Assessing kidney function in Asia

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ABSTRACT

An equation for accurate estimation of the glomerular filtration rate (GFR) is vital for staging and directing the treatment of chronic kidney disease (CKD), which is a source of considerable morbidity and mortality around the world. The Modification of Diet for Renal Disease (MDRD) equation, which includes a racial coefficient, is commonly used. The MDRD equation has been validated in Caucasian populations, but modifying the racial coefficient for Asian countries has resulted in substantially different values that may not be due to race alone. Moreover, it is sometimes difficult to define race, particularly in multi-ethnic populations and among offspring of inter-ethnic marriages. Furthermore, the precision of the MDRD equation is poorer at the early stages of CKD. New markers, such as cystatin C, and new equations may be needed to accurately assess wider ranges of GFR in multi-ethnic countries. We review the development of GFR-estimating equations from an Asian perspective.

Keywords: Asian Continental Ancestry Group, chronic kidney failure, creatinine, cystatin C, glomerular filtration rate

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INTRODUCTION

Chronic kidney disease (CKD) frequently leads to end-stage kidney disease requiring dialysis or transplantation, and is a "disease multiplier" that increases the risk of death from cardiovascular causes.[1] The detection, monitoring and treatment of CKD is essential, as it causes considerable morbidity and mortality. It is a growing problem in Asian countries, partly due to the rising prevalence of non-communicable diseases such as hypertension and diabetes, and partly due to the aging population.[2] Singapore is among those with the highest incidence of CKD cases, and the number of new patients on dialysis is increasing yearly.[3]

The most widely used classification of CKD severity and clinical practice guidelines is the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI), which classifies CKD by glomerular filtration rate (GFR) estimated by the Modification of Diet in Renal Disease (MDRD) equation.[1] The equation includes a factor for the American white or black race. Therefore, there is a movement to test its validity in Asian countries and modify its racial coefficient to better fit Asian populations. But to what extent is race responsible for the difference in the accuracy of the equation in different populations? What is the impact of "race" for cosmopolitan cities and multiracial countries? We review some studies that evaluated the performance of MDRD in Asian patients, examine the role of the race coefficient in improving GFR estimation using the MDRD equation and discuss other markers that can potentially increase the reliability of serum creatinine in estimating GFR.

CURRENT METHODS TO ESTIMATE GFR

CKD patients are often asymptomatic, and thus, a laboratory measurement of kidney function is required. The GFR gives a measure of the number of functioning nephrons. This can be measured from the urinary clearance of a marker, or estimated using equations incorporating one or more markers and other data. The ideal marker is freely filtered at the glomerulus, is not eliminated in extra-renal sites and is neither secreted nor absorbed by renal tubules. If an endogenous marker is used, it would ideally be produced at a constant rate in disease and in health. Although serum creatinine is most commonly used to assess kidney function, it has long been appreciated that creatinine concentration varies with muscle mass, dietary protein and gender.[4] Furthermore, creatinine is secreted by renal tubules, and this secretion varies substantially in the same individual over time, between individuals, and at low kidney function.[5] A 24-hour urine collection for clearance studies attempts to increase the accuracy by reducing reliance on a single serum creatinine and its variability with muscle mass. However, this advantage is obviated in clinical practice, as urine collection is often unreliable without supervision and in the patient groups who require them most (e.g. elderly, the incontinent).

When more accurate GFR estimation is required (e.g. potential kidney donors, patients at the extremes of body size) measurement of exogenous markers is used. It has been assumed that inulin, a polysaccharide derived from vegetables, has characteristics which approach the ideal exogenous marker. However, the complexity of administration (constant intravenous infusion), its poor commercial availability and the non-standardisation of

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laboratory detection methods have resulted in it being used only for research studies. In clinical practice, radionuclide-labelled markers such as ^{125}I-iothalamate, 51Cr-EDTA and ^{99m}Tc-DTPA are commonly measured instead.[6,7] There are also techniques using markers without radio-labelling.[8] The measurement of urinary clearance of these markers should theoretically give the most accurate GFR measurements, but incomplete bladder emptying reduces the accuracy. Therefore, many centres also use plasma-only methods to measure GFR. Calculating the GFR from plasma-only (or serum) methods can be made by fitting the entire clearance curve using multiple blood draws, or estimated using one to three samples that form the second part of a bi-exponential curve, and then applying correcting equations for ignoring the first exponential.[6,7] The correcting equations (e.g. Chantler and Brochner-Mortensen) improve the accuracy for higher GFRs.

