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CCL14 testing to guide clinical practice in patients with AKI: Results from an international expert panel

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ABSTRACT

Purpose: Urinary C-C motif chemokine ligand 14 (CCL14) is a strong predictor of persistent stage 3 acute kidney injury (AKI). Multiple clinical actions are recommended for AKI but how these are applied in individual patients and how the CCL14 test results may impact their application is unknown.
Methods: We assembled an international panel of 12 experts and conducted a modified Delphi process to evaluate patients at risk for persistent stage 3 AKI (lasting 72 hours or longer). Using a Likert scale, we rated 11 clinical actions based on international guidelines applied to each case before and after CCL14 testing and analyzed the association between the strength and direction of recommendations and CCL14 results.
Results: The strength and direction of clinical recommendations were strongly influenced by CCL14 results ($P < 0.001$ for the interaction). Nine (82%) recommendations for clinical actions were significantly impacted by CCL14 results ($P < 0.001$ comparing low to highest CCL14 risk category).
Conclusions: Most recommendations for care of patients with stage 2-3 by an international panel of experts were strongly modified by CCL14 test results. This work should set the stage for clinical practice protocols and studies to determine the effects of recommended actions informed by CCL14.

1. Background

For patients with stage 2-3 acute kidney injury (AKI), the urinary biomarker chemokine ligand CCL14 is a strong predictor of persistent stage 3 AKI [1-5]. Given the considerable uncertainty regarding the course of AKI, the ability to predict kidney recovery could significantly impact the care of patients. However, the approach to patients with AKI and therefore at risk for persistent stage 3 AKI is not standardized. The

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KDIGO clinical practice guideline for AKI [6] recommends multiple clinical actions but how these are applied in individual patients and how the CCL14 test results may influence their application is unknown.

Accordingly, we sought to understand what clinical actions are recommended by experts in specific cases of AKI and how CCL14 test results might influence these recommendations. To this end, we assembled a panel of clinical experts representing nephrology and critical care from both Europe and North America and asked them to evaluate a series of real clinical vignettes of patients where stage 2 or 3 AKI was already present, and patients were at risk for persistent stage 3 AKI (lasting 72 hours or longer)—the clinical endpoint used in studies of CCL14 [1-5]. Next, we asked them to rate their recommendations using a 9-point Likert scale ranging from "strongly against" to "strongly for" a clinical action, respectively. We then asked them to re-rate each recommendation assuming three different CCL14 results corresponding to lowest risk, increased risk, or highest risk for the development of persistent stage 3 AKI. Finally, we performed a single-stage Delphi process where all cases were discussed as a group and participants were asked to repeat the exercise.

Our primary analysis tested the association between the strength and direction of recommendations for clinical actions and CCL14 levels and our secondary analysis tested whether changes in recommendations from the pre-test condition, were associated with CCL14 levels. We also examined whether the primary analysis varied by specialty or by geographic location.

2. Methods

2.1. Study subjects

We assembled a panel of twelve experts in AKI from Europe (LF, MJ, MO, JP, CR, AS, AZ) and North America (SMB, SD, JAK, JLK, AT), representing Critical Care and Nephrology. Experts were all practicing clinicians, selected from the top 0.3% of published authors on AKI worldwide between 2013 and 2023 (expertscape.com accessed October 4, 2023). Additional criteria included balancing specialty, and country of origin to the extent possible. Written informed consent was obtained from each participant.

2.2. Patient data

We selected clinical cases from a prior study, the RUBY study, which included adult critically ill patients who met KDIGO [6] stage 2-3 AKI criteria from 21 clinical sites across Europe and the United States [1]. Investigational review boards (or the equivalent) approved the study, and written informed consent was obtained from subjects or their legally authorized representatives. We selected six clinically diverse cases (Table 1) after review of the clinical data, including demographics, medical history, serial serum creatinine and urine output, and urinary CCL14 results from the RUBY subjects. Clinical cases were prepared for review by the expert panel using deidentified data with minor modifications to ensure anonymity and clarify relevant gaps in the clinical data. Prior to presentation to the full panel, the cases were reviewed by four members of the panel to optimize content and presentation of the data.

