A Comparative Study of Different Methods of Estimating Glomerular Filtration Rate in a Subset of Filipinos with Normal Renal Function

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ABSTRACT

Kidney function is commonly quantified using the glomerular filtration rate (GFR). However, the gold standard of measuring GFR, inulin clearance, is not practical for daily clinical use. This study compares different methods of GFR estimation based on serum creatinine, plasma levels of ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA), and camera acquisition of ^{99m}Tc-DTPA uptake. Seventy-five Filipino adults between ages 20 and 35 presumed to have normal kidneys were recruited. Each subject underwent gamma camera scintigraphy using the Gates and Inoue protocols after receiving a dose of ^{99m}Tc-DTPA. Blood samples were subsequently extracted at 1 hour and 3 hours after tracer injection, and GFRs were calculated based on single- and double-plasma sampling methods (SPSM and DPSM, respectively). Serum creatinine was also measured to derive GFR using the CKD-EPI, MDRD, and Cockroft-Gault equations. Each method was correlated with a reference standard (DPSM) based on accuracy, linear regression, bias, and precision. SPSM tends to overestimate GFR unlike the other methods evaluated, but otherwise shows the most favorable diagnostic performance among the six methods when correlated with DPSM. The Inoue method appears modestly better than the routinely utilized Gates protocol, though both methods exhibit lack of precision. The CKD-EPI formula shows similar, if not slightly superior, diagnostic properties to the MDRD and Cockroft-Gault equations, thus confirming its validity for use in this Filipino population subset. Further studies are needed, particularly involving SPSM and CKD-EPI, to determine the applicability of our findings in Filipinos with varying degrees of kidney function. It is hoped that modifications to these methods can be made that are tailor-fit to derive more accurate and population-specific GFR values.

***Keywords**:* glomerular filtration rate, creatinine, plasma sampling, ^{99m}Tc-DTPA, CKD-EPI equation, method-comparison study

INTRODUCTION

Glomerular filtration rate (GFR) is known to be the best index of kidney function. It is defined as the volume of fluid filtered from the glomerular capillaries into the Bowman's capsule per unit time (1). Through the years, different methods have been established with the objective of estimating GFR as accurately as possible.

Inulin clearance is considered as the gold standard for determining GFR. However, inulin is not readily available in the local market. In addition, inulin clearance is relatively invasive, too time-consuming to measure, and requires a steady-state plasma concentration and urine collection to obtain accurate measurements (2). It is thus deemed unsuitable for routine clinical use.

^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) is a radiopharmaceutical that is excreted solely by filtration (3). The plasma sample-based or *in-vitro* technique is based on the good correlation between the renal clearance values of ^{99m}Tc-DTPA and inulin (4). Some studies show no significant difference between the *in-vitro* method and the *in-vivo* camera-based method among normal individuals. However, the *in-vitro* method is said to give more accurate GFR values and is thus regarded as an alternative reference standard to inulin clearance (2, 3, 5). Multiple formulas have been developed over the years for GFR estimation based on the number of plasma samples collected. The single plasma sample method (SPSM) by Christensen and Groth, as rewritten by Watson, is simple and convenient, but it tends to yield inaccurate results when the surface area normalized GFR goes below 30 mL/min/1.73 m² (4, 6). As such, many nuclear medicine institutions in the country have adopted the double plasma sample method (DPSM) as the standard for in-vitro GFR determination. Plasma samples are collected at 1 hour and 3 hours after tracer injection, and GFR is estimated

using Russell's formula with Brøchner-Mortensen correction (2, 7).

Camera-based renal scintigraphy is a less invasive method that not only estimates GFR but also is able to give relative kidney function (3). The Gates method is routinely used by nuclear medicine centers in the country (8). Nevertheless, one study found it to be less precise than the creatinine-based Cockroft-Gault formula (9). The Gates method is also said to severely overestimate GFR in pediatric patients, a problem duly addressed by the Inoue method developed at the turn of the century (10). More recent studies have validated the Inoue method to be specific for adult and pediatric Filipinos, making it a robust alternative to the Gates protocol (11, 12).

