Journal of Critical Care 52 (2019) 227–232

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

The incidence, characteristics, outcomes and associations of small short-term point-of-care creatinine increases in critically ill patients

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ARTICLE INFO

Keywords:
Acute kidney injury
Adult
Creatinine
Critical illness
Intensive care unit
Point-of-care testing

ABSTRACT

Purpose: We assessed the incidence, characteristics, outcomes and associations of small, short-term point-of-care creatinine increases in critically ill patients.
Methods: We prospectively identified the first episode of small (>1 μmol/L/h) short-term (3–4 h) point-of-care creatinine increase between two sequential arterial blood gas measurements. We followed patients for the subsequent development of Kidney Disease: Improving Global Outcomes (KDIGO) defined acute kidney injury (AKI) in the intensive care unit (ICU).
Results: Of 387 patients, 279 (72.1%) developed an episode of small short-term point-of-care creatinine increase and 212 (54.8%) developed AKI. Such episodes occurred at a median of 5 (IQR 2–10) hours after ICU admission, while AKI occurred at a median of 15 (IQR 9–28) hours after admission. Patients with such episodes were more likely to be mechanically ventilated on admission (83.9 vs. 44.4%; $p < .001$) and had higher hospital mortality (10.9 vs. 3.7%, $p = .03$). Creatinine increase episodes had a sensitivity of 86% (95% CI 78–95) and specificity of 31% (95% CI 26–36) for subsequent AKI stages 2 and 3 in 24 h.
Conclusions: Small, short-term point-of-care creatinine increase episodes are common. They are associated with illness severity, occur early, precede AKI by 10 h and are sensitive rather than specific markers of AKI.

1. Introduction

Acute kidney injury (AKI) is common among critically ill patients and associated with increased mortality [1-4]. AKI is also associated with long-term sequelae such as chronic kidney disease and end-stage kidney disease [5,6].

Failure to improve the outcome of patients with AKI has often been ascribed to delayed detection of AKI by serum creatinine [7,8]. However, the concept of such delayed detection of AKI is typically based on both our understanding of the relationship between serum creatinine and glomerular filtration rate and on the use of daily creatinine measurements [9,10]. It is possible that more frequent measurement of serum creatinine would provide a different perspective about its diagnostic and predictive value. Frequent and rapid assessment of creatinine is now possible with point-of-care creatinine measurement together with arterial blood gases. This approach has been validated in critically ill patients as accurate, equivalent to central laboratory measurement and suitable for clinical use [11-13].

Frequent (every 3 to 4 h) point-of-care creatinine measurements might theoretically allow detection of small short-term creatinine increases, which in turn, may indicate deteriorating renal function much earlier than daily measurements. Thus, we conducted a prospective observational study to examine the incidence, characteristics, outcomes and associations of small, short-term creatinine increases with subsequent AKI in the intensive care unit (ICU). We hypothesized that such measurements would be sensitive and earlier markers of subsequent AKI.

2. Methods

This single-centre prospective observational study received ethics approval with a waiver for consent from the Austin Health and Monash University Human Research Ethics Committees.

Abbreviations: ABG, arterial blood gas; AKI, acute kidney injury; APACHE, acute physiology and chronic health evaluation; AUROC, area under the receiver operating characteristic; CI, confidence interval; ICU, intensive care unit; IDMS, isotope dilution mass spectrometry; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; NRI, net reclassification index; OR, odds ratio; RRT, renal replacement therapy.

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https://doi.org/10.1016/j.jcrc.2019.05.007
0883-9441/

2.1. Study population

We screened all patients admitted to a tertiary referral centre ICU between 5 February and 16 July 2018 for enrolment. Exclusion criteria were age < 18 years, AKI (as per Kidney Disease: Improving Global Outcomes [KDIGO] definition) on ICU admission, end-stage kidney disease, kidney transplant, weekend admission, end-of-life care and no urinary catheter nor arterial line in situ [14].

