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Cystatin C and Kidney Function Recovery in Patients Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury

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Abstract:	Background Plasma cystatin C is a reliable marker to estimate kidney function; however, it is unknown whether this remains true in patients receiving continuous kidney replacement therapy (CKRT). Herein, we tested the hypothesis that lower concentrations of plasma cystatin C during the first three days of CKRT would predict kidney function recovery. Methods We performed a retrospective observational study of 72 patients from a 126-patient, single-center CKRT study. We studied two a priori defined cohorts of patients without advanced CKD who had acute kidney injury requiring CKRT (AKI-CKRT): 1) with early kidney function recovery defined as liberation from KRT within seven days of CKRT initiation versus 2) with delayed kidney function recovery defined as receipt of KRT for >21 days or death while on KRT. Subsequent analysis included patients with advanced CKD and intermediate kidney function recovery (liberation between 8 and 21 days). Cystatin C was then measured on stored plasma, urine, and dialysis effluent collected prior to CKRT initiation and on days 1, 2, and 3 of CKRT. Results Plasma cystatin C was significantly lower in patients with early kidney function recovery in comparison to patients with delayed kidney function recovery on days 1 (1.79 vs. 2.39mg/L), 2 (1.91 vs. 2.38mg/L) and 3 (2.04 vs. 2.67mg/L) of CKRT. Sieving coefficient and CKRT clearance of cystatin C were similar for patients with early and delayed kidney function recovery. The lowest plasma cystatin C concentration on days 1-3 of CKRT predicted early kidney function recovery with an area under the receiver operating curve of 0.77 (P = 0.002), positive likelihood ratio of 5.60 for plasma cystatin C <1.30mg/L, and negative likelihood ratio of 0.17 for plasma cystatin C ≥1.88mg/L. Conclusion Lower plasma cystatin C concentrations during the first three days of CKRT are associated with early kidney function recovery.
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Cystatin C and Kidney Function Recovery in Patients Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury

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ABSTRACT

Background

Plasma cystatin C is a reliable marker to estimate kidney function; however, it is unknown whether this remains true in patients receiving continuous kidney replacement therapy (CKRT). Herein, we tested the hypothesis that lower concentrations of plasma cystatin C during the first three days of CKRT would predict kidney function recovery.

Methods

We performed a retrospective observational study of 72 patients from a 126-patient, single-center CKRT study. We studied two a priori defined cohorts of patients without advanced CKD who had acute kidney injury requiring CKRT (AKI-CKRT): 1) with early kidney function recovery defined as liberation from KRT within seven days of CKRT initiation versus 2) with delayed kidney function recovery defined as receipt of KRT for >21 days or death while on KRT. Subsequent analysis included patients with advanced CKD and intermediate kidney function recovery (liberation between 8 and 21 days). Cystatin C was then measured on stored plasma, urine, and dialysis effluent collected prior to CKRT initiation and on days 1, 2, and 3 of CKRT.

Results

Plasma cystatin C was significantly lower in patients with early kidney function recovery in comparison to patients with delayed kidney function recovery on days 1 (1.79 vs. 2.39mg/L), 2 (1.91 vs. 2.38mg/L) and 3 (2.04 vs. 2.67mg/L) of CKRT. Sieving coefficient and CKRT clearance of cystatin C were similar for patients with early and delayed kidney function recovery. The lowest plasma cystatin C concentration on days 1-3 of CKRT predicted early kidney function recovery with an area under the receiver operating curve of 0.77 (P = 0.002), positive likelihood ratio of 5.60 for plasma cystatin C <1.30mg/L, and negative likelihood ratio of 0.17 for plasma cystatin C ≥1.88mg/L.

Conclusion

Lower plasma cystatin C concentrations during the first three days of CKRT are associated with early kidney function recovery.

Supplemental Digital Content: http://links.lww.com/CJN/C5

INTRODUCTION

Acute kidney injury (AKI) is an abrupt decrease in kidney function defined by an increase in serum creatinine (increase of 0.3mg/dL or 150% above baseline) and/or a decrease in urine output (less than 0.5ml/kg/hour for six hours) [1]. AKI is common, affecting approximately 20% of hospitalized patients, and confers increased morbidity and mortality [2]. Approximately 10% of patients with AKI will lose substantial enough kidney function to require kidney replacement therapy (KRT), which portends an especially poor prognosis [2-4]. It would be advantageous for both patients and providers to have techniques to assess the prognosis of patients with AKI-KRT; however, few tools are clinically available.

Two strategies have been employed to predict outcomes of AKI-KRT. Most tools utilize clinical variables and biomarkers to predict mortality or KRT liberation, while few have aimed to estimate glomerular filtration rate (GFR) during KRT [5-10]. Receipt of KRT during AKI complicates GFR estimation and identification of kidney function recovery since typical filtration markers like creatinine and blood urea nitrogen (BUN) (molecular weight (MW) <200Da) are removed by KRT. Larger molecules, including cystatin C and β-2 microglobulin (MW 13,300 and 11,600Da respectively), are thought to be less readily cleared by KRT and may thus reliably estimate kidney function in patients receiving KRT particularly in patients receiving intermittent hemodialysis for end-stage kidney disease (ESKD) [11, 12]. A recent study also suggests a role for cystatin C in patients with AKI requiring continuous KRT (AKI-CKRT), showing that a lower plasma cystatin C concentration measured at the time of CKRT discontinuation predicted successful KRT liberation defined as no additional KRT performed within the next 14 days [13]. However, whether cystatin C is significantly removed by CKRT and whether plasma cystatin C is a reliable tool to estimate GFR *during* CKRT remains unclear [14, 15]. To date, there are only four reports that have addressed whether cystatin C is cleared by CKRT or if cystatin C is a useful marker of kidney function during CKRT [15-18]. These reports generated controversy on whether cystatin C could or could not be reliably used during CKRT to identify kidney function recovery – two reaching the conclusion that

cystatin C cannot be used reliably during CKRT because it may be removed by CKRT [14, 17] and two suggesting that since removal was limited, that cystatin C would be useful to identify kidney function recovery [15, 16].

Given this controversy, we sought to quantify the clearance of cystatin C during CKRT and test the hypothesis that plasma cystatin C concentrations during the first three days of CKRT would predict early kidney function recovery in AKI-CKRT as defined by liberation from CKRT within seven days.

