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# Procalcitonin levels in septic and nonseptic subjects with AKI and ESKD prior to and during continuous kidney replacement therapy (CKRT)

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## Abstract

**Background** Procalcitonin is a 14.5 kDa protein used clinically as a marker of sepsis and therapeutic response to antibiotic therapy. However, its utility in critically ill patients with either acute kidney injury (AKI) or end-stage kidney disease (ESKD) who require continuous kidney replacement therapy (CKRT) is unknown. The aim of this study was to determine if plasma levels of procalcitonin could reliably distinguish septic from nonseptic status in patients with AKI or ESKD prior to or during CKRT.

**Methods** Procalcitonin concentrations were measured in plasma of 41 critically ill septic or non-septic subjects with AKI or ESKD prior to CKRT (pre-CKRT) and on days 1, 2, and 3 of CKRT in this retrospective cohort study (n = 111 total plasma measurements). Continuous venovenous hemodialysis was the modality of CKRT in these patients. Sepsis status was stringently defined based on culture results. Effluent procalcitonin levels were ascertained on days 1, 2, and 3 of CKRT to assess the clearance of procalcitonin and effects on plasma levels.

**Results** 92% (66/72) of the plasma procalcitonin measurements among nonseptic patients with either AKI or ESKD were ≥ 0.5 ng/mL (the diagnostic threshold beyond which bacterial infection is very likely). Prior to CKRT initiation, procalcitonin levels were (median (IQR), ng/mL) 5.6 (1.5–18.9) in nonseptic AKI and 58.1 (6.9–195.5) in septic AKI ($P = 0.03$) and were 3.3 (1.2–8.3) in nonseptic ESKD and 3.7 (1.4–209.8) in septic ESKD ($P = 0.79$). However, despite being significantly elevated in septic patients with AKI, substantial overlap among procalcitonin levels was present and ROC curve analysis found no cut point that could reliably separate septic from nonseptic patients. Effluent procalcitonin levels were consistently ~ 20% of plasma levels throughout the course of CKRT (i.e., sieving coefficient was 0.2) suggesting that clearance occurs during therapy. However, plasma procalcitonin levels did not significantly decline during CKRT in either AKI or ESKD.

**Conclusion** Procalcitonin levels are markedly elevated in nonseptic critically ill patients with either AKI or ESKD and do not effectively distinguish sepsis from nonseptic status prior to or during CKRT. We conclude that procalcitonin testing should be avoided in critically ill patients with kidney failure since results are nonspecific in this population.

**Keywords** AKI, ESKD, CKRT, Procalcitonin, Sepsis

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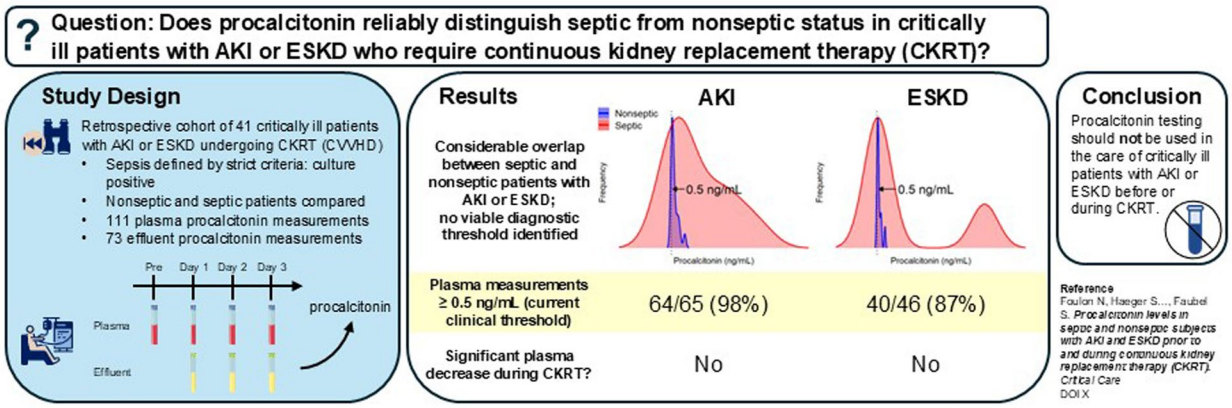
**Graphical abstract**




## Background

Procalcitonin is a 14.5 kDa protein which is used clinically as a marker of bacterial infection [1, 2] with levels above 0.5 ng/ml consistent with clinical sepsis. Procalcitonin is also used to evaluate the effectiveness of antibiotic therapy and inform de-escalation [3]. Consensus guidelines recommend that procalcitonin should be checked in critically ill patients with an initial sepsis diagnosis and that repeat levels should be checked after 2 or 3 days. If repeat levels drop below 0.5 ng/mL or decrease 80% from peak levels, treatment is considered effective and antibiotic de-escalation or discontinuation may be considered.

Although increased during sepsis [4], procalcitonin levels are also increased in non-infectious inflammatory conditions such as trauma, burns, cardiogenic shock, malignancy and surgery [5–7], as well as kidney disease (including acute kidney injury (AKI) and end-stage kidney disease (ESKD)) [8]. AKI occurs in approximately half of critically ill patients [9] and up to 70% of cases are associated with sepsis [10]. Similarly, patients with ESKD frequently require ICU care [11] with a risk of ICU admission four-fold greater than the general population [12]. Like AKI, sepsis is common in patients with ESKD [13] and is the second-leading cause of death in this population [14, 15]. Accordingly, appropriate diagnostic thresholds for procalcitonin specific to critically ill patients with AKI or ESKD are needed.

In critically ill patients with AKI or ESKD, continuous kidney replacement therapy (CKRT) is the typical KRT modality, particularly for patients with hemodynamic instability. Since sepsis is commonly considered as a cause of hemodynamic instability at the onset of CKRT 16 but is often difficult to diagnose in real time, procalcitonin is a potentially vital laboratory test in this population both for initiating and tapering antibiotic therapy. To date, while some studies have examined serial procalcitonin levels in critically ill patients requiring CKRT [17–20], none have included patients with ESKD and none have compared septic to nonseptic patients. Thus, procalcitonin levels typical of septic versus nonseptic status in the CKRT population with either AKI or ESKD have not been established. Additionally, many studies employed filters not commonly used in clinical practice [21–23]. Of the studies using typical filters, conclusions were mixed, with some studies suggesting that clearance was minimal and that plasma procalcitonin retained clinical utility, and others suggesting caution with its use [17–19]. Thus, while testing procalcitonin in patients with an initial sepsis diagnosis is recommended [24], there are no specific guidelines for or against its use in patients with kidney failure requiring CKRT. We conducted the present study to address this knowledge gap.

Herein, we assessed procalcitonin levels in septic and nonseptic critically ill patients with kidney failure due to either AKI or ESKD prior to the initiation of CKRT and for three subsequent days during the receipt of CKRT. This study is the largest to assess serial levels of procalcitonin during several days of CKRT, the first to include patients with ESKD, and the first to compare procalcitonin levels in septic versus non-septic patients. Our data reveal practice-changing results regarding the use of procalcitonin in this critically ill population.

