The kidney is essential for maintaining water and electrolyte homeostasis in the body. It acts as a filter, allowing the ‘recycling’ of extracellular fluid and excretion of waste products, through a combination of glomerular filtration, tubular reabsorption and tubular secretion. The glomerular filtration rate (GFR) is the most widely accepted measure of renal function in both health and disease. In critical illness, determination of renal function informs several issues, including overall mortality and morbidity, optimisation of drug dosing and the initiation of renal replacement therapy. It is widely accepted that many critically ill patients will develop acute kidney injury (AKI) due to many factors including sepsis, use of nephrotoxic agents and obstruction to urinary flow.

However, perhaps just as frequently, certain patients will manifest elevated renal function or augmented renal clearance (ARC). ARC often occurs in those who do not have renal impairment and have achieved adequate resuscitation during their intensive care unit (ICU) admission. Mostly for convenience, ARC is defined by an elevated creatinine clearance (Cr_cl), which is used as a surrogate of GFR. Values $\geq 130$ ml/minute/1.73m$^2$ have been proposed as a useful threshold, given the association with low antibiotic concentrations when using standard doses, and inferior clinical outcomes. However, this requires further validation, as the prevalence of ARC in ICU patients varies significantly (17.9% to 51.6%), depending on the definition employed and case-mix studied. Patients considered to be at risk of ARC include young, traumatised and postoperative patients with low...
illness severity scores. Systemic inflammation, coupled with peripheral vasodilation, increased cardiac output and greater renal blood-flow are thought to be important mechanisms. Traumatic brain-injured patients receiving vasopressor therapy have also been noted to have an elevated Cr_cl.

The most accurate method of identifying ARC among critically ill patients is still controversial. Commonly employed parameters, such as serum creatinine concentrations, may be misleading in the critically ill, as low values may be a reflection of reduced protein stores and malnourishment, rather than altered renal function. Therefore, equations that only use serum creatinine concentrations to estimate glomerular filtration (such as The Modification of Diet in Renal Disease and Cockcroft-Gault [CG] Equation) have been demonstrated to be inaccurate in this setting. Consequently, measuring a timed urinary Cr_cl is probably the most pragmatic and reliable method to identify ARC in the critical care setting.

The primary aim of this study was to describe the prevalence of ARC in a selected cohort of critically ill patients admitted to the ICU of Sungai Buloh Hospital, Malaysia, over a two-month period. We also aimed to compare the prevalence of ARC in our cohort with previous reports from other ICUs, while attempting to identify clinical characteristics that may help to identify these patients in a timely fashion. In addition, we also compared CG calculated creatinine clearance (CG Cr_cl) with measured urinary Cr_cl to determine whether these two methods can be used interchangeably.

**MATERIALS AND METHODS**

This prospective observational study was conducted in a 36-bed tertiary level adult ICU of a 620-bed public hospital in Malaysia. Ethics approval was obtained from the Malaysian Medical Research Ethics Committee (NMRR ID NMRR-12-137-11118 S4RO). The requirement for individual informed consent was waived for this study.
Patients were enrolled according to the following inclusion criteria: 1) admission to the ICU with expected length-of-stay >24 hours, 2) admission serum creatinine concentration <120 µmol/l and 3) no history of chronic kidney disease or renal replacement therapy. Patients were excluded from the study if one or more of the following criteria were met: 1) absence of invasive haemodynamic monitoring as part of routine management, 2) absence of an indwelling urinary catheter as part of routine management and 3) “Risk” stage of AKI (>1.5 fold increase in serum creatinine from baseline or urine output <0.5 ml/kg/hour for >six hours prior to enrolment)\(^\text{16}\). Our study cohort therefore, represents a selected group of ICU patients: those without AKI, requiring invasive monitoring and with an expected length-of-stay >24 hours.

