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Call for the use of a common equation for glomerular filtration rate estimation in East and South-East Asia

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ABSTRACT

Background: Estimated glomerular filtration rate (eGFR) is currently calculated using various equations and serum creatinine (Scr) value measured by different assays. Differences among these eGFRs deserve further study.

Methods: Volunteers from eight Asian regions (n = 3283; age 20–65 years, 1454 men, 1829 women) were recruited. The Chronic Kidney Disease Epidemiology Collaboration equation (EPI), Modification of Diet in Renal Disease Study equation (MDRD) for Japanese ($MDRD_{Jap}$) and MDRD for Chinese ($MDRD_{Chi}$) were selected. Jaffe and enzymatic assays were used to measure Scr. Six eGFRs were obtained for each volunteer: EPI equation using Scr value of enzymatic assay (EPI/E) and Jaffe assay (EPI/J); $MDRD_{Jap}$ equation using Scr value of the two assays ($MDRD_{Jap}$/E, $MDRD_{Jap}$/J); and $MDRD_{Chi}$ equation using Scr value of the two assays ($MDRD_{Chi}$/E, $MDRD_{Chi}$/J).

Results: Neither Scr nor eGFR showed significant regional difference. We compared eGFR calculated using the same equation but with different assays. The medians (2.5%, 97.5%) of eGFR difference were 2.0 (−7, 14) mL/min/1.73 m^2 for EPI, 3.0 (−12.0, 18.0) mL/min/1.73 m^2 for $MDRD_{Jap}$, and 5.0 (−18, 30) mL/min/1.73 m^2 for $MDRD_{Chi}$. We also compared eGFR calculated using different equations but with the same assay. The medians (2.5%, 97.5%) of eGFR difference were 11 (−6, 56) mL/min/1.73 m^2 between $MDRD_{Chi}$/E and EPI/E; 26 (9, 35) mL/min/1.73 m^2 between EPI/E and $MDRD_{Jap}$/E; and 39 (22, 65) mL/min/1.73 m^2 between $MDRD_{Chi}$/E and $MDRD_{Jap}$/E, respectively.

Conclusions: eGFR difference caused by using different equations is much larger than that caused by using different Scr assays. A common equation for GFR estimation is encouraged for use in Asians.

Introduction

In general, a glomerular filtration rate (GFR) that is lower than 60 mL/min/1.73 m^2 or a urine albumin to creatinine ratio that is higher than 30 mg/g is considered to be an indicator of chronic kidney disease (CKD) [1]. Early diagnosis and treatment of CKD can prevent or slow progression of the disease, which could reduce the incidences of end-stage kidney and cardiovascular diseases [2,3]. When such benefit is accepted by the clinical community, physicians are more likely to send a patient to a specialist if they identify such a sign on laboratory reports. It is suspected that the automated laboratory reporting of estimated GFR (eGFR) is associated with a significant increase in the rate of referral of patients to nephrologists [4]. At present, many equations to estimate GFR have been developed, but they were established on the basis of various populations and various serum creatinine (Scr) measurement assays, and referred to various "gold standards" for GFR measurement. A fundamental aspect related to GFR estimation deserves thorough investigation: that is, to what extend do the equation and Scr measurement assay affect values of eGFR.

A multicenter study titled "The Asian Project for Collaborative Derivation of Reference Intervals" was conducted in East and South-East Asia from 2009 to 2010, aiming at collaborative derivation of reference intervals. The initial report of the study [5] showed that no regional difference was found in Scr level in East and South-East Asians. The present paper reports our follow-up work on this previous study [5]. The objectives of this study were to investigate differences of eGFR among various equation–assay combinations and to study the feasibility of using a common equation in Asian populations. Our hypothesis of using a common equation among all Asians is motivated by the accepted understanding that the Modification of Diet in Renal Disease Study equation (MDRD) is suitable to be used in all Caucasians.

In this paper, because Japanese accounted for 46% and Chinese accounted for 28% of all volunteers, we selected 3 equations that contain ethnic considerations: the first is the MDRD equation for Japanese ($MDRD_{Jap}$) [6], which is recommended for use in Japanese by the Japan Society of Nephrology; the second is the MDRD equation for Chinese ($MDRD_{Chi}$), which had been used to investigate the prevalence of CKD in China [7]; and the third is the two-level Chronic Kidney

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Disease Epidemiology Collaboration equation (EPI) [8], which has been proved not to require additional ethnic factors and which can be used directly in Asians [9,10]. These three equations all use Scr in their calculation. Two common types of assays were used to measure Scr: the Jaffe assay and enzymatic assay.

Materials and methods

Participant enrollment, sample collection and measurement

This study further explored the data of an existing database created in a comprehensive survey among many cities in eight Asian regions. Participant recruitment, sample collection, specimen transportation, the assay's performance validation and target analyte measurement of the survey were described in a previous report [5].

The study was approved by the Ethical Committee of Yamaguchi University Graduate School of Medical Sciences in December 2008. All the volunteers were duly informed of the medical treatment and procedures associated with this study, and all gave their written consent to participate in this research.

