CJASN®
Clinical Journal of the American Society of Nephrology

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Title: Comparison of Cystatin C and Creatinine in the Assessment of Measured Kidney Function during Critical Illness

Manuscript Type: Original Article

Manuscript Category: Acute Kidney Injury and ICU Nephrology

Funders:

Disclosures:

Author Contributions:

Study Group/Organization Name:

Study Group Members' Names:

Clinical Trial Registry Name and Registration Number:

Data Sharing Statement:
All data are included in the manuscript and/or supporting materials.

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Methods: To assess kidney function during prolonged critical illness we enrolled 38 mechanically ventilated patients with expected length of stay of >72h near admission to ICU in a single academic medical center. We assessed sequential kidney function using creatinine, cystatin C, and iohexol clearance measurements. The primary outcome was

difference between eGFR creatinine and eGFR cystatin C at ICU discharge using Bayesian regression modelling. We simultaneously measured muscle mass by ultrasound of rectus femoris to assess the confounding effect on serum creatinine generation.

Results: Longer length of ICU stay was associated with greater difference between eGFR creatinine and eGFR cystatin C at a predicted rate of 2 ml/min/1.73m^2/day (95% confidence interval 1–2). By ICU discharge the posterior mean difference between creatinine and cystatin C eGFR was 33 ml/min/1.73m^2 (95% credible interval 24–42). In 27 patients with iohexol clearance measured close to ICU discharge, eGFR creatinine was on average 2-fold greater than the iohexol gold-standard, posterior mean difference 59 ml/min/1.73m^2 (95% credible interval 49–69). The posterior mean for eGFR cystatin C suggested a 22 ml/min/1.73m^2 (95% credible interval 13–31) overestimation of measured GFR. Each day in ICU resulted in a predicted 2% (95%CI 1-3%) decrease in muscle area. Change in creatinine-to-cystatin C ratio showed good longitudinal, repeated measures correlation with muscle loss, *R*=0.61 (95% confidence interval, 0.50–0.72).

Conclusions: eGFR creatinine systematically over-estimated kidney function after prolonged critical illness. Cystatin C better estimated true kidney function as it appeared unaffected by the muscle loss of prolonged critical illness.

Clinical Journal of the American Society of Nephrology
Doi:10.2215/CJN.0000000000000203

Comparison of Cystatin C and Creatinine in the Assessment of Measured Kidney Function during Critical Illness

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Conclusions: eGFR creatinine systematically over-estimated kidney function after prolonged critical illness. Cystatin C better estimated true kidney function as it appeared unaffected by the muscle loss of prolonged critical illness.

Introduction

An increasing number of critically ill patients require prolonged admission to intensive care (ICU).[1,2] For those surviving to ICU discharge, many experience prolonged hospital stays, complex rehabilitation, and a higher risk of long-term mortality.[3,4] Two organs consistently impacted by prolonged critical illness are the kidneys and skeletal muscle, importantly these are clinically interconnected as, respectively, the sites of generation and clearance of serum creatinine.[5]

There is good epidemiological evidence and pathophysiological rationale linking overt or subclinical episodes of acute kidney injury (AKI) with subsequent persistent decline in kidney function and the development of chronic kidney disease (CKD) with an associated higher risk of long-term morbidity and mortality.[6,7] Similarly, muscle wasting is a prominent feature of prolonged critical illness,[8] and is believed to contribute to poor short and longer-term outcomes.[9,10] These factors suggest that reliance on serum creatinine based estimated glomerular filtration rate (eGFRcreat) to assess recovery of kidney function may be confounded by co-existent pathophysiological reduction in muscle mass and creatinine generation, potentially masking persistent kidney dysfunction after critical illness.

Inaccuracy in the measurement of kidney function during and after prolonged critical illness has several clinical implications. First, reconciliation of chronic medications and new

administration of pharmacological treatments[11] depend on accurate estimations of GFR. Second, poor management of AKI and its recovery, through under-recognition of secondary kidney injury may contribute to worse outcomes during and after critical illness.[12] Third, non-recovery of kidney dysfunction may be missed resulting in missed opportunities for evidence based interventions to limit CKD progression and reduce cardiovascular risk.[6]

More generally, it remains unclear to what extent the trajectory of health after discharge from ICU is determined by the development of underlying comorbidity[13] or the ongoing detrimental contribution of prolonged critical illness. In ICU survivors, cystatin C, a marker of GFR independent of muscle mass, has been shown to strongly associate with post-ICU survival and the later development of overt kidney dysfunction.[14,15] Furthermore, cystatin C in combination with serum creatinine, may enable estimation of muscle mass and thus quantification of muscle wasting.[16]

Accordingly, we used a sample of general critically ill patients to assess in parallel the impact of critical illness on both kidney function and muscle mass. Our aims were twofold. First, to assess the difference between cystatin C based assessment of kidney function and the current best practice using creatinine-based measurements. Second, to assess the degree of muscle loss in patients with prolonged critical illness and the impact of this on creatinine and cystatin C measurements.

