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COMPARISON OF EIGHT METHODS FOR ESTIMATION OF CREATININE CLEARANCE IN MALAYSIA PATIENTS WITH UNSTABLE KIDNEY FUNCTION – A MULTI-CENTER, PROSPECTIVE, OBSERVATIONAL STUDY

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ABSTRACT: Estimation of creatinine clearance (Clcr) has long been a problem in critically ill patients with unstable kidney function. The commonly used methods like the Cockcroft-Gault method require a stable kidney function. A reliable and more accurate tool is needed to estimate Clcrto to guide drug dosage adjustment. The study aimed to compare the eight methods to estimate Clcr with measured Clcr. In addition, the study also aimed to determine the agreement between estimated Clcr with measured Clcr. This was a multicentre, prospective, observational study. Three intensive care units in Malaysia tertiary public hospitals. Two serum creatinine samples over 24 hours apart and simultaneously 24 hours urine collection. A total of 43 patients were recruited. During the early phase of unstable kidney functions (regardless of acute deteriorating or acute improving), only the modified Cockcroft-Gault method showed a non-significant different with the measured Clcr ($p = 0.741$). A sub-set analysis on 23 patients with acute deteriorating kidney functions was performed. Only the modified Cockcroft-Gault revealed a non-significant different with the measured Clcr ($p = 0.843$). Sub-set analysis performed on 20 patients with rapid improving kidney functions, the Chiou method greatly underestimated the Clcr by approximately 34%, $p < 0.001$. Bland-Altman analysis revealed that Clcr estimated with modified Cockcroft-Gault method showed agreement to measured Clcr, $p > 0.05$. Owing to the precision of estimation and the consistency (reproducibility) as well as the simplicity of the modified Cockcroft-Gault method, it should be the reliable method to assess renal function in critically ill patients with unstable kidney function.

INTRODUCTION: Acute kidney injury (AKI) is a common complication in hospitalized patients and is associated with a high mortality rate.

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The incidence of AKI is markedly higher in critically ill patients and those admitted to intensive care unit (ICU) settings [1].

An estimated 5 to 20% of critically ill patients experience an episode of AKI during their illness in all admission to ICU [2]. Critically ill patients normally have to fluctuate renal function with serum creatinine fluctuating from day to day [3]. Over 95% of practitioners use the Cockcroft-Gault equation to estimate creatinine clearance (Clcr) for

drug dosage adjustment in a patient with kidney disease, as shown in a survey of 204 members of the American College of Clinical Pharmacy (ACCP) Nephrology and Critical Care Practice and Research Network in 2009 [4]. The Cockcroft-Gault equation is the most widely used equation as most of the approved dosing information from the manufacturer of drugs was developed from pharmacokinetics studies using Cockcroft-Gault equation [5].

Nevertheless, the Cockcroft-Gault equation is not designed for patients with unstable kidney function, leading to the overestimation of renal clearance by using a steady state equation. Drug dosing in critically ill patients with unstable kidney function has been problematic. Several unique issues in this population include the rapid changes in serum creatinine and the time required to reach a new steady state concentration. Besides, the influence of aggressive volume resuscitation that ultimately led to increased volume of distribution (Vd) is another challenge among critically ill patients. Creatinine is a hydrophilic substance whose concentration changes with the fluctuations in total body water. Its Vd increases due to aggressive fluid resuscitation, resulting in overestimating one's kidney function [6]. Drug doses need to be adjusted appropriately with the correct estimation of kidney function to reduce potential toxicity [7].

Developing a rapid, accurate, safe, user-friendly, and inexpensive method of creatinine clearance estimation is highly important as employing isotopic methods is cumbersome and impractical. Equations potentially to be used to assess one's kidney function during unstable kidney function such as Jelliffe, Modified Jelliffe, Chiou and Brater are complex and involve various steps in performing the calculation. The 24 hours urine collection method remains the second best method of estimating one's GFR after the isotopic method. It does not involve exogenously administered substances such as inulin, iothlamate, iohexol, or radioisotopes, which are expensive, not readily available, and not practical in daily use, especially in an intensive care setting. This method is indeed validated in critically ill patients [8, 9]. As such, the 24 hours urinary creatinine clearance still offers values close to the real renal function of the patients [10, 11]. However, the 24 hours urine method is not practical to be used in daily practice as it involves the collection of the patient's urine for 24 hours and unable to offer a very prompt estimation of one's kidney function. Josee Bouchard *et al.* (2010) reported in the Programme to Improve Care in Acute Renal Dysfunction (PICARD) [12] study that the degree of over-estimation of GFR in critically ill patients with unstable kidney function by Cockcroft-Gault was 80%; 4-variable modification of diet in renal disease (MDRD) was 33% and 10% with Jelliffe equation. The relative overestimation of GFR by Cockcroft-Gault and MDRD was reported to be even more prominent if the baseline GFR is higher. In addition, Cockcroft-Gault and MDRD overestimating the GFR in most patients with fluid accumulation [12]. This study aimed to investigate the mean differences of estimated creatinine clearance computed by Cockcroft & Gault, MDRD, CKD-EPI, Jelliffe, modified Jelliffe, Chiou, Brater, and an empiric estimating equation (modified Cockcroft-Gault) equations with 24 hours urinary creatinine clearance (standard control) in critically ill and unstable kidney function patients.

