Blood Purification

Critical Care Nephrology – Research Article

Blood Purif 2024;53:548–556
DOI: 10.1159/000538898

Received: December 18, 2023
Accepted: April 9, 2024
Published online: April 18, 2024

CCL14 Predicts Oliguria and Dialysis Requirement in Patients with Moderate to Severe Acute Kidney Injury

Sevag Demirjian[a] Lakhmir Chawla[b] Danielle Davison[c] Lui G. Forni[d, e] Michael Heung[f] Eric A.J. Hoste[g, h] Jay Koyner[i] J. Patrick Kampf[j] Thomas Kwan[j] Paul McPherson[j] John A. Kellum[k]

[a]Department of Kidney Medicine, Cleveland Clinic, Cleveland, OH, USA; [b]Department of Medicine, Veterans Affairs Medical Center, San Diego, CA, USA; [c]Departments of Anesthesiology and Critical Care Medicine, George Washington University, Washington, DC, USA; [d]Department of Intensive Care, Royal Surrey Hospital, Guildford, UK; [e]Department of Clinical and Experimental Medicine, Faculty of Health Sciences, University of Surrey, Guildford, UK; [f]Division of Nephrology, Department of Medicine, University of Michigan, Ann Arbor, MI, USA; [g]Intensive Care Unit, Department of Internal Medicine and Pediatrics, Ghent University Hospital, Ghent University, Ghent, Belgium; [h]Research Foundation-Flanders (FWO), Brussels, Belgium; [i]Section of Nephrology, University of Chicago, Chicago, IL, USA; [j]Astute Medical Inc. (a bioMérieux company), San Diego, CA, USA; [k]Center for Critical Care Nephrology, University of Pittsburgh, Pittsburgh, PA, USA

Keywords
Acute kidney injury · CCL14 · Diuretics · Oliguria · Dialysis

Abstract

Introduction: AKI is a frequent complication of critical illness and portends poor outcome. CCL14 is a validated predictor of persistent severe AKI in critically ill patients. We examined the association of CCL14 with urine output within 48 h. ***Methods:*** In pooled data from 2 studies of critically ill patients with KDIGO stage 2–3 AKI, CCL14 was measured by NEPHROCLEAR™ CCL14 Test on the Astute 140® Meter (low, intermediate, and high categories [1.3 and 13 ng/mL]). Average hourly urine output over 48 h, stage 3 AKI per urine output criterion on day 2, and composite of dialysis or death within 7 days were examined using multivariable mixed and logistic regression models. ***Results:*** Of the 497 subjects with median age of 65 (56–74) years, 49% (242/497) were on diuretics. CCL14 concentration was low in 219 (44%), intermediate in 217 (44%), and high in 61 (12%) patients. In mixed regression analysis, hourly urine output over time was different within each CCL14 risk category based on diuretic use due to significant three-way interaction ($p < 0.001$). In logistic regression analysis, CCL14 risk category was independently associated with low urine output on day 2 per KDIGO stage 3 (adjusted for diuretic use and baseline clinical variables), and composite of dialysis or death within 7 days (adjusted for urine output within 48 h of CCL14 measurement). ***Conclusions:*** CCL14 measured in patients with moderate to severe AKI is associated with urine output trajectory within 48 h, oliguria on day 2, and dialysis within 7 days.

karger@karger.com
www.karger.com/bpu

Correspondence to:
Sevag Demirjian, demirjs@ccf.org

Introduction

Acute kidney injury (AKI) is a frequent complication in critical illness and following major procedures [1]. Although moderate to severe AKI often persists and necessitates extracorporeal kidney support, it is challenging for clinicians to predict trajectory of AKI at the bedside. Several well-designed multicenter randomized trials investigating timing of kidney replacement therapy (KRT) initiation have highlighted the challenges clinicians face when predicting progression to KRT in patients with moderate to severe AKI [2–5]. Importantly, a "non-personalized" approach of early KRT for all patients with AKI is not beneficial and may even be harmful. Conversely, delayed initiation in patients that ultimately require KRT is also potentially harmful. Notably, fluid burden and persistent oliguria were often the leading clinical indications for KRT initiation.

Urinary C-C-motif chemokine ligand 14 (CCL14) has been validated to predict persistent severe AKI in critically ill patients. In patients who sustain moderate to severe AKI (stage 2–3 per Kidney Disease: Improving Global Outcomes [KDIGO] classification), standardized cut-offs have been established at 1.3 (high sensitivity) and 13 ng/mL (high specificity) that predict individual patient trajectory and support clinical decision-making at the bedside [6]. However, the decision to initiate mechanical kidney support involves multiple variables. A more fundamental question is whether a fluid-overloaded patient is likely to respond to diuretics. Urine output with or without diuretic use may have prognostic and management implications [7, 8]. The current study sought to examine (1) the association of CCL14 with urine output over 48 h with or without diuretic exposure in critically ill patients with moderate to severe AKI and (2) the association of CCL14 with need for dialysis or death within 7 days.

Methods

Subjects

The current analysis includes 497 subjects from two prior studies: the Ruby study which included adult critically ill patients who met KDIGO stage 2–3 AKI criteria and a subgroup from the Sapphire study with first urine sample collected within 36 h of stage 2–3 AKI classification. Both studies enrolled subjects from multiple clinical sites across Europe and the USA, following approval by investigational review boards (or the equivalent) and obtaining written informed consent from subjects [9, 10].

