



OPEN Change in platelet and leukocyte counts and hospital mortality in adults with acute kidney injury receiving continuous renal replacement therapy

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Background Changes in platelet and white blood cell (WBC) counts during CRRT could identify patients at risk for adverse outcomes. We examined the association of change in platelet and WBC from pre-CRRT to during-CRRT with hospital mortality.

Methods This multicenter, retrospective cohort study included 1,413 adults with AKI requiring CRRT at two tertiary medical centers (2011–2021). Platelet and WBC change from pre- to during CRRT were assessed as a percentage and categorized by standard deviation (SD). Multivariable LASSO regression and interaction analyses investigated associations with hospital mortality.

Results A > 1 SD platelet count drop during CRRT was independently associated with hospital mortality (aOR: 1.82, 95% CI: 1.06, 3.13). A > 1 SD WBC count increase during CRRT did not significantly increase mortality (aOR 1.41, 95% CI: 0.88, 2.29). Interaction analyses revealed four sub-groups associated with increased mortality: pre-CRRT low platelet count that remained low, pre-CRRT normal platelet count that decreased, pre-CRRT elevated WBC count that remained high, and normal or elevated pre-CRRT WBC count that increased.

Interpretation In critically ill adults, a drop in platelets after CRRT initiation was associated with increased hospital mortality. Monitoring platelet and WBC during CRRT in reference to pre-CRRT levels could help identify high-risk patients.

Keywords Acute kidney injury, AKI, Continuous renal replacement therapy, CRRT, Leukocytes, Platelets

Abbreviations

AKI	acute kidney injury
aOR	adjusted odds ratio
CI	confidence interval

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CRRT	continuous renal replacement therapy
ICU	intensive care unit
SD	standard deviation
SOFA	Sequential Organ Failure Assessment
WBC	white blood cell

Background

Critically ill adult patients with acute kidney injury (AKI) may require extracorporeal organ support, which includes continuous renal replacement therapy (CRRT). This vulnerable patient population has high morbidity and mortality^{1–3}. Among different strategies to improve the care of these patients, accurate and actionable risk classification and sub-phenotyping to support more patient-specific interventions have gained recognition in critical care^{4–6}. In this context, time-varying data during the provision of CRRT may be informative for clinical sub-phenotyping, particularly if linked to pathobiological pathways that could guide specific interventions⁷.

Platelet, white blood cell (WBC), and WBC subtype counts are essential indicators of hemostasis and immunoinflammatory responses^{8–12}. In this context, some studies have examined the role of platelet and WBC parameters as predictors of mortality and renal function impairment in diverse critically ill populations, including those receiving CRRT^{11–19}. Nevertheless, many of these studies have used static time points to assess platelet and WBC counts during CRRT treatment^{14,15,17–21}. This approach may overlook the dynamic changes in these parameters as acute illness evolves. Notably, little is known about the association of change in platelet and WBC counts, specifically from pre- to during CRRT, with relevant clinical outcomes, such as hospital mortality.

The main objective of this study was to examine the association of change in platelet and WBC counts from pre-CRRT to during CRRT with hospital mortality in critically ill adults with AKI requiring CRRT. We hypothesized that a drop in platelet count and a rise in WBCs potentially signal dire underlying pathophysiology and hence associated with increased hospital mortality in this vulnerable patient population.

Methods

Study design and participants

This multicenter retrospective cohort study included critically ill adults with AKI who required CRRT during their intensive care unit stay at the University of Kentucky (UKY) Albert B. Chandler Hospital and the University of Texas Southwestern (UTSW) Medical Center between 2011 and 2021. Specifically, these two institutions used continuous veno-venous hemodiafiltration as the CRRT modality of choice and primarily regional citrate anticoagulation with acid citrate dextrose solution. HF1400[®] (UKY) and M100/M150[®] filters (UTSW) were used during the study period. Patients with coronavirus disease 2019 (COVID-19), end-stage renal disease or prior kidney transplant were excluded.

The study was approved, and the need to obtain informed consent was waived by the University of Kentucky and the University of Texas Southwestern Institutional Review Boards (IRBs 43159 and STU112015-069, respectively). All research in the study was performed in accordance with relevant guidelines/regulations and in accordance with the Declaration of Helsinki²².

Data extraction

Data were collected through automatic digital extraction from electronic health records, and ~10% of data were manually validated by individual record review. Patient demographics, comorbidities, laboratory tests, acute illness parameters, and final vital status were collected. The comorbidities were assessed by the Charlson Comorbidity Index²³ and the severity of acute illness by the Sequential Organ Failure Assessment (SOFA) score²⁴ on ICU admission and CRRT initiation days.