MATERIALS AND METHODS: This was a multicentre, prospective, observational study carried out in three tertiary government hospitals with ICU settings. Serum creatinine (key biomarker), blood urea nitrogen, fluid balances, and 24 hours urinary creatinine clearance from day 1 to day 7 were collected.

Mean calculated values of estimated creatinine clearance based on the Cockcroft-Gault, 4 variables MDRD, CKD-EPI, Jelliffe, Brater, Chiou, modified Jelliffe, and our empiric formula (modified Cockcroft-Gault) (Appendix 1) [12-18] were compared with 24 hours urinary creatinine clearance. The 24 hours urines were collected from eligible patients by the use of the indwelling urinary catheter. The ICU monitoring chart recorded urine output every hour (in ml). Plasma creatinine was also obtained on the same day. The plasma creatinine measurement obtained on the morning of the urine collection day was used to compute the measured Clcr. This study was approved by the Malaysian medical research ethical committee (MREC) – NMRR-16-736-29621 (IIR). The study was performed by the Declaration of Helsinki, as revised in Washington in 2013. Patients were

recruited based on the inclusion and exclusion criteria specified in the study protocol. Patients who were admitted to ICU and older than 18 years old; patients with unpredictable serum creatinine or unstable kidney function; patients with indwelling urinary catheters and consented were recruited. Unstable kidney function is defined as a change in the serum creatinine (Scr) of more than 50% over 1 day (24 hours) for patients with previously normal kidney function. Meanwhile, for patients with pre-existing chronic kidney disease with a baseline serum creatinine of greater than 2.0 mg/dL, it is defined as an increase in Scr by 30% or more than 1.0 mg/dL over a 24 to 48 hours period [19]. Patients with the following criteria were excluded from the study. These criteria include documented kidney transplant; pregnancy; previous dialysis; serum creatinine > 400 µmol/L; AKI from urinary tract obstruction; anuric; seizure disorder; psoriasis; rhabdomyolysis; myasthenia gravis; pyelonephritis; frank hematuria; concurrently receiving cimetidine, trimethoprim, probenecid and cisplatin; and documented augmented kidney function.

The sample size was calculated to address the primary objective of the study. Suppose the true difference in the mean response of matched pairs is 5 ml/min. In that case, we need to study 33 pairs of patients to be able to reject the null hypothesis that this response difference is zero with a probability (power) of 0.8. The Type I error probability associated with this null hypothesis test is 0.05. With an additional dropout rate of 20%, the minimum sample size required was 40.

The total number of patients recruited in this study was 43. In this study, statistical analysis was performed using SPSS version 26.0 software. All data was analyzed for normality using skewedness and kurtosis. For outcome measures of continuous data, paired t-test was used for groups' comparison and student t-test for between groups comparison. Mann Whitney U test was used for between-groups comparison for data that were not normally distributed. Descriptive statistics such as mean, median, standard deviation, interquartile range (IQR), minimum and maximum was used to summarize continuous variables. Counts and percentages were used to summarize categorical variables. Bland-Altman analysis was used to determine the agreement between calculated creatinine clearances based on different methods with measured urinary creatinine clearance (as reference). All the differences were considered statistically significant if 2-tailed tests estimated at a *p*-value were less than 0.05.

RESULTS AND DISCUSSION: Baseline characteristics of the total of 43 patients recruited into the study were summarized in **Table 1**. Most recruited patients were Malay (55.8%), followed by the Indian and non-Malay Bumiputera from east Malaysia (18.6% and 16.3%, respectively), while 9.3% of the studied population was Chinese. Regarding gender distribution, more than half of the studied population were female (58.1%). Indeed, female patients were 38.9% more than male patients, χ^2 (1) = 1.140, p= 0.286. The mean age of the patient was 62.51± 7.03 years old. The mean body mass index (BMI) for male patients was 23.80± 0.98 kg/m^2. The means $SAPS_2$ score in the studied population was 39.02± 4.46.