Study Design

KDIGO staging was based on serum creatinine and urine output criteria in both studies. Critically ill patients with established KDIGO stage 2 or 3 AKI were recruited in the Ruby study, in the absence of prior kidney transplantation or imminent need for KRT, whereas critically ill patients in the Sapphire study cohort who developed stage 2–3 AKI within a week of enrollment were included in the present study (Fig. 1, flowchart). In the Ruby study, urine samples were collected twice daily for 3 days from enrollment and then once daily for 4 days. In the Sapphire study, urine samples were collected twice daily for 4 days from enrollment and then once daily for 3 days. KDIGO stage at time of sample collection based on retrospective re-adjudication of AKI status (as opposed to prospective classification by the enrolling site) was determined.

In both studies, urine samples were centrifuged, flash frozen, stored at or below −70°C, and thawed prior to sample testing. Technicians who were blinded to the clinical data measured CCL14 concentrations in the samples using the NEPHROCLEAR™ CCL14 Test on the Astute 140® Meter (Astute Medical Inc., San Diego, CA, USA). Urinary CCL14 results were divided to low-, intermediate-, and high-risk categories based on 1.3 and 13 ng/mL concentration cut-offs. Diuretic use was defined as any diuretic use from a day prior to 1 day following CCL14 measurement (dose or mode of administration was not available). Hourly urine output within 48 h following urinary CCL14 collection was used as the primary endpoint in a mixed regression model. AKI stage 3 per urine output criterion on the second day of 48 h observation period (sooner if died or started dialysis) was also used in a logistic regression model. Finally, a composite of KRT or death at 7 days following CCL14 measurement was used in a logistic regression model.

Statistical Analysis

Continuous variables were presented as medians (interquartile range) and were compared using Spearman's rank correlation. Categorical variables were presented as count (%) and compared using the Cochran-Armitage test for trend where appropriate. Cumulative urine output over 48 h following urinary CCL14 measurement per CCL14 levels and diuretic exposure was presented in boxplots (online suppl. eFig. 1; for all online suppl. material, see https://doi.org/10.1159/000538898). Generalized linear mixed regression analyses were used to model the average hourly urine output (repeated measures) as a function of CCL14 level and diuretics use over time. A saturated model consisting of three 2-way and one 3-way interactions along with the linear terms was built using CCL14 level, diuretics use, and time. Random effect at subject level was used in the model to account for multiple measurements of urine output for each subject over time. Akaike and Bayesian information criteria were compared for the saturated model (diuretic use, CCL14 category, as fixed variables), versus the simpler models (diuretic use alone or CCL14 category alone as fixed variables) to compare model fit; and marginal R^2 calculated to assess variation explained by the fixed effects [11]. Multivariable logistic regression models were used to examine the association of urine output-based stage 3 AKI on the second day of 48 h observation period with CCL14 risk category adjusted for diuretic use, and baseline estimated glomerular filtration rate (eGFR) and fluid balance. An additional multivariable logistic regression model was constructed to assess the association of the

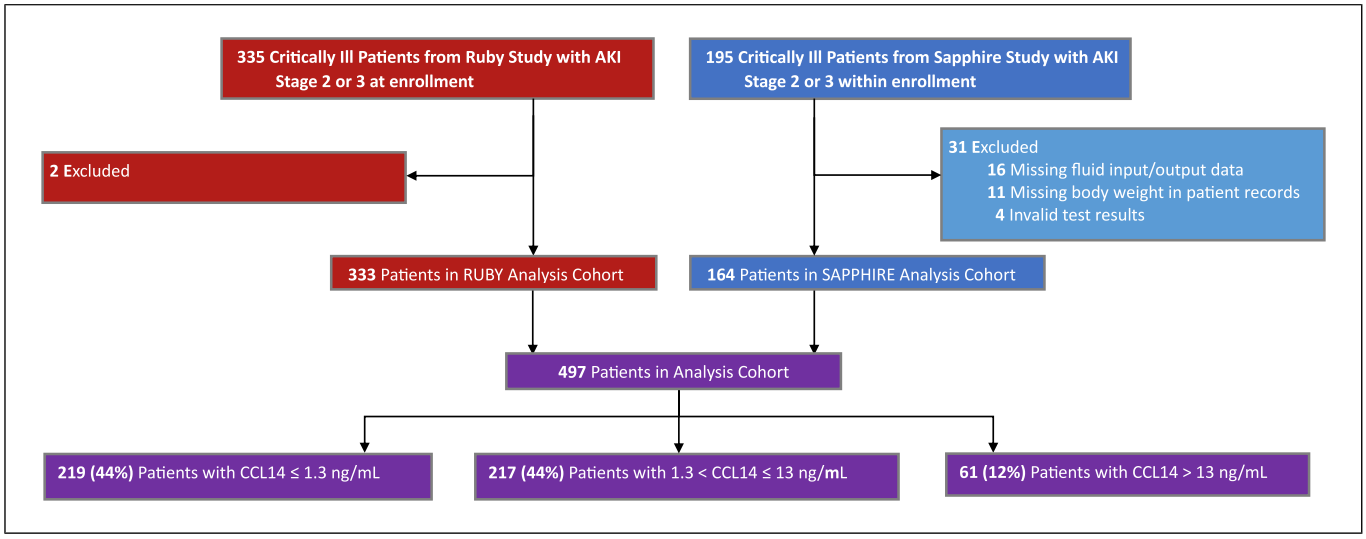

Fig. 1. Patient flow diagram.

composite endpoint of KRT or death within 7 days, with CCL14 risk category adjusting for average urine output (<0.5 mL/kg/h) within 48 h of CCL14 measurement. The logistic regression models included baseline eGFR and fluid balance as covariates, which remained statistically significant on univariate analysis with urine output, and subsequent one-by-one inclusion in the generalized linear mixed model described above.