## Methods

### Patient selection and definitions

Patients with AKI or ESKD with and without sepsis were selected from a parent study for the analysis herein. The

parent study was a prospective observational study that enrolled 126 subjects requiring CKRT that was conducted at the University of Colorado Hospital over two recruitment periods: 5/2019 to 6/2019 (n = 14) and 2/2020 to 12/2022 (n = 112, NCT04458571) [25]. Study approval was obtained locally from the Colorado Multiple Institutional Review Board, and consent was obtained from the subject directly when possible, or from a legally authorized representative if the subject was unable to consent. Subjects were considered for inclusion if they were ≥ 18 years of age, not pregnant, not incarcerated, and needed CKRT as recommended by the nephrology consult service, which was independent of the research team. Additionally, a group of pre-operative patients with no evidence of kidney disease nor sepsis were included as controls.

Four groups of patients were identified a priori for the present study: (1) AKI patients without sepsis, (2) AKI patients with sepsis, (3) ESKD patients without sepsis, and (4) ESKD patients with sepsis. AKI was defined as an increase in serum creatinine ≥ 0.3 mg/dL above baseline. Baseline creatinine was obtained from the electronic health record (EHR) and defined as the median of the lowest of ≥ 3 of the most recent consecutive stable outpatient creatinine concentrations within one year prior to initiation of CKRT. If outpatient values were not available, then the median of the lowest of ≥ 3 consecutive stable creatinine concentrations during the index hospitalization was used. Patients with AKI were excluded from all analysis if they had hemodialysis within a week prior to beginning CKRT and were excluded from CKRT analysis if they died within 2 days following CKRT initiation.

ESKD was defined as requiring KRT for at least 90 days prior to admission. Two subjects with ESKD and delayed graft function (DGF) necessitating CKRT after kidney transplant were included in the ESKD cohort. All ESKD patients were included in the pre-CKRT analysis regardless of recency of KRT or date of expiration, although patients were excluded from CKRT analysis if they died within 2 days following CKRT initiation.

Sepsis was defined as clinical evidence of sepsis as determined by documentation of sepsis in the electronic health record within the week prior to CKRT initiation with either of the following: (1) two out of two positive blood cultures from separate draws collected within a week pre-CKRT or (2) positive cultures identifying a pathogenic organism from a suspected site of infection collected within a week pre-CKRT. Nonsepsis status required meeting all three of the following criteria: (1) no clinical evidence of sepsis documented in the EHR within a week prior to CKRT initiation, (2) lack of two out of two positive blood cultures within a week prior to the initiation of CKRT, and (3) lack of positive cultures identifying a pathogenic organism from a site other than blood within a week prior to initiation of CKRT. While more stringent than current Sepsis-3 guidelines in which sepsis without positive cultures is included if there is clinical suspicion [26], these strict criteria were designed to reliably separate septic from nonseptic subjects.

After applying the above inclusion and exclusion criteria, 16 patients were selected for the nonseptic AKI group and 9 patients for the septic AKI group. Together, these patients constituted 20% (25/126) of the AKI patients in the parent cohort. 12 patients were selected for the nonseptic ESKD group, and 4 patients were selected for the septic ESKD group. Together, these patients constituted 100% (16/16) of ESKD patients in the parent cohort. Finally, a group of healthy control subjects (pre-operative cardiac patients with no evidence of kidney disease nor sepsis) were included (n = 9).

Two analyses were performed. First, pre-CKRT procalcitonin levels were determined to assess the effects of AKI and ESKD independent of KRT (N = 41 plus 9 controls). Then, patients were assessed for up to 3 days of CKRT to determine the impact of CKRT (N = 26) (patients with only one day of CKRT samples were not included; lack of samples was due to death or CKRT liberation). In total, 65 AKI and 46 ESKD plasma procalcitonin levels were assessed.

Demographic data was collected from the EHR. Baseline creatinine, baseline eGFR, duration of AKI, and SOFA score were determined as previously described.[27]

#### Plasma and effluent collection

Blood was collected prior to KRT initiation in all patients studied and additional blood and CKRT effluent were collected at 10:00 AM on days 1, 2, and 3 from patients still receiving CKRT at that time. Blood and effluent samples were kept on ice prior to centrifugation at 3600 rpm at 4 °C for 10 min. Effluent and the supernatant plasma were stored at − 80 °C for further studies.

#### Procalcitonin, creatinine, IL-6, and NGAL measurement

Procalcitonin levels were determined in stored samples using the validated clinical platform by the clinical laboratory personnel at the University of Colorado Hospital at Anschutz Medical Center using an Abbot Architect i2000SR. Plasma and effluent creatinine concentrations were measured via high-performance liquid chromatography tandem mass spectrometry as previously described [28]. Plasma IL-6 was measured via ELISA (R&D Systems, cat# D6050B, inter-assay coefficient of variance < 2.3%, limit of determination = 0.120 pg/mL) according to manufacturer instructions. Plasma neutrophil gelatinase-associated lipocalin (NGAL) was measured via ELISA

(RayBiotech, cat# ELH-Lipocalin2, inter-assay coefficient of variance < 12%, limit of determination = 4 pg/mL) according to manufacturer instructions.

### CKRT protocol and parameters

CKRT was performed using the NxStage® System One™ S CKRT machines and NxStage Purema H filters which are biocompatible polyethersulfone membranes. All of the patients received continuous venovenous hemodialysis (CVVHD) as the modality of CKRT. CKRT was typically initiated at a blood flow rate of 300 mL/min and without heparin; none of the patients in this study received citrate anticoagulation.

At our institution, CKRT parameters including delivered dose and total effluent volume are recorded hourly in the EHR as part of a standard protocol [29]. Data regarding hours on CKRT, average 24 h dose, and total effluent volume were collected from the EHR. Hours on CKRT was the number of hours that the patient received CKRT within the 24 h prior to 10 am (the time at which plasma and effluent were collected). Dose of CKRT was the average of all the hourly doses within the 24 h prior to 10 am and represents *delivered* dose of CKRT; specifically, this average included time off CKRT (which was recorded as "0") as may occur during filter clotting, procedures, etc. Total effluent volume was the sum of the hourly recorded effluent volume (including therapy fluid and ultrafiltration) within the 24 h prior to 10 am.

### Sieving coefficient and CKRT clearance calculations

The sieving coefficient (SC) and CKRT clearance of procalcitonin and creatinine were calculated using the following equations as previously described. [25, 27]

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

$$\text{Marker Clearance} = \text{Total Effluent Volume} \times \text{Marker SC}$$

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

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

### Statistical analysis

Subject characteristics and other parameters were gathered and combined in a secure database. Continuous variables were expressed as median ± interquartile range. Categorical variables were expressed as raw counts and percentages. Comparisons of creatinine and procalcitonin were completed with unpaired nonparametric *t* tests (Mann–Whitney) or one-way ANOVA. Receiver operating curves were generated by calculating sensitivity and 1-specificity for each patient value and plotting against one another. Plasma levels of procalcitonin were assessed for their correlation to levels of plasma IL-6 and plasma NGAL using Pearson's correlation test after log transformation of values. All statistical analysis was completed with GraphPad Prism and Microsoft Excel.