TABLE 1: DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF STUDIED SUBJECTS

Total (N= 43)	
Age – year*	62.51± 7.03
Weight – kg*	65.19± 5.12
Height – cm*	165.12± 5.32
BMI – kg/ m^2*	23.98± 2.38
BSA – m^2*	1.73± 0.07
$SAPS_2$ score - %*	39.02± 4.46
Gender – no. (%)	
Male	18 (41.9)
Female	25 (58.1)
Race or ethnicity background – no. (%)†	
Malay	24 (55.8)
Chinese	4 (9.3)
Indian	8 (18.6)
Non Malay Bumiputera	7 (16.3)
Reasons admitted to ICU – no. (%)	
Surgery	2 (4.7)
Respiratory diseases	2 (4.7)
Infectious diseases	31 (72.0)
Others	8 (18.6)
Past medication history‡ - no. (%)	
Not on any	16 (37.1)
RAAS blocker	19 (44.2)
RAAS blocker & Aspirin	2 (4.7)
RAAS blocker, aspirin & diuretic	6 (14.0)
Dialyzed (in ward) – no. (%)	0 (0.0)

* Plus-minus values are means ± SD † Race or ethnic background was reported in the patient's bed head ticket ‡ Refer to drugs that may worsen the renal function BMI: Body mass index; BSA: Body surface area; CKD: Chronic kidney disease; IHD: Ischemic heart disease; RAAS: Renal-angiotensin-angiotensinogen system (eg. ACEi or ARB)

TABLE 2: COMPARISON OF CREATININE CLEARANCE ACCORDING TO SERUM CREATININE TRENDS (GENERAL)

Measured Urinary Clcr (ml/min)	eGFR according to Jelliffe method (ml/min)		eGFR according to Brater method (ml/min)		eGFR according to Chiou method (ml/min)		eGFR according to CG method (ml/min)		eGFR according to mCG method (ml/min)		eGFR according to CKD-EPI method (ml/min)		eGFR according to MDRD method (ml/min)		eGFR according to mJelliffe method (ml/min)	
20.56 ± 18.47 Standard	22.38 ± 16.54	‡t = -3.90; *p*< 0.001	22.06± 16.42	‡t = -2.80; *p* = 0.008	16.90 ± 11.46	‡t = 2.32; *p* = 0.025	22.03 ± 14.52	‡t = -3.19; *p* = 0.003	20.12 ± 17.19	‡t = 0.333; *p* = 0.741	22.07 ± 17.52	‡t = -2.85; *p* = 0.007	22.73 ± 17.22	‡t = -3.49; *p* = 0.001	21.96 ± 16.34	‡t = -3.35; *p* = 0.002
Δ (ml/min) Compared to measured Clcr	3.20 ± 5.39	-	2.88 ± 6.76	-	- 2.28 ± 7.48	-	2.85 ± 5.86	-	- 0.43 ± 2.07	-	2.89 ± 6.65	-	3.55 ± 6.68	-	2.78 ± 5.45	-
% Δ Compared to measured Clcr	20.54 ± 32.12	-	19.47 ± 31.88	-	-2.88 ± 34.00	-	27.55 ± 32.25	-	0.37 ± 9.39	-	19.93 ± 30.95	-	27.06 ± 33.02	-	18.27 ± 32.53	-

Note: The central tendency and its dispersion is presented as mean ± SD since the skewedness is between -1.0 to 1.0 and kurtosis is between -3.0 to 3.0. Measured urinary creatinine clearance is the standard reference. Clcr: Creatinine clearance; CG: Cockcroft-Gault; mCG: modified Cockcroft-Gault; mJelliffe: modified Jelliffe. % Δ: Percentage of difference between the measured urinary creatinine clearance and estimated creatinine clearance through various methods [(EstimatedClcr – Measured Clcr) / Measured Clcr] x 100% ‡ Paired samples T test (2- tailed).

The estimated glomerular filtration rate (eGFR) from the eight mathematical methods was compared with the measured 24 hours urinary creatinine clearance (as the standard) (see **Table 2**).