2.2. Definition of an episode of increase in serum creatinine

Patients were considered for inclusion daily during weekdays. During ICU admission, we identified the first occurrence of an episode of small short-term point-of-care creatinine increase. This was defined as a small increase of >1 μmol/L/h between two sequential arterial blood gases (ABGs) (typically separated by a short period of 3–4 h). The rate of rise used to define an episode of small creatinine increase was determined by taking twice the rate required for the KDIGO-defined AKI Stage 1 criterion. The minimum creatinine increase required to fulfil the KDIGO AKI criteria is 26.5 μmol/L over 48 h which is equivalent to a rate of 0.55 μmol/L/h or a 2 μmol/L increase over 4 h [14]. This small rate of increase falls within the instrument error of the creatinine analyser. Therefore, we chose to double the rate of increase to >1 μmol/L/h and identified all creatinine increases greater than this threshold.

2.3. Creatinine measurement

Episodes of small creatinine increase were observed on point-of-care creatinine measurements from ABGs. ABG samples were performed only for clinical purposes as directed by the treating team, which were typically 3–4 hourly. ABG samples were processed on the Radiometer ABL800 Flex® analyser (Radiometer Medical ApS, Brønshøj, Denmark). This measured creatinine using a non-isotope dilution mass spectrometry (non-IDMS) enzymatic assay and a two-electrode amperometric technique [15]. This involved enzymatic conversion of creatinine and creatine to hydrogen peroxide which was subsequently oxidised ($H_2O_2 \rightarrow 2H^+ + O_2 + 2e^-$) [15]. The difference in the electrical current between the two electrodes gave the creatinine concentration [15].

2.4. Outcomes

Patients who developed an episode of creatinine increase were monitored for AKI until ICU discharge. AKI was defined and classified by both the urinary output and creatinine KDIGO criteria [14]. The primary outcome was development of AKI stages 2 and 3 within 24 h of the small short-term point-of-care creatinine increase episode. As additional sensitivity analysis, the development of AKI was also assessed within 12 and 48 h following the creatinine increase episode and for the entirety of the ICU admission. Baseline creatinine was defined as the lowest creatinine measured in the 3 months prior to ICU admission. Secondary outcomes were renal replacement therapy use, ICU and hospital length of stay and ICU and hospital mortality.

2.5. Statistical analysis

Statistical analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria, version 3.5.0). Categorical data were expressed as percentages and compared using chi square tests or Fisher's exact test if >20% of the contingency table had frequencies < 5. Non-parametric data were summarised with median and interquartile range and compared using Mann-Whitney *U* tests.

The predictive value of small short-term point-of-care creatinine increase episodes and continuous creatinine increases for AKI were assessed using univariate and multivariable logistic regressions, area under the receiver operating characteristic (AUROC) and continuous net reclassification index (NRI). Covariates for the multivariable logistic regression were age, Acute Physiology and Chronic Health Evaluation (APACHE) III score, baseline renal function and cardiac surgery. Optimal cut-offs on the receiver operating characteristics were determined using the Youden Index. Confidence interval estimation for the NRI was determined using the percentile bootstrap method. An alpha of <0.05 was used to reject the null hypothesis.

3. Results

3.1. Study population

We screened 830 patients and included 387 patients (Fig. 1). Of these, 236 (61.0%) were male and 246 (63.6%) were surgical admissions. Baseline characteristics of patients are presented in Table 1.

3.2. Incidence and characteristics of patients with a creatinine increase episode

Of the 387 patients, 279 (72.1%) developed an episode of small short-term point-of-care creatinine increase. Patients with such a creatinine increase episode were more likely to be male, mechanically ventilated on ICU admission and have higher APACHE II and III scores (Table 1).

Additionally, patients with a small short-term point-of-care creatinine increase episode were more likely to be a surgical admission, especially for cardiovascular surgery. ICU admission for sepsis was less common in patients with small short-term point-of-care creatinine increase compared to those without a creatinine increase.

