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Estimating creatinine clearance for Malaysian critically ill patients with unstable kidney function and impact on dosage adjustment

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ABSTRACT

It is an essential requirement to estimate glomerular filtration rate in dosing adjustment of drug treatment for critically ill patients with unstable kidney function. Previous studies showed that Cockcroft-Gault equation was not appropriate for the assessment of unstable kidney function. However, there is a lack of assessment on other equations specifically designed for fluctuating kidney functions. This study is aimed to evaluate the differences between estimated creatinine clearances by using Cockcroft-Gault, Jelliffe, Brater, and Chiou equations and the impact on dosing adjustment of renally excreted drugs for critically ill patients with unstable kidney function. A retrospective observational study was conducted among 103 patients with unstable kidney function who were admitted to intensive care unit of Taiping Hospital, Malaysia. Serum creatinine levels from day 1 to 7 of admission were collected. The median differences of estimated creatinine clearance based on the four different equations were analysed by Friedman-ANOVA test. The median estimated creatinine clearances when patients were having fluctuating kidney functions showed 35.69 ml/min (IQR: 22.57 – 53.97) by Cockcroft-Gault and 22.64 ml/min (IQR: 10.46 – 38.49) by Jelliffe equation, while Brater and Chiou equations showed 35.88 ml/min (IQR: 19.46 – 56.04) and 30.10 ml/min (IQR: 16.55 – 46.82) respectively. Jelliffe and Chiou equation showed a significant 36.56% and 15.66% lower estimated creatinine clearance respectively as compared to Cockcroft-Gault ($p < 0.001$). Jelliffe equation demonstrated the lowest estimated creatinine clearance value with a more intense dosage adjustment required for patients' drug regimen involving renally excreted drugs. In conclusion, there were clinically significant variations in the estimated creatinine clearance from the different equations.

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INTRODUCTION

Acute renal failure or more recently known as acute kidney injury is a common complication in hospitalized patients and is associated with high mortality rate (Mehta *et al.*, 2004; Uchino *et al.*, 2005). The incidence of acute kidney injury is markedly higher in critically ill patients with fluctuating kidney function (Chertow *et al.*, 2005; Mehta *et al.*, 2004). The decline in kidney function contributes to the accumulation of renally excreted drugs, leading to potential drug toxicity (Peyrière *et al.*, 2001). Besides, the

reduced kidney function may also cause an impairment in hepatic and intestinal drugs metabolism. Prominent changes in pharmacokinetics particularly protein bindings and serum amino acid levels may also be observed in patients with unstable kidney function. Consequently, the concentration of free drugs will increase concurrently with an altered volume of distribution and could possibly lead to drug toxicity (Blanco *et al.*, 2019).

Several studies suggested that the Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault equations are both highly correlated with measured glomerular filtration rate (Golik and Lawrence, 2008; Nguyen *et al.*, 2009). Nevertheless, the use of the MDRD equation often overestimates creatinine clearance, leading to errors in drug dosing compared with doses calculated by using Cockcroft-Gault equation (Hermsen *et al.*, 2009; Wargo *et al.*, 2006). For instance, a study involving 409 chronic kidney disease (CKD) stage 3 to 5 patients found that kidney function estimates using MDRD equation were approximately 13% to 26% higher than Cockcroft-Gault derived creatinine clearance estimates (Wargo *et al.*, 2006). The Cockcroft-Gault equation is the most widely recognized method for drug dosage adjustment. However, it is not the most accurate equation to be used in acute kidney injury as the derivation of this equation involved only males with stable kidney function (Awdishu *et al.*, 2018; Cockcroft and Gault, 1976).

Estimation of creatinine clearance has been a challenge in critical care due to the fluctuations in patients' kidney function, creatinine production, and fluid balance (Jelliffe and Jelliffe, 1972). There was no consensus on the most appropriate equation to be applied in clinical practice. The 24-hour urine creatinine clearance is the standard. The commonly used Cockcroft-Gault equation is considered inaccurate as compared to the 24-hour urine creatinine clearance (Giles and Fitzmaurice, 2007). Nevertheless, the 24-hour urine creatinine clearance involves timed urine collections which are cumbersome to perform (Giles and Fitzmaurice, 2007). Inaccurate creatinine clearance estimation for dosing adjustment may lead to ineffective drug therapy or toxicity. Therefore, there is a need for careful individualization of drug dosage. The equations by Jelliffe (Jelliffe and Jelliffe, 1972; Brater, 1983) or Chiou (Chiou and Hsu, 1975) are options but these equations were not robustly tested and there was a debate on accuracy (Bouchard *et al.*, 2010). These equations are better choices for unstable kidney functions since they involve the use of two consecutive serum creatinine values in the estimation of creatinine clearance. Meanwhile, Cockcroft-Gault equation uses only one serum creatinine value in the estimation and tends to overestimate and underestimate the glomerular filtration rate in patients with deteriorating and improving kidney functions respectively (Dager and Halilovic, 2014). A previous study revealed that estimated glomerular filtration rate computed using Jelliffe equation correlated best with urinary creatinine clearance as compared to the Cockcroft-Gault equation in critically ill patients with acute kidney injury (Bouchard *et al.*, 2010). The Jelliffe and Cockcroft-Gault equations overestimated urinary creatinine clearance by 10% and 80% respectively (Bouchard *et al.*, 2010). Therefore, the Jelliffe equation is more accurate in creatinine clearance estimation for patients with unstable kidney function as compared to the Cockcroft-Gault equation. Meanwhile, studies assessing the use of Brater and Chiou equations in the clinical setting and studies involving Asian population are limited.

