Urinary CXCL10 is Associated with Acute Kidney Injury and Sepsis, and Predicts Mortality in Critically Ill Children

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Research

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Abstract

Background: Acute kidney injury (AKI) biomarkers are often susceptible to confounding factors, limiting their utility as a specific biomarker, in the prediction of AKI, especially in heterogeneous population. The urinary CXCL10 motif chemokine 10 (uCXCL10), as an inflammatory mediator, has been proposed to be a biomarker for AKI in a specific setting. Whether uCXCL10 is associated with AKI and predicts AKI in critically ill patients remains unclear. The aims of the study were to investigate clinical variables potentially associated with uCXCL10 levels and determine the associations of uCXCL10 with AKI, sepsis and PICU mortality in critically ill children, as well as its predictive values of aforementioned issues.

Methods: Urinary CXCL10 levels were serially measured in a heterogeneous group of children during the first week after pediatric intensive care unit (PICU) admission. AKI diagnosis was based on the criteria of Kidney Disease: Improving Global Outcomes with serum creatinine and urine output. Sepsis was diagnosed according to surviving sepsis campaign international guidelines for children. Mortality was defined as all-cause death occurring during the PICU stay.

Results: Among 342 critically ill children, 52 (15.2%) developed AKI during the first week after PICU admission, and 132 (38.6%) were diagnosed as sepsis and 30 (12.3%) died during PICU stay. Both the initial and peak values of uCXCL10 remained independently associated with AKI with adjusted odds ratios (AORs) of 1.791 ($P = 0.010$) and 2.002 ($P = 0.002$), sepsis with AORs of 1.679 ($P = 0.003$) and 1.752 ($P = 0.002$), septic AKI with AORs of 3.281 ($P < 0.001$) and 3.172 ($P < 0.001$), and PICU mortality with AORs of 2.779 ($P = 0.001$) and 3.965 ($P < 0.001$), respectively. The AUCs of the initial uCXCL10 for predicting AKI, sepsis, septic AKI, and PICU mortality were 0.63 (0.53-0.72), 0.62 (0.56-0.68), 0.75 (0.64-0.87), and 0.77 (0.68-0.86), respectively. The AUCs for prediction by using peak uCXCL10 were as follows: AKI 0.65 (0.56-0.75), sepsis 0.63 (0.57-0.69), septic AKI 0.76 (0.65-0.87), and PICU mortality 0.84 (0.76-0.91).

Conclusions: Urinary CXCL10 is independently associated with AKI and sepsis, and may be a potential indicator of septic AKI and PICU mortality in critically ill children.

Introduction

Acute kidney injury (AKI) is a common complication in clinical settings and associated with high morbidity and mortality [1–3], especially in critically ill patients [4–6]. The clinical diagnosis of AKI is delayed and the development of therapeutic strategies to improve outcomes of AKI is greatly impeded. Studies on AKI have focused on novel injury biomarkers, contributing to earlier diagnosis of AKI. Although many urinary biomarkers have been reported in adults and children [1, 7, 8], these early biomarkers have not been widely accepted and adopted to clinical practice, especially in children. Strong evidence is still needed to confirm that early urinary biomarkers of AKI have beneficial effects on the clinical outcomes in a general pediatric intensive care unit (PICU) population.

A growing body of evidence demonstrates that many chemokines play an active role in injury and inflammation during AKI development [9, 10]. The CXC motif chemokine ligand 10 (CXCL10), also known as IFN- γ -inducible protein of 10 (IP-10), is released by inflammatory cells and various epithelial cells including renal tubular epithelial cells, and is upregulated in kidney tissue exposed to ischemic, nephrotoxic or inflammatory stress [11–15]. It is reported that CXCL10 levels in urine (uCXCL10) were elevated in adult patients with biopsy-proven acute tubular injury after renal transplantation [16] and patients undergoing cardiac surgery [17], and had an association with AKI after hematopoietic cell transplantation (HCT) in children [18]. In addition, a clinical cross-sectional study indicated that urinary CXCL10 were significantly higher in patients with documented AKI and performed well in differentiating between adult patients with and without AKI [19]. Taken together, however, researches on the relationship between uCXCL10 and AKI were relatively small and conducted in a specific setting [16–18]. It still remains unclear whether uCXCL10 could be used to discriminate AKI of the critically ill patients, because that AKI biomarkers are often susceptible to confounding factors, limiting their utility as a specific biomarker, in the prediction of AKI, especially in heterogeneous population. AKI is frequently associated with sepsis, and sepsis is the most common cause of AKI in critically ill patients, which may limit the use of uCXCL10 as a specific biomarker of AKI in the critically ill patients [5]. Several studies have revealed that serum CXCL10 is early diagnosis of sepsis in adults [20, 21]. There has been little previous evidence for the association between uCXCL10 and sepsis. In this study, we firstly investigated clinical variables potentially associated with uCXCL10 levels and determined the associations of uCXCL10 with AKI, sepsis and PICU mortality in critically ill children. Moreover, we evaluated whether uCXCL10 could serve as an early predictor of AKI, septic AKI or mortality in this population, independently of potential confounders.