3.3. Characteristics of creatinine increase episodes

Characteristics of small short-term point-of-care creatinine increase episodes are presented in Table 2. Patients had a median increase of 7 μmol/L over 3 h which occurred 5 h into their ICU admission. The median urine output during this period was 0.8 mL/kg/h and the median fluid balance was +19 mL. Finally, 79 (28.3%) patients were on vasopressors during the creatinine increase episode.

3.4. Outcomes

Of the 387 patients, 212 (54.8%) developed AKI in ICU (Table 3). Overall, 61 patients (15.8%) developed AKI stages 2 and 3 within 24 h of their small short-term point-of-care creatinine increase episode. Of these, 24 patients developed AKI defined by creatinine criteria, 26 patients defined by oliguria criteria. and 10 patients by both the creatinine and oliguria criteria. Median time from ICU admission to AKI diagnosis was 15 h. Patients with a small short-term point-of-care creatinine increase episode were significantly more likely to develop AKI than those without a creatinine increase. Patients with a small short-term point-of-care creatinine increase episode also had longer ICU length of stay and higher hospital mortality than patients without such episodes (Table 3).

3.5. Associations of creatinine increase episodes

Small short-term point-of-care creatinine increase episodes were associated with a six-fold increase in the odds of subsequent AKI in ICU (odds ratio [OR] 5.9; 95% confidence interval [CI] 3.6–9.9) (Fig. 2). Small short-term point-of-care creatinine increase episodes had a sensitivity of 87% and specificity of 46% for subsequent AKI in ICU (Table 4). Such episodes were associated with a 2 day increase in ICU length of stay (beta coefficient 2.0; 95% CI 0.7–3.2; p value < .01); a six-fold increase in risk of death in ICU (OR 5.7; 95% CI 1.1–103.1) and a three-fold increase in risk of death in hospital (OR 3.2; 95% CI 1.2–10.9).

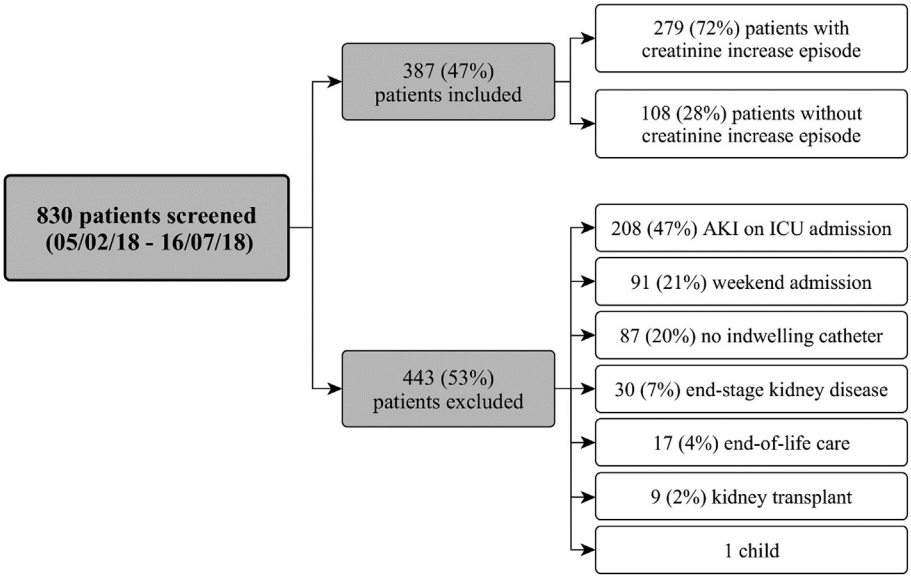

Fig. 1. Flow diagram of study patients screened, included and excluded.

Finally, a short-term point-of-care creatinine increase of 10 μmol/L was associated with a near-doubling of the risk of AKI in 12 h (Supplementary appendix Table S1). Despite the above observations, the AUROC of time-weighted creatinine increase to predict AKI stages 2 and 3 in 24 h was 0.54 (Supplementary appendix Table S2). The optimal cut-off of 5 μmol/L/h change in short-term point-of-care creatinine on this AUROC, had a sensitivity of 32% (95% CI 20–46) and specificity of 88% (95% CI 83–92). The positive continuous NRI for a 10% creatinine increase in predicting AKI stages 2 and 3 in 24 h was 0.08 (95% CI 0.00–0.17).

