Augmented Renal Clearance in the ICU: Results of a Multicenter Observational Study of Renal Function in Critically Ill Patients With Normal Plasma Creatinine Concentrations*

Andrew A. Udy, BHB, MBChB, FCICM[1,2]; João P. Baptista, MD[3]; Noelle L. Lim, MBBS, MMed, FAMS[4]; Gavin M. Joynt, MBBCh, FFA, FHKCA, FHKCA (IC), FHKAM, FCICM[1,5]; Paul Jarrett, DipHE[2]; Leesa Wockner, PhD[6]; Robert J. Boots, MBBS, PhD, MMedSci, MHAIS, FRACP, FCICM[1,2]; Jeffrey Lipman, MBBCh, DA, FFA, FFA (Crit Care), FCICM, MD[1,2]

Objective: To describe the prevalence and natural history of augmented renal clearance in a cohort of recently admitted critically ill patients with normal plasma creatinine concentrations.

Design: Multicenter, prospective, observational study.

Setting: Four, tertiary-level, university-affiliated, ICUs in Australia, Singapore, Hong Kong, and Portugal.

Patients: Study participants had to have an expected ICU length of stay more than 24 hours, no evidence of absolute renal impairment (admission plasma creatinine < 120 µmol/L), and no history of prior renal replacement therapy or chronic kidney disease. Convenience sampling was used at each participating site.

Interventions: Eight-hour urinary creatinine clearances were collected daily, as the primary method of measuring renal function. Augmented renal clearance was defined by a creatinine clearance more than or equal to 130 mL/min/1.73 m^2. Additional demographic, physiological, therapeutic, and outcome data were recorded prospectively.

Measurements and Main Results: Nine hundred thirty-two patients were admitted to the participating ICUs over the study period, and 281 of which were recruited into the study, contributing 1,660 individual creatinine clearance measures. The mean age (95% CI) was 54.4 years (52.5–56.4 yr), Acute Physiology and Chronic Health Evaluation II score was 16 (15.2–16.7), and ICU mortality was 8.5%. Overall, 65.1% manifested augmented renal clearance on at least one occasion during the first seven study days; the majority (74%) of whom did so on more than or equal to 50% of their creatinine clearance measures. Using a mixed-effects model, the presence of augmented renal clearance on study day 1 strongly predicted ($p = 0.019$) sustained elevation of creatinine clearance in these patients over the first week in ICU.

Conclusions: Augmented renal clearance appears to be a common finding in this patient group, with sustained elevation of creatinine clearance throughout the first week in ICU. Future studies should focus on the implications for accurate dosing of renally eliminated pharmaceuticals in patients with augmented renal clearance, in addition to the potential impact on individual clinical outcomes. (*Crit Care Med* 2014; 42:520–527)

***See also p. 728.**

[1]Burns, Trauma, and Critical Care Research Centre, The University of Queensland, Royal Brisbane and Women's Hospital, Herston, QLD, Australia.

[2]Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Herston, QLD, Australia.

[3]Serviço de Medicina Intensiva, Hospitais da Universidade de Coimbra, EPE Praceta Prof. Mota Pinto, Coimbra, Portugal.

[4]Anaesthesia and Surgical Intensive Care, Changi General Hospital, Singapore.

[5]Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin NT, Hong Kong SAR.

[6]Statistics Unit, Level 3 Clive Berghofer Cancer Research Centre, Queensland Institute of Medical Research, Herston, QLD, Australia.

This work was performed at Royal Brisbane and Women's Hospital, Hospitais da Universidade de Coimbra, Changi General Hospital, and The Chinese University of Hong Kong, Prince of Wales Hospital.

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For information regarding this article, E-mail: andrew_udy@health.qld.gov.au

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Accurate assessment of organ function in the critically ill remains uniquely challenging. Such patients routinely manifest an inflammatory response, which in combination with invasive interventions results in physiology that is infrequently encountered in other settings (1). Regular clinical examination and use of select biomarkers dominate modern critical care practice, being primarily employed to identify and monitor evolving organ dysfunction. Enhanced or augmented organ performance is often of less concern, based on the premise that this is unlikely to lead to adverse outcomes.

