CRITICAL CARE

## RESEARCH

# Four hour creatinine clearance is better than plasma creatinine for monitoring renal function in critically ill patients

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## Abstract

**Introduction:** Acute kidney injury (AKI) diagnosis is based on an increase in plasma creatinine, which is a slowly changing surrogate of decreased glomerular filtration rate. We investigated whether serial creatinine clearance, a direct measure of the glomerular filtration rate, provided more timely and accurate information on renal function than serial plasma creatinine in critically ill patients.

**Methods:** Serial plasma creatinine and 4-hour creatinine clearance were measured 12-hourly for 24 hours and then daily in 484 patients. AKI was defined either as $\geq 50\%$ increase in plasma creatinine from baseline, or $\geq 33.3\%$ decrease in creatinine clearance. The diagnostic and predictive performance of the two AKI definitions were compared.

**Results:** Creatinine clearance decrease diagnosed AKI in 24% of those not diagnosed by plasma creatinine increase on entry. These patients entered the ICU sooner after insult than those diagnosed with AKI by plasma creatinine elevation ($P = 0.0041$). Mortality and dialysis requirement increased with the change in creatinine clearance-acute kidney injury severity class ($P = 0.0021$). Amongst patients with plasma creatinine < 1.24 mg/dl on entry, creatinine clearance improved the prediction of AKI considerably (Net Reclassification Improvement 83%, Integrated Discrimination Improvement 0.29). On-entry, creatinine clearance associated with AKI severity and duration ($P < 0.0001$) predicted dialysis need (area under the curve: 0.75) and death (0.61). A $\geq 33.3\%$ decrease in creatinine clearance over the first 12 hours was associated with a 2.0-fold increased relative risk of dialysis or death.

**Conclusions:** Repeated 4-hour creatinine clearance measurements in critically ill patients allow earlier detection of AKI, as well as progression and recovery compared to plasma creatinine.

**Trial Registration:** Australian New Zealand Clinical Trials Registry ACTRN012606000032550.

## Introduction

Acute kidney injury (AKI) is common in critically ill patients and is frequently fatal [1-5]. Although defined as an abrupt decrease in glomerular filtration rate (GFR) [6,7] there are no real time measures of GFR to enable timely diagnosis. In practice, diagnosis depends on observing an increase in plasma creatinine (pCr); according to creatinine kinetics, this may not become apparent until 24 to 72 hours after a decrease in GFR [8]. This temporal disconnect between changed GFR

and pCr is readily observable, particularly where there is a clearly defined time of injury, such as cardiopulmonary bypass surgery. The relationship is less clearly demonstrated following multiple or continuing injury and after vigorous resuscitation. The relationship between change in GFR and change in plasma creatinine has not been investigated in critically ill patients at high risk of AKI. In contrast, numerous urinary and plasma biomarkers of kidney injury are under investigation, and are usually assessed by their ability to predict an increase in creatinine [9,10]. Although, many biomarkers show promise as predictors of change in renal function, of dialysis need and of mortality, their primary biological role is to mark the presence of renal injury. With the exception of

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plasma cystatin C, these biomarkers are not markers of function.

Creatinine clearance (CCl) is an easy to estimate GFR in the intensive care unit, since most patients are catheterised and have frequent measurements of pCr. In patients with normal creatinine a low CCl may be an early indicator of AKI [11]. Several studies have shown that short duration (1 to 4 h) CCl measures are feasible in the critically ill [11-14]. Several of these evaluated CCl by comparing short duration clearance with 24-h clearance [12-14]. While validating the brief clearance technique, these studies did not evaluate the use of brief CCl in the detection of AKI.

Evaluation of 4-h CCl was a planned component of the two-centre Early intervention in Acute Renal Failure (EARLYARF) randomised controlled trial of high dose erythropoietin for the prevention of AKI in the ICU [15]. We hypothesised that CCl would give more timely and accurate information on renal function than pCr. We compared these metrics in the diagnosis of AKI and AKI severity and as predictors of the need for dialysis and mortality. We also compared these metrics with urine output. Finally, we compared serial measurements of CCl with serial measurements of pCr.

## Materials and methods
The study was approved by the multiregional ethics committee of New Zealand (MEC/050020029) and registered under the Australian New Zealand Clinical Trials Registry (ACTRN012606000032550 [16]). Screening on entry to the ICU was by presumptive consent, followed by written consent from the patient or family.

Inclusion and exclusion criteria, consent procedures, estimation of time after renal injury, and creatinine assays have been described in detail elsewhere [15]. Briefly, patients were excluded if they were not expected to remain in the ICU for 24 h or to survive 72 h; anuric; receiving renal replacement therapy, or had obvious haematuria, rhabdomyolysis or polycythemia. There was no significant difference between means or standard deviations of creatinine reference samples between the laboratories at the two centres. Since erythropoietin had no effect on outcome in the EARLYARF trial, this analysis includes patients in both observation and intervention arms [15]. Plasma and urine samples were taken for assay and a 4-h urine collection commenced on entry to ICU at 12 and 24 h post-entry and then daily for 7 days. CCl was calculated in ml/min (Table 1). Baseline renal function in patients with known baseline creatinine was determined by the Cockcroft-Gault (CG) equation [17]. The average urine output per kg of body-weight (UO in ml/kg/hr) was measured on entry to the ICU (Table 1).

### Cohorts with known and unknown baseline creatinine
The cohort was divided into those with a known baseline creatinine ($n = 182$) and those without ($n = 302$). Known baseline creatinine was defined as a measured value within one year of entry to the ICU ($n = 162$), or for elective surgery patients, the pre-surgery sample ($n = 20$).

### Definitions of AKI
The known baseline creatinine cohort was used to test the hypothesis that the estimated change in CCl was a better predictor of outcomes than the change in creatinine ($\Delta pCr$). AKI was defined by an increase in pCr ($\Delta pCr_{AKI}$), or an estimated decrease in CCl ($\Delta CCl_{AKI}$),

