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GFR Estimation in Japan and China: What Accounts for the Difference?

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A primary goal for staging chronic kidney disease (CKD) with glomerular filtration rate (GFR) has been to risk stratify patients for adverse outcomes.(1) A somewhat arbitrary threshold (<60 ml/min/1.73 m^2) defines chronic kidney disease and another somewhat arbitrary threshold (<15 ml/min/1.73 m^2) defines kidney failure. The literature based on a uniform CKD staging system supports various screening and intervention guidelines. GFR is usually estimated from serum creatinine, age, sex, and ethnicity (African American [ND1]compared to white) with the Modification of Diet in Renal Disease (MDRD) Study equation.(2) Notably, there have always been concerns with the ethnicity coefficient since it does not address non-white, non-African American ethnic groups. Several studies have sought to address this problem in order to apply GFR estimation in non-white, non-African American populations. Ma and colleagues developed a new coefficient (1.23) that estimates a 23% higher GFR in Chinese than whites (the arbitrary reference group) at the same serum creatinine level.(3) In this issue of the American Journal of Kidney Diseases, Matsuo and colleagues developed a new coefficient (0.81) that estimates a 19% lower GFR in Japanese than whites at the same serum creatinine level (4), which is similar to a previously reported Japanese coefficient (0.76).(5) To put these coefficients into perspective, a 60 year-old man with a serum creatinine of 1.4 mg/dl would have an estimated GFR of 52 ml/min/1.73 m^2 if white, but 64 ml/min/1.73 m^2 if Chinese and 42 ml/min/1.73 m^2 if Japanese. What accounts for the difference?

In order to make sense of these ethnicity coefficients, it is important to understand their biological framework. Creatinine is generated from skeletal muscle catabolism (6) and a lesser extent from dietary protein (particularly cooked meat).(7,8) Besides glomerular filtration, creatinine is eliminated by tubular secretion and a nearly negligible fraction by intestinal excretion.(9) GFR estimating equations attempt to account for the variation in serum creatinine due to these non-GFR determinants. The MDRD Study equation models the non-GFR determinants of serum creatinine with demographic variables (age, sex, and ethnicity). One explanation is that coefficients for demographic variables model variation in muscle mass, since muscle mass declines with age consistent with the age −0.203 exponential coefficient in the MDRD Study equation, women have less muscle mass then men consistent with the female sex 0.74 coefficient, and African-American have higher muscle mass than whites, consistent with the African-American race coefficient of 1.21.(10) Thus, it is surprising that the ethnicity

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coefficients should be so different between Chinese and Japanese patients. If demographic coefficients are interpreted as muscle mass differences, then one would expect that Chinese compared to Japanese patients have the same difference in skeletal muscle as 33 year-old men compared to 60 year-old women.

Another consideration is that one or both of the coefficients for Japanese and Chinese patients may be inaccurate due to study design differences with the MDRD Study. The Japanese coefficient is actually a “Japanese compared to white ethnicity” coefficient, but it was only developed using patients from Japan with the comparison group, whites, based on historical data. This same problem exists for the Chinese coefficient. There are several differences in the study protocols used to determine the relationship between serum creatinine and GFR in each of these ethnicity groups (Table). To compare the relationship between serum creatinine and GFR between two ethnic groups, an ideal study would use identical methods to measure serum creatinine and GFR, identical methods to identify and recruit study patients, and the same statistical approach for both groups. Both the Japanese coefficient and the Chinese coefficient studies addressed calibration differences with their serum creatinine assay compared to the MDRD Study reference laboratory.(3,4) However, recent data suggests differences in creatinine assay calibration may still have led to inaccuracy in the Chinese coefficient.(11)

