Comparison of various creatinine-based estimates of glomerular filtration rate equations in the Malaysian setting

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ABSTRACT

Introduction: Kidney disease is a worldwide health concern with an increasing mortality in the past 10 years. The Kidney Disease Improving Global Outcomes (KDIGO) guideline advocates the use of estimated glomerular filtration rate equation (eGFR) to estimate renal function. We evaluated the performance of Cockroft Gault (CG), Modified Diet of Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations to measured GFR ^{99m}Tc-DTPA taking into account body mass index (BMI) and age group.

Materials and methods: This is a cross-sectional study of patients referred for ^{99m}Tc-DTPA scan at the Nuclear Medicine Centre of International Islamic University Malaysia. The record was taken from patients visiting the centre from January 2016 to December 2019.

Results: The mean measured GFR by ^{99m}Tc-DTPA scan was 42.2 ± 20.38 ml/min. These were lower than that estimated by CG, MDRD, and CKD-EPI equations. CKD-EPI had the highest correlation of 0.72, least bias (mean bias of 11.08 ± 23.08) and was more precise (r^2 = 0.4) as compared to MDRD and CG. In patients < 65 years old, CKD-EPI had the highest correlation; however, MDRD had the least bias and highest accuracy. In terms of BMI, CKD-EPI had the least bias and highest accuracy for BMI >30 and with the highest correlation for all classes of BMI.

Conclusion: CKD-EPI has the best estimation of GFR taking into account the effect of BMI and age. A further study can be done to determine the correlation of estimated GFR equations with different ethnicity in Malaysia.

KEYWORDS:
Chronic kidney disease, Chronic Kidney Disease Epidemiology equation, Modified Diet in Renal Disease equation, Cockroft Gault equation

INTRODUCTION

Kidney disease is a major concern as it contributes towards global mortality and morbidity.[1] According to The Global Burden disease 2015 study, there was a rise of death by 31.7% in 2015 as compared to 2005 which was estimated about 1.2 millions death.[2] For Malaysian population, number of patients on dialysis increased by two and a half folds from 15087 to 37183 patients in 2015.[3] According to the Kidney Disease Improving Global Outcomes (KDIGO), chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function for more than 3 months with implication for health. A reduction of glomerular filtration less than 60 ml/min/1.73m^2 alone is diagnostic of CKD.[4] KDIGO 2012 guideline advocated the use of glomerular filtration rate (GFR) estimating equation rather than serum creatinine alone to estimate GFR.[4] GFR estimating equations such as Cockroft Gault (CG), Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease-Epidemiology Collaboration (CKD–EPI) had been studied extensively and validated in different populations.[5-8]

There were conflicting data with regards to estimated glomerular filtration for different age group and BMI. Age plays an important role in predicting the equation that best estimated the glomerular filtration rate. A study by Carter et al. showed no difference between MDRD and CKD-EPI equations in determining GFR for the elderly.[9] Another study stated that CKD-EPI formula was more accurate in predicting estimated GFR for elderly.[10] With regard to BMI, study done by Michels et al. 2010 showed that CKD-EPI was most accurate for obese patient compared to other equations; however, Poggio et al 2005 and Verhave et al 2005 stated no difference in terms of BMI.[8,11] In comparison, a study done in Bangladeshi patients in both lean and obese patients showed that estimated glomerular filtration rate by MDRD formula was more accurate than CKD EPI.[12] We embark on this study to evaluate the performance of the three most commonly used estimated glomerular filtration rate equations which are Cockroft Gault, MDRD, and CKD-EPI and the effect of difference BMI and age group to the equations.

MATERIALS AND METHODS

This was a cross-sectional study using an existing record of cases conducted at the Nuclear Medicine Centre of International Islamic University Malaysia, Kuantan. The data were collected retrospectively from the patients' clinical records in which patients were referred for ^{99m}Tc-DTPA for various reasons. The records were taken from patients visiting the centre from January 2016 to December 2019.