## Table 1 Definitions

| Name | Abbreviation | Calculation |
|---|---|---|
| Creatinine Clearance | CCl | (Urine creatinine concentration/Plasma creatinine concentration) × (Volume of urine collected over 4 hours in ml/(4 × 60)) |
| Cockcroft-Gault clearance [17] | CG | [(140-Age in years) × weight in kg/(72 × Plasma creatinine concentration in mg/dl)] × 0.85 if female |
| Average urine output | UO | Volume of urine collected over 4 hours in ml/(4 × Patient weight in kg) |
| Change in CCl | $\Delta CCl$ | 100 × (Measured CG on entry - baseline CCl)/Baseline CG |
| Change in plasma creatinine | $\Delta pCr$ | 100 × (On entry creatinine - baseline creatinine)/Baseline creatinine |
| AKI plasma creatinine | $\Delta pCr_{AKI}$ | $\Delta pCr > 50\%$ |
| AKI creatinine clearance | $\Delta CCl_{AKI}$ | $\Delta CCl < -33.3\%$ |
| AKI urine output (oliguria) | $UO_{AKI}$ | Urine output $\leq 0.5$ ml/kg/hr on average over 4 hours |
| RIFLE class R | R | $\Delta pCr > 50\%$ and $\leq 100\%$, or $\Delta CCl < -33.3\%$ and $\geq -50\%$ |
| RIFLE class I | I | $\Delta pCr > 100\%$ and $\leq 200\%$, or $\Delta CCl < -50\%$ and $\geq -66.7\%$ |
| RIFLE class F | F | $\Delta pCr > 200\%$ or $\Delta CCl < -66.7\%$ |
| AKI from entry (AKIN) | $AKI_{AKIN}$ | (Plasma creatinine - on entry plasma creatinine) > 0.3 mg/dl or 50% within 48 hours |

AKI: acute kidney injury; RIFLE: Risk, Injury, Failure, Loss, End stage.

or as oliguria ($UO_{AKI}$). Each component approximates a diagnostic criterion of the Risk, Injury, Failure, Loss, End stage (RIFLE) definition [6,18]. Because urine output was measured over 4 h only, oliguria was only defined over this duration rather than the 6-h RIFLE period. Patients were further classified into (i) no AKI ($\Delta pCr_{No-AKI}$ and $\Delta CCl_{No-AKI}$); (ii) AKI by the clearance criterion only ($\Delta pCr_{No-AKI}$ and $\Delta CCl_{AKI}$); (iii) AKI by the pCr criterion only ($\Delta pCr_{AKI}$ and $\Delta CCl_{No-AKI}$) or (iv) AKI by both criteria ($\Delta pCr_{AKI}$ and $\Delta CCl_{AKI}$). Finally, patients were classified according to AKI RIFLE severity class (Table 1).

### CCl and pCr cut-points and risk prediction models
The area under the receiver operator characteristic curve (AUC) was used to determine the predictive value of on-entry CCl for $\Delta CCl_{AKI}$ and on-entry pCr for $\Delta pCr_{AKI}$. For each metric the optimal cut-point was determined as the value nearest to a sensitivity and specificity of one. We were most interested in whether the addition of CCl to existing measurements of pCr and UO helps identify patients with AKI when pCr is low. Therefore, in the cohort with pCr less than the optimal cut-point, a reference risk prediction model (logistic regression) for AKI (either $\Delta CCl_{AKI}$ or $\Delta pCr_{AKI}$) was constructed using pCr, UO and other variables associated with AKI on univariate analysis. The model calculates for each patient the probability of having AKI. To assess the added benefit of CCl, a new model was constructed by adding CCl to the reference model and was compared with the reference model.

Using the entire cohort, the on-entry creatinine and on entry CCl and pCr were compared as predictors of AKI and severity stage according to the AKIN (Acute Kidney Injury Network) criteria [7] ($AKI_{AKIN}$), duration of $AKI_{AKIN}$, death within 30 days and 365 days, need for dialysis, and length of ICU stay.

### Statistical analysis
Results are presented as means ± SD or medians and inter-quartile range (IQR), or incidence presented as number (n). Cohorts were compared with the Student's *t*-test (for normally distributed continuous variables), the Mann-Whitney *U*-test (for variables not normally distributed), and the chi square ($\chi^2$) or Fisher's exact test for categorical variables. Length of ICU stay was log transformed as necessary for assessment of association with AKI severity class, using one-way analysis of variance (ANOVA). Diagnostic and prognostic performance was assessed by calculating the AUC and odds ratios. The reference and new AKI risk prediction models were compared by the continuous (category-free) net reclassification improvement (NRI) and integrated discrimination improvement statistics [19-21] and difference in

AUC [22]. GraphPad Prism 5.0a for Mac OS (GraphPad Software, San Diego, CA, USA) and Matlab 2011a (MathWorks, Natick, MA, USA) were used for statistical analyses. All confidence intervals (CIs) are 95%.

## Results
Of the 528 patients enrolled in the EARLYARF trial, 484 had a CCl measure on entry to the ICU. Of the remainder, 30 were a sub-cohort of high-risk patients who had undergone cardio-thoracic surgery, and whose first clearance measure was 8 to 11 h after entry to ICU, and 14 patients had no clearance measurement because they were anuric or because clinical events prevented measurement. The analysis is based on 484 patients. Patient characteristics are shown in Table 2.

### AKI on entry to ICU (known baseline creatinine cohort)
On entry to the ICU, 182 patients had a pre-admission baseline creatinine from which the change in creatinine ($\Delta pCr$) and change in creatinine clearance ($\Delta CCl$) to

**Table 2 Patient demographics (*n* = 484) on entry to the ICU**

| | |
|---|---|
| Age, yrs | 60 ± 17 |
| Female, % (n) | 39 (190) |
| Weight, kg | 79 ± 19 |
| Baseline pCr, mg/dl | 0.86 (0.71, 1.06) |
| Baseline estimated CCl, ml/min | 89 (66, 125) |
| APACHE II score | 18 ± 6 |
| SOFA score | 6.3 ± 2.8 |
| Hypotension, % (n) | 23 (111) |
| pCr, mg/dl | 1.0 (79.0, 1.36) |
| 4-h CCl, ml/min | 78 (48, 122) |
| Urine output, ml/kg/hr | 1.0 (52, 2.14) |
| Urine creatinine, mg/dl | 62 (30, 107) |
| Plasma cystatin C, mg/dl | 86 (66, 1.2) |
| CKD, % (n) | 14 (66) |
| Primary diagnosis, % (n) | |
| Abdominal aortic aneurysm rupture & repair | 5 (22) |
| Abdominal surgery or inflammation | 11 (51) |
| Burns | 1 (5) |
| Cardiac arrest or failure | 13 (63) |
| Cardiac surgery | 13 (64) |
| Collapse, cause unknown | 1 (3) |
| Neurological surgery, injury or seizure or haemorrhage | 15 (71) |
| Other | 1 (3) |
| Pulmonary or thoracic surgery or failure | 13 (63) |
| Sepsis | 20 (97) |
| Trauma[a] | 9 (42) |