2.3. Clinical actions

The KDIGO clinical practice guideline for AKI [6] was used as the basis for developing a list of potential clinical actions. Table 2 shows the mapping of KDIGO recommendations to specific clinical actions. The final list of eleven clinical actions was developed based on input from the four participants (LF, JAK, MO, AZ) who performed a preliminary review of the clinical cases. For some clinical actions, the wording as presented to the panel was modified as appropriate for the clinical context of the case and later harmonized before statistical analysis.

2.4. Survey design

The survey contained formatted clinical case data which is provided in supplemental Fig. S1 and a questionnaire with the 11 clinical actions for each of the six clinical cases. For each clinical action, four separate scenarios were presented: 1. initial recommendation (pre-test), i.e. without knowledge of CCL14 test result, 2. CCL14 $\leq$ 1.3 ng/mL (lowest risk), 3. CCL14 $>$ 1.3 and $\leq$ 13 ng/mL (increased risk), and 4. CCL14 $>$ 13 ng/mL (highest risk) [3]. Each scenario was hypothetical as the panel was blinded to the actual CCL14 result. A 9-point Likert scale ranging from "Strongly against" to "Strongly for" a clinical action was used for

Table 1
Patient characteristics for each case.

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age	54	72	61	59	32	75
Sex	Female	Female	Female	Male	Female	Female
Weight (kg)	60	80	74	112	128	60
Height (cm)	170	160	160	172	159	164
Baseline serum creatinine (mg/dL)	0.7	0.5	0.8	0.9	0.6	0.8
Estimated GFR (mL/min/1.73m^2)	104	101	83	71	124	76
Reason for hospital admission	Perforated viscus, surgery, sepsis	Pneumonia, sepsis	Aortic aneurysm, respiratory insufficiency, AKI	CABG X3, multi-vessel CAD	Pneumonia, ARDS	Non ST-elevated MI, nasal hemorrhage
Reason for ICU admission	Post-op, septic shock, closed-loop obstruction	Pneumonia, sepsis	Left aortorenal bypass, repair of type 4 thoraco-abdominal aortic aneurysm	Post-op	VV ECMO, H1N1, pneumonia, ARDS	Post-coronary stenting
Medical history	Hypothyroid, alcoholic gastritis, no CKD, no diabetes	Hypertension, no CKD, no diabetes	Diabetes, hypothyroid, hypertension, no CKD	Type 2 diabetes, CKD, hypertension, diverticulitis (colonic), cellulitis	Type 1 diabetes, morbid obesity, hypertension, asthma, no CKD	CAD, hypertension, emphysema, COPD, no CKD, no diabetes
KDIGO Stage at time of urinary CCL14 sample collection	Stage 3 by serum creatinine	Stage 3 by serum creatinine	Stage 3 by serum creatinine	Stage 2 by both serum creatinine and urine output	Stage 2 by serum creatinine	Stage 2 by serum creatinine

Formatted cases are shown in supplemental Fig. S1.
Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; ICU, intensive care unit; MI, myocardial infarction; VV, veno-venous.

Table 2
Clinical Actions based on the KDIGO guideline for Acute Kidney Injury

KDIGO*	Clinical Action	Comments
Discontinue nephrotoxic agents when possible	Avoid nephrotoxic medications	Various nephrotoxic drugs were examined. For 2 cases there were questions on vancomycin and piperacillin/ tazobactam. For these cases, vancomycin was used for the primary analysis and piperacillin/ tazobactam in a secondary analysis.
Ensure volume status and perfusion pressure	Give fluid	
	Administer furosemide	
Consider functional hemodynamic monitoring	Use functional hemodynamic monitoring	
Monitor serum creatinine	Measure serum creatinine at least daily	
Monitor urine output	Keep foley catheter, 1-2 hourly Urine Output	
Consider alternatives to radiocontrast procedures	Avoid IV radiocontrast	
Check for changes in drug dosing	Adjust non-nephrotoxic, renally cleared medications	
Consider renal replacement therapy	Consult nephrology	These two actions were used as surrogates for consider renal replacement therapy
	Discuss RRT with patient/family	
Non-invasive diagnostic workup	Perform renal ultrasound	

Abbreviations: RRT, renal replacement therapy, IV, intravenous.
* KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International. 2012;2(1): Fig. 4 page 8.

each scenario.