## Results

### Patient demographics

The initial clinical characteristics of all patients are shown in Table 1. Data for individual patients regarding type of kidney failure, sepsis status (with organism and infectious source for septic patients), and daily plasma procalcitonin levels are presented in Supplemental Table 1.

### Plasma procalcitonin in patients with AKI and ESKD without and with sepsis

Pre-CKRT procalcitonin levels were significantly elevated in patients with AKI or ESKD versus healthy controls, regardless of sepsis status (Fig. 1). Pre-CKRT plasma procalcitonin was significantly increased in septic AKI versus nonseptic AKI (Fig. 1A). Pre-CKRT plasma procalcitonin of septic ESKD patients was not significantly different compared to nonseptic ESKD patients (Fig. 1B).

The pre-CKRT procalcitonin values of all of the septic AKI patients and 15/16 (94%) nonseptic AKI patients were ≥ 0.5 ng/mL which is the threshold used to aid in the clinical assessment of sepsis in hospitalized patients. When all plasma values for AKI patients were considered (i.e., pre-CKRT to day 3), 27/27 (100%) of septic AKI and 37/38 (97%) of nonseptic AKI procalcitonin levels were ≥ 0.5 ng/mL.

The pre-CKRT procalcitonin values of all the septic ESKD patients and 10/12 (83%) of the nonseptic ESKD patients were ≥ 0.5 ng/mL. When all plasma values were considered (i.e., pre-CKRT to day 3), 12/12 (100%) of septic ESKD and 28/34 (82%) of nonseptic ESKD procalcitonin levels were ≥ 0.5 ng/mL.

In total, 92% (66/72) of the plasma procalcitonin measurements in the *nonseptic* patients with either AKI or ESKD were ≥ 0.5 ng/mL (Supplemental Table 1).

In sum, these data demonstrate that the vast majority of procalcitonin measurements in critically ill nonseptic patients with kidney failure prior to and during CKRT were above the current clinical standard threshold of 0.5 ng/mL.

### Application of different procalcitonin thresholds to distinguish septic from nonseptic status.

Published data have suggested that different procalcitonin thresholds be applied for patients with either AKI

**Table 1** Baseline characteristics and demographics

| | Control | AKI | | ESKD | |
|---|---|---|---|---|---|
| | | Nonseptic | Septic | Nonseptic | Septic |
| Total patients | 9 | 16 | 9 | 12 | 4 |
| Age | 58 (52.5–65) | 49 (34–60) | 67 (59.5–73) | 60 (53–70) | 66 (55.5–76.5) |
| Male (%) | 5 (56) | 9 (56) | 5 (56) | 7 (58) | 3 (75) |
| Female (%) | 4 (44) | 7 (44) | 4 (44) | 5 (42) | 1 (25) |
| Baseline Cr (mg/dL) | 0.84 (0.72–0.99) | 0.94 (0.81–1.20) | 0.72 (0.53–0.89) | ESKD | ESKD |
| Baseline eGFR (mL/min/1.73 $m^2$) | 92 (85–100) | 84 (72–110) | 98 (79–108) | ESKD | ESKD |
| Duration of AKI, hrs (IQR) | N/A | 34 (4–54) | 40 (33–68) | ESKD | ESKD |
| Pre-CKRT creatinine (mg/dL) | N/A | 2.60 (1.86–3.74) | 2.27 (1.79–3.18) | 6.00 (4.07–7.65) | 6.12 (3.38–8.82) |
| SOFA score, average (IQR) | N/A | 11 (7.25–13) | 10 (9.5–12.5) | 5 (3.25–10.50) | 9.50 (9–12.25) |
| Delayed graft function (%) | N/A | N/A | N/A | 2 (17) | N/A |
| *Comorbidities (%)* | | | | | |
| HTN | 5 (56) | 9 (56) | 7 (78) | 5 (42) | 1 (25) |
| DM | 3 (33) | 2 (13) | 4 (44) | 4 (33) | 4 (100) |
| CHF | 0 (0) | 10 (63) | 6 (67) | 2 (17) | 2 (50) |
| CAD | 1 (11) | 4 (25) | 2 (22) | 4 (33) | 2 (50) |
| Cirrhosis | 0 (0) | 0 (0) | 0 (0) | 1 (8) | 0 (0) |
| COPD | 2 (22) | 0 (0) | 2 (22) | 2 (17) | 1 (25) |
| Alcohol use disorder | 0 (0) | 0 (0) | 0 (0) | 1 (8) | 0 (0) |
| Solid cancer | 3 (33) | 0 (0) | 2 (22) | 1 (8) | 1 (25) |
| Hematologic cancer | 0 (0) | 0 (0) | 5 (56) | 0 (0) | 0 (0) |
| CVA/TIA | 0 (0) | 2 (13) | 2 (22) | 0 (0) | 0 (0) |

Data are median (IQR) or n (%). AKI = acute kidney injury. CAD = coronary artery disease. CHF = congestive heart failure. COPD = chronic obstructive pulmonary disease. Cr = creatinine. CVA = cerebrovascular accident. DM = diabetes mellitus. eGFR = estimated glomerular filtration rate. ESKD = end-stage kidney disease. HTN = hypertension. N/A = not applicable. SOFA = Sequential Organ Failure Assessment score. TIA = transient ischemic attack.

or ESKD in the inpatient (but not critical care) setting [30–33]. Therefore, we examined whether these thresholds would accurately identify sepsis in our cohort of AKI and ESKD patients. As shown in Table 2, none of the evaluated thresholds provide sensitivity and specificity with a sum greater than 170% (a typical cutoff for clinical test usefulness) [34].

### Plasma levels of interleukin 6 (IL-6) and neutrophil gelatinase-associated lipocalin (NGAL) and their association with procalcitonin

Given plausible similarities among procalcitonin and IL-6 and NGAL with respect to inflammation and effects of impaired kidney function [35–37], we hypothesized that levels of IL-6 and NGAL would correlate with procalcitonin levels suggesting a shared mechanism of increase. As shown in Fig. 2, IL-6 and NGAL levels were significantly elevated in both septic and nonseptic patients with AKI and ESKD versus controls. We then assessed the correlation of procalcitonin with IL-6 and NGAL. In patients with AKI, plasma levels of IL-6 and procalcitonin were significantly correlated (Pearson's r = 0.69, $p = 0.02$), as were NGAL and procalcitonin (Pearson's r = 0.58, $p = 0.002$) (Fig. 3). In patients with ESKD, plasma levels of IL-6 and procalcitonin were also significantly correlated (Pearson's r = 0.57, $p = 0.02$), but not NGAL and procalcitonin (Pearson's r = 0.20, $p < 0.46$).