However, changes in renal function, and therefore drug handling, can significantly distort the normal pharmacokinetic profile of many commonly prescribed agents (2, 3). As a consequence, the clinician may adjust the dosing regimen. Usually, progressive acute kidney injury (AKI), often recognized by a rising plasma creatinine concentration, will impair the elimination of renally cleared agents, leading to drug accumulation. Consequently, dose reduction is generally appropriate to avoid drug toxicity.

The converse, dose escalation in the presence of augmented renal drug elimination, is infrequently reported in clinical practice (4). This largely results from the lack of "visibility" of this phenomenon, due to the poor discrimination of plasma creatinine concentrations, when reported within the "normal" reference range (5). There is, however, increasing evidence supporting the presence of augmented renal clearance (ARC) in critically ill patients (6). ARC is defined as the enhanced renal elimination of circulating solute (7). Specifically, elevated creatinine clearance (CL_{CR}), has been reported in burns (8), traumatic brain injury (9), polytrauma (10), sepsis (11), ventilator-associated pneumonia (12), and general intensive care practice (13, 14).

Although there is a paucity of specific data detailing renal drug clearance in the critically ill, CL_{CR} is a routinely used surrogate, representing a key covariate describing renal drug elimination (3). Mathematical estimates of CL_{CR} have been proposed; however, these were principally designed for use in an ambulatory or ward-based setting and are inaccurate in the critically ill (15, 16). As such, a directly measured urinary CL_{CR} is the most accurate and reproducible measure of renal function routinely available (17).

Currently little data exist that describe the epidemiology of ARC, particularly in respect to its prevalence and natural history. The impact of ARC on drug pharmacokinetics is not only relevant for daily practice but also the implementation and interpretation of clinical trials of new or emerging pharmaceuticals (4). As such, there is significant uncertainty regarding the design of robust investigations that account for this phenomenon. The aims of this multicenter prospective observational study were therefore to examine the prevalence and natural history of ARC in a cohort of critically ill patients with normal plasma creatinine concentrations, with a view to informing future clinical study and current prescribing practice.

MATERIALS AND METHODS

Setting

This multicenter observational study was undertaken in four, tertiary-level, university-affiliated, ICUs in Australia, Singapore, Hong Kong, and Portugal. Ethical approval was obtained from the institutional review board of each participating site, with written informed consent obtained from either the patient or their nominated substitute decision maker. The lead site was the Royal Brisbane and Women's Hospital, Australia, with ethical approval granted by the Human Research Ethics Committee (HREC/09/QRBW/192).

Study Population

Study participants had to have an expected ICU length of stay (LOS) more than 24 hours, no evidence of absolute renal impairment (admission plasma creatinine < 120 μmol/L), and no history of prior renal replacement therapy or chronic kidney disease. Patients were excluded if 1) either invasive hemodynamic monitoring (principally an intraarterial cannula) or an indwelling urinary catheter (IDC) was not used as part of standard management; 2) they were younger than 18 years; 3) they were pregnant; 4) rhabdomyolysis was clinically suspected or the admission plasma creatinine kinase was more than 5,000 IU/L; or 5) they were in the "risk" category or greater for AKI, as defined by the Risk, Injury, Failure, Loss, and End-stage criteria (18). Convenience sampling was used at each participating site. Patients undergoing an operative procedure within 24 hours prior to admission were classified as "surgical." Planned postoperative admissions were considered "elective."

Interventions

Demographic and outcome data, including age, gender, anthropometric measures, admission diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, ICU and hospital LOS, and ICU mortality, were recorded prospectively. Modified (excluding the neurological and renal components) Sequential Organ Failure Assessment (SOFA) scores, physiological variables, ventilation variables, 24-hour fluid balance, vasopressor/inotrope administration, diuretic use, and antibacterial administration were recorded daily. Data collection commenced within 48 hours of ICU admission and were discontinued at 1) ICU discharge; 2) death; 3) development of severe renal impairment (CL_{CR} < 30 mL/min/1.73 m^2); 4) institution of renal replacement therapy; 5) removal of invasive monitoring or IDC; 6) withdrawal of informed consent; or 7) day 28, whichever came first.