Admission type was classified as ‘Elective’ when a routine ICU bed was requested postoperatively. All other cases were treated as ‘Emergency admissions’. Independently, all cases were also categorised as being trauma or non-trauma related. Additional demographic, therapeutic and outcome data were collected while the patient was in ICU via the institutional computerised medical record system. Sequential organ failure assessment\(^\text{17}\) scores were obtained from a national database (the Malaysian Registry of Intensive Care).

**Cr\(_{\text{cl}}\) measurement**

A 24-hour Cr\(_{\text{cl}}\) study was commenced within 24 hours of ICU admission. Serum creatinine concentrations obtained from routine morning blood samples were used to calculate Cr\(_{\text{cl}}\). ARC was defined as >130 ml/minute. A CG Cr\(_{\text{cl}}\) was also calculated for comparison (CG Cr\(_{\text{cl}}\)=\([140-\text{age}] \times \frac{\text{weight in kg}}{0.85 \text{ for females}} \times \frac{\text{Serum creatinine mmol/l}}{0.814}\)).

**Statistical analysis**

For continuous variables, data are presented as the median and interquartile range. Qualitative variables are presented as frequencies and percentages. A Mann–Whitney U or chi-square test was used to compare independent subgroups, for continuous and categorical variables respectively. Comparisons between measured and estimated clearances used the Wilcoxon Sign Rank test, Spearman correlation (rs), linear regression and Bland–Altman analysis. A P-value <0.05 was considered statistically significant. All statistical analyses employed SPSS v.21.0 (IBM, Armonk, NY, USA).

**RESULTS**

From 272 patients admitted to the ICU during the study period, a total of 49 eligible patients were included in this study. Figure 1 illustrates the common reasons for patients excluded from this study. Demographic and clinical data of the 49 patients included in this study are presented in Table 1. The majority of participants were young (median age 34 years) male trauma patients. All trauma patients suffered traumatic brain injury and also underwent emergency surgery prior to ICU admission. Overall
### Table 2
Comparison of patients with and without augmented renal clearance

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Category</th>
<th>ARC (n=19)</th>
<th>Non-ARC (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)/N (%)</td>
<td>Median (IQR)/N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>35 (25–45)</td>
<td>34 (24–50)</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>17 (89.5)</td>
<td>20 (66.7)</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2 (10.5)</td>
<td>10 (33.3)</td>
<td></td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>6 (3–19)</td>
<td>9 (6–12)</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>17 (5–25)</td>
<td>11 (7–21)</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>SOFA Score</td>
<td>9 (7–10)</td>
<td>9 (6–11)</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Trauma admission</td>
<td>No</td>
<td>5 (26.3)</td>
<td>16 (53.3)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>14 (73.7)</td>
<td>14 (46.7)</td>
<td></td>
</tr>
<tr>
<td>Admission type</td>
<td>Elective</td>
<td>2 (10.5)</td>
<td>12 (40.0)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Emergency</td>
<td>17 (89.5)</td>
<td>18 (60.0)</td>
<td></td>
</tr>
<tr>
<td>ICU outcome</td>
<td>Discharge</td>
<td>16 (84.2)</td>
<td>26 (86.7)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Death</td>
<td>3 (15.8)</td>
<td>4 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>66 (59–79)</td>
<td>66 (61–72)</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Cr_cl (ml/min)</td>
<td>173 (141–223)</td>
<td>91 (64–112)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Vasopressors (during Cr_cl collection)</td>
<td>Yes</td>
<td>11 (57.9)</td>
<td>21 (70.0)</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>8 (42.1)</td>
<td>9 (30.0)</td>
<td></td>
</tr>
</tbody>
</table>

ARC=augmented renal clearance, IQR=interquartile range, LOS=length-of-stay, ICU=intensive care unit, SOFA=Sequential Organ Failure Assessment, Cr_cl=creatinine clearance.