### Receiver operator characteristic (ROC) curve

Since the majority of the suggested procalcitonin thresholds to distinguish septic from nonseptic status in kidney failure were derived in non-ICU populations, we assessed whether a diagnostic threshold could be established using the data from our cohort and generated receiver operating characteristic (ROC) curves for AKI and ESKD (Supplemental Fig. 1**).** The procalcitonin thresholds with the highest sensitivity + specificity were 9.215 ng/mL and 3.26 ng/mL with 140% and 125% for AKI and ESKD, respectively, neither of which meet guidelines for an acceptable diagnostic test). [34]

### Changes in procalcitonin levels during CKRT

To determine the effect of CKRT on plasma procalcitonin levels, plasma procalcitonin levels were assessed pre-CKRT and on Days 1, 2, and 3 of CKRT. As shown in Fig. 4, procalcitonin levels were variable over the

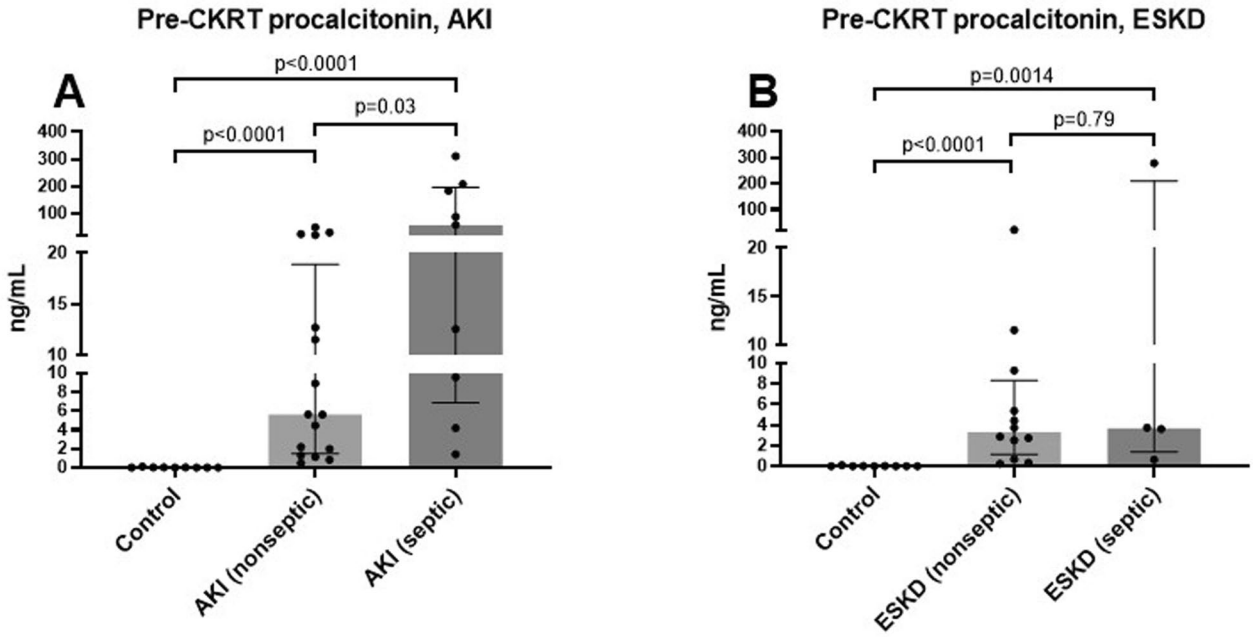



**Fig. 1** Plasma procalcitonin levels in patients with AKI or ESKD prior to the initiation of continuous kidney replacement therapy (CKRT). Plasma levels of procalcitonin were determined in controls and patients with AKI and ESKD without sepsis or with sepsis. **A** Procalcitonin in control (n = 9), nonseptic AKI (n = 16), and septic AKI (n = 9); **B** Plasma procalcitonin in control (n = 9), nonseptic ESKD (n = 12), and septic ESKD (n = 4). Data are shown as median and interquartile range (25th to 75th percentiles). Statistics via Mann–Whitney comparing the groups indicated. *P* value is shown above the bracket

**Table 2** Comparison of published procalcitonin thresholds

| Threshold (ng/mL) | Reference | Population | Clinical Setting | AKI | | ESKD | |
|---|---|---|---|---|---|---|---|
| | | | | Sensitivity | Specificity | Sensitivity | Specificity |
| 0.5 | Clinical standard | n/a | n/a | 100(%) | 6(%) | 100(%) | 17(%) |
| 0.75 | Lee et al. | ESKD | Inpatient | 100(%) | 6(%) | 75(%) | 25(%) |
| 1.5 | Bowman et al. | AKI | Inpatient | 89(%) | 25(%) | 75(%) | 25(%) |
| 1.75 | Bowman et al. | ESKD | Inpatient | 89(%) | 25(%) | 75(%) | 25(%) |
| 2.86 | Han et al | AKI | Inpatient | 89% | 38% | 75% | 42% |
| 3.2 | El-sayed et al. | ESKD | ICU | 89(%) | 38(%) | 75(%) | 50(%) |

Published procalcitonin thresholds [30–33] applied to studied AKI and ESKD cohorts from procalcitonin levels obtained prior to CKRT initiation. Sensitivity = true positives/true positives + false negatives. Specificity = true negatives/true negatives + false positives. Accuracy = true positives + true negatives/total

course of CKRT with no consistent pattern of increase or decrease, and the vast majority of values remained above 0.5 ng/mL. In particular, no significant decline in procalcitonin levels was observed from day to day over the CKRT course. In contrast, creatinine levels were consistently and significantly reduced by Day 1 of CKRT and remained low during each day of therapy regardless of AKI or ESKD status.

### CKRT clearance characteristics

Tables 3 and 4 show the sieving coefficient, delivered dose, and CKRT clearance among the AKI and ESKD populations over three days of therapy. While some patients received a dose below the recommended 20 mL/kg/h, it is important to note these data represent *delivered* CKRT dose, which is generally lower than the prescribed dose most commonly reported in the literature. Thus, these doses likely represent doses similar to general practice. Significant differences were identified between day 1 and day 2 as well as day 1 and day 3 clearance values among the AKI patients. However, the total effluent volumes on day 2 and 3 always exceeded those of day 1, as day 2 and day 3 typically involved a full 24 h of therapy whereas day 1 involved a median 16.4 h.