An 8-hour CL_{CR} was the primary method of measuring renal function. Urine was collected via the IDC between midnight and 08:00 AM daily, following which urinary volume and creatinine concentration were determined by laboratory analysis. Concurrent plasma creatinine concentrations

were obtained, following which CL_{CR} was calculated using the standard formula. Creatinine measurement in plasma and urine used automated analyzers employing a modified Jaffe (alkaline picrate) technique, representing an isotope dilution mass spectrometry traceable assay. As per convention, CL_{CR} values were subsequently normalized to a body surface area (BSA) of 1.73 m^2. ARC was defined as an 8-hour CL_{CR} more than or equal to 130 mL/min/1.73 m^2, given the association with subtherapeutic antibacterial concentrations, when using standard doses (19).

Statistical Analysis

Continuous data are presented as the mean (95% CI). Where continuous data were nonnormal, a log transformation was applied; all summary statistics were calculated on the log scale and back transformed for ease of interpretation. When a log transform was not appropriate, data are presented as median (interquartile range). Categorical data are presented as counts (%). Nonpaired analysis of continuous data used an independent Student *t* test for two groups or one-way analysis of variance for multiple groups. When data exhibited nonnormality and could not be transformed, a Mann-Whitney *U* or Kruskal-Wallis *H* test was used alternatively. Paired comparisons used a paired Student *t* test. Independent associations between categorical data were explored by chi-square test or Fisher exact test, where appropriate. To model changes in CL_{CR} over time, a mixed-effects model with a random intercept and random slope was constructed. These models are desirable in situations where data are missing not at random (due to patients being discharged from the ICU). As there are limited baseline data concerning ARC in critical illness, no specific power analysis was possible. A priori a sample size more than 250 patients was deemed sufficient for exploratory analysis. No assumptions were made for missing data, and proportions were adjusted for the number of patients with available data. A two-sided *p* value of less than 0.05 was considered as statistical significance, and all analyses were performed using SPSS version 21 (IBM Corporation, Armonk, NY).

RESULTS

Demographic Data

During the study period, 932 patients were admitted to participating ICUs, of which 281 patients were recruited into the study, contributing 1,660 individual CL_{CR} measures. Demographic, admission, and illness severity data are presented in **Table 1**. The cohort was relatively young (54.4 yr [52.5–56.4 yr]), with most requiring admission to ICU on an emergent basis, with or without an antecedent operation. Routine admissions were scarce (< 10%). Illness severity scores were moderately low, despite the nonelective nature of the cohort. Data collection commenced on day 1 (1–2), with patients remaining in the ICU for a median of 4 days (2–10 d). As determined by protocol, admission plasma creatinine concentrations were within the normal range (mean, 72 µmol/L [69–75 µmol/L]). ICU mortality was 8.5%.

TABLE 1. Demographic, Admission, and Illness Severity Data

Variable	Summary Data
Age, yr, mean (95% CI)	54.4 (52.5–56.4)
Gender, male, *n* (%)	178 (63.3)
Weight, kg, mean (95% CI)	72.4 (70.1–74.6)
Height, m, mean (95% CI)	1.66 (1.65–1.68)
Body mass index, kg/m^2, mean (95% CI)	26.0 (25.3–26.6)
Body surface area, m^2, mean (95% CI)	1.80 (1.77–1.83)
Acute Physiology and Chronic Health Evaluation II score, mean (95% CI)	16.0 (15.2–16.7)
Modified Sequential Organ Failure Assessment score (max), median (IQR)	3 (2–6)
Mechanical ventilation (at any point), *n* (%)	206 (73.8)
Vasopressor/inotropes (at any point), *n* (%)	111 (39.5)
Participating site, *n* (%)	
Australia	116 (41.3)
Singapore	81 (28.8)
Hong Kong	59 (21.0)
Portugal	25 (8.9)
Admission category, *n* (%)	
Elective	26 (9.3)
Emergency	93 (33.1)
Surgical emergency	126 (44.8)
Trauma	36 (12.8)
ICU day of enrolment, median (IQR)	1 (1–2)
Plasma creatinine concentration (day 1), µmol/L, mean (95% CI)	72 (69–75)
Creatinine excretion rate, mg/kg/d, (day 1), mean (95% CI)	19.2 (17.8–20.5)
Creatinine clearance, mL/min/1.73 m^2 (day 1), mean (95% CI)	108 (102–115)
ICU length of stay (d), median (IQR)	4 (2–10)
ICU mortality, *n* (%)	24 (8.5)

IQR = interquartile range.

