGFRs from aCKD-EPI and cCKD-EPI equations were better associated with hypertensive TOD compared with other eGFR equations. aCKD-EPI and cCKD-EPI equations may be more helpful for risk stratification.

eGFRs and hypertensive TOD in the previous studies

As mentioned earlier, CKD affects a large part of the aging population, which has a considerable prevalence of TOD. The associations between eGFR and other TOD have been widely investigated in previous studies and in our analysis, including cf-PWV, UACR, ABI, IMT and LVH.

In our analysis, decreased eGFRs calculated from all the equations were significantly associated with arterial stiffening (increased cf-PWV). This result was consistent with the Health Aging and Body Composition (ABC) study. In the Health ABC study, which consisted of 2,129 elderly adults, PWV was associated with a rapid decline in renal function over a median of 8.9 years (incident rate ratio [IRR], 95% CI, 1.39, 1.09–1.77). ABC investigators emphasized the adjustment for blood pressure (BP), and we also adjusted BP in our analysis.[27]

As for UACR, the association of reduced eGFR and increased albumin to creatinine ratio (ACR) was consistent with previous studies. Reduced eGFR and increased ACR are always accompanied by each other and are also consistent in a trend of risk prediction.[28,29]

Previous studies also proved that low ABI was associated with the decline in eGFR calculated from CKD-EPI equation. In a prospective cohort study consisting of 2,592 participants from the Framingham Offspring cohort, investigators found that, compared to normal ABI, low ABI was associated with 5.73-fold increased odds of rapid eGFR decline (95% CI, 2.77–11.85; $P<0.001$).[30] This trend was also consistent with our results.

On the other hand, investigators revealed that for a general community population of 3,629 participants, reduced eGFR calculated from CKD-EPI-derived equations was independently associated with carotid artery thickening. The odds ratio for increased IMT was 1.299 (95% CI, 1.062–1.588).[31] This result was in line with our finding when taking the community elderly population of our analysis into account.

As for LVH, it was positively associated with renal function decline. Furthermore, in a retrospective study consisting of 300 in- and outpatients, Chinese investigators found that renal function decline (calculated from CKD-EPI) would contribute to pathological LVH in the elderly.[3] Their finding suggests that LVH is associated with reduced eGFR calculated from the CKD-EPI equation. This conclusion was in accordance with the trend in our analysis.

