CLINICAL RESEARCH

Check for updates

An Evaluation of Commonly Used Surrogate Baseline Creatinine Values to Classify AKI During Acute Infection

Daniel J. Cooper[1,2], Katherine Plewes[3,4,5], Matthew J. Grigg[1,2], Aatish Patel[2], Giri S. Rajahram[2,6], Timothy William[2,6,7], Thomas F. Hiemstra[8,9], Zhiqiang Wang[1], Bridget E. Barber[1,2,10] and Nicholas M. Anstey[1,2]

[1]Menzies School of Health Research and Charles Darwin University, Darwin, Northern Territory, Australia; [2]Infectious Diseases Society Sabah-Menzies School of Health Research Clinical Research Unit, Kota Kinabalu, Sabah, Malaysia; [3]Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand; [4]Centre for Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK; [5]Division of Infectious Diseases, Department of Medicine, University of British Columbia, Vancouver, Canada; [6]Infectious Diseases Unit and Clinical Research Centre, Queen Elizabeth Hospital, Kota Kinabalu, Malaysia; [7]Gleneagles Hospital, Kota Kinabalu, Malaysia; [8]Cambridge Clinical Trials Unit, Cambridge, UK; [9]Division of Experimental Medicine and Immunotherapeutics, Department of Medicine, University of Cambridge, Cambridge, UK; and [10]QIMR Berghofer Institute of Medical Research, Brisbane, Australia

Introduction: Classification of acute kidney injury (AKI) requires a premorbid baseline creatinine, often unavailable in studies in acute infection.

Methods: We evaluated commonly used surrogate and imputed baseline creatinine values against a "reference" creatinine measured during follow-up in an adult clinical trial cohort. Known AKI incidence (Kidney Disease: Improving Global Outcomes [KDIGO] criteria) was compared with AKI incidence classified by (1) back-calculation using the Modification of Diet in Renal Disease (MDRD) equation with and without a Chinese ethnicity correction coefficient; (2) back-calculation using the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation; (3) assigning glomerular filtration rate (GFR) from age and sex-standardized reference tables; and (4) lowest measured creatinine during admission. Back-calculated distributions were performed using GFRs of 75 and 100 ml/min.

Results: All equations using an assumed GFR of 75 ml/min underestimated AKI incidence by more than 50%. Back-calculation with CKD-EPI and GFR of 100 ml/min most accurately predicted AKI but misclassified all AKI stages and had low levels of agreement with true AKI diagnoses. Back-calculation using MDRD and assumed GFR of 100 ml/min, age and sex-reference GFR values adjusted for good health, and lowest creatinine during admission performed similarly, best predicting AKI incidence (area under the receiver operating characteristic curves [AUC ROCs] of 0.85, 0.87, and 0.85, respectively). MDRD back-calculation using a cohort mean GFR showed low total error (22%) and an AUC ROC of 0.85.

Conclusion: Current methods for estimating baseline creatinine are large sources of potential error in acute infection studies. Preferred alternatives include MDRD equation back-calculation with a population mean GFR, age- and sex-specific GFR values corrected for "good health," or lowest measured creatinine. Studies using surrogate baseline creatinine values should report specific methodology.

T he estimation of AKI incidence in clinical trials presents a number of challenges. Composite endpoints of major adverse outcomes such as mortality,

Correspondence: Daniel Cooper, Global Health Division, Menzies School of Health Research, John Mathews Building (Building 58), Royal Darwin Hospital Campus, Rocklands Drive, Tiwi, NT 0810, Australia. E-mail: Dancooper@doctors.net.uk

need for renal replacement therapy (RRT) or progression to chronic kidney disease (CKD) are not always logistically feasible or appropriate. The significance of under- or overestimation of AKI has significant implications as the long-term sequelae of even small rises in creatinine are becoming clearer.[1,2] Consensus definitions of AKI[3–5] allow classification of small short-term changes in creatinine; however, all require a premorbid baseline creatinine as a reference point. The steady state of creatinine is influenced by many factors during AKI, including catabolic states,[6] total fluid

Table 1. Abbreviations, definitions, and methods for imputed and surrogate creatinine values

Abbreviation	Derivation	Equation used	eGFR (ml/min per 1.73 m²)	Notes
Cr_{Ref}	Reference	-	-	Reference creatinine (nadir follow-up creatinine)
eCr_{75M}	Estimate	MDRD	75	-
eCr_{100M}	Estimate	MDRD	100	-
eCr_{75c}	Estimate	MDRD	75	Chinese ethnicity[23] correction coefficient applied
eCr_{100c}	Estimate	MDRD	100	Chinese ethnicity[23] correction coefficient applied
eCr_{75EPI}	Estimate	CKD-EPI	75	-
eCr_{100EPI}	Estimate	CKD-EPI	100	-
$eCr_{adjusted}$	Estimate	MDRD	Assigned[a]	Corrected for "good health"[30]
eCr_{Cohort}	Estimate	MDRD	Calculated[b]	The cohort mean eGFR, defined as the mean of all individually calculated eGFR values using the follow-up creatinine
eCr_{Rnd}	Estimate	-	-	Randomly assigned creatinine value using a number generator along a lognorml curve
mCr_{admit}	Measured	-	-	Lowest measured creatinine during 72-hour admission (measured 12-hourly)

CKD-EPI, Chronic Kidney Disease–Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.
[a]Assigned using reference values for age and sex.[29]
[b]A calculated glomerular filtration rate based on patient age and sex using the MDRD equation.
Prefixes:
Prefix e denotes an estimated creatinine value.
Prefix m denotes a measured creatinine value.
Suffixes:
Suffix 75 denotes an assumed eGFR of 75 ml/min per 1.73 m².
Suffix 100 denotes an assumed eGFR of 100 ml/min per 1.73 m².
Suffix M denotes a back-calculation using an MDRD-derived formula.
Suffix c denotes a back-calculation using an MDRD-derived formula and a Chinese correction coefficient.
Suffix EPI denotes a back-calculation using an CKD-EPI derived formula.

distribution,[7,8] and critical illness,[9] and is therefore heavily influenced by, and variable between, different clinical presentations.[10,11] Due to this non–steady state, back-calculation is also necessary to allow a comparison of creatinine, and changes in creatinine, rather than simply relying on a comparison of measured and estimated baseline GFRs.

Among the methods proposed to determine baseline creatinine, the mean outpatient creatinine assessed 7 days before admission is thought to be the best.[12,13] However, AKI associated with infection frequently affects patients who are unlikely to have documented prehospitalization creatinine measurements. In addition, follow-up of patients from clinical trials in these settings is logistically challenging.

It is often necessary, therefore, to estimate a baseline creatinine by back-calculation; however, this process is not standardized or uniform throughout studies.[14] The most frequently used approach,[15–17] recommended by the Acute Dialysis Quality Initiative working group,[3] is to back-calculate estimated baseline creatinine using the MDRD equation with an assumed GFR of 75 ml/min per 1.73 m². This method has numerous sources of potential error.

The more recently derived CKD-EPI equation uses the same 4 variables as the MDRD equation; however, models a different relationship of age, sex, and race with creatinine.[18] Although the CKD-EPI equation improves the accuracy of GFR estimates, particularly at higher GFR values,[19] back-calculation using an assigned GFR of 75 ml/min per 1.73 m² demonstrates a poor agreement between measured and back-calculated baseline creatinine values in surgical patients.[20] It is not known how these methods perform in acute infection.