Patients who came were advised to be well hydrated and requested to void just prior to the procedure. The patient must be in supine position and 0.8–10 mCi of ^{99m}Tc-DTPA was

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administered intravenously. The acquisition protocol was then performed immediately after the injection. The renal dynamic imaging measurements were acquired in 128 x 128 frame matrix. Region of interest for each kidney will then be drawn manually and a semi-lunar background was placed around the lower outer renal margin. By computing the patient's height and weight, the computer was able to calculate measured GFR using Gates method. The measured GFR was standardized to the body surface area of 1.73 m^2

Estimated GFR was calculated based on the CG, MDRD, and CKD-EPI equations. Demographics data of the patients that were collected include age, gender, height, weight, and ethnicity. The clinical data that was collected include: CKD aetiology, background comorbidities, vitals sign, and laboratory data which included the renal function test. The serum creatinine was measured using Jaffé method and traceable to isotope dilution mass spectrometry (IDMS). The ^{99m}Tc-DTPA-measured GFR readings were also recorded. If there were multiple measurements of scans done, the latest ^{99m}Tc-DTPA-measured GFR was taken. Renal function test must be within 3 months of when the ^{99m}Tc-DTPA scan was done. The study has been approved by IIUM research committee (IREC). Inclusion criteria include patients with age more than 18 years old and being not pregnant.

Statistical Analysis

For statistical analysis, SPSS® Statistics version 21 (IBM, New York, USA) was used. Results were presented for categorical data as frequency and percentage while for numerical data, results were presented as mean ± standard deviation (SD) if normally distributed or median (inter-quartile range) if the data was not normally distributed. For categorical data, we used Chi-squared test and for numerical data, we used Independent t-test for normally distributed data and Mann–Whitney U test for non-normally distributed data. ANOVA test was done if there were more than two categorical variables. Performance of different estimated GFR equations was assessed against measured GFR. Pearson rank correlation and linear regression were used to assess the relationship between estimated GFR and measured GFR. Bland–Altman analysis was used to assess concordance between different estimated GFR equations to measure GFR.[13,14]

RESULTS

A total of 153 data of patients who underwent ^{99m}Tc-DTPA scan was collected. After exclusions due to incomplete data, the remaining eligible data was 126 patients.

Demographic data of the patients

Table I shows the demographic of the patients. Of the 126 patients, 54% (n=68) were male and 46% (n=58) were female. The mean age was 55.04 ± 13.73 with the youngest of 18 years old and the oldest of 85 years old. About 72 % of the patients were below 65 years old while 28% of the patients were above 65 years old. All of the mean estimated GFR equations overestimated the mean of measured GFR. CG had the highest GFR of 53.81 ± 36.11 and CKD-EPI had the lowest of 53.28 ± 32.9.

Performance of CG, MDRD and CKD-EPI to measured GFR

CKD-EPI had the highest correlation to the measured GFR, with a correlation coefficient of 0.72 compared to the correlation for MDRD of 0.69 and CG of 0.64 (all $p < 0.0001$). MDRD had the highest accuracy at 30% and 50% of measured GFR which was between 45.2% and 67.4%, respectively, compared to CG and CKD-EPI (Table II). However, CKD-EPI had the highest precision with r^2 of 0.4 and the least bias of 11.08. Bland–Altman analysis was also performed to look for concordance between estimated GFR and measured GFR. (Figures 1–3) CKD-EPI had the lowest limit of agreement which was 90 compared to MDRD with a limit agreement of 98 and CG with a limit agreement of 112.

Comparison of estimated GFR for elderly and non elderly

Table III shows mean and standard deviation of all estimated GFR and measured GFR according to the subgroup of age. Patients > 65 years old had statistically significantly lower GFR estimation compared to younger patients < 65 years old for all three equations. (all $p < 0.0001$. Table III) CKD-EPI had the strongest correlation to measured GFR which was 0.75 for patient < 65 years old. For patients > 65 years old, the correlation was at moderate strength and the highest was MDRD which is 0.564. (all $p < 0.0001$)

We also looked at bias, accuracy, and precision of each equation for the different age groups. In patients <65 years old, MDRD had the least bias of 14.35 compared to CKD-EPI of 14.63 and CG of 16.69. For accuracy, MDRD had the highest accuracy of 43.96% at 30% and of 67.03% at 50% accuracy. CG had the highest precision of 0.457. For patients >65 years old, CG had the least bias of -1.61 compared to CKD-EPI and MDRD. For accuracy, CG also had the highest accuracy at 30% of 57.14% and 71.43% at accuracy of 50% of measured GFR. In addition, CG had the highest precision of 0.1 followed by CKD-EPI and MDRD.

