

# Comparative Performance of Creatinine-Based GFR Estimation Equations in Exceptional Longevity: The Rugao Longevity and Ageing Study

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**Purpose:** Reduced kidney function has been associated with an increased risk for adverse outcomes. Accurate assessment of glomerular filtration rate (GFR) is key to diagnosis and management of kidney dysfunction. Debate exists on the best GFR estimation equation for elderly people. This study aimed to compare the predictive validity and discriminative ability of four GFR equations in relation to 2-year and 6-year mortality in exceptional longevity (EL) (those over 95 years old with intact health) individuals and is an ideal model to address factors relating to life span and age-related diseases.

**Patients and Methods:** This study used 6 years' data of 278 EL from the Rugao longevity cohort. Baseline GFR was estimated using four equations: Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, Modification of Diet in Renal Disease Study (MDRD) equation, Berlin Initiative Study-1 (BIS) equation, and modified MDRD equation. Predictive validity was tested using Cox proportional hazards analysis. Overall improvement in reclassification based on estimated GFR (eGFR) was assessed applying net reclassification improvement (NRI).

**Results:** Mean age of participants was 97±2 years with median follow-up of 2.6 years. Median (IQR) eGFR by CKD-EPI, MDRD, BIS, and modified MDRD equations were 73.9 (62.2–77.6), 82.3 (67.4–98.6), 56.4 (47.9–63.9), and 101.5 (83.1–121.6) mL/min per 1.73 m<sup>2</sup>, respectively. Higher eGFR<sub>EPI</sub> was associated with lower mortality after multivariate adjustment (for continuous eGFR<sub>EPI</sub>, HR<sub>two-year</sub> 1.018, 95% CI 1.002–1.033, *P*=0.023; HR<sub>six-year</sub> 1.013, 95% CI 1.002–1.025, *P*=0.022), while eGFR from other equations did not show any associations with mortality. NRI for two-year mortality was 0.14 and approximately significant, which may favor the CKD-EPI when compared to BIS equation (*P*=0.052).

**Conclusion:** The CKD-EPI equation showed more accurate estimation of kidney function in the elderly with respect to GFR distribution and predictability of mortality risk.

**Keywords:** glomerular filtration rate, kidney function, equation, exceptional longevity, mortality

## Introduction

Over the past two decades, China's population has been aging rapidly. The population aged over 80 years has reached 23 million.<sup>1</sup> According to Centers for Disease Control and prevention (CDC) of the US, of those born in the year 2000, at least 15% of men and 20% of women are projected to reach the age of 90 years, presenting a major challenge for health care systems.<sup>2,3</sup> Older adults suffer high rates of reduced kidney function which may occur as part of the normal ageing

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process or be related to comorbid disease.<sup>4,5</sup> Glomerular filtration rate (GFR) is the best measure of kidney function. It is reported that 62.2% of those aged 80 and older had GFR < 60 mL/min/1.73 m<sup>2</sup> in NHANES 1999–2002 surveys, and this prevalence of reduced GFR in the United States is still going to increase in future decades.<sup>6,7</sup>

Attention should be paid to GFR decrease in older individuals since reduced GFR has been associated with an increased risk for adverse outcomes including disability, cardiovascular disease (CVD), and mortality.<sup>8–12</sup> Thus, accurate GFR assessment is key to the diagnosis and management of kidney dysfunction. The real GFR can be directly measured by the clearance of exogenous filtration markers (eg, inulin and iothexol), however, due to inconvenience of this measurement, GFR is always estimated by a series of equations using serum creatinine which results in estimated GFR (eGFR). The eGFR in older patients is based on equations largely derived from young adults including Epidemiology Collaboration (CKD-EPI) equation and Modification of Diet in Renal Disease (MDRD) Study equation. There is a less frequently used Berlin Initiative Study (BIS) equation which was developed from older people, aged 70+ years.<sup>13–15</sup> Until now, debate has continued with regards to which equation is superior in elderly individuals (mostly 70 to 85 years old) based on comparison with gold standard measurements or based on mortality prediction.<sup>16–19</sup> The underlying reason for diverse results may be related to the population they used, either people admitted to hospital or the elderly in the community with different comorbidities.

Exceptional longevity refers to those who survive to an advanced old age (EL, 95 years old and over) with intact health or function. EL is an ideal model to address factors that are related to life span and age-related diseases and, therefore, targeted prevention and health promotion.<sup>20</sup> Thus in this study, we aimed to screen the best GFR estimation equation for the elderly by comparing the predictive validity and discriminative ability of four commonly used and creatinine-based equations: the CKD-EPI equation, the MDRD study equation, the BIS equation, and the modified MDRD equation in relation to short-term (two-year) and long-term (six-year) mortality using data from a prospective cohort of community-dwelling EL people and to further investigate the distribution of GFR in these individuals with healthy aging.<sup>20,21</sup>