Although there are guidelines for the performance of these reference GFR methods, there is wide variation for the timing of urine and plasma sampling between centres.[6,7] When measured GFRs are higher (e.g. in potential kidney donors), shorter sampling times are needed since clearance of the marker would be rapid. However, longer sampling times from the time of administering the marker are required when GFR is less than 30 ml/min. This is because renal clearance of the marker is low, and early sampling times may erroneously attribute clearance to kidney function when the marker declines as a result of distribution in the body. There are thus more GFR errors when patients have oedema, a common finding in kidney disease patients.

Furthermore, the coefficient of variation for repeated measurements of exogenous markers in the same individual may be up to 10%.[6] This variation is due to physiology, and may also be contributed by the pre-procedure preparation of the patients. Many centres perform GFR measurements in patients who have fasted, but these procedures can take up to six hours or longer. Therefore, some centres do the procedures after the patient has taken a protein-light meal (amino acids increase GFR). Because of physiological variation, coupled with the systematic differences in the measurement and calculation of GFR, clinically significant differences can be detected only when GFR measurements differ by more than 20% consistently. The inconvenience to patients (time and multiple blood sampling), costs and radiation exposure reduce the clinical utility of reference GFR measurements, and in practice, equations that estimate GFR using a spot serum sample of an endogenous marker are used.

KDOQI recommends the use of the "abbreviated" MDRD equation, which was derived from 1,628 chronic kidney disease patients who underwent GFR measurement with ^{125}I-iothalamate by urine clearances.[9] It was able to predict 90.3% of the variability in measured GFR in the validation sample.[9] The formula uses four variables only, namely, serum creatinine, age, race and gender, and takes the form: estimated GFR = $186 \times \text{creatinine}^{-1.154} \times \text{Age}^{-0.203}$ × (0.742, if female) × (1.21, if African-American) (age in years and serum creatinine in mg/dL).

However, the MDRD study population consisted of mostly white patients, and had few patients with diabetic kidney disease. Its validity has been extensively evaluated, and it was observed that while it was reasonably accurate in patients with moderate to advanced kidney disease (< 60 ml/min per 1.73 m^2), it was not as accurate in diabetic patients, obese patients, kidney transplant recipients, and as a screening test among healthy individuals. Furthermore, laboratory measurement technique and calibration affect serum creatinine determinations. Standardised creatinine measurements have only started recently with the SRM 967 programme of the National Institute of Standards and Technology (USA), resulting in the re-expression of the MDRD equation: GFR = $175 \times \text{creatinine}^{-1.154} \times \text{Age}^{-0.203}$ × (0.742, if female) × (1.21, if African-American).[10] The same group, in collaboration with other investigators, recently developed another equation, the Chronic Kidney Disease Epidemiology (CKD-EPI) equation, which aims to overcome some of the disadvantages of the MDRD-equation.[11]

PERFORMANCE OF THE MDRD EQUATION IN ASIAN COUNTRIES

Chinese and Japanese investigators have found that modifying the racial coefficient for the abbreviated MDRD equation improved the estimation of the GFR and increased the accuracy of CKD classification (Table I).[12-14] GFR estimation also improved when new equations are derived from their data. However, there was a 30% difference between the Chinese and Japanese coefficients for the MDRD equation, suggesting that race alone accounted for a 30% difference in the GFR of a Chinese and Japanese CKD patient with the same age, gender and serum creatinine.

Although age and gender are invariable in the four-variable MDRD equation, there can be considerable systematic error in measuring serum creatinine when different methods (enzymatic vs. kinetic Jaffe) are used in different studies.[15] The two studies attempted to correct this by indirectly calibrating their measurements to those of the Cleveland Clinic laboratory, but it is likely that not all errors were removed.[16] One major issue in all of these studies is the use of different reference GFR techniques; the

Table I. Chronological development of creatinine-based GFR-estimating equations.