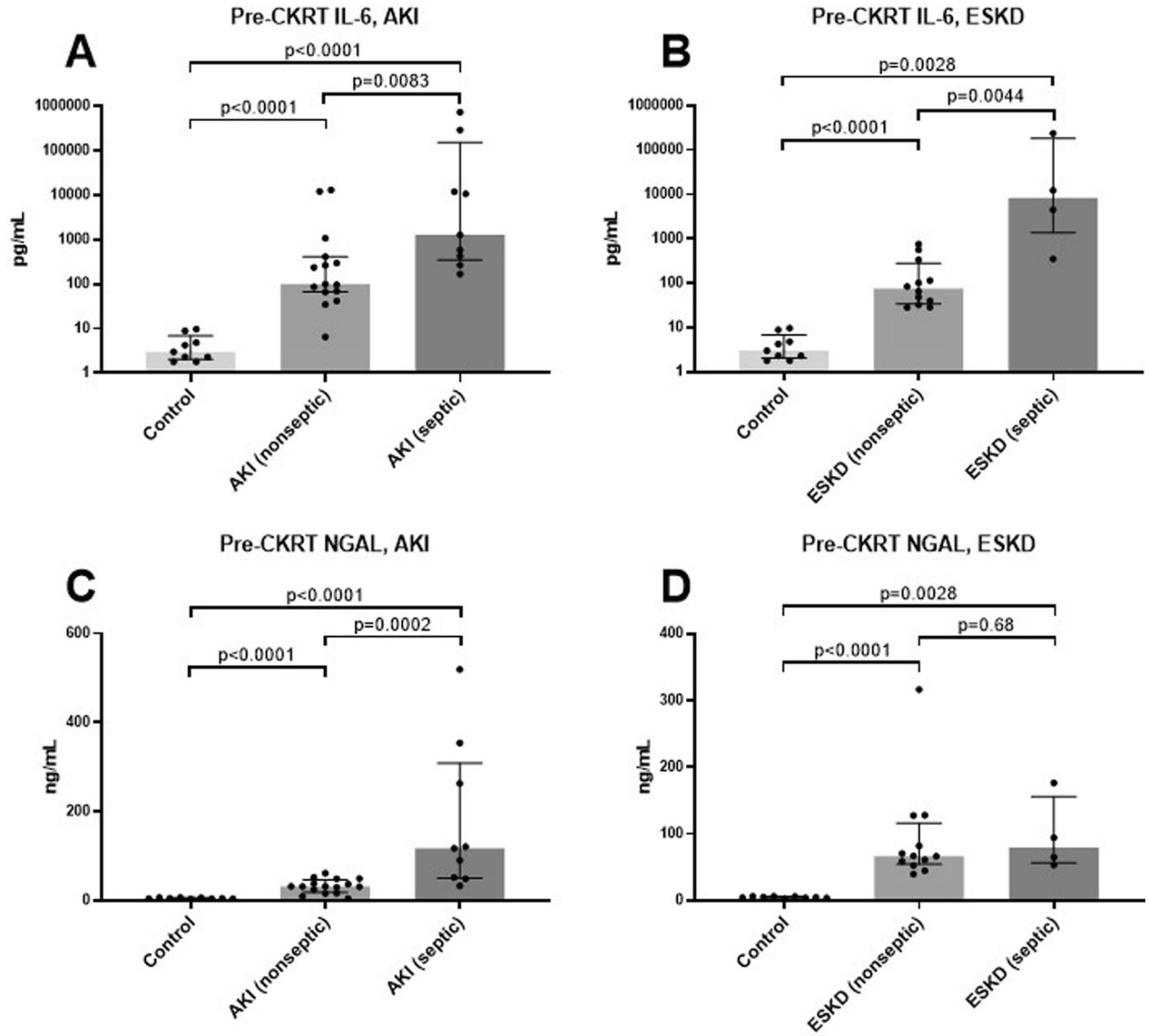



**Fig. 2** Plasma IL-6 and NGAL levels in patients with AKI or ESKD prior to initiation of continuous kidney replacement therapy (CKRT). Plasma levels of IL-6 and NGAL were determined in controls and patients with AKI and ESKD without sepsis or with sepsis. **A** Plasma IL-6 in control (n = 9), nonseptic AKI (n = 16), and septic AKI (n = 9); **B** Plasma IL-6 in control (n = 9), nonseptic ESKD (n = 12), and septic ESKD (n = 4). **C** Plasma NGAL in control (n = 9), nonseptic AKI (n = 16), and septic AKI (n = 9); **D** Plasma NGAL in control (n = 9), nonseptic ESKD (n = 12), and septic ESKD (n = 4). Data are shown as median and interquartile range (25th to 75th percentiles). Statistics via Mann–Whitney comparing the groups indicated. P value is shown above the bracket

## Discussion

We performed the study herein to address the use of procalcitonin in critically ill patients with AKI or ESKD prior to and during CKRT. The major conclusions from this study are (1) procalcitonin does not reliably distinguish septic from nonseptic critically ill patients with either AKI or ESKD, (2) procalcitonin levels are significantly correlated with the proinflammatory cytokine IL-6 in patients with AKI or ESKD with and without sepsis, and (3) plasma procalcitonin levels do not decrease during CKRT despite consistent clearance, suggesting ongoing production. Based on these data, we conclude that the use of procalcitonin in critically ill patients with either AKI or ESKD will lead to inaccurate conclusions regarding sepsis status and treatment response and therefore it should not be measured.

Procalcitonin is a commonly used test by clinicians to aid the diagnosis of sepsis and is typically used as a