Limited access to nuclear medicine facilities in the country makes the camera-based and plasma sample-based methods nonviable for everyday clinical use. As such, creatinine-based methods remain the most practical and clinician-friendly way of estimating the GFR. The Cockroft-Gault equation normalized for body surface area was historically the first formula developed for such purpose. It is no longer recommended for use because it is not expressed using standardized creatinine values (13). Nowadays, the four-variable modification of diet in renal disease (MDRD) equation and the recently described formula by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) are more extensively used. Both these formulas take a patient's age, gender and race into account. The MDRD and CKD-EPI formulas have been validated for Caucasians (5). However, limited data exists on the performance of these equations among Asians, more specifically among Filipinos. The Philippine Society of Nephrology endorses the use of the CKD-EPI equation but does not have a definite clinical practice guideline (14).

Previous efforts have been made to compare a variety of combinations of the above methods using different sets of sample populations (Table 1). A study that takes all seven methods into consideration has not been undertaken, particularly on a normative subset of the Filipino population.

Filipino individuals from 20 to 35 years old with presumed normal kidney function are chosen as the preferred sample population for this study. It is hoped that the presumptively normative values obtained would reduce the confounding effect of decreased intrinsic kidney function, thereby lessening the probability of untoward bias.

This study aims to establish a correlation between DPSM and the other methods of GFR estimation among Filipinos with normative kidney function. DPSM was chosen as the reference standard for this study both for its accuracy relative to inulin clearance and accessibility in our institution. Incidentally, this study also provides an opportunity to validate the CKD-EPI formula against a nuclear medicine-based technique and compare its diagnostic performance against the other creatinine-based equations. Findings from this study may serve as reference for future research relating to GFR, both in (a) evaluating Filipinos with impaired renal function, and (b) improving the accuracy and specificity of the methods evaluated toward Filipinos.

MATERIALS AND METHODS

A prospective, clinical observational study was performed, with data collection running from February 2018 to July 2019.

Study Subjects and Recruitment

Seventy-five (75) Filipinos no younger than 20 years old and no older than 35 years old, presumed to have normal renal function, were recruited for this study. These include the following:

- Those referred by private clinics and social service to the nuclear medicine department for any imaging study not related to kidney diseases
- Those referred for renal studies (for pre-employment check-up, kidney allograft donor evaluation, and the like)

Individuals with the following were excluded from the study:

- Pre—existing condition/s that can influence kidney function. These include, but are not limited to, the following:
  - Hypertension
  - Diabetes
  - Urinary tract obstruction
  - Renal artery stenosis
  - Polycystic kidney disease
  - Nephrolithiases
  - Hydronephrosis and/or pelvocaliectasia of the kidney/s
  - Infections of the kidney and urinary tract
  - Congenital anomalies of the kidney and urinary tract
  - Kidney neoplasms

Table 1. Review of some current literature comparing different methods of GFR estimation, listed in order of reference citation. CKD: chronic kidney disease; SPSM: single plasma sample method; DPSM: double plasma sample method; MPSM: multiple plasma sample method.