2.5. Delphi process

The format of the clinical cases, the clinical action questionnaire, and the performance characteristics of urinary CCL14 [3] were reviewed with each member of the expert panel prior to administering the survey. Each participant then completed the survey independently online. The survey results were summarized and then presented to the expert panel for guided discussion, after which each participant completed the survey a second time. After resolving any data queries or missing scores the results from the second round were analyzed as described below.

2.6. Statistical analyses

The responses for each clinical action from the twelve experts across the six cases were presented in boxplots stratified by the pre-test condition and three hypothetical CCL14 results. For our primary analysis of testing whether the clinical recommendations were influenced by CCL14 levels, the responses were treated as an ordinal variable from -4 to +4, corresponding to "Strongly against" to "Strongly for", and modeled using mixed ordinal regression with clinical actions, CCL14 results (three risk categories), and their interaction as fixed effects and cases and experts as random effects to account for the hierarchical structure of the survey design. Because all the experts responded with a "Strongly for" rating for the clinical action, "At least daily serum creatinine measurement", across all cases and CCL14 scenarios, this clinical action was removed from the dataset prior to regression procedure to avoid convergence error. *Post hoc* pairwise comparisons were used to explore the mean difference in Likert scores from the regression model between the CCL14 levels for each clinical action. To characterize the variability in the expert responses pre- and post-CCL14 test, the Likert scores (-4 to +4) were treated as numerical values, and variances were computed for each clinical action and CCL14 level across the cases and experts. The Brown-Forsythe test [7] was used to detect heterogeneity in variances among the CCL14 results for each clinical action, and a *post hoc* pairwise comparison between the three CCL14 risk categories and the pre-test condition was used to find those pairs with significantly different variances. Two-sided p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using R 4.0.2 (R Foundation for Statistical Computing. Vienna, Austria).

3. Results

3.1. Recommended actions and associations with CCL14 risk categories

Our primary analysis tested whether clinical recommendations were influenced by CCL14 results (categorized as Lowest, Increased or Highest Risk) defined by two clinical cutoff values described previously [3]. This analysis revealed that overall, the strength and direction of clinical recommendations were strongly influenced by CCL14 results ($P < 0.001$ for CCL14, clinical action, and their interaction). Given this result, we examined pairwise comparisons between the three CCL14 risk categories and between each CCL14 category and the pre-test condition for each clinical action (Fig. 1). Most recommendations for clinical actions were significantly influenced by CCL14 results ($P < 0.001$ comparing low to highest CCL14 risk category); the exceptions being measurement of serum creatinine (not shown) and use of furosemide (Fig. 1). Measurement of serum creatinine was always strongly recommended and was not affected by CCL14 results. Furosemide use was highly variable and overall, recommendations were not significantly different with different CCL14 results.

Recommendations for each case along with changes based on CCL14 results are shown in the supplement (Fig. S2) with examples shown in Fig. 2. As shown in Table 3, overall, only two actions, measure urine output and measure serum creatinine, achieved >50% "strongly for" rating in the pre-test (no CCL14) condition and no actions achieved a "strongly against". Thus, most clinical actions including those recommended by the KDIGO guideline were not strongly recommend in individual cases. When the CCL14 result was >13 ng/mL corresponding to the highest risk, three additional actions, avoid/discontinue potentially nephrotoxic drugs, adjust drug dosing of renally cleared drugs and use functional hemodynamic monitoring achieved >50% "strongly for". Conversely, when CCL14 was ≤1.3 ng/mL, corresponding to the lowest risk, there were still no actions rated as >50% "strongly against".