Two-sided p values less than 0.05 were considered statistically significant, with no adjustments for multiple comparisons. Statistical analyses were performed using R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Our final analysis cohort consisted of 333 subjects from the Ruby study and 164 from the Sapphire study (Fig. 1, flowchart). The median age was 65 (56–74) years, and 304/497 (39%) were female. Forty-nine percent of patients (242/497) were exposed to diuretic use. Within the overall cohort, 219 (44%) patients had measured CCL14 in low, 217 (44%) in intermediate, and 61 (12%) in the high category.

Baseline clinical and acute illness characteristics stratified by CCL14 levels are shown in Table 1. Patients with elevated CCL14 levels were less likely to be exposed to diuretic use ($p = 0.002$), more likely to have higher net positive fluid balance ($p < 0.001$), and more likely to have higher APACHE III scores ($p < 0.001$). KDIGO stage at time of sample collection is displayed in online supplementary eTable 1. In addition, diuretic use and fluid balance were correlated ($p < 0.001$).

As depicted in online supplementary eTable 2, patients who were exposed to diuretic use within a day pre- and post-CCL14 collection were more likely to be older in age 67 (57–75) versus 64 (55–72) ($p = 0.04$), have higher incidence of heart failure 30 versus 15% ($p < 0.001$), and have lower eGFR 70 (53–91) versus 79 (57–97) mL/min/1.73^2 at baseline ($p = 0.03$). Average hourly urine output increased over the 48 h following the CCL14 sample collection (online suppl. eFig. 1), and the rate of the increase differed by CCL14 category ($p < 0.001$ for the interaction between CCL14 category and time in mixed regression model, online suppl. eTable 3). The rate of increase in average hourly urine output was significantly greater for the intermediate (0.68 mL/h, 95% confidence interval [CI]: 0.59, 0.77) than for the low (0.11 mL/h, 95% CI: 0.01, 0.21) and high (0.31 mL/h, 95% CI: 0.15, 0.47) CCL14 categories (online suppl. eTable 3).

The addition of diuretic exposure (yes or no) to the mixed regression model resulted in lower Akaike and Bayesian information criteria indicating better fit compared to the model without diuretics (online suppl. eTable 4). The conditional R^2 of the saturated model with diuretics, CCL14, and time, which is the proportion of the total variation explained by the fixed and random effects, was 0.969, of which 39% (marginal $R^2 = 0.381$) was accounted by the fixed effects (diuretic use, CCL14 risk category, and time) [11].

In the mixed regression model with both CCL14 and diuretic use, urine output trajectory over time was different within each CCL14 risk category based on diuretic exposure as indicated by the significant three-way

Table 1. Clinical characteristics of all patients and grouped by CCL14 risk group at time of enrollment[1]

	All patients	CCL14 ≤ 1.3	1.3 < CCL14 ≤ 13	CCL14 > 13	*p* value
Total patients	497	219	217	61	
Male, *n* (%)	304 (61)	137 (63)	130 (60)	37 (61)	0.6
Age, years	65 (56–74)	65 (55–74)	66 (57–74)	64 (53–72)	0.8
BMI[2], kg/m^2	30 (25–36)	31 (26–36)	29 (25–36)	28 (24–32)	0.09
Race[3], *n* (%)					
Black or African American	55 (11)	30 (14)	19 (9)	6 (10)	0.4
Other/unknown	35 (7)	14 (6)	15 (7)	6 (10)	
White or Caucasian	407 (82)	175 (80)	183 (84)	49 (80)	
Chronic comorbidities, *n* (%)					
Chronic kidney disease	76 (15)	27 (12)	38 (18)	11 (18)	0.1
Diabetes mellitus	173 (35)	75 (34)	81 (37)	17 (28)	0.7
Heart failure	110 (22)	52 (24)	48 (22)	10 (16)	0.2
Coronary artery disease	179 (36)	92 (42)	71 (33)	16 (26)	0.009
Hypertension	345 (69)	158 (72)	151 (70)	36 (59)	0.08
COPD	96 (19)	44 (20)	46 (21)	6 (10)	0.2
Cancer	126 (25)	46 (21)	61 (28)	19 (31)	0.055
Reason for ICU admission, *n* (%)					
Respiratory	172 (35)	74 (34)	77 (35)	21 (34)	0.8
Surgery	163 (33)	79 (36)	67 (31)	17 (28)	0.1
Cardiovascular	209 (42)	85 (39)	93 (43)	31 (51)	0.101
Sepsis	110 (22)	39 (18)	52 (24)	19 (31)	0.022
Neurological	29 (6)	14 (6)	13 (6)	2 (3)	0.4
Trauma	14 (3)	5 (2)	7 (3)	2 (3)	0.6
Other	133 (27)	52 (24)	64 (29)	17 (28)	0.33
Baseline creatinine, mg/dL	1.0 (0.8–1.2)	0.9 (0.7–1.2)	1.0 (0.8–1.3)	1.0 (0.8–1.2)	0.005
Baseline eGFR[4], mL/min	74 (54–94)	78 (61–100)	70 (50–90)	80 (50–94)	0.006
Non-renal APACHE III score	55 (43–75)	51 (38–68)	58 (45–78)	65 (47–90)	<0.001
Fluid balance, mL[5]	2939 (916–5,996)	1,969 (273–4,342)	4,076 (1,534–6,840)	4,267 (2121–7,473)	<0.001
Fluid accumulation, %[6]	3.4 (1.1–6.8)	2.2 (0.3–4.7)	4.2 (1.7–8.5)	5.7 (2.5–8.3)	<0.001
Vasopressors[5], *n* (%)	303 (61)	123 (56)	143 (66)	37 (61)	0.22
Diuretics[5], *n* (%)	242 (49)	121 (55)	100 (46)	21 (34)	0.002
Mechanical ventilation[5], *n* (%)	325 (65)	146 (67)	147 (68)	32 (52)	0.1
CCL14, ng/mL	1.6 (0.6–5.9)	0.6 (0.3–0.9)	3.5 (2.0–6.7)	28.5 (17.7–30.0)	<0.001