Methods

Study design

This was a prospective study conducted from September to December 2016 and from December 2017 to January 2018 in the PICU and critically ill children aged between 1 month and 16 years were eligible for enrollment in the study. Exclusion criteria included: known congenital abnormality of the kidney and a failure to collect urine samples before discharge from the PICU or death. This study was approved by the Institutional Review Board at the Children's Hospital of Soochow University and performed in accordance with the Declaration of Helsinki. Informed parental consent was obtained on admission.

Clinical data collection

We reviewed and recorded demographic and clinical characteristics, including age, body weight, gender, clinical diagnosis, the use of mechanical ventilation (MV), hemofiltration, furosemide, antibiotics, steroids and inotrope during PICU stay. The diagnosis of multiple organ dysfunction syndrome (MODS), shock, and disseminated intravascular coagulation (DIC) that developed during the PICU stay were defined clinically and diagnosed by the attending PICU physicians as the criteria described previously [22]. The duration of MV and the length of PICU stay were also recorded. In addition, the pediatric risk of mortality

III (PRISM III) score was calculated within 24 h after PICU admission to assess the severity of illness in the critically ill children, as described previously [23].

Diagnosis of AKI

The diagnosis of pediatric AKI developed during the first 7 days after PICU admission was based on the increase of serum creatinine (SCr) and/or the reduction of the urine output according to the criteria of Kidney Disease: Improving Global Outcome (KDIGO) [24]. The baseline SCr was defined as the lowest level obtained within 3 months prior to PICU admission. If the baseline SCr value was not available, admission SCr was used. For the critically ill children with $\text{SCr} \geq 1.2 \text{ mg/dL}$ ($106.0 \text{ }\mu\text{mol/L}$) at PICU admission, the lowest value of SCr within 2 weeks during the PICU stay was considered as the baseline SCr, which was in accordance with our previous studies [23, 25]. The SCr level was routinely measured daily during the first week after PICU admission, followed by measurement every 48–72 hours during the PICU stay.

Diagnosis of sepsis

Sepsis was diagnosed by a chief physician and two attending physicians specialized in pediatric critical care medicine, who were completely blinded to the urinary biomarker results, retrospectively, in accordance with the international guidelines for management of septic shock and sepsis-associated organ dysfunction in children (Surviving Sepsis Campaign International Guidelines) [26].

Clinical outcomes

The primary outcome measure was PICU mortality defined as all-cause death occurring during the PICU stay, including death resulting from withdrawal of therapy.

Measurement of urinary CXCL10

Urine samples were collected at predetermined time points for all children: within 24 h after PICU admission, followed by every 48–72 h within the first week of the PICU stay. All samples were immediately stored at $-80 \text{ }^{\circ}\text{C}$ until testing. The urine samples were centrifuged for 15 min at $1500 \times g$ at $4 \text{ }^{\circ}\text{C}$, and the supernatants were used for measurement of uCXCL10 and urine creatinine (uCr). The concentration of uCXCL10 was measured by means of ELISA (human CXCL10/IP-10 Duo Set ELISA DIP100, R&D Systems, USA). The minimum detectable level of CXCL10 was $< 1.67 \text{ pg/mL}$, and the coefficient of variation of intra-assay and inter-assay were less than 5 and 10%, respectively. The uCXCL10 for analysis were adjusted by uCr (ng/mg uCr). The concentration of uCr was determined by sarcosine oxidase assay using an automatic biochemical analyzer (Hitachi 7600, Tokyo, Japan).

Statistical analysis

All data were analyzed using SPSS statistical software Version 22. The assumptions of normality and homogeneity of variance were checked. Continuous data were presented as median and interquartile range (IQR), as they were not-normally distributed. Categorical data were presented as counts and percentage. To compare differences among groups, the Mann-Whitney U test or Kruskal-Wallis H test was