Study predictor variables

The predictor (independent) variables were percentage changes in platelet and WBC counts before and during CRRT. We calculated the average counts of platelets and WBCs during two specific timeframes on a per patient basis: up to 7 days preceding the initiation of CRRT and up to 7 days post-initiation of CRRT. The 'up to 7 days' period included all available laboratory values within those windows, without requiring the full 7-day data. The frequency of observations during the referred period is depicted in e-Figure 1. The percentage change was determined by dividing the difference in means between the two timeframes (delta) by the pre-CRRT mean. Next, we categorized the changes in platelet and WBC counts based on their deviation from the mean, using standard deviation (SD) as a benchmark: changes less than one SD (< 1 SD), within one SD (± 1 SD), and greater than one SD (> 1 SD) from the mean.

Study outcomes

The primary outcome was hospital mortality, defined as death recorded at the time of hospital discharge.

Statistical analyses

Means, SDs, medians, and interquartile ranges were used for describing continuous variables and counts and percentages for categorical variables. Baseline characteristics were stratified and compared by survival status. The comparisons were made using a t-test or Mann-Whitney U test for continuous variables and chi-squared test for categorical variables. Linear associations between platelet/WBC count change and hospital mortality were assessed with box-plot figures.

To address multicollinearity among ICU covariates and reduce the risk of overfitting in a high-dimensional dataset, we applied Least Absolute Shrinkage and Selection Operator (LASSO) regression for the primary analysis. This approach promotes model parsimony and enhances interpretability by shrinking less informative coefficients toward zero²⁵. Multivariable LASSO regression analyses were performed using the percentage difference between means of platelets and WBCs before and during CRRT as the predictor variables and hospital mortality as the outcome of interest. The following candidate covariates were included based on clinical relevance and availability across both study sites: age, sex, race, study site, weight, Charlson Comorbidity Index (as a measure of comorbidity burden), SOFA score at ICU admission, SOFA score at CRRT initiation (to assess illness severity), mechanical ventilation status, baseline serum creatinine (as a proxy for kidney function), hospital length of stay, ICU length of stay, and CRRT duration. From this list, the following covariates were retained in the final multivariable models: age, Charlson Comorbidity Index, baseline serum creatinine (closest value 7–365 days prior to index admission with missing values back-calculated by resolving the estimated glomerular filtration rate [eGFR] EPI²⁶ to 75 ml/min/1.73m²), SOFA score at ICU admission and SOFA score at CRRT initiation.

Statistical analyses were performed using R version 4, and $p < 0.05$ was considered statistically significant.

Interaction analyses

Given that thrombocytopenia and leukocytosis before CRRT initiation might also be associated with hospital mortality, as supported by prior literature^{14,16,17,19,21,27,28}, we used a combination of novel clustering exploratory tools and clinical insight to identify the 4-way interaction between platelet and WBC counts before CRRT and drop in platelets and rise in WBCs during CRRT.

Sensitivity analyses

Sensitivity analyses were conducted to assess the robustness of the primary findings by¹ using a shorter 3-day window before and after CRRT initiation to calculate changes in platelet and WBC counts, and² including patients with COVID-19 who were excluded from the primary analysis.

Results

Clinical characteristics

A total of 1413 critically ill adults with AKI on CRRT comprised the study cohort (Fig. 1). Among these, 753 (53.2%) died during the index hospitalization. Table 1 describes the cohort's baseline and clinical characteristics, stratified by hospital mortality status. Supplemental e-Table 1 describes baseline and clinical characteristics data stratified by study location, while e-Table 2 presents non-parametric measurements. Patients who died were similar to those who survived regarding sex, race, study location, and CRRT duration. In contrast, patients who died were older and had higher Charlson Comorbidity Index, weight, SOFA score, and more frequent use of mechanical ventilation (Table 1).