METHODS

Study Design and Population

Two cohorts of patients, all of which received continuous venovenous hemodialysis using a polyethersulfone membrane, were selected a priori from a parent study (described in supplemental methods) for the analysis herein: 1) patients with AKI and early kidney function recovery defined as liberation from KRT within seven days of CKRT initiation, and 2) patients with AKI and delayed kidney function recovery defined as requiring KRT for >21 days or death while on KRT. Seven days was selected as the timepoint for early kidney function as plasma cystatin C is likely to only reflect kidney function during the immediate timeframe following its measurement, and as described below, cystatin C was measured on the first three days of CKRT. Twenty-one days was selected as the timepoint for delayed kidney function recovery to ensure that the comparator group did not have a possibility of kidney function recovery on a similar timeframe as the patients with early kidney function recovery. Timing of KRT liberation and death for all patients can be found in **Supplemental Table 1.** AKI was defined as an increase in serum creatinine of 0.3mg/dL or 150% above baseline. Baseline creatinine was obtained from the electronic health record and defined as the median of the lowest of three or more of the most recent consecutive stable outpatient creatinine concentrations within one year prior to initiation of CKRT. If outpatient values were not available, then the median of the lowest of three or more

consecutive stable creatinine concentrations during the index hospitalization was used. CKRT discontinuation was based on the clinical discretion of the providers caring for the patient. While liberation was not standardized, early kidney function recovery required that patients were successfully liberated from KRT and did not need additional KRT within the next 30 days.

Patients were excluded if they had stage 3 or greater CKD or received KRT within one week of CKRT initiation, as these factors may affect plasma cystatin C concentrations. Stage 3 CKD was defined based on an estimated GFR (eGFR) of less than 60ml/min/1.73m^2 in men and in women <65 years and an eGFR less than 45 ml/min/1.73m^2 in women ≥ 65 years. The different eGFR cut off for women >65 years old was used due to known age and sex-related differences in eGFR [19, 20]. eGFR was calculated using the non-race corrected 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula using baseline creatinine [21]. Patients that died within 24 hours of CKRT initiation were also excluded, given accurate plasma cystatin C clearance via CKRT could not be measured/calculated.

Baseline demographic data and CKRT data (time on CKRT, hourly effluent volume, and average CKRT dose per interval) were obtained from the electronic health record. Total effluent volume was determined by summing the hourly recorded therapy fluid volume and ultrafiltrate volumes during each time interval.

To determine if advanced CKD affected the use of cystatin C to predict early kidney function recovery and whether cystatin C may predict early kidney function recovery versus not-early kidney function recovery (liberation from KRT after seven days of CKRT initiation, progression to ESKD, or death while on KRT), we performed several post-hoc analyses that included patients with advanced CKD (GFR <45ml/min/1.73m^2) and patients with intermediate kidney function recovery (liberation from KRT between eight and 21 days of CKRT initiation). Timing of KRT liberation and death for these additional patients can be found in **Supplemental Table 2.**

Plasma, Urine, and Effluent Collection and Cystatin C, IL-6, BUN and creatinine measurements.

Please see Supplemental Methods.

Clearance and Sieving Coefficient Calculations

The sieving coefficient (SC) and CKRT clearance of cystatin C were calculated using the following equations as previously described [22]:

$$Marker\ SC = \frac{Effluent\ Marker\ Concentration}{Plasma\ Marker\ Concentration}$$

$$Marker\ Clearance = Total\ Effluent\ Volume\ \times Marker\ SC$$

The mass amount of cystatin C removed by CKRT during each time interval was also calculated using the following equation:

$$Mass\ Amount\ of\ Marker\ Removed\ by\ CKRT = Total\ Effluent\ Volume\ \times Effluent\ Marker\ Concentration$$

Statistical Analyses

All statistics were performed using GraphPad Prism. Patient characteristics/demographics are displayed as counts and percentages or means +/- standard error of the mean as appropriate. Chi-square analysis was used to compare patient characteristics/demographics that are displayed as counts and percentages. Student's unpaired t-test was used to compare patient characteristics/demographics that are displayed as means. Student's unpaired t-test was used to compare plasma, effluent, and urine cystatin C, BUN, and creatinine concentrations, sieving coefficients, all CKRT parameters, and urine output. A receiver operating curve (ROC) analysis was performed, and sensitivities and specificities were obtained from this curve to determine the test characteristics of the minimum (lowest) plasma cystatin C concentration from days 1-3 of CKRT and the maximum average hourly urine output from days 1-3 of

CKRT. The lowest plasma cystatin C concentration and the maximum average hourly urine output were used for this analysis as these values would be most likely to reflect kidney function recovery. A linear regression analysis was also performed to determine the slope of plasma cystatin C concentration change over the study period for each subject.

RESULTS

Study Design and Baseline Patient Characteristics

The baseline clinical characteristics of the patients are shown in **Table 1**. There were no statistical differences of any recorded characteristics, including baseline estimated GFR, severity of illness, risk factor for AKI, or prevalence of common comorbidities observed between the two groups. No patients in the study had vasculitis or glomerulonephritis. Thyroid dysfunction and corticosteroid administration can both affect cystatin C [23-26]; however, there was no difference in plasma TSH concentration, history of hypothyroidism, levothyroxine receipt, corticosteroid receipt or administered corticosteroid dose (during and 5 days prior to the study period) between the two groups.

Plasma Cystatin C is Decreased in Patients with AKI-CKRT with Early Kidney Function Recovery

Plasma cystatin C concentration was significantly decreased on day 1 (1.79 vs. 2.39mg/L), day 2 (1.91 vs. 2.38mg/L), and day 3 (2.04 vs. 2.67mg/L) of CKRT in patients with early kidney function recovery in comparison to patients with delayed kidney function recovery (**Figure 1A**). There was no difference in plasma creatinine (**Figure 1B**) or BUN (**Figure 1C**) between groups at any time point. Average hourly urine output was significantly greater between CKRT initiation and day 1 (50 vs. 21ml/hour) and between day 1 and day 2 (37 vs. 13ml/hour) of CKRT in patients with early kidney function recovery (**Figure 1D**). Interestingly, there was no difference in plasma cystatin C, creatinine, or BUN between groups prior to CKRT initiation. The percent decrease in plasma cystatin C from CKRT initiation to day 1 was significantly greater in patients with early kidney function recovery; however,

there was no difference in the percent change of plasma cystatin C between CKRT initiation and days 2 and 3 of CKRT between groups. There was also no difference in the slope of cystatin C change throughout the study period between groups as obtained by linear regression analysis (**Supplemental Figure 1**).