Prevalence of ARC

Overall, 65.1% ($n = 183$) of the cohort manifested ARC on at least one occasion during the first seven study days. On study day 1, ARC was evident in 108 patients (prevalence = 38.4%), with the majority of new cases occurring on study day 2 ($n = 41$) and day 3 ($n = 13$). The number of evaluable patients fell to 231 on study day 2, with the prevalence of ARC increasing to 49.4% ($n = 114$). Of the 50 patients not completing a second CL_{CR}, 64% ($n = 32$) did not manifest ARC. **Figure 1** demonstrates the prevalence of ARC, as a fraction of the patients

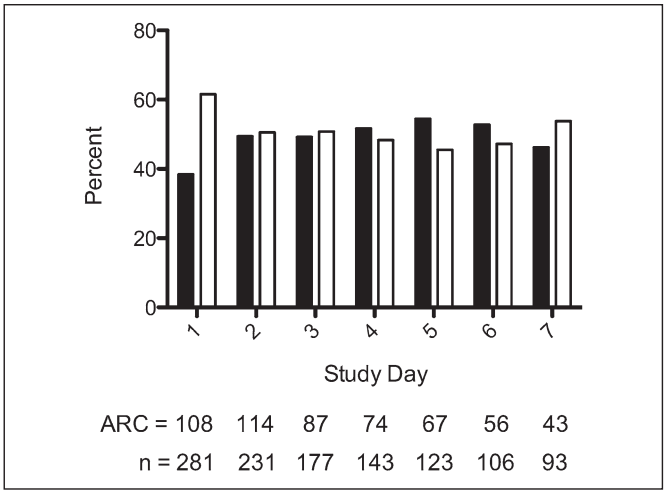

Figure 1. Daily prevalence of augmented renal clearance (ARC) to study day 7. Percentage of patients with ARC (*solid bars*) compared with no ARC (*open bars*) on each study day. The total number (*n*) of patients remaining in the study and those manifesting ARC are provided.

remaining in the study, through day 7. From day 2, the prevalence of ARC remained relatively constant (~50%) with the highest prevalence (54.5%, $n = 67$) recorded on study day 5. Of those patients who did not manifest ARC on day 1 and remained in the ICU, 43.4% did so at least once in the next 6 days. Thirty-four point nine percent (34.9%) of patients never displayed ARC on any CL_{CR} measure. Of those patients manifesting ARC, the majority (74%) did so on more than or equal to 50% of their CL_{CR} measures.

Characteristics of Patients Displaying ARC

Comparison of admission, demographic, and illness severity data between groups (ARC vs no ARC) are presented in **Table 2**. Differences in physiological and treatment variables on study days 1, 4, and 7 are provided in **Appendix A** (Supplemental Digital Content 1, http://links.lww.com/CCM/A755). Patients manifesting ARC (at any point in the first seven study days) tended to be younger, men, and multitrauma victims, receiving mechanical ventilation. On study day 1, the absence of ARC was associated with higher modified SOFA scores ($p = 0.007$), the application of vasopressor or inotropic support ($p = 0.015$), and a lower 24-hour urine output ($p = 0.004$). Frusemide use was more common in those not manifesting ARC. Differences in the minimum mean arterial pressure (study day 1) and body temperatures (study day 4) were also observed, although these deviations are unlikely to be clinically meaningful. No

TABLE 2. Demographic, Therapeutic, and Illness Severity Data in Those With and Without Augmented Renal Clearance at Any Time During the First Seven Study Days