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CCL14, C-C-motif chemokine ligand 14; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes. [1]Continuous variables presented by median (interquartile range), and categorical variables as count (%). [2]BMI was calculated using patient's weight in kilograms divided by higher in meter square. [3]*p* value for race categories was calculated using χ^2 test. [4]eGFR was calculated based on CKD-EPI creatinine-based equation without race. [5]Fluid balance, mechanical ventilation, diuretic, and vasopressor use were assessed over 48 h (day pre- and day post-CCL14 collection). [6]Percent fluid accumulation is fluid balance over 48 h normalized by patient body weight at enrollment.

interaction ($p < 0.001$) (Table 2). In the low CCL14 risk category, urine output was higher in the diuretic versus non-diuretic group at the start of the observation period (difference of 49 mL, 95% CI: 30.1, 67.8) and the difference decreased over time (−0.63 mL/h, 95% CI: −0.83, −0.44), largely due to an increase in average urine output for the non-diuretic group over time (0.44 mL/h, 95% CI: 0.30, 0.58) (Fig. 2a). In contrast, within the intermediate CCL14 risk category, urine output was similar in the two diuretic arms at the beginning of the observation period (difference of 7.9 mL, 95% CI −12.0, 27.7), but diverged over time based on diuretic use (0.56 mL/h, 95% CI: 0.38, 0.74) with the average urine output increasing more quickly over time for those who received diuretics (Fig. 2b). In the high CCL14 risk category, urine output based on diuretic use was not significantly different at the start (difference of −7.5 mL, 95% CI −46.8, 31.7). Although the rate of increase in

Table 2. The effect of time and diuretic exposure within CCL14 risk categories per mixed linear regression analysis[1]

	CCL14 reference category[2]					
	low		intermediate		high	
	coefficient (95% CI)	*p* value	coefficient (95% CI)	*p* value	coefficient (95% CI)	*p* value
Main effects						
Intercept	63.3 (49.2, 77.4)	<0.001	50.3 (36.8, 63.8)	<0.001	42 (19.0, 65.0)	<0.001
CCL14 risk category		0.222		0.222		0.222
CCL14 low	REF		13 (−6.5, 32.5)		21.3 (−5.72, 48.3)	
CCL14 intermediate	−13 (−32.5, 6.49)		REF		8.28 (−18.4, 35.0)	
CCL14 high	−21.3 (−48.2, 5.63)		−8.3 (−34.9, 18.3)		REF	
Diuretic use versus no use	49.0 (30.1, 67.8)	<0.001	7.90 (−12.0, 27.7)	0.437	−7.50 (−46.8, 31.7)	0.709
Time variable	0.44 (0.30, 0.59)	<0.001	0.42 (0.30, 0.54)	<0.001	0.18 (−0.02, 0.38)	0.073
First-order interactions						
Diuretic use and CCL14 risk interaction		0.003		0.003		0.003
CCL14 low	REF		41.1 (13.8, 68.4)		56.5 (12.9, 100)	
CCL14 intermediate	−41.1 (−68.4, −13.8)		REF		15.4 (−28.6, 59.3)	
CCL14 high	−56.5 (−99.8, −13.1)		−15.3 (−59.1, 28.4)		REF	
Time and CCL14 risk interaction		0.087		0.087		0.087
CCL14 low	REF		0.02 (−0.16, 0.21)		0.26 (0.01, 0.51)	
CCL14 intermediate	−0.02 (−0.21, 0.16)		REF		0.24 (0.00, 0.47)	
CCL14 high	−0.26 (−0.51, −0.01)		−0.24 (−0.47, 0.00)		REF	
Diuretic use and time interaction	−0.63 (−0.83, −0.44)	<0.001	0.56 (0.38, 0.74)	<0.001	0.37 (0.03, 0.71)	0.03
Second-order interaction						
Diuretic use, time, and CCL14 risk interaction		<0.001		<0.001		<0.001
CCL14 low	REF		−1.19 (−1.45, −0.92)		−1.00 (−1.39, −0.61)	
CCL14 intermediate	1.19 (0.92, 1.45)		REF		0.19 (−0.20, 0.57)	
CCL14 high	1.00 (0.61, 1.39)		−0.19 (−0.57, 0.20)		REF	