## Materials and Methods

### Study Population

We extracted, refined, and examined data from 278 long-lived individuals enrolled in the Rugao longevity cohort, a population-based prospective study conducted between December 2007 and February 2008 in Rugao city of Jiangsu Province in China. Individuals in this study were followed through April, 2014.<sup>20</sup> Details regarding the cohort are provided elsewhere.<sup>20</sup> Briefly, after strict four-step age verifications, 705 persons aged over 95 years (149 men and 556 women) including 102 centenarians, were identified in Rugao city. Of them, 463 (103 men and 360 women) participants were recruited, with a response rate of 65.7%. No significant difference in age and gender was found between non-responders and responders according to a previous study of Rugao longevity cohort.<sup>22</sup> Of the 463 individuals, we excluded 177 individuals who had missing baseline data on serum creatinine; 7 individuals who were lost to follow-up, and 1 who was diagnosed with cancer during recruitment of the cohort ([Supplementary Figure S1](#)). Our final study population consisted of 278 EL individuals. This study was approved by the Human Ethics Committee of the School of Life Sciences of Fudan University, Shanghai, China. The ID number of the approval was 278. Written informed consent was obtained from each participant or a member of his or her immediate family prior to participation.

### Demographic, Clinical, and Laboratory Measures

A structured questionnaire was administered by trained field staff that delved into areas including demographic characteristics, histories of chronic disease (eg, cardiovascular disease, cerebrovascular disease, hypertension, chronic obstructive pulmonary disease, malignancy), functional status (measured by activities of daily living (ADL)), and medications. Physical examinations were also performed by the trained staff. All interviews were tape-recorded, and 5% of the recorded interviews were evaluated for interviewing quality.<sup>20</sup>

The Katz Index, which was based on six daily tasks: eating, dressing, bathing, indoor transferring, going to the toilet and cleaning oneself afterwards, was used to assess ADL in this study.<sup>23</sup> Each task has the following three response alternatives: strongly independent, somewhat dependent, and strongly dependent, with a score of 1, 2, and 3 points, respectively. Lower scores indicated better

functional status. Based on the total summed scores, a nominal variable with three categories of functional disability, “none” (total score=6), “moderate” (total score=7–9), “severe” (total score  $\geq 10$ ), was constructed.<sup>24</sup>

Fasting blood samples were drawn using uniform techniques for laboratory examination at recruitment for the study. All laboratory values were measured using Olympus AU5811 clinical chemistry analyzer (Tokyo, Japan) with standard laboratory techniques (performed by a technician in the biochemistry laboratory of Jiangsu Rugao Hospital of Traditional Chinese Medicine).

## Outcome Assessment

Dates of death were obtained through the Bureau of Civil Affairs of Rugao. Survival time (in months) was calculated from February 2008 to the date of death or of censoring on April 2014. The Bureau of Civil Affairs in Rugao is responsible for providing pensions for persons aged 80 years or over every month. The penalty for any family trying to conceal the death of an elderly family member is high.

## Estimation of GFR

Serum creatinine concentration was measured according to an enzymatic method with the Cica Creatinine reagent (KANTO Chemical, Tokyo, Japan) and Hitachi 7600 analyzer (Hitachi, Tokyo, Japan). We calculated eGFR using the following 4 equations:

1.  $eGFR_{MDRD} = 175 \times (\text{serum creatinine [mg/dL]})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female})^{25,26}$
2.  $eGFR_{EPI} = 144 \times (\text{serum creatinine [mg/dL]}/0.7)^{-0.329} \times (0.993)^{Age}$  if female and serum creatinine  $\leq 0.7$  or  $eGFR_{EPI} = 144 \times (\text{serum creatinine [mg/dL]}/0.7)^{-1.209} \times (0.993)^{Age}$  if female and serum creatinine  $> 0.7$  or  $eGFR_{EPI} = 141 \times (\text{serum creatinine [mg/dL]}/0.9)^{-0.411} \times (0.993)^{Age}$  if male and serum creatinine  $\leq 0.9$  or  $eGFR_{EPI} = 141 \times (\text{serum creatinine [mg/dL]}/0.9)^{-1.209} \times (0.993)^{Age}$  if male and serum creatinine  $> 0.9$ <sup>14</sup>
3.  $eGFR_{BIS} = 3736 \times (\text{serum creatinine [mg/dL]})^{-0.87} \times \text{age}^{-0.95} \times (0.82 \text{ if female})^{15}$
4.  $eGFR_{\text{modified MDRD}} = 175 \times (\text{serum creatinine [mg/dL]})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.233 \text{ if Chinese})^{21}$  We changed the coefficient of 186 to 175 based on the calibration factor used to adjust non-standardized MDRD study samples to isotope dilution mass spectrometry (IDMS).<sup>25</sup>

## Statistical Analyses

Continuous variables of patients' characteristics were expressed as mean  $\pm$  standard deviation (SD), and categorical variables were expressed as percentages or ratios. eGFR was treated as continuous or categorical variables with the cut-off value at 40, 60, and 80 mL/min/1.73 m<sup>2</sup> according to the distribution of eGFR in longevity cohort. The association of eGFR with all-cause mortality was examined by fully adjusted Cox proportional hazard models. We also examined potential non-linear relationships by using restricted cubic spline functions with four knots at the 5th, 35th, 65th, 95th percentile of each index and the reference for eGFR was 80 mL/min/1.73 m<sup>2</sup>. The fully adjusted model included age, gender, marital status, education, smoking, ADL, body mass index (BMI), hypertension, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, systolic blood pressure, serum albumin, and serum low-density lipoprotein cholesterol (LDL-C).