A previous survey from the ACCP Nephrology and Critical Care Practice and Research Network showed approximately 95% of critical care pharmacists used Cockcroft-Gault equation to estimate creatinine clearance for dosage adjustment (Dowling *et al.*, 2010). In Malaysia, estimating creatinine clearance using Cockcroft-Gault equation remained as the preference for most practicing clinical pharmacists and clinicians. The mortality in critical care could be partly contributed by the inappropriate drug dosing due to inaccurate prediction of patients' kidney function. The critical care population is exceptionally vulnerable for which underdosing of antibiotics will lead to poor response and mortality; while overdosing will lead to undesired side effects, permanent damages or even death secondary to multiple complications (Ali *et al.*, 2019). Hence, clinicians and pharmacists should consider using more reliable alternative methods in guiding drug dosing for patients with unstable kidney function (Jelliffe and Jelliffe, 1972).

There is a need for conducting a study to conclude an appropriate equation for estimating kidney function in critically ill patients. This study aimed to investigate the differences between estimated creatinine clearances with Cockcroft-Gault, Jelliffe, Chiou, and Brater equations for critically ill patients with unstable kidney function. This study finding will provide an insight for dosage adjustment of renally excreted drugs in critical care.

MATERIALS AND METHODS

This was a single-centred, retrospective study involving a total of 103 patients admitted to

Table 1: Equations for estimating of creatinine clearance (CrCl) in adults with unstable kidney function

Equation 1: Cockcroft-Gault (ml/min)	
Male	Female
$CrCl\ (male) = \frac{(140-age)\times Wt}{72\times Scr}$	$CrCl\ (female) = \frac{(140-age)\times Wt}{72\times Scr} \times 0.85$
Equation 2: Jelliffe (ml/min per 1.73m^2)	
Male	Female
$Ess(males) = Wt \times [29.3 - 0.203(age)]$	$Ess(females) = Wt \times [25.1 - 0.175(age)]$
Correct Ess for nonrenal creatinine excretion in chronic kidney disease:	Correct Ess for nonrenal creatinine excretion in chronic kidney disease:
$Esscorr = Ess \times [1.035 - 0.0337(Scr)]$	$Esscorr = Ess \times [1.035 - 0.0337(Scr)]$
Scr = If serum creatinine values are rising, enter the most recent Scr. If Scr values are declining enter the average value between the two Scr values.	Scr = If serum creatinine values are rising, enter the most recent Scr. If Scr values are declining enter the average value between the two Scr values.
$E = Esscorr - \frac{[4\times Wt\times(Scr2-Scr1)]}{Time\ in\ days\ between\ Scr1\ and\ Scr2}$	$E = Esscorr - \frac{[4\times Wt\times(Scr2-Scr1)]}{Time\ in\ days\ between\ Scr1\ and\ Scr2}$
Scr2 = latest serum creatinine;	Scr2 = latest serum creatinine;
Scr1 = earlier serum creatinine	Scr1 = earlier serum creatinine
$CrCl\ (ml/min/1.73m^2) = \frac{E}{14.4\times Scr}$	$CrCl\ (ml/min/1.73m^2) = \frac{E}{14.4\times Scr}$
Body surface area (BSA) (m^2) = $\sqrt{(Wt\ (kg) X\ Height\ (cm))/3600}$	Body surface area (BSA) (m^2) = $\sqrt{(Wt\ (kg) X\ Height\ (cm))/3600}$
Convert CrCl (ml/min/1.73m^2) to CrCl (ml/min) = $(CrCl\ X\ BSA\ (m^2))/(1.73\ m^2)$	Convert CrCl (ml/min/1.73m^2) to CrCl (ml/min) = $(CrCl\ X\ BSA\ (m^2))/(1.73\ m^2)$
Equation 3: Brater (ml/min per 70kg)	
Male	Female
$CrCl\ (ml/min/70kg) = \frac{[293-2.03(age)]\times[1.035-0.01685(Scr1+Scr2)]}{(Scr1+Scr2)} + \frac{49(Scr1-Scr2)}{(Scr1+Scr2)\times time\ in\ days\ between\ Scr1\ and\ Scr2}$	CrCl = Male value x 0.86
Convert CrCl (ml/min/70kg) to CrCl (ml/min) = $(CrCl\ x\ Wt\ (kg))/(70\ kg)$	Convert CrCl (ml/min/70kg) to CrCl (ml/min) = $(CrCl\ x\ Wt\ (kg))/(70\ kg)$
Equation 4: Chiou (ml/min)	
Male	Female
$Volume\ distribution\ of\ creatinine,\ Vd = 0.6\ L/kg \times Wt$	$Volume\ distribution\ of\ creatinine,\ Vd = 0.6\ L/kg \times Wt$
$CrCl(ml/min) = \frac{2\times Wt\times[28-0.2(age)]}{14.4(Scr1+Scr2)} + \frac{2[Vd(Scr1-Scr2)]}{(Scr1+Scr2)\times times\ in\ minutes\ between\ Scr1\ and\ Scr2} - (Nonrenal\ Clcr \times Wt)$	$CrCl(ml/min) = \frac{2\times Wt\times[22.4-0.16(age)]}{14.4(Scr1+Scr2)} + \frac{2[Vd(Scr1-Scr2)]}{(Scr1+Scr2)\times times\ in\ minutes\ between\ Scr1\ and\ S} - (Nonrenal\ Clcr \times Wt)$
Non-renal CrCl = 0.048 ml/min/kg	Non-renal CrCl = 0.048 ml/min/kg

