Estimating glomerular filtration rates in elderly Chinese patients with chronic kidney disease: performance of six modified formulae developed in Asian populations

Xun Liu1,2,*
Haixia Xu3,*
Zebin Zheng4,5,*
Cheng Wang1
Cailian Cheng1
Chenggang Shi1
Yihong Gong4,5
Ming Li1
Tanqi Lou1

1Division of Nephrology, Department of Internal Medicine, The Third Affiliated Hospital of Sun Yat-sen University, 2College of Biology Engineering, South China University of Technology, 3Division of Endocrinology, Department of Internal Medicine, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, People’s Republic of China; 4Department of Biomedical Engineering, School of Engineering, Sun Yat-sen University, Guangzhou, Guangdong, People’s Republic of China; 5Guangdong Provincial Key Laboratory of Sensor Technology and Biomedical Instruments, Sun Yat-sen University, Guangzhou, Guangdong, People’s Republic of China

*These authors contributed equally to this work

Objectives: The aim of the present study was to evaluate modified glomerular filtration rate (GFR) prediction formulae in an elderly Chinese population with chronic kidney disease (CKD).

Methods: A total of 378 elderly Chinese patients with CKD were enrolled. The GFR was estimated with six modified GFR prediction formulae. The performances of the estimated GFRs were compared with those of the standard GFRs measured by technetium-99m diethylenetriaminepentaacetic acid.

Results: Biases were similar for Chinese formula 1, the Asian formula, and Chinese formula 2 (median difference, 2.22 mL/min/1.73 m² and 2.59 mL/min/1.73 m² for Chinese formula 1 and the Asian formula, respectively, versus (vs) 3.69 mL/min/1.73 m² for Chinese formula 2 [P = 0.298 and P = 0.913, respectively]). Precision was improved with the Japanese formula (interquartile range of the difference, 3.14 mL/min/1.73 m² of the Japanese formula versus 15.53–23.06 mL/min/1.73 m² of the other formulae). The accuracy of Chinese formula 2 was the highest (30% accuracy, 59.3% vs range 37.8–54.0% [P < 0.05 for all comparisons]). However, none of the modified formulae surpassed the acceptable tolerance (>70%), and the GFR category misclassification rates for all the formulae exceeded 50%.

Conclusion: Our findings suggest that all six modified formulae developed in Asian populations may show great bias in elderly Chinese patients with CKD. Also, our study suggests the need for uniform measures for the assessment of CKD in the elderly to guarantee better sensitivity and specificity.

Keywords: formula, CKD, Asian, GFR

Introduction

Accurate estimation of glomerular filtration rate (GFR) is essential for the detection, diagnosis, and management of patients with chronic kidney disease (CKD).1 The incidence of CKD is markedly high in elderly populations.2 The Modification of Diet in Renal Disease (MDRD) formula and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula are the most frequently used formulae for estimating GFR but are known to be less accurate for racial and ethnic groups outside North America, Europe, and Australia.3 Taking this into account, six GFR prediction formulae, the Asian formula,4 Korean formula,5 Japanese formula,6 Thai formula,7 Chinese formula 1,8 and Chinese formula 2,9 were developed based on Asian populations either by adding a coefficient into the original MDRD formula or developing a new equation using the same variables as the MDRD formula. These modified formulae
have not been validated in elderly CKD patients. The current
study was designed to compare the performance of different
modified formulae for the estimation of GFR in elderly
Chinese patients with CKD.

Materials and methods

Sample size calculation

Based on the findings of a pilot study (Tables S1 and S2), the
minimum sample size was calculated in accordance with the
formula\(^\text{10}\) for a cross-sectional survey. A significance level
of 95% and 80% power was used. We therefore estimated
that the sample size should be 360 subjects.

Study design

A cross-sectional, single-center study design was used. The
study, approved by the institutional review board at the
Third Affiliated Hospital of Sun Yat-sen University, was
conducted in accordance with the ethical guidelines of the
Helsinki Declaration. Informed consent was obtained from
each patient before the study.