Comparison of estimated GFR for different BMI groups

We divided the BMI according to WHO criteria of normal weight <25, pre-obesity which is 25–29 and obese BMI >30. ANOVA test was done to look for the significance of estimating GFR for different classes of BMI. The mean measured GFR was 43.54 ± 19.76 for BMI >25, 40.14 ± 20.23 for BMI 25–29, and 42.59 ± 22.99 for BMI >30. For BMI <25, all the estimated GFRs overestimated measured GFR with CG being the least that overestimated with a mean of 47.77 ± 29.32. For BMI 25–29, CKD-EPI had the best estimation to measure GFR with mean of 49.41 ± 34.82. For obese patient (BMI >30), all equations overestimated measured GFR with the least being MDRD formula where the mean was 52.03 ± 30.37. CKD-EPI had the highest correlation to mGFR compared to CG and MDRD with a correlation coefficient of 0.82 ($p < 0.0001$) for all classes of BMI. For BMI <25, CG has the highest accuracy at 30% and 50%, least bias with the highest precision. For BMI 25–29, CKD-EPI had the least bias, highest accuracy at 30% and 50% but CG had the highest precision. Similarly, for BMI >30, CKD-EPI had the least bias, highest accuracy at 30% and 50% while CG had the highest precision.

Table I: Demographic data of the patients

	N (%)/mean ± SD
Gender	
Male	68 (54%)
Female	58 (46%)
Age	55.04 ± 13.73
Below 65 years old	91 (72.2%)
Above 65 years old	35 (27.8%)
Ethnicity	
Malay	109 (86.5%)
Non-Malay	17 (13.5%)
Height (M)	1.59 ± 0.10
Weight	64.67 ± 14.66
BMI	25.67 ± 5.42
Less than 25	61 (48.4%)
25–30	41 (32.5%)
More than 30	24 (19%)
Renal/urological diseases	
Renal calculi	91 (72.2%)
Obstructive uropathy secondary to tumour infiltration	6 (4.8%)
Diabetic nephropathy	12 (9.5%)
Polycystic kidney	4 (3.2%)
Others	13 (10.3%)
Stages of chronic kidney disease	
≥90	17 (13.5%)
60–90	28 (22.2 %)
30–59	45 (35.7%)
15–29	25 (19.8%)
≤15	11 (8.8%)
Measured glomerular filtration rate by Tc DTPA (mGFR)	42.2 ± 20.38
Estimated GFR by Cockroft Gault (eGFRCG)	53.81 ± 36.11
Estimated GFR by MDRD (eGFRMDRD)	53.65 ± 34.24
Estimated GFR by CKD EPI (eGFRCKD-EPI)	53.28 ± 32.9

Data expressed as mean ± SD and n (%). BMI, body mass index; mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration; CG, Cockcroft Gault; MDRD, modification of diet in renal disease; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration

Table II: Bias, precision, and accuracy for estimated glomerular filtration rate

GFR Equations	Mean Bias	SD Bias	r^2 (Precision)	Accuracy within	
				30%	50%
eGFRCG	11.61	27.98	0.42	42.86	63.49
eGFRMDRD	11.45	25.02	0.48	45.24	67.46
eGFRCKD-EPI	11.08	23.18	0.40	42.06	64.29

eGFR, estimated glomerular filtration rate; CG, Cockcroft Gault; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration

Table III: Mean and standard deviation of subgroup of age

	Less than 65 Mean ± SD	More than 65 years old Mean ±SD	*p* value
mGFR	45.11 ± 20.43	34.62 ± 18.44	<0.0001
eGFRCG	61.80± 38.35	33.01± 16.85	<0.0001
eGFRMDRD	59.45± 36.94	38.56 ± 19.30	<0.0001
eGFRCKD EPI	59.73± 34.92	36.47± 18.63	<0.0001

eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; CG, Cockcroft Gault; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration

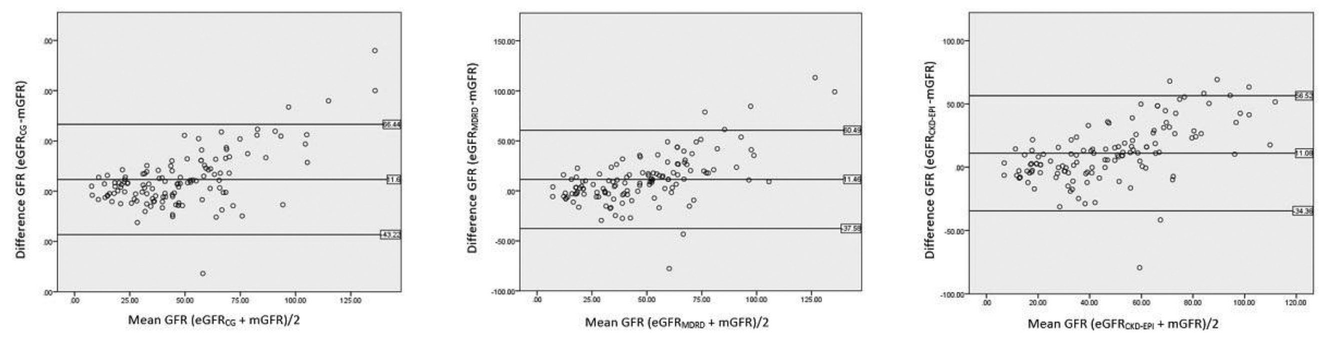

Figure 1a: Bland–Altman analysis for CG and mGFR

Figure 1b: Bland–Altman analysis for MDRD and mGFR

Figure 1c: Bland–Altman analysis for CKD-EPI and mGFR

Fig. 1: Bland-Altman analysis for estimated glomerular filtration rate and measured glomerular filtration rate

DISCUSSION

GFR is an important indicator in evaluating kidney function. However, it is difficult to measure GFR in a clinical setting. Thus, estimating GFR equations play an important role in determining the extent of a kidney injury. This study assessed the performance of the estimated GFR of CG, MDRD, and CKD-EPI equations as compared to mGFR of ^{99m}Tc-DTPA scan. ^{99m}Tc-DTPA GFR was used for measuring GFR and previous study showed that it is a good marker for GFR and comparable to inulin infusion.[15,16,17]

In general, we observed that all of the estimated GFR equations overestimated measured GFR. This finding was similar to a study by Jessani et al for the Pakistani population comparing MDRD and CKD-EPI against measured GFR.[18] According to Lamb et al., the degree of dissociation of ^{99m}Tc-DTPA can be variable which will lead to imprecision and bias. Furthermore, ^{99m}Tc bind to protein which also contributes towards GFR underestimation.[19] This study demonstrated that MDRD had the highest accuracy within 30% and 50% of measured GFR while CKD-EPI had shown the highest precision with the least bias. The findings were similar to previous study done in Malaysia by Jalalonmuhali where MDRD had the highest accuracy while CG had the least bias and highest precision. However, CKD-EPI was not tested in this particular study.[20]

We also performed Bland–Altman analysis to look at the agreement between estimated GFR and measured GFR. This study demonstrated that CKD-EPI has the lowest limit of agreement as compared to MDRD and CG. CKD-EPI had better performance in general compared to MDRD and CG as it was developed and validated using a large database with diverse clinical characteristics and it also comprises patients with and without kidney disease.[21]

Influence of Age

We divided the patients as young and elderly according to WHO classification where we took the limit of age considered as elderly as 65 years old. In this study, for patients less than 65 years old, MDRD had the least bias with the highest accuracy while for elderly more than 65 years old, CG had the least bias, highest accuracy, and least precision. Our study also demonstrated that the younger patients have higher GFR and with higher GFR, estimated GFR may be inaccurate. Variations among laboratories in the calibration of serum creatinine assay had larger effects at higher GFR level thus producing a wider variation in the results.[22,23] These inter-laboratory variations were also influenced by muscle mass, the influence of drug on creatinine clearance, dietary intake, and the differences in creatinine excretions between individuals.[22] In our study, the distribution between elderly and non-elderly is incomparable as only 27.8% of the patients had age above 65 years old. The GFR equations in elderly tends to be underrepresented as all the samples were mostly include less of the elderly populations.[24] A further research with regard to finding the best equations for the elderly is warranted.

Influence of BMI

The estimated GFR of CG, MDRD, and CKD-EPI were also compared according to the subgroup of BMI. This study showed that for both BMI 25–30 and BMI more than 30, CKD-EPI showed the highest accuracy and the least bias. However, we observed that there was no significant difference between all the three estimated GFR equations for all subgroup of BMI. The reason was the number of patients in each subgroup was too small to make a difference. Interestingly in this study, the bias of CG increased significantly with increased BMI denoting that there is a relationship between body composition and performance of estimated GFR. This finding is similar to a few previous studies done earlier.[25,26]

There were several limitations to this study. This study was done in a single centre whereby all of the patients were referred from Urology clinic. Thus, the population study did not reflect the general population in Malaysia. Furthermore, as this was a retrospective study, we could only use the available recorded data. The sample size was particularly small for certain subcategories such as the different classes of BMI and in the elderly population more than 65 years old.

CONCLUSION

Of the three estimated GFR equations studied, MDRD is the most accurate; however, CKD-EPI has a smaller bias and a better precision when compared with measured GFR. When we included the influence of BMI, age, and looking at the performance of each estimated GFR equations for different stages of CKD, CKD-EPI gives the best estimation of GFR with almost comparable performance of MDRD.

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CONFLICTS OF INTEREST

Nil

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