used for continuous variables and the Chi-Square test or Fisher's exact test was used for categorical variables, as appropriate. Spearman's correlation tests were performed to investigate correlations between uCXCL10 and clinical variables. To determine clinical variables potentially associated with the levels of uCXCL10, variables with $P < 0.05$ in Spearman's test were analyzed by the generalized linear model (GLM), and the beta coefficient (β), standard error (SE) and odds ratio (OR) with a 95% confidence interval (CI) were calculated. Continuous variables were log-transformed (base10) to meet approximate normality. Multicollinearity of variables was evaluated via tolerance and variance inflation factor (VIF), and tolerance ≤ 0.5 and the VIF value ≥ 2 indicated the presence of multicollinearity. Univariate and multivariate logistic regression analysis were used to evaluate the association between uCXCL10 and AKI, sepsis, septic AKI and mortality. The predictive values of uCXCL10 for AKI, sepsis, septic AKI and mortality were assessed by the receiver operating characteristic (ROC) curve and area under the curve (AUC). The sensitivity, specificity and Youden index were also calculated, and the optimal cutoff values were determined by the maximum Youden index. A 2-tailed $P < 0.05$ was considered significant.

Results

Patient characteristics

A total of 351 critically ill children admitted to the PICU during the study period, 9 were excluded: including 1 child who was admitted to the PICU at age < 1 month, 4 children who had a failure in collecting urine samples before discharge from the PICU or death, and 4 children with multiple PICU admission during one hospitalization and only the last admission to PICU was used for analysis. Admission diagnoses included respiratory diseases (42.4%), neurological diseases (16.1%), hematologic/oncologic diseases (9.9%), gastrointestinal diseases (9.7%), trauma or postoperative acute care (8.8%) and others (13.1%)

Among the 342 critically ill children, 52 (15.2%) developed AKI during the first week after admission, including 23 with KDIGO stage 1, 14 with stage 2, and 15 with stage 3. One hundred and thirty-two (38.6%) critically ill children were diagnosed with sepsis during the PICU stay. A Comparison of demographic and clinical characteristics between patients with and without AKI or sepsis are presented in Table 1.

Table 1

Comparison of demographic and clinical characteristics between patients with and without AKI or sepsis.

	Non-AKI n = 290	AKI n = 52	P value	Non-sepsis n = 210	Sepsis n = 132	P value
Age, months	14.0 [3.0–46.3]	37.5 [11.5–81.8]	0.001	20.0 [3.0–60.0]	12.5 [3.0–45.0]	0.114
Body weight, kg	10.0 [6.0–16.0]	13.5 [9.3–22.5]	0.003	11.3 [6.5–19.0]	10.0 [6.0–15.8]	0.050
Male, n	192 (66.2)	34 (65.4)	0.908	140 (66.7)	86 (65.2)	0.773
PRISM III score	3 [0–8]	10 [5–16]	0.001	2 [0–8]	6 [2–13]	0.001
AKI ^a , n		52 (100)	NA	30 (14.3)	22 (16.7)	0.551
AKI stage 1, n		23 (44.2)	NA	16 (7.6)	7 (5.3)	0.370
AKI stage 2, n		14 (26.9)		6 (2.9)	8 (6.1)	
AKI stage 3, n		15 (28.8)		8 (3.8)	7 (5.3)	
Sepsis ^b , n	110 (37.9)	22 (42.3)	0.551		132 (100)	NA
MODS ^b , n	18 (6.2)	17 (32.7)	<0.001	16 (7.6)	19 (14.4)	0.044
Shock/DIC ^b , n	18 (6.2)	16 (30.8)	<0.001	10 (4.8)	24 (18.2)	<0.001
MV ^b , n	69 (23.8)	25 (48.1)	<0.001	39 (18.6)	55 (41.7)	<0.001
Duration of MV ^b , hours	0 [0–0]	0 [0–100.3]	0.001	0 [0–0]	0 [0–131.8]	<0.001
Hemofiltration ^b , n	9 (3.1)	8 (15.4)	<0.001	12 (5.7)	5 (3.8)	0.425
Furosemide ^b , n	22 (7.6)	17 (32.7)	<0.001	21 (10.0)	18 (13.6)	0.303
Steroid ^b , n	164 (56.6)	29 (55.8)	0.917	101 (48.1)	92 (69.7)	<0.001
Antibiotic ^b , n	234 (80.7)	39 (75.0)	0.346	148 (70.5)	125 (94.7)	<0.001

Values are median [interquartile range]. Numbers in parentheses denote percentages.

AKI acute kidney injury, DIC disseminated intravascular coagulation, LOS length of stay, MODS multiple organ dysfunction syndrome, MV mechanical ventilation, N/A not applicable, PICU pediatric intensive care unit, PRISM III pediatric risk of mortality III. uCXCL10 urinary CXCL10, uCr urinary creatinine.

^aDeveloped during the first week after PICU admission. ^bAdministered and developed during PICU stay.