CrCl= Creatinine clearance; E = Creatinine excretion; Ess = Steady state creatinine excretion;Esscorr = Corrected steady state creatinine excretion; Scr = Serum creatinine value; Scr1= First serum creatinine value; Scr2 =Second serum creatinine value; Vd = Volume of distribution;Wt = Body weight (use ideal bodyweight, IBW if weight > 30% above IBW)

Table 2: Baseline characteristics of the patients

Characteristics	n (%)
Gender	
Female	53 (51.5)
Male	50 (48.5)
Ethnic background	
Malay	73 (70.9)
Indian	17 (16.5)
Chinese	12 (11.7)
Others	1 (1.0)
Reasons for ICU admission	
Infectious Disease	75 (72.8)
Surgery	14 (13.6)
Respiratory diseases	6 (5.8)
CVD	6 (5.8)
CVA	2 (1.9)
Medical history	
Diabetes & hypertension	15 (14.6)
Diabetes	11 (10.7)
Diabetes, hypertension & dyslipidemia	9 (8.7)
CKD, diabetes & hypertension	8 (7.8)
Hypertension	6 (5.8)
Dyslipidemia & hypertension	5 (4.9)
CVD, diabetes & hypertension	5 (4.9)
Diabetes, hypertension, dyslipidemia & CKD	4 (3.9)
CVD	4 (3.9)
Hyperlipidemia	2 (1.9)
Liver disease	1 (1.0)
CKD	1 (1.0)
COPD	1 (1.0)
No known co-morbidity	31 (30.1)
Medication history	
ACEi/ARB & platelet aggregation inhibitor	21 (20.4)
ACEi/ARB	18 (17.5)
ACEi/ARB & platelet aggregation inhibitor & diuretic	5 (4.9)
Platelet aggregation inhibitor	3 (2.9)
Diuretic	2 (1.9)
ACEi/ARB & diuretic	1 (1.0)
Not on any medication	53 (51.5)

ACEi = Angiotensin converting enzyme inhibitor; ARB =Angiotensin II receptor antagonist; CVA = Cerebrovascular accident; CVD =Cardiovascular disease; CKD = Chronic kidney disease; COPD = Chronic obstructive pulmonary disease

Table 3: Comparison of estimated creatinine clearance (CrCl) based on Cockcroft-Gault, Jelliffe, Brater and Chiou equations