Subjects

A total of 378 elderly CKD patients were referred consecu-
tively to our department in the Third Affiliated Hospital of
Sun Yat-sen University, People’s Republic of China, for mea-
surement of their GFR from January 2005 through December
2010. The mean age of the patients was 72.8 ± 5.7 (range
65–93) years, with standard glomerular filtration rate (sGFR)
measured by technetium-99m diethylenetriaminepentaacetic
acid (\(^{99m}\)Tc-DTPA) renal scintigraphic analysis found to be
39.5 ± 20.2 (range 4.5–95.1) mL/min/1.73 m\(^2\) (Table 1).
Inclusion criteria were age 65 years or older and CKD
diagnosed and categorized according to the Kidney Disease:
Improving Global Outcomes clinical practice guidelines.\(^\text{11}\)
Exclusion criteria are described elsewhere.\(^\text{12}\)

Measurements

The sGFR was determined by \(^{99m}\)Tc-DTPA renal scintigraphic
analysis,\(^\text{13}\) measured using a commercial SPECT/CT system
(Discovery VH, GE Healthcare, Waukesha, WI, USA). A high
correlation was observed in comparison to renal scintigraphic
analysis with inulin clearance, the reference standard of GFR
measurement.\(^\text{14}\) Serum creatinine (SC) was analyzed using the
enzymatic method on a Hitachi 7180 analyzer (Tokyo, Japan;
reagents from Roche Diagnostics, Mannheim, Germany),
traceable to isotope dilution mass spectrometry.

We used six modified formulae to calculate the estimated
glomerular filtration rate (eGFR):

- The Asian formula:\(^\text{4}\)
  \[ \text{GFR} = 1.086 \times 175 \times \text{SC}^{-1.154} \times \text{age}^{-0.203} \times [0.742 \text{ if patient is female}] \]
- The Korean formula:\(^\text{5}\)
  \[ \text{GFR} = 87.832 \times \text{SC}^{-0.882} \times \text{age}^{-0.061} \times [0.653 \text{ if patient is female}] \]
- The Japanese formula:\(^\text{6}\)
  \[ \text{GFR} = 194 \times \text{SC}^{-1.094} \times \text{age}^{-0.287} \times [0.739 \text{ if patient is female}] \]
- The Thai formula:\(^\text{7}\)
  \[ \text{GFR} = 1.129 \times 175 \times \text{SC}^{-1.154} \times \text{age}^{-0.203} \times [0.742 \text{ if patient is female}] \]
- Chinese formula 1:\(^\text{8}\)
  \[ \text{GFR} = 175 \times \text{SC}^{-1.234} \times \text{age}^{-0.179} \times [0.79 \text{ if patient is female}] \]
- Chinese formula 2:\(^\text{9}\)
  \[ \text{GFR} = 234.96 \times \text{SC}^{-0.926} \times \text{age}^{-0.280} \times [0.828 \text{ if patient is female}] \]

Statistical analysis

The difference between the eGFR and sGFR was defined as
eGFR minus sGFR. Accuracy was measured as the percent-
age of eGFR not deviating more than 30% from the sGFR.
A Wilcoxon Mann–Whitney test was used for the
difference, bootstrap method for IQR for difference, and \(\chi^2\)
test for accuracy, respectively. In a pilot study (Tables S1