Methods

Study population and setting

The study was conducted at The Royal London Hospital, a tertiary academic ICU serving a major trauma center in London, United Kingdom between January 2019 to August 2020 (https://clinicaltrials.gov/ct2/show/NCT03736005). The Joint Research and Management Office at Queen Mary University of London approved and sponsored the study protocol and ethical approval was granted by a national research ethics committee (Wales REC 6, ref: 18/WA/0304). Informed consent was obtained from patients or their decision makers prior to enrolment.

We identified eligible patients by regular screening (Monday-Friday). We enrolled patients ≥18 years admitted to ICU, anticipated to be mechanically ventilated for ≥48 hours and considered likely to survive to ICU discharge by the treating physician. We excluded patients with major traumatic brain injury (abbreviated injury scale head injury score ≥ 5), spinal cord injury with paralysis, lower limb amputation, end stage kidney disease or disseminated cancer and lack of independence with activities of daily living or non-ambulatory status prior to admission. We defined a subset of patients with major trauma, defined as a new injury severity score of ≥15.

Study procedures

Serum creatinine and serum cystatin C were used to calculate estimated glomerular filtration rate (eGFRcreat and eGFRcys) in ml/min/1.73m^2 using the new CKD-EPI formula.[17] Creatinine was measured in mg/dL and analysed with isotope dilution mass spectrometry (IDMS) calibrated methods in The Royal London Hospital laboratory. Cystatin C was

determined with a turbidimetric method (Gentian Cystatin-c UDR-Kit for Beckman-Coulter Synchron and UniCel Systems, Ref A52761, Moss, Norway). We excluded cystatin C and creatinine measurements during or shortly after kidney replacement therapy (KRT). Measurements of eGFR occurred at regular timepoints (days 1, 3, 5, 7, 10, ICU discharge, and at 1 week after ICU discharge). In a subset of patients, measured GFR at ICU discharge was assessed using a single timepoint (4 hour) iohexol clearance method. Iohexol plasma clearance has been endorsed as a gold standard method for the evaluation of GFR in patients with CKD by the National Institute of health and Care Excellence (NICE) CKD guideline (G73 1.1.6). Serum iohexol concentration was determined by ultra-high performance liquid chromatography separation and UV detection in Uppsala, Sweden. The formula for single timepoint iohexol clearance by Jacobsson was used.[18]

Rectus femoris cross-sectional area was measured using B-mode ultrasound on study assessment days as previously described.[8] Further sample processing and muscle measurement details are provided in the supplementary methods.

Clinical risk factors

Demographic data, comorbidities, and admission diagnosis were collected at baseline by investigators. Ethnicity was reported using the NHS standard categorisation as there are potential ethnicity imbalances in the incidence of AKI and CKD in our population.[19] We screened electronic health records for historical creatinine measurements and for any pre-recorded CKD diagnoses. Severity of Organ Failure Assessment (SOFA) score and AKI stages, using the KDIGO 2012 criteria, were calculated daily for the first 7 days of the study. We assessed patients for acute kidney disease at ICU discharge (defined as the presence of AKI

stage, or increase in serum creatinine by >50% or an acute eGFRcreat < 60ml/min/1.73m^2).[20] Kidney replacement therapy was delivered as a continuous KRT for all patients. All patients are fed enterally as soon as possible, unless contraindicated. This follows the European Society for Clinical Nutrition and Metabolism guidelines in terms of calories delivered, feed constitution, and the use of pro-kinetic drugs.

Statistical Analysis

Data processing, analyses and plotting were made in R version 3.6.1 with packages used detailed in the supplement. Data were expressed as mean (SD), median (interquartile range [IQR]), and absolute and relative frequencies, as indicated. The cohort were divided into 2 groups based on being a trauma or non-trauma admission to ICU. Clinical characteristics, changes in eGFR and muscle mass trajectory are reported for the whole cohort and compared between groups. We originally planned to enroll 62 mechanically ventilated patients (see online supplement for sample size considerations), however, planned recruitment curtailed due to the COVID-19 pandemic.