Year	Study	Equation
1976	Cockroft-Gault[39]	[(140 − Age) × Weight] / (72 × SCr) × 0.85, if patient is female
1999	MDRD[9]	$170 \times (SCr)^{-0.999} \times (Age)^{-0.176} \times (0.762$, if patient is female) $- (1.180$, if patient is black) $\times (SUN)^{-0.170} \times (Alb)^{0.318}$
2002	4-variable MDRD[1]	$186 \times (SCr)^{-1.154} \times (Age)^{-0.203} \times (0.742$, if patient is female)
2006	Chinese-modified MDRD[14]	(4-variable MDRD) × 1.233
2007	Japanese-modified MDRD[12]	(4-variable MDRD) × 0.741
2007	MDRD re-expressed for standardised creatinine[10]	$175 \times (SCr)^{-1.154} \times (Age)^{-0.203} \times (1.212$, if patient is black) × (0.742, if patient is female)
2009	Revised Japanese-modified MDRD[25]	(Re-expressed MDRD) × 0.808
2009	CKD-EPI equation[11]	Refer to paper for details

Note: Age in years and weight in kg.
SCr: serum creatinine (mg/dL) [multiply by 88.4 for μmol/L]; SUN: serum urea nitrogen (mg/dL) [multiply by 0.357 for mmol/L]; Alb: serum albumin (g/dL)

Japanese study used urinary clearance of inulin, while the Chinese study used plasma clearance of ^{99m}Tc-DTPA. GFR by plasma clearance methods has been variously reported as underestimating or overestimating urinary clearance by up to 8%.[17,18] Furthermore, the suitable sampling time after its intravenous administration may vary among patients with different kidney functions.[19,20] Finally, the development of the equations relied on different CKD populations (body size, kidney disease type, gender, age and kidney function distributions), which may affect serum creatinine levels and consequently, the regression equation. For all the reasons discussed previously, the validity of the racial coefficients for the MDRD equation derived so far is therefore questionable. It is probably preferable to use the newly derived equations that are specific to the Chinese and Japanese populations, as the estimations reflect the method of GFR measurement in their respective countries (health authority licensing requirements limits the availability of markers), and if widely adopted, pegging these measurements to clinical outcomes would improve clinical utility.

IMPORTANCE OF RACE IN CALCULATING ESTIMATED GFR

Even if serum creatinine calibration and the GFR reference technique were identical, could race alone cause such a disparity between the two studies? It may become more difficult to define race in a highly globalised world with migration and inter-racial marriages. Moreover, even within the same race, body composition may be different because of environmental influences.[21] Thus, an equation derived from Chinese in the People's Republic of China may not fit an ethnic Chinese population in Singapore.

GFR estimated by the MDRD equation is normalised to body surface area (BSA), usually using the DuBois equation.[22] However, this equation was derived from only nine non-Asians in the 1900s, and may not be reflective of body morphology at this time in a Singaporean population. Moreover, a single height-weight formula may be insufficient for use in patients with a wide range of body shapes. In fact, the British guidelines for GFR determination in nuclear medicine recommended an alternative formula.[6] Furthermore, is BSA the appropriate factor for normalising GFR for comparisons between individuals? Other investigators have proposed using extracellular fluid volume, assuming that it reflects the role of GFR.[23] Therefore, the standardisation of GFR measurement technique, serum creatinine and body surface area estimation are required before it would be possible to ascertain true racial differences in GFR as well as the requirement of racial factors for GFR-estimating equations.

Assuming appropriate study methods are used, a statistically important race coefficient that is obtained would be clinically important in improving the estimation of GFR during the assessment of patients with CKD, only if the magnitude is large enough (probably > 10%, i.e. multiply by a factor of 1.1 and above). Race may indeed be significant and important, since the coefficient for African-Americans (but reduced to 1.159) persisted for the newly developed CKD-EPI equation.[11] In 2005, 65% of patients started dialysis urgently in a Singapore hospital, and one possible contributory factor is the inaccurate point-estimates of GFR in Asians and thus, CKD staging, and the lack of prediction of the trajectory of GFR declines during follow-ups.[24] Current studies on the accuracy of GFR-estimating equations have reported that 30%–50%, 60%–85%, and > 90% of patients achieve eGFR to within 15%, 30%, and 50% of the measured GFR, respectively.[14,25] Accuracy to within 30% and 50% is inadequate for practice, based

on guideline paradigms. Patients in slowly progressive Stage 3 CKD (i.e. GFR > 30 mL/min/1.73m^2) are usually seen at less frequent intervals, but those in Stage 4 require preparation for transition to end-stage kidney disease care, which may be dialysis, kidney transplantation or palliative care. A misclassification to Stage 3 results in inadequate transition time for dialysis and poorer clinical outcomes. For example, a patient with an actual GFR of 30 mL/min/1.73m^2 ± 30% of estimation error can have an estimated GFR of 39 mL/min/1.73m^2 (should have a longer time between follow-ups for slowly progressive declines, thereby reducing healthcare costs), but a GFR of 21 mL/min/1.73m^2 would clearly require closer follow-up and preparation for end-stage kidney disease care. Therefore, race coefficients that correct significantly biased estimated GFR will make a difference in clinical management.