CKRT Clearance of Cystatin C is Similar in Patients with Early versus Delayed Kidney Function Recovery

To determine if cystatin C clearance by CKRT was responsible for the decreased plasma cystatin C concentrations in patients with early kidney function recovery, we examined the sieving coefficient and CKRT clearance of cystatin C. Cystatin C was detected in the CKRT effluent and cystatin C sieving coefficients (mean±SEM) were 0.59±0.03, 0.60±0.02, and 0.60±0.02 on days 1, 2, and 3, respectively. The cystatin C sieving coefficient was not different in patients with early versus delayed kidney function recovery (**Figure 2A**).

There was no difference in CKRT cystatin C clearance on day 1 (21.5 vs. 18.2 L), day 2 (27.9 vs. 26.5 L), or day 3 (25.2 vs. 25.9 L) of CKRT in patients with early versus delayed kidney function recovery (**Figure 2B**). There was also no difference in the mass amount of cystatin C removed by CKRT on day 1 (37.7 vs. 41.0 mg) or day 2 (52.3 vs. 62.0 mg) of CKRT in patients with early versus delayed kidney function recovery. There was paradoxically an increase in the mass amount of cystatin C removed by CKRT on day 3 of CKRT (66.0 vs. 49.7 mg) in patients with delayed kidney function recovery (**Figure 2C**). Furthermore, there was no difference in total effluent volume and CKRT dose in patients with early versus delayed kidney function recovery (**Figures 2D and 2E**). Together these findings suggest that the decrease in plasma cystatin C concentration in patients with early kidney function recovery is not due to increased cystatin C clearance by CKRT.

Urinary Excretion of Cystatin C is Similar in Patients with Early versus Delayed Kidney Function Recovery

To determine if patients with early kidney function recovery had increased urinary cystatin C excretion, we performed several analyses of urinary cystatin C clearance. There was no difference in the urine cystatin C concentration (**Figure 3A**), daily urinary cystatin C excretion (**Figure 3B**), urine cystatin C/urine creatinine ratio (**Figure 3C**), or fractional urinary excretion of cystatin C (**Figure 3D**) in patients with early versus delayed kidney function.

Plasma Cystatin C as a Clinical Test to Predict Early Kidney Function Recovery in Patients with AKI-CKRT

To assess the utility of plasma cystatin C as a clinical test, we compared the minimum (lowest) plasma cystatin C concentration from days 1-3 of CKRT between the two groups, as the lowest plasma cystatin C concentration would be most likely to reflect kidney function recovery. We developed a ROC and analyzed the test characteristics of the lowest plasma cystatin C concentration from days 1-3 of CKRT in all patients included in this study. The minimum cystatin C concentration was significantly lower in patients with early kidney function recovery (**Figure 4A**). The area under the curve of the ROC (AUROC) was 0.77 (95% CI = 0.61-0.93, P = 0.002) (**Figure 4B**). Using ideal cutoff points from the ROC, a plasma cystatin C concentration of 1.30mg/L or less correlated with a positive likelihood ratio (LR) of 5.60 of having early kidney function recovery, and a plasma cystatin C concentration of greater than 1.88mg/L correlated with a negative LR of 0.17 of having early kidney function recovery (**Figure 4C**). These findings suggest that plasma cystatin C could be used as a clinical tool to predict early kidney function recovery in patients with AKI-CKRT.

Plasma Cystatin C Predicts Early Kidney Function Recovery in Patients with Advanced CKD and Predicts Early Versus Not-Early Kidney Function Recovery in Patients with and without Advanced CKD with AKI-CKRT

To determine if the presence of advanced CKD affects the ability of cystatin C to predict early kidney function recovery and if cystatin C can predict early kidney function recovery versus not-early kidney function recovery in all patients (including those with advanced CKD), we also measured plasma cystatin C in patients with advanced CKD (N=3 with early kidney function recovery, N=8 with delayed kidney function recovery or death while on KRT) and with intermediate kidney function recovery (KRT liberation between days 8 and 21 of CKRT initiation, N=4). There was no difference in baseline patient characteristics including these additional patients (**Supplemental Tables 3 & 4**). Plasma cystatin C remained significantly decreased on days 1 and 2 of CKRT in patients with early kidney function recovery in both analyses (**Supplemental Figures 2A & 3A**). The minimum (lowest) plasma cystatin C concentration remained significantly decreased in patients with early kidney function recovery (**Supplemental Figures 2B & 3B**) and still predicted kidney function recovery (**Supplemental Figures 2C, 2D, 3C, & 3D**).

Urine Output as a Clinical Test to Predict Early Kidney Function Recovery in Patients with AKI-CKRT

We also studied the utility of the maximum average hourly urine output from days 1-3 of CKRT to predict early kidney function recovery. The maximum average hourly urine output was greater in patients with early kidney function recovery in comparison to patients with delayed kidney function or those that died while on KRT (60.82 vs. 26.26ml/hr) (**Supplemental Figure 4A**). The AUROC was 0.72 (95% CI = 0.58-0.85, P = 0.01) (**Supplemental Figure 4B**). Using ideal cutoff points from the ROC, a maximum hourly urine output of equal to or greater than 109.2ml/hr correlated with a positive likelihood ratio (LR) of 8.40 of having early kidney function recovery, and a maximum hourly urine output

of less than 6.3ml/hr correlated with a negative LR of 0.15 of having early kidney function recovery (**Supplemental Figure 4C**).

DISCUSSION

In this study we examined the utility of plasma cystatin C to predict kidney function recovery in patients with AKI-CKRT. The major findings are that 1) plasma concentrations of cystatin C are lower in patients with early kidney function recovery after CKRT initiation, 2) CKRT clearance did not interfere with the utility of cystatin C to predict kidney function recovery despite removal of cystatin C by CKRT with a sieving coefficient of ~0.6, and 3) the lowest plasma cystatin C concentration on days 1-3 of CKRT may be a useful clinical test to predict early kidney function recovery. To our knowledge, there are only four other reports that have assessed plasma cystatin C concentrations during CKRT (as in our study) which included 62 patients combined [14-17]. Only two of these reports assessed cystatin C CKRT clearance [16, 17] and none addressed whether cystatin C predicts kidney function recovery as we did. Thus, our study of 72 patients is larger than all the prior reports combined and is the most comprehensive as our study addressed both CKRT clearance and kidney function recovery. This study lays the foundation for future investigations of the use of plasma cystatin C to estimate GFR during CKRT.