In studies of AKI associated with infection, populations are generally younger with a lower body mass index and expected to have a normal, or near-normal GFR at baseline, with these accuracies compounded by ethnic and regional differences in muscle mass and diet.[21] Although efforts have been made to provide correction coefficients to existing GFR formulae in Japanese[22] and Chinese[23] populations, these modified formulae have not been evaluated for back-calculation of estimated baseline creatinine. Furthermore, the large variation in these coefficients suggests that differences may be due to methodological issues rather than purely genetic factors.[24]

In this study, we use different methods to estimate baseline creatinine values in a heterogeneous Southeast Asian population with acute infection, and then compare the accuracy of these back-calculation methods with a measured "baseline" creatinine at follow-up. We further evaluate the accuracy of these methods in classifying AKI.

METHODS

Population

Patients with *Plasmodium knowlesi* malaria were recruited consecutively as part of an adjunctive therapy clinical trial (PACKNOW),[25] conducted across 4 hospital sites in Sabah, Malaysian Borneo, between October 2016 and February 2018. Infection with *P. knowlesi* is now the commonest cause of endemic malaria for people living in Malaysia,[26] and commonly causes AKI.[27] Full details of the PACKNOW trial protocol have been published.[25] The 2010 Malaysian

Derivation	Assumed GFR (ml/min)	Sex	Age	Equation
MDRD equation	75			$esCr = \left(\dfrac{75}{sex \times 186 \times Age^{0.203}}\right)^{-\frac{1}{1.154}}$
	100			$esCr = \left(\dfrac{100}{sex \times 186 \times Age^{0.203}}\right)^{-\frac{1}{1.154}}$
MDRD with Chinese coefficient	75			$esCr = \left(\dfrac{75}{sex \times 1.233 \times 186 \times Age^{0.203}}\right)^{-\frac{1}{1.154}}$
	100			$esCr = \left(\dfrac{100}{sex \times 1.233 \times 186 \times Age^{0.203}}\right)^{-\frac{1}{1.154}}$
CDK-EPI	75	Female	<92.9	$esCr = 0.7 \times \left(\dfrac{144 \times 0.993^{Age}}{75}\right)^{\frac{1}{1.209}}$
			≥92.9	$esCr = 0.7 \times \left(\dfrac{144 \times 0.993^{Age}}{75}\right)^{\frac{1}{0.329}}$
		Male	<89.9	$esCr = 0.9 \times \left(\dfrac{141 \times 0.993^{Age}}{75}\right)^{\frac{1}{1.209}}$
			≥89.9	$esCr = 0.9 \times \left(\dfrac{141 \times 0.993^{Age}}{75}\right)^{\frac{1}{0.329}}$
	100	Female	<51.9	$esCr = 0.7 \times \left(\dfrac{144 \times 0.993^{Age}}{100}\right)^{\frac{1}{1.209}}$
			≥51.9	$esCr = 0.7 \times \left(\dfrac{144 \times 0.993^{Age}}{100}\right)^{\frac{1}{0.329}}$
		Male	<48.9	$esCr = 0.9 \times \left(\dfrac{141 \times 0.993^{Age}}{100}\right)^{\frac{1}{1.209}}$
			≥48.9	$esCr = 0.9 \times \left(\dfrac{141 \times 0.993^{Age}}{100}\right)^{\frac{1}{0.329}}$

Figure 1. Equations used for back-calculation of creatinine. CKD-EPI, Chronic Kidney Disease–Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

census[28] reported that 67.4% of Malaysian citizens in Sabah were classified as Indigenous, 24.6% were of Chinese origin, 7.3% of Indian origin, and 0.7% as "others."

Design

Patients older than 18 years were included in the analysis if they had a follow-up creatinine measurement at ≥7 days from study enrollment. Serum creatinine was measured at study enrollment (hour 0), then 12-hourly for 72 hours. Malaysian Ministry of Health guidelines for the management of malaria mandate 2 consecutive negative blood slides for malaria parasites before discharge. In addition, the PACKNOW trial had an initial study duration of 72 hours. Participants were invited to attend study follow-up at 7, 14, and 28 days, where serum creatinine was measured as part of study procedures. No participants had a documented premorbid baseline creatinine.

Accuracy of Estimated Surrogate Creatinine Methods Compared With a Reference Creatinine Value in a Heterogeneous Southeast Asian Population With Acute Infection

As no premorbid baseline creatinine values were available, each patient's reference baseline creatinine (Cr_{Ref}) for all comparisons was defined as the nadir creatinine measured at follow-up.

Surrogate baseline creatinine values for each patient were estimated using the following methods (Method summaries Table 1; detailed equations in Figure 1):

1. eCr_{75M}: Back-calculation using the modified MDRD equation assuming all patients had a GFR of 75 ml/min.
2. eCr_{100M}: Back-calculation using the modified MDRD equation assuming all patients had a GFR of 100 ml/min.
3. eCr_{75c}: Back-calculation using the modified MDRD equation with correction coefficient for Chinese

ethnicity[23] assuming all patients had a GFR of 75 ml/min.

4. eCr_{100c}: Back-calculation using the modified MDRD equation with correction coefficient for Chinese ethnicity[23] assuming all patients had a GFR of 100 ml/min.

5. eCr_{75EPI}: Back-calculation using the CKD-EPI creatinine equation assuming all patients had a GFR of 75 ml/min.

6. eCr_{100EPI}: Back-calculation using the CKD-EPI creatinine equation assuming all patients had a GFR of 100 ml/min.

7. $esCr_{adjusted}$: Back-calculation using the modified MDRD equation with GFR assigned using reference values for age and sex[29] and corrected for "good health."[30]

8. eCr_{Cohort}: The mean of individual follow-up estimated GFR (eGFR) values calculated using the MDRD equation and lowest measured follow-up creatinine to provide a population mean eGFR at follow-up.

9. eCr_{Rnd}: Assigning a creatinine value using a random number generator along a lognorml curve. Input parameters were derived by fitting a lognormal curve to baseline creatinine values ($\mu = 0.194$, $\sigma = 0.182$).

10. mCr_{Admit}: lowest measured creatinine during 72-hour admission (measured 12-hourly).

The performance of each surrogate baseline creatinine value was then evaluated against the reference creatinine value (Cr_{Ref}). Patients requiring RRT were excluded from this analysis due to potential confounding from subsequent iatrogenic alterations in creatinine kinetics during admission and follow-up.

Evaluation of the Accuracy of Estimated Baseline Creatinine Methods in Predicting AKI

The presence of AKI was determined for each patient using KDIGO criteria based on the increase from the reference baseline creatinine (mCr_{Ref}) by ≥ 0.3 mg/dl or an increase in serum creatinine to ≥ 1.5 times baseline; presumed to have occurred within the prior 7 days (in the context of acute *P. knowlesi* infection).

Each method of estimating a surrogate baseline creatinine was then used to predict the presence of AKI for each patient using the same criteria.

The performance of the predicted AKI (including severity and incidence) for each estimated baseline creatinine method was then evaluated against the reference AKI result.