When the 9-point Likert scale is collapsed so that strongest (+4) and second strongest (+3) rating in favor of an action are pooled, we see that three actions achieve a majority rating in favor for the pre-test (no CCL14) condition: measure urine output and creatinine but also adjust non-nephrotoxic, renally cleared medications (Table 3). When CCL14 was >13 ng/mL the number of actions achieving a majority in favor rose to eight with use functional hemodynamic monitoring, avoid nephrotoxic medications, consult nephrology, discuss possible renal replacement therapy (RRT) with the patient/family and avoid IV contrast all added to the list. Notably, for consult nephrology and discuss possible RRT, <10% and 0% achieved this rating in the pre-test condition. The largest effect of a CCL14 result ≤1.3 ng/mL, lowest risk, was seen with adjust non-nephrotoxic, renally cleared medication where in the pre-test condition 72% rated the action +3 or +4. When CCL14 ng/mL was ≤1.3 only 56% rated it this highly.

3.2. Secondary analyses

3.2.1. Clinical specialty and geographic location

We tested in secondary analysis whether clinical specialty (intensivist vs. nephrologist, N=6 each) or geographic location (North America, N=5 vs. Europe, N=7) of experts were associated with clinical

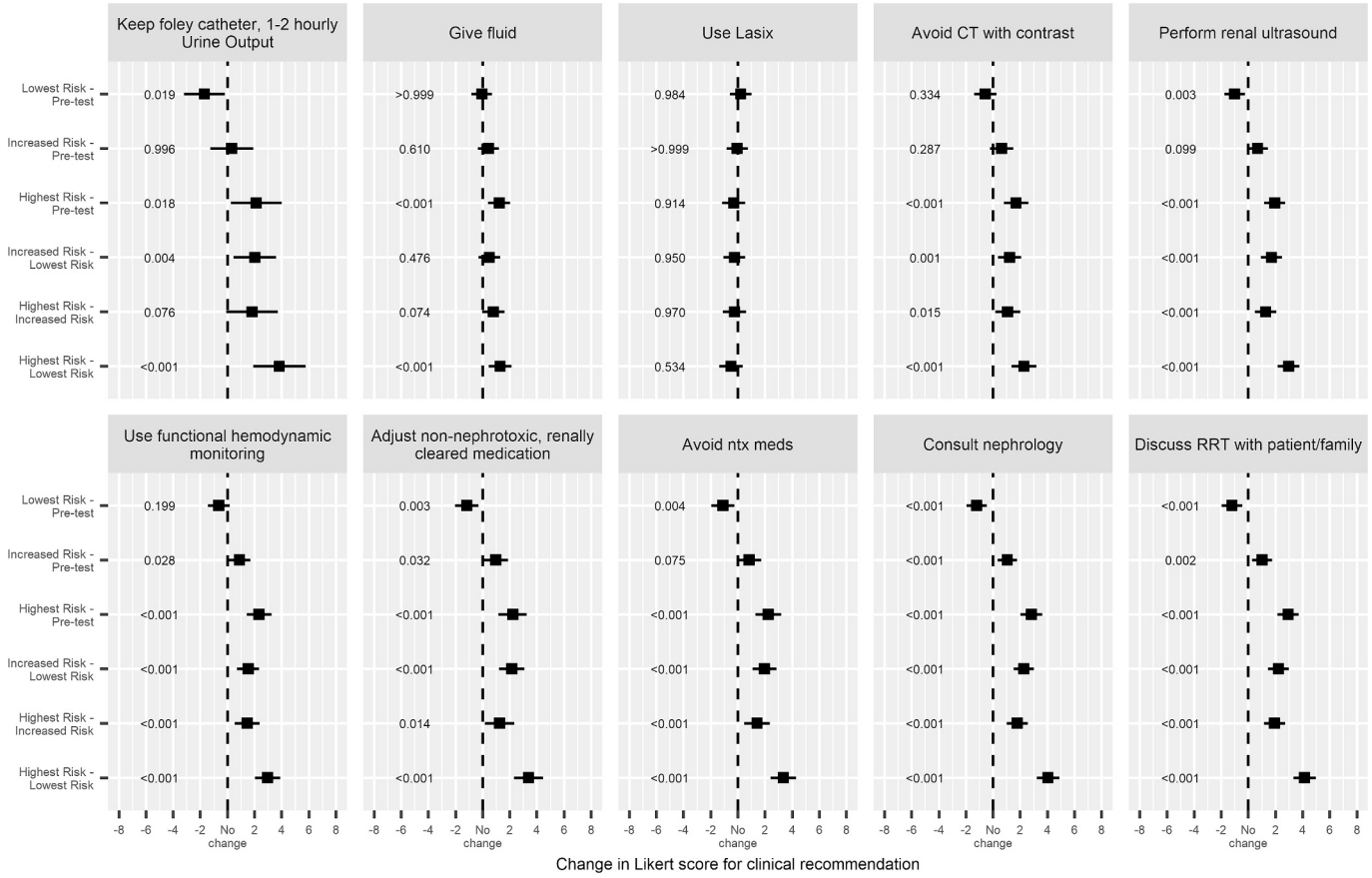

Fig. 1. Change in Likert scores as a function of persistent stage 3 AKI risk for each clinical action.
Change in the fitted Likert scores from mixed ordinal regression between the indicated pairs (y-axis) in the format, "A – B", where "A" and "B" is one of the following: Pre-test, Lowest Risk, Increased Risk, and Highest Risk. The p-value (left of ■) is the probability that the change is zero (dotted vertical line). The x-axis is in units of Likert scores where a negative number denotes a Likert score for "A" that is lower than that for "B" in the pair, and a positive number denotes a Likert score for "A" that is higher than that for "B". For example, the recommendation to perform a renal ultrasound was significantly different from the pre-test condition when the CCL14 result indicated lowest risk (more against) with a p-value of 0.003; and in the opposite direction when CCL14 indicted highest risk (more in favor) with a p-value < 0.001.

recommendations or influence of CCL14 results. Neither clinical specialty nor location had an impact on their own or through an interaction with CCL14 levels although power was limited for each analysis ($p > 0.05$, see supplement Table S1).