This study was crafted to allow for interpretation of plasma cystatin C to identify kidney function recovery during CKRT. For a plasma marker to estimate kidney function in patients on CKRT, marker clearance by CKRT should be known, and changes in plasma marker concentrations should be indicative of differences in kidney function. Our data demonstrate that while cystatin C is meaningfully removed by CKRT, this does not confound its ability to identify patients with early kidney function recovery. This is important as removal by CKRT has been thought to a limiting factor for cystatin C to reflect kidney function during CKRT [11, 27, 28].

In addition to assessing CKRT clearance, we also examined urinary cystatin C excretion to provide further evidence to support, or refute, the utility of plasma cystatin C as a marker to estimate kidney function in patients on CKRT. We examined urinary cystatin C excretion via many methods, all of which showed no difference in urinary cystatin C excretion in patients with early kidney function recovery. At first glance it appears these data suggest that there is no difference in glomerular filtration of cystatin C in patients with early kidney function recovery; however, urinary cystatin C excretion may not be proportional to the amount of cystatin C filtered by the glomerulus. Cystatin C is freely filtered by the glomerulus, but subsequently binds megalin on the proximal tubule epithelial cell surface, is endocytosed, and catabolized [29-34]. As such, patients with impaired filtration and proximal tubule injury will filter less cystatin C by the glomerulus but will also reabsorb and catabolize less cystatin C in the proximal tubule (**Supplemental Figure 5**)[34]. Therefore, urinary cystatin C excretion may not be proportional to the amount of cystatin C that is filtered by the glomerulus. Given the mechanism of cystatin C clearance by the kidney (i.e., both by GFR or proximal tubular metabolism), we suggest that lower levels of plasma cystatin C in the patients with early kidney function recovery reflects an improvement in both GFR and proximal tubule function. These results are consistent with other studies which demonstrate that urine cystatin C may have limited utility to identify and predict the prognosis of AKI [35].

Finally, we investigated the potential for plasma cystatin C to be implemented as a clinical test. We determined plasma cystatin C cutoff values that correlate with positive and negative LRs that could impact the probability of a patient having early kidney function recovery. Putting the identified LRs into clinical practice (+LR 5.60 for cystatin C≤ 1.30, -LR for cystatin C >1.88), if a patient with a ~50% pre-test probability of early kidney function recovery has an elevated plasma cystatin C concentration (≥1.88mg/L), this decreases the patient's probability of having early kidney function recovery to 15%. In comparison, if the plasma cystatin C is low (<1.30mg/L), this would increase the patient's probability of

having early kidney function recovery to 85%. We also studied the utility of the maximum average hourly urine output from days 1-3 of CKRT to predict early kidney function recovery, as urine output is the most commonly used tool in clinical practice to identify kidney function recovery in patients on CKRT. While the maximum average hourly urine output was greater in patients with early kidney function recovery, the AUROC of the maximum average hourly urine output was modestly lower than the AUROC for minimum plasma cystatin C. Furthermore, while average hourly urine output cutoff values were able to be determined that corresponded to impactful likelihood ratios, most study patients fell between these two cutoff values and thus would have an indeterminate test result. Adjustments to the cutoff values could be made to allow a positive or negative result in more patients; however, this would compromise the likelihood ratio strength. Together, these findings suggest that cystatin C has the potential to help inform clinical decision-making regarding attempts to discontinue CKRT and that minimum cystatin C may be an equivalent or superior clinical test as maximum urine output. These data are in line with the growing body of data indicating that urine output has limitations in predicting kidney function recovery and successful CKRT liberation, and that additional tools are needed [18, 36].

While this study demonstrates several strengths, it also has limitations. Though larger than the prior studies of cystatin C during CKRT, this study is still relatively small and should be replicated in a larger and multi-institutional validation cohort. Unfortunately, a validation cohort with plasma samples collected prior to initiation of CKRT, and plasma and effluent samples serially collected after CKRT initiation does not exist at this time. Additionally, while cystatin C is increasingly available for measurement in clinical labs, not all healthcare systems are able to measure cystatin C and its measurement is not standardized across institutions. As more studies show beneficial uses for cystatin C, it is important that clinical labs adopt and standardize this technology. Finally, the only form of CKRT studied was continuous venovenous hemodialysis (CVVHD) – which is a diffusive therapy. Based on available data, it does not appear that CKRT modality will be a major confounding factor that affects

cystatin C removal. Similar cystatin C sieving coefficients [15, 17] and clearance [15] during continuous venovenous hemofiltration (CVVH), a convective therapy, have been observed. Additionally, cystatin C is a middle molecular weight molecule, similar to cytokines, for which no significant difference in serum concentrations or CKRT clearance of five different cytokines were observed with CVVHD vs. CVVH [37].

In summary, this study demonstrates that plasma cystatin C concentrations are lower in patients with AKI-CKRT with early kidney function recovery. The lowest concentration of plasma cystatin C in the first three days of CKRT has the promise to be a clinically useful test that could help inform prognostic conversations and possibly provide guidance as to when KRT discontinuation can be attempted.

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TABLE LEGENDS

Table 1. Baseline Patient Characteristics. Baseline characteristics of patients by group.