	Non-AKI n = 290	AKI n = 52	<i>P</i> value	Non-sepsis n = 210	Sepsis n = 132	<i>P</i> value
Inotrope ^b , n	24 (8.3)	10 (19.4)	0.015	16 (7.6)	18 (13.6)	0.070
PICU LOS, hours	91.0 [48.0-158.3]	106.0 [41.2-200.0]	0.553	71.6 [43.6-133.4]	132.4 [78.0-210.6]	<0.001
PICU death, n	14 (4.8)	16 (30.8)	<0.001	16 (7.6)	14 (10.6)	0.342
Initial uCXCL10, ng/mg uCr	0.096 [0.040-0.257]	0.186 [0.054-1.068]	0.004	0.079 [0.032-0.227]	0.151 [0.064-0.453]	<0.001
Peak uCXCL10, ng/mg uCr	0.117 [0.055-0.382]	0.500 [0.078-1.806]	0.001	0.104 [0.042-0.334]	0.192 [0.083-0.767]	<0.001
Values are median [interquartile range]. Numbers in parentheses denote percentages.						
AKI acute kidney injury, DIC disseminated intravascular coagulation, LOS length of stay, MODS multiple organ dysfunction syndrome, MV mechanical ventilation, N/A not applicable, PICU pediatric intensive care unit, PRISM III pediatric risk of mortality III. uCXCL10 urinary CXCL10, uCr urinary creatinine.						
^a Developed during the first week after PICU admission. ^b Administered and developed during PICU stay.						

Urinary CXCL10

Seven hundred and six urinary samples were collected within the first week after PICU admission. Of the 342 critically ill children, 111 (32.4%) had one sample, 140 (40.9%) had two samples, and 90 (26.3%) had three or more than three samples. Urinary CXCL10 values were detectable in 689 (97.6%) samples. The concentrations of undetectable uCXCL10 were assumed at 1.67 pg/mL, which were equivalent to the mean minimum detectable dose of the assay. Seven (1.0%) urinary samples were diluted 2, 5 or 20 times to maintain the enzymatic reactions within a linear range.

The uCXCL10 level from the first 24 h after admission to PICU was denoted as the initial uCXCL10. The highest uCXCL10 level among all collected samples during the first 7 days after PICU admission was denoted the peak uCXCL10. The initial and the peak values of uCXCL10 were used for analysis.

Correlation of urinary CXCL10 levels with clinical variables

All variables in Table 1 were analyzed for association with uCXCL10. Spearman's correlation analysis showed that both the initial and peak levels of uCXCL10 were significantly correlated with age, body

weight, PRISM III score, AKI, AKI stage, sepsis, MODS, Shock/DIC, MV, duration of MV, the use of furosemide, steroid and antibiotic ($P < 0.05$).

Variables with $P < 0.05$ under the Spearman's test were included in the GLM to confirm factors significantly associated with the uCXCL10 levels after checking the multicollinearity. As listed in Table 2, the initial uCXCL10 was independently associated with body weight ($P = 0.020$), PRISM III score ($P = 0.007$), sepsis ($P = 0.026$) and AKI stage ($P = 0.047$); the peak uCXCL10 was independently associated with body weight ($P = 0.003$), PRISM III score ($P = 0.007$), sepsis ($P = 0.038$), AKI stage ($P = 0.006$) and Shock/DIC ($P = 0.046$).

Table 2
Generalized linear model analysis of urinary CXCL10 with clinical variables.

	β	SE	OR	95%CI	Pvalue
Initial uCXCL10					
Body weight, kg	-0.270	0.116	0.763	0.607–0.958	0.020
PRISM III score	0.013	0.005	1.014	1.004–1.024	0.007
AKI stage ^a	0.105	0.053	1.111	1.001–1.232	0.047
Sepsis ^b	0.173	0.077	1.188	1.021–1.383	0.026
MODS ^b	0.255	0.144	1.290	0.972–1.711	0.078
Shock/DIC ^b	0.179	0.137	1.196	0.913–1.565	0.193
Duration of MV ^b , hours	-0.027	0.044	0.973	0.893–1.060	0.535
Furosemide ^b	0.057	0.122	1.059	0.834–1.345	0.639
Steroid ^b	0.082	0.074	1.086	0.940–1.254	0.262
Antibiotic ^b	0.055	0.094	1.056	0.879–1.269	0.558
Peak uCXCL10					
Body weight, kg	-0.333	0.112	0.717	0.576–0.893	0.003
PRISM III score	0.013	0.005	1.013	1.004–1.023	0.007
AKI stage ^a	0.141	0.051	1.152	1.042–1.273	0.006
Sepsis ^b	0.155	0.075	1.167	1.009–1.351	0.038
MODS ^b	0.201	0.139	1.223	0.932–1.606	0.147
Shock/DIC ^b	0.264	0.132	1.303	1.005–1.688	0.046
Duration of MV ^b , hours	0.003	0.042	1.003	0.923–1.089	0.949
Furosemide ^b	0.226	0.118	1.253	0.996–1.578	0.055
Variables in Table 1 with a <i>P</i> value < 0.05 (Spearman's analysis) were taken into the generalized linear model analysis after checking the multicollinearity. Continuous variables were log-transformed.					
AKI acute kidney injury, DIC disseminated intravascular coagulation, MODS multiple organ dysfunction syndrome, MV mechanical ventilation, PRISM III pediatric risk of mortality III.					
^a Developed during the first week after PICU admission. ^b Administered and developed during PICU stay.					