Assays

Serum creatinine was measured at hospital laboratories by the Jaffe reaction using Abbot reagents on an
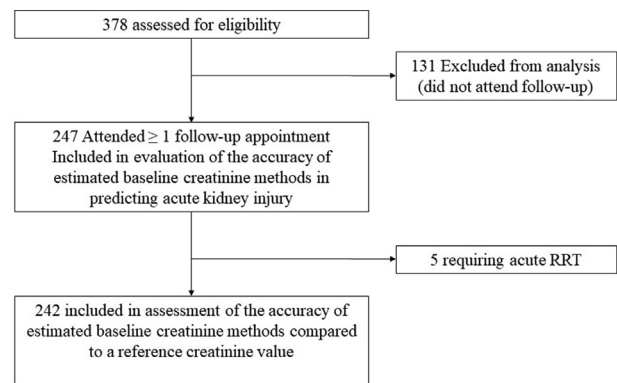

Figure 2. Participant flow diagram. RRT, renal replacement therapy.

Architect c4000 Clinical Chemistry Analyzer (Abbot Laboratories, Chicago, IL).

Statistical Analysis

Each method was compared against the reference creatinine (Cr_{Ref}) using a Bland-Altman analysis, by plotting the mean of the reference creatinine and the estimated baseline creatinine ([reference + estimated]/2) against the difference (reference − estimated baseline creatinine) for each patient. An ideal model would give the difference between the 2 measurements as zero, thereby having all plotted points along the y = 0 axis. Bias is defined as the average of the differences, with a bias farther from zero indicating the estimate is systematically producing different results (i.e., one method consistently gives values that are higher or lower than those from the other by a constant amount). Precision is defined as 1 SD of the bias, and 95% limits of agreement as ± 1.96 SD from the mean. Proportional bias is calculated as the slope of the regression line of the Bland-Altman plots and illustrates whether the difference between estimated baseline creatinine and reference creatinine is proportional to the reference creatinine. Wilcoxon signed rank test (matching pairs, non-normal distribution) was used to compare the entire estimated baseline distribution with the entire reference distribution, for each of the different methods.

Sensitivity and specificity were calculated for each estimate by comparing true KDIGO classification (using measured reference creatinine) with the classification by each estimation method. Kappa statistic (95% confidence interval [CI]) was used to report the level of agreement between AKI classification and classification using the reference creatinine. The AUC ROC was used to compare the accuracy of each method for identifying AKI compared with the reference creatinine.

All analyses were undertaken with Stata version 12 (StataCorp, College Station, TX) and GraphPad Prism 8 (GraphPad, La Jolla, CA).

Table 2. Baseline characteristics of study population ($n = 247$)

Characteristic	Male ($n = 208$)	Female ($n = 39$)	Cohort ($n = 247$)
Age	39.1 ± 14.3	48.2 ± 16.3	40.5 ± 14.9
Weight (kg)	63.2 ± 11.4	56.9 ± 13.4	62.2 ± 11.9
Follow-up CKD or nonresolved AKI,[a] n (%)	3 (1.4)	0 (0)	3 (1.2)
Severe malaria, n (%)	18 (8.7)	4 (10.3)	22 (8.9)
Number of admission creatinine values available (Median [Range])	7 (3–7)	7 (4–7)	7 (3–7)
Number of follow-up creatinine values available (Median [Range])	2 (1–3)	2 (1–3)	2 (1–3)
Follow-up creatinine[b] **(μmol/l)**			
Mean $\pm$ SD	0.86 ± 0.18	0.72 ± 0.13	0.84 ± 0.18
Median (IQR)	0.83 (0.77–0.92)	0.73 (0.65–0.78)	0.80 (0.75–0.89)
Min, max	0.49, 2.09	0.54, 1.28	0.49, 2.09
Follow-up eGFR[c] (ml/min)	104.5 ± 20.1	90.1 ± 18	102.2 ± 20.9
Maximum admission creatinine (μmol/l)			
Mean $\pm$ SD	1.39 ± 1.76	0.92 ± 0.25	1.32 ± 1.63
Median (IQR)	1.03 (0.93–1.2)	0.89 (0.79–1.02)	1.0 (0.91–1.18)
Min, max	0.77, 16.1	0.54, 2.1	0.54, 16.1
Required renal replacement therapy, n (%)	5 (2.4)	0 (0)	5 (2.0)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; min, max, minimum, maximum.
[a]Composite of preexisting CKD and/or nonrecovery of AKI as no previous creatinine results available. Defined as eGFR <60 ml/min and uACR >3.0 mg/mmol at 28 days follow-up. The 3 CKD diagnoses included 40-, 48-, and 65-year-old men. Two had KDIGO stage 3 AKI requiring renal replacement therapy during admission.
[b]Lowest of all creatinine measurements throughout follow-up measurements at 7, 14, or 28 days.
[c]Calculated using MDRD equation and the lowest of all creatinine measurements throughout follow-up measurements at 7, 14, or 28 days.
Conversion factors for units: serum creatinine in mg/dl to μmol/l, $\times 88.4$.

RESULTS

The PACKNOW study recruited 378 patients, 247 of whom attended a follow-up appointment and were included in this analysis (Figure 2). Of these, 92% of patients returned for day 7 follow-up, 23% for day 14, and 76% for day 28, with a median number of follow-up visits of 2 (range 1–3). At follow-up, 62% ($n = 153$), 8% ($n = 20$), and 30% ($n = 74$) of creatinine values were identified as being the lowest on days 7, 14, and 28, respectively. There was no statistical difference in median creatinine at day 7 compared with day 28 (0.8 mg/dl [interquartile range 0.72–0.88] vs. 0.88 mg/dl [interquartile range 0.8–0.1]; $P = 0.66$). Five patients had a length of stay >72 hours; each of them requiring RRT and intensive care unit admission. The patients' baseline characteristics are summarized in Table 2. Men and women are presented separately in Table 2 because (1) creatinine values are imputed using a different coefficient depending on sex, and (2) the epidemiology of *P. knowlesi* malaria[31,32] results in different median ages of men and women within this population. Five (2.4%) patients required acute RRT and were excluded from the evaluation of the estimated baseline creatinine values against Cr_{Ref}. All 247 patients were included in the classification of AKI analysis as, by definition, those requiring acute RRT were classified as stage 3 AKI by KDIGO criteria.

Accuracy of Estimated Baseline Creatinine Methods Compared With a Reference Creatinine Value

The Bland-Altman plot distribution of all estimated baseline creatinine methods differed significantly from the reference Cr_{Ref} distribution (Table 3 and Figure 3),

with the exception of eCr_{100M} (Wilcoxon signed rank $P = 0.09$). The distribution of the lowest creatinine during the first 72 hours of admission (mCr_{Admit}) also differed significantly to the distribution of the Cr_{Ref} ($P < 0.001$).

All distributions of estimated baseline creatinine values back-calculated using an assumed GFR of 75 ml/min displayed both large absolute and proportional bias and poor precision (Figures 3a and c, and 4e). The eCr_{100M} distribution had the smallest bias (-0.002 mg/dl; Figure 3b) and good precision (0.16 mg/dl). The eCr_{100EPI} distribution (Figure 3f) was the next best performing in terms of bias (-0.05 mg/dl); however, had poorer precision than all other methods (0.26 mg/dl). The eCr_{100c} distribution (Figure 3d) had a large negative bias and low precision. The $eSCr_{adjusted}$ (Figure 4g) method had a bias of 0.06 mg/dl and precision of 0.14 mg/dl. The measured lowest creatinine during admission (mCr_{Admit}; Figure 4h) correlated better with Cr_{Ref} than the estimated distributions ($r = 0.71$), had a relatively small bias of 0.05 mg/dl, the highest precision of all methods at 0.1 mg/dl, and a small proportional bias that did not differ from zero.