Shown are means ± SD or medians (lower quartile, upper quartile) for normal and non- normally distributed data, or percentage (n).
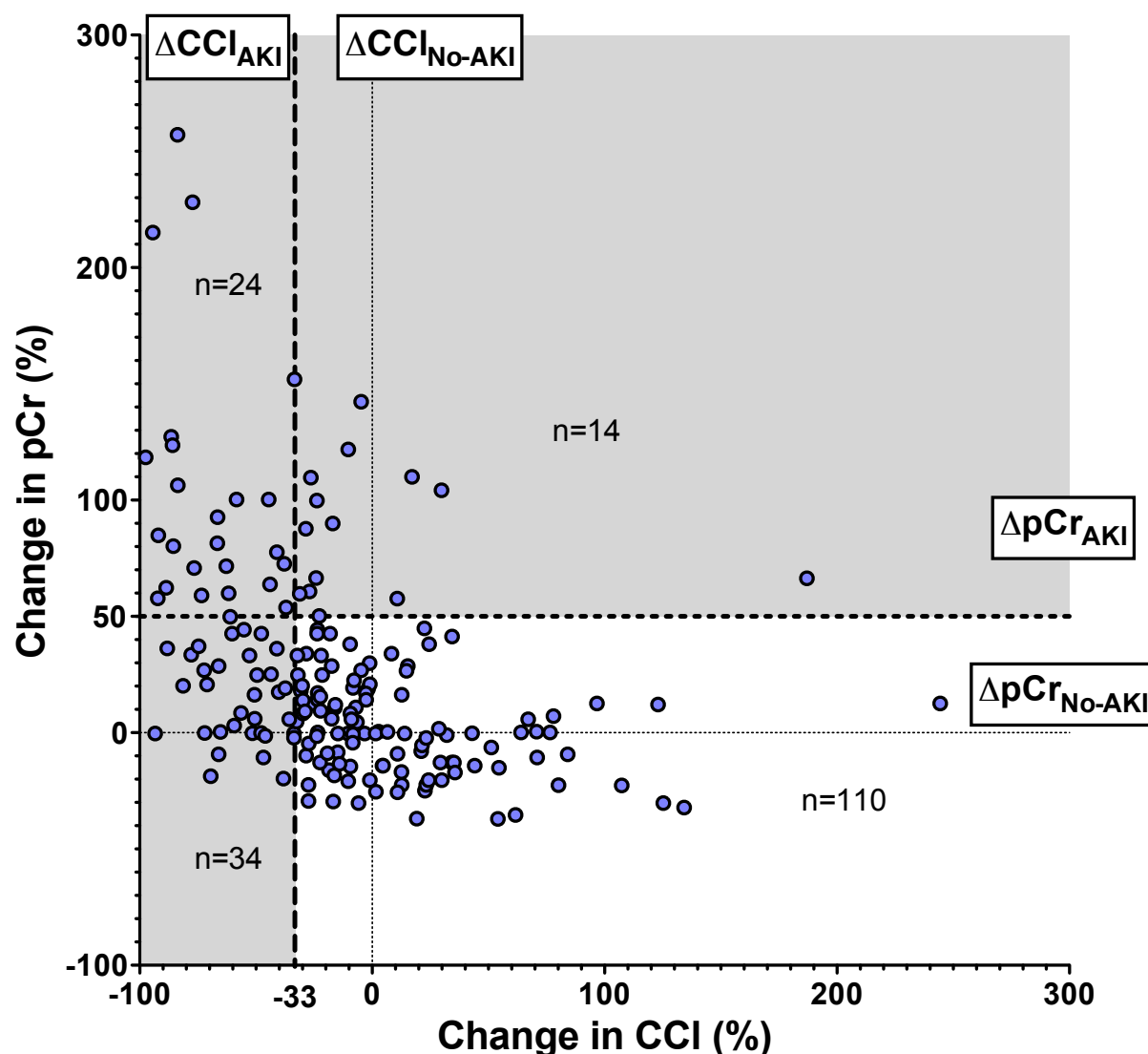pCr: plasma creatinine; CCl: creatinine clearance; CKD: chronic kidney disease; APACHE: acute physiology and chronic health evaluation SOFA: Sequential Organ Failure Assessment.

determine AKI status on entry was calculated (Figure 1). The $\Delta pCr$ only poorly approximated that expected from $\Delta CCl$ ($r^2 = 0.18$) according to the creatinine kinetic model [23]:

$$\Delta pCr = 100*[1/(1 + \Delta CCl/100) - 1]$$

Ninety-two patients (51%) had AKI according to $\Delta CCl_{AKI}$, $\Delta pCr_{AKI}$ or $UO_{AKI}$. Thirty-seven percent ($n = 14$) of $\Delta pCr_{AKI}$ were not simultaneously $\Delta CCl_{AKI}$, whereas 24% ($n = 34$) of $\Delta pCr_{No-AKI}$ had AKI according to $\Delta CCl_{AKI}$ (Table 3). Twenty more patients were classified as AKI by $\Delta CCl_{AKI}$ than by $\Delta pCr_{AKI}$ (McNemar's test $P < 0.01$). Although 14 more patients were classified as $UO_{AKI}$ than $\Delta pCr_{AKI}$, and a 6 more by $\Delta CCl_{AKI}$ than $UO_{AKI}$, the differences were not significant ($P = 0.07$ and $P = 0.49$ respectively). Sixteen patients had AKI by all three definitions. Ten of these sixteen patients died or needed dialysis within 30 days (relative risk (RR) 4.1 compared with not meeting all three definitions; 95% CI, 2.7 to 6.4). $\Delta CCl_{AKI}$ severity classifications were



**Figure 1 Comparison of percentage increase in plasma creatinine (pCr) with percentage decrease in creatinine clearance (CCl) from known baseline to entry into the ICU**. Four quadrants are shown: (i) No AKI ($\Delta pCr_{No-AKI}$ and $\Delta CCl_{No-AKI}$), (ii) AKI by the clearance criterion only ($\Delta pCr_{No-AKI}$ and $\Delta CCl_{AKI}$), (iii) AKI by the pCr criterion only ($\Delta pCr_{AKI}$ and $\Delta CCl_{No-AKI}$) or (iv) AKI by both criteria ($\Delta pCr_{AKI}$ and $\Delta CCl_{AKI}$). AKI: acute kidney injury; No-AKI ($CCl_{No-AKI}$): without AKI; $\Delta pCr$: relative change in pCr from baseline; $\Delta CCl$: relative change in CCl from Cockcroft-Gault (CG) baseline; AKI ($pCr_{AKI}$): with AKI.