The current estimation equations are also inaccurate for mildly depressed GFR in the 60–90 mL/min/1.73m^2 ranges, the purported "creatinine-blind" range, and this has implications for clinical research, clinical practice and public health resource allocation, particularly in screening for CKD. Undetected early kidney disease will result in inadequate treatment and may lead to end-stage renal disease with its associated problems of high costs and mortality with renal replacement therapy.

Ideally, equations that are not reliant on a race factor should be developed. The racial coefficients derived in the Chinese and Japanese studies most likely reflect a summative "correction factor" for all the factors (body composition) that adjust for serum creatinine and differences in GFR measurement techniques. When using only one GFR technique for a large enough multiracial population, an objective method for measuring muscle mass that can be introduced into a serum creatinine-based GFR-estimating equation may obviate the "race" factor and reduce inaccuracies of GFR estimation as a result of difficulties in classifying "race".[26] This would be particularly true for a multiracial population like Singapore.

LONGITUDINAL STUDIES OF GFR ESTIMATION

Increased accuracy of GFR estimation is only useful if it is linked to longitudinal clinical outcomes. Studies evaluating the effectiveness of therapeutic intervention on CKD progression should compare two or more experimental groups, as changes in the rate of decline in GFR of a single group may be attributed to regression to the mean.[27] Analyses may be time-to-endpoint-based (a popular one being the doubling of serum creatinine) or slope-based (based on serial determinations of GFR). A time-to-endpoint approach does not make the assumption that kidney function decline is linear in all patients, and avoids problems of premature dropout.[28] If doubling of serum creatinine is used, data analysis must account for end-stage kidney disease that may develop before the endpoint so as to avoid erroneous conclusions.[29] An alternative analysis of data from the African-American Study of Kidney Disease and Hypertension compared the validity of an equation derived from the study by examining the concordance of the relationships of CKD risk factors with the outcomes on creatinine-based estimated GFR, against the corresponding relationships of risk factors with outcomes based on radionuclide-measured GFR. It was concluded that outcomes based on creatinine-based GFR estimates were satisfactory surrogates, albeit for analyses in risk factors for CKD progression.[30] There are currently no studies conducted in Asians evaluating the longitudinal performance of serum creatinine-based estimated GFR in CKD progression.

CYSTATIN C, A POTENTIAL NEW MARKER IN ESTIMATING GFR

Although CKD Stages 1 and 2 may be considered "pre-clinical" diseases, there is little evidence that they are associated with poorer clinical outcomes.[31] There may indeed be a true threshold, or it may be due to the imprecision of the abbreviated MDRD equation at higher GFR values.[32,33] Several low-molecular-weight endogenous proteins have been evaluated as alternative markers to creatinine. Cystatin C, a cysteine protease inhibitor produced by nucleated cells, has received the most attention. Studies have shown that serum cystatin C may be more sensitive in identifying mild reductions in kidney function than serum creatinine.[34,35] Two studies showed that equations incorporating both serum cystatin C and creatinine improved GFR estimations and reduced the misclassification of CKD, especially at milder degrees of kidney dysfunction.[36,37] However, owing to its relatively recent introduction, there are only a limited number of longitudinal studies for cystatin C, and no validation in Asian populations.[37] More importantly, there is no standard for serum cystatin C measurement; at present, the particle-enhanced turbidimetric and particle-enhanced nephelometric latex immunoassays are employed.[38] Furthermore, serum cystatin C levels have been found to be affected by corticosteroid use, thyroid disease and inflammation. Therefore, more studies are needed before serum cystatin C can be used in routine clinical practice.

CONCLUSION

There has been some research in adapting the MDRD equation for use in Asian countries, but more research

is required to assess kidney function over a wider GFR range and in multi-ethnic Asian populations. Clinically indicated GFR measurements should be performed with the GFR technique available in the country (or institution) according to best practices espoused by guidelines. Laboratories should standardise their serum creatinine assays because calibration is crucial in improving the accuracy of GFR estimations. As the MDRD equation has been widely adopted since its publication and used in countless studies globally, we recommend that the MDRD equation, re-expressed for standardised serum creatinine, be used for clinically important kidney function estimations (GFR < 60 ml/min) without consideration of racial adjustments in multiracial Asian populations, such as in Singapore.

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