To assess reclassification, we created a  $4 \times 4$  cross-tabulation of the  $eGFR_{EPI}$  and the  $eGFR_{MDRD}$  or  $eGFR_{BIS}$  or  $eGFR_{\text{modified MDRD}}$  categories, calculated the proportion of participants reclassified by  $eGFR_{EPI}$  in each category of  $eGFR_{MDRD}$  or  $eGFR_{BIS}$  or  $eGFR_{\text{modified MDRD}}$ , and assessed whether risk of death differed between participants reclassified and those not reclassified. Overall improvement in reclassification based on clinical  $eGFR_{EPI}$  categories was assessed applying net reclassification improvement,<sup>27,28</sup> which was calculated as follows:

Net reclassification improvement (NRI) = clinically correct reclassification (proportion of participants reclassified upward among those who died + proportion of participants reclassified downward among those who survived) - clinically incorrect reclassification (proportion of participants reclassified upward among those who survived + proportion of participants reclassified downward among those who died)

Differences in baseline characteristics between included versus excluded patients were compared by Student's *t*-test or  $\chi^2$  test. The frequency of missing data was low [ $<1$ ], and multiple imputation methods with five data-sets were used in all regression analyses (Supplementary Table S10). Analyses were conducted using STATA MP version 13.1 (StataCorp, College Station, TX).

## Results

### Characteristics of the Study Population

Table 1 shows the demographic and clinical characteristics of participants. The mean $\pm$ SD age was 97 $\pm$ 2 years. The

**Table 1** Baseline Characteristics of the Rugao Longevity Population

Characteristics N=278	Mean $\pm$ SD or n (%)
Age (years)	97 $\pm$ 2
Male (%)	64 (23%)
Marital status (%)	
Married	14 (5%)
Widowed	261 (94%)
Divorced	0
Never married	3 (1%)
Education (%)	
Illiterate	225 (81.2%)
Primary school	37 (13.4%)
Middle School	1 (0.4%)
High School	1 (0.4%)
University or college	0
Others	13 (4.7%)
Comorbidities (%)	
Diabetes	0
Hypertension	45 (16%)
Cardiovascular disease	13 (5%)
Cerebrovascular disease	8 (3%)
Chronic obstructive pulmonary disease	25 (9%)
ADL Disability (%)	
None	125 (45%)
Moderate	65 (23%)
Severe	88 (32%)
Smoking	29 (10%)
Body mass index (kg/m <sup>2</sup> )	21.6 $\pm$ 4.1
Systolic blood pressure (mmHg)	137.7 $\pm$ 23.7
Laboratory Variables	
White blood cells (10 <sup>9</sup> /L)	5.4 $\pm$ 1.7
Hemoglobin (g/dL)	127.1 $\pm$ 21.0
Albumin (mg/dL)	41.0 $\pm$ 3.8
Triglyceride (mmol/L)	1.06 $\pm$ 0.44
Cholesterol (mmol/L)	4.78 $\pm$ 0.88
Low-density lipoprotein cholesterol (mmol/L)	2.57 $\pm$ 0.68
High-density lipoprotein cholesterol (mmol/L)	1.37 $\pm$ 0.34
Creatinine ( $\mu$ mol/L)	65.6 $\pm$ 19.8
Uric acid ( $\mu$ mol/L)	275.5 $\pm$ 96.5
Sodium (mmol/L)	140.6 $\pm$ 4.5
Calcium (mmol/L)	2.1 $\pm$ 0.1
Phosphorus (mmol/L)	1.0 $\pm$ 0.2

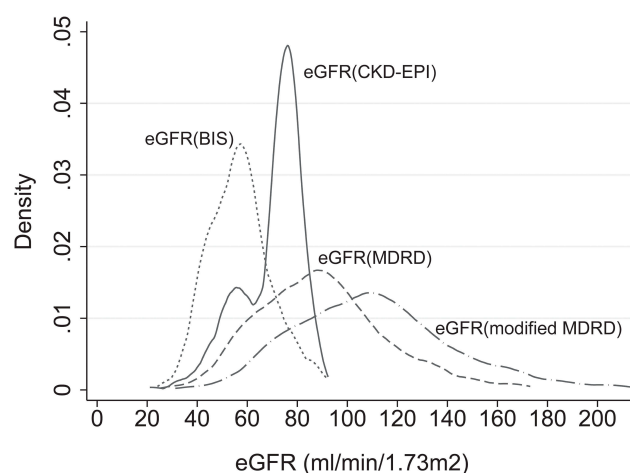
**Notes:** Values are expressed as mean  $\pm$  SD or number (percent). Conversion factors for units: LDL-C and HDL-C in mmol/L to mg/dL,  $\times 38.67$ ; triglycerides in mmol/L to mg/dL,  $\times 88.6$ ; creatinine in  $\mu$ mol/L to mg/dL,  $\times 0.01131$ ; eGFR in mL/min/1.73m<sup>2</sup> to mL/s/1.73 m<sup>2</sup>,  $\times 0.01667$ .