**Table 3 Cross-tabulation of Risk, Injury, Failure, Loss, End stage (RIFLE) on entry in the known baseline creatinine cohort according to the definition**

| | $\Delta CCl_{No-AKI}$ | $\Delta CCl_{AKI}$ | $UO_{No-AKI}$ | $UO_{AKI}$ |
|---|---|---|---|---|
| $\Delta pCr_{No-AKI}$ | 110 | 34 | 111 | 33 |
| $\Delta pCr_{AKI}$ | 14 | 24 | 19 | 19 |
| $\Delta CCl_{No-AKI}$ | | | 101 | 23 |
| $\Delta CCl_{AKI}$ | | | 29 | 29 |

AKI: acute kidney injury; AKI ($pCr_{AKI}$): with AKI; No-AKI ($CCl_{No-AKI}$): without AKI; CCl: creatinine clearance; pCr: plasma creatinine.

associated with increased 30-day mortality or need for dialysis ($\chi^2$ test for trend, $P$ = 0.0021), but not $\Delta pCr_{AKI}$ ($P$ = 0.12) (Figure 2). Length of ICU stay was not associated with $\Delta CCl_{AKI}$ ($P$ = 0.49) or $\Delta pCr_{AKI}$ severity classifications ($P$ = 0.95).

The time from insult until entry to the ICU differed between groups ($P$ = 0.0041, Kruskal Wallis non-parametric ANOVA). Thirty-four patients were $\Delta CCl_{AKI}$ and $\Delta pCr_{No-AKI}$. Their median time from insult until entry to the ICU, 10.8 h (IQR, 5.0 to 20.0 h), was less than those classified as $\Delta pCr_{AKI}$ and $\Delta CCl_{AKI}$, for whom the equivalent figure was 24.6 h (IQR, 17.0 to 50.0 h) ($P$ = 0.0037; Mann-Whitney $U$-test) and was less than $\Delta pCr_{AKI}$ and $\Delta CCl_{No-AKI}$, at 18.7 h (IQR, 9.8 to 48.0 h), but not significantly so ($P$ = 0.079). Four $\Delta CCl_{AKI}$ and $\Delta pCr_{No-AKI}$ patients developed AKI according to $\Delta pCr$ at a later time point, and three further patients died within seven days.

### CCl as a risk factor for AKI on entry to ICU when pCr is low (known baseline creatinine cohort)

The optimal cut-point for CCl to diagnose $\Delta CCl_{AKI}$ was 48.6 ml/min (AUC, 0.87; 95% CI, 0.81 to 0.94) calculated using 1/CCl) in the known baseline creatinine cohort (Figure 3). The optimal cut-point for pCr to diagnose $\Delta pCr_{AKI}$ was 1.24 mg/dl (AUC, 0.91; 95% CI, 0.85 to 0.98). Below this cut-point adding CCl to a risk prediction model comprising pCr, UO and acute physiology and chronic health evaluation (APACHE) II scores (all $P$ < 0.1 in a univariate analysis) for AKI ($\Delta CCl_{AKI}$ or $\Delta pCr_{AKI}$) considerably improved the model: in the known baseline creatinine cohort the AUC increased by 0.23 to a moderate 0.77; a net 23% of those with AKI had greater risk whilst 60% of those without AKI had less risk, resulting in an NRI of 83%; the average increase in risk of those with AKI was 0.22 ($IDI_{AKI}$) and the average decrease in risk of those without AKI was 0.074 ($IDI_{No-AKI}$) indicating the model worked best to improve identification of those with AKI rather than exclude those without (Table 4). At a cut-point of CCl = 48.6 ml/min, the positive predictive value (PPV) was 0.88 and the negative predictive value (NPV) was 0.65.

### Prognosis on entry to ICU (entire cohort)

On-entry CCl, pCr, and UO were associated with maximum severity of AKI observed over the next 48 h ($AKI_{AKIN}$: $P$ < 0.0001, $P$ < 0.0001, $P$ = 0.035 respectively, Mann-Whitney $U$- test) (Figure 4). CCl and pCr, but not UO were also associated with duration of $AKI_{AKIN}$ ($P$ < 0.0001, $P$ < 0.0001, $P$ = 0.79 respectively).

On entry to the ICU, CCl moderately predicted the need for dialysis marginally better (AUC, 0.75; 95% CI, 0.59 to 0.91; $P$ = 0.018) than pCr (AUC, 0.72; 95% CI, 0.56 to 0.89); UO was not predictive (AUC, 0.50; 95% CI, 0.41 to 0.75). CCl was predictive of death within 30 days, but with a lower AUC value of 0.61 (95% CI, 0.54 to 0.68). Neither pCr (AUC, 0.55; 95% CI, 0.48 to 0.62) nor UO (AUC, 0.55; 95% CI, 0.47 to 0.62) were predictive of death.

### Change in CCl after entry to ICU

CCl decreased by > 33.3% over the first 12 hours in 72 patients (14.9%) following ICU entry. These patients were more likely to require dialysis or die within 30 days than patients with smaller decreases (29% vs 15%, $P$ = 0.0057; RR, 2.0; 95% CI, 1.3 to 3.0). Only sixteen patients (22%) had a subsequent increase in pCr of more than 50% as would be expected by creatinine kinetic modelling. The median (IQR) time for this increase from the on-entry sample was 25 (17 to 44) h. This was greater than the 16 h required to measure the 33.3% decrease in 4-h CCl required to diagnose AKI; $P$ = 0.0046, Mann Whitney $U$-test. Of the other 56 patients, 21 had very high on-entry CCl (> 140 ml/min), two-thirds of whom were admitted following head injury, neurological surgery, stroke or Guillian Barre syndrome; 22 had a transient decrease in CCl (resolved by 24 h) which may explain the lack of increase in pCr; 3 exhibited elevations in pCr of 29 to 47% (that is, less than the 50% required for AKI classification); 3 patients did not exhibit any significant changes in pCr and seven had no subsequent CCl measurements.

Thirty-six patients exhibited a rise in pCr > 50% but no decrease in CCl over 12 h. Of these, 27 had a decrease in CCl on entry (23) or by 24 h (4) from the CG baseline greater than 33.3% (determined retrospectively); 5 had decreases of CCl > 33.3% between later time points (between day 2 and day 3) followed by an increase in pCr, and 4 showed no decrease in CCl preceding a increase in pCr.