3.2.2. *Variability among experts*

We also analyzed whether CCL14 levels impacted the variance in clinical recommendations across experts compared with not having a CCL14 result (pre-test condition). These results are summarized in supplemental Table S2. When CCL14 was >13 ng/mL corresponding to the highest risk for persistent stage 3 AKI, variance in scoring significantly decreased for 3 clinical actions, avoid/discontinue potentially nephrotoxic drugs, adjust drug dosing of renally cleared drugs, and use of functional hemodynamic monitoring. Conversely, variance significantly increased for use of furosemide. Variance also increased when CCL14 was ≤1.3 ng/mL for maintain Foley catheter and adjust drug dosing of renally cleared drugs.

3.2.3. *Sensitivity analysis for nephrotoxic drugs*

For Cases 1 and 5, the respondents considered 2 separate actions for "avoid nephrotoxic drugs". Responses for Vancomycin were used in primary analysis. However, responses for piperacillin/tazobactam were used in sensitivity analysis. This change had no material effect on the results; i.e., the strength and direction of clinical recommendations remained strongly influenced by CCL14 results ($P < 0.001$ for the interaction).

4. Discussion

For six clinical cases, twelve experts from Europe and North America significantly modified their recommendations for care based on urinary CCL14 test results corresponding to three categories of risk (lowest, increased, and highest) for developing persistent stage 3 AKI. However, some clinical actions were clearly more impacted than others. Effects of CCL14 on expert recommendations were highly significant ($P < 0.001$) for all clinical actions except measuring serum creatinine and use of furosemide.

Recommendations on avoiding potentially nephrotoxic drugs and adjusting drug dosing of renally cleared drugs were significantly impacted and also less variable when CCL14 was >13 ng/mL (highest risk). This is consistent with the well-recognized impact of nephrotoxic medication [8] on the development of AKI and the potential as a target to modify AKI rates, especially among the critically ill. However, this area is not without controversy and the risk of specific drugs may be difficult to weigh against the potential benefit. This uncertainty has placed nephrotoxic drug research as a priority for AKI [9].