mean $\pm$ SD BMI was 21.6 $\pm$ 4.1 kg/m<sup>2</sup>. The participants were more likely to be women (77%), widowed (94%), and illiterate (81%). Mean serum baseline hemoglobin, albumin, and creatinine levels were 127.1 $\pm$ 21.0 g/dL, 41.0 $\pm$ 3.8 mg/dL, and 65.6 $\pm$ 19.8  $\mu$ mol/L, respectively (Table 1). A total of 256 (92%) participants died during the median follow-up of 2.6 years (IQR, 1.2–4.1 years) with an incidence of 33 deaths per 100 person-years.

Compared to 185 excluded persons who lacked data on serum creatinine, 278 included persons were more likely to smoke, had lower albumin, and had higher LDL-C and calcium (Supplementary Table S1).

### Distribution of eGFR by CKD-EPI Equation, MDRD Study Equation, BIS Equation, and Modified MDRD Equation

Median (IQR) eGFR by CKD-EPI, MDRD study, BIS equation, and modified MDRD equations were 73.9 (62.2–77.6), 82.3 (67.4–98.6), 56.4 (47.9–63.9), and 101.5 (83.1–121.6) mL/min per 1.73m<sup>2</sup>, respectively. The distribution of eGFR<sub>EPI</sub> and eGFR<sub>BIS</sub> were more concentrated and on the left side of the axis, while the distribution of eGFR<sub>MDRD</sub> and eGFR<sub>modified-MDRD</sub> were more dispersed and on the right side (Figure 1). The prevalence of chronic kidney disease (CKD) stage 3–5 (defined as eGFR < 60 mL/min/1.73 m<sup>2</sup>) at baseline were 23%, 16%, 63% and 4% by CKD-EPI equation, MDRD equation, BIS equation, and modified MDRD equation, respectively.



**Figure 1** Kernel density estimates of eGFR by four equations in Rugao longevity population.

High discrepancy of eGFR by 4 equations was seen after GFR of approximate 80 mL/min/1.73 m<sup>2</sup> where much higher GFR values were obtained by MDRD and modified MDRD equations compared to CKD-EPI and BIS equations ([Supplementary Figure S2](#)).

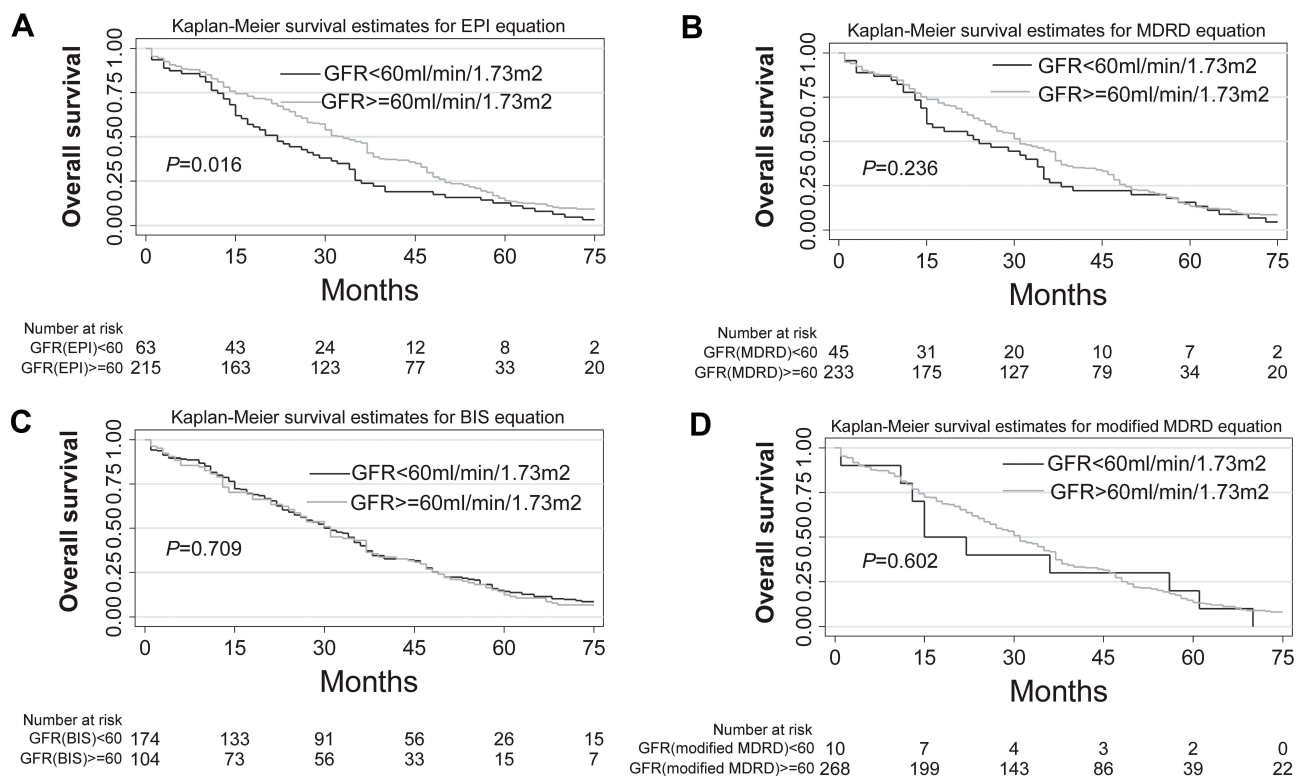
### Prognostic Value of eGFR<sub>EPI</sub>, eGFR<sub>MDRD</sub>, eGFR<sub>BIS</sub>, and eGFR<sub>modified-MDRD</sub> for Short-Term and Long-Term Mortality

