Glomerular Filtration Rates in Asians

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The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommended the Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate (GFR) for the classification of CKD, but its accuracy was limited to North American patients with estimated GFR <60 mL/min per 1.73 m^2 body surface area of European (White) or African (Black) descent. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) developed another equation for estimating GFR, derived from a population that included both participants without kidney disease and with CKD. But many ethnicities were inadequately represented. The International Society of Nephrology, Kidney Disease Improving Global Outcomes committee promulgated clinical practice guidelines, which recommended the CKD-EPI equation. Investigators in Asia subsequently assessed the performance of these GFR estimating equations—the Modification of Diet in Renal Disease study equation, the CKD-EPI equation (creatinine only), and the CKD-EPI equations (creatinine and cystatin C). In this review, we summarize the studies performed in Asia on validating or establishing new Asian ethnicity GFR estimating equations. We included both prospective and retrospective studies which used serum markers traceable to reference materials and focused the review of the performance of GFR estimation by comparisons with the GFR estimations obtained from the CKD-EPI equations.

Key Words: Asian, Glomerular filtration rate, Chronic kidney failure, Creatinine, Cystatin C

INTRODUCTION

The U.S. National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines originally recommended the Modification of Diet in Renal Disease study (MDRD) equation for estimating glomerular filtration rate (GFR) as part of the identification and classification of kidney disease (CKD).[1] Due to the inherent limitations of the original derivation patient population, the accuracy of the MDRD study equations was limited to patients with CKD and with estimated GFR <60 mL/min per 1.73 m^2 body surface area.[2] Moreover, as the study was in a North American population, estimated GFR was only valid in American CKD patients of European (White) and African (Black) descent. The originally published MDRD study equation required more variables than was thought to be practicable for routine clinical practice (needed serum urea nitrogen and serum albumin additionally), and an abbreviated 4-variable equation was eventually adopted in clinical practice.[3] The variables needed were age, gender, serum creatinine, and ethnicity. Under the auspices of the International Society of Nephrology, the Kidney Disease Improving Global Outcomes committee promulgated clinical practice guidelines, which recommended the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimating GFR.[4] This equation was derived from a population that included both healthy participants without kidney disease and CKD.[5] It also included a more diverse ethnic population. Nonetheless, many ethnicities were inadequately represented, and the validity of estimations of GFR was uncertain with the CKD-EPI equation in non-European and non-African ethnicities.

As a result of the known limitations of using ethnicity as a part of an estimating equation, many investigators looked at other methods of improving the accuracy of the estimating equations including the use of a different serum marker, using another (or more) serum markers in combination, and also muscle mass quantification to adjust serum creatinine, believing that the ethnicity component of equations is in part related to differences in body composition.[6] Thus, the CKD-EPI collaboration group further expressed an equation that used both serum creatinine and cystatin C.[7] Since then, many different investigators in Asia set about to assess the performance of the various GFR estimating equations, in particular, the MDRD study equation, the CKD-EPI equation (creatinine only), and the CKD-EPI equations (creatinine and cystatin C).

In this review, we summarize the various studies performed in Asia on validating or establishing GFR estimating equations, and the clinical practice recommendations established by the various national professional societies, Ministries of Health, or other regulatory agencies, where available. We included both prospective and retrospective studies that indicated serum biomarkers which were traceable to standardized reference materials (serum creatinine and serum cystatin C) and CKD and/

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or healthy participants without kidney disease were clearly stated. We excluded studies that used radionuclide dynamic kidney imaging to estimate GFR instead of plasma sampling. As the more current KDIGO guidelines recommend the CKD-EPI serum creatinine-based GFR estimating equation, we focused the review of the performance in these populations to comparisons with the CKD-EPI equations. However, our comparisons are limited by the various ways for which accuracy and performance were reported in these studies.