The primary outcome was difference between eGFRcreat and eGFRcys at ICU discharge compared using Bayesian regression modelling. The results include the posterior distribution of the difference between eGFRcreat and eGFRcys, given data, and the priors, from which we calculated the posterior mean difference and a 95% credible interval (95% probability that the value of the unknown parameter falls in this credible interval). We adopted a Bayesian approach as the calculated estimates would be less affected by the relatively small sample size and allow clearer interpretation of results.[21]

We used the *brms*[22] package in R to define a regression model with a normality parameter to include the *t* distribution to reduce the impact of outliers [23] and chose sceptical priors, representing the prior belief that results of eGFR equations for creatinine and cystatin c would not normally be expected to markedly differ.

There was no missing data for assessment of the primary outcome. To further investigate difference in eGFRcreat and eGFRcys over multiple timepoints and explore determinants of difference we used linear mixed effects models. This analysis is intended to compare relative magnitude over time between both filtration markers, recognising that estimated GFR equations will not directly reflect true underlying GFR in the absence of steady state of kidney function which may be present during the acute phase of critical illness and its recovery.[24] Linear mixed effect models incorporate repeated longitudinal measurements from all patients and allow for patient-specific random effects and can robustly handle missing data.[25] We used restricted cubic splines with 3 knots to capture any non-linearity from a relatively small sample size.[26]

As a secondary outcome we assessed correlation between creatinine-to-cystatin C ratio and muscle loss as measured by rectus cross sectional area. We analysed within patient correlation between creatinine-to-cystatin C ratio using multiple regression as outlined by Bland and Altman[27] using the *rmcorr* package in R.

Results

A total of 38 patients, comprising 22 (58%) trauma and 16 (42%) non-trauma admissions were enrolled (Supplemental Figure 1). Three patients died and did not complete the primary outcome but were included in longitudinal modelling. Paired, serum creatinine and cystatin C measurements were recorded on 181 patient days. Rectus femoris measurements were recorded on a total of 169 patient days. Demographic and clinical characteristics of the study are shown in Table 1. All patients were mechanically ventilated at enrolment with a median ICU admission SOFA of 4.5 [IQR 3.0 - 6.8], and median length of ICU stay of 16.5 days [10.3 - 27.3]. 35/38 were discharged to the ward.

Time course of changes in estimation of kidney function

At admission median eGFRcreat and eGFRcys were comparable, respectively 79 [IQR 51 - 102] and 78 [36-117] ml/min/1.73m^2, however over time course of the study there was an increasing separation between eGFRcreat and eGFRcys (Figure 1A and Supplemental Table 1). Modelling using restricted cubic splines demonstrated a non-linear relationship with an increase in eGFR difference over the first 30 days from ICU admission, plateauing thereafter (Figure 1B). Each day in ICU in the first 30 days resulted in a predicted 2 ml/min/1.73m^2 (95% CI 1–2) increase in difference in eGFR between creatinine and cystatin C based measurements.

Eighteen patients had a diagnosis of AKI. Of these 15 survived to ICU discharge. Two of these patients had acute kidney disease using discharge creatinine values. However, when using eGFRcys, 10 patients had a potential diagnosis of acute kidney disease (eGFRcys < 60ml/min/1.73m^2). These data suggest 8 of the 10 patients with potential acute kidney

disease based on creatinine criteria (80%) were potentially misclassified as having recovered AKI by ICU discharge.

Only 3 patients had a reported or recorded diagnosis of CKD pre-admission. However, 10 patients (2 trauma) had evidence of acute or chronic kidney impairment at hospital admission with first eGFRcreat of <60 ml/min/1.73m^2. By ICU discharge median eGFRcreat (105 ml/min/1.73m^2 [IQR 97–122]) was markedly higher than eGFRcys (70 [37–99]), (Figure 2, Supplemental Figure 2). Iohexol measured GFR was performed at ICU discharge in 27/38 patients, with median value of 58 ml/min/1.73m^2 [IQR 39–70]. At ICU discharge three (9%) patients had an eGFRcreat of <60 ml/min/1.73m^2 compared to 16 (46%) with an eGFRcys <60 ml/min/1.73m^2.

In Bayesian models, at ICU admission the posterior mean for difference between eGFRcreat and eGFRcys was -2 ml/min/1.73m^2 (95% credible interval [CrI] -11–7), (Supplemental Figure 3A). However, by ICU discharge the posterior mean for difference between eGFRcreat and eGFRcys was 33 ml/min/1.73m2 (95% CrI 24–42), (Supplemental Figure 3B). The posterior mean for eGFRcys suggested a 22 ml/min/1.73m^2 (95% CrI 13–31) overestimation of measured GFR. Similarly, the posterior mean for eGFRcreat suggested a 59 ml/min/1.73m^2, (95% CrI 49–69) overestimation of measured GFR. There was a better agreement between eGFRcys and measured GFR than between eGFRcreat and measured GFR suggesting less systemic bias in eGFRcys values (Supplemental Figure 4).