Table 1.		Early Kidney Recovery		Delayed Kidney Recovery or Died	
		N or Avg +/- SEM	%	N or Avg +/- SEM	%
Total Patients	Early Kidney Recovery	15			
	Delayed Kidney Recovery			19	
	Died			23	
Age (years)		58.3 +/- 3.9		55.9 +/- 2.6	
Weight (kg)		85.8 +/- 5.0		96.0 +/- 4.9	
BMI		29.0 +/- 1.6		30.0 +/- 1.3	
Sex	M	8	53%	26	62%
	F	7	47%	16	38%
Baseline eGFR (ml/min/m2)		92.7 +/- 5.8		83.4 +/- 3.4	
SOFA-Renal Score		9.1 +/- 0.9		10.1 +/- 0.6	
IL-6 (pg/ml)		22173 +/- 19255		1909 +/- 1377	
Thyroid Dysfunction	TSH (mIU/L)	3.32 +/- 0.96		3.97 +/- 1.20	
	History of Hypothyroidism	3	20%	12	29%
	# Receiving Levothyroxine	1	7%	8	19%

Corticosteroid Administration	# Receiving corticosteroids	7	47%	26	62%
	Average Daily PO Prednisone Equivalent Corticosteroid Administration Dose (mg)	51.0 +/- 30.4		39.7 +/- 12.1	
Comorbidities	Hypertension	7	47%	20	48%
	Diabetes	6	40%	10	24%
	Heart Failure or Pulmonary Hypertension	6	40%	17	41%
	Coronary Artery Disease	2	13%	8	19%
	Cirrhosis	1	7%	7	17%
	Cancer (Solid Tumor)	2	13%	3	7%
	Cancer (Hematologic)	2	13%	3	7%
	CVA/TIA	2	13%	4	10%
	COPD	2	13%	2	5%
Risk Factor(s) for AKI	Sepsis	8	53%	19	45%
	Decompensated Heart Failure	4	27%	13	31%
	Hepatorenal Syndrome	1	7%	4	10%
	Cardiac or Vascular Surgery	1	7%	9	21%
	Tumor Lysis Syndrome	1	7%	0	0%
	Rhabdomyolysis	0	0%	1	2%
	Nephrotoxin Administration	0	0%	1	2%
	Hypertensive Emergency	0	0%	1	2%
ICU Type	Medical ICU	10	67%	23	55%

	Cardiac or Cardiothoracic Surgery ICU	**1**	**7%**	**12**	**29%**
	Surgical and Trauma ICU	**4**	**27%**	**6**	**14%**
	Neuro ICU	**0**	**0%**	**1**	**2%**

FIGURE LEGENDS

Figure 1. Measurements of Kidney Function in Patients with AKI Requiring CKRT. Plasma cystatin C (**A**), creatinine (**B**), and BUN (**C**) on the day prior to CKRT initiation and on days 1, 2, and 3 of CKRT in patients with early kidney function recovery (gray) versus delayed kidney function recovery (white). Hourly urine output (**D**) between time of enrollment to day 1, day 1 to day 2, and day 2 to day 3 of CKRT in patients with early kidney function recovery (gray) versus delayed kidney function recovery (white). Boxes represent 25^{th} – 75^{th} percentile results with a bar at the median result, Whiskers extend from the minimum to maximum value, **+** = Mean result. ***** = P<0.05. p-values between 0.05 and 0.10 reported above each comparison.

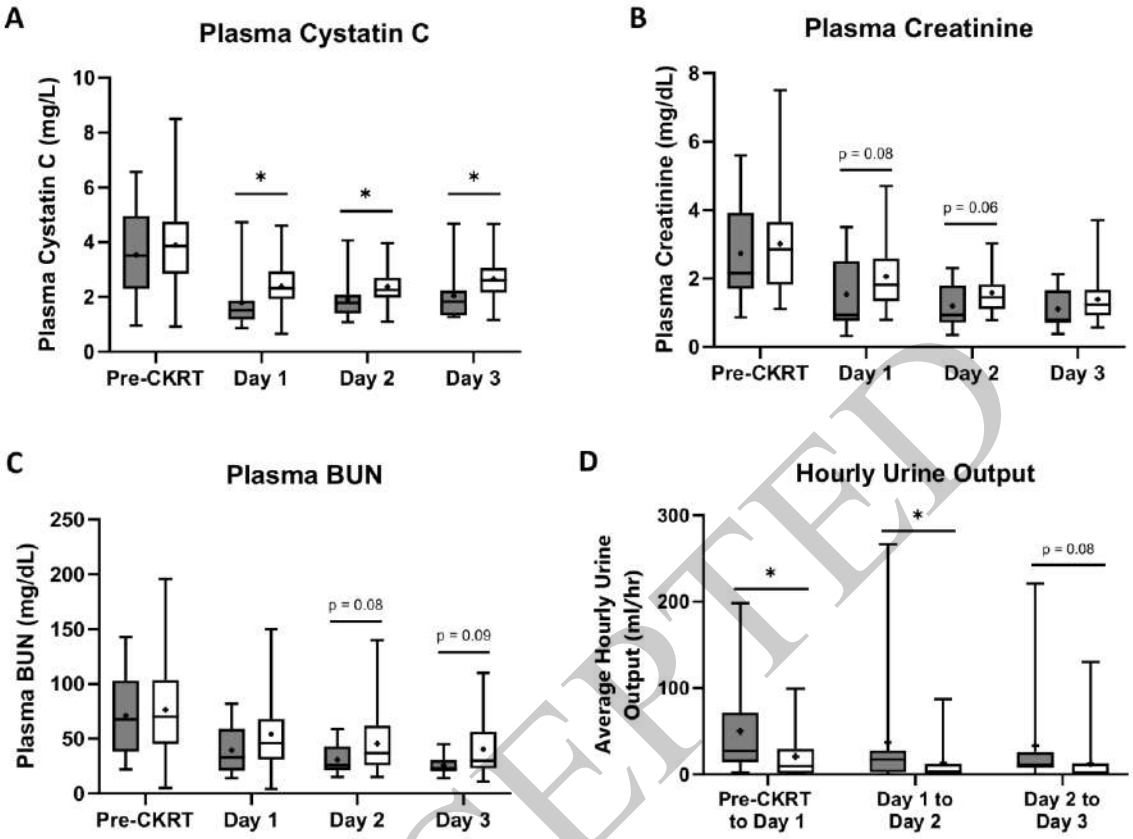


Figure 1. Measurements of Kidney Function in Patients with AKI Requiring CKRT. Plasma cystatin C (**A**), creatinine (**B**), and BUN (**C**) on the day prior to CKRT initiation and on days 1, 2, and 3 of CKRT in patients with early kidney function recovery (gray) versus delayed kidney function recovery (white). Hourly urine output (**D**) between time of enrollment to day 1, day 1 to day 2, and day 2 to day 3 of CKRT in patients with early kidney function recovery (gray) versus delayed kidney function recovery (white). Boxes represent 25th – 75th percentile results with a bar at the median result, Whiskers extend from the minimum to maximum value, **+** = Mean result. * = P<0.05. p-values between 0.05 and 0.10 reported above each comparison.