	β	SE	OR	95%CI	<i>P</i> value
Steroid ^b	0.074	0.071	1.077	0.937–1.237	0.298
Antibiotic ^b	0.093	0.090	1.097	0.920–1.309	0.303
Variables in Table 1 with a <i>P</i> value < 0.05 (Spearman's analysis) were taken into the generalized linear model analysis after checking the multicollinearity. Continuous variables were log-transformed.					
AKI acute kidney injury, DIC disseminated intravascular coagulation, MODS multiple organ dysfunction syndrome, MV mechanical ventilation, PRISM III pediatric risk of mortality III.					
^a Developed during the first week after PICU admission. ^b Administered and developed during PICU stay.					

Association between urinary CXCL10 and AKI

The initial and peak uCXCL10 levels were significantly higher in the AKI than in the non-AKI (Table 1). Comparisons of the initial and peak uCXCL10 levels among different stages of AKI in critically ill children are displayed in Additional file 2: Figure. S1 (a, b).

Univariate and multivariate logistic regression analysis were performed to identify whether uCXCL10 levels were independently associated with AKI in critically ill children. As shown in Table 3 and Figure.1 (a, b), both the initial and peak uCXCL10 levels remained significantly associated with AKI (initial: AOR = 1.791, 95% CI 1.152–2.785, *P* = 0.010; peak: AOR = 2.002, 95% CI 1.284–3.123, *P* = 0.002) after adjustment for body weight, PRISM III score and sepsis. The AUCs of the initial and peak uCXCL10 for predicting AKI was 0.63 (0.53–0.72) and 0.65 (0.56–0.75), respectively.

Table 3
Association of urinary CXCL10 with AKI, sepsis, septic AKI and PICU mortality.

	AKI	Sepsis	Septic AKI	PICU mortality
Initial uCXCL10				
OR (95% CI)	2.127 (1.413–3.202)	1.835 (1.322–2.546)	3.679 (2.062–6.564)	4.091 (2.387–7.012)
P value	<0.001	<0.001	<0.001	<0.001
AOR (95% CI)	1.791 (1.152–2.785) ^a	1.679 (1.189–2.371) ^b	3.281 (1.788–6.018) ^c	2.779 (1.487–5.195) ^d
P value	0.010	0.003	<0.001	0.001
AUC (95% CI)	0.63 (0.53–0.72)	0.62 (0.56–0.68)	0.75 (0.64–0.87)	0.77 (0.68–0.86)
Optimal cutoff value, ng/mg	0.40	0.09	0.15	0.54
Sensitivity	42.3%	70.5%	81.8%	56.7%
Specificity	82.4%	52.4%	60.3%	86.5%
Peak uCXCL10				
OR (95% CI)	2.319 (1.542–3.485)	1.908 (1.378–2.641)	3.570 (2.008–6.345)	5.947 (3.292–10.741)
P value	<0.001	<0.001	<0.001	<0.001
AOR (95% CI)	2.002 (1.284–3.123) ^a	1.752 (1.231–2.494) ^b	3.172 (1.735–5.799) ^c	3.965 (2.037–7.717) ^d
P value	0.002	0.002	<0.001	<0.001
AUC (95% CI)	0.65 (0.56–0.75)	0.63 (0.57–0.69)	0.76 (0.65–0.87)	0.84 (0.76–0.91)
Optimal cutoff value, ng/mg	0.45	0.09	0.94	0.54
Sensitivity	53.8%	75.0%	59.1%	73.3%
Specificity	79.0%	43.8%	87.8%	81.1%
AKI acute kidney injury. AOR adjusted odds ratio, AUC the area under the ROC curve, CI confidence interval.				
^a After adjustment for body weight, pediatric risk of mortality III (PRISM III) score and sepsis. ^b After adjustment for body weight, PRISM III score and AKI stage. ^c After adjustment for body weight and PRISM III score. ^d After adjustment for body weight, PRISM III score, sepsis and AKI stage.				