Another potential sources of *bias* is that each study used a different method to measure GFR. If there are systematic differences between methods of GFR measurement, the ethnicity coefficient will reflect these differences in addition to any true ethnic differences in the non-GFR determinants of serum creatinine. The study in Japan used inulin clearance whereas the MDRD Study used iothalamate clearance. Several investigators,(12–14) but not all,(15) have found iothalamate clearance to give higher values than a simultaneous inulin clearance and this could contribute to a Japanese coefficient <1.0. The Chinese coefficient study used plasma clearance, a method that can vary depending on body distribution effects of the exogenous marker and on the model used to account for these distribution effects.(16,17) Recently, Agarwal and colleagues found a plasma clearance over 4 hours (as used in the Chinese study) overestimated GFR (plasma clearance over 10 hours) by 22 to 50% and this could contribute to a Chinese coefficient >1.0.(18) A morning meal preceded the GFR measurement in the Chinese coefficient study,(19) and any dietary protein in this meal could have raised GFR (20) and contributed to a Chinese coefficient >1.0. There is not necessarily one correct approach to measuring GFR in all settings, as time, cost, and convenience are important factors. However, it is important in studies that compare groups to measure GFR the same way in each group.

These studies also differed with respect to how they identified patients. The Chinese coefficient study specifically excluded patients with muscle atrophy, but muscle is the primary source of creatinine generation and this could contribute to a Chinese coefficient >1.0. Patients who were selected by physicians to undergo direct GFR measurement as part of their health care (Japanese and Chinese coefficient studies) may differ from patients who underwent GFR measurement as part of a clinical trial (the MDRD Study). It is also important to consider that Japan, China, and America all have different health care systems and possibly different referral patterns to centers where direct GFR measurement would be obtained and this could potentially affect these ethnicity coefficients. Further, these equations and ethnicity coefficients were developed using patients who had a diagnosis of CKD and may perform differently in settings where most patients are healthy and are being screened for CKD.(21–23)

If study design differences had little impact on these coefficients, are the putative ethnic differences inferred for the non-GFR determinants of serum creatinine plausible? For an equation to estimate GFR per body surface area (BSA), there needs to be parity in the units on both sides of the equation, which requires the demographic coefficients to model the non-GFR

determinants of serum creatinine indexed to BSA.(23) Matsuo et al suggests that the lower creatinine generation (mg/day) in Japanese compared to whites is consistent with a Japanese ethnicity coefficient that is <1.0.(4) However, a more relevant comparison would be with creatinine generation per BSA (mg/day/1.73 m^2), particularly since BSA is lower in Japanese compared to whites (Table). Besides ethnic differences in muscle mass, there may be differences in other non-GFR determinants of serum creatinine. Ethnic differences in dietary protein could contribute to these ethnicity coefficients, particularly if there were practice differences with regard to protein restriction for treatment of CKD.(24,25) There may also be ethnic differences in the tubular secretion of creatinine, a possibility that has been suggested for differences between African Americans and whites.(26)

In addition to Japanese and Chinese ethnicity coefficients for the MDRD Study equation, Matsuo and colleagues developed a separate Japanese equation and Ma and colleagues developed a separate Chinese equation.(3,4) Unlike the ethnicity coefficients used to modify the MDRD Study, these new equations optimize the serum creatinine, age, and sex coefficients to the Japanese and Chinese population. For the specific purpose of managing patients in Japan or China, one could argue that these new equations are preferred. These equations are optimized to the regional assays for serum creatinine, the regional method for measuring GFR, and the regional CKD patient population. It would be important to study these new equations with regard to their impact on risk prediction of outcomes such as mortality and end-stage renal disease.

How do we improve estimation of GFR in multi-ethnic settings? The ethnicity coefficients developed in these studies (3,4) may not be adequate for managing patients in multi-ethnic settings.(27) Additional studies of CKD patients that differ by ethnicity are needed, but these studies should use standardized serum creatinine, the same GFR measurement protocol, and the same inclusion criteria. Further work on ethnic differences with the non-GFR determinants of serum creatinine (indexed to BSA) may provide insight into the biological basis of ethnicity coefficients. Even if ethnicity coefficients are developed and well-validated in CKD populations, it would also be important to assess their validity in representative populations where screening for CKD occurs. Further work to improve estimation of GFR and its interpretation will ultimately benefit the patients we look after.