Recommendations for use of functional hemodynamic monitoring were also significantly impacted and less variable when CCL14 was >13 ng/mL (highest risk). The use of functional hemodynamic monitoring to guide fluid resuscitation has been studied extensively in major surgery and in septic shock and has been incorporated in various interventional trials [10-13]. Indeed, in a secondary analysis of data from the Prev-AKI [10] and Prev-AKI2 [11] trials, Von Groote et al. found using logistic

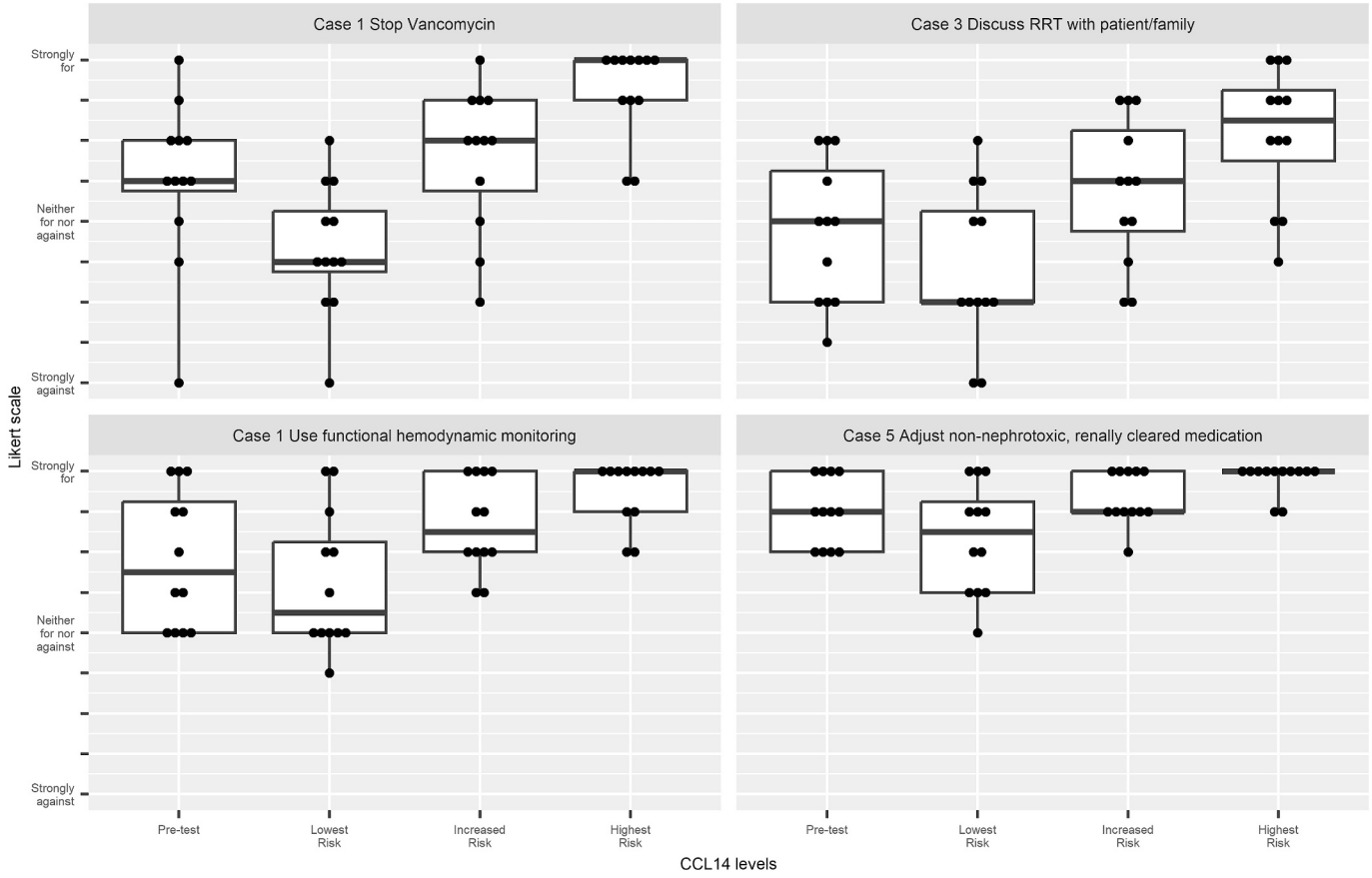

Fig. 2. Example boxplots of responses for four clinical recommendations.
Example boxplots of responses for four clinical recommendations stratified by CCL14 test results. The bottom and top boxes are the 1st and 3rd quartiles, respectively. The bottom and top whiskers are the minimum and maximum, respectively. The middle bars within the boxes are the medians. The dots are the individual responses from the experts.