Table 1
Baseline characteristics of study patients.

	All patients N = 387	Creatinine increase N = 279	No creatinine increase N = 108	P-value
Age	64.0 (52.5–73.0)	64.0 (54.0–73.0)	60.0 (46.0–71.0)	0.054
Male	236 (61.0%)	188 (67.4%)	48 (44.4%)	<0.001
Weight	80.0 (68.0–90.0)	80.0 (69.1–90.0)	77.3 (65.0–89.5)	0.24
Weight measured	331 (85.5%)	240 (86.0%)	91 (84.3%)	0.71
Mechanically ventilated	282 (72.9%)	234 (83.9%)	48 (44.4%)	<0.001
APACHE II	13.0 (10.0–16.0)	13.0 (10.0–17.0)	12.0 (9.0–14.0)	0.01
APACHE III	42.0 (32.0–52.0)	44.0 (33.5–54.5)	38.0 (29.0–48.0)	<0.01
Admission type				
Medical	141 (36.4%)	93 (33.3%)	48 (44.4%)	0.04
Surgical	246 (63.6%)	186 (66.7%)	60 (55.6%)	
Admission diagnosis				
Non-operative				
Cardiovascular	36 (9.3%)	21 (7.5%)	15 (11.6%)	0.053
Respiratory	26 (6.7%)	18 (6.5%)	8 (8.4%)	0.74
Gastrointestinal	10 (2.6%)	8 (2.9%)	2 (2.1%)	0.73
Neurological	23 (5.9%)	18 (6.5%)	5 (3.2%)	0.50
Sepsis	18 (4.7%)	7 (2.5%)	11 (10.5%)	<0.01
Trauma	5 (1.3%)	3 (1.1%)	2 (2.1%)	0.62
Metabolic	19 (4.9%)	14 (5.0%)	5 (5.3%)	0.87
Renal	4 (1.0%)	4 (1.4%)	0 (0.0%)	0.58
Operative				
Cardiovascular	158 (40.8%)	135 (48.4%)	23 (21.1%)	<0.001
Respiratory	13 (3.4%)	8 (2.9%)	5 (5.3%)	0.39
Gastrointestinal	37 (9.6%)	24 (8.6%)	13 (11.6%)	0.30
Neurological	12 (3.1%)	6 (2.2%)	6 (5.3%)	0.08
Renal	5 (1.3%)	3 (1.1%)	2 (2.1%)	0.62
Gynaecological	1 (0.3%)	0 (0.0%)	1 (1.1%)	0.28
Musculoskeletal/skin	19 (4.9%)	10 (3.6%)	9 (9.5%)	0.053
Metabolic	1 (0.3%)	0 (0.0%)	1 (1.1%)	0.28

Data are presented as median (interquartile range) or N (%). P values are expressed to 2 digits, except when highly significant (<0.001) or immediately around the alpha. APACHE: acute physiology and chronic health evaluation.

4. Discussion

4.1. Key findings

In this prospective observational cohort study of the incidence, characteristics, outcomes and associations of small short-term point-of-care creatinine increase episodes, we found that such episodes were common in critically ill patients and were more frequently seen in more acutely ill patients. Moreover, such episodes occurred rapidly, over a short duration and early during ICU admission with a median of 10 h before AKI development. Finally, small short-term point-of-care creatinine increase episodes were significantly associated with increased risk of AKI, length of stay and mortality. However, despite a high sensitivity, their specificity was low and their overall predictive value poor.

Table 2
Characteristics of creatinine increase episodes.