Of the 9 patients who received KRT, 2 died and the remaining 7 were not dependent on KRT at ICU discharge. Nine paired cystatin C and creatinine measurements were excluded in the

cohort on KRT due to ongoing continuous KRT at a study timepoint. For this KRT cohort, difference between eGFRcreat and eGFRcys at ICU discharge showed a similar trend to the whole cohort (posterior mean for difference 51 ml/min/1.73m^2, 95% CrI 26–76).

Time course of changes in muscle mass and association with creatinine and creatinine-to-cystatin C ratio

Rectus femoris cross sectional area decreased over time, Figure 3A and B. Significant rhabdomyolysis was rare, only 3 patients had a creatine kinase measurement of over 10000 U/L (median 171 U/L, total of 473 measurements). Linear mixed effects modelling suggested each day in ICU resulted in a predicted 2% (95% CI 1–3%) daily decrease in rectus femoris cross sectional area (Supplemental Table 2). Decrease of rectus femoris cross sectional area showed a similar trend for trauma and non-trauma patients (Supplemental Figure 6). Repeated measures correlation between rectus femoris cross sectional area and change in serum creatinine over time was 0.22 (0.06 – 0.50), (Supplemental Figure 5A). There was a stronger correlation between change in creatinine-to-cystatin C ratio and change in rectus femoris cross sectional area, repeated measures correlation of 0.61 (95% CI, 0.50–0.72), (Supplemental Figure 5B).

Discussion

In this study we found that in patients surviving to ICU discharge, serum creatinine and eGFRcreat overestimated underlying kidney function by a large margin of clinical significance including missed diagnosis of a large proportion of patients with persistent kidney dysfunction. Our findings suggest creatinine-based assessment of kidney function is inadequate to guide clinical management and stratify follow-up of patients after critical

illness. By contrast, cystatin C based estimations provided a more accurate reflection of kidney function and identified more cases of persistent kidney dysfunction. Additionally, we found that the ratio of creatinine to cystatin C may be a useful surrogate of muscle mass changes during critical illness.

The limitations of serum creatinine to estimate kidney function during critical illness have consistently been demonstrated.[20,28-30] The bias and imprecision associated with eGFRcreat appears most evident in patients with prolonged ICU stays.[31] Acute muscle wasting has been proposed as a potential cause of the inaccuracies associated with eGFRcreat.[32] The findings in our study of consistent longitudinal reductions in muscle mass, support reduced muscle generation of serum creatinine as the dominant mechanism for inaccuracies in eGFRcreat at ICU discharge. In addition reduced creatinine generation due to altered de novo hepatic synthesis of creatinine precursors (creatine and phosphocreatine),[5] or the transient dilutional effects of intravenous fluid[33,34] are likely, if at all, to have a greater impact during the acute phase of critical illness rather than at the end of an ICU admission.

In previous studies of a combined total of 190 patients with near normal kidney function (eGFR 80 to 96 ml/min/1.73m^2) and minimal exposure to AKI, eGFRcys consistently outperformed eGFRcreat in relation to measured GFR.[31,35-37] Importantly, we confirmed these findings in critically ill patients with variable exposure to AKI with a median measured GFR of less than 60 ml/min/1.73m^2 representing a cohort at greater risk of persistent decline in kidney function and subsequent CKD.

There are limitations to eGFRcys in recovering critically ill patients. In our study eGFRcys overestimated measured GFR. Factors behind inaccuracies in eGFRcys such as diabetes, body size, and inflammation have been previously identified.[38] In particular over-estimation of GFR by cystatin C might be associated with loss of adipose tissue mass during critical illness, a significant determinant of cystatin C production.[39] In addition, eGFR equations were designed and tested in outpatients settings with kidney function in steady state. However these limitations of cystatin C are small compared to the consistent and dramatic overestimations of kidney function provided by creatinine during and after critical illness. For example, when measured by eGFRcreat patients who survive prolonged critical illness appear to have better kidney function by ICU discharge than at premorbid baseline, a biologically implausible finding.[28] In addition, inaccuracies in eGFRcys that are associated with the acute phase of illness, such as inflammation, should become less prominent as patients are discharged from ICU and hospital. Similarly, during recovery from critical illness the majority of weight gained is acquisition of fat rather than muscle.[40] Thus, the interpretation of eGFRcreat would be expected to remain confounded due to persistent reduction of muscle mass in patients during the weeks and months after critical illness, persistently precluding clinical assessment of kidney function.