Association between urinary CXCL10 and sepsis

The sepsis group in critically ill children had higher initial and peak levels of uCXCL10 than the non-sepsis group (Table 1). Comparisons of the initial and peak uCXCL10 levels between non-sepsis and sepsis in critically ill children are displayed in Additional file 3: Figure. 2 (a, b). To identify the association between uCXCL10 and sepsis, univariate and multivariate logistic regression analysis were performed. As shown in Table 3 and Figure.1 (a, b), the initial and peak uCXCL10 were both independently associated with sepsis (initial: AOR = 1.679, 95% CI 1.189–2.371, P = 0.003; peak: AOR = 1.752, 95% CI 1.231–2.494, P = 0.002) after adjustment for body weight, PRISM III score and AKI stage. The AUCs of the initial and peak uCXCL10 in predicting sepsis were 0.62 (0.56–0.68) and 0.63 (0.57–0.69), respectively.

Association between urinary CXCL10 and septic AKI

Since the initial and peak uCXCL10 levels were both independently associated AKI and sepsis (Table 2), the relationship between uCXCL10 and septic AKI was further investigated. Children were divided into four groups according to the presence/absence of AKI and sepsis: sepsis/AKI (septic AKI, n = 22), non-AKI/sepsis (n = 110), AKI/non-sepsis (n = 30), non-sepsis/non-AKI (n = 180). As displayed in Figure. 2 (a, b), both the initial and peak uCXCL10 levels in septic AKI group were the highest. Comparison of clinical characteristics among four groups according to the status of AKI and sepsis are shown in Additional file 1: Table S1.

Univariate and multivariate logistic regression analysis were used to determine the association between uCXCL10 and septic AKI (n = 342). As shown in Table 3 and Figure.1 (a, b), the initial and peak uCXCL10 were both independently associated with septic AKI after adjustment for body weight and PRISM III (initial: AOR = 3.281, 95% CI 1.788–6.018, P < 0.001; peak: AOR = 3.172, 95% CI 1.735–5.799, P < 0.001). The AUCs of the initial and peak uCXCL10 in predicting septic AKI were 0.75 (95% CI 0.64–0.87) and 0.76 (95% CI 0.65–0.87). The ROC curves of the initial and peak uCXCL10 and PRISM III for predicting septic AKI are displayed in Figure. 3a.

In addition, univariate and multivariate logistic regression analysis indicated that the uCXCL10 was robustly associated with septic AKI in the critically ill children with sepsis (n = 132), as shown in Additional file 1: Table S2. The performances of the initial and peak uCXCL10 in predicting septic AKI were 0.72 (95% CI 0.59–0.85) and 0.73 (95% CI 0.60–0.85), respectively, in this population in Additional file 1: Table S2.

Association between urinary CXCL10 and mortality

A comparison of demographic and clinical characteristics between survivors and non-survivors is shown in Additional file 1: Table S3. Out of the 342 children, 30 (8.8%) died during PICU stay. The values of uCXCL10 were significantly higher in those who died within PICU than in survivors as displayed in Additional file 4: Figure. 3 (a, b). In order to explore whether uCXCL10 levels were independently associated with mortality in critically ill children, univariate and multivariate logistic regression analysis

were performed. After adjustment for body weight, PRISM III score, sepsis and AKI stage, the initial and peak uCXCL10 levels remained independently associated with mortality, with adjusted odds ratios of 2.779 (95% CI 1.487–5.195, $P = 0.001$) and 3.965 (95% CI 2.037–7.717, $P < 0.001$) as listed in Table 3 and Figure.1(a, b).

The initial and peak uCXCL10 displayed AUCs of 0.77 (95% CI 0.68–0.86) and 0.84 (95% CI 0.76–0.91), and PRISM III score displayed the AUC of 0.83 (95% CI 0.75–0.91) in predicting mortality. The ROC curves of the initial and peak uCXCL10 and PRISM III for predicting mortality are shown in Figure. 3b.

Discussion

This study prospectively assessed uCXCL10 in a typical heterogeneous PICU population. Our data revealed that elevated uCXCL10 was independently associated with AKI and sepsis after adjustment for confounding factors, and uCXCL10 could be a potential indicator of septic AKI and PICU mortality in critically ill children.

In normal condition, CXCL10 is expressed at low levels in the kidney, but their expression levels are upregulated in renal tubular cells after insult, involving in the pathogenesis of AKI [11, 12, 27]. Higher uCXCL10 levels were found among the critically ill children with AKI in our study, which was in consistent with a prospective nested case-control study performed by Ho J et al [17]. They compared urinary proteomes of adults before, during, and after cardiopulmonary bypass surgery, discovering that uCXCL10 levels were upgraded in patients with AKI postoperatively [17]. In a recent study on urinary biomarkers of AKI, uCXCL10 was discovered and validated to be associated with AKI in children after HCT [18]. However, these data are limited to small studies originally designed for AKI prediction in a specific setting. Our results confirmed the significant association of uCXCL10 with AKI regardless of illness severity and the presence of sepsis, in critically ill children.