[Figure 2](#) shows the Kaplan–Meier curve for overall six-year survival of groups with eGFR higher or less than 60 mL/min/1.73 m<sup>2</sup>. Those with eGFR<sub>EPI</sub> higher than 60 mL/min/1.73 m<sup>2</sup> had a statistically significant higher survival rate compared to those with eGFR<sub>EPI</sub> less than 60 mL/min/1.73 m<sup>2</sup> ( $P=0.02$  for CKD-EPI equation) ([Figure 2](#)). After adjusting for case-mix and laboratory variables, reduced eGFR<sub>EPI</sub> was significantly associated with two-year and six-year mortality (for continuous eGFR<sub>EPI</sub>, two-year estimates: HR 1.018, 95% CI 1.002–1.033,  $P=0.02$ ; six-year estimates: HR 1.013, 95% CI 1.002–1.025,  $P=0.02$ ); however, GFR estimated by three other equations did not show any significant association with all-cause mortality ([Tables 2 and 3](#), [Supplementary](#)

[Table S8, S9](#)). Models using spline functions yielded consistent results in which a trend toward lower mortality risk across higher eGFR was observed when GFR was estimated by CKD-EPI equation ([Figures 3 and 4](#)). Cox regression analysis was also carried out by considering eGFR > 60 mL/min/1.73 m<sup>2</sup> as a reference category, and it showed that reduced kidney function (eGFR < 60 mL/min/1.73 m<sup>2</sup>) estimated by only CKD-EPI was significantly associated with increased two-year and six-year mortality ([Tables 2 and 3](#)).

### Net Reclassification Improvement

The detailed table for calculating net reclassification improvement for death based on eGFR categories is shown in [Supplementary Table S2–S7](#). During the two-year follow-up, 61% ( $n=101$ ) of 166 participants who did not die were reclassified correctly to a lower risk (higher eGFR) category by CKD-EPI equation compared to BIS equation. On the other hand, among 112 participants who died during follow-up, 46% ( $n=52$ ) were reclassified incorrectly to a lower risk (higher eGFR) group by CKD-EPI equation ([Supplementary Table S2](#)). In sum, net reclassification improvement for death by the CKD-EPI equation



**Figure 2** Kaplan–Meier survival estimates and 95% confidence intervals for long term by GFR level using CKD-EPI (A), MDRD (B), BIS (C), and modified MDRD (D) equations.

**Table 2** Adjusted Hazard Ratio (95% CI) for Short-Term (Two-Year), All-Cause Mortality According to Estimated GFR (eGFR) Determined by CKD-EPI or MDRD or BIS or Modified MDRD Equations

	Hazards <sup>b</sup> Ratio	95% Confidence Interval		P <sup>a</sup>
eGFR (continuous)				
By EPI equation	1.018	1.002	1.033	0.023
By MDRD equation	1.006	0.997	1.014	0.206
By BIS equation	1.011	0.995	1.029	0.176
By modified MDRD equation	1.005	0.998	1.011	0.206
eGFR ( $\geq 60$ mL/min/1.73 m <sup>2</sup> as reference)				
By EPI equation ( $< 60$ mL/min/1.73 m <sup>2</sup> )	1.97	1.28	3.02	0.002
By MDRD equation ( $< 60$ mL/min/1.73 m <sup>2</sup> )	1.54	0.95	2.51	0.081
By BIS equation ( $< 60$ mL/min/1.73 m <sup>2</sup> )	1.01	0.68	1.52	0.947
By modified MDRD equation ( $< 60$ mL/min/1.73 m <sup>2</sup> )	1.91	0.82	4.43	0.134

**Notes:** <sup>a</sup>Adjusted for the following covariates: age, gender, marital status, education, smoking, body mass index, systolic blood pressure, serum albumin, low-density lipoprotein cholesterol, activities of daily living, hypertension, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease. <sup>b</sup>Every 1 mL/min/1.73 m<sup>2</sup> decrease of GFR or compared to GFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>.