Author	Year + Country	Type of Study	Sample Population	GFR Estimation Methods Compared		
				Camera-Based	*Plasma Sample-Based*	*Creatinine-Based*
Dias et al. (1)	2013 Portugal	Retrospective	Kidney donors + patients treated with nephrotoxic chemotherapy	Gates	DPSM	MDRD, CKD-EPI
Younis et al. (3)	2014 Egypt	Prospective	Normal + patients with obstructive uropathy	Gates	DPSM	Cockroft-Gault, CKD-EPI
Mulay and Gokhale (5)	2017 India	Prospective	Kidney donors + CKD patients	Gates	MPSM	Cockroft-Gault, MDRD, CKD-EPI
Hephzibah et al. (7)	2013 India	Prospective	Kidney donors + renal transplant recipients	Gates	DPSM, SPSM	Cockroft-Gault
Itoh (9)	2003 Japan	Prospective	Various degrees of renal function	Gates	DPSM, SPSM	Cockroft-Gault
Mendoza et al. (11)	2014 Philippines	Retrospective	Various degrees of renal function	Gates, Inoue	DPSM	None
Carbonell et al. (12)	2014 Philippines	Retrospective	Pediatric patients with various degrees of renal function	Gates, Inoue	DPSM	None
Ayan et al. (15)	2016 Turkey	Prospective	Kidney donors	Gates	DPSM	Cockroft-Gault, MDRD
Santoro et al. (16)	2014 Italy	Retrospective	CKD patients	Gates	None	MDRD, CKD-EPI
Muhammad (17)	2014 Pakistan	Prospective	Kidney donors	Gates, Inoue	None	Cockroft-Gault
Anil Kumar et al. (18)	2013 India	Prospective	Patients with diabetic nephropathy	Gates	None	Cockroft-Gault
Jahan et al. (19)	2013 Bangladesh	Prospective	Kidney donors	Gates	None	Cockroft-Gault, MDRD
Jardeleza et al. (20)	2004 Philippines	Retrospective	Various degrees of renal function	Gates	DPSM	Cockroft-Gault

- Serum creatinine values that are significantly above or below the normal reference range (defined as being more than 0.2 mg/dL above upper limit or below lower limit of the normal range). Reference intervals set by the institution's pathology department were adopted, as follows:
  Males: 0.80 – 1.50 mg/dL
  Females: 0.60 – 1.20 mg/dL

Recruitment was done during the study period by the primary investigators in the nuclear medicine department upon encountering patients that meet the inclusion criteria. An entry interview was conducted by a member of the study team for prospective participants. The benefits and advantages of participation were emphasized to them, and the procedure explained. Upon voluntary agreement to join the study, informed consent was obtained.

Patient Preparation and Injection of Radiopharmaceutical

Patients were advised to hydrate at least 2 hours prior to the procedure, with no fasting limitations. Prior to the procedure, parameters such as age, weight, height were collected, and used to derive body mass index (BMI) and body surface area (BSA).

Intravenous administration of 111-148 MBq (3-4 mCi) of ^{99m}Tc-DTPA was done prior to scintigraphic imaging. The plasma sample-based and camera-based methods were performed on the same day.

GFR Determination Using Plasma Sample-Based Methods

Blood samples were extracted at 1 hour and 3 hours after injection of radiopharmaceutical. Afterwards, plasma was separated using a centrifuge and activity (in counts per minute) was measured using a gamma well counter. GFR values were measured using the following formulas:

Single Plasma Sample Method (SPSM)

Method by Christensen and Groth, modified by Watson (6). *3-hour plasma sample was used for calculation.*

$$GFR = \frac{-b + \sqrt{b^2 - 4ac}}{2a}$$

where a = t (0.0000017t - 0.0012)
b = t (-0.000775t + 1.31)
c = ECV x ln (ECV/V_t)
ECV = extracellular volume (mL) = (8116.6 x BSA) – 28.2
V_t = tracer apparent volume (mL) of distribution at time t
t = sampling time (min)
BSA = body surface area (m^2)

Double Plasma Sample Method (DPSM)

