Glomerular filtration rates in Asians

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Clinical Summary

Performance of GFR estimating equations have been assessed in Asia.

The CKD-EPI 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.

Key Words

Asian continental ancestry group

Glomerular filtration rate

Chronic renal failure

Creatinine

Cystatin C

Inulin

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Abstract

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommended the Modification of Diet in Renal Disease study (MDRD) equation for estimating glomerular filtration rate (GFR) for the classification of chronic kidney disease (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 MDRD 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.

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 chronic kidney disease.[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/or healthy participants without kidney disease were clearly stated. We excluded studies that used radionuclide dynamic renal 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, radio-isotopes 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]

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 (NIST SRM 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. But a study 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 more interestingly is the persistence of 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 non-standardized 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% CI 0.794-0.833).[16] This is similar to the previously determined coefficient for the MDRD study equation.[14] But 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 (ACOS-CG-FREE) 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 amongst 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 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 are shown in Table 1. As is to be expected, the newly developed equations performed similar or better than the MDRD study equation(s) or the CKD-EPI equation. The performance of the GFR estimations in Asian ethnicities can be compared in Table 2.

Validity of Asian GFR estimation equations

While the validity of externally derived coefficients for Asians for the MDRD and CKD-EPI equations are suspect for a variety of reasons, the newly developed equations from these prospective studies (if serum markers are standardized) are valid for their respective populations (Table 3). Certainly, if these countries have reference laboratories for measured GFR, a well designed study with an adequate sample size,

an appropriately constituted (CKD patients and normal individuals) sample population, should lead to more accurate equations predicting the GFR in the different ethnic populations. Therefore, it is very important that the larger centers in China and Japan perform the derivation and validation studies. Methodologically, there is no perfect way of performing measured GFR, as all methods introduce certain errors and imprecision.[18, 24, 25] Urinary clearance methods will be less accurate if the collection is from a research participant with incomplete bladder emptying, and most methods reflect a short-term clearance period, which differs from an individual's average GFR because of physiologic day-to-day and diurnal fluctuation.

Nonetheless, for the purposes of epidemiologic studies and international comparisons, it would be more reasonable to accept systematic "errors" or rather "ethnicity bias". Arguably, in usual clinical practice the knowledge of the exact GFR is not required but more importantly a relatively accurate estimate throughout the entire GFR range in CKD patients is needed to plot trajectories of GFR over time.[25, 26] And also to link the estimated GFR to clinically important outcomes like dialysis initiation and death.

Cystatin C and combination biomarkers

The presence of "ethnicity" coefficients may be due to the effects of non-GFR factors affecting the serum biomarker used in the GFR estimating equations. The CKD-EPI group developed GFR estimating equations incorporating serum cystatin C alone and in combination with serum creatinine.[7] Interestingly, the cystatin C alone equation obviates the "Black" coefficient, and a combination biomarker approach reduced the "Black" adjustment coefficient to 1.08. This suggests that indeed the ethnicity coefficient may be contributed to a large measure by non-GFR determinants,

which can be more objectively accounted for by using other methods besides the term "ethnicity". Asian investigators studied serum cystatin C in GFR estimating equations but these studies also predated the standardization of serum cystatin C (International Federation of Clinical Chemistry certified reference material, ERM-DA471/IFCC).[27, 28] More recent studies assessed the performance of serum cystatin C alone and in combination with serum creatinine in the CKD-EPI equations.[29, 30] While further assessment work is required, it appears that serum creatinine and cystatin C in combination may reduce the imprecision of either marker alone.

Nonetheless, the common findings in these studies are that the various equations performed differently within different GFR categories (<30, 30-60, 60-90, >90 mL/min per 1.73 m^2). On an overall basis, in a multiethnic Asian population, using 2 biomarkers in estimating GFR (taking the average or using the combination equation) improved GFR estimation.[29] Obviously, obviating the need to consider ethnicity in multi-ethnic populations is attractive in practical implementation. The Chinese study found that accuracy was better in individuals with higher (>90) GFR or very low GFR (<30).[30] But a Japanese study showed that the CKD-EPI cystatin C alone equation performed better.[31] In fact, using the development set, the derived Japanese ethnic coefficient for the equation was 0.977 (95% confidence interval 0.853 to 1.002) versus a coefficient of 0.908 (95% CI 0.889 to 0.928) for the CKD-EPI combination serum creatinine and cystatin C equation.