Figure 2. Continuous Kidney Replacement Therapy Clearance of Cystatin C. Cystatin C sieving coefficient (**A**), cystatin C CKRT clearance (**B**), cystatin C CKRT mass removed (**C**), CKRT total effluent volume (**D**), and CKRT dose (**E**) between time of enrollment to day 1, day 1 to day 2, and day 2 to day 3 of CKRT in patients with early kidney function recovery (gray) versus delayed kidney function recovery (white). Boxes represent 25^{th} – 75^{th} percentile results with a bar at the median result, Whiskers extend from the minimum to maximum value, **+** = Mean result. ***** = P<0.05. p-values between 0.05 and 0.10 reported above each comparison.

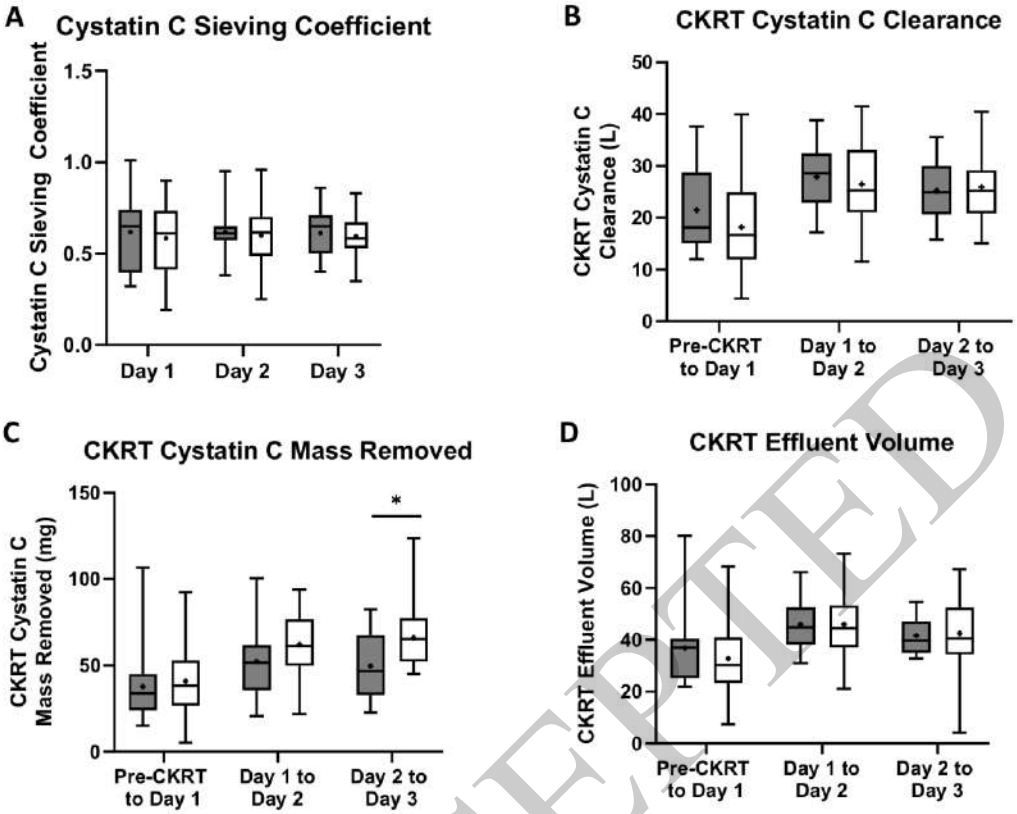


Figure 2. Continuous Kidney Replacement Therapy Clearance of Cystatin C. Cystatin C sieving coefficient (**A**), cystatin C CKRT clearance (**B**), cystatin C CKRT mass removed (**C**), CKRT total effluent volume (**D**), and CKRT dose (**E**) between time of enrollment to day 1, day 1 to day 2, and day 2 to day 3 of CKRT in patients with early kidney function recovery (gray) versus delayed kidney function recovery (white). Boxes represent 25^{th} – 75^{th} percentile results with a bar at the median result, Whiskers extend from the minimum to maximum value, **+** = Mean result. * = P<0.05. p-values between 0.05 and 0.10 reported above each comparison.

Figure 3. Urinary Clearance of Cystatin C. Urine cystatin C (**A**), urine cystatin C/urine creatinine ratio (**C**), and urinary fractional excretion of cystatin C (**D**) on the day prior to CKRT initiation and on days 1, 2, and 3 of CKRT in patients with early kidney function recovery (gray) versus delayed kidney function recovery (white). Urine cystatin C clearance (**B**) between time of enrollment to day 1, day 1 to day 2, and day 2 to day 3 of CKRT in patients with early kidney function recovery (gray) versus delayed kidney function recovery (white). Boxes represent 25^{th} – 75^{th} percentile results with a bar at the median result, Whiskers extend from the minimum to maximum value, **+** = Mean result. ***** = P<0.05. p-values between 0.05 and 0.10 reported above each comparison.