Method by Russell, with Brøchner-Mortensen correction (2, 7). *GFR in mL/min; normalized GFR in mL/min/1.73 m^2.*

$$D = \left(\frac{Di - Pi}{Standard}\right) \times \left(cpm_{standard} - cpm_{background}\right) \times 10^4$$

$$GFR_{uncorrected} = \frac{D \ln\left(\frac{P_1}{P_2}\right)}{T_2 - T_1} \exp \frac{(T_1 \ln P_2) - (T_2 \ln P_1)}{T_2 - T_1}$$

$$GFR_{normalized} = \frac{GFR_{uncorrected} \times 1.73}{\frac{Weight^{0.125} \times Height^{0.725} \times 71.81}{10^4}}$$

$$GFR_{corrected} = 0.990778\,(GFR) - 0.001218\,(GFR)^2$$

where D = dose activity (cpm)
P_1 = 1st blood sample activity (cpm/mL)
P_2 = 2nd blood sample activity (cpm/mL)
Di = injected dose activity (mCi)
Pi = post-injection activity (mCi)
Standard = standard dose activity (mCi)
T_1 = time of 1st blood sample collection = 60 min
T_2 = time of 2nd blood sample collection = 180 min

GFR Determination Using Camera-Based Methods

Image acquisition and processing was done on the same day as the plasma sample-based methods, as per the institution's work protocol.

Image Acquisition

Images obtained and their corresponding instructions are listed in Table 2. A Siemens Symbia gamma camera fitted with a low-energy all-purpose collimator set at a 20% energy window at 140 keV was used.

Table 2. Images acquired for the camera-based estimation of GFR.

IMAGES	IMAGE ACQUISITION
Pre-injection syringe	A 60-second spot image was taken with the syringe positioned 30 cm from the center of the collimator.
6-minute post - injection	With the patient positioned supine, dynamic imaging of the kidneys in the posterior view was done after injection of radiotracer. Images were acquired at 15 seconds per frame in a 128 x 128 matrix.
Post-injection syringe	*(same as pre-injection syringe protocol)*
Injection site	*(same as pre-injection syringe protocol)*

Image Processing: Gates Protocol

After the images were acquired, composite images were generated reflecting renal radioactivity 2-3 minutes after tracer entry into the kidneys. Regions of interest (ROIs) were drawn around the kidneys, with background-corrected kidney counts obtained using ROIs drawn along the inferolateral aspect of each kidney. The SyngoMI VA50B software was used to obtain the GFR and surface area normalized GFR values based on Gates' method (8).

Image Processing: Inoue Protocol

Utilizing the same software, another composite image was generated, this time reflecting renal radioactivity 120-150 seconds after tracer entry into the kidneys. Background-corrected kidney counts were obtained using ROIs drawn along the periphery of each kidney, excluding the calyceal areas. The raw count values from the images were then used to calculate GFR values using the formula by Inoue et al. (10).

For both camera-based methods, images were processed twice by two different technologists (i.e. two trials per method per subject). Kidney counts, GFR, and surface area normalized GFR values were noted and averaged between the two trials for each method.

GFR Determination Using Serum Creatinine-Based Methods

For each of the subjects, a portion of the blood sample extracted for *in-vitro* GFR determination was sent to the pathology department for serum creatinine measurement. Results were duly recorded and used to

calculate GFR using each of the formulas listed. Note that age *a* is in years, weight *w* is in kilograms, and serum creatinine *crea* is in mg/dL.

Cockroft and Gault Equation for GFR

Male:

$$GFR_{C-G} = \frac{(140 - a) \times w}{crea \times 72}$$

Female:

$$GFR_{C-G} = \frac{(140 - a) \times w}{crea \times 72 \times 0.85}$$

Four-Variable MDRD Equation

Male:

$$GFR_{MDRD} = \frac{186.3}{a^{0.203} \times crea^{1.154}}$$

Female:

$$GFR_{MDRD} = \frac{186.3 \times 0.742}{a^{0.203} \times crea^{1.154}}$$

CKD-EPI Equation

Male:

$$GFR_{CKD-EPI} = \frac{141 \times 0.993^{a}}{\left[min\left(\frac{crea}{0.9}, 1\right)\right]^{0.411}\left[max\left(\frac{crea}{0.9}, 1\right)\right]^{1.209}}$$

Female:

$$GFR_{CKD-EPI} = \frac{141 \times 0.993^{a} \times 1.018}{\left[min\left(\frac{crea}{0.7}, 1\right)\right]^{0.329}\left[max\left(\frac{crea}{0.7}, 1\right)\right]^{1.209}}$$

Min and *max* pertain to the minimum and maximum between the two expressions indicated in parentheses, respectively.