The discriminative power of uCXCL10 for AKI in our study was less well comparing with the study of Vaidya et al [19]. Our result suggested that uCXCL10 may not be a good predictor of AKI in critically ill children. Different from the patients without AKI in the present study, 102 individuals without AKI in previous study were from 3 types: 50 healthy volunteers, 39 patients undergoing cardiac catheterization and 13 patients admitted to the intensive care unit [19]. The healthy volunteers accounted for half of those who were non-AKI, which may partly explain the discrepancy. In critically ill patients, AKI development is characterized with heterogeneity, and the predictive value of AKI is highly dependent on the underlying conditions. Our study indicates that although it is undisputed that uCXCL10 is associated with kidney injury, similar association has been identified between uCXCL10 and sepsis, which makes uCXCL10 measurements generally a poor diagnostic tool in complex contexts in critically ill children. Moreover, the levels of uCXCL10 were influenced by age and body weight, which might be another explanation for the poor performance in the clinical utility of uCXCL10 as an AKI biomarker in PICU population.

Sepsis is a well-known main cause of AKI in critically ill patients [5, 28]. The CXCL10 has been reported to regulate the pathogenesis of sepsis [29, 30]. In our present study, uCXCL10 levels were higher in critically ill children with sepsis, suggesting that the levels of uCXCL10 were influenced by inflammation and infection. Urinary CXCL10 remained independently associated with both sepsis and AKI, indicating that the increases of uCXCL10 due to AKI and sepsis are additive. These results were supported by animal research in which a marked upregulation of CXCL10 was detected within kidney in septic acute renal failure model [31].

In this study, uCXCL10 had an ability to discriminate septic AKI in all critically ill children and in children with sepsis. These findings suggested that uCXCL10 could be diagnostic of septic AKI. Considering that septic AKI is a frequent complication in critically ill patients, and associated with higher risk of in-hospital mortality [28, 32], the identification of early biomarkers of septic AKI is extremely important. Urinary biomarker neutrophil gelatinase-associated lipocalin and cell cycle biomarkers of tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 are the frequently investigated and have been proved to predict septic AKI in patients with sepsis [32–34]. Our finding emphasizes that uCXCL10, as any other biomarker, must be interpreted in the specific clinical context. Although, to our knowledge, this is the first report about the relationship of uCXCL10 and septic AKI, this was a single cohort study and 22 (6.4%) critically ill children were septic AKI, a multi-center study with more cases would be needed to confirm our findings. Additional studies are also required to delineate the specific mechanism of CXCL10 in septic and non-septic AKI.

As uCXCL10 has been related to different conditions of inflammation and injury and proven as a reliable marker for septic AKI, it has been consequentially evaluated as a prognostic marker. Our study firstly proved that uCXCL10 levels had independent associations with PICU mortality in critically ill patients. Clinical studies about the association between CXCL10 and mortality have been limited and predominantly investigated in blood rather than in urine of adult patients [21, 35, 36]. As regards to CXCL10 in urine, a pilot study conducted in patients with ischemic AKI suggested that uCXCL10 might predict renal functional outcome at various times along the course of ischemic AKI and predict mortality of AKI patients within 3 months [37]. However, in adult patients with established AKI, uCXCL10 was a good biomarker of AKI as mentioned earlier, but it was not predictive of in-hospital mortality [19]. Both AKI and sepsis are established risk factors for mortality, and AKI and sepsis increase mortality synergistically [2, 38]. In our study, patients with septic AKI had a similar mortality compared to non-septic AKI, suggesting that non-septic etiologies may also contribute to the high mortality rate in AKI patients. The relationship between elevated uCXCL10 levels and increased risk of all-cause PICU death in our cohort was independent of the presence of sepsis and/or AKI and illness severity assessed by the PRISM III score, indicating that uCXCL10 is not simply associated with AKI and sepsis, but also a potential indicator of PICU mortality in critically ill children. Thus, elevated uCXCL10 levels in ICU patients should not be simply viewed as a risk indicator for AKI but rather should prompt a thorough investigation for coexisting conditions, which will ultimately determine the prognosis of the ICU patients. Furthermore, the predictive abilities of the peak uCXCL10 for PICU mortality was better than the initial uCXCL10. These

results suggest that dynamic monitoring of uCXCL10 levels upon PICU admission is valuable for clinicians in guiding preventive strategies and improving prognosis.