Possible reasons for the better associations between equations and TOD

Our results suggested that the aCKD-EPI equation and cCKD-EPI equation were associated better with hypertensive
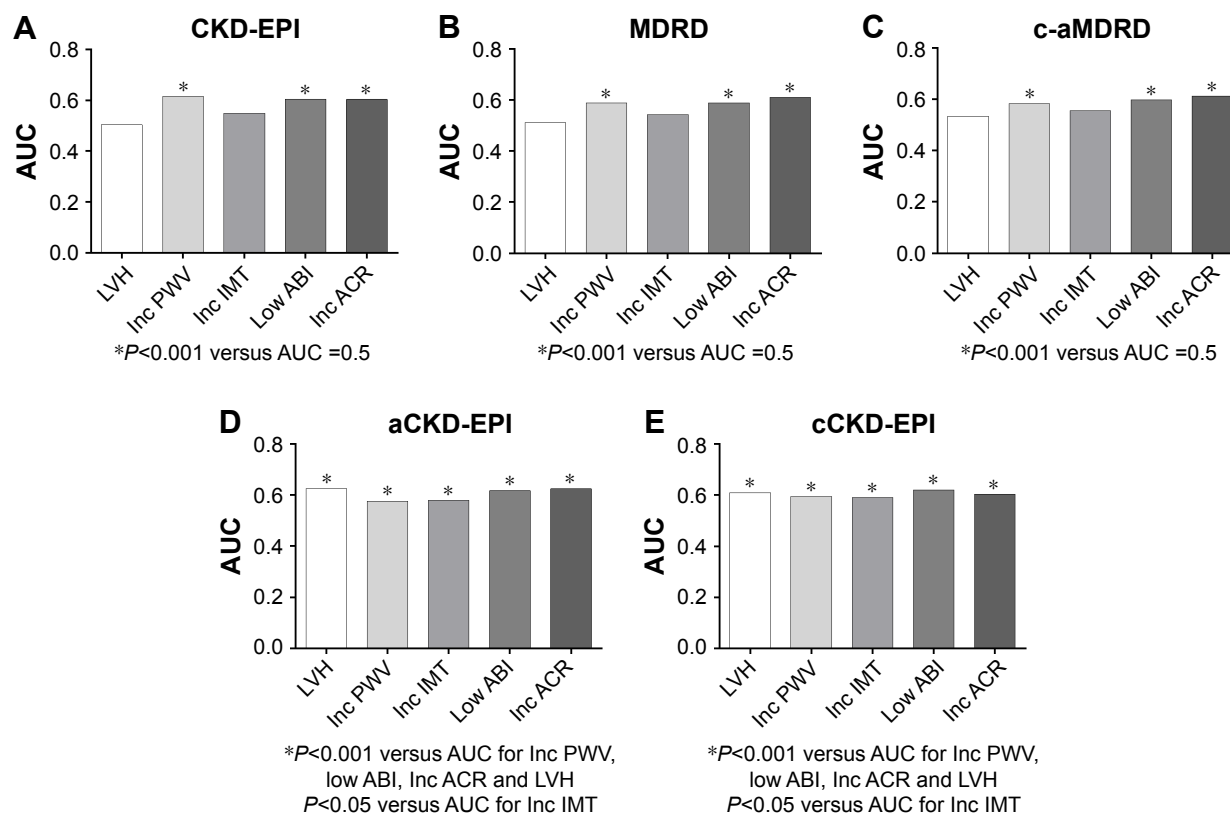
Figure 2 The performance (AUC of the ROC curve) of eGFRs from a specific equation to detect a series of cardiovascular TOD.
Notes: (**A–C**) eGFRs (calculated from CKD-EPI, MDRD and c-aMDRD equations) versus AUC =0.5 have statistical differences with PWV, ABI and UACR. (**D** and **E**) The AUCs of eGFR (calculated from aCKD-EPI and cCKD-EPI equations) versus AUC =0.5 have statistical differences with all the listed hypertensive TOD. AUCs were classified by each eGFR equation. AUCs of different TODs are presented as histograms of different colors. The abbreviation for each TOD is under the x-axis. The significance is presented at bottom.
Abbreviations: AUC, area under the curve; ROC, receiver operator characteristic; eGFR, estimated glomerular filtration rate; TOD, target organ damage; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; c-aMDRD, Chinese-abbreviated MDRD; PWV, pulse wave velocity; ABI, ankle–brachial index; UACR, urine albumin to creatinine ratio; aCKD-EPI, Asian-modified CKD-EPI; cCKD-EPI, Chinese-modified CKD-EPI; LVH, left ventricular hypertrophy; IMT, intima-media thickness; ACR, albumin to creatinine ratio.

TOD than the other equations in the elderly Chinese community-dwelling population. Such associations have some underlying reasons.

The superiority of CKD-EPI equation-derived eGFR in detecting an increased PWV and left ventricular hypertrophy has been validated. The investigators argued more on the associations between the MDRD equation and the CKD-EPI equation.[32] Especially, the four-level ethnicity CKD-EPI equation significantly decreased bias in Asians, including Chinese, although the original CKD-EPI equation may not be accurate for Asians.[15,33] Thus, in the four-level ethnicity CKD-EPI equation, the aCKD-EPI equation may be more accurate for elderly Chinese.

In terms of the detection value of eGFR, age and race are important factors that should be considered, as age and race played a vital role in the eGFR calculation. The superiority of cCKD-EPI to detect the elderly's TOD may come from the influence of the population's age profile. The population from which the cCKD-EPI was derived had an average age

of 61±12.7 years, and our target population had an average age of 72.7±6.0 years, both of which were >60 years old. Although the populations of other equations also had elderly participants, the average age was relatively younger. Thus, from the age point of view, the population of the cCKD-EPI study was the most adjacent one to our investigated population (Table S4).