TABLE 3: COMPARISON OF CREATININE CLEARANCE ACCORDING TO INCREASING SERUM CREATININE TRENDS (DETERIORATING)

Measured Urinary Clcr (ml/min)	eGFR according to Jelliffe method (ml/min)		eGFR according to Brater method (ml/min)		eGFR according to Chiou method (ml/min)		eGFR according to CG method (ml/min)		eGFR according to mCG method (ml/min)		eGFR according to CKD-EPI method (ml/min)		eGFR according to MDRD method (ml/min)		eGFR according to mJelliffe method (ml/min)	
11.77 ± 6.27 Standard	16.22 ± 11.85	‡t = 3.21; *p* = 0.004	15.92 ± 10.99	‡t = 3.66; *p* = 0.001	14.66 ± 8.27	‡t = -3.99; *p* = 0.001	17.71 ± 9.26	‡t = 8.81; *p*< 0.001	12.72 ± 6.01	‡t = 0.200; *p* = 0.843	16.70 ± 9.79	‡t = 6.15; *p*< 0.001	17.51 ± 9.55	‡t = 7.61; *p*< 0.001	15.86 ± 11.79	‡t = -2.92; *p* = 0.008
Δ (ml/min) Compared to measured Clcr	4.44 ± 6.65	-	4.15 ± 5.44	-	2.89 ± 3.47	-	5.94 ± 3.24	-	- 0.07 ± 1.17	-	4.92 ± 3.84	-	5.74 ± 3.61	-	4.08± 6.71	-
% Δ Compared to measured Clcr	30.83 ± 38.07	-	29.26 ± 31.98	-	21.13 ± 25.61	-	51.84 ± 13.94	-	0.89 ± 10.60	-	39.09 ± 16.80	-	49.19 ± 16.07	-	27.83 ± 39.11	-

Note: The central tendency and its dispersion is presented as mean ± SD since the skewedness is between -1.0 to 1.0 and kurtosis is between -3.0 to 3.0, Measured urinary creatinine clearance is the standard reference. Clcr: Creatinine clearance; CG: Cockcroft-Gault; mCG: modified Cockcroft-Gault; mJelliffe: modified Jelliffe % Δ: Percentage of difference between the measured urinary creatinine clearance and estimated creatinine clearance through various methods [(Estimated Clcr – Measured Clcr) / Measured Clcr] x 100% ‡ Paired samples T-test (2- tailed).

The comparison was done regardless of the serum creatinine trend (acute deterioration or acute kidney function improvement). The mean value of urinary creatinine clearance was 20.56 ± 18.47 ml/min. Among the equations, only the modified Cockcroft-Gault (20.12 ± 17.19 ml/min) showed a non-significant difference with the urinary creatinine clearance. The modified Cockcroft-Gault method was 0.37% deviated from the urinary creatinine clearance. Meanwhile, the estimated creatinine

clearances by the remaining seven equations were significantly different from the 24 hours urine collection method. The CG method has the highest mean deviation (27.55%) from the urinary method. Whereas the Chiou method has the lowest mean deviation (-2.88%) from the urinary creatinine clearance. A subset analysis was performed on 53.5% of the cohort (23 out of 43 patients recruited) with increasing serum creatinine or deteriorating renal function trends. The mean value of urinary creatinine clearance was 11.77 ± 6.27 ml/min. Among the equations, only the modified Cockcroft-Gault (12.72 ± 6.01 ml/min) showed a non-significant difference with the urinary creatinine clearance. The modified Cockcroft-Gault method was 0.89% or -0.07 ± 1.17 ml/min deviated from the urinary creatinine clearance.

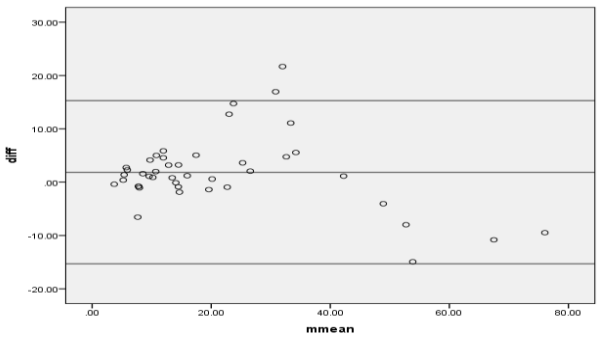
Meanwhile, the estimated creatinine clearances by the remaining seven equations were significantly different from the 24 hours urine collection method. The Cockcroft-Gault method has the highest mean deviation (51.84% or 5.94 ± 3.24 ml/min) from the urinary method. In contrast, the Chiou method has the lowest mean deviation (21.13% or 2.89 ± 3.47 ml/min) from the urinary creatinine clearance.