Evaluation of the Accuracy of Estimated Baseline Creatinine Methods in Predicting AKI

Of the 247 patients, 71 (29%) had AKI according to KDIGO criteria (Table 4). All estimated and measured methods led to an overestimation of total AKI incidence when compared with AKI classification using the reference creatinine (Cr_{Ref}). The eCr_{100EPI} method had the lowest total percentage error for correctly

Table 3. Comparison of the baseline reference serum creatinine distribution to those estimated using different back-calculated or measured methods (mg/dl)

	Reference[b]	Estimated[c]								Measured[d]	Mean[e]
	mCr_Ref	eCr_75M (75 ml/min)	eCr_100M (100 ml/min)	eCr_75c (75 ml/min)	eCr_100c (100 ml/min)	eCr_75EPI (75 ml/min)	eCr_100EPI (100 ml/min)	eCr_adjusted		mCr_Admit	eCr_Cohort
Mean ± SD (mg/dl)	0.83 ± 0.15	1.06 ± 0.13	0.83 ± 0.10	1.35 ± 0.16	1.05 ± 0.12	1.19 ± 0.15	0.87 ± 0.22	0.77 ± 0.06		0.77 ± 0.14	0.81 ± 0.01
Median (IQR) (mg/dl)	0.80 (0.75–0.88)	1.08 (1.02–1.15)	0.85 (0.80–0.89)	1.34 (1.29–1.46)	1.06 (1.0–1.13)	1.21 (1.11–1.3)	0.96 (0.76–1.03)	0.78 (0.76–0.80)		0.77 (0.69–0.84)	0.83 (0.78–0.87)
Wilcoxon[a]	-	<0.001	0.09	<0.001	<0.001	<0.001	<0.001	<0.001		<0.001	0.3
Min, max (mg/dl)	0.49, 1.77	0.72, 1.24	0.57, 0.97	0.92, 1.57	0.71, 1.22	0.32, 1.38	0.14, 1.09	0.62, 0.87		0.43, 1.63	0.54, 0.94
Correlation, pCr_m (r)		0.22**	0.22**	0.22**	0.22**	0.13*	0.13*	0.29**		0.71**	0.21**
Bias (mg/dl)		−0.24	−0.002	−0.52	−0.22	−0.36	−0.05	0.06		0.05	0.02
Precision (mg/dl)		0.17	0.16	0.19	0.17	0.20	0.26	0.14		0.10	0.16
Proportional bias		0.24*	0.62**	−0.14 (NS)	0.27*	−0.07 (NS)	−0.7**	1.3**		0.074 (NS)	0.67**

IQR, interquartile range; NS, not significant.

[a]P-value of comparison between reference creatinine (mCr_Ref) and the estimated baseline creatinine method.

[b]The lowest measured follow-up creatinine ≥ 7 days since enrollment.

[c]Estimated baseline creatinine for each estimation method.

[d]Lowest measured creatinine during 72-hour admission.

[e]Estimated creatinine using the inverse Modification of Diet in Renal Disease (MDRD) back-calculation method and the population mean glomerular filtration rate at follow-up (calculated using the MDRD equation and lowest measured creatinine at follow-up at 7, 14, and 28 days).

Wilcoxon signed rank test (paired) for comparison of entire distribution with reference creatinine.

*$P < 0.05$.

**$P < 0.001$.

Precision = 1 SD of the mean

95% limits of agreement = ±1.98 × SD of the mean

r: Spearman's rho

Bias: total mean difference between estimated and reference creatinine.

Precision: 1 SD of the Bias

Proportional bias: the slope of the regression line of the differences between estimated and reference creatinine against the average of estimated and reference creatinine. A slope of 0 means no proportional bias. P value is the significance of the deviation of the slope from 0: ***$P < 0.0001$.

mCr_Ref : Reference baseline creatinine.

eCr_75M: estimated baseline serum creatinine using the MDRD formula with estimated glomerular filtration rate (eGFR) of 75 ml/min.

eCr_100M: estimated baseline serum creatinine using the MDRD formula with eGFR of 100 ml/min.

eCr_75c: estimated baseline serum creatinine using the MDRD formula and Chinese correction coefficient with eGFR of 75 ml/min.

eCr_100c: estimated baseline serum creatinine using the MDRD formula and Chinese correction coefficient with eGFR of 100 ml/min.

eCr_75EPI: estimated baseline serum creatinine using the CKI-EPI formula with eGFR of 75 ml/min.

eCr_100EPI: estimated baseline serum creatinine using the CKI-EPI formula with eGFR of 100 ml/min.

eCr_adjusted: Back-calculation using the modified MDRD equation with eGFR assigned using reference values for age and sex[29] and corrected for "good health."[30]

mCr_Admit: Lowest measured creatinine during 72-hour admission.

eCr_Cohort: estimated baseline serum creatinine using the MDRD formula with population mean eGFR of 103 ml/min.

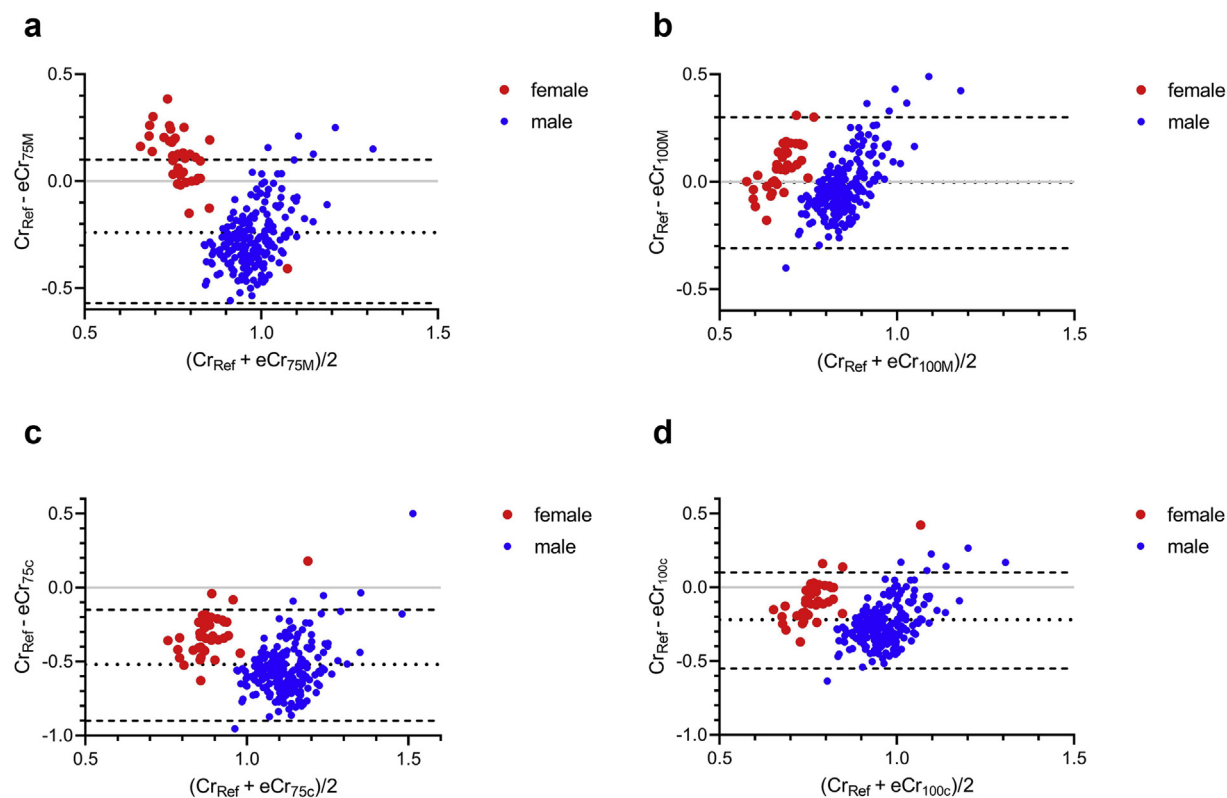Conversion factors for units: serum creatinine in mg/dl to μmol/l, ×88.4.