Characteristic	Creatinine increase episodes N = 279
Creatinine increase (μmol/L)	7 (5–10)
Time-weighted creatinine increase (μmol/L/h)	2.3 (1.7–3.9)
Percentage creatinine increase (%)	10 (7–15)
Time-weighted percentage creatinine increase (%/h)	3.6 (2.4–5.7)
Time from ICU admission to creatinine increase episode (hours)	5 (2−10)
Episode duration (hours)	3 (2–4)
Urine output over episode (mL)	283 (185–484)
Weight and time-adjusted urine output (mL/kg/h)	0.8 (0.5–1.5)
Fluid balance during creatinine increase episode (mL)	19 (−225–301)
Fluid balance ≤ 500 mL during creatinine increase episode (N)	20 (7.2%)
Fluid balance > 500 mL during creatinine increase episode (N)	29 (10.4%)
Vasopressor use during creatinine increase episode (N)	79 (28.3%)

Data are presented as median (interquartile range) or N (%). ICU: intensive care unit.

Table 3
Outcomes of study patients.

	All patients N = 387	Creatinine increase N = 279	No creatinine increase N = 108	P-value
AKI	212 (54.8%)	185 (66.3%)	27 (25.0%)	<0.001
Stage 1	144 (67.9%)	124 (67.0%)	20 (74.1%)	0.46
Stage 2	53 (25.0%)	47 (25.4%)	6 (22.2%)	0.72
Stage 3	15 (7.1%)	14 (7.6%)	1 (3.7%)	0.70
Time from ICU admission to AKI (hours)	15 (9–28)	15 (9–28)	16 (11−32)	0.58
RRT	6 (2.8%)	6 (3.2%)	0 (0%)	1
ICU length of stay (days)	2.1 (1.1–3.8)	2.4 (1.5–4.6)	1.6 (0.8–2.7)	<0.001
Hospital length of stay (days)	11.8 (7.2–19.6)	11.8 (7.4–18.7)	11.8 (6.2–22.7)	0.90
ICU mortality	15 (3.9%)	14 (5.0%)	1 (0.9%)	0.08
Hospital mortality	34 (8.8%)	30 (10.9%)	4 (3.7%)	0.03

Data are presented as median (interquartile range) or N (%). P values are expressed to 2 digits, except when highly significant (<0.001) or immediately around the alpha. AKI: acute kidney injury; ICU: intensive care unit; RRT: renal replacement therapy.

4.2. Relationship with previous studies

This is the first study to describe the epidemiology and AKI predictive value of small, short-term point-of-care creatinine increase episodes detected on ABG-based frequent measurements. This study, with such frequent creatinine assessment, removes the "delayed ascertainment" bias generated by daily creatinine measurement for the detection of an outcome which occurred, on average, 15 h into ICU admission in this study population.

Frequent creatinine measurement using point-of-care ABGs has previously been validated for clinical use in critically ill patients [11-13]. Such studies found that point-of-care enzymatic creatinine measurements had a very small negative bias compared to central laboratory measurements which used the Jaffé (alkaline picrate) method [11,12]. This difference was attributed to interference with the Jaffé method by chromogens such as ketones, ascorbic acid, bilirubin, acetoacetate, glucose, haemoglobin and cephalosporins [11,12,16-18]. These confounders have little impact on point-of-care creatinine measurements with the enzymatic method, as used in this study [11].

The overall AKI rate in our study is congruent with the range in AKI incidence reported internationally by Hoste et al., Nisula et al. and Kellum et al. [1,19,20]. The distribution of AKI severity reported by Hoste et al. was 18.4%, 8.9% and 30.0% for Stages 1, 2 and 3 respectively while that of Nisula et al. was 17.2%, 8% and 14.1% [1,19]. In contrast, our study population had a preponderance of Stage 1 AKI and a smaller proportion of Stage 3 AKI. This discrepancy could be explained by the exclusion of patients in whom AKI was already present on ICU admission.

4.3. Study implications

Our findings imply that small short-term point-of-care creatinine increase episodes are common in the ICU and are rapidly and readily assessable by clinicians at the bedside.