There are some limitations in this study. First, the AKI incidence may be underestimated when SCr at PICU admission was considered as a baseline, given that the majority of critically ill children did not have baseline SCr prior to PICU admission. In consistent with our previous studies [23, 25], the lowest SCr value within 2 weeks during the PICU stay was used as a baseline for patients with elevated SCr $\geq 106.1 \mu\text{mol/L}$ at PICU admission, which, however, has not been validated in critically ill children. Nevertheless, a previous study suggests that the lowest SCr within the first week in the ICU better approximates the true baseline distribution and leads to more accurate diagnosis of AKI, as compared with the estimation methods of back-calculating baseline SCr [39]. Second, although it is a challenge to evaluate the performance of biological indicators on the diagnosis of septic AKI based on the recommendations applying to children [26, 32] and the relevance of this finding of uCXCL10 in predicting septic AKI is limited by the small sample size, the diagnostic accuracy of uCXCL10 persisted in all critically ill children and in a subgroup analysis of children with sepsis. Third, we did not perform an etiological analysis for developing AKI. Since our study was carried out in a general and mixed PICU population, it was difficult to distinguish the exact causes of AKI from the existence of complex comorbidities. Fourth, it is unclear whether uCXCL10 is truly causatively involved in pathophysiologic mechanisms of underlying conditions resulting in high mortality or whether it reflects general inflammation and injury in critical illness. Further studies are required for understanding of the biochemical properties and regulatory mechanisms of uCXCL10 in critical illness. Fifth, the single-center study design represents a main limitation. Although we add novel insights to the literature, we did not compare other kidney injury biomarkers, and could not prove the statistical superiority of initial uCXCL10 value overall other standard parameters in early predicting adverse outcome. A multi-center study with a larger quantity of samples is necessary for further validation.

Conclusions

Urinary CXCL10 levels are independently associated with increased risk for AKI, sepsis, septic AKI and PICU mortality even after adjustment for confounding factors. A higher uCXCL10 may be predictive of septic AKI and PICU mortality in critically ill children.

Abbreviations

AKI, Acute kidney injury; AOR, Adjusted odds ratio; AUC, Area under the receiver operating characteristic curve; CI, Confidence interval; Cr, Creatinine; CXCL10, CXC motif chemokine ligand 10; DIC, Disseminated intravascular coagulation; GLM, Generalized linear model; HCT, Hematopoietic cell transplantation; IQR, Interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; LOS, Length of stay; MODS, Multiple organ dysfunction syndrome; MV, Mechanical ventilation; OR, Odds ratio; PICU, Pediatric intensive care unit; PRISM III, Pediatric risk of mortality III; ROC, Receiver operating characteristic curve;

SCr, Serum creatinine; SE, Standard error, uCr, Urinary creatinine; uCXCL10, Urinary CXCL10; VIF, Variance inflation factor.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board at the Children's Hospital of Soochow University, and performed in accordance with the Declaration of Helsinki. Informed parental consent was obtained at enrollment.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Hui Huang performed the experiments and data analysis and drafted the manuscript. Huiting Zhou participated in data analysis and revised the manuscript. Wenwen Wang, Jiao Chen and Zhenjiang Bai had primary responsibility for diagnosis of sepsis and participated in clinical data collection. Xiaomei Dai and Wenjing Li participated in collecting the data and samples. Jian Pan and Xiaozhong Li participated in data analysis and interpretation. Jian Wang participated in the design of the study and coordination. Yanhong Li had primary responsibility for study design, performing the experiments, data analysis, interpretation of data, and writing the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Figure 1

The correlation between uCXCL10 and AKI, sepsis, septic AKI and mortality in multivariate logistic regression. Adjusted odds ratio: AKI, after adjustment for body weight, PRISM III score and sepsis. Sepsis,

after adjustment for body weight, PRISM III score and AKI stage. Septic AKI, after adjustment for body weight and PRISM III score. Mortality, after adjustment for body weight, PRISM III score, sepsis and AKI stage. a Initial uCXCL10, b Peak uCXCL10. AKI acute kidney injury, PRISM III pediatric risk of mortality III, uCXCL10 urinary CXCL10.

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Figure 2

Figure 2

Median uCXCL10 differences among children with and without AKI and with and without sepsis. a Initial uCXCL10, b Peak uCXCL10. AKI acute kidney injury, uCXCL10 urinary CXCL10, uCr urinary creatinine.

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Figure 3

Figure 3

ROC curves of PRISM III and uCXCL10 to predict septic AKI and mortality. a Septic AKI, b Mortality. AKI acute kidney injury, PICU pediatric intensive care unit, PRISM III pediatric risk of mortality III, uCXCL10 urinary CXCL10.

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