Correction for Body Surface Area

All GFR values were corrected for body surface area to account for differences in body size. The following formulas were used:

$$BSA = 0.024265 \times weight^{0.5378} \times height^{0.3964}$$

$$GFR_{corrected} = GFR \times \frac{1.73}{BSA}$$

Note that BSA is expressed in m^2, weight in kg and height in cm.

Data Analysis

Aside from descriptive statistics, i.e. measures of central tendency and dispersion, the six methods under evaluation (SPSM, Gates, Inoue, CKD-EPI, MDRD, Cockroft and Gault) were compared against the reference standard based on four criteria: accuracy, correlation, bias, and precision. Surface area normalized GFRs were utilized for this purpose. Statistical significance was defined as $P < 0.05$ when applicable.

Accuracy

The accuracy of each method was calculated based on the proportion of patients with estimated GFR within 30% above or below the measured GFR_{DPSM}, as per the definition set by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) (21).

Correlation

Linear regression analyses were performed to calibrate the association between DPSM and the other methods. For each of the six methods, the regression coefficient (± 95% confidence interval) and Pearson's correlation coefficient were calculated.

Bias and Precision

Bland-Altman analysis was done to determine the difference between DPSM and the other methods in terms of bias and precision. Bias pertained to the difference between the mean GFR estimated by each of the other methods (the minuend) and the mean GFR_{DPSM} (the subtrahend). Precision was assessed based on the standard deviation of the difference and limits of agreement (confidence limits for the bias). Assumption of normality of differences was calculated using the Shapiro-Wilk test; normality was rejected when $P < 0.05$.

For the purpose of validating the CKD-EPI formula, the three creatinine-based methods were compared against each other based on the criteria presented.

Statistical analyses were performed using Microsoft Excel and NCSS 2019 software.

Withdrawal of Subjects from the Study

A patient was withdrawn from the study if any of the following conditions were met:

- Patient has an allergic reaction to the radiopharmaceutical
- Patient is not able to have his/her blood extractions within the time parameters set (i.e. 1 hour and 3 hours after radiopharmaceutical injection)
- Patient voluntarily withdraws from the study during the procedure

Ethical Considerations

The clinical protocol and all relevant documents were reviewed and approved by our institution's Ethics Review Committee. Patient confidentiality was respected by ensuring anonymity of patient records. Study codes were assigned to each of the participants, with the corresponding identifiers (PIN, name, etc.) only accessible to the primary investigators. No prominent patient identifiers were placed in the data collection forms.

All study data were recorded, and investigators ensured data integrity (i.e. accuracy, completeness, legibility, etc.). Physical and electronic data records were kept for the sole use of the investigators.

RESULTS

Study Population

The demographic profile of the 75 recruited subjects are shown in Table 3. None of the conditions for withdrawal were met; as such, no study subjects were withdrawn. Roughly three-fourths of the study participants are male, and almost three-fourths (73.3%) are within normal range of BMI.

Descriptive Statistics

Summary statistics for the GFR values obtained using the different methods described are shown in Table 4. Mean GFRs are graphically plotted in Figure 1. All GFR values used are surface area normalized and are thus expressed in mL/min/1.73 m².

Based on Table 4 and Figure 1, it can be deduced that SPSM tends to overestimate GFR while the rest of the methods tend to underestimate GFR, particularly the creatinine-based methods.

Accuracy

The proportion of patients with estimated GFR within 30% above or below the measured GFR_{DPSM} was obtained

Table 3. Demographic profile of the subjects recruited for this study (n = 75).