They also imply that such episodes are markers of illness severity and are associated with subsequent AKI development and mortality. Their timing in relation to AKI and their sensitivity presents a window of opportunity for increased surveillance and a possible target population for future randomised controlled trials of early intervention.

Despite the above observations, the limited specificity, AUROC and NRI imply the need to refine the definition and cut-off value of this signal in terms of magnitude and duration and to consider combining such findings with data on simultaneous urinary output. Such synergistic evaluation of creatinine increase episodes and urinary output data may help distinguish episodes of oliguria that do or do not progress to AKI. This potential clinically useful implication would require further evaluation.

4.4. Strengths and limitations

This study has several strengths. First, it is prospective in design and involves assessment of 588 point-of-care creatinine values, lending a degree of robustness to our observations. Moreover, it was conducted in a mixed medical and surgical tertiary referral centre ICU, resulting in recruitment of a heterogeneous population, which would likely reflect the broad spectrum of disease.

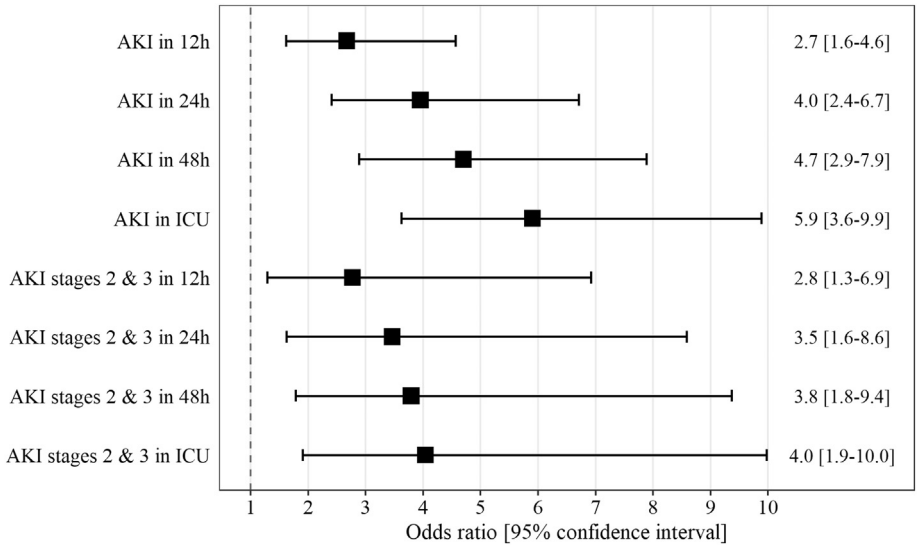

Fig. 2. The occurrence of an episode of point-of-care rise in serum creatinine increases the odds of AKI outcomes at 12, 24 and 48 h and during ICU admission.

Table 4
Diagnostic test characteristics of creatinine increase episodes.

Outcome	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Positive likelihood ratio	Negative likelihood ratio
AKI in ICU	87 (82–91)	46 (39–54)	66 (60–72)	75 (66–83)	1.6 (1.4–1.9)	0.3 (0.2–0.4)
AKI in 12 h	84 (76–89)	34 (29–41)	42 (36–48)	79 (70–86)	1.3 (1.1–1.4)	0.5 (0.3–0.7)
AKI in 24 h	86 (80–91)	39 (33–46)	53 (47–59)	78 (69–85)	1.4 (1.2–1.6)	0.4 (0.2–0.5)
AKI in 48 h	87 (81–91)	42 (35–50)	60 (54–66)	76 (67–84)	1.5 (1.3–1.7)	0.3 (0.2–0.5)
Stages 2 and 3 AKI	90 (80–96)	32 (27–37)	22 (17–27)	94 (87–97)	1.3 (1.2–1.5)	0.3 (0.2–0.7)
Stages 2 and 3 AKI in 12 h	87 (1–94)	30 (0–35)	16 (0−21)	94 (1–97)	1.2 (1.1–1.4)	0.4 (0.2–0.9)
Stages 2 and 3 AKI in 24 h	86 (78–95)	31 (26–36)	19 (15–24)	94 (87–97)	1.3 (1.1–1.4)	0.4 (0.2–0.8)
Stages 2 and 3 AKI in 48 h	89 (79–96)	31 (26–37)	21 (16–26)	94 (87–97)	1.3 (1.2–1.5)	0.3 (0.2–0.7)

Data are presented with 95% confidence intervals. AKI: acute kidney injury; ICU: intensive care unit.