Development of Ethnicity Coefficients

Following the introduction of the MDRD study equation, investigators in China and Japan quickly performed validation studies.[8] They discovered that the equations had some bias in their respective populations and developed ethnic coefficients for adjusting the MDRD study equation and subsequently the CKD-EPI equation. The Chinese study was published in the year 2006 demonstrating an ethnic coefficient of 1.233.[9] The Japanese study followed soon after, however, showing a much lower coefficient of 0.763.[10] This is to say that for the same creatinine, age, and gender, the estimated GFR between a Chinese and Japanese individual is different by over 40%! This finding was thought to be biologically less plausible and challenged by many investigators. There are many technical issues which may account for ascribing bias in GFR estimation to ethnicity. These include the use of different reference GFR measurement methods (urinary vs plasma clearance, radioisotopes vs inulin), the lack of serum creatinine standardization, the different methods of assaying serum creatinine (alkaline picrate vs enzymatic), and the sample size, distribution of GFR, and constitution of the study sample (CKD patients vs healthy individuals).[11] Chinese investigators subsequently presented their findings of creatinine standardization as partly accounting for the bias in GFR estimates.[12]

CLINICAL SUMMARY

- Performance of glomerular filtration rate (GFR) estimating equations has been assessed in Asia.
- The Chronic Kidney Disease Epidemiology Collaboration equation may require an ethnicity coefficient to adjust the estimated GFR to an Asian reference GFR laboratory.
- The use of serum cystatin C in combination with serum creatinine may obviate the need for an ethnicity coefficient.

Creatinine Standardization and New Ethnic Coefficients

A crucial element in improving the accuracy of GFR estimating equations is the development of a reference standard for serum creatinine by the National Institute for Standards and Technology Standard Reference Material 967 using isotope dilution mass spectrometry (IDMS).[13] This resulted in the re-expression of the MDRD study equation, where standardized serum creatinine was 0.95 times the original MDRD study serum creatinine. Unless otherwise indicated, the more recent publications where standardized serum creatinine was reported are referenced in this review.

Realizing the limitations of the earlier validation and equation development studies, Chinese and Japanese groups published further studies. Japanese investigators repeated the validation studies aiming to overcome some of the previous limitations by including central laboratory measurement of the GFR and serum creatinine.[14] This study yielded a Japanese ethnic coefficient of 0.808 for the IDMS MDRD study equation. However, in Korea, using inulin clearance (blood sampling) showed a coefficient for the 4-variable IDMS MDRD equation of 0.99096, in between the Chinese and the Japanese results. Thus, despite using standardized creatinine, it was uncertain if ethnicity coefficients for 3 East Asian countries in close proximity were valid or which were more "correct."

The MDRD study equation was limited to only estimating GFR in CKD patients, as GFR is underestimated when applied to patients with kidney function better than 60 mL/min per 1.73 m^2. The CKD-EPI equation was developed to overcome this but continues to include an ethnic adjustment coefficient for African-Americans (Black), albeit smaller at 1.159.[5] The most recent Chinese study on GFR estimation compared the 2-level CKD-EPI equation (Black, White), 4-level CKD-EPI equation (Black, Asian, Native American and Hispanic, White and other), the MDRD study equation (all using standardized serum creatinine), and the Chinese equation (using their previously published nonstandardized serum creatinine-based equation).[15] In this study, they concluded that both the 2-level CKD-EPI equation and the Chinese equation performed equally well and suggested that both could be used in the Chinese population. However, the Japanese examination of the CKD-EPI (creatinine only equation) modeled a Japanese ethnic coefficient of 0.813 (95% confidence interval (CI): 0.794-0.833).[16] This is similar to the previously determined coefficient for the MDRD study equation.[14] The Japanese coefficient modified CKD-EPI equation performed better.[16]

Because of the technical issues resulting in seemingly different ethnicity coefficients obtained in different Asian ethnicities, the Asian Collaborative Study for Creating GFR Estimation Equation was started in 2007 to explore the possibility of creating a common GFR estimation equation for Asian people.[17] Using the same technique (urinary clearance of inulin), it may be possible to ascertain if there are any adjustment coefficients among different Asian ethnicities.[18] There has not been a publication on this endeavor yet.

Pakistani, Taiwanese, and Thai investigators also assessed the performance of the MDRD study and CKD-EPI equations, developed ethnic coefficients adjusting these equations, and/or derived new GFR estimating equations for their respective populations.[19-23] Newly developed GFR estimating equations in Asian ethnicities