TABLE 4: COMPARISON OF CREATININE CLEARANCE ACCORDING TO DECREASING SERUM CREATININE TRENDS (IMPROVING)

Measured Urinary Clcr (ml/min)	eGFR according to Jelliffe method (ml/min)		eGFR according to Brater method (ml/min)		eGFR according to Chiou method (ml/min)		eGFR according to CG method (ml/min)		eGFR according to mCG method (ml/min)		eGFR according to CKD-EPI method (ml/min)		eGFR according to MDRD method (ml/min)		eGFR according to mJelliffe method (ml/min)	
30.66 ± 22.53 Standard	29.47 ± 18.53	‡t = 0.94; *p* = 0.361	29.13± 18.93	‡t = 0.64; *p* = 0.527	19.48 ± 14.08	‡t = 4.75; *p*< 0.001	26.99 ± 17.83	‡t = 1.76; *p* = 0.095	29.79 ± 20.68	‡t = 1.42; *p* = 0.171	28.26 ± 22.19	‡t = 1.17; *p* = 0.256	28.74 ± 21.88	‡t = 0.903; *p* = 0.378	28.99 ± 18.22	‡t = 1.29; *p* = 0.213
Δ (ml/min) Compared to measured Clcr	-1.19 ± 5.67	-	-1.53 ± 10.66	-	-11.18 ± 10.52	-	-3.67 ± 9.36	-	-0.88 ± 2.75	-	-2.62 (IQR: 6.92)	-	-1.67 (IQR: 6.86)	-	-1.67± 5.81	-
% Δ Compared to measured Clcr	3.69 ± 20.87	-	3.66 ± 31.37	-	-33.84 ± 18.91	-	-11.43 (IQR: 20.50)	-	-0.36 ± 7.07	-	-14.99 (IQR: 27.15)	-	-13.28 (IQR: 23.03)	-	2.34 ± 20.91	-

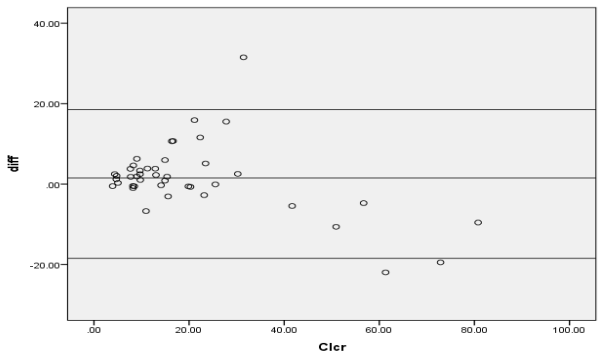
Note: The central tendency and its dispersion is presented as mean ± SD if the skewedness is between -1.0 to 1.0 and kurtosis is between -3.0 to 3.0.Otherwise as median (IQR). Measured urinary creatinine clearance is the standard reference. Clcr: Creatinine clearance; CG: Cockcroft-Gault; mCG: modified Cockcroft-Gault; mJelliffe: modified Jelliffe. % Δ: Percentage of difference between the measured urinary creatinine clearance and estimated creatinine clearance through various methods [(Estimated Clcr – Measured Clcr) / Measured Clcr] x 100% ‡ Paired samples T-test (2- tailed).

Subset analysis was performed on patients with decreasing trends of serum creatinine or improving renal function. The mean value of urinary creatinine clearance was30.66 ± 22.53 ml/min. All predicting equations, except the Chiou equation, showed no statistically significantly different from the standard method. Jellife (29.47± 18.12 ml/min), Brater (29.13 ± 18.93 ml/min), Cockcroft-Gault (26.99 ± 17.83 ml/min), modified Cockcroft-Gault (29.79 ± 20.68 ml/min), CKD-EPI (28.26 ± 22.19 ml/min), MDRD (28.74 ± 21.88 ml/min) and modified Jelliffe (28.99 ± 18.22 ml/min) showed non-significant different with the urinary creatinine clearance. The CKD-EPI method revealed the greatest deviation from the standard (-14.99%) while the modified Cockcroft-Gault method showed the smallest deviation of -0.36%. Meanwhile, the estimated creatinine clearances by the Chiou method were significantly different from the 24 hours urine collection method, $p < 0.001$. The Chiou method has the highest mean deviation (-33.84%) from the urinary method. Bland-Altman plots were performed on the eight methods. The results **Fig. 1** showed that Clcr predicted by MDRD method, CKD-EPI method, mCG method, Jelliffe method and Brater method has good agreement with the standard method. Meanwhile, there is no agreement between Clcr predicted by CG method, mJelliffe method and Chiou method, $p < 0.05$.