Figure 3. Bland-Altman plots of estimated and measured distributions (a–d). Bland-Altman plots of the mean of measured and estimated creatinine against the difference between measured recovery and estimated creatinine for (a) eCr_{75M}; (b) eCr_{100M}; (c) eCr_{75c}; (d) eCr_{100c}. Dotted line shows bias (mean difference) and dashed lines show 95% limits of agreement ($\pm 1.96 \times$ SD of the mean). eCr_{75M}: estimated baseline serum creatinine using the MDRD formula with estimated glomerular filtration rate (eGFR) of 75 ml/min. eCr_{100M}: estimated baseline serum creatinine using the MDRD formula with eGFR of 100 ml/min. eCr_{75c}: estimated baseline serum creatinine using the MDRD formula and Chinese correction coefficient with eGFR of 75 ml/min. eCr_{100c}: estimated baseline serum creatinine using the MDRD formula and Chinese correction coefficient with eGFR of 100 ml/min.

identifying AKI overall (3%), although misclassified all KDIGO stages. The difference in classification of AKI was statistically significant between all estimated and measured methods and the reference creatinine. The eCr_{100M} and eCr_{100EPI} methods overestimated AKI by 16% and 3%, respectively; however, sensitivity was higher for eCr_{100M} (83% compared with 65%), and eCr_{100M} had a significantly higher area under the ROC curve (0.85 [95% CI 0.80–0.90] compared with 0.75 [95% CI 0.69–0.81]; $P < 0.001$). The $eCr_{adjusted}$ had a high sensitivity of 94% and specificity of 79%, with the highest AUC ROC (0.87 [95% CI 0.83–0.91]). However, $eCr_{adjusted}$ had a large total percentage error (47%) for correctly identifying AKI, with a predominant overclassification of stage 1 AKI. mCr_{Admit} overestimated AKI by 22%; however, had a relatively high sensitivity and specificity of 85% for each, and an AUC ROC of 0.85 (95% CI 0.80–0.90). There were no statistically significant differences among the AUC ROC for eCr_{100}, $eCr_{adjusted}$, and mCr_{Admit}. Although all estimated methods were highly specific for the detection of stage 3 AKI, false positives were also present for each

method, and mCr_{Admit} failed to identify 1 of 7 (14%) patients with stage 3 AKI. The AUC ROC curves are shown in Supplementary Figures S1 and S2.

The eCr_{100EPI} method had the lowest percentage error of estimating total AKI incidence; however, also had the lowest kappa statistic of 0.49 (95% CI 0.45–0.53). This demonstrates that despite identifying similar numbers with AKI compared with the reference group, agreement between individual AKI cases was low, similar to that seen with eCr_{75M}. The eCr_{100M}, $eCr_{adjusted}$, and mCr_{Admit} methods demonstrated similar interrater agreement, with eCr_{100M} marginally better than the other 2 methods with a kappa statistic of 0.67 (95% CI 0.64–0.70).

Population Mean GFR
A follow-up eGFR value was calculated using the MDRD equation and inputting the lowest measured follow-up creatinine. The mean of these eGFR values was calculated to provide a cohort mean eGFR at follow-up. We used the inverse MDRD equation (Figure 3) to back-calculate a baseline creatinine for
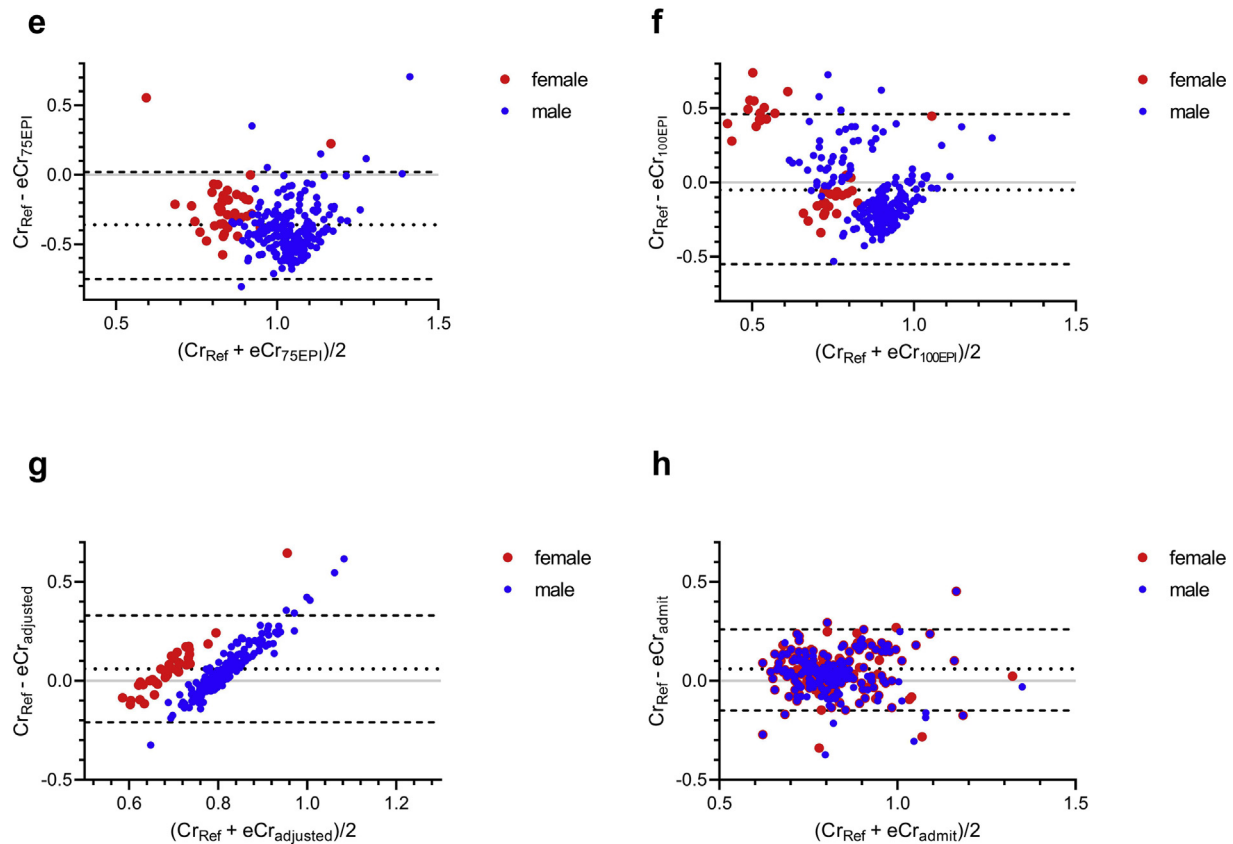
Figure 4. Bland-Altman plots of estimated and measured distributions (e–h). Bland-Altman plots of the mean of measured and estimated creatinine against the difference between measured recovery and estimated creatinine for (e) eCr_{75EPI}; (f) eCr_{100EPI}; (g) $eCr_{adjusted}$; (h) mCr_{Admit} $eCr75_{EPI}$: estimated baseline serum creatinine using the CKI-EPI formula with eGFR of 75 ml/min. eCr_{100EPI}: estimated baseline serum creatinine using the CKI-EPI formula with eGFR of 100 ml/min. $eCr_{adjusted}$: Back-calculation using the modified MDRD equation with eGFR assigned using reference values for age and sex[29] and corrected for "good health."[30]. mCr_{Admit}: Lowest measured creatinine during 72-hour admission.