Official recommendations

With the validation studies, some professional societies and public health organizations have made recommendations for the choice of GFR estimating equations for their populations, which is summarized in Table 4. The Philippine

Society of Nephrology endorses the CKD-EPI equation but does not have a clinical practice guideline. The Korean Society of Nephrology recommends using the original IDMS MDRD and CKD-EPI equations without ethnic adjustment for estimating GFR, and now is in the process of revising its clinical practice guidelines of CKD management. Malaysia recommended the MDRD study equation but is also in the process of updating their clinical practice guidelines.[32] The Japanese Society of Nephrology recommends using the Japanese formula for estimating GFR.[33] At the time of this review, Hong Kong, Taiwan, the Philippines, and India were developing guidelines and recommendations.

Pending validation studies

There are many countries in Asia with different ethnicities. The countries vary in their resources and ability to assess the performance of the MDRD study and CKD-EPI equations. Studies which are pending publication at the time of this review include those from India and the Philippines.

Summary

Currently recommended GFR estimating equations are probably valid in Asian ethnicities. When benchmarked to a reference GFR laboratory, certain ethnicities may require "ethnic" coefficients for adjusting the KDIGO recommended CKD-EPI equation. Estimating GFR using a combination of serum creatinine and cystatin C may obviate the need to consider an ethnicity adjustment.

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Table 1 Asian GFR validation studies

							Validated serum marker type					Equations validated	
Ethnicity	**GFR validation study**	**Cohort** (Healthy or CKD or Mixed)	**Age (years)**	**Average GFR** (mL/min per 1.73 m^2)	**Reference GFR method**	**Clearance method**	**Creatinine**	**Standardized to NIST SRM 976**	**Cystatin C**	**Standardized to ERM-DA471/IFCC**	**Creatinine + Cystatin C**	**MDRD**	**CKD-EPI**
CKD-EPI	-	Mixed N= 5352	47±15	68 ± 39	I-iothalamate	Urinary	Yes	Yes	Yes	Yes	Yes	-	-
Chinese	Kong et al [15]	Mixed N = 977	48.3 ± 16.0	68.3 ± 37.1	Tc-DTPA	Plasma (2 and 4 hours)	Yes	Yes	-	-	-	Yes	Yes
Chinese	Zhang et al [30]	Mixed N = 617	47.11 ± 17.25	73.80 ± 37.55	Tc-DTPA	Plasma (2 and 4 hours)	Yes	Yes	Yes	Yes	Yes	No	Yes
Japanese	Matsuo et al [14]	Mixed Development N = 413 Validation N = 350	51.4 ± 16.5 53.9 ± 17.5	59.1 ± 35.4 57.2 ± 34.7	Inulin	Urinary	Yes	Yes	-	-	-	Yes	No
Japanese	Horio et al [16]	Mixed Development N = 413 Validation N = 350	51.4 ± 16.5 53.9 ± 17.5	59.1 ± 35.4 57.2 ± 34.7	Inulin	Urinary	Yes	Yes	-	-	-	-	Yes
Japanese	Horio et al [31]	Mixed Development N = 413 Validation N = 350	51.4 ± 16.5 53.9 ± 17.5	59.1 ± 35.4 57.2 ± 34.7	Inulin	Urinary	Yes	Yes	Yes	Yes	Yes	No	Yes
Korean	Lee et al [34]	Mixed N = 147	48 ± 14.99	55.60 ± 27.79	Inulin	Plasma (curve fitting)	Yes	Yes	-	-	-	Yes	No
Korean	Chung et al [35]	Healthy N = 207	40.4 ± 11	110.3 ± 20.7	Tc-DTPA	Plasma (0.16, 0.5, 3, and 4	Yes	Yes	-	-	-	Yes	Yes