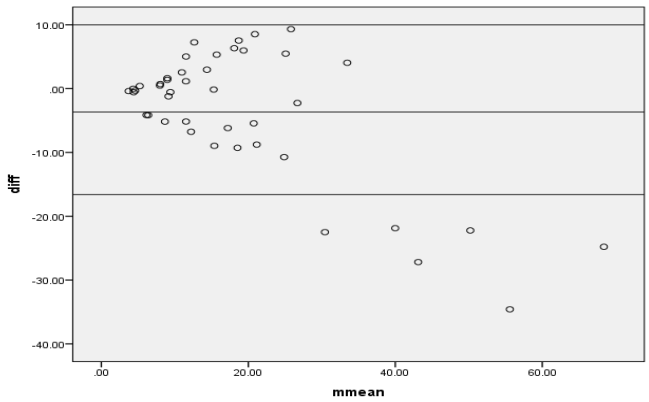
24 hours urinary Clcr vs Jelliffe method

B= 4.276 t = -1.943 P-value =0.059



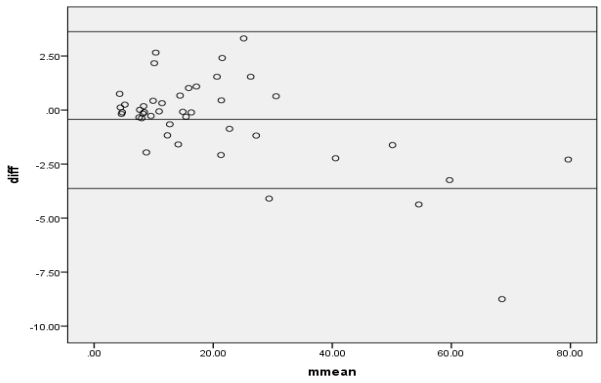
24 hours urinary Clcr vs Brater method

B= 4.161 t = -1.943 P-value =0.116



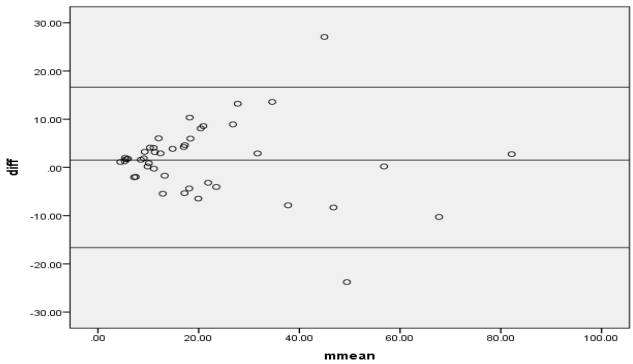
24 hours urinary Clcr vs Chiou method

B= 5.714 t = -6.292 P-value < 0.001



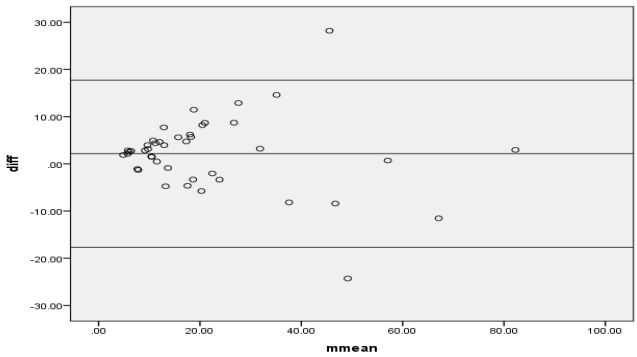
24 hours urinary Clcr vs mCG method

B= 1.033 t = 2.689 P-value = 0.218



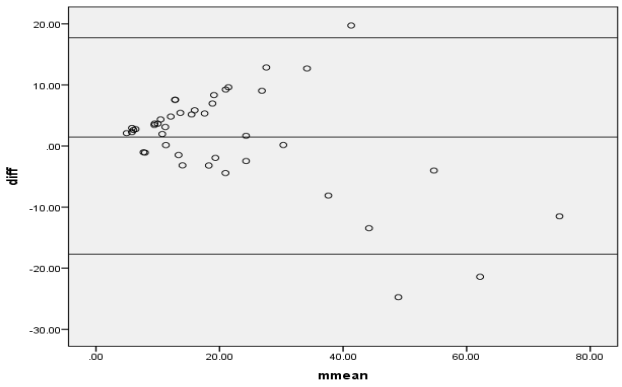
24 hours urinary Clcr vs CKD-EPI method

B= 2.693 t = -0.812 P-value = 0.422



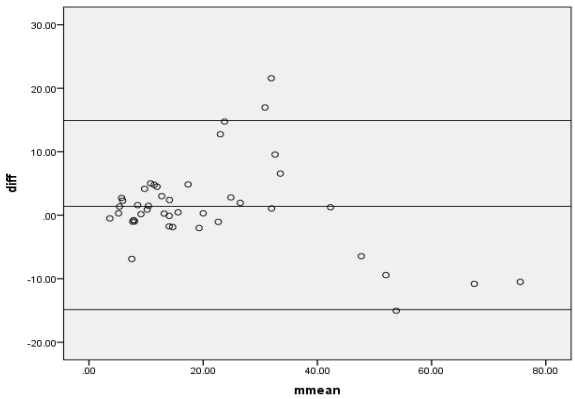
24 hours urinary Clcr vs MDRD method

B= 3.774 t = -1.051 P-value = 0.299



24 hours urinary Clcr vs CG method

B= 6.836 t = -3.593 P-value = 0.001



24 hours urinary Clcr vs mJelliffe method

B= 4.109 t = -2.133 P-value = 0.039

FIG. 1: BLAND-ALTMAN PLOT FOR AGREEMENT BETWEEN MEASURED CLCR AND ESTIMATED CLCR BY THE EIGHT ESTIMATING METHODS.

In general, the present study found out that during the early phase of unstable kidney function regardless of the trends of serum creatinine; either increasing or decreasing, all creatinine clearance predicting equations revealed slight deviation (< 5ml/min) except the modified Cockcroft-Gault equation which shown an insignificant different by -0.43 ml/min compared to the measured 24 hours urinary creatinine clearance. The Chiou method showed the lowest estimated creatinine clearance among the eight methods. It was noted that it underestimated the creatinine clearance by 2.88% compared to the measured 24 hours urinary creatinine clearance. The slight deviations of all the equations observed in general trends of serum creatinine may be due to the dilution effects of a mixture of acute improving and acute deteriorating of one's kidney function.

However, during the acute deterioration of one's kidney function, the creatinine clearance estimated by Cockcroft-Gault method showed the greatest deviation from the standard used in this study. Deviations of estimated creatinine clearance of greater than 5 ml/min were observed in the Cockcroft-Gault and the MDRD method. By converting the difference observed in ml/min to % of different using the 24 hours creatinine clearance as a point of reference, the Cockcroft-Gault and MDRD method overestimated the creatinine clearances by 51.8% and 49.2%, respectively.