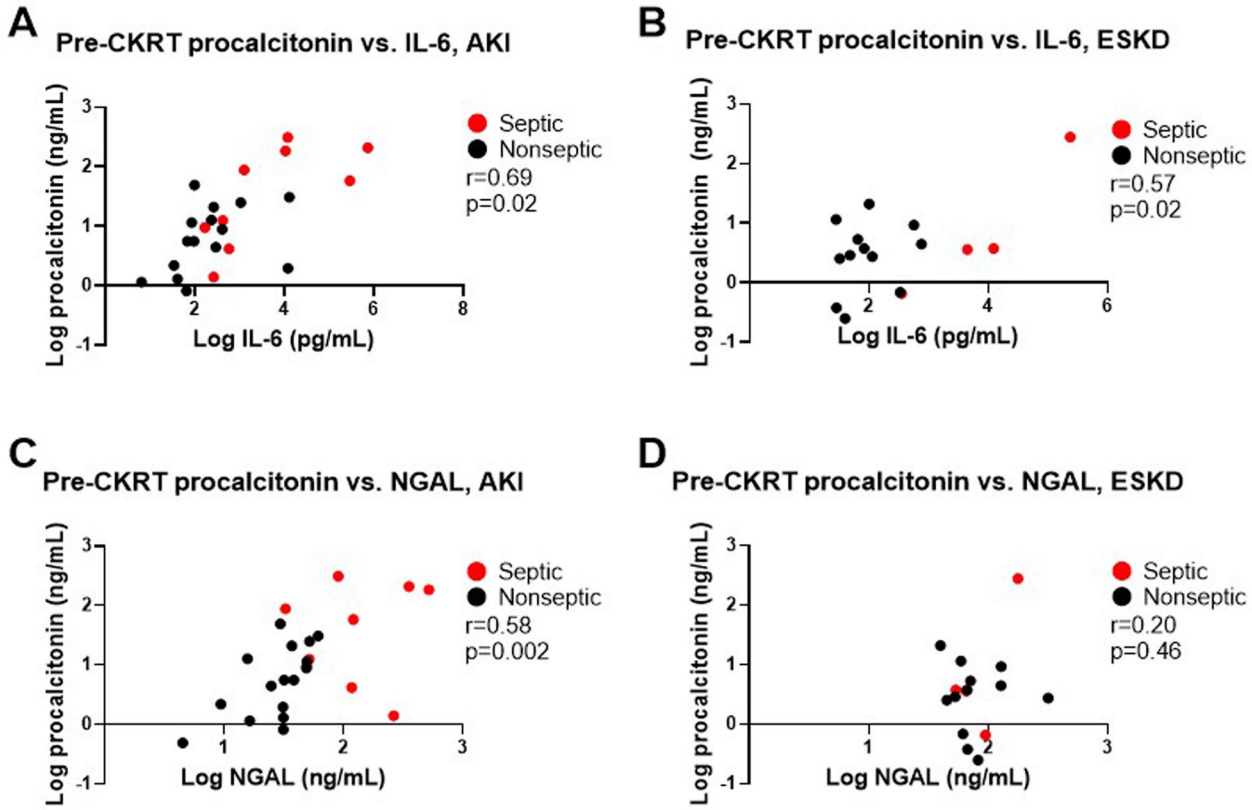



**Fig. 3** Plasma procalcitonin and its association with plasma IL-6 and NGAL. Plasma levels of IL-6 and NGAL in patients with either AKI or ESKD were assessed for their correlation to plasma levels of procalcitonin. **A** IL-6 and procalcitonin in AKI, **B** IL-6 and procalcitonin in ESKD, **C** NGAL and procalcitonin in AKI, and **D** NGAL and procalcitonin in ESKD. Pearson r for log transformed values and *P* values via Mann Whitney analysis are indicated. AKI: acute kidney injury. ESKD: end-stage kidney disease. IL-6: interleukin 6. NGAL: neutrophil gelatinase-associated lipocalin

"spot-check" to identify infection and confirm clinical gestalt [38]. Procalcitonin is also used to monitor clinical response antibiotic treatment for infection and inform antibiotic discontinuation, as recommended by the 2021 Surviving Sepsis guidelines [24]. Of note, no specific recommendations are made for or against the use of procalcitonin in patients with kidney failure. To address the use of procalcitonin in critically ill patients with kidney failure, we first examined procalcitonin levels in critically ill patients with AKI or ESKD just prior to the initiation of CKRT. Our data demonstrate that procalcitonin levels are profoundly elevated in both AKI and ESKD regardless of sepsis status. In fact, 94% of procalcitonin levels in the nonseptic AKI cohort prior to CKRT were above the typical threshold associated with sepsis (> 0.5 ng/mL). Similarly, 83% of procalcitonin levels in nonseptic ESKD patients were above this cutoff prior to CKRT. When considering all of the values measured in patients with either AKI or ESKD (prior to and during CKRT), 92% (66/72) of the plasma procalcitonin measurements in the *nonseptic* patients were ≥ 0.5 ng/mL. Together, these data indicate that the current diagnostic threshold of 0.5 ng/mL for procalcitonin in the general population cannot be applied to critically ill patients with AKI or ESKD prior to or during CKRT.

Our data is consistent with other studies which had suggested that procalcitonin levels may be higher in patients with either AKI or ESKD, with levels being greater in patients with AKI. Prior studies have generally been conducted in patients with AKI or ESKD in the inpatient (but not ICU) setting [30–32]. Similar to the study herein, however, a recent study of critically ill AKI patients prior to CKRT found the median procalcitonin level of nonseptic patients to be 5.78 ng/mL. In this study, serial levels of procalcitonin were not determined and sepsis was defined by Sepsis 3 criteria [33]. We tested the diagnostic thresholds from this and other prior studies in our cohort and found that none could reliably distinguish septic and nonseptic patients [30–33]. Finally, we constructed receiver operator characteristic plots for both AKI and ESKD populations and found that even the best-performing procalcitonin thresholds were inaccurate (sensitivity + specificity = 140% and 125% for AKI and ESKD), reflecting the substantial overlap between

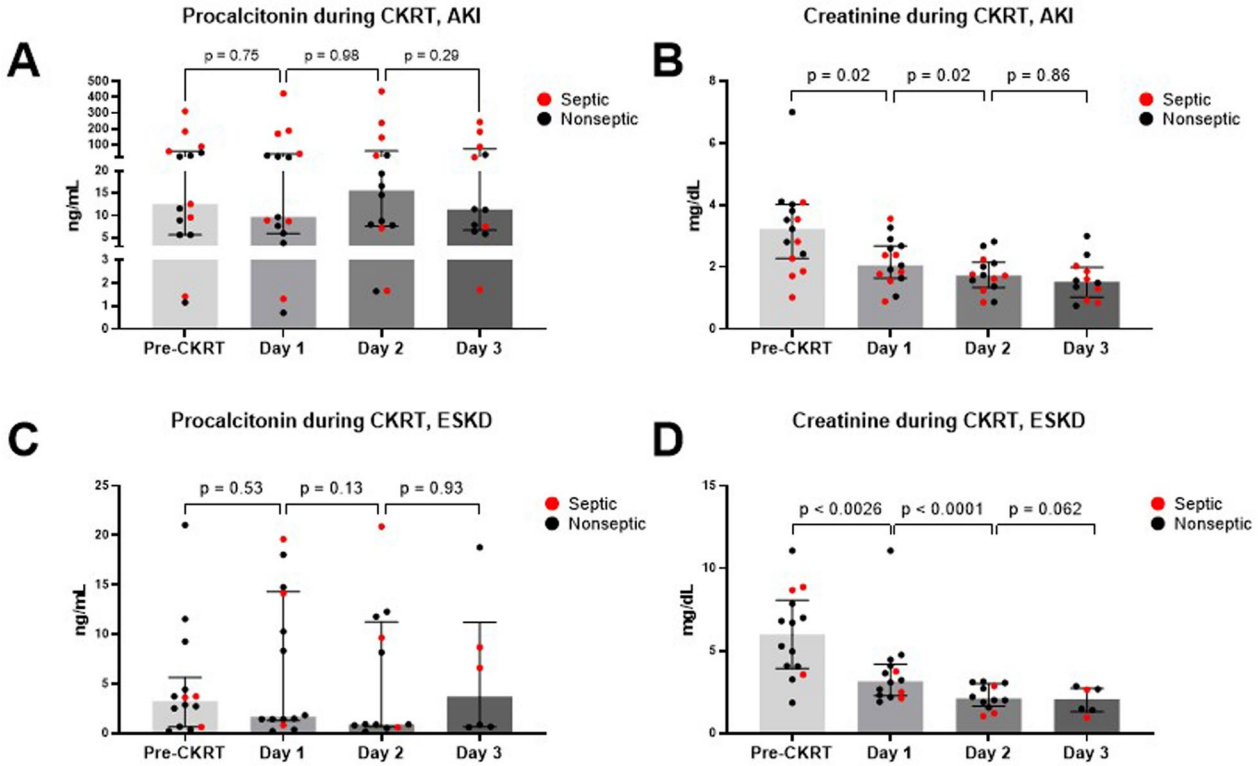



**Fig. 4** Plasma procalcitonin and creatinine levels prior to and during CKRT in patients with AKI or ESKD. Plasma levels of procalcitonin and creatinine were determined in patients with AKI or ESKD prior to CKRT initiation (Pre-CKRT) and on Day 1, Day 2, and Day 3 of CKRT. Regardless of AKI or ESKD status, plasma levels of procalcitonin (**A**, **C**) did not significantly change, while levels of creatinine (**B**, **D**) decreased significantly after 1 day of therapy. Data are shown as median and interquartile range (25th to 75th percentiles). Statistics via ANOVA using Šídák's multiple comparisons test comparing the groups indicated. *P* value is shown above the bracket

septic and nonseptic patients [34, 39]. Together, these data suggest that no procalcitonin threshold is suitable for use in critically ill patients with kidney failure.