Equation to estimate CrCl	Median CrCl (ml/min)	Friedman-ANOVA test statistic, χ2(df) & p value	Post-hoc analysis (Wilcoxon signed rank test)
Day 1 (Baseline) (N = 103)			
Cockcroft-Gault	55.80 (IQR: 37.41-84.90)	χ2(3) = 215.82; p < 0.001	CG vs J (Z = -8.797, p < 0.001)
Jelliffe	28.39 (IQR: 17.51-50.60)		CG vs B (Z = -7.080, p < 0.001)
Brater	40.69 (IQR: 25.48-61.38)		CG vs C (Z = -8.521, p < 0.001)
Chiou	36.70 (IQR: 27.78-59.79)		J vs B (Z = -8.636, p < 0.001)
			J vs C (Z = -8.299, p < 0.001)
			B vs C (Z = -0.405, p = 0.686)
Deteriorating trend[a] (N = 390)			
Cockcroft-Gault	34.03 (IQR: 21.74 – 52.33)	χ2(3) = 684.72; p < 0.001	CG vs J (Z = -16.993, p < 0.001)
Jelliffe	19.99 (IQR: 10.19 – 35.64)		CG vs B (Z = -4.978, p < 0.001)
Brater	32.13 (IQR: 17.63 – 47.82)		CG vs C (Z = -14.690, p < 0.001)
Chiou	27.79 (IQR: 15.69 – 41.64)		J vs B (Z = -16.508, p < 0.001)
			J vs C (Z = -14.805, p < 0.001)
			B vs C (Z = -8.935, p < 0.001)
Rapid deteriorating trend[b] (N = 38)			
Cockcroft-Gault	26.13 (IQR: 13.44 – 39.23)	χ2(3) = 63.32; p < 0.001	CG vs J (Z = -5.272, p < 0.001)
Jelliffe	16.99 (IQR: 4.68 – 29.49)		CG vs B (Z = -1.385, p = 0.166)
Brater	27.77 (IQR: 17.05 – 44.53)		CG vs C (Z = -3.879, p < 0.001)
Chiou	21.75 (IQR: 10.22 – 34.79)		J vs B (Z = - 5.098, p < 0.001)
			J vs C (Z = -4.198, p < 0.001)
			B vs C (Z = -4.546, p < 0.001)
Improving trend[c] (N = 171)			
Cockcroft-Gault	39.39 (IQR: 26.87 – 57.09)	χ2(3) =302.78; p < 0.001	CG vs J (Z = -10.440, p < 0.001)
Jelliffe	29.43 (IQR: 12.70 – 50.16)		CG vs B (Z =-6.524, p < 0.001)

Continued on next page

Table 3 continued

Brater	49.39 (IQR: 29.11 – 68.76)		CG vs C (Z = -5.241, p < 0.001)
Chiou	37.59 (IQR: 22.88 – 56.16)		J vs B (Z = -11.152, p < 0.001)
			J vs C (Z = -9.821, p < 0.001)
			B vs C (Z=-10.343, p < 0.001)
Rapid improving trend[d]			
(N = 43)			
Cockcroft-Gault	51.19 (IQR: 35.22 – 84.79)	χ2(3) = 60.35; p < 0.001	CG vs J (Z = -4.552, p < 0.001)
Jelliffe	37.98 (IQR: 24.67 – 70.50)		CG vs B (Z = -2.946, p = 0.003)
Brater	56.60 (IQR: 41.90 – 95.60)		CG vs C (Z = -2.258, p = 0.024)
Chiou	45.15 (IQR: 32.60 – 76.05)		J vs B (Z = -5.567, p < 0.001)
			J vs C (Z = -4.051, p < 0.001)
			B vs C (Z = -4.951, p < 0.001)
Overall trend (N = 561)			
Cockcroft-Gault	35.69 (IQR: 22.57 – 53.97)	χ2(3) = 929.90; p < 0.001	CG vs J (Z = -19.961, p < 0.001)
Jelliffe	22.64 (IQR: 10.46 – 38.49)		CG vs B (Z = -0.425, p = 0.671)
Brater	35.88 (IQR: 19.46 – 56.04)		CG vs C (Z = -15.494, p < 0.001)
Chiou	30.10 (IQR: 16.55 – 46.82)		J vs B (Z = -19.921, p < 0.001)
			J vs C (Z = -17.747, p < 0.001)
			B vs C (Z = -13.791, p < 0.001)

[a]Creatinine clearance in deteriorating trend (serum creatinine at increasing trend). [b]Creatinine clearance for patients with more than 50% increase in serum creatinine within 24 hours. [c]Creatinine clearance in improving trend (serum creatinine at decreasing trend). [d]Creatinine clearance for patients with more than 50% decreased in serum creatinine within24 hours

Table 4: Dosage adjustment requirement based on estimated creatinine clearance (CrCl) using all four equations