**Abbreviations:** CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease Study; BIS, Berlin Initiative Study-1.

compared to BIS equation was 0.14 ( $P=0.05$ ). Results were obtained when comparing CKD-EPI equation with MDRD equation or modified MDRD equation (EPI vs MDRD, NRI=0.05,  $P=0.3$ ; EPI vs modified MDRD, NRI=0.002,  $P=0.5$ ) (Supplementary Table S3–S4). The NRI were 0.14 ( $P=0.4$ ),  $-0.02$  ( $P=0.5$ ), and  $-0.05$  ( $P=0.5$ ) when comparing CKD-EPI equation with BIS, MDRD, and modified MDRD equation using the six-year follow-up data (Supplementary Table S5–S7).

## Discussion

Overall, our results suggest that it might be more appropriate to use the CKD-EPI equation when estimating GFR level in an elderly population according to its predictive validity and discriminative ability in relation to short-term and long-term mortality risk, in comparison to MDRD, BIS, and revised MDRD equation. Accordingly, ageing kidneys result in a decreased GFR with an average of 74 mL/min/1.73 m<sup>2</sup> for extremely longevous population

**Table 3** Adjusted Hazard Ratio (95% CI) for Long-Term (Six-Year), All-Cause Mortality According to eGFR Determined by CKD-EPI or MDRD or BIS or Modified MDRD Equations

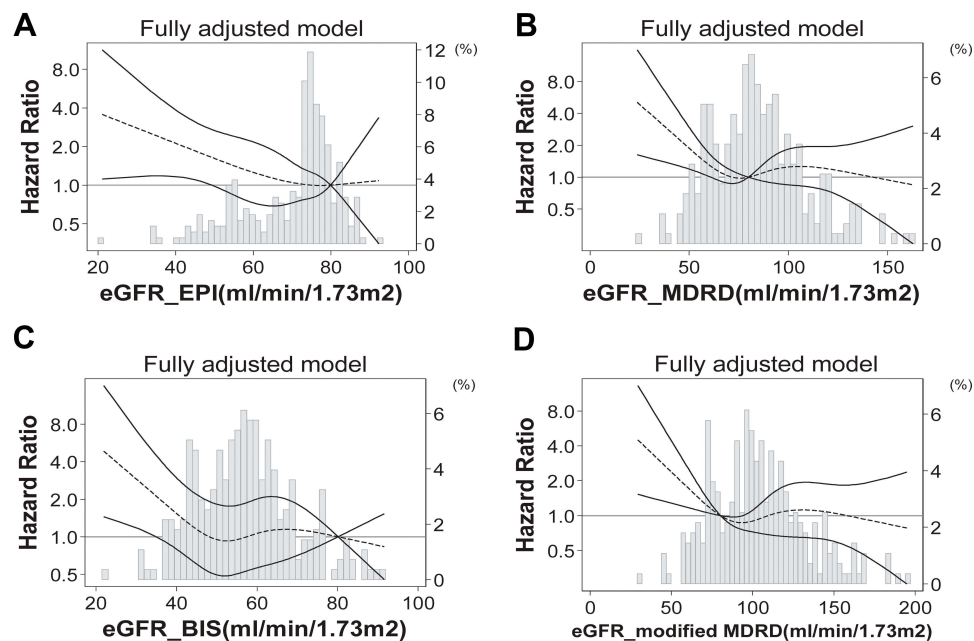
	Hazards <sup>b</sup> Ratio	95% Confidence Interval		P <sup>a</sup>
eGFR (continuous)				
By EPI equation	1.013	1.002	1.025	0.022
By MDRD equation	1.004	0.998	1.010	0.167
By BIS equation	1.009	0.997	1.021	0.148
By modified MDRD equation	1.003	0.999	1.008	0.167
eGFR ( $\geq 60$ mL/min/1.73 m <sup>2</sup> as reference)				
By EPI equation ( $< 60$ mL/min/1.73 m <sup>2</sup> )	1.62	1.18	2.23	0.003
By MDRD equation ( $< 60$ mL/min/1.73 m <sup>2</sup> )	1.33	0.93	1.89	0.119
By BIS equation ( $< 60$ mL/min/1.73 m <sup>2</sup> )	0.95	0.73	1.25	0.728
By modified MDRD equation ( $< 60$ mL/min/1.73 m <sup>2</sup> )	1.38	0.71	2.69	0.337

**Notes:** <sup>a</sup>Adjusted for the following covariates: age, gender, marital status, education, smoking, body mass index, systolic blood pressure, serum albumin, low-density lipoprotein cholesterol, activities of daily living, hypertension, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease. <sup>b</sup>Every 1 mL/min/1.73 m<sup>2</sup> decrease of GFR or compared to GFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>.