The combination of cystatin C and serum creatinine to assess muscle mass has been investigated in ICU cohorts and has been associated with malnutrition[41] and adverse ICU outcomes.[16] Previous research has examined a ratio of creatinine to cystatin C or "sarcopaenic index" but has been limited to single timepoint assessments of muscle mass in the context of stable kidney function to stratify patients risk near admission to ICU. Evidence from our study suggests longitudinal measurements of muscle mass strongly correlate with

creatinine-cystatin C ratio. Importantly, due to the limited pre-existing comorbidities and defined beginning of critical illness episode in the trauma cohort, our data suggests changes in muscle mass due to the impact of critical illness led to measurable changes in creatinine-to-cystatin C ratio. Strategies to address changes in muscle mass attributable to critical illness could benefit from a simple, cheap surrogate marker of muscle loss and with further validation creatinine-to-cystatin C ratio could fulfil this role.

The consensus report of the Acute Disease Quality Initiative (ADQI) initiative on kidney recovery recommends against creatinine-based formula estimates of GFR and highlights a need for better biomarkers to diagnose and risk stratify patients recovering from AKI.[14] Despite this current national treatment guidelines recommend basing follow-up of kidney function on hospital discharge eGFRcreat.[42] Our data suggest this approach is misinformed and will miss opportunities detect and treat many patients with or at risk of CKD. Poor longer-term outcomes of ICU survivors are consistently linked to cardiovascular mortality, as demonstrated in observational studies after sepsis.[43,44] Decreases in GFR are associated with a higher risk of cardiovascular events in patients with CKD[45] and eGFRcys better associates with clinical outcomes in both the general population and ICU cohorts.[15] The diagnosis and progression of CKD is likely underestimated in survivors of critical illness. Early detection and treatment of modifiable risk factors in ICU survivors is potential target to reduce the excess morbidity and mortality. Furthermore, substantial reductions in GFR were seen in subgroup of major trauma admissions with little prior comorbidity, suggesting considerable potential to intervene to alter healthcare trajectory. In addition, during ICU admission, drug dosing based on creatinine based equations could potentially be harmful and may be improved by incorporation of cystatin C.[46]

Cystatin C is widely available and is recommended by the National Institute for Health and Clinical Excellence to confirm CKD.[47] However, it remains to be utilised in clinical practice potentially due to cost (US$3.4) per test compared with creatinine at US$0.35)[48] and clinical uncertainty as to the optimal cohorts to benefit.[49] Considering the severe limitations of eGFRcreat in critically ill patients and risk of progressive or new CKD, wider use of cystatin C could be beneficial. However, the implementation of cystatin C in clinical practice requires further research and these data should highlight to clinicians its potential role in a cohort of patients with a specific phenotype.

Strengths of this study include prospective design and testing of a pre-specified hypothesis. We have demonstrated that cystatin C is closer to gold standard measured GFR and that changes in muscle mass can account for the developing discrepancy in estimation of GFR. In the acute setting we are novel in assessing measured GFR and muscle mass changes simultaneously. However, there are several limitations. First, the estimate of the population difference between eGFRcys and eGFRcreat in patients with prolonged critical care admissions cannot be certain from these data due to risk of confounding in a sample of patients from a single center. The COVID-19 pandemic curtailed recruitment and the initial sample size was not achieved. In addition, 7 (18%) were discharged from ICU before day 10 and 3 died before evaluation further restricting our cohort. However, using a Bayesian approach with a weakly informative prior, models provide substantial evidence to support a clinically significant difference exists between eGFRcys and eGFRcreat at ICU discharge. This is supported by longitudinal modelling that robustly incorporated patient specific trajectories, varying baseline differences, and repeated measurements of eGFR.[25] Second, we were unable to determine the reasons behind the overestimation of measured eGFR by

cystatin C. Third, measured GFR was only available for a subgroup of patients (discharged from ICU between 0800 and 1700 on week days) and used a single timepoint method that may have reduced precision compared to multiple timepoint approaches. However, any systemic bias in single timepoint iohexol methods would be expected in patients with low GFR (<30 ml/min/1.73m^2),[50] likely in only a small proportion of patients in this study. Fourth, ultrasonographers were not blinded to creatinine measurements during the ICU admission. However, the reported muscle loss is similar in magnitude to other studies. [8]

Finally, we cannot make conclusions regarding the impact of eGFRcreat inaccuracies on clinical outcomes. By providing a more reliable measurement of eGFR and estimate of muscle mass, cystatin C adds additional insights to one part of the phenotype of patients discharged from ICU.

We have provided further evidence that cystatin C can detect clinically important changes in kidney function and muscle mass in survivors of prolonged critical illness while conversely the standard test, creatinine, is not fit for purpose in this context. Use of cystatin C could enhance the clinical management of such patients throughout the recovery phases and warrants investigation in studies aimed at optimising interventions for the prevention and mitigation of CKD in this vulnerable patient population.