Patient No.	Drug Regimen (Name, dose, frequency)	Calculated CrCl (ml/min) based on different method				Dose adjustment requirement			
		C-G	J	B	C	C-G	J	B	C
1.	IV Tazosin 4.5 g TDS	32.69	8.85	13.60	18.28	✓	✓*	✓*	✓*
2.	IV Tazosin 4.5 g QID	22.57	11.41	12.46	16.12	✓	✓*	✓*	✓*
3.	IV Imipenem 500 mg QID	31.14	18.07	44.64	30.20	✓*	✓*	✓	✓*
4.	IV Meropenem 1g TDS	24.01	11.36	29.11	21.57	✓*	✓*	✓	✓*
5.	T. Digoxin 0.25 mg OD	14.23	7.77	8.77	10.14	✓	✓*	✓*	✓
6.	IV Meropenem 500 mg BD	17.71	3.20	2.91	10.54	✓	✓*	✓*	✓
7.	IV Imipenem 500 mg QID	22.06	7.80	25.55	20.10	✓	✓*	✓	✓*
8.	IV Imipenem500 mg QID	53.67	38.72	51.85	44.33	✓	✓*	✓	✓
9.	IV Imipenem 500 mg QID	31.80	14.10	34.45	28.94	✓	✓*	✓	✓
10.	IV Imipenem 1 g QID	44.10	34.18	59.25	43.70	✓	✓*	✓	✓
11.	IV Meropenem 1 g TDS	36.78	23.93	47.55	36.97	✓	✓*	✓	✓
12.	IV Meropenem 1 g TDS	21.13	8.60	26.01	18.86	✓	✓*	✓	✓
13.	IV Meropenem 1 g TDS	39.54	25.33	46.58	38.25	✓	✓*	✓	✓
14.	IV Meropenem 2 g TDS	28.20	15.69	37.14	26.86	✓	✓*	✓	✓

Continued on next page

Table 4 continued

15.	IV Imipenem 500 mg TDS	23.29	21.85	22.33	19.57	✓	✓	✓	✓*
16.	IV Meropenem 1 g BD	28.44	18.22	22.79	21.12	X	✓	✓	✓
17.	IV Meropenem 1 g TDS	24.08	16.66	51.04	29.62	✓*	✓*	X	✓
18.	IV Tazosin4.5 g QID	30.86	22.31	51.43	32.79	✓	✓	X	✓
19.	IV Meropenem 1 g TDS	42.34	32.62	57.62	42.70	✓	✓	X	✓
20.	IV Meropenem 1 g TDS	44.34	31.80	53.91	43.84	✓	✓	X	✓
21.	IV Tazosin 2.25 g TDS	44.74	31.42	53.83	40.76	X	✓	X	X
22.	IV Cefepime 2 g BD	33.60	23.34	49.92	35.01	X	✓	X	X
23.	IV Meropenem 1 g BD	38.69	22.89	30.37	28.41	X	✓	X	X
24.	IV Meropenem 1 g BD	31.20	15.96	35.88	27.76	X	✓	X	X
25.	IV Sulper-azone 2 g QID	36.04	19.14	40.60	33.49	X	✓	X	X

C-G = Cockcroft-Gault equation; J = Jelliffe equation;B = Brater equation; C = Chiou equation; ✓ = Dosage adjustment required; * = Dosage adjustment required at higherintensity; X =No dosage adjustment required

intensive care unit (ICU) of Taiping Hospital, state of Perak, Malaysia from year 2010 to 2012. This study was granted ethics approval by the Medical Research & Ethics Committee, Malaysia on 20^{th} May 2013 (NMRR-12-1299-14330).

The inclusion criteria were adult ICU patients (older than 18 years) with documented acute kidney injury or unstable kidney function. Acute kidney injury is defined as an acute decrease in kidney function (Glomerular filtration rate) over a period of hours, days, or even weeks, associated with an accumulation of waste products and (usually) volume. Unstable kidney function is defined as an increase in serum creatinine of 0.5 mg/dl (44.2 μmol/L) or a decrease of 25% or greater in the glomerular filtration rate of patients with a previously normal kidney function; or an increase of 1.0 mg/dl or greater in patients with chronic kidney disease within 48 hours (Dager and Halilovic, 2014). It is also defined based on urine output, which is less than 0.5 ml/kg/hour for at least 6 hours (Dager and Halilovic, 2014). The patients with incomplete data, documented kidney transplantation, pregnancy, previous history of renal replacement therapy, receiving dialysis from the ICU, serum creatinine more than 400 μmol/L, acute kidney injury from urinary tract obstruction, oliguric or anuric, seizure disorders, hypovolemic responsive to fluid, and psoriasis were excluded.

Patients' demographic, ICU admission reasons, past medical history, past medication history and drug treatment in the ICU were recorded. Besides, Simplified Acute Physiology Score II (SAPS II) score, laboratory data and urine output were also recorded. The serum creatinine as a key biomarker was collected from day 1 to day 7. This was owing to serum creatinine needs a week to stabilize when there is a change in kidney function as shown by a previous study (Bouchard *et al.*, 2010).