Table 3
Effect of AKI risk on percentage of experts who were strongly for each clinical action

Clinical Recommendation	Percent experts who chose the highest "for" rating (+4)				Percent experts who chose the highest and second highest "for" rating (+3 or +4)			
	Pre-test	Lowest Risk	Increased Risk	Highest Risk	Pre-test	Lowest Risk	Increased Risk	Highest Risk
Measure serum creatinine at least daily	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**
Keep foley catheter, 1-2 hourly Urine Output	**85%**	**76%**	**82%**	**92%**	**90%**	**82%**	**93%**	**97%**
Adjust non-nephrotoxic, renally cleared medication	42%	33%	**57%**	**78%**	**72%**	**56%**	**86%**	**92%**
Use functional hemodynamic monitoring	25%	19%	33%	**64%**	46%	32%	**58%**	**79%**
Avoid nephrotoxic medications	33%	21%	40%	**57%**	44%	32%	**50%**	**72%**
Avoid CT with contrast	18%	15%	29%	47%	36%	28%	47%	**65%**
Consult nephrology	0%	0%	6%	31%	8%	7%	15%	**54%**
Discuss RRT with patient/family	0%	0%	0%	24%	0%	0%	14%	**54%**
Give fluid	4%	6%	10%	22%	14%	17%	26%	44%
Perform renal ultrasound	4%	3%	8%	25%	13%	4%	24%	47%
Use Furosemide	1%	4%	0%	4%	1%	8%	4%	15%

Percentage of experts who chose the highest "for" rating (+4), and the highest and second highest "for" rating (+4 or +3) by clinical recommendations and CCL14 levels. Values in **bold** are greater than 50%.
Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy; CT, computerized tomography.

regression, hemodynamic optimization (and avoidance of nephrotoxic drugs) were the most important measures to prevent AKI [14]. A meta-analysis including 65 randomized trials and 9308 patients concluded that goal-directed hemodynamic therapy, including various forms of functional hemodynamic monitoring, was effective in reducing AKI in patients undergoing major abdominal and orthopedic surgery [15]. In a modified intent-to-treat analysis that included 83 patients with septic shock randomized to receive fluids as indicated by passive leg raise results and 41 usual care patients, fluid balance at 72 hours or ICU discharge was significantly lower (-1.37 L favoring the intervention arm; 0.65 ± 2.85 L intervention arm vs 2.02 ± 3.44 L usual care arm; P = 0.02) [16]. Fewer patients required RRT (5.1% vs 17.5%; P = 0.04) or mechanical ventilation (17.7% vs 34.1%; P = 0.04) in the intervention arm compared with usual care.

Decision making around use of RRT was also significantly impacted. Consult nephrology and discuss possible RRT with the patient/family were not recommended by a majority of experts in the pre-test condition but became recommendations when CCL14 was >1.3 ng/mL. Given that

timing of RRT initiation remains controversial and likely only benefits patients developing persistent AKI [17] it is perhaps unsurprising that experts felt that results of a biomarker for persistent stage 3 AKI could help guide them. Importantly, in the Ruby study [1], just over half of patients with persistent stage 3 AKI received RRT whereas RRT was distinctly unusual (3.2%) in patients without persistent stage 3 AKI. Furthermore, nearly 60% of patients with CCL14 >13 ng/mL received RRT while fewer than 10% received RRT when CCL14 was 1.3 ng/mL or less [3].

By contrast, CCL14 results had no effect on the already strong, unanimous recommendation for monitoring of serum creatinine. The recommendation for urine output monitoring (maintain Foley catheter) was statistically different when CCL14 was ≤1.3 vs >13 ng/mL, and both were significantly different from the pre-test condition (Fig. 1). Interestingly, recommendations for treatment with furosemide did not differ across CCL14 results. This may have reflected differences in indications for diuretics across cases. Additionally, while diuretics have an important role in managing the complications of kidney dysfunction, their use is determined more by the patient's volume status than by persistence of AKI per se.