### Discussion

The measurement of a brief CCl, relative to a known baseline value (or when unknown, relative to a calculated CG baseline value), provided earlier diagnostic and prognostic information, compared with change in pCr alone. AKI on entry to the ICU was identified in
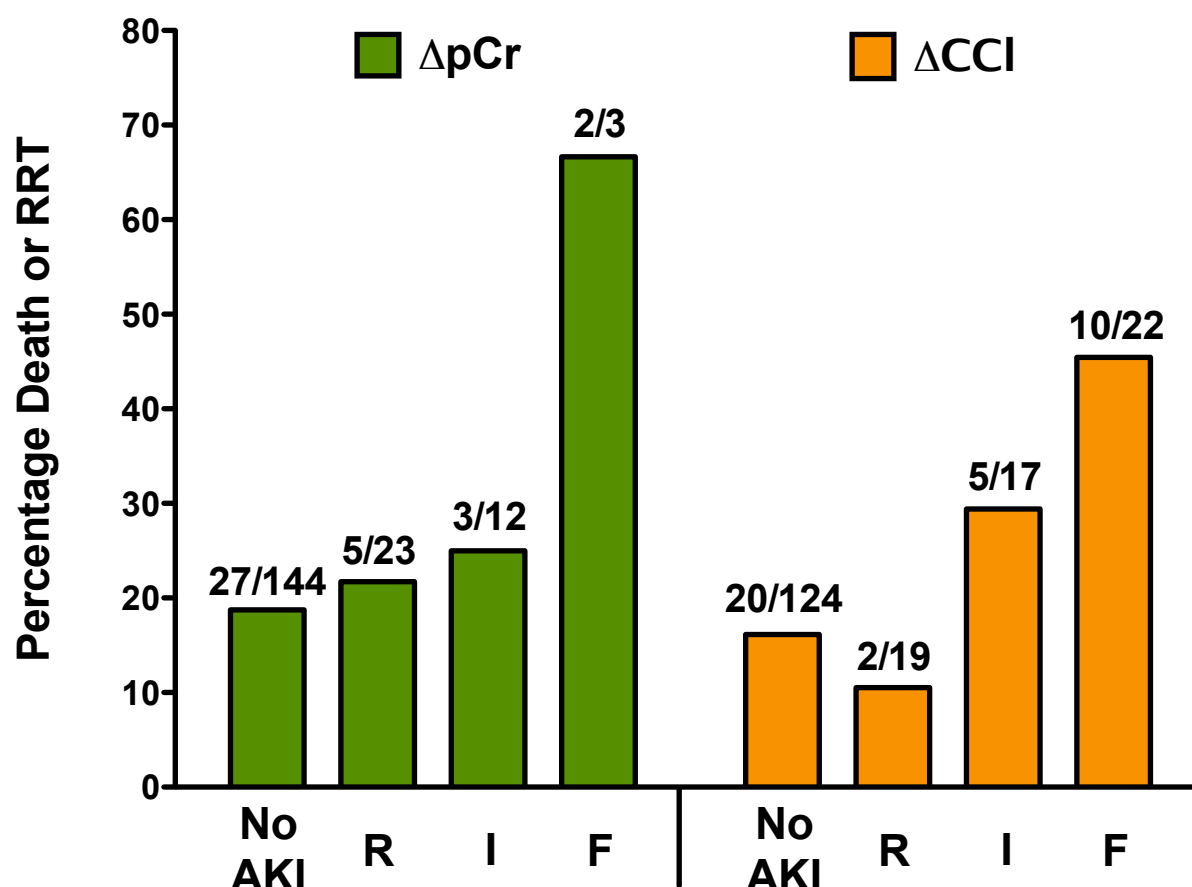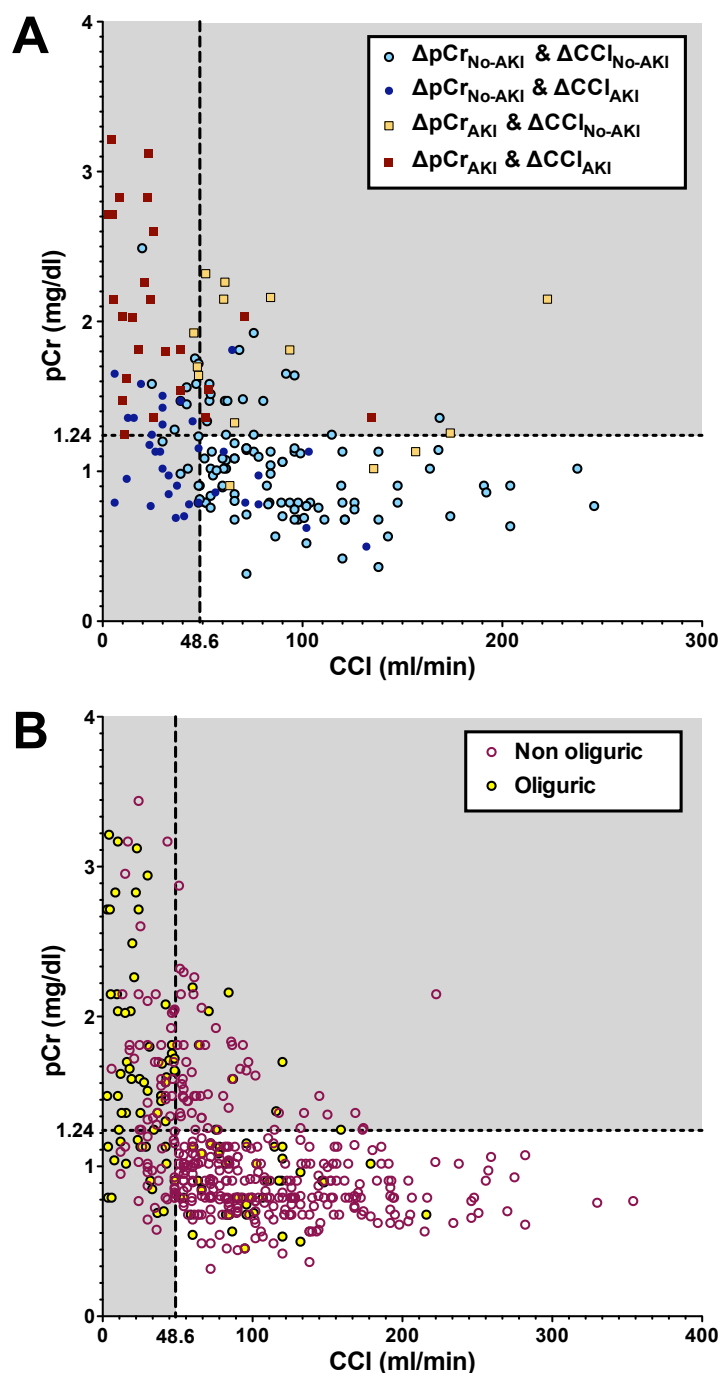
**Figure 2 Comparison of plasma creatinine (pCr) change with estimated creatinine clearance (CCl) change acute kidney injury (AKI) severity classes (No-AKI, R, I or F) on entry to the ICU in the known baseline creatinine cohort**. Percentage of patients who died or needed dialysis; ΔpCr, $P = 0.12$, ΔCCl, $P = 0.0055$ ($\chi^2$ test for trend). The number above each bar is the number of patients who died/total number.

one third of patients not identified by pCr. After admission to the ICU, these patients were identified earlier than those identified by ΔpCr, consistent with the delay in pCr equilibration suggested by creatinine kinetics. ΔCCl also identified a cohort of patients, the (ΔpCr$_{AKI}$ and ΔCCl$_{No-AKI}$) group, with normal renal clearance but with an increased pCr, consistent with recovering renal function after an earlier loss of GFR. This mistiming between CCl measurement and steady state pCr potentially explains the poor correlation ($r^2 = 0.18$) observed. The probability of death or dialysis was more closely associated with the ΔCCl RIFLE severity grade than with ΔpCr severity grade. Serial measurements of CCl provided a diagnosis of AKI and of improving renal function earlier than serial measurements of pCr and also identified patients at risk of dialysis.