Acknowledgments

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

We thank the patients and their families for their individual contributions during difficult times. We thank the Critical Care and Perioperative Medicine Research Group (CCPMG) staff including Maria Fernandez, Tim Jones Mari-Liis Pakats, Tim Martin, Filipa Alexandra Pereira dos Santos, Tasnin Shahid, and Tim Stephens. We also thank the Royal London ICNARC audit office and Royal London critical care consultants.

Supplemental Material

Supplemental Figure 4. Bland Altman plots for estimated glomerular filtration rate based on CKD-EPI creatinine (A) and CKD-EPI cystatin C (B) versus measured iohexol glomerular filtration rate.

Supplemental Figure 5. Rectus femoris cross sectional area measurements correlated with serum creatinine (A) and creatinine-cystatin C ratio (B).

Supplemental Figure 6. Rectus femoris cross sectional area decreased over time in ICU trauma patients.

Table 1. Clinical characteristics of study cohort and patient subgroups according to non-trauma and trauma admissions.

	Overall study population (n=38)	Non-trauma (n=16)	Trauma (n=22)
Age, yr	51 [38, 63]	52 [48, 64]	48 [29, 61]
Sex, % male	25 (66)	7 (44)	18 (82)
Body mass index, admission, kg/m^2	26.2 [23.5, 28.2]	27.0 [23.5, 29.2]	25.9 [23.8, 27.1]
Charlson comorbidity index	1.0 [0.3, 1.0]	1.0 [1.0, 2.0]	1.0 [0.0, 1.0]
Ethnicity (%)			
Black	3 (8)	2 (13)	1 (5)
South Asian	8 (21)	3 (19)	5 (23)
White	27 (71)	11 (68)	16 (73)
Primary diagnosis (%)			
Cardiovascular	1 (3)	1 (6)	
Gastrointestinal	3 (8)	3 (19)	
Liver	1 (3)	1 (6)	
Neurological	5 (13)	5 (31)	
Respiratory	3 (8)	3 (19)	
Sepsis	3 (8)	3 (19)	
Chronic kidney disease stage 3 (%)*	10 (26)	7 (44)	3 (14)
Admission eGFR, ml/min/1.73^2	79 [51, 102]	61 [47, 93]	89.0 [63, 111]
APACHE 2, admission	12.5 [9.0, 18.8]	17.0 [12.8, 22.0]	9.5 [8.0, 15.5]
SOFA, admission	4.5 [3.0, 6.8]	4.5 [3.0, 7.3]	4.5 [4.0, 6.0]
AKI stage, maximum†			
0	20 (53)	7 (44)	13 (59)
1	7 (18)	2 (13)	5 (23)
2	1 (3)	0 (0.0)	1 (5)
3	10 (26)	7 (44)	3 (14)
Kidney replacement therapy	9 (24)	6 (38)	3 (14)
Invasive mechanical ventilation days	9.0 [6.0, 14.0]	8.0 [2.8, 14.3]	9.0 [7.3, 13.8]
Tracheostomy	11 (29)	4 (25)	7 (32)
Advanced cardiovascular days§	2.0 [0.0, 3.0]	0.0 [0.0, 2.0]	2.0 [0.3, 4.8]
Basic cardiovascular days§	11.5 [6.0, 13.8]	11.0 [6.0, 14.5]	12.0 [7.8, 13.0]
Pre-ICU length of stay, days	0.0 [0.0, 0.0]	0.0 [0.0, 1.3]	0.0 [0.0, 0.0]
ICU length of stay, days	16.5 [10.3, 27.3]	14.9 [7.2, 28.6]	17.7 [15.4, 23.6]
Hospital length of stay	44.0 [20.5, 68.3]	24.5 [16.5, 93.8]	50.5 [31.0, 61.5]
Hospital discharge location^			
Died	5 (13)	2 (13)	3 (14)

Home	20 (53)	10 (63)	10 (46)
Nursing home	2 (5)	0 (0)	2 (9)
Rehabilitation facility	11 (29)	4 (25)	7 (32)
3-month post-discharge location			
Home	21 (64)	10 (71)	11 (58)
Nursing home	3 (9)	1 (7)	2 (11)
Rehabilitation facility	9 (27)	3 (21)	6 (31)

*Chronic kidney disease defined by baseline creatinine as first documented in hospital.
†Acute kidney injury stage as per Kidney Disease Improving Global Outcomes criteria.
§ Based on the Intensive Care National Audit & Research Centre definitions: Advanced cardiovascular; multiple IV/rhythm controlling drugs (at least one vasoactive), continuous observation of cardiac output, intra-aortic balloon pump, temporary cardiac pacemaker; Basic cardiovascular: central venous catheter, arterial line, single IV vasoactive/rhythm controlling drug.
^Hospital discharge location 3 months after hospital discharge.
The Acute Physiology and Chronic Health Evaluation II (APACHE 2) score ranges from 0-71. The Sequential Organ Failure Assessment (SOFA) score ranges from 0-24. ICU=intensive care unit. AKI=acute kidney injury.