Variable	ARC ($n = 183$)	No ARC ($n = 98$)	p
Age, yr, mean (95% CI)	49.1 (46.8–51.4)	64.4 (61.6–67.2)	< 0.001
Gender, male, *n* (%)	124 (67.8)	54 (55.1)	0.036
Weight, kg, mean (95% CI)	73.3 (70.6–76.0)	70.6 (66.6–74.7)	0.266
Height, m, mean (95% CI)	1.67 (1.66–1.69)	1.65 (1.63–1.67)	0.077
Body mass index, kg/m^2, mean (95% CI)	26.0 (25.3–26.8)	25.8 (24.5–27.1)	0.750
Body surface area, m^2, mean (95% CI)	1.82 (1.78–1.85)	1.77 (1.72–1.81)	0.106
Acute Physiology and Chronic Health Evaluation II, mean (95% CI)	15.7 (14.7–16.6)	16.6 (15.3–17.8)	0.265
Modified Sequential Organ Failure Assessment score (max), median (IQR)	3 (2–6)	3 (2–6)	0.711
Mechanical ventilation (at any point), *n* (%)	150 (82.4)	56 (57.7)	< 0.001
Vasopressor/inotropes (at any point), *n* (%)	76 (41.5)	35 (35.7)	0.342
Norepinephrine (at any point), *n* (%)	66 (36.1)	30 (30.6)	0.358
Dopamine (at any point), *n* (%)	14 (7.7)	5 (5.1)	0.417
Admission category, *n* (%)			
Elective	13 (7.1)	13 (13.3)	0.089
Emergency	54 (29.5)	39 (39.8)	0.081
Surgical emergency	86 (47.0)	40 (40.8)	0.321
Trauma	30 (16.4)	6 (6.1)	0.014
ICU length of stay (d), median (IQR)	5 (3–11)	3 (2–6)	< 0.001
ICU mortality, *n* (%)	14 (7.7)	10 (10.2)	0.465

ARC = augmented renal clearance, IQR = interquartile range.

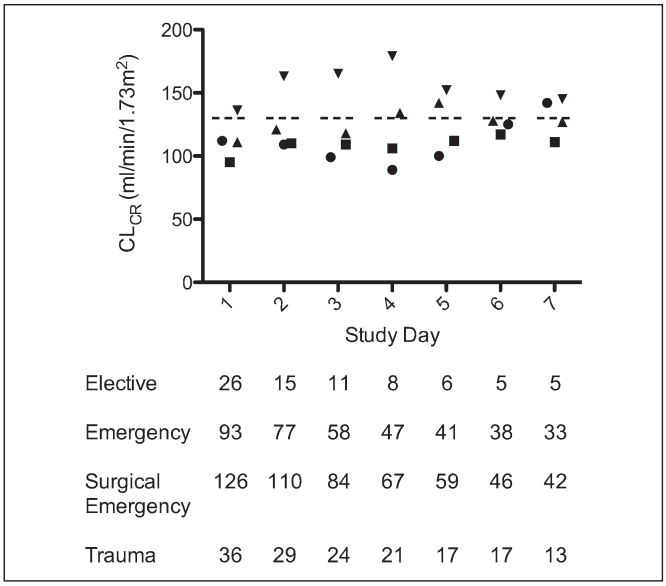

Figure 2. Daily creatinine clearance (CL_{CR}) measures by admission type to study day 7. Mean CL_{CR} in elective (*solid circle*), emergency (*solid square*), surgical emergency (*solid triangle*), and trauma (*inverted solid triangle*) patients to study day 7. The *dashed line* represents the cutoff for augmented renal clearance (130 mL/min/1.73 m^2). The number of patients of each admission type remaining in the study per day is provided.

difference was observed in the provision of enteral nutrition between groups. Significantly lower plasma creatinine concentrations ($p < 0.01$) and high creatinine excretion rates ($p < 0.001$) were consistently noted in those manifesting ARC (Appendix A, Supplemental Digital Content 1, http://links.lww.com/CCM/A755).