A low on-entry CCl was associated with poor outcome, including death. In contrast, neither UO nor pCr predicted death. The moderate AUCs indicate that CCl is not a useful stand-alone predictor of death. When added to a risk prediction model for AKI in patients with low on-entry pCr (< 1.24 mg/dl), CCl greatly improved the model. A sub-threshold CCl predicted the development of AKI and was associated with severity of AKI when AKI was determined using the on-entry creatinine as baseline. The combination of a normal pCr (< 1.24 mg/dl) and low CCl (< 48.6 ml/min) had a moderately high predictive value (0.88) for the early detection of AKI.

Patients with a low CCl and increased pCr need additional information to distinguish on-entry AKI from chronic kidney disease (CKD) in the absence of a pre-admission baseline creatinine. The presence or absence

**Figure 3 Comparison of creatinine clearance (CCl) with plasma creatinine (pCr) on entry into the ICU in the (A) known baseline cohort and (B) entire cohort.** Dashed lines represent optimum cut-points for diagnosis of acute kidney injury (AKI) according to a change in CCl (CCl < 48.6 ml/min) or change in pCr (pCr > 1.24 mg/dl). **(A)** The four possible diagnoses (i) No AKI ($\Delta pCr_{No-AKI}$ and $\Delta CCl_{No-AKI}$), (ii) AKI by the clearance criterion only ($\Delta pCr_{No-AKI}$ and $\Delta CCl_{AKI}$), (iii) AKI by the pCr criterion only ($\Delta pCr_{AKI}$ and $\Delta CCl_{No-AKI}$) or (iv) AKI by both criteria ($\Delta pCr_{AKI}$ and $\Delta CCl_{AKI}$) are illustrated by squares for $\Delta pCr_{AKI}$ and closed circles or squares for $\Delta CCl_{AKI}$. **(B)** Oliguric (urine output < 0.5 ml/kg/h average over 4 h, closed circles), and non-oliguric (open circles) for the entire cohort. No-AKI (CCl$_{No-AKI}$): without AKI; $\Delta pCr$: relative change in pCr from baseline; $\Delta CCl$: relative change in CCl from Cockcroft-Gault (CG) baseline; AKI (pCr$_{AKI}$): with AKI.

**Table 4 Risk reclassification using creatinine clearance plus clinical predictors (plasma creatinine, urine output, and APACHE II) compared with the clinical model alone for AKI on entry.**

|  | Known baseline creatinine cohort, pCr ≤ 1.24 mg/dl (*n* = 111) |
|---|---|
| Comparison of model performance | |
| $IDI_{AKI}$ | 0.22 (0.09 to 0.38) |
| $IDI_{No-AKI}$ | 0.074 (0.029 to 0.13) |
| IDI | 0.29 (0.12 to 0.49) |
| $NRI_{AKI}$ | 23 (-9.2 to 56) |
| $NRI_{No-AKI}$ | 60 (34 to 76) |
| NRI | 83 (29 to 125) |
| Increase in AUC | 0.23 (0.015 to 0.41) |
| Combined CCl and clinical predictors model performance | |
| AUC | 0.77 (0.66 to 0.88) |
| IS | 0.45 (0.29 to 0.61) |
| IP | 0.16 (0.099 to 0.25) |
| PPV at < 48.6 ml/min | 0.88 (0.81 to 0.94) |
| NPV at < 48.6 ml/min | 0.65 (0.46 to 0.85) |
| Cut-point (ml/min) for PPV > 90% | < 78 |
| Cut-point (ml/min) for NPV > 90% | < 38.7 |

Values in brackets represent 95% confidence intervals. APACHE: acute physiology and chronic health evaluation; IDI: integrated discrimination improvement; NRI: net reclassification improvement (continuous/category free); AUC: Area under the receiver operator characteristic curve (ideally = 1); Increase in AUC: difference in AUC between the combined model and the clinical predictors only model; CCl: creatinine clearance; IS: integrated sensitivity (ideally = 1); IP: integrated 1-specificity (ideally = 0); PPV: positive predictive value; NPV: negative predictive value.

of oliguria alone in this group was not sufficient to distinguish patients with CKD from those with AKI (data not shown). Underlying CKD causes the relative increase in pCr to be lower, potentially delaying diagnosis of AKI if a relative change in creatinine is used for diagnosis [24]. An absolute rise in creatinine allows diagnosis to be independent of the underlying function [24]. However, for early diagnosis, injury biomarkers not associated with CKD are needed to identify on-entry AKI from CKD without AKI. Unfortunately, amongst the injury markers we measured in this cohort (with time course of sufficient duration to be increased when pCr was increased) biomarker performance depended on baseline renal function [10] which makes interpretation difficult when the patient has CKD. Only 22% of patients (*n* = 16) with an initial one third decrease in CCl subsequently developed a 50% increase in pCr as predicted by the creatinine kinetic model. Serial measurements were needed to identify patients with only a transient decrease in CCl. Some of the false positives in this group reflected a high initial CCl, suggesting caution when interpreting a decrease in CCl if the initial CCl baseline is high (> 140 ml/min).

The optimum frequency for monitoring loss of GFR remains to be determined, and near real-time measurements of GFR are possible [8]. In this study, CCl was measured on entry to the ICU and then 12 hourly. Since urine output is measured hourly in most ICUs, the frequency of CCl measurements could easily be increased with more frequent plasma and urine

creatinine sampling. CCl would then have the potential to provide earlier information on worsening of AKI severity and to facilitate interpretation of changes in pCr. For example, while a modest increase in pCr suggests progression of severity, for example, from RIFLE stage R to stage I, renal function may remain unchanged. An unchanged CCl would demonstrate that the apparent progression represented a prior, rather than a continuing decrease in GFR. Detection of a true decline in renal function requires demonstration of incremental loss of GFR, which may be detected by serial CCl measurements but not initially by serial pCr measurement. CCl may also be preferable to pCr for other clinical purposes, such as calculation of dose for renal-excretion drugs [25], or for triaging patients in trials in AKI, aiming to intervene after a decrease in GFR but prior to creatinine increase, so-called secondary prevention [26].