CCL14, C-C-motif chemokine ligand 14; CI, confidence interval. [1]The generalized mixed regression model includes time of urine output measurement, diuretic use (yes vs. no), CCL14 (low, intermediate, and high), and their interaction terms (2 and 3 ways) as fixed effects, patient as random effect, and hourly urine output as dependent variable. [2]CCL14 ≤ 1.3 and CCL14 > 13 ng/mL were used to define low, intermediate, and high categories.

urine output was statistically significantly greater with diuretics exposure than without (0.37 mL/h, 95% CI: 0.028, 0.71), this difference did not result in a meaningful difference (10 mL or less per hour) in average hourly urine output at any time during the course of the observation the period (Fig. 2c). When analyzed as cumulative over the 48-h period following CCL14 collection, mean urine output did not differ significantly by diuretic exposure in the high CCL14 risk category (Fig. 3). Diuretic exposure was associated with higher cumulative urine output in the low CCL14 risk category only.

In a multivariable logistic regression model which included diuretic use, baseline eGFR, and fluid balance, CCL14 risk category was independently associated with AKI stage 3 per urine output criterion during the second day of the 48-h observation period; odds ratio for CCL14 intermediate versus low was 6.49 (1.77, 41.8), and high versus low was 31.8 (8.36, 208.9) (online suppl. eTable 5). Moreover, CCL14 was associated with the composite endpoint of KRT or death within 7 days, despite adjustment for weight-adjusted average urine output (<0.5 mL/kg/h) over 48 h following CCL14 measurement;

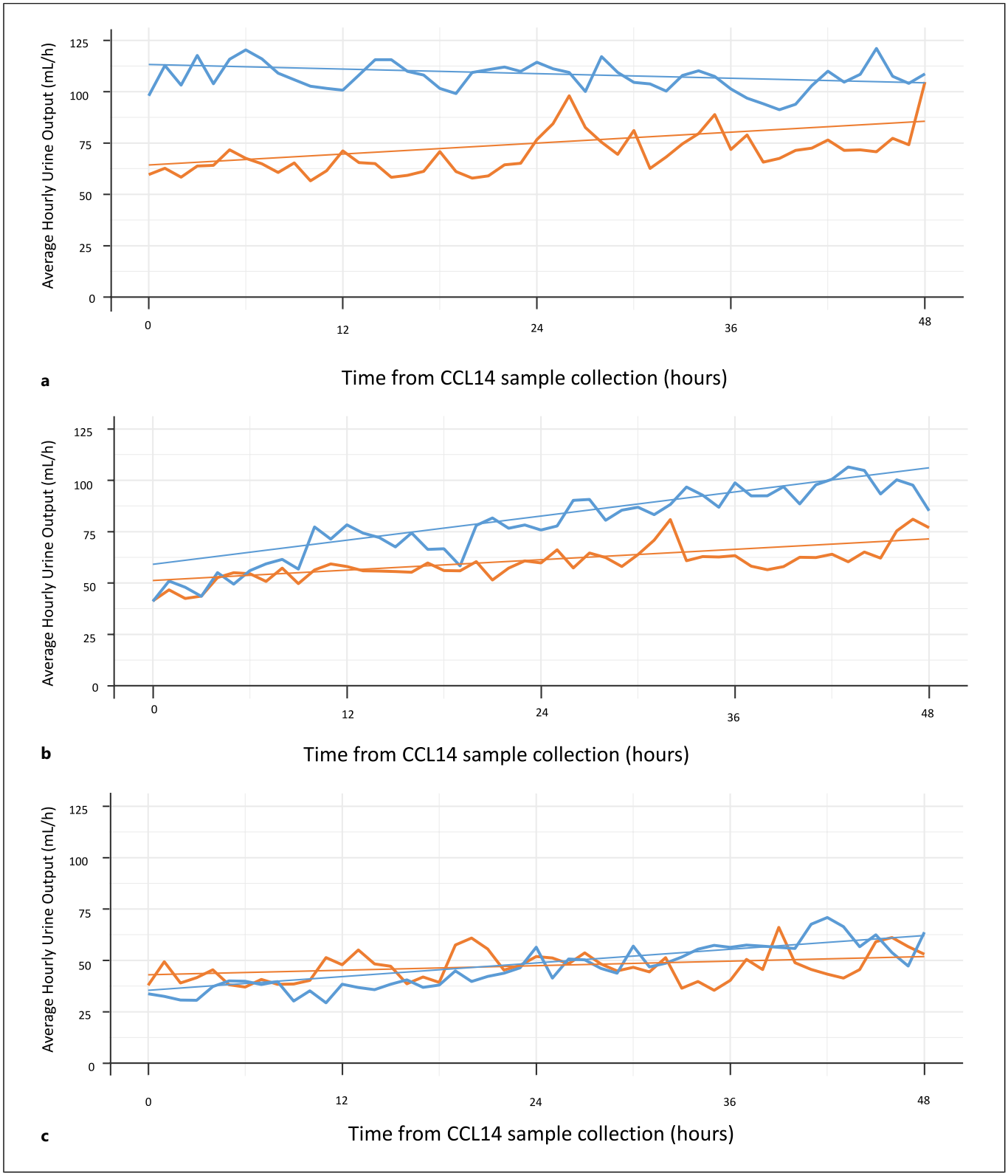

Fig. 2. Average hourly urine output versus time with and without diuretics in patients with low (**a**), intermediate (**b**), and high (**c**) CCL14 risk categories. CCL14 ≤ 1.3, 1.3 < CCL14 ≤ 13, and CCL14 > 13 ng/mL were used to define low, intermediate, and high categories. Blue color denotes diuretics and orange color no diuretics.