The study by Bouchard (2010) found a similar trend of overestimation. Bouchard (2010) reported that the Cockcroft-Gault method overestimated the urinary creatinine clearance by 80% while MDRD by 33% [12]. The differences observed between this study and study conducted by Bouchard (2010) is most likely contributed by the different studied population in term of ethnicity and body weight of the patients since all creatinine clearance predicting equations include variables such as age, gender, ethnicity and body weight into its calculation [11, 12, 19, 20, 21]. Only 12 patients with urinary creatinine clearances were recruited and analyzed in the PICARD study[12]by which 75% of this population were Caucasian; 8.3% African American; and 16.7% Hispanic (none of the studied population was Asian). Poggio and colleagues (2005) [22] studied the accuracy of the Cockcroft-Gault and MDRD equations (steady state estimating equations) in predicting creatinine clearance compared to measured creatinine clearance in hospitalized patients documented with kidney dysfunction. They reported that the MDRD and the Cockcroft-Gault equations overestimated the measured creatinine clearance, and the estimates' accuracy within 50% of the measured creatinine clearance was 49% and 40%, respectively. Bragadottir (2013)[23] also found out that the Cockcroft-Gault, MDRD, and CKD-EPI formulae performed poorly compared to the measured creatinine clearance in critically ill patients with unstable kidney function, and the biases observed were between 7.39 to 11.58 ml/min. A 5 ml/min deviation of estimated creatinine clearance shall produce a difference in drug dosing adjustment decision, which can be either under-dosed (during the recovery phase) or overdosed (during deteriorating phase) [24].

The validated formula to estimate one's kidney function during stable kidney function, CKD-EPI, also showed an overestimated urinary creatinine clearance by 39% [25]. In the current study, equations that were developed to estimate one's kidney function during AKI (but not robustly tested and not widely used), such as the Jelliffe, Brater, Chiou, and later modified Jelliffe, also overestimated the urinary creatinine clearances between 20% to 30%.