Alone, the urine output criterion for diagnosis of AKI was not a reliable alternative to CCl. Consistent with these findings, Prowle *et al.* recently demonstrated that most episodes (94%) of oliguria were not associated with AKI (RIFLE I by the creatinine- change criterion) the next day [27]. As discussed, there are many modifiers of urine output in critically ill patients, including the administration of fluids and diuretics, and impaired ability for urinary concentration in some patients with CKD.

The search for new biomarkers of AKI has aimed to identify injury that leads to significant loss of GFR, as
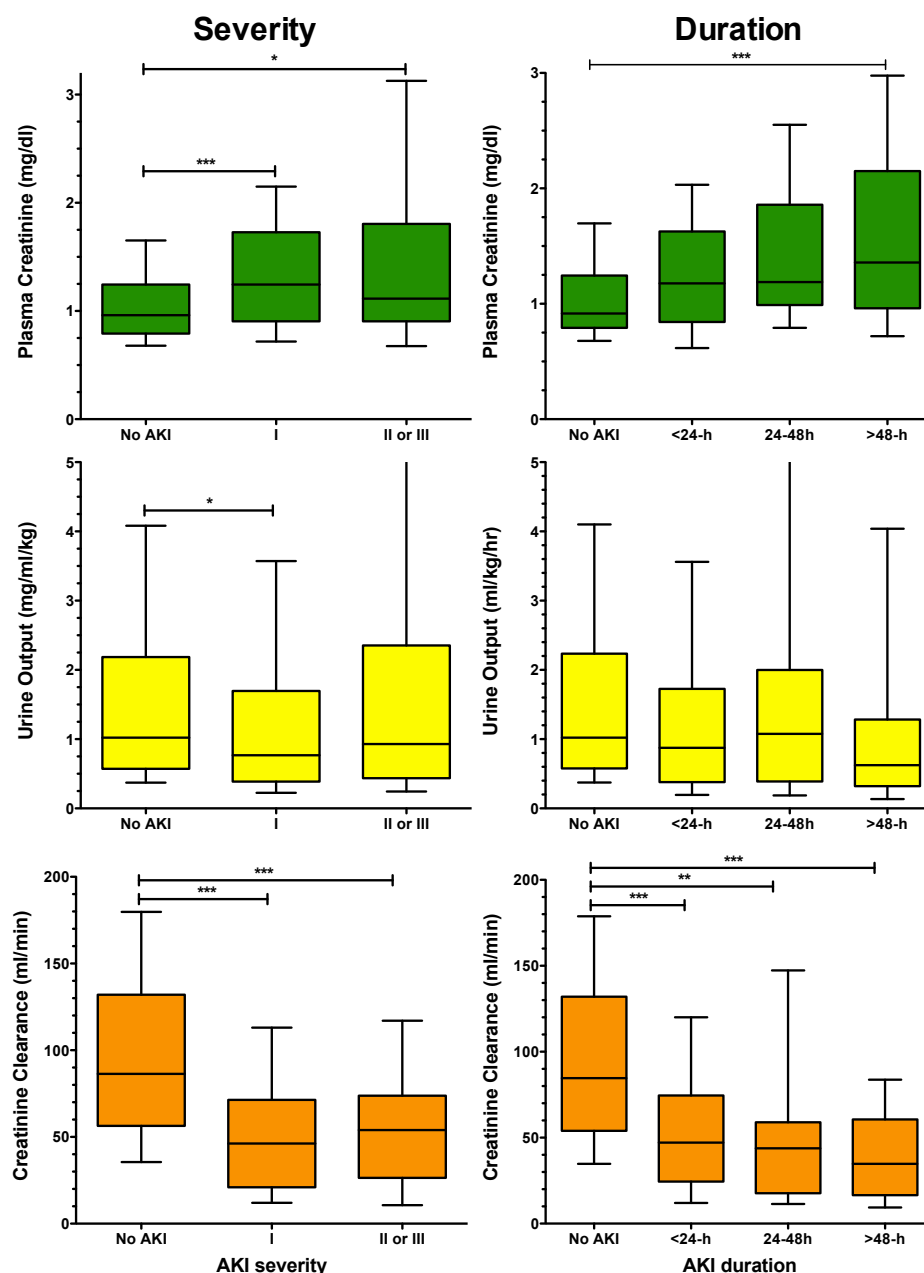
**Figure 4 Comparison of on entry plasma creatinine (pCr), urine output (UO), and creatinine clearance (CCl) in the entire cohort with:** **(i) AKI$_{AKIN}$ severity classes (No AKI, I, II or III) determined from on entry pCr and CCl and UO, (ii) Duration of AKI$_{AKIN}$.** Post-hoc *** $P <$ 0.001, ** $P < 0.01$, * $P < 0.05$.

an alternative to waiting for GFR-induced change in pCr. Nevertheless, most biomarker studies have relied on change in creatinine, the surrogate for change in GFR, on the assumption that pCr changes follow a simple creatinine kinetic model [28]. This was the assumption behind the RIFLE definition of equating a percentage increase in pCr with a percentage decrease in GFR [6,18]. Although the AKIN removed change in GFR from the RIFLE, we have argued that the principal of measuring a change in GFR should be retained as the gold standard in the definition of AKI [29]. While awaiting a commercially available real-time measure of GFR,

we postulate that serial CCl may allow identification of the specific phase of injury in AKI [26]. Brief CCl could also help determine whether a particular injury biomarker was increased before or after a decrease in GFR, which may also facilitate appropriate intervention. In a recent AKI biomarker study, the difference between the estimated baseline and 12-h CCl within 48 h of ICU admission was used to define patients with AKI [30]. This enabled the study to assess the effectiveness of a combination of pCr and urinary gamma-glutamyltranspeptidase in AKI detection. This suggests that change in CCl may be independently useful as a selection criterion for early intervention.