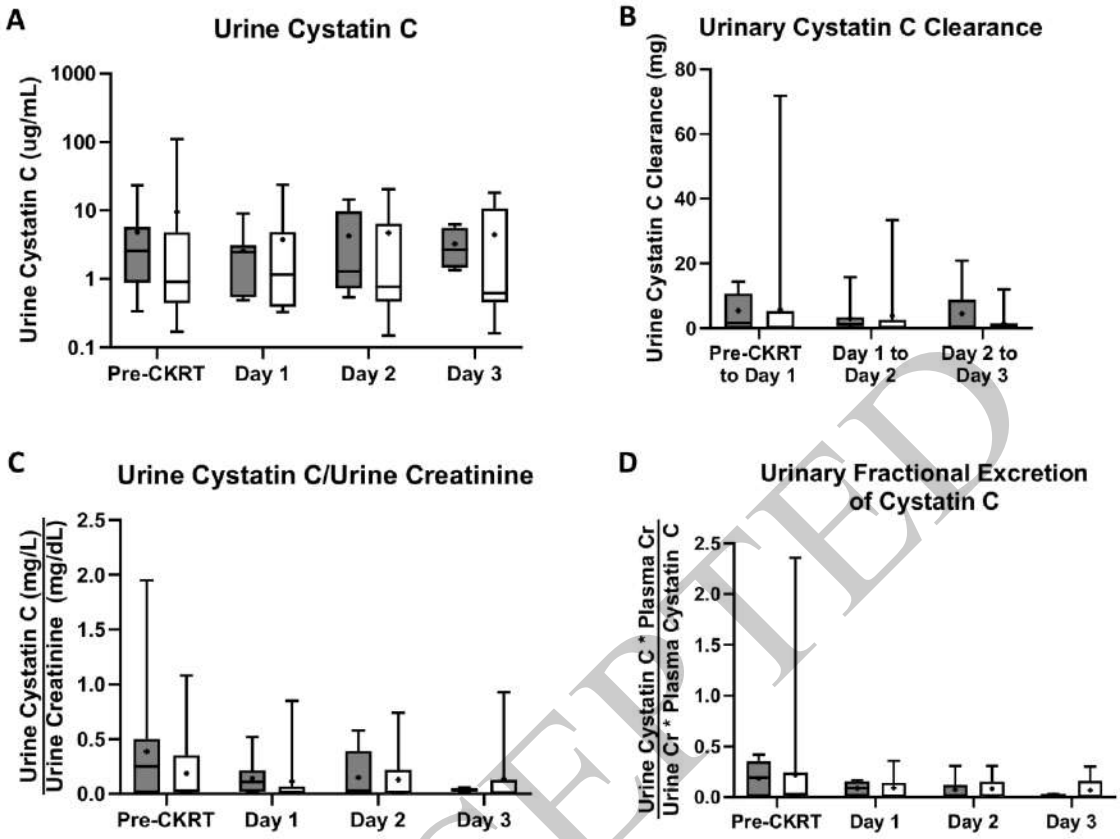
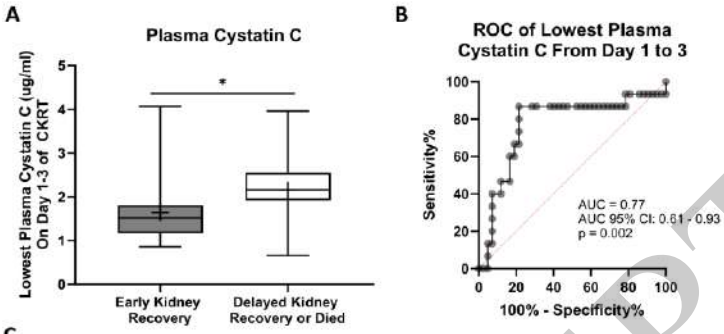


Figure 3. Urinary Clearance of Cystatin C. Urine cystatin C (**A**), urine cystatin C/urine creatinine ratio (**C**), and urinary fractional excretion of cystatin C (**D**) on the day prior to CKRT initiation and on days 1, 2, and 3 of CKRT in patients with early kidney function recovery (gray) versus delayed kidney function recovery (white). Urine cystatin C clearance (**B**) between time of enrollment to day 1, day 1 to day 2, and day 2 to day 3 of CKRT in patients with early kidney function recovery (gray) versus delayed kidney function recovery (white). Boxes represent 25^{th} – 75^{th} percentile results with a bar at the median result, Whiskers extend from the minimum to maximum value, **+** = Mean result. * = P<0.05. p-values between 0.05 and 0.10 reported above each comparison.

Figure 4. Minimum Cystatin C From Day 1 - Day 3 of CKRT Predicts Early Kidney Function Recovery in Patients with AKI-CKRT. Minimum (lowest) plasma cystatin C from days 1-3 of CKRT (**A**) in patients with AKI-CKRT with early kidney function recovery (gray) versus delayed kidney function recovery (white). Receiver operating curve of minimum plasma cystatin C in all patients (**B**) and optimal cutoff values with corresponding positive and negative likelihood ratios for early kidney recovery (**C**). For box and whisker plots, boxes represent 25^{th} – 75^{th} percentile results with a bar at the median result, Whiskers extend from the minimum to maximum value, **+** = Mean result. ***** = P<0.05.



C

Cystatin C Cutoff Value (mg/L)	# Early Kidney Recovery	# Delayed Recovery or Died	Likelihood Ratio
≤1.30	**6**	**3**	**+ LR: 5.60**
1.31-1.88	7	6	
>1.88	2	33	- LR: 0.17

Figure 4. Minimum Cystatin C From Day 1 - Day 3 of CKRT Predicts Early Kidney Function Recovery in Patients with AKI-CKRT. Minimum (lowest) plasma cystatin C from days 1-3 of CKRT (**A**) in patients with AKI-CKRT with early kidney function recovery (gray) versus delayed kidney function recovery (white). Receiver operating curve of minimum plasma cystatin C in all patients (**B**) and optimal cutoff values with corresponding positive and negative likelihood ratios for early kidney recovery (**C**). For box and whisker plots, boxes represent 25^{th} – 75^{th} percentile results with a bar at the median result, Whiskers extend from the minimum to maximum value, **+** = Mean result. ***** = P<0.05.

SUPPLEMENTAL MATERIALS LIST:

Does plasma Cystatin C predict kidney function recovery in subjects requiring continuous kidney replacement therapy for acute kidney injury?