| Table 1 | Patient characteristics* |
|--------|--------------------------|
| Subjects (n) | 378 |
| Age (years) | 72.8 ± 5.7 |
| Male sex (n, %) | 242 (64.0) |
| Diabetes (n, %) | 162 (42.8) |
| Body mass index |
| Mean (kg/m\(^2\)) | 23.3 ± 3.6 |
| <20 (n, %) | 67 (17.7) |
| 20–24 (n, %) | 196 (51.9) |
| 25–30 (n, %) | 97 (25.7) |
| >30 (n, %) | 18 (4.8) |
| Weight (kg) | 61.3 ± 11.5 |
| Height (cm) | 161.7 ± 8.1 |
| Body-surface area (m\(^2\)) | 1.64 ± 0.17 |
| Serum creatinine (mg/dL) | 2.5 ± 1.9 |
| Measured GFR (mL/min/1.73 m\(^2\)) |
| Mean | 39.5 ± 20.2 |
| <15 | 43 (11.4) |
| 15–29 | 94 (24.9) |
| 30–44 | 96 (25.4) |
| 45–59 | 87 (23.0) |
| 60–89 | 53 (14.0) |
| >90 | 5 (1.3) |

Note: *Quantitative data are expressed as mean ± standard deviation; categorical data, as number (percentage).
Abbreviation: GFR, glomerular filtration rate.
and S2), Chinese formula 2 performed better than the other formulae. Therefore, we chose eGFR measured by Chinese formula 2 as the reference against which all comparisons among formulae were made. Performances of the modified formulae were assessed in terms of four factors – bias, precision, accuracy, and GFR category misclassification rate. An optimal score system was developed. The formula that performed the best in each aspect in the entire population was scored as 1, and in each GFR subgroup the best scores were 0.5. The greater the total scores, the better the synthetic performance. All statistical analyses were performed using SPSS (v 11.0; IBM Corporation, Armonk, NY, USA) and Matlab (v 2011b; The MathWorks®, Natick, MA, USA) software.

Results
Biases were similar for Chinese formula 1, the Asian formula, and Chinese formula 2 (median difference, 2.22 mL/min/1.73 m² and 2.59 mL/min/1.73 m² for Chinese formula 1 and the Asian formula, respectively, vs 3.69 mL/min/1.73 m² for Chinese formula 2 [P = 0.298 and P = 0.913, respectively]), while bias for the Chinese equation 2 was less than those for the Korean formula, Japanese formula, and Thai formula (median difference, range −6.71 to 11.72 mL/min/1.73 m² [P < 0.001 for all comparisons]). Precision was improved with the Japanese formula (IQR of the difference, 13.14 mL/min/1.73m² of the Japanese formula versus 15.53–23.06 mL/min/1.73m² of the other formulae). The accuracy of Chinese formula 2 was the highest (30% accuracy, 59.3 vs range 37.8%–54.0%, [P < 0.05 for all comparisons]). There was also an improvement in the GFR category misclassification rate of Chinese formula 2 (54.0 vs range 57.4%–68.3% [P < 0.001 for the Asian formula, Korean formula, Thai formula and Chinese formula 1; P = 0.320 for the Japanese formula]). However, none of the modified formulae surpassed the acceptable tolerance (>70%), and the GFR category misclassification rate of all the formulae exceeded 50% (Table 2).

The performances of the six modified formulae in various GFR categories were analyzed. In the subgroup with sGFR <30 mL/min/1.73 m², the bias of Chinese formula 2 was more than those of the Thai formula and Asian formula (median difference, P < 0.001 for both comparisons), while it was less than those of Chinese formula 1, the Japanese formula, and the Korean formula (median difference, P < 0.001 for all comparisons). Chinese formula 2 showed the lowest GFR category misclassification rate (P < 0.01 for all comparisons except the Japanese formula, for which P = 0.272). Among all three subgroups, precision was improved with the Japanese formula (IQR, P < 0.001 for all comparisons), and accuracy with Chinese formula 2 (30% accuracy, P < 0.05 for all comparisons). In the subgroups with sGFR 30–59 mL/min/1.73 m² as well as >60 mL/min/1.73 m², there were improvements in both the bias and GFR category misclassification rate of Chinese formula 2 (P < 0.01 for all comparisons). Detailed performances are listed in Table 2.