Age	20 to 35 years old	*Average age: 26.9 years old*
Sex	Males: 56 (74.7 %)	Females: 19 (25.3 %)
Body Mass Index	17.6 – 36.4 kg/m² (27.0 ± 9.4 kg/m²)	*Average BMI: 23.2 kg/m²*
	Underweight (<18 kg/m²)	1
	Normal (18-24.9 kg/m²)	55
	Overweight (25-29.9 kg/m²)	12
	Obese (≥30 kg/m²)	7
Body Surface Area	1.23 – 2.16 m² (1.695 ± 0.465 m²)	*Average BSA: 1.66 m²*

Table 4. Summary statistics of the different methods used to obtain GFR in the study population. CI: confidence

METHOD	MEAN GFR ± 95% CI	STANDARD DEVIATION	RANGE OF GFRs OBTAINED	
			LOWER LIMIT	UPPER LIMIT
DPSM	121.8 ± 3.3	14.3	91.6	167.1
SPSM	135.2 ± 3.8	16.6	99.7	195.5
Gates	116.0 ± 6.5	28.4	46.9	187.5
Inoue	111.2 ± 5.2	22.4	49.2	159.1
CKD-EPI	106.1 ± 3.6	15.7	59.8	131.9
MDRD	100.3 ± 4.0	17.4	55.4	141.9
Cockroft-Gault	107.0 ± 4.1	17.8	65.8	158.6

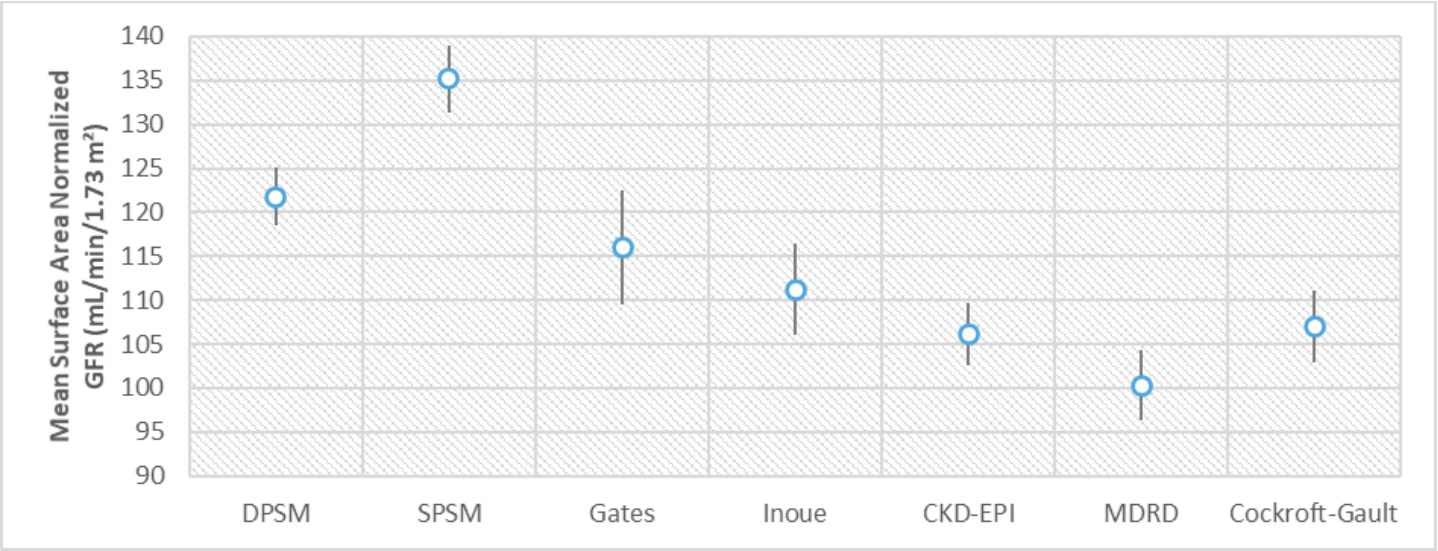

Figure 1. Plot showing the mean surface area normalized GFRs obtained for the different methods employed. Bars indicate 95% confidence interval.