Natural History of ARC and Comparison Between Admission Types

Figure 2 displays mean CL_{CR} as a function of admission type to study day 7. In the overall cohort, a significant rise is noted on study day 2 (day 2, 121 mL/min/1.73 m^2 [113–129 mL/min/1.73 m^2]; day 1, 108 mL/min/1.73 m^2 [102–115 mL/min/1.73 m^2]; $p = 0.001$). Significant differences in demographics, anthropometric measures, illness severity, and interventions exist between diagnostic groups (**Table 3**). In addition, CL_{CR} varies both between and within the groups. Of note, CL_{CR} on study day 2 rises significantly in trauma ($p = 0.013$) and surgical emergency admissions ($p = 0.015$), although no significant difference was identified in elective cases ($p = 0.916$) or emergency admissions ($p = 0.121$). Sustained increases in CL_{CR} appear to occur in trauma victims and surgical emergency admissions primarily (Fig. 2).

Variations in CL_{CR} as a function of ARC status on study day 1 are presented in **Figure 3**. Significant differences exist between groups on each study day, although greater within group variability is noted in those without ARC initially. Specifically, a significant increase in CL_{CR} is noted on study day 2 in those not previously manifesting ARC ($p < 0.001$), which is not the case in those with documented augmented clearances already. However, the presence of ARC initially is associated with a sustained elevation of CL_{CR}, over the first seven study days (Fig. 3).

TABLE 3. Comparison of Demographics, Anthropometric Measures, Illness Severity, and Interventions Between Admission Types

Variable	Elective	Emergency	Surgical Emergency	Trauma	*p*
Age, yr, mean (95% CI)	58.5 (53.8–63.3)	56.3 (53.0–59.6)	56.2 (53.4–59.0)	40.7 (34.5–46.9)	< 0.001
Gender, male, *n* (%)	15 (57.7)	50 (53.8)	79 (62.7)	34 (94.4)	< 0.001
Weight, kg, mean (95% CI)	73.7 (68.3–79.1)	72.7 (67.8–77.6)	69.8 (67.2–72.4)	79.5 (72.7–86.2)	0.059
Height, m, mean (95% CI)	1.68 (1.64–1.72)	1.65 (1.63–1.67)	1.66 (1.64–1.67)	1.72 (1.69–1.75)	0.001
Body mass index, kg/m^2, mean (95% CI)	26.1 (24.4–27.8)	26.5 (25.0–28.0)	25.3 (24.5–26.1)	26.8 (24.7–28.9)	0.344
Body surface area, m^2, mean (95% CI)	1.83 (1.76–1.90)	1.78 (1.73–1.84)	1.77 (1.73–1.81)	1.92 (1.84–1.99)	0.008
Acute Physiology and Chronic Health Evaluation II, mean (95% CI)	13.4 (11.4–15.4)	17.0 (15.6–18.4)	16.3 (15.2–17.4)	14.2 (12.2–16.1)	0.017
Modified Sequential Organ Failure Assessment score (max), median (IQR)	3 (1.5–5.5)	4 (2–6)	3 (2–5)	4 (3–6)	0.014
Vasopressor/inotrope (at any point), *n* (%)	7 (26.9)	46 (49.5)	45 (35.7)	13 (36.1)	0.089
Mechanical ventilation (at any point), *n* (%)	7 (26.9)	72 (78.3)	99 (78.6)	28 (80.0)	< 0.001
ICU length of stay (d), median (IQR)	3.5 (2–4.5)	4 (3–12)	5 (2–9)	4.5 (2–11.5)	0.239

IQR = interquartile range.

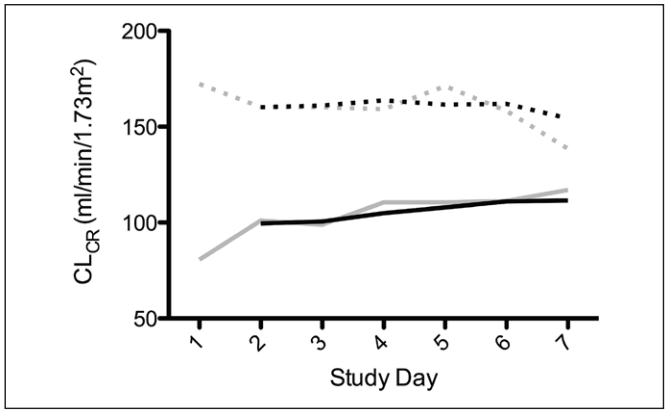

Figure 3. Mixed-effects model comparing those with and without augmented renal clearance (ARC) on study day 1. Mean creatinine clearance (CL_{CR}) (*gray lines*) and results from the model (*black lines*). The *solid lines* represent those without ARC on study day 1 and the *dotted lines* those with ARC on study day 1.