These associations may also come from the influence of the population's race. Our target population is community-based elderly Chinese. The cCKD-EPI study has a population of Chinese. The validation cohort of aCKD-EPI equation consisted of 675 Chinese and 248 Japanese, which means that the majority of the cohort is Chinese. Therefore, from the race point of view, the populations from which the aCKD-EPI and cCKD-EPI were derived were adjacent to our community-dwelling population (Table S4). Furthermore, both coefficients of these two equations were calculated from the local population. A previous study revealed that adjusting a coefficient based on the local population

would improve their accuracy.[33] Thus, these associations of these two equations in detecting hypertensive TOD may come from the adjusted coefficients based on the local population.

Strengths and limitations

The present analysis has several strengths. First, this study is the first study comparing the eGFR equations in their associations with preclinical TOD in elderly Chinese. Second, we had a good population consistency of various measurements. We analyzed five major hypertensive TOD in >97% (97%–99%) of the final 1,586 participants in our analysis. There are also limitations in this study. First, in this study, the serum creatinine concentrations were measured by the enzymatic method, so that we excluded the Cockcroft–Gault equation, which is based on the Jaffe method. Second, our target was to compare the associations between equation-derived eGFRs and TOD; we did not have the data of GFR from inulin clearance. Thus, the superiority is only for the associations with preclinical TOD. Finally, in this study, we should avoid overinterpretation of the present data as the present analysis was cross-sectional in nature; the ROC curves were not particularly impressive. Additionally, a limited number of participants had clinically significant increases in IMT (n=65, 4.12% of the total 1,586 participants). Therefore, future longitudinal analysis and a clinical sample with a high prevalence of TOD are required.

Conclusion

Considering that TOD is a good marker for risk stratification in the elderly, by showing that Chinese specific CKD-EPI equation derived eGFRs were associated better with 5 major preclinical TOD, cCKD-EPI equation and aCKD-EPI equation are more helpful for risk stratification. Future studies may give attention to the detection value of eGFR for future cardiovascular events. And prior interventions and managements for renal diseases in the elderly should also be considered.

Acknowledgments

Author contributions

Hongwei Ji, Han Zhang, Jing Xiong, Shikai Yu, Chen Chi and Jue Li acquired the original data for this study. Jacques Blacher, Yi Zhang and Yawei Xu formulated the methods and designed the protocol. Hongwei Ji and Han Zhang drafted the manuscript. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 The respectively calculated SDs of eGFR values for the logistic regression

Total (n=1,586) Equations	IMT (n=1,579) SD	ABI (n=1,553) SD	LVMI (n=1,577) SD	UACR (n=1,537) SD	Aortic PWV (n=1,533) SD
MDRD	20.5683668	20.5557993	20.5548362	20.4855702	20.5961544
CKD-EPI	14.2426876	14.2090751	14.2406751	14.1873433	14.1307789
aCKD-EPI	18.0208154	18.0347565	18.0355388	17.9665128	17.9131654
cCKD-EPI	14.9272658	14.9582379	14.9289286	14.8616948	14.9174066
c-aMDRD	24.4979976	24.5138248	24.4881662	24.3729941	24.5445129

Abbreviations: SD, standard deviation; eGFR, estimated glomerular filtration rate; IMT, intima–media thickness; ABI, ankle–brachial index; LVMI, left ventricular mass index; UACR, urine albumin to creatinine ratio; PWV, pulse wave velocity; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; aCKD-EPI, Asian-modified CKD-EPI; cCKD-EPI, Chinese-modified CKD-EPI; c-aMDRD, Chinese-abbreviated MDRD.