Taken together these results suggest efforts to standardize management of stage 2-3 AKI could be enhanced by use of CCL14. However, the largest effects will likely be on management of drugs including nephrotoxins and dosing of renally cleared medication and guiding the use of functional hemodynamic monitoring as well as planning for RRT. In this respect, it is somewhat surprising that recommendations for use of furosemide, a common treatment in patients developing persistent AKI, were not better informed by CCL14 results. Meersch and colleagues reported that combination of the furosemide stress test with CCL14 predicts the development of indications for RRT [5]. Furthermore, Demirjian and coworkers found that response to furosemide was significantly different among patients with CCL14 ≤1.3 vs >13 ng/mL [18]. The importance and ubiquity of diuretic therapy coupled with lack of strong consensus for when to use it in patients with stage 2-3 AKI may warrant further research to help optimize and standardize its use in these patients.

Our study represents the first investigation of how the information from urinary CCL14 testing can alter recommendations for patient management in specific cases of stage 2-3 AKI in the critically ill. Strengths of this analysis include the use of real cases from multiple different institutions and twelve experts in clinical AKI from multiple countries in Europe and North America. Our selection of clinical actions was based on the KDIGO guideline [6]. Several limitations should be mentioned. First, although our case studies were real, they were, by necessity, limited to data collected for the parent study. In the first phase of case review, we encouraged experts to ask for any additional data they deemed necessary, but we could only provide data that was collected in the case report forms. Second, the case review exercise could not completely replicate the clinical situation. Although the Delphi process incorporates group discussion as occurs among a health care team, the experts could not examine patients or interact with all of the different specialties typically represented in a health care team. The experts only had the case forms that we provided. Furthermore, we recognize that AKI experts may not practice the same way as non-experts. Biomarkers and other tests may be less helpful to clinical experts. Third, we made the conscious choice to investigate clinical actions that could reasonably be recommended in all cases. The reason for this was so that we could pool responses across cases and experts. Some of the clinical actions were more applicable and some less in a given case. In addition, we used clinical actions mainly from the KDIGO guideline, but this guideline addresses both prevention and management of AKI and does not even mention persistent AKI per se. However, all of the actions recommended by the guideline were still found to be relevant for persistent AKI by our expert panel. Finally, given the small number of cases and experts we chose to examine differences based on a somewhat arbitrary, simple majority (50%).

In conclusion, most recommendations for care of patients with stage 2-3 by an international panel of experts were strongly modified by CCL14 test results. This work should set the stage for clinical practice protocols and studies to determine the effects of recommended actions informed by this biomarker.

Ethics approval and consent to participate

All participants provided written consent.

Consent for publication

Not applicable.

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CRediT authorship contribution statement

John A. Kellum: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Sean M. Bagshaw:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Sevag Demirjian:** Writing – review & editing, Investigation, Conceptualization. **Lui Forni:** Writing – review & editing, Methodology, Investigation. **Michael Joannidis:** Writing – review & editing, Investigation, Conceptualization. **J. Patrick Kampf:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **Jay L. Koyner:** Writing – review & editing, Investigation, Conceptualization. **Thomas Kwan:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Paul McPherson:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Marlies Ostermann:** Writing – review & editing, Methodology, Investigation, Conceptualization. **John Prowle:** Writing – review & editing, Investigation, Conceptualization. **Claudio Ronco:** Writing – review & editing, Investigation, Conceptualization. **Julia de la Salle:** Writing – review & editing, Funding acquisition. **Antoine Schneider:** Writing – review & editing, Investigation, Conceptualization. **Ashita Tolwani:** Writing – review & editing, Investigation, Conceptualization. **Alexander Zarbock:** Writing – review & editing, Investigation, Conceptualization.

Declaration of competing interest

SB, SD, LF, MJ, JAK, JLK, MO, JP, CR, AS, AT, AZ disclose consulting fees paid by bioMérieux. JPK, TK, and PM were full-time employees of Astute Medical/bioMérieux when this work was conducted. JDLS is a full-time employee of bioMérieux.

Data availability

Not applicable.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2024.154816.

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