The creatinine clearances of the patients were subsequently calculated by using Cockcroft-Gault, Jelliffe, Chiou and Brater equations (Table 1). The creatinine clearance units for Jelliffe (ml/min/1.73m^2) and Brater (ml/min/70kg) were converted to ml/min. The conversion was conducted to standardise the values of estimated creatinine clearance to the same units for comparisons. Besides, ideal body weight (IBW) were used in this study for the creatinine clearance estimation as documented by the hospital dieticians in the patients' case notes (at the nutritional referral form). The patients' actual body weights (ABW) were untraceable in the case notes.

Statistical analysis was performed by using SPSS® version 20.0 software. Descriptive statistics such as mean and standard deviation were used to summarise the continuous variables which were normally distributed. Median and interquartile range (IQR) were used if the data was not normally distributed. Besides, the differences between calculated creatinine clearance based on Cockcroft-Gault, Jelliffe, Brater, and Chiou equations were analysed using Friedman-ANOVA test. Follow-up post-hoc analysis by using Wilcoxon Signed-Rank test was conducted to evaluate comparison between pairs of the calculated creatinine clearance. Statistically significant was set at a p value of less than 0.05.

The patients' drug regimen involving renally excreted drugs were evaluated for the need of dosage adjustment according to the creatinine clearance estimated by the four equations. The drug dosages were evaluated by using the IBM Micromedex® (an evidence-based, multi-database drug search engine).

RESULTS AND DISCUSSION

A total of 103 patients who fulfilled the inclusion criteria were selected from a pool of 1500 patients through convenient sampling. Majority (51.5%) of the patients were female. All the patients were from Asian population with most of them were Malays (70.9%) (Table 2). The patients had mean age of 57.91 $\pm$ 16.04 years old with mean body weight of 61.79 $\pm$ 9.55 kg and median height of 163.00 cm (IQR: 156.00 – 170.00 cm). The mean body weight for male patients was 67.43 $\pm$ 8.80 kg with a median height of 169.50 cm (IQR: 166.00 – 170.00 cm). Whereas, the mean weight for female patients was 56.47 $\pm$ 6.82 kg with a median height of 156.00 cm (IQR: 154.00 – 160.00 cm).

The most common complication that led to ICU admission was infectious disease (72.8%) either in the form of septicaemia or sepsis. Approximately 51.5% of the studied patients had no medication history or with no history of taking chronically any renal toxic medications. Meanwhile, 20.4% of the patients were taking both angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) and a platelet aggregation inhibitor (aspirin, aspirin plus glycine or clopidogrel). Patients who were taking ACEi or ARB prior to admission was documented as much as 17.5% (Table 2). The mean SAPS II score of the patients was 46.31 $\pm$ 18.96 which carries a meaning of 50% mortality rate. The studied patients had a median serum creatinine at baseline of 99.00 (IQR: 70.80 – 137.00) μmol/L and a median blood urea nitrogen (BUN) level of 7.10 (IQR: 4.40 – 10.10) mmol/L.

Both baseline serum creatinine and BUN were at the higher end of normal range.

The comparison of creatinine clearance determined by four different methods was made for day 1 or at baseline when patients were still having stable kidney functions. The median creatinine clearance for Cockcroft-Gault, Jelliffe, Brater and Chiou equations were significantly different between each other based on post hoc analysis except for the Brater and Chiou pair. Using Cockcroft-Gault equation as standard, the creatinine clearance calculated by Jelliffe, Brater and Chiou equations were 49.12%, 27.08%, and 34.23% lower as compared to Cockcroft-Gault respectively. When the creatinine clearance was in a deteriorating trend (serum creatinine at increasing trend), with a total of 390 sets of serum creatinine measurements, significant differences (post hoc analysis) were found between all the equations. The magnitude of differences when comparing Jelliffe, Brater and Chiou to Cockcroft-Gault were 41.26%, 5.58% and 18.34% lower respectively (Table 3).

A subgroup analysis was performed on 38 sets of serum creatinine measurements with most rapid deteriorating kidney functions (more than 50% increase in serum creatinine within 24 hours). The Brater equation showed the highest estimated creatinine clearance, followed by Cockcroft-Gault, Chiou and Jelliffe. The median calculated creatinine clearances by Brater was 6.28% higher, while Jelliffe and Chiou were 34.98% and 16.76% lower respectively when compared to the Cockcroft-Gault equation. There were statistically significant differences among all pairs comparison except for the Cockcroft-Gault and Brater pair (Table 3).