To gain insight into potential mechanisms underpinning the dramatic elevations of procalcitonin in the nonseptic AKI and ESKD cohorts, we examined IL-6 and NGAL levels and their correlation to procalcitonin. NGAL and IL-6 were both elevated in AKI and ESKD compared to healthy controls, regardless of sepsis status. Both IL-6 and NGAL were significantly correlated with procalcitonin levels in patients with AKI, and IL-6 and procalcitonin were also significantly correlated in patients with ESKD. IL-6 is a proinflammatory cytokine that is elevated in a wide variety of non-infectious and infectious inflammatory conditions such as trauma, hemorrhage, surgery, and sepsis. NGAL is a major component of the hepatic acute phase response and is similarly increased during inflammation and its production is mediated—in part—by IL-6 [36, 40]. IL-6 and NGAL are both affected by impaired kidney clearance, especially in AKI [41–43], although increased levels of IL-6 are also observed in patients with ESKD [44]. Kidney clearance of IL-6 [45] and NGAL [37] is thought to be dependent on both glomerular filtration rate and proximal tubule resorption and degradation which may be megalin dependent [46, 47]. Given that dozens of low molecular weight proteins that are cleared by the kidney in this way [46, 47], it is possible that procalcitonin is similarly handled. Thus, we suggest that kidney failure in the setting of critical illness is a unique combination in which increased procalcitonin production coupled with impaired kidney clearance results in dramatic and sustained elevations of plasma procalcitonin levels. This mechanism provides a plausible explanation for the particularly high levels of procalcitonin observed in both nonseptic and septic AKI patients.

We also examined CKRT clearance and plasma levels of procalcitonin on days 1, 2, and 3 of CKRT. We found that procalcitonin was detected in the effluent and was consistently ~ 20% of plasma levels (i.e., the sieving coefficient was ~ 0.20) for all three days of CKRT and was not affected by type of kidney failure or sepsis status [20]. For comparison, the sieving coefficient of creatinine, which is readily cleared by KRT, is 0.96 [48, 49]. Despite being

**Table 3** CKRT characteristics in AKI

| CKRT parameters | Pre CKRT | Day 1 | Day 2 | Day 3 |
|---|---|---|---|---|
| Dose, mL/kg/h | n/a | 20.46 (15.71–23.86) | 21.58 (16.58–26.65) | 20.66 (18.06–24.07) |
| Time on CKRT, h | n/a | 16.7 (11.38–20.5) | 23 (20.5–24) | 20.4 (18.83–23.35) |
| Total effluent volume, L | n/a | 31.49 (23.27–40.01) | 43.14 (33.38–54.74) | 37.56 (29.66–47.55) |
| *Procalcitonin values during CKRT* | | | | |
| Plasma procalcitonin, ng/mL | 9.54 (2.08–40.03) | 9.23 (5.39–66.50) | 15.57 (7.61–60.61) | 11.31 (6.67–73.69) |
| Effluent procalcitonin, ng/mL | n/a | 2.15 (0.70–16.55) | 3.09 (1.41–20.55) | 3.19 (1.96–20.31) |
| Sieving coefficient procalcitonin | n/a | 0.24 (0.19–0.31) | 0.26 (0.20–0.32) | 0.26 (0.23–0.36) |
| Procalcitonin CKRT clearance, L | n/a | 6.08 (3.97–10.2) | 12.34 (7.92–17.37) | 11.08 (9.18–14.46) |
| Procalcitonin CKRT mass removal, ug | n/a | 63.97 (16.16–196) | 152.1 (54.36–808) | 167.2 (89.04–669.1) |
| *Creatinine values during CKRT* | | | | |
| Plasma creatinine, mg/dL | 2.42 (1.86–3.53) | 1.99 (1.43–2.62) | 1.72 (1.12–2.07) | 1.43 (0.96–1.99) |
| Effluent creatinine, mg/dL | n/a | 1.58 (0.98–2.56) | 1.56 (1.02–1.84) | 1.32 (1.12–1.57) |
| Sieving coefficient creatinine | n/a | 0.87 (0.71–0.91) | 0.85 (0.8–1.01) | 0.91 (0.83–1.01) |
| Creatinine CKRT clearance, L | n/a | 22.88 (10.48–34.51) | 34.07 (11.27–50.3) | 26.58 (0–38.89) |
| Creatinine CKRT mass removal, mg | n/a | 394.7 (131–790.3) | 585.9 (111.6–877.7) | 397.1 (0–687.2) |

All parameters are reported as median (IQR). Dose is the median (IQR) of 24-h averages of hourly dose. Time, and effluent volume, clearance, and mass removal are the median (IQR) per time interval as follows: Day 1 is from the initiation of CRRT to 10:00 a.m. the following day, Day 2 is from 10:00 a.m. on Day 1 to 10 a.m. on Day 2, Day 3 is from 10 a.m. on Day 2 to 10 a.m. on Day 3. Plasma, effluent, and sieving coefficient are the values (median (IQR)) obtained at 10:00 am on the day indicated. Sieving coefficient (SC) is the effluent effluent level divided by the plasma level; CKRT clearance is the total effluent volume × SC; CKRT mass removal is the total effluent volume × effluent concentration