each patient using the population mean follow-up eGFR (103 ml/min) and individual age and weight. This method (eCr_{Cohort}) had a sensitivity and specificity for predicting AKI of 86% (95% CI 76%–93%) and 85%

(95% CI 79%–90%), respectively, an AUC ROC of 0.85 (95% CI 0.80–0.90) and a kappa of 0.66. The eCr_{Cohort} distribution (Figure 5i) did not differ significantly from the Cr_{Ref} distribution (Wilcoxon signed rank test $P =$

Table 4. Number of patients at each acute kidney injury stage based on Kidney Disease: Improving Global Outcomes staging

	Reference	Estimated						Measured
	mCr_{Ref}	eCr_{75M} (75 ml/min)	eCr_{100M} (100 ml/min)	eCr_{100EPI} (100 ml/min)	$eCr_{adjusted}$	eCr_{Cohort}	$esCr_{Rnd}$	mCr_{Admit}
Stage I (% error)	55	20 (−64)	67 (22)	34 (-38)	88 (60)	72 (31)	60 (9)	72 (31)
Stage II (% error)	9	5 (−44)	5 (−44)	17 (89)	6 (−33)	6 (−33)	15 (67)	9 (0)
Stage III (% error)	7	7 (0)	10 (43)	22 (68)	10 (43)	10 (43)	9 (29)	6 (−14)
Total (% error)	71	32 (−55)	82 (16)	73 (3)	104 (47)	88 (24)	84 (18)	87 (22)
Sensitivity, % (95% CI)		42 (31–55)	83 (80–86)	65 (53–76)	94 (86–98)	86 (76–93)	75 (71–78)	85 (74–92)
Specificity, % (95% CI)		99 (96–100)	87 (85–89)	85 (79–90)	79 (72–85)	85 (79–90)	84 (82–85)	85 (79–90)
Kappa, statistic (95% CI)		0.49 (0.37–0.61)	0.67 (0.57–0.77)	0.49 (0.37–0.61)	0.64 (0.55–0.74)	0.66 (0.56–0.76)	0.55 (0.52–0.59)	0.66 (0.56–0.76)
AUC ROC[a] (95% CI)		0.71 (0.65–0.76)	0.85 (0.80–0.90)	0.75 (0.69–0.81)	0.87 (0.83–0.91)	0.85 (0.80–0.90)	0.79 (0.77–0.81)	0.85 (0.80–0.90)

AUC ROC, area under the receiver operating characteristic curve; CI, confidence interval; esCrRnd, randomly assigned creatinine value along a lognormal curve.
[a]Area under the ROC curve for correctly identifying acute kidney injury (AKI).
Values are n (%) unless otherwise indicated.
mCr_{Ref} : Reference baseline creatinine.
eCr_{75M}: estimated baseline serum creatinine using the MDRD formula with estimated glomerular filtration rate (eGFR) of 75 ml/min.
eCr_{100M}: estimated baseline serum creatinine using the MDRD formula with eGFR of 100 ml/min.
eCr_{100EPI}: estimated baseline serum creatinine using the CKI-EPI formula with eGFR of 100 ml/min.
$eCr_{adjusted}$: Back-calculation using the modified MDRD equation with eGFR assigned using reference values for age and sex[29] and corrected for "good health."[30]
mCr_{Admit}: Lowest measured creatinine during 72-hour admission.
eCr_{Cohort}: estimated baseline serum creatinine using the MDRD formula with population mean eGFR of 103 ml/min.
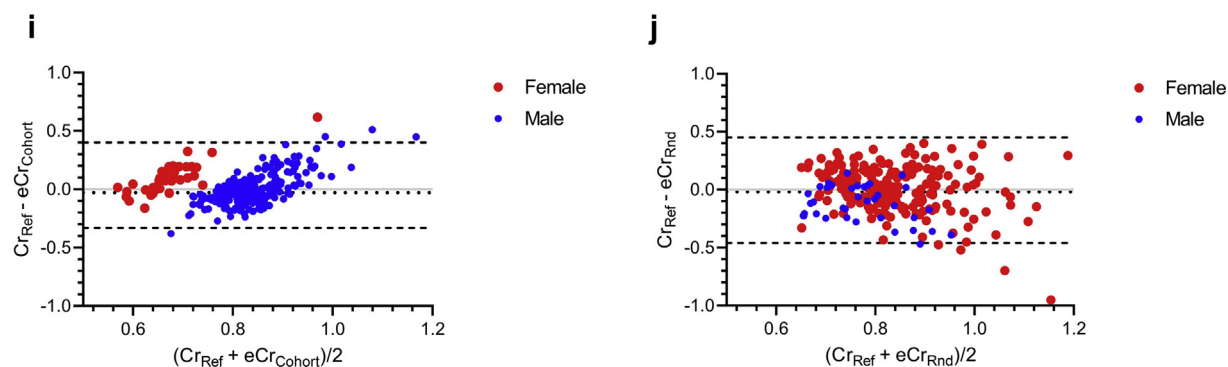% error defined as ([Estimated n with AKI − Reference n with AKI] / Reference n with AKI) × 100.

Figure 5. Bland-Altman plots of estimated and measured distributions (i and j). Bland-Altman plots of the mean of measured and estimated creatinine against the difference between measured recovery and estimated creatinine for (i) eCr_{Cohort}; (j) eCr_{Rnd}. eCr_{Cohort}: estimated baseline serum creatinine using the MDRD formula with population mean eGFR of 103 ml/min. eCr_{Rnd}: Assigning a creatinine value using a random number generator along a lognorml curve.

0.3), and had a small bias (0.02 mg/dl) with a precision of 0.16 mg/dl.

Randomly Assigned Creatinine Values Along a lognormal Curve

We randomly assigned a creatinine value along a lognormal curve for each participant using the Stata *rnormal* command, with input parameters generated by fitting a lognormal curve to the reference creatinine ($\mu = 0.194$, $\sigma = 0.182$). This method (eCr_{Rnd}) had a sensitivity and specificity for predicting AKI of 75% (95% CI 71%–78%) and 84% (95% CI 82%–85%), respectively, an AUC ROC of 0.79 (95% CI 0.77–0.81), and a kappa of 0.55.

We assessed the performance of eCr_{100M} (back-calculation using the MDRD equation and an assumed eGFR of 100 ml/min per 1.73 m^2) against that of randomly assigning a creatinine value against a lognormal curve by a comparison of both of these ROC curves to Cr_{Ref} (Figure 6). The χ^2 test of this comparison yielded a significance probability of 0.25, suggesting no significant difference between the 2 ROC areas, and therefore no difference in performance for predicting AKI.

Clinical Characteristics of Patients With Misclassified AKI Status

We compared relevant clinical characteristics of the patients who were incorrectly classified as either having, or not having, AKI according to the eCr_{100M}, eCr_{Admit}, $eCr_{adjusted}$, and eCr_{Cohort} methods (Supplementary Table 1). The age of patients with a misclassified AKI status was significantly lower than those correctly classified when assessed using the eCr_{Admit}, $eCr_{adjusted}$, and eCr_{Cohort} methods ($P = 0.015$, $P < 0.001$, and $P = 0.049$, respectively). There was no difference in sex or weight between the groups that

were classified correctly or incorrectly for any of the methods assessed.