### Table 3
Comparison of Cockcroft-Gault calculated creatinine clearance (CG Cr_cl) and measured creatinine clearance (Cr_cl) for all patients (n=49), augmented renal clearance (ARC) patients (n=19) and non-ARC patients (n=30)

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>ARC</th>
<th>Non-ARC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CG Cr_cl</td>
<td>Cr_cl</td>
<td>CG Cr_cl</td>
</tr>
<tr>
<td>Median</td>
<td>120</td>
<td>116</td>
<td>120</td>
</tr>
<tr>
<td>rs (P-value)</td>
<td>0.24 (0.05)</td>
<td>-0.04 (0.44)</td>
<td>0.48 (&lt;0.01)</td>
</tr>
<tr>
<td>Bias (SD)</td>
<td>3.9 (58)</td>
<td>57 (54)</td>
<td>-30 (27)</td>
</tr>
<tr>
<td>95% LOA</td>
<td>-110–118</td>
<td>-50–164</td>
<td>-83–23</td>
</tr>
</tbody>
</table>

rs=Spearman correlation, SD=standard deviation, LOA=limits of agreement.
sequential organ failure assessment scores were found to be moderate in this cohort of patients (median [interquartile range] 9 [6.0 to 10.0]).

Descriptive data analysis identified that 39% of patients in this study had ARC. Data were later separated into two categories, patients with ARC and those without ARC (Table 2). No significant differences were identified between the two groups other than in admission type (elective versus emergency admission). Although patients manifesting ARC were more frequently trauma victims, this did not reach statistical significance ($P=0.06$). Data were also separated into four quartiles based on the $Cr_q$ result. The age of patients in each quartile is presented in Figure 2. The first and second quartiles show a wider distribution as compared to the third and fourth quartiles.

Linear regression between CG $Cr_q$ and measured $Cr_q$ for non-ARC and ARC patients, is presented in Figure 3. As illustrated, significantly worse correlation was observed in ARC patients ($r_s=-0.04, P=0.44$) as compared to non-ARC patients ($r_s=0.48, P<0.01$). Furthermore, in those patients with ARC, measured $Cr_q$ values were significantly higher (173 [141 to 223] ml/minute) compared to CG $Cr_q$ (120 [89 to 154] ml/minute), $P<0.01$) (Figure 4). Figure 5 compares the different methods using Bland–Altman analysis. For all patients, it yielded an average bias of 3.9 ml/minute with broad limits of agreement, -110 to 118 ml/minute. A larger bias was observed in the ARC subgroup: 57 ml/minute (54 ml/minute), with similar limits of agreement (-50 to 164 ml/minute). All data are summarised in Table 3.

DISCUSSION

To our knowledge, this is the first study examining the epidemiology of ARC in a selected cohort of Malaysian critical care patients. Although 39% of study subjects had ARC on admission, the overall prevalence of this phenomenon in the wider Malaysian critical care population is likely to be lower, as only 18% of all admissions to the ICU were included over the study period (Figure 1). ARC was more likely to occur in emergent ICU admissions ($P=0.03$) and possibly also in trauma patients ($P=0.06$). Perhaps most significantly, poor agreement was noted between CG $Cr_q$ and measured $Cr_q$ in patients with ARC, suggesting that clinicians should be cautious when using mathematical estimates of renal function in this setting.

The reported prevalence of ARC from other studies ranges from 17.9% to 41.1% $^{7-9}$, albeit with varying definitions employed. Unlike this prior work, no significant differences were noted in demographic data between ARC and non-ARC patients in the current study. Specifically, previous authors have observed ARC as a frequent finding, predominantly in younger male patients $^{5,7,11}$. In our study cohort, this demographic was over-represented, such that age and gender were not identified as discriminatory variables. Although this is likely a reflection of our inclusion criteria and subsequent small sample size, significant differences in critical care case-mix in Malaysia may have also contributed. Of note, stratification of data into quartiles did illustrate a trend towards younger age in those with higher $Cr_q$ (Figure 2).

The association between ARC and emergent admission to the ICU, often in the setting of trauma, represents an observation consistent with previous
It is also interesting to note that all trauma victims in our study suffered traumatic brain injury, a previously reported risk factor for ARC. No significant differences were found for length-of-stay and ICU outcome between groups, although this study is significantly underpowered for such an observation.