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Table

Comparison of methods used to develop ethnicity coefficients for the Modification of Diet in Renal Disease Study equation.

	MDRD Study (87% whites, 13% African Americans) (2,28)	Chinese Study(3)	Japanese Study(4)
Ethnicity Coefficient	1.0 in American whites, 1.21 in African Americans	1.23 in native Chinese	0.81 in native Japanese
External Validation	Performed well in several other studies of whites and African Americans with CKD (reasonably unbiased).(21)	Coefficient was inaccurate in a recent Chinese study. (11)	Ethnicity coefficient was similar (0.76) in a prior Japanese study. (5)
Serum Creatinine			
Mean	2.1 mg/dl	2.0 mg/dl (not standardized)	1.6 mg/dl
Assay	Enzymatic (standardized)	Kinetic rate alkaline picrate (Jaffe) reaction	Enzymatic (standardized)
Calibration	Reference assay	Levels adjusted for calibration differences with the MDRD Study laboratory for the Chinese ethnicity coefficient, but not for the separate Chinese equation. This adjustment may not have been accurate.(11)	Levels were slightly lower than standardized assay used to develop MDRD Study equation. No adjustment was made.
Glomerular Filtration Rate			
Mean	40 ml/min/1.73 m^2	55 ml/min/1.73 m^2	58 ml/min/1.73 m^2
Exogenous marker	^{125}I-Iothalamate with SC injection	^{99m}Tc-DTPA with bolus IV injection	Inulin with IV infusion over 2 hours
Clearance method	Urinary clearance with 4 consecutive urine collections by voluntary voiding (no bladder catheter) and 5 plasma samples after a 1 hour equilibrium period	Plasma clearance with dual plasma sampling method (plasma samples at 2nd and 4th hour)	Urinary clearance with 3 plasma and 3 urine samples over 2 hours
Patient factors (physiological state)	Fasting except for a 10 ml/kg oral water load (29)	Post-prandial and 300 to 500 ml oral water load (19)	Fasting except for 500 ml oral water load (30)
Study Population			
Demographics	Mean age 51 years, 60% men	Mean age 50 years, 51% men	Mean age 51 years, 61% men
Body Surface Area	Mean 1.91 m^2	Mean 1.7 m^2	Mean 1.64 m^2
Sample Size	1628 patients	684 patients	763 patients
Target sample	CKD as identified by an elevated SCr level (>1.4 mg/dL in men and >1.2 mg/dL in women) at 15 centers. Extensive exclusion criteria as is common in clinical trials.(31)	CKD as diagnosed by KDOQI guidelines (1) at 9 renal institutes at university hospitals. Persons with skeletal muscle atrophy, edema, heart failure, pleural effusions, or ascites excluded.	Mostly nephrology inpatients at 80 centers undergoing a kidney biopsy or education on life style changes.
Case Mix (top 4 etiologies)	Glomerular disease, polycystic kidney disease, hypertensive nephrosclerosis, other kidney disease or not specified	Primary or secondary glomerular disease, hypertension, obstructive kidney disease, renovascular disease	Chronic glomerulonephritis, miscellaneous, diabetes mellitus, and nephrosclerosis (kidney donors/recipients also included)

	MDRD Study (87% whites, 13% African Americans) (2,28)	Chinese Study(3)	Japanese Study(4)
Statistical Methods	Regression of logarithmic GFR onto logarithmic SCr with a "African American compared with white ethnicity" indicator variable.	Measured GFR was regressed onto estimated GFR with the intercept forced to 0 and the slope as the Chinese coefficient.	Japanese coefficient calculated by minimizing the root-mean-squared error between measured GFR and estimated GFR.

Note: Conversion factors for units: serum creatinine in mg/dL to mol/L, x88.4; glomerular filtration rate in ml/min/1.73m^2 to ml/s/1.73m^2, multiply by 0.01667.

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease; KDOQI, Kidney Disease Outcomes Quality Initiative, SC, subcutaneous; IV, intravenous; SCr, serum creatinine.