DISCUSSION

In this assessment of defining surrogate baseline creatinine values in community-acquired AKI during acute infection, we have demonstrated that existing conventional research methods may result in a large source of potential error. Our results have significant implications for epidemiological studies and clinical trials conducted in these settings. AKI can result from a wide range of pathological processes, with varying clinical courses and outcomes. This analysis illustrates an additional pitfall when conducting studies requiring the evaluation and classification of AKI during a systemic infection.

The widely accepted practice of assuming a GFR of 75 ml/min and back-calculating an estimated baseline creatinine[15,33–37] using the methods described is inaccurate in this setting and population, leading to
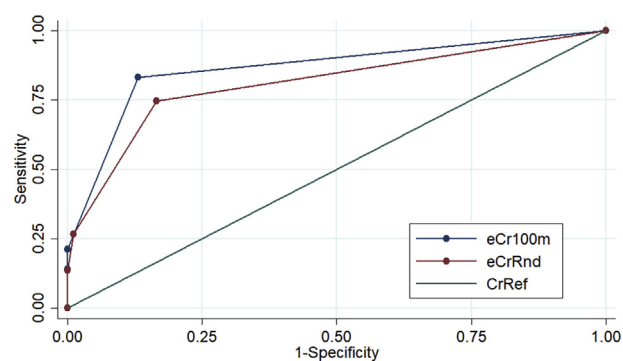

Figure 6. Receiver operating characteristic curve analysis of the performance of eCr_{Rnd} and eCr_{100M} at identifying acute kidney injury compared with Cr_{Ref}.

eCr_{Rnd}: Assigning a creatinine value using a random number generator along a lognorml curve.

eCr_{100M}: estimated baseline serum creatinine using the MDRD formula with eGFR of 100 ml/min. Cr_{Ref} : Reference baseline creatinine.

underestimation of AKI incidence by greater than 50%. This underestimation is not surprising given that 75 ml/min is lower than both the mean (103 ± 20 ml/min) and median (104 [IQR 90–115] ml/min) follow-up GFR. Despite being slightly lower than the median and mean GFR, an assumed GFR of 100 ml/min overestimates AKI incidence by 16% using the MDRD equation and misclassifies AKI at all stages using the CKD-EPI equation, despite having only a 3% total percentage error.

In an intensive care unit population in New Zealand, back-calculation using the MDRD equation and an assumed GFR of either 75 or 100 ml/min performed no better at estimating baseline creatinine than a random number generator over a lognormal curve, and led to an overestimation of AKI.[38] We found a similar effect in our dataset, with a randomly assigned creatinine over a lognormal curve performing no better than back-calculation methods. Most studies to date assessing back-calculation of baseline creatinine have been in the context of hospital-acquired AKI,[14] leaving the classification of a baseline creatinine in community-acquired AKI (as will be the case with most presentations of infection associated AKI) even less certain.

The MDRD and the more recently derived CKD-EPI equations were generated and validated in older North American populations with high body mass indexes and CKD.[18,39] This analysis shows they are not appropriate or accurate measures in younger and/or lower body mass index populations, or in those without CKD. The MDRD equation is known to have limitations for the estimation of GFR in healthy populations, with GFR on average 26% higher in healthy persons than those with CKD at the same serum creatinine concentration, age, and sex.[30] This limitation is evident from our analysis of clinical characteristics, whereby we demonstrate that participants with an incorrectly identified AKI status have a significantly younger age than those correctly identified.

The CKD-EPI equation is known to perform better at estimating GFR[19]; however, in this study we found that it is less accurate at back-calculating an estimated baseline creatinine and at classifying AKI than the MDRD equation. Further, this method involves more complicated calculations, including the derivation of individual age-specific reference points for each assumed GFR. This study found that assigning a GFR using age- and gender-specific values and correcting for a non-CKD population has the greatest sensitivity (94%), although at the expense of specificity (79%) and overestimates total AKI incidence by nearly 50%.

The lowest measured creatinine during the first 72 hours of admission appears to be an acceptable surrogate for recovery creatinine, especially at classifying

stage 2 and 3 AKI, with similar sensitivity and specificity to back-calculation with the MDRD equation and an assumed GFR of 100 ml/min, as well as similar interrater agreement (kappa statistic) and AUC ROC. It is not certain from these data, however, whether this surrogate measure would perform as well for shorter admissions, or less frequent creatinine measurements. The lowest measured creatinine during admission appears to be the preferable surrogate for higher admission creatinine values, as it showed the smallest proportional bias (which did not differ significantly from zero), indicating the distribution does not differ significantly from the measured distribution at higher creatinine values.

This study has several limitations. There is no accurate classification of the population distribution of baseline creatinine values in any Southeast Asian population in good health or during illness. This presents difficulties for accurate comparison of surrogate creatinine values. Given these limitations, the recovery creatinine at 28 days is likely the best estimate of premorbid baseline creatinine in most patients analyzed here. In a retrospective cohort study of critically ill North American adults in an intensive care unit, 88% of patients experienced renal recovery 3 months after discharge.[40] The patients in that study were older, with significant comorbidities and a lower median GFR at enrollment, and the degree of AKI was more severe and associated with a high mortality rate (25.6%). In contrast, most patients in this study had AKI stage 1 or 2, those requiring RRT were omitted, and there were no fatalities; thus, a higher proportion of patients would be expected to have recovered to a premorbid baseline in a shorter timeframe. The 5 patients requiring RRT acutely were excluded from comparison of back-calculation methods; however, interpretation of the creatinine kinetics, and therefore defining an expected absolute creatinine value, in the context of acute RRT of varying durations and modalities was not feasible for inclusion in this analysis. This study included patients from a very specific population and clinical context; however, acute infections frequently occur in younger populations and in low- and middle-income countries. These populations are unlikely to have a well-defined distribution of GFR in good health or disease, and therefore the need to carefully consider and report surrogate creatinine estimates in acute infection is a generalizable conclusion. Finally, there were relatively few women included; however, this is unlikely to have affected the inference due to sex coefficients included within the formulae assessed.

Epidemiological studies or clinical trials in acute infection are prone to errors in classification of AKI by

back-calculating using standard methods, and in particular may miss small, short-term changes in creatinine or small treatment effects. If back-calculation is necessary, assuming a GFR of 100 ml/min in a younger population with community-acquired acute infection without multiple comorbidities is likely to be more accurate than assuming a GFR of 75 ml/min, with the MDRD method preferable to CKD-EPI. This may reflect the fact that the mean population eGFR was 103 ml/min, also suggesting that using a mean population (or cohort) GFR for back-calculating creatinine is likely to be more accurate than assuming an arbitrary GFR value. Obtaining a population distribution of baseline GFR values or an estimate of a distribution using recovery values in a specific cohort would likely improve back-calculations of estimated baseline creatinine, and provide more accurate classifications of AKI.

Whichever method is chosen to define surrogate baseline creatinine values for classification of AKI in clinical trials or epidemiological studies, it is essential that investigators clearly define the chosen method, the definition of AKI, justify any assumptions made, and that methods used are consistent across and within studies where possible. These methodological issues will persist until improved baseline creatinine distributions exist for different populations, or until a superior biomarker for AKI becomes available.