During acute kidney function deterioration, the modified Cockcroft-Gault method (0.89% deviation from measured 24 hours urinary creatinine clearance) should be better than other methods. The Chiou method, the Brater method, the Jelliffe method, and the modified Jelliffe method should be considered acceptable methods (deviation between 21.1% to 30.8%). This statement is based on the criteria for acceptable agreement between two methods suggested by Critchley and Critchley (1999) [26]. The authors proposed that the acceptance of the new method should base on method errors of up to 30%. It is best to avoid using the Cockcroft-Gault method, the CKD-EPI method, and the MDRD method in patients with AKI, particularly in decreasing renal function. During the recovery phase of AKI, all predicting equations underestimated the kidney function with the degree of deviation less than 5 ml/min. The exception result was the Chiou method which recorded a negative deviation of 11.18

ml/min (33.84%). Nevertheless, the modified Cockcroft-Gault method provided a closed estimation of creatinine clearance to the measured urinary creatinine clearance. The difference between the measured urinary creatinine clearance and that estimated by the modified Cockcroft-Gault method was only -0.36 ± 7.07 ml/min (0.88%), and the difference observed was not statistically significant.

The magnitude of underestimation for the remaining methods was below 5 ml/min, except the Chiou method. It is noted that the Chiou method always yields a lower estimation of creatinine clearance at any conditions (increasing or decreasing trends of serum creatinine). At the point of early recovery of kidney function, the Chiou method showed a negative deviation of 11.18± 10.52 ml/min or equivalent to – 33.84± 18.91%, $p< 0.0001$.

If we take the cut-off point of acceptable between methods variation of 30% [26], all creatinine clearance estimating methods in this study are acceptable methods to estimate one's kidney function during the recovery phase of AKI, with the exception of Chiou method. The modified Cockcroft-Gault equation able to produce the closest estimation of one's kidney functions during acute deteriorating and acute improving of kidney function.

The Bland-Altman analysis result showed that the steady state equations validated to estimate creatinine clearance at stable kidney disease which includes the Cockcroft-Gault, CKD-EPI and MDRD did not achieve a good agreement with measured creatinine clearance in patients with deteriorating kidney functions. On the other hand, during improving kidney function, these steady-state methods achieve a good agreement with measured urinary creatinine clearance.

The same degree of agreement was also observed in equations specifically developed for unstable kidney function which include the Jelliffe method, Brater method, and modified Jelliffe method in all categories and conditions, except the Chiou method. The Chiou method failed to achieve any level of agreement with measured urinary creatinine clearance in either deteriorating or improving kidney functions. The modified Cockcroft-Gault method consistently showed good agreement of estimated creatinine clearance to the measure 24 hours of urinary creatinine clearance in all categories and conditions. This indicates that the modified Cockcroft-Gault is a better estimating method to predict the creatinine clearance in critically ill patients with unstable kidney function owing to its consistency of very high correlation to the measured urinary creatinine clearance.

CONCLUSIONS: During the early phase of acute deterioration of kidney function, all estimating methods overestimated the urinary creatinine clearance; the modified Cockroft-Gault is an exception. The steady-state estimating methods which include the Cockroft-Gault, MDRD, and the CKD-EPI method overestimated the urinary creatinine between 40 to 50%.

Among these three methods, the Cockroft-Gault method showed an overestimation of urinary creatinine clearance by 51.84 ± 13.94%. The non-steady state methods, including the Jellife, Brater, Chiou, and modified Jellife, also showed a positive deviation from the timed urine collection method. However, the magnitude of variations in estimated creatinine clearances by these non-steady state methods was less than 5 ml/min, which shall not have any clinically significant effects.

The modified Cockroft-Gault method can provide an estimate of creatinine clearance compared to the 24 hours urinary creatinine clearance method. On the other hand, during the early recovery of kidney function, all the steady state creatinine methods underestimated the urinary creatinine clearance, but the magnitude of differences was not clinically significant since all variations were less than 2 ml/min.

During the early recovery phase and deteriorating kidney function, the Chiou method should be avoided, as this method consistently yields a much lower estimation of creatinine clearance under all conditions. The Jellife, Brater, and modified Jellife could be a good alternative. Once again, the modified Cockroft-Gault revealed the ability to predict the creatinine clearance essentially comparable with the urinary creatinine clearance. Good agreement was observed between measured

urinary creatinine and the estimated creatinine clearance by the Jellife method, Brater method, modified Jellife method, Cockroft-Gault method, MDRD method, and CKD-EPI method in all conditions (both improving and deteriorating kidney functions).

The modified Cockroft-Gault method consistently demonstrated good agreement of estimated creatinine clearance to the measure 24 hours of urinary creatinine clearance in all conditions. The estimated Clcr using the Chiou method failed to agree to the measured 24 hours urinary creatinine method in all conditions.

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