Second, patients who had already developed any stage of AKI on ICU admission were excluded from the study. This enabled assessment of creatinine as a biomarker in an at-risk population during the development of AKI. Third, creatinine measurement on the blood gas analyser used the enzymatic, amperometric method which is not subject to interference by chromogens. Fourth, we assessed the relationship between small short-term point-of-care creatinine increase episodes in relation to AKI occurring within 12, 24 and 48 h or subsequently during ICU admission, thus obtaining a comprehensive assessment of the potential predictive value of such episodes.

This study also has several limitations. It was conducted in a single ICU, limiting its external validity. However, its tertiary referral status enabled recruitment of patients who would be representative of similar ICUs in high-income countries. Detection of small creatinine increases from ABGs performed for clinical purposes created ascertainment bias as ABGs were performed more frequently in unwell patients. However, eliminating this systematic bias was impossible in this study as it was approved as an observational study. Moreover, protocolized observations would only be justified if studies such as this were able to identify the optimal timing and frequency of such measurements. We acknowledge that the study population had a preponderance of cardiac surgery patients in whom the incidence of AKI is known to be higher. These patients, however, also have the benefit of a recent pre-operative creatinine value, which is helpful in establishing accurate baseline renal function. The predictive model for AKI development did not adjust for some confounders such as fluid balance, type of intravenous fluid used, blood product administration and medications including different vasopressors, diuretics and nephrotoxic exposures such as vancomycin, aminoglycosides and intravenous contrast. However, norepinephrine accounted for >90% of vasopressor drug use and there is no consensus in the literature on a reliable method for such statistical adjustment. Only the first creatinine increase episode was identified. We did not analyse the impact of subsequent episodes of creatinine increase and decrease which may have improved predictive ability for subsequent AKI development. We plan to investigate such episodes to understand the potential utility of frequent creatinine measurement.

The inherent measurement error of the Radiometer blood gas analyser used for the creatinine measurements in this study also poses a limitation. Although previously validated for clinical use, we acknowledge a poorer median imprecision of 3.3% for creatinine concentrations <120 μmol/L reported in the literature [11,12,21]. Concerns about the cost of repeated creatinine measurement may be raised. However, there was no patient cost of additional blood sampling as creatinine measurements were incorporated in the ABG test and the financial cost was minimal at 47 cents per measurement.

Finally, we acknowledge the limited specificity of this marker which produces an AUROC close to chance. However, the time interval between two creatinine measurements was very short and it is possible that longer periods of observation (e.g. 6–8 h) may provide a substantial improvement in the specificity and predictive power of the test and that combining such episodes with data from urinary output may also improve predictive performance. We plan such investigations as part of our future research agenda.

5. Conclusion

Small creatinine increase episodes, as observed from frequent point-of-care creatinine measurements, are common among the critically ill and are markers of illness severity. Such episodes are early and sensitive, rather than specific predictors of AKI and would benefit from refinement of duration and magnitude and simultaneous urinary output assessment to improve predictive value and ultimately provide a window of opportunity for intervention.

Author contributions

RB and LT designed the study. RB and GE supervised the data collection conducted by LT. LB and RB provided statistical advice for LT and LB to analyse the data. LT drafted the manuscript and all authors provided intellectual input to its revision.

Acknowledgements

The authors thank Leah Peck and Helen Young for their help in setting up the data collection process, and Alwin Wang for technical and coding support in the use of R.

Financial support

Supported by the Austin Hospital Intensive Care Trust Fund.

Conflict of interest

The authors declare they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.05.007.

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