A low CCl (in our study ≤ 48.6 ml/min) on entry to the ICU indicates that individuals are at high risk of AKI. We suggest this should lead to the appropriate management recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) consortium (see Figure 4 in [31]). This comprises: discontinuation of nephrotoxic agents, maintenance of perfusion pressure and volume status, further haemodynamic monitoring, continued monitoring of serum creatinine and urine output, avoidance of hyperglycaemia and contrast procedures, and additional diagnostic workups. In addition, we recommend further CCl monitoring. As a research tool, where available, measurement of biomarkers of kidney injury could assist in establishing the diagnosis of AKI [32,33]. In contrast, if CCl on entry to the ICU is normal in the presence of an increased pCr, patients may be stratified to lower risk. At this stage, we would recommend at least one more 4-h CCl to confirm normal clearance. Clearly, biomarkers of acute kidney injury could be helpful here too, if available. Clearly all patients who appear to have had a short episode of AKI prior to entry to ICU should have nephrology follow up after discharge to check for progression to CKD.

## Limitations

There are limitations in the use of a CCl to estimate GFR. A measured CCl is averaged over the collection period and requires pre- and post or mid-point pCr measurement. If the time interval is brief pCr is unlikely to change substantially. If the interval is too brief, relative errors in measurement of urine output may be increased. We suggest that 2 to 4 h is a reasonable and practical compromise. We recently demonstrated in these same patients that a 4-h clearance could detect the early phase decrease in CCl that characterises the initial phase of patients developing AKI [34]. The costs associated with CCl, are minimal, simply more frequent assays of urine and pCr, with careful attention to recording urine output accurately.

The optimal frequency for CCl measurements is uncertain. In a patient with oliguria, urine collection for less than 1 to 2 h will be relatively inaccurate. Assuming laboratory turnaround was 2 h or less, the maximum frequency of clearance measurements would be 3- to 4-hourly, which may set a reasonable minimum interval over which to review change based on creatinine excretion data. Clearly, given time and cost, these measurements should be undertaken on entry to the ICU to establish a baseline, but only repeated at this frequency in patients at high risk of, or already suspected of having AKI.

Few studies have compared short duration CCl in the ICU with direct measures of GFR. Robert *et al.* compared inulin clearance with 30-minute CCl in 20 consecutive ICU patients [35]. Whilst there was no statistically significant bias, the 95% CI of the difference was large (-88 to 74 ml/min) although halved by the removal of two apparent outliers. Wharton *et al.* compared inulin clearance, [99 mTc-DTPA] and 2-h CCl in 18 acute patients with AKI [36]. Again there was no bias. The 95% CI for the difference was from -33 to +16 ml/min for inulin and -20 to +11 ml/min for [99 mTc-DTPA]. Hilbrands *et al.* measured CCl during simultaneous inulin and EDTA clearance (1.5 h) [37]. CCl overestimated GFR by about 20%, a difference that disappeared following cimetidine administration. Hoste *et al.* compared 1-h CCl in ICU patients with normal pCr with CG and modified diet in renal disease (MDRD) estimations of GFR [11]. The difference between these equations and CCl was large and clinically significant. They concluded that these equations were not acceptable alternatives to measured CCl.

The rapid loss of GFR causes rapid changes in creatinine excretion [38]. Initially excretion falls in proportion to the loss of GFR followed by a gradual increase in excretion in proportion to the gradual increase in pCr concentration (see Figure five in [34]). CCl is therefore influenced initially by the fall in creatinine excretion, and later by any change in plasma concentration. Errors will be introduced by factors which independently alter creatinine excretion. For example, CCl overestimates GFR because of tubular secretion of creatinine, which approximates 10 to 20% at normal GFR but increases with declining GFR [37,39]. While cimetidine inhibition of tubular creatinine secretion improves GFR estimates [37,40], this may interfere with other drug excretion and is probably not useful in the timeframe of AKI. A change in renal blood flow which induces AKI may also directly modify creatinine secretion, but there is little evidence from which to quantify this. CCl is likely to be unreliable when there is polyuria, such as in diabetes insipidus or, when acute brain injury is causing cerebral salt wasting [41].

Finally, as with pCr, change in clearance requires a baseline value for interpretation. This will be absent in

many cases. Estimation equations perform poorly when used to estimate a baseline creatinine [42-44]. Similarly, it will not always be possible to decide if a measured CCl on admission to the ICU reflects baseline renal function or a loss of function. We used the CG formula to estimate baseline clearance. Whilst other formulas are more precise estimates of GFR, it was appropriate to use an estimate of CCl as a baseline for calculation of change in CCl, potentially minimising some of the error introduced by creatinine secretion. Using the MDRD formula made minimal difference (results not shown). Additional clinical information is also required to separate those with CKD from those with AKI on entry to the ICU.

## Conclusions

In a high-risk clinical setting, short duration CCl measurement is useful for patients with a known baseline creatinine for whom a CG estimation of baseline CCl can be made or when pCr is low. In this setting, low CCl suggests an acute loss of renal function and will influence drug dosing, initiate avoidance of known nephrotoxins, and trigger early nephrology consultation. Regular additional CCl would monitor recovery. Further, larger studies are required to determine the optimum frequency and duration of CCl measurement.

When pCr is increased in a patient with normal baseline values, 4-hourly CCl can distinguish resolving and ongoing renal impairment.

CCl may be useful in clinical trials by identifying patients soon after loss of renal function and before pCr is elevated, or by excluding patients when renal function is impaired.

## Key Messages

- Repeated 4-h CCl in the ICU are viable
- Low 4-h CCl in the presence of a normal pCr indicates recent loss of renal function
- Normal 4-h CCl in the presence of an increased pCr indicates renal recovery

## Abbreviations

AKI: acute kidney injury; AKI (eg $pCr_{AKI}$): with AKI; No-AKI (eg $CCl_{No-AKI}$): without AKI; AKIN: Acute Kidney Injury Network; ANOVA: one-way analysis of variance; APACHE: acute physiology and chronic health evaluation; AUC: area under the receiver operator characteristic curve; CCl: creatinine clearance; $\Delta$CCl: relative change in CCl from CG baseline; CG: Cockcroft-Gault; CKD: chronic kidney disease; EARLYARF: Early intervention in Acute Renal Failure trial; GFR: glomerular filtration rate; IDI: integrated discrimination improvement; IQR: interquartile range; KDIGO: Kidney Disease: Improving Global Outcomes; MDRD: modified diet in renal disease; pCr: plasma creatinine; $\Delta$pCr: relative change in pCr from baseline; RIFLE: Risk, Injury, Failure, Loss, End stage; NPV: negative predictive value; NRI: net reclassification improvement; PPV: positive predictive value; RR: relative risk; UO: urine output.

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## Authors' contributions

JP: analysis design, data analysis and manuscript drafting. CF: statistical design and manuscript approval. RW: EARLYARF trial design, data collection, and manuscript approval. GS: data collection, analysis design and manuscript approval. ZH: EARLYARF trial design, Principal Investigator, analysis design and manuscript drafting. All authors have approved the manuscript.

## Competing interests

The authors declare that they have no competing interests.

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