A mixed-effects model was generated to account for variable ICU LOS. Modeling occurred from study day 2, to mitigate the influence of factors outside ICU. Significant covariates included hospital location, age, ARC status on day 1, daily modified SOFA scores, and frusemide administration. Vasopressor use was not included, given the strong correlation with modified SOFA scores, while gender, mechanical ventilation, 24-hour fluid balance, and admission type were not predictive of daily CL_{CR}. As shown in Figure 3, ARC status on study day 1 significantly predicts CL_{CR} from day 2 to 7, with values being markedly lower in those without ARC initially ($p = 0.019$). Changes in modified daily SOFA scores are only significant in those without ARC, whereby increasing scores promote lower CL_{CR} values ($p < 0.001$). Age was highly significant, with patients 65 years old or older having log CL_{CR} values on average 0.46 units lower than those younger than 40 years ($p < 0.001$). Hospital location was included as an adjusting variable to account for differences in case-mix. Of note, frusemide administration was associated with lower CL_{CR} values ($p < 0.001$).

DISCUSSION

This article reports the findings of a multicenter observational study examining the frequency of ARC in critically ill patients with normal plasma renal indices at admission. Major observations include a high prevalence overall, with ~65% of patients manifesting ARC on at least one occasion in the first seven study days. ARC on day 1 is also strongly associated with higher clearances over the subsequent 6 days, a finding that is not simply related to ongoing fluid loading. Although plasma creatinine concentrations were consistently lower in those manifesting ARC, the sustained elevation in CL_{CR} and creatinine excretion rates, and the lack of any significant difference in 24-hour fluid balance, strongly supports this assertion.

These data suggest that a significant proportion of patients will manifest sustained augmented renal solute elimination over the first week in ICU, a consideration not immediately obvious to the clinician or prescriber. Importantly, ARC will significantly impact drug pharmacokinetics for a variety of renally eliminated pharmaceuticals (such as low–molecular weight heparins, aminoglycosides, glycopeptides, and β-lactams) (2), leading to subtherapeutic concentrations and potentially adverse clinical outcomes (20–22).

Brown et al (13) reported similar data in their work examining creatinine, osmolar, and free water clearance in 50 critically ill postoperative patients. In those patients admitted to the surgical ICU with trauma, CL_{CR} values were elevated on day 1 (mean, 140 mL/min/1.73 m^2), peaked on day 4 (mean, 190 mL/min/1.73 m^2), and returned to initial levels by day 7. A strong inverse relationship was also demonstrated between age and CL_{CR}, as measured on the second postoperative day (13). Similar observations have been reported in more contemporary research (6, 9, 10, 14), whereas this study confirms these findings in a larger multicenter dataset.

The mechanisms driving such variation in renal function in the critically ill remain poorly understood. Increased major organ blood flow has been demonstrated in large animal models of Gram-negative sepsis (23), similar to changes observed in human pregnancy (24), which may promote enhanced renal solute elimination. Recent clinical investigation, however, has demonstrated at best only a weak correlation between pulse contour–derived cardiac index and CL_{CR} in critical illness (6). Of note, the high prevalence of ARC in this patient group suggests that this might represent the "expected" response to systemic inflammation, as an indicator of accessible physiological reserve. Whether the absence of ARC can be used as a useful diagnostic or prognostic indicator represents an important area for future clinical investigation.

The true biological influence of trauma and surgery in the pathogenesis of ARC remains uncertain, given the confounding influence of age (25). Specifically, age was identified as the most significant covariate in predicting the development of ARC in mixed-effects modeling, suggesting that the high prevalence in trauma may simply be a reflection of the underlying demographic. As illustrated, the trauma subgroup was almost exclusively young men, with greater body size, who were frequently ventilated. As such, systemic inflammation coupled with a greater physiological reserve may account for the higher clearances observed, rather than any unique mechanism. Although an increase in glomerular filtration in response to protein loading may also be implicated (26, 27), no difference in the provision of enteral nutrition was noted between patients with and without ARC.