						hours)							
Korean	Oh et al [21]	Mixed N = 266	49.0 ± 15.8	58.4 ± 31.7	Inulin	Plasma (curve fitting)	Yes	Yes	-	-	-	Yes	No
Korean	Jeong et al [20]	Mixed N = 960	63.0 ± 13.0	67.8 ± 34.7	Cr-EDTA	Plasma (3 and 5 hours)	Yes	Yes	-	-	-	Yes	Yes
South Asian (Pakistani)	Jessani et al [19]	Mixed	50.6 ± 10	91.0 [36.7]	Inulin	Urinary	Yes	Yes	-	-	-	Yes	Yes
South Asian (Indian)	Prasad et al [36]	Mixed N = 897	44.8 (Range: 18 to 70)	Reported as means by GFR categories	Tc-DTPA	Plasma (1 and 3 hours)	Yes	No	-	-	-	Yes	No
Singapore (Chinese, Malay, Indian, Others)	Teo et al [29]	Mixed N = 335	53.5 ± 15.1	67 ± 33	Tc-DTPA	Plasma (2, 3.5 and 5 hours)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Taiwanese (Chinese)	Chen et al [22]	Mixed Development N = 556 Validation N = 139	 47 ± 0.7 51 ± 1	67 ± 1.6 68.8 ± 3.0	Inulin	Urinary	Yes	Yes	-	-	-	Yes	Yes
Thai	Praditpornsilpa et al [23]	CKD	59.5 ± 13. 6	55.86 ± 30.40	Tc-DTPA	Plasma (Curve fitting)	Yes	Yes	-	-	-	Yes	Yes

Average GFR is reported as mean standard deviation or median (25% to 75% or inter-quartile range).

I-iothalamate = ^{125}I-iothalamate

DTPA = ^{99m}Tc- diethylenetriamine pentaacetic acid

EDTA = ^{51}Cr-ethylenediaminetetraacetic acid

Table 2 Accuracy of CKD-EPI equations in Asians

		Overall		
Ethnicity/Equation	**GFR validation study**	**Bias Median (95% CI)**	**Precision IQR (P25, P75 or 95% CI)**	**Accuracy P30 (or reported as 1 – P30, 95% CI)**
CKD-EPI Creatinine only	Inker et al [7]	3.7 (2.8 to 4.6)	15.4 (14.3 to 16.5)	12.8 (10.9 to 14.7)
CKD-EPI Cystatin C only	Inker et al [7]	3.4 (2.3 to 4.4)	16.4 (14.8 to 17.8)	14.1 (12.2 to 16.2)
CKD-EPI Creatinine-cystatin C	Inker et al [7]	3.9 (3.2 to 4.5)	13.4 (12.3 to 14.5)	8.5 (7.0 to 10.2)
CKD-EPI Average of creatinine and cystatin C	Inker et al [7]	3.5 (2.8 to 4.1)	13.9 (12.9 to 14.7)	8.2 (6.7 to 9.9)
Chinese Creatinine only	Kong et al [15]	0.2	20.5	73.4
Chinese Creatinine only	Zhang et al [30]	5.399	20.636 (−4.122, 16.514)	72.61
Chinese Cystatin C only	Zhang et al [30]	4.417	23.87 (−6.374, 17.496)	72.12
Chinese Creatinine-cystatin C	Zhang et al [30]	2.614	20.078 (−5.516, 14.562)	76.66
Japanese Cystatin C only	Horio et al [31]	-1.1 (-1.9 to 0.9)	14.5	79 (74 to 83)
Japanese Creatinine-cystatin C	Horio et al [31]	-4.7 (-5.7 to -3.1)	13.2	77 (72 to 81)
Korean Creatinine only	Chung et al [35]	0.4 (-55.5, -45.1)	-	91.8
Korean Creatinine only	Jeong et al [20]	−0.9	15.5	82.8
South Asian (Pakistani)	Jessani et al [19]	26.8 (28.2 to 25.4)	22.6 (19.9 to 25.3)	76.1 (72.7 to 79.5)
Singapore (Chinese, Malay, Indian, Others) Creatinine only	Teo et al [29]	–0.036 (–1.23 to 1.58)	15.37 (13.26 to 17.69)	13.73 (10.05 to 17.42)
Singapore (Chinese, Malay, Indian, Others) Cystatin C only	Teo et al [29]	–2.93 (–3.82 to –1.20)	14.03 (12.23 to 16.83)	12.84 (9.25 to 16.42)
Singapore (Chinese, Malay, Indian, Others) Creatinine-cystatin C	Teo et al [29]	–1.21 (–2.77 to –0.16)	13.74 (11.30 to 15.92)	9.85 (6.66 to 13.04)
Singapore (Chinese, Malay, Indian, Others) Average of creatinine and cystatin C	Teo et al [29]	–1.17 (–2.12 to 0.11)	13.70 (10.82 to 15.31)	8.96 (5.90 to 12.01)