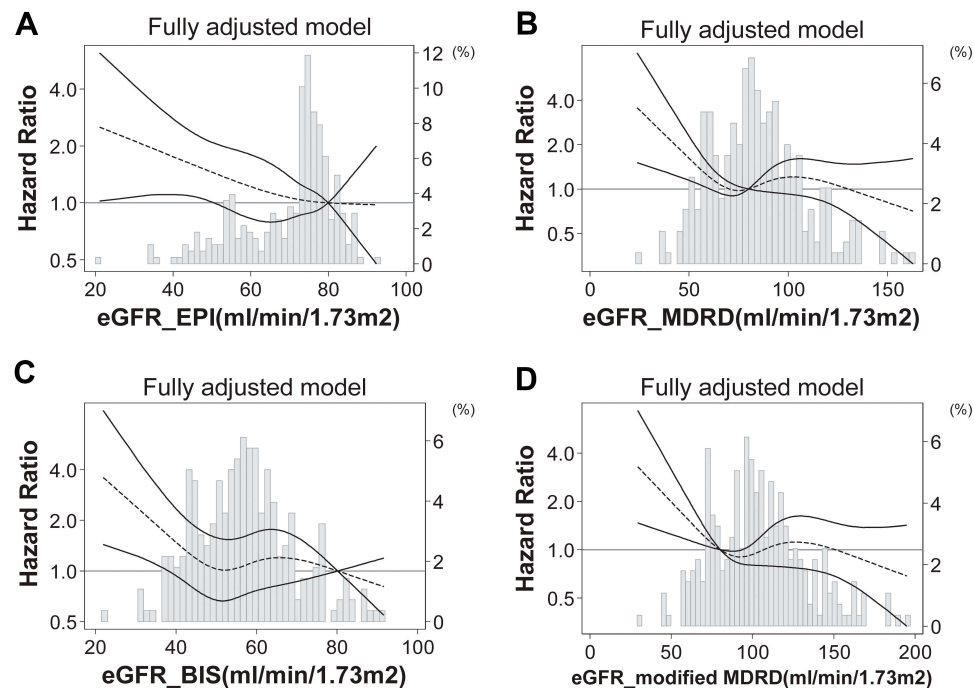
**Abbreviations:** CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease Study; BIS, Berlin Initiative Study-1.

aged over 95 years according to CKD-EPI equation, and intervention of reducing GFR decrease may still be necessary for improving survival. Though not all NRI results support better overall reclassification by the CKD-EPI equation, a larger sample size may be needed to further test our hypothesis.

It is well-known that kidney function has a physiological decline in individuals without comorbid conditions and without intrinsic renal disease or proteinuria. The magnitude of this decline has been reported as an average of 0.75 mL/min per year.<sup>29</sup> Comparing against previous studies which showed GFR by gold standard method in older individuals,<sup>17,18,30</sup> the estimated value of GFR from modified MDRD appeared less reasonable. This may be attributed to the developing process of the equation by adding a racial factor based on the MDRD equation in a cohort of younger CKD patients. In studies that evaluated accuracy of estimated GFR by equations with measured GFR in an older population, overestimation of GFR was often reported for MDRD and CKD-EPI



**Figure 3** Association of eGFR with short-term (2-year), all-cause mortality in fully adjusted model using splines in Rugao longevity population with GFR estimated by (A) CKD-EPI equation, (B) MDRD equation, (C) BIS equation, (D) modified MDRD equation.



**Figure 4** Association of eGFR with long-term (6-year), all-cause mortality in fully adjusted model using splines in Rugao longevity population with GFR estimated by (A) CKD-EPI equation, (B) MDRD equation, (C) BIS equation, (D) modified MDRD equation.

equations, with the bias of MDRD being slightly higher than those observed in the CKD-EPI equation,<sup>15,18,30,31</sup> especially at higher GFRs.<sup>15,32</sup> In contrast, underestimation of GFR was reported for BIS equation.<sup>16–18</sup> These were in accordance with the current study which showed

GFR estimated by MDRD was higher than CKD-EPI and BIS equation, and greater discrepancy of eGFR was seen after eGFR of approximate 80 mL/min/1.73 m<sup>2</sup> where MDRD and modified MDRD equations resulted in much higher eGFR than CKD-EPI and BIS equations. The

CKD-EPI equation includes two parts according to serum creatinine level which might avoid the resultant very high GFR in case of very low creatinine. This was especially important in older adults whose muscle mass may reduce dramatically.<sup>14,33</sup> Besides, The MDRD equation was developed in CKD patients (mean GFR, 40 mL/min/1.73 m<sup>2</sup>; mean age, 50.6),<sup>13</sup> the external validation in older individuals might not perform as well as CKD-EPI equation which was developed in a broader cohort with better kidney function (68 mL/min/1.73 m<sup>2</sup>) and BIS equation which was developed predominantly in cohorts of older people.<sup>14,15</sup>