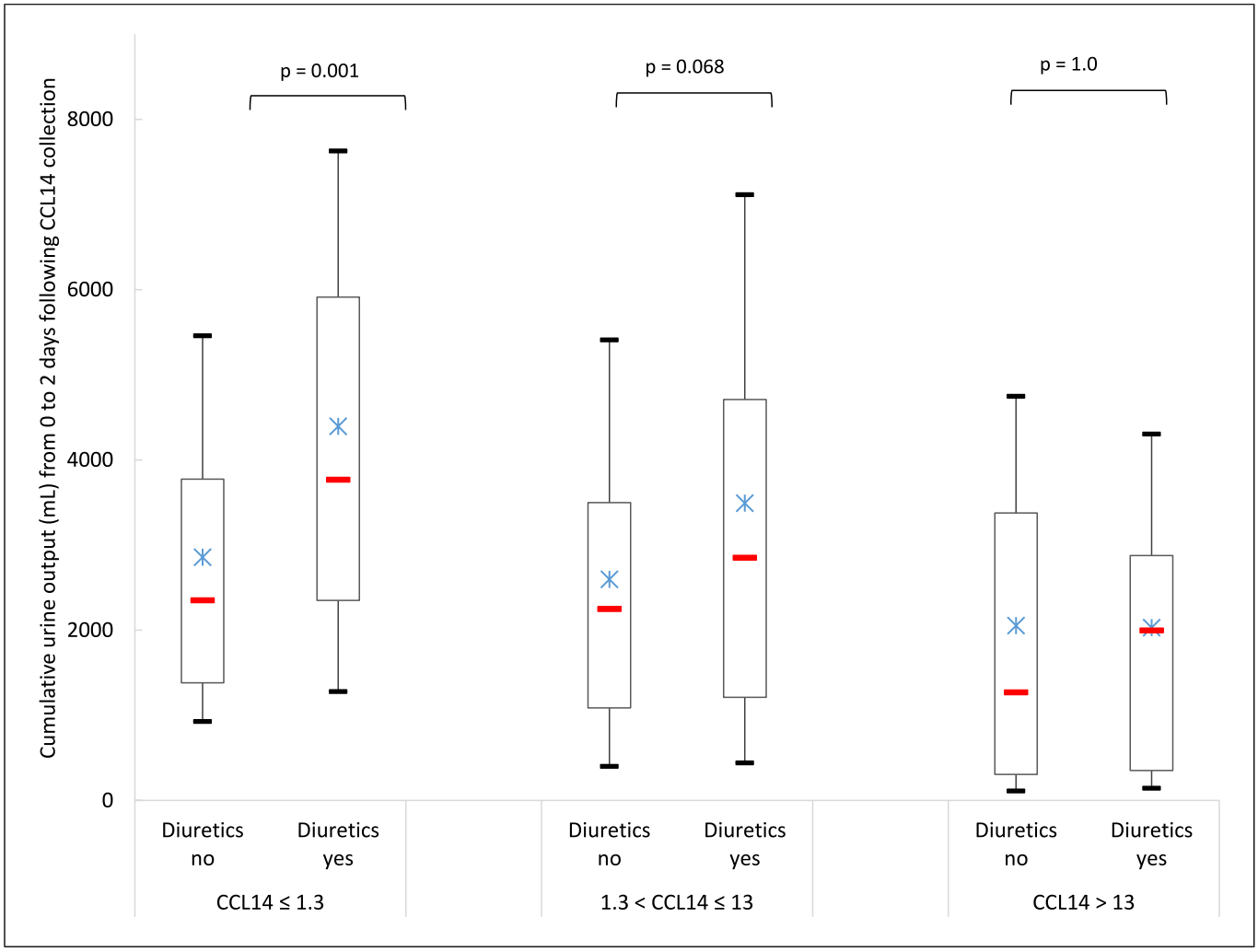

Fig. 3. Cumulative urine output over 48 h stratified by diuretic use and CCL14 risk categories. Bottom and top whiskers represent the 10th and 90th percentiles of the CCL14 concentrations in that group, respectively. Bottom and top boxes represent the 1st and 3rd quartiles, respectively. The red bars and blue asterisks are the median and mean concentrations, respectively. *p* values for the difference in mean concentrations within each CCL14 risk category were computed by the Tukey's multiple comparison test following a generalized linear model fit of CCL14 concentrations with diuretics exposure, CCL14 risk categories, and their interaction.

odds ratio for CCL14 intermediate versus low was 2.47 (1.51, 4.08), and high versus low was 5.3 (2.76, 10.30) (online suppl. eTable 5).