An additional major finding from this work is the poor relationship between CG Crcl and measured urinary Crcl in ARC patients, as illustrated in Figures 3 and 4. A similar positive bias (between 17 and 39 ml/minute) has been reported by others in this setting, while some have identified a negative bias. Importantly, the bias becomes significantly larger in patients exhibiting ARC, such that dose adjustment of renally excreted drugs is unlikely to be accurate on the basis of CG Crcl. In this respect, it has been suggested that a measured Crcl represents a more accurate surrogate of GFR in the ICU setting.

Although our study did not attempt to quantify the clinical implications of ARC, the observation that approximately two out of five participants in this study manifested this phenomenon represents an important consideration in drug dose selection, particularly antibiotics. While decreasing renal function is a common trigger for dose reduction of renally cleared agents, ARC should also trigger increased dosing to avoid subtherapeutic concentrations. Failure to consider this in dose selection may increase the likelihood of treatment failure, or promote colonisation and infection by multi-drug-resistant organisms. In this context, several studies have demonstrated that beta-lactam antibiotics are more rapidly cleared in septic patients without organ dysfunction, resulting in subtherapeutic levels and associated poor clinical outcomes.

Applying the results of our study suggests that significantly altered dosing may be required for patients with ARC. Our data describing the range of Crcl that can be observed in the critically ill serves as an important reminder that a simple ‘one dose fits all’ approach for renally cleared drugs in patients without renal dysfunction is likely to be grossly flawed. Such variation in Crcl between critically ill patients supports an individualised drug dosing approach that may not be necessary in a ward environment. To this end, therapeutic drug monitoring has been strongly advocated as a tool for optimised dosing of antibiotics in critically ill patients.

We wish to acknowledge the following limitations of this work. Only 18% of patients admitted to the ICU over the study period were enrolled. Rapid clinical turnover (resulting in a shorter expected length-of-stay), and a high percentage of patients with comorbid disease predisposing to the development of AKI appeared to be the key factors contributing to the low rate of patient enrolment. As such, a post hoc power analysis suggests that this study has only 80% power to detect a difference in incidence in risk factors between 20% and 60% or 40% and 80% (with a higher prevalence in the ARC group), if we assume P <0.05 is statistically significant. In addition, even though a measured Crcl is considered a reliable method of assessing renal function, it is not a gold standard measurement of GFR. Furthermore, we have only examined a single Crcl per patient and as such, we cannot confirm how common ARC would be in our patients in the whole ICU stay.

CONCLUSION
In conclusion, in a selected population of critically ill patients without AKI requiring invasive monitoring admitted to a Malaysian ICU with an expected length-of-stay greater than 24 hours, ARC was identified in a significant proportion of patients. This represents an important finding, as ARC is a key predictor of subtherapeutic drug concentrations, such that these patients are at risk of inadequate drug exposure. Patients admitted emergently appeared to be at particular risk, although unlike prior studies, there was no significant difference in age and gender between ARC and non-ARC patients. Significant
bias and imprecision was also noted between CG \( \text{Cr}_{cl} \) and measured urinary \( \text{Cr}_{cl} \) in this setting, suggesting that clinicians should be cautious in modifying dosing on the basis of mathematical estimates of \( \text{Cr}_{cl} \) from plasma creatinine concentrations alone.

**ACKNOWLEDGEMENTS**

We would like to thank all the personnel of the Department of Anaesthesiology/Critical Care and Clinical Research Centre of Sungai Buloh Hospital, Malaysia, for their kind cooperation and assistance throughout the study period. Jason Roberts is funded in part by a National Health and Medical Research Council of Australia Research Fellowship [NHMRC APP1048652].

**Figure 5**: Bland–Altman plot of Cockcroft-Gault calculated creatinine clearance (\( \text{Cr}_{cl} \)) for (A) ARC patients (n=19) and (B) non-ARC patients (n=30). The dashed lines represent the bias (mean difference) and the dotted lines represent the 95% limits of agreement. ARC=augmented renal clearance.
REFERENCES