Taiwanese (Chinese) Creatinine only	Chen et al [22]	-8.0	25	60.4
Thai Creatinine only	Praditpornsilpa et al [23]	-8.0	15.6	68.0

Average GFR is reported as mean standard deviation or median (25% to 75% or inter-quartile range).

I-iothalamate = ^{125}I-iothalamate

DTPA = ^{99m}Tc- diethylenetriamine pentaacetic acid

Bias is the median of the difference between estimated GFR and measured GFR.

Precision is the inter-quartile range.

Accuracy is the percentage (P30) of estimates of GFR within ±30% of the measured GFR.

Results were reported differently; please refer to the original article for details of the statistical methods.

Table 3 Asian GFR equations and ethnic coefficients for creatinine-based MDRD Study and CKD-EPI equations

Country/Ethnicity	MDRD ethnicity coefficient	CKD-EPI ethnicity coefficient	Modified MDRD equation*	Modified CKD-EPI equation† (2-level)	Modified CKD-EPI equation (4-level)
China (non-standardized creatinine)	1.223 [9]		$175 \times (Cr^{-1.234} \times (Age)^{-0.179}$ ($\times 0.79$ if female) [9]		
Japan	0.808 [14]	0.813 [16]	$194 \times SCr^{-1.094} \times Age^{-0.287}$ ($\times$ 0.739 if female)		
Korea	1.02046 [21] 0.99096 [34]			Refer to paper.[20]	
Pakistan				0.686 × CKD-EPI$^{1.059,\ [19]}$	
Taiwan			1.309 × MDRD$^{0.912,\ [22]}$	1.262 × CKD-EPI$^{0.914,\ [22]}$	1.205 × CKD-EPI$^{0.914,\ [22]}$
Thailand	1.129 [23]		$375.5 \times Cr^{-0.848} \times Age^{-0.364} \times$ (0.712 if female) [23]		

* New equation in the format of the MDRD study equation, or incorporates the IDMS MDRD study equation for the ethnicity (only the 4-variable equation is considered)

† New equation in the format of the CKD-EPI equation, or incorporates the CKD-EPI equation for the ethnicity (only the 2-level equation is considered)

Table 4 National/Regional Recommendations/guidelines for Asian ethnicities

Country/Ethnicity	**Guidelines**	**Source of Guidelines** (Government or Professional Society)	**Guidelines reference(s), if any**
China	No		Chinese eGFR Investigation Collaboration. Modification and evaluation of MDRD estimating equation for Chinese patients with chronic kidney disease. [37]
Hong Kong	No	-	-
India	No	-	-
Japan	Yes	Japanese Society of Nephrology	Evidence-based Practice Guideline for the Treatment of CKD.[33]
Korean	Yes	Korean Society of Nephrology	Clinical Practice Guidelines of Chronic Kidney Disease (currently under revision)
Malaysia	Yes	Ministry of Health; Academy of Medicine	Clinical Practice Guidelines Management of chronic kidney disease in adults. [32]
Pakistan	No	-	-
Singapore	No	-	-
Taiwan	No	-	-
Thailand	Yes	Nephrology Society of Thailand	Booklet published in Thai