To our knowledge, this is the first study which compared the ability of different eGFR equations to predict short-term and long-term mortality in EL populations. Actually, CKD-EPI equation had already been shown to have improved risk prediction compared to MDRD equation in a large community-based, middle-aged population.<sup>27,34</sup> Though debate exists around older populations, in some studies, they found creatinine-based BIS and MDRD equation was not superior to creatinine-based CKD-EPI equation for predicting all-cause mortality.<sup>34-36</sup> Here we demonstrated that CKD-EPI was the only equation with ability of predicting mortality among EL populations when using Cox regression method. The assumption is that the mortality risk predicted by eGFR is based upon the impact on death by measured renal function. GFR estimated by CKD-EPI equation might be closer to measured renal function by gold standard method. It is more stable and less biased since the cohorts used to develop the CKD-EPI equation were larger, more racially diverse and with broader range of age.<sup>14</sup> Though BIS equation was developed from European elderly population, the single race draws into question BIS' accuracy in Asian people with different muscle compositions and dietary habits. Besides, the BIS equation tended to estimate GFR lower than other equations. This helped to reclassify those who died to more advanced GFR categories, but may have, to a larger extent, inappropriately reclassified those who survived to more advanced GFR categories, giving less accurate outcome predictions.<sup>37</sup> Thus, we also found that the NRI of CKD-EPI compared with BIS was positive and with marginal significance. The persistent predictive value of reduced eGFR<sub>EPI</sub> in short-term and long-term follow-up highlights the strengths of baseline renal function estimated by CKD-EPI equation as an important factor in risk-stratifying EL population. Since EL is an ideal model of healthy aging without various comorbidities that interfere with the association of GFR

and mortality, we believe CKD-EPI equation is superior to other equations for categorizing the risk for mortality in elderly population.

The mean GFR of the current study population estimated by BIS, CKD-EPI or MDRD equations was 5 to 10 mL/min/1.73 m<sup>2</sup> higher than the averages reported in previous studies for older people,<sup>6,16,38-43</sup> perhaps due to survival bias in our exceptional longevity setting.<sup>29</sup> People with severe disease are more likely to die earlier. This phenomenon of compressed morbidity in centenarians compared to younger referent individuals was also seen in both the New England Centenarian Study (NECS) and Longevity Genes Project (LGP) cohorts.<sup>44</sup> More than 80% of the EL individuals had delayed or escaped most lethal diseases of the elderly population including heart disease, non-skin cancer, and stroke.<sup>45</sup> Thus, we speculated that the decrease of GFR in the current cohort was mostly due to physiological change. According to the low morbidity of EL individuals, the declining rate of GFR in healthy ageing, the accuracy of GFR estimated by CKD-EPI demonstrated in previous studies, and the conclusion, we found that GFR estimated by CKD-EPI was the predictor of mortality; the range of eGFR (IQR 62.2–77.6 mL/min/1.73 m<sup>2</sup>) by CKD-EPI equation might be a reference of successful aging kidney function of EL population. Besides, intervention may not be needed if estimated GFRs are above or near this range. However, future studies are needed to further verify these findings.

One of the strengths of the present study is the inclusion of a large community cohort of EL population followed prospectively over 6 years. To control for potential confounding factors, results were adjusted for the main clinical conditions of elderly population associated with mortality. Moreover, we revealed again that the age-adapted CKD definition should be changed to people without evidence of kidney injury, especially for elderly people with healthy ageing. Some limitations of the present study should be mentioned. First, creatinine-based equation might affect accurate GFR estimation in EL individuals who suffer from sarcopenia. However, mean BMI was 21.6±4.1 kg/m<sup>2</sup> in our study which is very similar to the reported BMI of elderly adults from Chinese community.<sup>46</sup> We speculate that few participants suffered from sarcopenia. Second, the creatinine measured in the current study was measured using enzymatic method with the Cica Creatinine reagent and Hitachi 7600 analyzer which was not calibrated to the recognized Roche enzymatic method. Finally, proteinuria was not measured at baseline. Thus, we could not evaluate

eGFR and proteinuria simultaneously along with other factors for the most accurate risk prediction.

## Conclusion

In conclusion, GFR decreased in EL population with an average of 74 mL/min/1.73 m<sup>2</sup> by CKD-EPI equation. The CKD-EPI equation showed more accurate estimation of GFR in EL individuals with respect to predictability of mortality risk compared to the other equations, indicating greater clinical utility among older population in China.

## Data Sharing Statement

Data were obtained by the staff and participants of the Rugao Longevity Cohort. Prof Xiaofeng Wang, one of our corresponding authors, would need to be emailed for available data.

## Ethics Approval and Informed Consent

This study was approved by the Human Ethics Committee of the School of Life Sciences of Fudan University, Shanghai, China. Written informed consent was obtained from each participant or a member of his or her immediate family prior to participation.

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare that they have no conflict of interest.

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