Discussion

In the current study, three risk categories based on previously standardized and validated CCL14 cut-offs were associated, in a graded manner, with sustained or improving urine output over 48 h in patients with moderate to severe AKI [6]. Conversely, in patients with high CCL14 (>13 ng/mL), urine output remained low regardless of diuretic use, whereas patients with low CCL14 levels (≤1.3 ng/mL) had higher and sustained urine output when managed with diuretics. Moreover, CCL14 risk category was not only associated with oliguria (urine output-based AKI stage 3) on the 2nd day, but also predicted the need for dialysis or death within 7 days independent of oliguria during the 48-h observation period.

Functional markers such as serum creatinine have a delayed response following injury and do not reflect strained electrolyte, acid/base, and fluid homeostasis.

Urine output rate (with or without diuretics), on the other hand, although an unreliable marker if not sustained, is a pivotal clinical parameter in patient management. Indeed, for patients not randomized to immediate KRT, oliguria with positive fluid balance was invariably the most common indication for KRT receipt in the trials which investigated strategies for timing of KRT initiation [2–5]. Patients with sustained or improving urine output with or without diuretics, and regardless of conventional biochemical indicators (creatinine and BUN), are often managed conservatively (i.e., without KRT). Furthermore, patients with adequate urine output are more likely to maintain neutral fluid balance, respond to medical management of hyperkalemia, and tolerate volume infusion with buffer administration for metabolic acidosis. In the current study, CCL14 risk category was associated with KRT or death within 7 days of measurement independent of urine output. The latter indicates that CCL14, in addition to being associated with urine output trajectory within the observation period, may independently predict progression to KRT in the current study. Our findings are consistent with a recent report, where the combination of a negative furosemide stress test with CCL14 measurement improved prediction of KRT indications in critically ill patients with AKI [12].

Although transient fluctuations in urine output may reflect physiologic adaptive response to hemodynamic changes [13, 14], sustained oliguria more than 12 h (KDIGO stage 2 or 3) is associated with poor outcomes irrespective of concomitant serum creatinine-based AKI staging [8, 15]. Moreover, oliguria not responsive to diuretics is likely indicative of more severe and progressive kidney injury [7]. In the current study, patients with low CCL14 and exposed to diuretics maintained elevated urine output for the duration of the study. Furthermore, those in the intermediate category, which represent 44% of the cohort, showed an increase in urine output approximately 12 h post-CCL14 measurement. Prediction of urine output trajectory over an extended time period of 48 h in patients with moderate to severe AKI may help treating clinician in timely initiation of appropriate intervention. Current clinical practice for critically ill patients' volume overload is a trial of diuretics. The current results suggest that diuretic response may be significantly delayed in patients with intermediate CCL14 and absent all together in patients with high levels. Thus, measuring the biomarker offers an attractive alternative to a prolonged "wait and see" approach that risks exposing patients to unnecessary KRT or continued exposure to fluid overload.

The current study has strengths and limitations. The study uses an assembled cohort of critically ill patients recruited from multiple international medical centers from mixed medical and surgical units. Due to large sample size, the study was able to not only examine the association of urine output with CCL14 risk categories, but also observe the downstream clinical implications by analyzing their impact on KRT, a patient-centered outcome and invasive procedure. Although the study recorded daily diuretic use on individual patients during the observation period, details of the type of drug, mode of administration, and dosing were not available. Indication for dialysis initiation was not protocolized due to observational nature of the study. Due to the observational nature of the study, diuretic used was not randomized but was assumed to be clinically indicated. Of note also, not all patients enrolled, upon further adjudication, had reached stage 2 or 3 per inclusion criteria, but ultimately were included in the current analysis following an "intention to diagnose" principle.

In conclusion, the current study demonstrates the association of CCL14 with urine output over the course of 48 h in critically ill patients with moderate to severe AKI with and without diuretic treatment. It also shows the complementary role of CCL14 to urine output in the ensuing need for KRT in these patients.

Statement of Ethics

The Ruby and Sapphire study protocol and ethics approval were obtained from the Western Institutional Review Board (Puyallup, WA), approval numbers 20101176 and 20130523, and individual investigational review boards or Ethics Committees as required by each enrolling site. Written informed consent was obtained from all individual participants included in the studies or their legally authorized representatives.

Conflict of Interest Statement

Sevag Demirjian is an employee of Cleveland Clinic and has consulted for Baxter, Outset Medical, bioMérieux, and MediBeacon. Dr. Demirjian and Cleveland Clinic Innovations Center hold the US patent No. 10281455 for post-procedure AKI prediction algorithms. Lakhmir S. Chawla is an employee and stockholder in Stavro Medical and has consulted for ExThera Medical, AcelRx, CalciMedica, and Silver Creek Pharma. Danielle Davison declares no competing interests. Lui Forni has received research funding from Baxter, has received honoraria from Baxter, Jafron, and bioMérieux, and has been an advisory board member for Sphingotec and Novartis. Michael Heung has been a consultant for CardioSounds Inc., Potrero Inc., and Wolters Kluwer Inc. and has received grant funding from CardioSounds Inc., Astute

Medical/ bioMérieux Inc., and Spectral Inc. Eric A.J. Hoste has been a member of the steering committee for a CSA study for AMPharma. Jay L. Koyner has received grants/research funding from the NIH, Fresenius, and bioMérieux, has consulted for Baxter, bioMérieux (Astute), Mallinckrodt, Seastar, Alexion, Novartis, and Guard Therapeutics, and has received honoraria from ASN. J. Patrick Kampf, Thomas Kwan, and Paul McPherson were employees of Astute Medical, have owned stock in bioMérieux, have consulted for bioMérieux, and are inventors on patents assigned to Astute Medical/ bioMérieux. John A. Kellum is an employee and stockholder in Spectral Medical and has consulted for Alexion, Astellas, bioMérieux, CSL Behring, Chugai Pharma, GE Healthcare, Mitsubishi Tanabe, and Novartis.