Figure 1. Difference in estimated glomerular filtration measurements (serum creatinine - cystatin C) by study timepoint (A). Includes a loess smoother with 95% confidence intervals. A marginal-effects plot of predicted modelled difference in estimated glomerular filtration rate by days (B) fitted with restricted cubic spline. Bands represent 95% confidence interval. Actual data points are overlayed on the modelled trend line. Median length of ICU stay was 16.5 days [IQR 10.3 - 27.3].

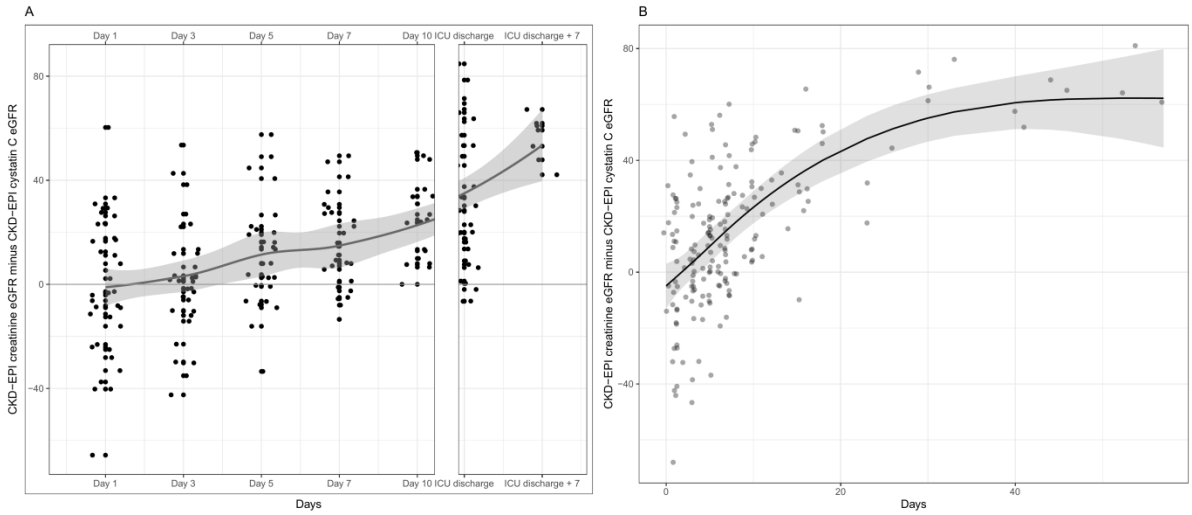


Figure 2. ICU discharge eGFR comparisons, including iohexol measured glomerular filtration rate in (n = 27).