Table S2 Assessment of the discrimination abilities of adjusted logistic models to detect the cardiovascular TOD

Total (n=1,586) Equations	Carotid hypertrophy (n=1,579) C-statistic (95% CI)	P-value	Lower limb atherosclerosis (n=1,553) C-statistic (95% CI)	P-value	Cardiac hypertrophy (n=1,577) C-statistic (95% CI)	P-value	Microalbuminuria (n=1,537) C-statistic (95% CI)	P-value	Arterial stiffening (n=1,533) C-statistic (95% CI)	P-value
MDRD	0.618 (0.543, 0.693)	<0.001	0.640 (0.604, 0.676)	<0.001	0.685 (0.656, 0.713)	<0.001	0.738 (0.657, 0.819)	<0.001	0.709 (0.682, 0.736)	<0.001
CKD-EPI	0.613 (0.536, 0.690)	0.002	0.647 (0.611, 0.682)	<0.001	0.686 (0.657, 0.714)	<0.001	0.747 (0.667, 0.828)	<0.001	0.723 (0.696, 0.749)	<0.001
aCKD-EPI	0.615 (0.538, 0.692)	0.002	0.647 (0.612, 0.681)	<0.001	0.685 (0.656, 0.713)	<0.001	0.729 (0.646, 0.812)	<0.001	0.707 (0.680, 0.734)	<0.001
cCKD-EPI	0.624 (0.550, 0.699)	<0.001	0.649 (0.614, 0.684)	<0.001	0.685 (0.656, 0.714)	<0.001	0.724 (0.643, 0.805)	<0.001	0.713 (0.685, 0.740)	<0.001
c-aMDRD	0.620 (0.545, 0.694)	<0.001	0.644 (0.608, 0.680)	<0.001	0.685 (0.656, 0.713)	<0.001	0.736 (0.654, 0.817)	<0.001	0.707 (0.680, 0.734)	<0.001

Notes: Adjusted confounders: SBP, smoking, BMI and DM for carotid hypertrophy, lower limb atherosclerosis, microalbuminuria and arterial stiffening and sex, SBP, smoking, BMI and DM for cardiac hypertrophy. Considering an increased IMT (IMT $\geq$0.9 mm) as carotid hypertrophy, a lower ABI ($\leq$0.9) as lower limb atherosclerosis, left ventricular hypertrophy ($>$115 g/m^2 for males and $>$95 g/m^2 for females) as cardiac hypertrophy, an increased UACR ($>$30 mg/g) as microalbuminuria and an increased PWV ($>$10 m/s) as arterial stiffening.
Abbreviations: TOD, target organ damage; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; aCKD-EPI, Asian-modified CKD-EPI; cCKD-EPI, Chinese-modified CKD-EPI; c-aMDRD, Chinese-abbreviated MDRD; SBP, systolic blood pressure; BMI, body mass index; DM, diabetes mellitus; IMT, intima–media thickness; ABI, ankle–brachial index; UACR, urine albumin to creatinine ratio; PWV, pulse wave velocity.

Table S3 Goodness-of-fit among the different models

Total (n=1,586) Equations	Carotid hypertrophy (n=1,579) AIC	P-value	Lower limb atherosclerosis (n=1,553) AIC	P-value	Cardiac hypertrophy (n=1,577) AIC	P-value	Microalbuminuria (n=1,537) AIC	P-value	Arterial stiffening (n=1,533) AIC	P-value
MDRD	521.247	ns	1,421.704	<0.01	1,736.528	ns	302.080	ns	1,711.694	<0.01
CKD-EPI	521.392	ns	1,411.528	Reference	1,737.047	ns	299.038	Reference	1,690.964	Reference
aCKD-EPI	520.530	ns	1,415.310	ns	1,732.407	Reference	303.961	ns	1,707.235	<0.01
cCKD-EPI	519.782	Reference	1,415.070	ns	1,734.270	ns	306.967	0.02	1,701.476	<0.01
c-aMDRD	521.030	ns	1,419.735	0.02	1,738.172	ns	303.390	ns	1,713.643	<0.01

Abbreviations: AIC, Akaike information criterion; MDRD, Modification of Diet in Renal Disease; ns, not significant; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; aCKD-EPI, Asian-modified CKD-EPI; cCKD-EPI, Chinese-modified CKD-EPI; c-aMDRD, Chinese-abbreviated MDRD.