Ethics

The study was approved by the Malaysian Research Ethics Committee (protocol number NMRR-16-356-29088) and the Ethics Committee of Menzies School of Health Research, Darwin, Australia (reference number 2016-2544).

DISCLOSURE

ACKNOWLEDGMENTS

AUTHOR CONTRIBUTIONS

DJC, BEB, NMA, MJG, TW, AP, and GSR conceived and designed the study and led data collection. DJC, BEB, NMA, MJG, KP, and ZW analyzed the data and interpreted results. DJC, BEB, NMA, MJG, and KP wrote and revised the manuscript. TFH contributed to analysis and revised the manuscript. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)
Figure S1. ROC curves for correctly identifying AKI for (A) cCr_{75M}, (B) eCr_{100M}, (C) eCr_{100EPI}, and (D) $eCr_{adjusted}$.
Figure S2. ROC curves for correctly identifying AKI for (A) cCr_{Cohort}, (B) eCr_{Rnd}, and (C) eCr_{Admit}.
Table S1. Comparison of clinical characteristics of patients misclassified as having AKI.

REFERENCES

1. Chawla LS, Amdur RL, Shaw AD, et al. Association between AKI and long-term renal and cardiovascular outcomes in United States veterans. *Clin J Am Soc Nephrol*. 2014;9:448–456.

2. Hsu RK, Hsu CY. The role of acute kidney injury in chronic kidney disease. *Semin Nephrol*. 2016;36:283–292.

3. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8:R204–R212.

4. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:R31.

5. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2:1–138.

6. Doi K, Yuen PS, Eisner C, et al. Reduced production of creatinine limits its use as marker of kidney injury in sepsis. *J Am Soc Nephrol*. 2009;20:1217–1221.

7. Pickering JW, Ralib AM, Endre ZH. Combining creatinine and volume kinetics identifies missed cases of acute kidney injury following cardiac arrest. *Crit Care*. 2013;17:R7.

8. Macedo E, Bouchard J, Soroko SH, et al. Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. *Crit Care*. 2010;14:R82.

9. Prowle JR, Kolic I, Purdell-Lewis J, et al. Serum creatinine changes associated with critical illness and detection of

persistent renal dysfunction after AKI. *Clin J Am Soc Nephrol.* 2014;9:1015–1023.

10. Murata K, Baumann NA, Saenger AK, et al. Relative performance of the MDRD and CKD-EPI equations for estimating glomerular filtration rate among patients with varied clinical presentations. *Clin J Am Soc Nephrol.* 2011;6:1963–1972.

11. Moran SM, Myers BD. Course of acute renal failure studied by a model of creatinine kinetics. *Kidney Int.* 1985;27:928–937.

12. Thomas ME, Blaine C, Dawnay A, et al. The definition of acute kidney injury and its use in practice. *Kidney Int.* 2015;87:62–73.

13. Siew ED, Ikizler TA, Matheny ME, et al. Estimating baseline kidney function in hospitalized patients with impaired kidney function. *Clin J Am Soc Nephrol.* 2012;7:712–719.

14. Gaiao S, Cruz DN. Baseline creatinine to define acute kidney injury: is there any consensus? *Nephrol Dial Transplant.* 2010;25:3812–3814.

15. Bagshaw SM, George C, Dinu I, et al. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant.* 2008;23:1203–1210.

16. Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. *Crit Care Med.* 2007;35:1837–1843. quiz 1852.

17. Uchino S, Bellomo R, Goldsmith D, et al. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit Care Med.* 2006;34:1913–1917.

18. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604–612.

19. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis.* 2010;55:622–627.

20. Kork F, Balzer F, Krannich A, et al. Back-calculating baseline creatinine overestimates prevalence of acute kidney injury with poor sensitivity. *Acta Physiol (Oxf).* 2017;219:613–624.

21. Levey AS, Inker LA, Coresh J. GFR estimation: from physiology to public health. *Am J Kidney Dis.* 2014;63:820–834.

22. Horio M, Imai E, Yasuda Y, et al. Modification of the CKD epidemiology collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. *Am J Kidney Dis.* 2010;56:32–38.

23. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol.* 2006;17:2937–2944.

24. Rule AD, Teo BW. GFR estimation in Japan and China: what accounts for the difference? *Am J Kidney Dis.* 2009;53:932–935.

25. Cooper DJ, Plewes K, Grigg MJ, et al. The effect of regularly dosed paracetamol versus no paracetamol on renal function in *Plasmodium knowlesi* malaria (PACKNOW): study protocol for a randomised controlled trial. *Trials.* 2018;19:250.

26. World Health Organization. World Malaria Report. 2019. Available at: https://www.who.int/malaria/publications/world-malaria-report-2019/en/. Accessed May 1, 2020.

27. Grigg MJ, William T, Barber BE, et al. Age-related clinical spectrum of *Plasmodium knowlesi* malaria and predictors of severity. *Clin Infect Dis.* 2018;67:350–359.

28. Malaysian Department of Statistics. Population distribution and basic demographic characteristics. 2010. Kuala Lumpur, Malaysia: Malaysian Department of Statistics.

29. Wetzels JF, Kiemeney LA, Swinkels DW, et al. Age- and gender-specific reference values of estimated GFR in Caucasians: the Nijmegen Biomedical Study. *Kidney Int.* 2007;72:632–637.

30. Rule AD, Larson TS, Bergstralh EJ, et al. Using serum creatinine to estimate glomerular filtration rate:accuracy in good health and in chronic kidney disease. *Ann Intern Med.* 2004;141:929–937.

31. Cooper DJ, Rajahram GS, William T, et al. *Plasmodium knowlesi* malaria in Sabah, Malaysia,. 2015–2017: ongoing increase in incidence despite near-elimination of the human-only *Plasmodium* species. *Clin Infect Dis.* 2020;70:361–367.

32. Grigg MJ, Cox J, William T, et al. Individual-level factors associated with the risk of acquiring human *Plasmodium knowlesi* malaria in Malaysia: a case-control study. *Lancet Planet Health.* 2017;1:e97–e104.

33. Joannidis M, Metnitz B, Bauer P, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med.* 2009;35:1692–1702.

34. Bagshaw SM, George C, Bellomo R, et al. Early acute kidney injury and sepsis: a multicentre evaluation. *Crit Care.* 2008;12:R47.

35. Cruz DN, Bolgan I, Perazella MA, et al. North East Italian Prospective Hospital Renal Outcome Survey on Acute Kidney Injury (NEiPHROS-AKI): targeting the problem with the RIFLE Criteria. *Clin J Am Soc Nephrol.* 2007;2:418–425.

36. Constantin JM, Futier E, Perbet S, et al. Plasma neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in adult critically ill patients: a prospective study. *J Crit Care.* 2010;25:176 e171–e176.

37. Udy A, O'Donoghue S, D'Intini V, et al. Point of care measurement of plasma creatinine in critically ill patients with acute kidney injury. *Anaesthesia.* 2009;64:403–407.

38. Pickering JW, Endre ZH. Back-calculating baseline creatinine with MDRD misclassifies acute kidney injury in the intensive care unit. *Clin J Am Soc Nephrol.* 2010;5:1165–1173.

39. Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem.* 2007;53:766–772.

40. Bernier-Jean A, Beaubien-Souligny W, Goupil R, et al. Diagnosis and outcomes of acute kidney injury using surrogate and imputation methods for missing preadmission creatinine values. *BMC Nephrol.* 2017;18:141.