Author Contributions

Sevag Demirjian contributed to the study design and interpretation of results, acquired study data, and drafted the work. Thomas Kwan analyzed the study data and contributed to interpretation of data and drafting of the work. J. Patrick Kampf, Paul McPherson, and John A. Kellum contributed to study design, interpretation of results, and drafting of the work. Lakhmir Chawla contributed to the clinical study design and reviewed and made critical revisions to the work. Danielle Davison, Lui Forni, Michael Heung, Eric A.J. Hoste, and Jay L. Koyner acquired study data and reviewed and made critical revisions to the work. All authors have provided final approval of the work for publication.

Funding Sources

The Ruby and Sapphire studies were funded by Astute Medical (Astute Medical, Inc.), a bioMérieux company. J.P. Kampf, T. Kwan, and P. McPherson were employees of Astute Medical. No other author received recompense for their contributions to this study.

Data Availability Statement

The data that support the findings of this study are not publicly available due to containing information that might compromise the privacy of research participants, but are available from the study sponsor (bioMérieux company) upon reasonable request on case-by-case basis.

References

1 Ronco C, Bellomo R, Kellum JA. Acute kidney injury. Lancet. 2019;394(10212):1949–64. https://doi.org/10.1016/S0140-6736(19)32563-2.

2 Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med. 2016;375(2):122–33. https://doi.org/10.1056/NEJMoa1603017.

3 Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. JAMA. 2016;315(20):2190–9. https://doi.org/10.1001/jama.2016.5828.

4 STARRT-AKI Investigators, Canadian Critical Care Trials Group, Australian and New Zealand Intensive Care Society Clinical Trials Group, United Kingdom Critical Care Research Group, Canadian Nephrology Trials Network, Irish Critical Care Trials Group, et al. Timing of initiation of renal-replacement therapy in acute kidney injury. N Engl J Med. 2020;383(3):240–51. https://doi.org/10.1056/NEJMoa2000741.

5 Gaudry S, Hajage D, Martin-Lefevre L, Lebbah S, Louis G, Moschietto S, et al. Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial. Lancet. 2021;397(10281):1293–300. https://doi.org/10.1016/S0140-6736(21)00350-0.

6 Koyner JL, Chawla LS, Bihorac A, Gunnerson KJ, Schroeder R, Demirjian S, et al. Performance of a standardized clinical assay for urinary C-C motif chemokine ligand 14 (CCL14) for persistent severe acute kidney injury. Kidney360. 2022;3(7):1158–68. https://doi.org/10.34067/KID.0008002021.

7 Chawla LS, Davison DL, Brasha-Mitchell E, Koyner JL, Arthur JM, Shaw AD, et al. Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. Crit Care. 2013;17(5):R207. https://doi.org/10.1186/cc13015.

8 Bianchi NA, Stavart LL, Altarelli M, Kelevina T, Faouzi M, Schneider AG. Association of oliguria with acute kidney injury diagnosis, severity assessment, and mortality among patients with critical illness. JAMA Netw Open. 2021;4(11):e2133094. https://doi.org/10.1001/jamanetworkopen.2021.33094.

9 Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care. 2013;17(1):R25. https://doi.org/10.1186/cc12503.

10 Hoste E, Bihorac A, Al-Khafaji A, Ortega LM, Ostermann M, Haase M, et al. Identification and validation of biomarkers of persistent acute kidney injury: the RUBY study. Intensive Care Med. 2020;46(5):943–53. https://doi.org/10.1007/s00134-019-05919-0.

11 Nakagawa S, Schielzeth H. A general and simple method for obtaining R2 from generalized linear mixed-effects models. Methods Ecol Evol. 2013;4(2):133–42. https://doi.org/10.1111/j.2041-210x.2012.00261.x.

12 Meersch M, Weiss R, Gerss J, Albert F, Gruber J, Kellum JA, et al. Predicting the development of renal replacement therapy indications by combining the furosemide stress test and chemokine (C-C motif) ligand 14 in a cohort of postsurgical patients. Crit Care Med. 2023;51(8):1033–42.

13 Prowle JR, Liu YL, Licari E, Bagshaw SM, Egi M, Haase M, et al. Oliguria as predictive biomarker of acute kidney injury in critically ill patients. Crit Care. 2011;15(4):R172. https://doi.org/10.1186/cc10318.

14 Myles PS, McIlroy DR, Bellomo R, Wallace S. Importance of intraoperative oliguria during major abdominal surgery: findings of the restrictive versus liberal fluid therapy in major abdominal surgery trial. Br J Anaesth. 2019;122(6):726–33. https://doi.org/10.1016/j.bja.2019.01.010.

15 Kellum JA, Sileanu FE, Murugan R, Lucko N, Shaw AD, Clermont G. Classifying AKI by urine output versus serum creatinine level. J Am Soc Nephrol. 2015;26(9):2231–8. https://doi.org/10.1681/ASN.2014070724.