An optimal score system was developed to synthetically evaluate the performances of different modified formulae (Table 3). Chinese formula 2 achieved the greatest total scores (5.5 vs range 0.0–2.5 for the rest of the formulae).

Discussion
In this study, for the first time as far as we are aware, six modified formulae derived from Asian populations were validated for the estimation of GFR in elderly Chinese patients with CKD. We found that none of the formulae had 30% accuracy up to the acceptable tolerance (>70%), and the GFR category

Table 2 Performance between measured glomerular filtration rate (GFR) and estimated GFR

| Variable | Measured GFR (mL/min/1.73 m²) |
|----------|-------------------------------|
|          | Overall | <30 | 30–59 | ≥60 |
| Bias, median difference (mL/min/1.73 m²) |         |     |       |     |
| Asian formula | 2.59  | −1.48* | 5.31† | 10.79* |
| Korean formula | 11.72* | 7.17* | 17.25* | 14.85* |
| Japanese formula | −6.71* | −4.94* | −7.49* | −12.38* |
| Thai formula  | 3.74*  | −0.98* | 7.43* | 14.47* |
| Chinese formula 1 | 2.22  | −2.66* | 5.58* | 18.47* |
| Chinese formula 2 | 3.69  | 1.80  | 4.85  | 4.38  |
| Precision, IQR of the difference (mL/min/1.73 m²) |         |     |       |     |
| Asian formula | 21.40* | 10.96* | 23.28* | 36.10* |
| Korean formula | 22.06* | 13.90* | 25.52* | 30.08* |
| Japanese formula | 13.14* | 9.77* | 14.48* | 25.61* |
| Thai formula  | 22.48* | 11.25* | 24.07* | 37.71* |
| Chinese formula 1 | 23.06* | 10.62* | 24.98* | 42.59* |
| Chinese formula 2 | 15.53* | 10.68* | 17.70* | 28.05* |
| Accuracy, 30% accuracy (%) |       |     |       |     |
| Asian formula | 49.2*  | 45.3* | 53.0*  | 46.6* |
| Korean formula | 37.8*  | 33.6* | 37.2*  | 50.0* |
| Japanese formula | 54.0† | 42.3† | 58.5† | 67.2† |
| Thai formula  | 48.4*  | 46.0* | 50.3*  | 48.3* |
| Chinese formula 1 | 47.4* | 44.5* | 50.3* | 44.8* |
| Chinese formula 2 | 59.3  | 48.9  | 63.9  | 69.0  |
| GFR category misclassification rate (%) |         |     |       |     |
| Asian formula | 57.4*  | 43.8* | 68.3*  | 55.2* |
| Korean formula | 68.3*  | 57.7* | 80.3*  | 55.2* |
| Japanese formula | 58.5 | 48.2 | 65.0* | 62.1* |
| Thai formula  | 59.5*  | 43.8* | 72.1*  | 56.9* |
| Chinese formula 1 | 58.7* | 41.6* | 70.5* | 62.1* |
| Chinese formula 2 | 54.0 | 43.8 | 63.4 | 48.3 |

Notes: *P<0.001 compared with Chinese formula 2-GFR; †P<0.01 compared with Chinese formula 2-GFR; ‡P<0.05 compared with Chinese formula 2-GFR.

Abbreviations: GFR, glomerular filtration rate; IQR, interquartile range.
misclassification rate of all formulae exceeded 50%. Such results are consistent with previous findings and suggest that other factors in addition to race or ethnicity may affect the performance of GFR prediction formulae.

Study population was the first of these suggested factors. All the currently available modified formulae were derived from the general Asian population. However, the validation population in this study was elderly CKD patients. Intrinsic factors, such as the loss of muscle mass with aging, affect the evaluation of GFR in elderly CKD patients. Other studies have reported mean sGFRs ranging from 50.7 to 59.1 mL/min/1.73 m², which is much higher than that of the validation population in this study. The distribution of the GFR categories in our study was also different from the other studies. Differences in the study population characteristics between the original development dataset and the validation dataset led to bias in the modified GFR-estimating formulae.