Performance of serum creatinine assays

Scr was measured by UniCell DxC 800 analyzer (Beckman-Coulter, USA) using a kinetic Jaffe assay. The enzymatic assay was performed on a Hitachi 917 analyzer, P module, and the reagent was provided by Shino, Japan. All measurement procedures followed the manufacturer's specifications. The accuracy of the two assays was validated by measuring a certified reference material (JCCRM521-10, serum matrix; see the Supplementary material for its certification). The biases of the Jaffe assay and enzymatic assay were −2.7 μmol/L and −2.7 μmol/L, respectively, when the Scr level is 78.7 μmol/L, and −5.3 μmol/L and −3.5 μmol/L, respectively, when the Scr level is 194.5 μmol/L. The within-run coefficient of variation was 2.41% for the Jaffe assay and 1.41% for the enzymatic assay, and the day-to-day coefficient of variation was 2.97% for the Jaffe assay and 1.58% for the enzymatic assay during the study period.

Estimation of glomerular filtration rate

Three equations, the EPI, $MDRD_{Jap}$ and $MDRD_{Chi}$, were used. When EPI is used to calculate eGFR, the following equations are used for males and females.

For males:

$$Scr \le 0.9 : eGFR = 141 \times (Scr/0.9)^{-0.411} \times 0.993^{Age}$$

$$Scr > 0.9 : eGFR = 141 \times (Scr/0.9)^{-1.209} \times 0.993^{Age}.$$

For females:

$$Scr \le 0.7 : eGFR = 144 \times (Scr/0.7)^{-0.329} \times 0.993^{Age}$$

$$Scr > 0.7 : eGFR = 144 \times (Scr/0.7)^{-1.209} \times 0.993^{Age}.$$

When the $MDRD_{Jap}$ is used to calculate eGFR, the following equation is used for males and females.

$$eGFR = 194 \times (Scr)^{-1.094} \times (Age)^{-0.287} \text{ [if female, } \times 0.739\text{]}$$

When the $MDRD_{Chi}$ is used to calculate eGFR, the following equation is used for males and females.

$$eGFR = 175 \times (Scr)^{-1.234} \times (Age)^{-0.179} \text{ [if female, } \times 0.79\text{]}$$

For each volunteer, the following six eGFRs were obtained: EPI using the Scr value of the enzymatic assay (EPI/E) and Jaffe assay (EPI/J); $MDRD_{Jap}$ using the Scr value of the enzymatic assay ($MDRD_{Jap}$/E) and Jaffe assay ($MDRD_{Jap}$/J); and $MDRD_{Chi}$ using the Scr value of the enzymatic assay ($MDRD_{Chi}$/E) and Jaffe assay ($MDRD_{Chi}$/J).

Statistical analysis

The same statistical methods as reported in the previous study [5] were used. The magnitudes of variation due to sex, age and region were analyzed by three-level nested ANOVA. In brief, the magnitude of variation due to each factor (sex, age and region) was expressed as standard deviations (SD) including between-region SD (SD_{region}), between-sex SD (SD_{sex}) and between-age SD (SD_{age}). The relative magnitude of each factor to that of the residual SD representing a net between-individual SD ($SD_{net\text{-}btw\text{-}indiv}$) was computed as the SD ratio (SDR) by the following formula:

$$SDR_{factor} = SD_{factor}/SD_{net\text{-}btw\text{-}indiv}.$$

The SDR of each factor indicates its degree of influence on the target analyte. An SDR of ≥0.3 was regarded as high, an SDR between 0.26 and 0.29 was considered moderate, and an SDR of ≤0.25 was considered low.

The Harris and Boyd algorithm [11] was used to determine whether regional groups could be merged. Distribution of eGFR was analyzed based on nonparametric descriptive statistics, by use of a general-purpose statistical software, Statflex Version 6.0 (Artech Co., Osaka, Japan).

Results

Sex, age and regional difference of Scr and eGFR

Sex difference was significant for the Scr value because the SDR for Scr was approximately 1.83. However, the sex difference was relatively subdued for the eGFR value because the SDR for eGFR was approximately 0.32.

Age difference was significant for eGFR because the SDRs for eGFR were 1.24 for males and 1.42 for females. In contrast, age difference showed no significant effect for the Scr value because the SDRs for Scr were only 0.08 for males and 0.00 for females.

Both Scr and eGFR showed no noticeable regional differences by three-level nested ANOVA. The SDR_{region} for Scr and eGFR was all below 0.25 and was considered not significant (Table 1).

Scr distribution (by enzymatic assay) in eight Asian regions

The Scr value at each percentile in the eight Asian regions studied was shown in Table 2. The Scr value was obtained from the enzymatic assay. The Harris–Boyd method was applied, and an az value greater than 3.0 was deemed to represent a significant difference. Taking Japan as the comparison region, the az values, which ranged from 0.0 to 2.5, suggested no significant regional differences among the eight regions.

Table 1
SD_{ratio} of Scr and eGFR (EPI/E) by nested ANOVA.

	SDR_{sex}	SDR_{age}		SDR_{region}	
		Male	Female	Male	Female
Scr	1.83	0.08	0.00	0.24	0.22
eGFR by EPI/E	0.32	1.24	1.42	0.00	0.00

Standard deviation ratio (SDR) of each factor indicates the degree of influence on the target analyte. SDR ≥0.3 was regarded as high, SDR between 0.26 and 0.29 was considered moderate, and SDR ≤0.25 was considered low [5].

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