A total of 171 sets of serum creatinine measurements which showed recovery of kidney function with an improving trend (decreasing trend in serum creatinine) were analysed. The Brater equation estimated the highest creatinine clearance. The calculated creatinine clearance by Jelliffe was 25.29% lower, Brater was 25.39% higher and Chiou was 4.57% lower as compared to Cockcroft-Gault. Post hoc analysis showed statistically significant difference in all pair's comparison. A total of 43 sets of serum creatinine measurements with most rapid improving kidney functions (more than 50% decrease in serum creatinine within 24 hours) were identified. The estimated creatinine clearance by Brater equation was again higher than the other equations. The estimated creatinine clearances by Chiou and Jelliffe equations were 11.80% and 25.81% lower respectively when compared to Cockcroft-Gault. Meanwhile, the Brater estimated creatinine clearance was 10.57% higher than Cockcroft-Gault. Statistically significant differences were found among all the pairs comparison. Considering the overall trend of estimated creatinine clearance from all four equations with a total of 561 sets of measurements, significant difference was found between all pair's comparisons except for the Cockcroft-Gault and Brater pair. Jelliffe and Chiou estimated the creatinine clearance lower than Cockcroft-Gault by 36.56% and 15.66% respectively. Whereas, Brater estimated creatinine clearance were slightly higher (0.53%) than Cockcroft-Gault (Table 3).

Patients' drug regimen involving renally excreted drugs with distinct dosage adjustment recommendations according to the four equations were illustrated in Table 4. The estimated creatinine clearance using all four equations were also examined if dosage adjustment was required for patients' different drug regimen. Jelliffe equation estimated the lowest creatinine clearance, hence it required dosage adjustment for all the 25 selected cases. Out of the 25 cases, 15 cases required the dose to be adjusted to a greater intensity as compared to the other equations. Meanwhile, Brater equation estimated creatinine clearance were mostly the highest, thus it only showed 16 cases needed dosage adjustment. Cockcroft-Gault and Chiou showed 19 and 20 cases needed dosage adjustment respectively. There was a case (case number 16) that required dose adjustment according to Jelliffe, Chiou and Brater equations but not by the Cockcroft-Gault equation. Meanwhile, there were four cases (case number 17-20) that required dosage adjustments by Cockcroft-Gault, Jelliffe and Chiou equations but not by the Brater equation. Besides, a total of five cases (case number 21-25) showed only dosage adjustments required by Jelliffe equation and not with the other three equations (Table 4).

This was among the first study comparing the differences among the estimated creatinine clearances calculated by Cockcroft-Gault, Jelliffe, Brater and Chiou equations for critically ill patients who developed acute kidney injury during the ICU stay that involved Asian population in Malaysia. Acute kidney injury is one of the most serious adverse events that can develop in ICU patients which may lead to a higher mortality rate (Chertow *et al.*, 1998). Accurate estimation of kidney function is required to optimize drug administration. Despite being the gold standard for glomerular filtration rate estimation, inulin clearance is however very difficult and impractical for daily clinical use. This is because a constant intravenous infusion is needed to maintain a consistent level of inulin for its clearance mea-

surement (Langlois, 2008). Besides, inulin is expensive for daily routine use. Hence, the most common way for accurate measurement of kidney function is 24 hours urine collection (Nguyen *et al.*, 2009). However, this method might lead to inaccuracy secondary to urine collection error or anuria when patients were critically ill (Awdishu *et al.*, 2018).

Several equations such as Cockcroft-Gault and MDRD have been developed for rapid estimation of patients' kidney function (Golik and Lawrence, 2008; Nguyen *et al.*, 2009). Cockcroft-Gault and MDRD use serum creatinine and other characteristics to provide an estimate of kidney function. Nevertheless, patients who are critically ill have fluctuating serum creatinine and kidney functions. Besides, there are certain patients' characteristics which influence the creatinine production. For instance, severe liver disease, altered muscle mass or disposition secondary to unstable kidney function may render the creatinine-based equations inaccurate (Nyman *et al.*, 2011). Poorer kidney function caused the creatinine clearance to overestimate the glomerular filtration rate due to the additional creatinine cleared by tubular secretion (Hermsen *et al.*, 2009; Wargo *et al.*, 2006). Both Cockcroft-Gault and MDRD equations require stable kidney function and serum creatinine concentration for glomerular filtration rate estimation. These two equations for creatinine clearance estimation may overestimate the kidney function in critically ill acute kidney injury patients based on the results from a previous study (Bouchard *et al.*, 2010).

The estimation of creatinine clearance would be affected if patients were taking drugs that were affecting creatinine secretion through inhibition of active tubular secretion of creatinine (Zaltzman *et al.*, 1996). For instance, drugs such as cimetidine, trimethoprim or probenecid would result in falsely low estimates of creatinine clearance when serum creatinine is solely used in the creatinine clearance estimation (Israni and Kasiske, 2007). In this study, none of the studied patients were prescribed with the above-mentioned drugs. However, 20.4% of the studied patients in this study were taking drugs that might worsen the kidney function, namely ACE inhibitors, ARB, diuretics and platelet aggregation inhibitor. However, the use of these drugs would not affect the creatinine secretion and the subsequent estimation of creatinine clearance.