Table S4 List of the eGFR equations in our study

Equations	eGFR (mL/min/1.73 m^2)	Participant	Race	Reference
MDRD	$186\times Scr^{-1.154}\times age^{-0.203}\times 0.742$ (if female) $\times 1.212$ (if black)	Middle aged CKD patients Age =50.6±12.7 years[1]	Black and White	Group TMoDiRDS[2]
c-aMDRD	$175\times Scr^{-1.234}\times age^{-0.179}\times 0.79$ (if female)	Middle aged CKD patients Age =49.9±15.8 years	Chinese	Collaboration Cel[3]
CKD-EPI	Female & Scr ≤0.7: 144 (166 if black) $\times (Scr/0.7)^{-0.329}\times (0.993)^{age}$ Female & Scr >0.7: 144 (166 if black) $\times (Scr/0.7)^{-1.209}\times (0.993)^{age}$ Male & Scr ≤0.9: 141 (163 if black) $\times (Scr/0.9)^{-0.411}\times (0.993)^{age}$ Male & Scr >0.9: 141 (163 if black) $\times (Scr/0.9)^{-1.209}\times (0.993)^{age}$	Middle aged CKD patients Age =47±15 years	Black and White or other	Levey et al[4]
aCKD-EPI	Female & Scr ≤0.7: $151\times (Scr/0.7)^{-0.328}\times (0.993)^{age}$ Female & Scr >0.7: $151\times (Scr/0.7)^{-1.210}\times (0.993)^{age}$ Male & Scr ≤0.9: $149\times (Scr/0.9)^{-0.412}\times (0.993)^{age}$ Male & Scr >0.9: $149\times (Scr/0.9)^{-1.210}\times (0.993)^{age}$	Middle aged CKD patients Age =49±15 years	Asian (675 Chinese and 248 Japanese)	Stevens et al[5]
cCKD-EPI	Female & Scr ≤0.7: $94\times (Scr/0.7)^{-0.511}\times (0.998)^{age}$ Female & Scr >0.7: $128\times (Scr/0.7)^{-0.543}\times (0.992)^{age}$ Male & Scr ≤0.9: $117\times (Scr/0.9)^{-0.277}\times (0.994)^{age}$ Male & Scr >0.9: $102\times (Scr/0.9)^{-0.558}\times (0.994)^{age}$	T2DM CKD patients Age =61.0±12.7 years	Chinese	Liu et al[6]

Abbreviations: eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD, chronic kidney disease; c-aMDRD, Chinese-abbreviated MDRD; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; aCKD-EPI, Asian-modified CKD-EPI; cCKD-EPI, Chinese-modified CKD-EPI.

Table S5 Crude relations between equation-eGFR and cardiovascular TOD indicators

Equations	IMT (n=1,579)		ABI (n=1,553)		LVMI (n=1,577)		UACR (n=1,537)		Aortic PWV (n=1,533)	
	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
MDRD	−0.005	0.84	0.11	<0.001	−0.06	0.01	−0.07	0.004	−0.15	<0.001
CKD-EPI	−0.03	0.19	0.15	<0.001	−0.09	<0.001	−0.11	<0.001	−0.22	<0.001
aCKD-EPI	−0.10	<0.001	0.12	<0.001	−0.09	<0.001	−0.07	0.005	−0.17	<0.001
cCKD-EPI	−0.08	0.002	0.10	<0.001	−0.07	0.003	−0.06	0.03	−0.15	<0.001
c-aMDRD	−0.02	0.41	0.10	<0.001	−0.06	0.01	−0.07	0.009	−0.13	<0.001

Note: Crude linear regression was performed without adjustment.
Abbreviations: eGFR, estimated glomerular filtration rate; TOD, target organ damage; IMT, intima-media thickness; ABI, ankle–brachial index; LVMI, left ventricular mass index; UACR, urine albumin to creatinine ratio; PWV, pulse wave velocity; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; aCKD-EPI, Asian-modified CKD-EPI; cCKD-EPI, Chinese-modified CKD-EPI; c-aMDRD, Chinese-abbreviated MDRD.

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