for each method (Table 5). While almost all GFR values obtained by SPSM are higher than those obtained by DPSM (by 11.12% on the average), all GFR_{SPSM} values obtained are within 30% of GFR_{DPSM} – something which cannot be said for the camera-based and creatinine-based methods. The large deviation of the camera-based methods from GFR_{DPSM} (up to more than 50% in some cases) is compatible with a relatively larger standard deviation from the mean (Table 4). At 92%, the CKD-EPI method exhibits the greatest number of subjects within 30% of GFR_{DPSM} among the creatinine-based methods.

Correlation

Regression and Pearson's correlation coefficients for each of the methods relative to DPSM are listed in Table 6. All P-values are less than 0.05. Graphical regression representation for each of the method comparisons are shown in Appendix 1.

SPSM appears to show the best linear correlation with DPSM compared to the other methods, given high regression and correlation coefficients, and a low standard error. The rest of the methods have lower correlation coefficients, implying a less linear relationship with DPSM; this is duly supported by the plots in Appendix 1. However, the significant p-values supports the presence of relationships between DPSM and the other methods. The creatinine-based methods exhibit better correlation with DPSM compared to the camera-based methods based on the values obtained.

Bias and Precision

Data derived from Bland-Altman analysis of each of the methods when compared to DPSM are listed in Table 7. Disagreement plots for each of the method comparisons are shown in Appendix 2. Comparison of bias and limits of agreement among the different methods is graphically represented in Figure 2.

Like the data on linear regression and correlation, the calculated numbers on SPSM are unique to the rest (Table 7). Positive bias is expected given that the mean GFR_{SPSM} is higher than the mean GFR_{DPSM}. Also, the standard deviation and limits of agreement are much smaller than the rest of the methods. However, assumption of normality of differences is rejected based on the Shapiro-Wilk test (P = 0.0398); the rest of the methods evaluated showed P-values greater than 0.05.

In general, the camera-based methods are noted to have marginally smaller bias (i.e. closer to zero) than the creatinine-based methods. However, precision is better for the creatinine-based methods, as exhibited by the relatively lower standard deviation values and smaller limits of agreement. There is no significant variation in the Bland-Altman findings among the three creatinine-based methods.

DISCUSSION

To the knowledge of the authors, this is the first study to simultaneously compare six different methods of estimating GFR vis-à-vis a reference standard (DPSM). This is also the first study to focus on the renal function of normal Filipino subjects in a relatively young age group (20 to 35 years old). Additionally, this appears to be the first study to validate the CKD-EPI

formula in any given subset of Filipinos using a nuclear medicine-based technique.

Single Plasma Sampling Method

While multiple plasma sampling (e.g. DPSM) is considered the reference standard for GFR determination, the authors chose to explore the possibility of deriving a normal subject's GFR using a single plasma sample collected 3 hours after tracer injection and see how it compares with that of DPSM. While there are many formulas available for this purpose (6), the method by Christensen and Groth, modified by Watson, was chosen to represent SPSM. A separate study by Itoh et al. (4) attests to its accuracy, technical simplicity, and utility in clinical practice among patients expected to have GFRs above 30 mL/min/1.73 m^2.

Among all the GFR estimation methods that were evaluated, SPSM is the only one which overestimates GFR, but never beyond 30% of the GFR_{DPSM}. Linear correlation with DPSM also appears much better than the others. While the average difference between mean GFR_{SPSM} and mean GFR_{DPSM} is relatively high (hence the relatively higher bias), the standard deviation is lowest of all the methods, implying relatively good precision.

However, it is the only method of GFR estimation which does not statistically follow the assumption of normality of differences. This implies that estimates may not be as reliable as when the normality assumption is met.