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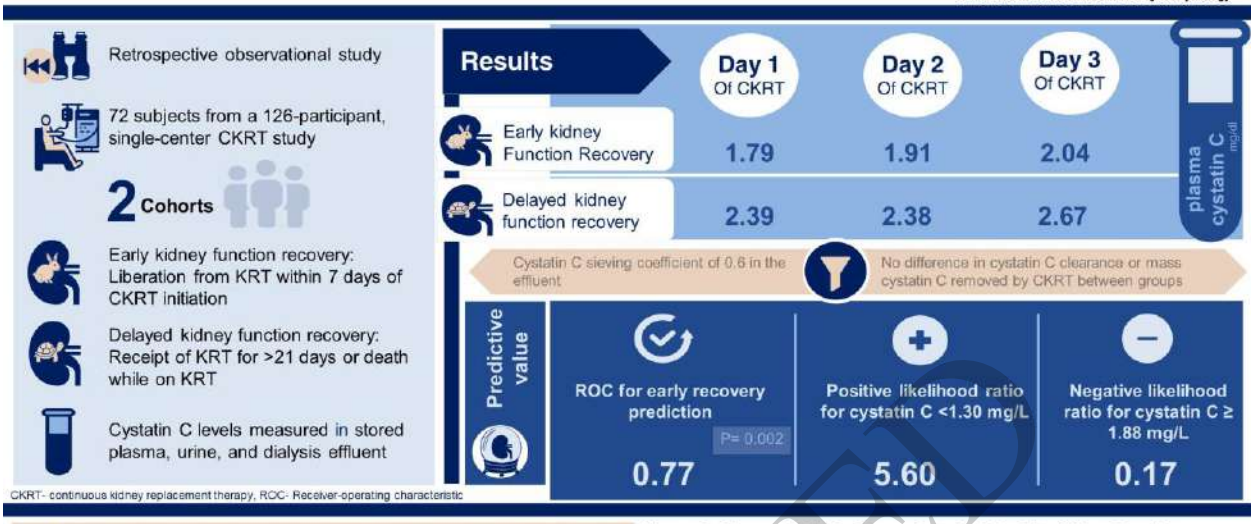

CKRT- continuous kidney replacement therapy, ROC- Receiver-operating characteristic

Conclusion: Lower plasma cystatin C concentrations during the first 3 days of CKRT are associated with early kidney function recovery. Despite being partially dialyzed, cystatin C still predicted kidney function recovery in patients on CKRT.

Haeger S, Okamura K, Li AS, ***Plasma Cystatin C Predicts Kidney Function Recovery in Subjects Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury***. CJASN DOI 10.2215/CJN.0000000000000531
Visual abstract by Cristina Popa, MD

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Manuscript ID: CJASN-2024-000396R1
Manuscript Title: Plasma Cystatin C Predicts Kidney Function Recovery in Subjects Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury
Date of Completion: June 25, 2024
Disclosure Updated Date: June 25, 2024

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Date of Completion: July 29, 2024
Disclosure Updated Date: July 29, 2024

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Manuscript ID: CJASN-2024-000396R3
Manuscript Title: Cystatin C and Kidney Function Recovery in Patients Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury
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Disclosure Updated Date: May 15, 2024

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Date of Completion: July 31, 2024
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Manuscript Title: Cystatin C and Kidney Function Recovery in Patients Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury
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Name: Sarah Faubel
Manuscript ID: CJASN-2024-000396R3
Manuscript Title: Cystatin C and Kidney Function Recovery in Patients Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury
Date of Completion: July 31, 2024
Disclosure Updated Date: May 17, 2024

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N. Foulon reports the following:
Employer: University of Colorado School of Medicine

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: North Foulon
Manuscript ID: CJASN-2024-000396R1
Manuscript Title: Plasma Cystatin C Predicts Kidney Function Recovery in Subjects Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury
Date of Completion: June 11, 2024
Disclosure Updated Date: May 7, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

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B. Griffin reports the following:
Employer: University of Iowa

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Name: Benjamin R. Griffin
Manuscript ID: CJASN-2024-000396R3
Manuscript Title: Cystatin C and Kidney Function Recovery in Patients Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury
Date of Completion: August 2, 2024
Disclosure Updated Date: August 2, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

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S. Haeger reports the following:
Employer: University of Washington

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Sarah Haeger
Manuscript ID: CJASN-2024-00396R3
Manuscript Title: Cystatin C and Kidney Function Recovery in Patients Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury
Date of Completion: July 31, 2024
Disclosure Updated Date: July 31, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

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Z. He reports the following:
Employer: University of Colorado Denver Anschutz Medical Campus; Ownership Interest: 1. Apple Inc.; 2. Tesla Inc.; 3. Gilead Sciences Inc.; 4. Delta Air Lines, Inc.; 5. United Airlines Holdings, Inc.; and Research Funding: Xortex therapeutics.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Zhibin He
Manuscript ID: CJASN-2024-000396R3
Manuscript Title: Cystatin C and Kidney Function Recovery in Patients Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury,
Date of Completion: August 2, 2024
Disclosure Updated Date: May 15, 2024

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JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

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D. Jalal reports the following:
Employer: University of Iowa; Iowa City VA; Consultancy: Meridian Health Comms; Research Funding: AstraZenica; Corvidia;; Honoraria: K-INBRE; Reata; Sullivan conference- University of Kansas; PER (Physicians Education Resource); and Advisory or Leadership Role: Reata; CSL Behring.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Diana I. Jalal
Manuscript ID: CJASN-2024-000396R1
Manuscript Title: Plasma Cystatin C Predicts Kidney Function Recovery in Subjects Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury
Date of Completion: June 12, 2024
Disclosure Updated Date: May 6, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

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M. Kennis reports the following:
Employer: University of Colorado Anschutz Medical Campus; and Ownership Interest: Neurocrine Biosciences.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Matt Robert Kennis
Manuscript ID: CJASN-2024-000396R1
Manuscript Title: Plasma Cystatin C Predicts Kidney Function Recovery in Subjects Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury
Date of Completion: June 11, 2024
Disclosure Updated Date: April 21, 2024

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JASN Journal of the American Society of Nephrology
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A. Li has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Amy Shijia Li
Manuscript ID: CJASN-2024-000396R1
Manuscript Title: Plasma Cystatin C Predicts Kidney Function Recovery in Subjects Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury
Date of Completion: June 11, 2024
Disclosure Updated Date: May 10, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
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M. Miyazaki reports the following:
Employer: University of Colorado-Denver

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Makoto Miyazaki
Manuscript ID: CJASN-2024-000396R1
Manuscript Title: Plasma Cystatin C Predicts Kidney Function Recovery in Subjects Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury
Date of Completion: June 11, 2024
Disclosure Updated Date: May 8, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
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K. Okamura has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Kayo Okamura
Manuscript ID: CJASN-2024-000396R3
Manuscript Title: Cystatin C and Kidney Function Recovery in Patients Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury
Date of Completion: August 1, 2024
Disclosure Updated Date: May 10, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

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B. Park reports the following:
Employer: University of Colorado

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Bryan Park
Manuscript ID: CJASN-2024-000396R1
Manuscript Title: Plasma Cystatin C Predicts Kidney Function Recovery in Subjects Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury
Date of Completion: June 13, 2024
Disclosure Updated Date: June 13, 2024