**Table 4** CKRT characteristics in ESKD

| CKRT parameters | Pre CKRT | Day 1 | Day 2 | Day 3 |
|---|---|---|---|---|
| Dose, mL/kg/h | n/a | 19.07 (15.01–23.12) | 20.81 (17.74–23.86) | 21.50 (17.76–24.15) |
| Time on CKRT, h | n/a | 16.3 (12.33–20.8) | 23.5 (8.125–24) | 11.5 (0–22.28) |
| Total effluent volume, L | n/a | 27.49 (21.59–34.83) | 41.26 (14.64–45.76) | 22.94 (0–41.25) |
| *Procalcitonin values during CKRT* | | | | |
| Plasma procalcitonin, ng/mL | 3.69 (1.15–8.30) | 1.67 (1.30–14.30) | 0.92 (0.66–11.26) | 3.75 (0.67–11.21) |
| Effluent procalcitonin, ng/mL | n/a | 0.78 (0.27–2.73) | 0.37 (0.17–2.76) | 0.47 (0.16–2.72) |
| Sieving coefficient procalcitonin | n/a | 0.22 (0.14–0.27) | 0.24 (0.2–0.31) | 0.19 (0.13–0.35) |
| Procalcitonin CKRT clearance, L | n/a | 7.11 (3.65–8.46) | 11.16 (9–13.28) | 8 (6.43–13.65) |
| Procalcitonin CKRT mass removal, ug | n/a | 18.73 (6.909–106.9) | 13.88 (7.47–117.6) | 26.52 (6.628–108.9) |
| *Creatinine values during CKRT* | | | | |
| Plasma creatinine, mg/dL | 5.99 (3.69–8.48) | 3.16 (2.29–4.19) | 2.47 (1.82–3.07) | 2.86 (1.46–3.31) |
| Effluent creatinine, mg/dL | n/a | 2.3 (1.85–3.89) | 2.36 (1.77–2.64) | 1.67 (1.12–1.98) |
| Sieving coefficient creatinine | n/a | 0.85 (0.68–1) | 0.87 (0.84–1.33) | 0.82 (0.68–0.96) |
| Creatinine CKRT clearance, L | n/a | 27.14 (16.34–34.03) | 38.12 (33.94–62.3) | 29.88 (22.7–46.98) |
| Creatinine CKRT mass removal, mg | n/a | 768.3 (516.1–1234) | 1034 (809.6–1080) | 608.4 (421.9–791.7) |

All parameters are reported as median (IQR). Dose is the median (IQR) of 24-h averages of hourly dose. Time, and effluent volume, clearance, and mass removal are the median (IQR) per time interval as follows: Day 1 is from the initiation of CRRT to 10:00 a.m. the following day, Day 2 is from 10:00 a.m. on Day 1 to 10 a.m. on Day 2, Day 3 is from 10 a.m. on Day 2 to 10 a.m. on Day 3. Plasma, effluent, and sieving coefficient are the values (median (IQR)) obtained at 10:00 am on the day indicated. Sieving coefficient (SC) is the effluent effluent level divided by the plasma level; CKRT clearance is the total effluent volume × SC; CKRT mass removal is the total effluent volume × effluent concentration.

consistently cleared during CKRT, plasma levels of procalcitonin did not decline and were markedly variable (unlike creatinine), which is similar to previous studies that examined septic patients with AKI [19, 20, 22] and suggests that ongoing production of procalcitonin during CKRT may occur.

This study has several strengths. Both AKI and ESKD patients are included, and it is specifically focused on

the critically ill population. It is unique in tracking serial levels of plasma procalcitonin in septic versus nonseptic patients over several days of CKRT therapy. Importantly, patients were strictly separated into septic and nonseptic groups, providing a high level of confidence that septic patients were not misclassified as nonseptic and vice versa. Procalcitonin levels were measured by hospital laboratory personnel using the hospital laboratory clinical platform, increasing the clinical relevance of this study. We report a high level of detail regarding the CKRT prescription which includes delivered dose of CKRT and an accurate calculation of total effluent volume. Finally, it encompasses over 100 measurements of procalcitonin across the cohort and is the largest study of its kind to date.

The study also carries certain limitations. First, while larger than prior studies [17, 19–23, 50], our cohorts are relatively small. It is possible that with a very large cohort of AKI or ESKD patients, a procalcitonin threshold capable of reliably distinguishing septic from nonseptic patients could be found—although our data suggest that this threshold would apply to only a minority of patients due to the considerable overlap between septic and nonseptic levels. Second, while our inclusion and exclusion criteria reliably separated septic from nonseptic patients, patients with culture negative sepsis (constituting approximately half of septic patients) [51] were not included. Data suggest that sepsis severity does not differ between culture positive and culture negative sepsis [52], so it is likely that our results will apply to culture negative sepsis. Third, the septic and nonseptic groups were heterogenous demographically, which is relevant given the myriad factors causing procalcitonin elevation outside of infection. For example, malignancy rates were increased in the septic AKI cohort relative to the nonseptic AKI cohort (although this is more in favor of our results and does not confound our findings) [6, 7]. Fourth, our study was not designed to assess whether procalcitonin may be useful for *monitoring* sepsis status. Currently, guidelines suggest that antibiotic discontinuation should be considered if a patient's plasma procalcitonin falls below either 0.5 ng/mL or 80% from their peak level [3, 53]. Since the vast majority of procalcitonin levels during the course of CKRT were above these thresholds regardless of septic or nonseptic status, we surmise that procalcitonin also loses reliability for serial monitoring during CKRT, and its use would lead to inappropriate continuation of antibiotic treatment if used to monitor for antibiotic de-escalation. Finally, this was a single center study and particularities of our center and CKRT prescription (e.g., blood flow rates are higher, anticoagulation is uncommon) may have affected results. Furthermore, CVVHD was the only modality of CKRT studied. However, our results are generally in line with previous studies and it does not appear that modality has a major effect on procalcitonin clearance or circulating levels. For example, a prior study of AKI patients with sepsis using continuous venovenous hemofiltration (CVVHF) found similar results with sieving coefficient of 0.24 and no significant effect on plasma levels [20]. In addition, procalcitonin has a molecular weight similar to many cytokines and no significant difference in clearance or serum levels of five different cytokines occurred when CVVHD and CVVHF were compared [54]. Thus, we suggest that our findings are generalizable to the wider scope of CKRT practice.

In summary, we have investigated the reliability of procalcitonin to identify sepsis among critically ill patients with AKI or ESKD prior to and during CKRT. We have demonstrated that in these populations of critically ill patients, plasma procalcitonin is neither accurate nor specific for the diagnosis of sepsis. Because of these data, we suggest that the use of procalcitonin in critically ill patients with kidney failure should be suspended.

**Abbreviations**

| | |
|---|---|
| AKI | Acute kidney injury |
| CKRT | Continuous kidney replacement therapy |
| ESKD | End-stage kidney disease |
| IL-6 | Interleukin 6 |
| KRT | Kidney replacement therapy |
| NGAL | Neutrophil gelatinase associated lipocalin |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05414-7.

Supplementary material 1: Figure 1. Receiver operating characteristic (ROC) curves for procalcitonin diagnosing sepsis in patients with AKI (A) and ESKD (B). Area under curve (AUC) shown with standard error.

Supplementary material 2 Table 1. Data for individual patients regarding type of kidney failure, sepsis status (with organism and infectious source for septic patients), and daily plasma procalcitonin levels.

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None.

**Author contributions**
The authors confirm contribution to the paper as follows: study conception and design: NF and SF; data collection: KO and ZH; analysis and interpretation of results: NF and SF; draft manuscript preparation: NF and SF. All authors read and approved the final manuscript.

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**Availability of data and materials**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
Study approval was obtained locally from the Colorado Multiple Institutional Review Board, and consent was obtained from the subject directly when possible, or from a legally authorized representative if the subject was unable to consent.

**Consent for publication**
Consent for publication was obtained from participants. Our institutional consent form is available upon request.

**Competing interests**
The authors declare no competing interests.

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