Camera-Based Methods

In contrast to SPSM, the Gates method performs poorly on accuracy assessment and linear correlation studies. Bland-Altman analysis shows negative bias (i.e. tendency to underestimate the GFR) that is of lesser magnitude than any of the other methods. However, given the higher standard deviation values and wider limits of agreement compared to the others, the Gates method proves to be the most imprecise of all the methods evaluated. This finding is in line with prior published literature (5, 11). Given that the sample population of this study already excludes subjects with impaired renal function, our findings perhaps support its lack of reliability as a stand-alone method in ascertaining an individual's GFR.

Compared to the Gates method, the Inoue method exhibits slightly better accuracy and linear correlation. It tends to underestimate the GFR a little more than the Gates method, but with marginally lower standard deviation, and thus slightly better precision. As such, the Inoue protocol appears somewhat superior and preferable to the Gates protocol in deriving the GFR based on gamma camera acquisition, at least for the population in question. This appears in line with the findings of Mendoza et al. (11) using a population with both normal and below-normal kidney function.

Creatinine-Based Methods and Validation of the CKD-EPI Formula

Among the creatinine-based methods, the CKI-EPI formula exhibits the highest accuracy (second only to SPSM), followed by the Cockroft-Gault formula. On linear regression and correlation analysis, the Cockroft-Gault formula appears marginally better than either CKD-EPI or MDRD, though all three formulas exhibit better correlation with respect to DPSM than the camera-based methods. On Bland-Altman analysis, the three creatinine-based methods show slightly higher magnitude of bias compared to the camera-based methods, but with smaller standard deviation. Of note, the MDRD formula shows slightly higher bias and standard deviation compared to the CKD-EPI and Cockroft-Gault equations.

So, does this study validate the CKD-EPI formula in this normative subset of Filipinos? When the three creatinine - based equations are compared against a reference standard, all three meet the KDOQI definition of accuracy and appear to exhibit no significant difference in terms of correlation, bias, and precision. In this context, all three equations are valid for use in the Filipino population under study. A more specific observation is that CKD-EPI does not have a definite performance advantage over the Cockroft - Gault formula in deriving the GFR, with MDRD being modestly behind in terms of the parameters assessed.

Study Limitations

In retrospect, several aspects of the study might have been improved. Hydration could have been standardized across all the subjects. The accuracy of the DPSM values may have been improved by having another technologist do a second processing of the collected blood samples; however, this is not logistically feasible. Also, to improve heterogeneity of the population, an equal number of

males and females could have been re-determined for recruitment, but such move may have delayed the subject recruitment process.

CONCLUSIONS AND RECOMMENDATIONS

Our study shows that single plasma sampling using the Christensen and Groth method is a viable alternative to the double plasma sampling protocol. Apart from its tendency to overestimate GFRs, it shows superior accuracy, good correlation with DPSM, and high precision. Among the camera-based methods, the Inoue protocol appears slightly better than the Gates protocol, though both are generally imprecise. The CKD-EPI equation performs similar, if not slightly superior, to the more established MDRD and Cockroft-Gault formulas and is thus deemed valid for use in this Filipino population subset.

Neighboring Asian countries have developed ethnicity - specific modifications to the CKD-EPI formula (13). We therefore recommend further studies, particularly involving subjects with impaired kidney function, in order to come up with a modified CKD-EPI equation specifically for Filipinos that will yield GFR values with better precision and accuracy. A similar recommendation can be made for SPSM, given the favorable result of this study, to provide a feasible alternative to DPSM in patients with trypanophobia or in cases where multiple blood extractions are technically difficult.

ACKNOWLEDGMENTS

The authors would like to thank the following:

Our technologists, both past and present, for going above and beyond their call of duty to obtain the data presented in this study;

The Research and Biotechnology Group of St. Luke's Medical Center, for supporting this study; and

Our department chair, Dr. Jonas Francisco Y. Santiago, and research committee head, Dr. Eduardo Erasto S. Ongkeko, for inspiring research.

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