The second factor is the method used to measure GFR. Renal inulin clearance was used as the sGFR in the Korean formula and Japanese formula, which was different from the plasma clearance of diethylenetriaminepentaacetic acid (DTPA) used for the Asian formula, and both the modified Chinese formula and the DTPA renal dynamic imaging in both Chinese formula and in this study as well. Rehling et al found that renal dynamic imaging gave more accurate values than the renal clearance of inulin, whereas Zuo et al indicated that the plasma clearance of DTPA was systemically higher than that of modified inulin. Variability in the measurement of GFR introduces error into the estimation of GFR.

Calibration of SC assays was the third factor. The SC value was measured by the enzyme method calibrated to the Cleveland Clinic Laboratory for both the Japanese formula and Chinese formula. The SC value in Chinese formula was obtained by Jaffe’s kinetic method. SC levels in the Asian and Chinese formula were all calibrated to an assay traceable to isotope dilution mass spectrometry. The inaccuracy in the modified formulae may be due in part to the differences in the calibration of SC assays.

### Conclusion

Our findings suggest that all six modified formulae developed in Asian populations may show great bias in elderly Chinese patients with CKD. Our study also suggests the need for uniform measures for the assessment of CKD in the elderly to guarantee better sensitivity and specificity. Further studies should compare different GFR-estimating formulae in similar population cohorts with the same GFR measurement and SC calibration.

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### Disclosure

The authors declare no conflicts of interest in this work.

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Supplementary tables

**Table S1** Clinical characteristics* of a subgroup of patients selected from January 2005 to December 2008

| Subject (n) | 215 |
|---|---|
| Age (years) | 72.9 ± 5.9 |
| Male sex (n, %) | 130 (60.5) |
| Diabetes (n, %) | 95 (44.1) |
| Body mass index | 23.7 ± 3.7 |
| Mean (kg/m²) | 32 (14.9) |
| <20 (n, %) | 110 (51.2) |
| 20–24 (n, %) | 58 (27.0) |
| ≥30 (n, %) | 15 (7.0) |
| Weight (kg) | 61.9 ± 12.1 |
| Height (cm) | 161.3 ± 8.7 |
| Body-surface area (m²) | 2.4 ± 0.18 |
| Serum creatinine (mg/dL) | 2.4 ± 0.2 |
| Measured GFR (mL/min/1.73 m²) | 39.4 ± 20.2 |
| Mean | 4 (1.9) |
| <15 | 24 (11.2) |
| 15–29 | 56 (26.0) |
| 30–44 | 53 (24.7) |
| ≥45 | 53 (24.7) |
| >90 | 25 (11.6) |

**Note:** *Plus-minus values are means ± standard deviation.

**Abbreviation:** GFR, glomerular filtration rate.

**Table S2** Performance between the estimated glomerular filtration rate (GFR) and standard GFR in a subgroup of patients selected from January 2005 to December 2008

| Equation | Median of difference (mL/min/1.73m²) | IQR of the difference (mL/min/1.73m²) | 30% accuracy (%) | GFR category misclassification rate (%) |
|---|---|---|---|---|
| Asian | 2.61 | 21.55 | 47.0 | 58.1 |
| Korean | 11.30 | 22.41 | 37.7 | 67.9 |
| Japanese | −6.30 | 13.88 | 52.6 | 54.9 |
| Thai | 3.72 | 22.88 | 46.0 | 60.9 |
| Chinese 1 | 2.18 | 24.30 | 46.5 | 58.6 |
| Chinese 2 | 4.00 | 16.40 | 57.7 | 56.3 |

**Abbreviation:** IQR, interquartile range.

**Notes:** Chinese 1 formula was developed by Ma et al. Chinese 2 formula was developed by Shi et al.