The estimation of creatinine clearance also depends on the production of creatinine. Long term bedridden critically ill patients will experience muscular dystrophy, thus having low muscle mass. Creatinine is produced from the metabolism of muscle. Hence, lesser creatinine will be produced with low muscle mass, leading to low serum creatinine level. Creatinine clearance will be overestimated particularly by the Cockcroft-Gault equation due to the inverse proportional relationship between serum creatinine and creatinine clearance (O'Connell *et al.*, 1992; Smythe *et al.*, 1994). This was reflected in the present study findings whereby the estimated creatinine clearance by the Cockcroft-Gault equation was generally higher than the Jelliffe and Chiou equations. The Jelliffe and Chiou equations were affected to a lesser extent by the low muscle mass in ICU patients since these equations involved the changes of serum creatinine between two consecutive days and not solely depending on one serum creatinine value. Additionally, the nonrenal creatinine excretion is corrected in both the Jelliffe and Chiou equations (Chiou and Hsu, 1975; Jelliffe and Jelliffe, 1972). Although the Brater equation involved the use of two consecutive serum creatinine values, the nonrenal creatinine excretion is not corrected (Brater, 1983). This could be the reason for higher estimated creatinine clearance value by the Brater equation as compared to Jelliffe and Chiou equations.

A previous study conducted by Bouchard *et al.* which compared the estimated glomerular filtration rate calculated by Cockcroft-Gault and Jelliffe equations found that the estimation by Cockcroft-Gault equation was 49% higher than Jelliffe equation in acute kidney injury (Bouchard *et al.*, 2010). Besides, glomerular filtration rate estimation by Jelliffe equation demonstrated a small deviation from urinary creatinine clearance as compared to Cockcroft-Gault (Bouchard *et al.*, 2010). The present study also showed an overall trend of huge difference between Cockcroft-Gault and Jelliffe for the estimation of creatinine clearance. The Cockcroft-Gault estimated creatinine clearance was higher than Jelliffe by 36.6%. However, Brater and Chiou equations were not included in the Bouchard *et al.* study (Bouchard *et al.*, 2010). Thus, the comparisons of estimated creatinine clearance using Cockcroft-Gault, Jelliffe, Brater and Chiou equations in this study will complement the results of Bouchard *et al.* study. As Brater and Cockcroft-Gault did not show significant difference in the estimated creatinine clearance, while only a small difference (15.7%) was observed between Chiou and Cockcroft-Gault equations, Jelliffe would be the most appropriate equation for unstable kidney function. However, there were differences in the demographic characteristics between the Bouchard *et al.* and this study. The Bouchard *et al.* study had only 2.8% of patients from Asian population and the mean base-

line body weight (81.9 + 19.7 kg) was higher as compared to the present studied patients due to the greater body sizes of Caucasians. These differences might have contributed to the deviation between the difference of Jelliffe and Cockcroft-Gault estimated creatinine clearance between these two studies.

During the acute kidney injury, the kidney function will initially in the deteriorating phase. After a few days, the kidney function will start to recover. The kidney is considered deteriorating if the serum creatinine level is increasing and vice versa (Dager and Halilovic, 2014). It is essential to specifically assess the most accurate equation to be used for the estimation of creatinine clearance in both deteriorating and recovering phases of acute kidney injury. The Jelliffe equation showed the lowest estimated creatinine clearance among the four equations and demonstrated the highest deviation from the Cockcroft-Gault equation for both deteriorating and improving trends of kidney function. This was consistent with the overall trend that Jelliffe estimated the lowest creatinine clearance. Hence, Jelliffe equation would tend to have a more intense dosage adjustment as compared to the other three equations. Brater, Chiou and Cockcroft-Gault equations estimated higher creatinine clearance. Thus, there would be a higher tendency of overdosing if the three equations were used, leading to dose dependent adverse effects or Type A reactions (Pirmohamed and Park, 2003).

Strength and Limitations

As this is a retrospective study, it relied on the written record accuracy. Some important data might be missing, thus leading to the exclusion of many potential patients. This study was also limited with the absence of the use of 24-hour urine creatinine clearance and Modified Jelliffe equation for the assessment of unstable kidney function. Besides, this retrospectively designed study could not assess the clinical outcomes of dosage adjustment based on different equations. Hence, there is a need for future prospective studies to compare more equations used to assess unstable kidney functions including the use of Modified Jelliffe equation and the gold standard urine creatinine collection method. The evaluation of clinical outcomes on dosage adjustments based on various unstable kidney function equations should also be carried out in future studies.

CONCLUSIONS

Jelliffe equation might be a more suitable equation to assess patients with unstable kidney functions. The Brater and Chiou equations might lead to higher doses of renally excreted drugs due to higher estimated creatinine clearances.

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