Of note is the significant increase in CL_{CR} between day 1 and 2, which appears to drive some of the within subject variability, particularly in those not manifesting ARC initially. Interpreting this finding is complex, given the number of patients not completing a second CL_{CR} and the potential impact of pre-ICU care. Relatively poor renal function despite normal plasma creatinine concentrations at admission to the ICU has been previously reported (28) and may suggest the presence of "occult" AKI, in parallel with a greater disease burden. This is reflected in the higher modified SOFA scores, greater vasopressor requirements, and lower urine outputs in patients without ARC on day 1. In those remaining in the study, renal function

appears to improve, possibly associated with ICU intervention or disease evolution.

Identifying a specific pattern of intrapatient variation, particularly in relation to ICU intervention, remains complex. Vasopressor administration increases renal blood flow and glomerular filtration in large animal models (29), although the relationship in critical illness is much more dynamic. The inverse association between vasopressor administration and CL_{CR} on day 1 illustrates this. Of interest, the majority of participants received norepinephrine, such that exploring the influence of differing vasoactive agents is limited in the current dataset. The true clinical significance of mechanical ventilation is also uncertain, and likely it reflects the ubiquitous nature of this intervention and longer LOS in patients with ARC. The association between frusemide administration and lower CL_{CR} is also unclear; although this may represent clinician directed diuretic therapy in the context of worsening azotemia, or overly aggressive attempts at fluid diuresis.

LIMITATIONS

To maximize data efficiency, a mixed-effects model was generated to infer results, despite participants contributing an unequal number of CL_{CR} measures. This represents a well-recognized statistical technique uniquely suited to dealing with missing information and strengthens the overall study findings. Four separate institutions contributed data, significantly improving the generalizability and external validity of our findings. We recognize, however, that the prevalence of ARC will vary significantly with case-mix, and in this manner, assessment of CL_{CR} in individual institutions is highly recommended.

Eight-hour collections were used as the primary outcome measure, as prior research has suggested that this time period provides the best balance between feasibility and accuracy (30). In addition, the observed creatinine excretion rates are within the range reported for the general populous (31). We acknowledge that CL_{CR} is not a "gold standard" measure of glomerular filtration (such as inulin clearance), although tubular creatinine secretion is unlikely to confound the results at higher filtration rates (32). Of note, we have not collected data on patient ethnicity, which represents an unexplored variable in this analysis.

The prevalence of ARC reported is consistent with recent data (22), although the exclusion of patients unlikely to remain in the ICU for more than 24 hours, and those with established or evolving AKI, has resulted in a select study population. This is reflected in the moderate overall APACHE II score and ICU mortality, although the majority of patients were mechanically ventilated and ~40% received vasopressor or inotrope therapy. As such, although the prevalence of ARC may be lower in the wider ICU population, this analysis provides a unique longitudinal view of CL_{CR} in a significant fraction of critically ill patients. We do not report on specific pharmacokinetic endpoints, therapeutic outcomes, or antibiotic resistance patterns; as such data were beyond the aims of this study. In addition, although ARC was associated with a longer ICU LOS, it should be recognized that this study was not designed to assess any specific clinical outcomes.

CONCLUSIONS

The findings from this prospective, multicenter, observational study suggest that a substantial group of patients will manifest significantly elevated renal solute elimination over the first 7 days in ICU, not overtly obvious to the clinician. In addition, the observation of relatively low CL_{CR} in some patients reinforces the concept that an assessment of "renal function," as opposed to simply identifying "kidney injury," is necessary. Recognition of patients at risk of ARC allows the targeted use of CL_{CR} measurement (not routine in most units) to monitor changes in renal function. Future studies should focus on expanding current knowledge regarding the implications for accurate dosing of renally eliminated pharmaceuticals in patients with ARC. In addition, given the high prevalence of ARC in this study (65.1%), further investigation to assess the potential impact on individual clinical outcomes is warranted.

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