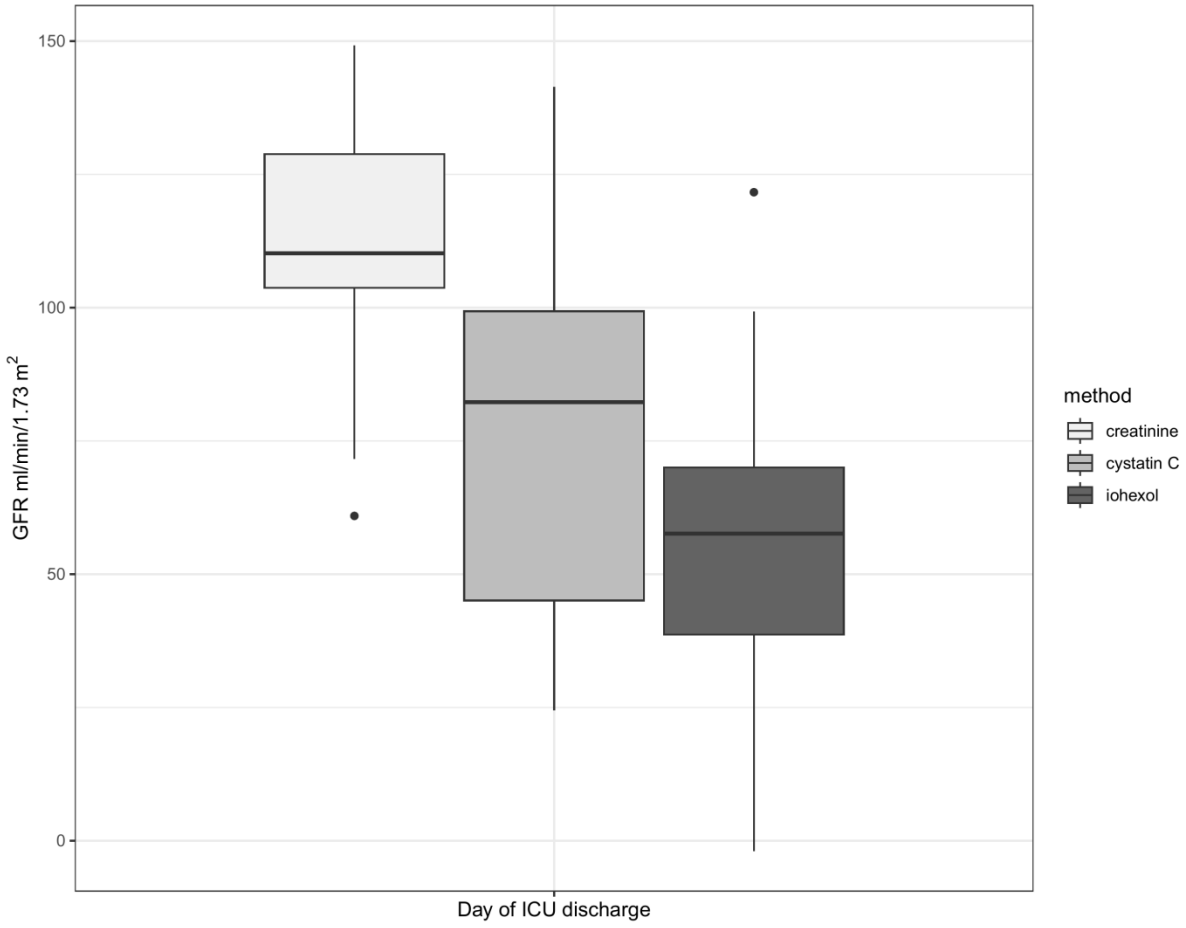
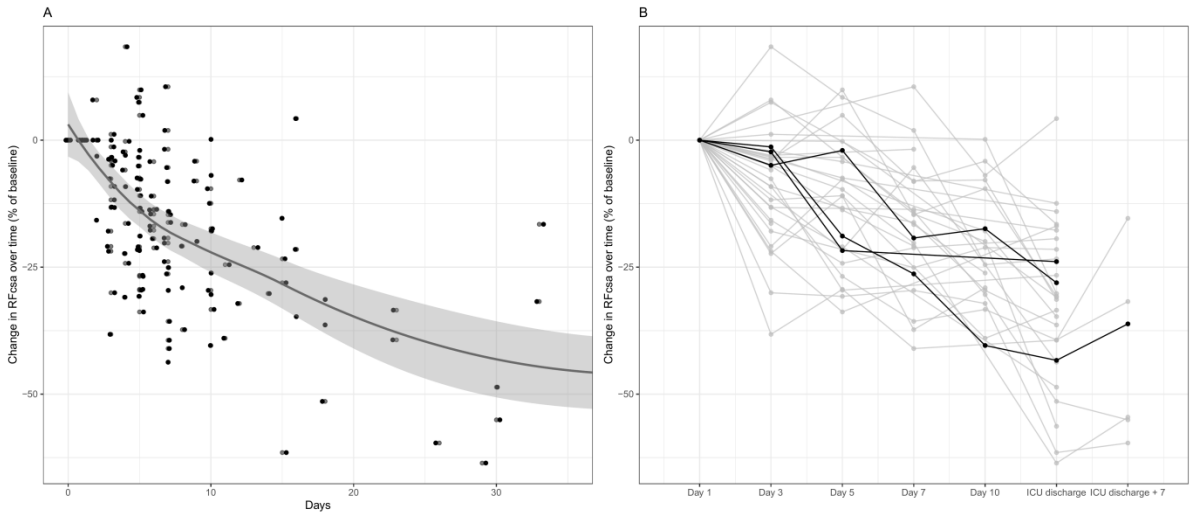


Figure 3. Rectus femoris cross sectional area decreased over time in ICU patients. Trend line and confidence intervals using loess smoother in A. There was variation in baseline (day 1) rectus femoris cross sectional area and trajectory of loss over time. Three example patient trajectories highlighted in B.



CJASN-2022-001141R3 supplemental material ----
http://links.lww.com/CJN/B776

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