Study outcomes

Non-survivors had lower mean platelets and higher mean WBCs before and during CRRT than patients who survived (Table 1). The mean platelet count dropped 14% from pre-CRRT to during CRRT in the whole cohort

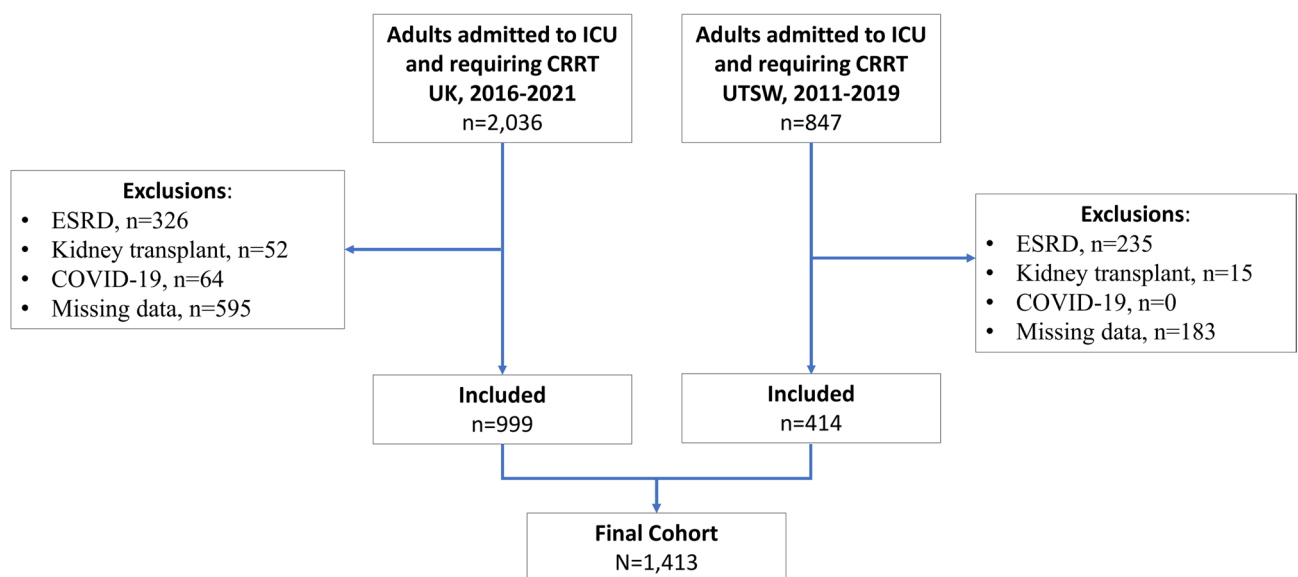


Fig. 1. Cohort derivation diagram. ICU: intensive care unit, CRRT: continuous renal replacement therapy, UK: University of Kentucky, UTSW: University of Texas Southwestern, ESRD: end-stage renal disease, COVID-19: Coronavirus Disease 2019.

Variables	Overall (n = 1413)	Survived (n = 660)	Died (n = 753)	P value
Age, mean years (SD)	56.32 (14.71)	54.23 (14.99)	58.10 (14.24)	< 0.001
Men, n (%)	895 (63.3)	418 (63.3)	477 (63.3)	1.000
Race, n (%)				0.662
White	1166 (82.5)	551 (83.5)	615 (81.7)	
Black	155 (11.0)	69 (10.5)	86 (11.4)	
Other	92 (6.5)	52 (6.9)	40 (6.1)	
Study site				
UK	999 (70.7)	466 (70.6)	533 (70.8)	0.988
UTSW	414 (29.3)	194 (29.4)	220 (29.2)	
Weight, kg, mean (SD)	95.71 (31.33)	93.76 (28.38)	97.39 (33.60)	0.037
Baseline Serum Creatinine, mean (SD)	1.74 (1.77)	1.90 (2.08)	1.60 (1.40)	0.005
Charlson Comorbidity Index, mean (SD)	4.27 (2.64)	4.05 (2.67)	4.45 (2.61)	0.005
Mechanical ventilation, n (%)	1280 (90.6)	585 (88.6)	695 (92.3)	0.024
SOFA at ICU admission, mean (SD)	9.55 (4.98)	8.83 (4.99)	10.16 (4.90)	< 0.001
SOFA at CRRT initiation, mean (SD)	12.73 (4.81)	11.73 (5.00)	13.58 (4.48)	< 0.001
Hospital LOS, mean days (SD)	26.63 (25.83)	35.94 (30.41)	18.67 (17.61)	< 0.001
ICU LOS, mean days (SD)	17.22 (18.64)	20.43 (22.62)	14.44 (13.75)	< 0.001
Time from ICU admission to CRRT initiation, mean days (SD)	5.36 (8.91)	5.07 (9.26)	5.62 (8.57)	0.250
CRRT duration, mean days (SD)	7.57 (9.46)	7.54 (9.65)	7.60 (9.30)	0.894
Platelets before CRRT, ^a x 10 ⁹ /L, mean (SD)	159.04 (103.78)	166.25 (109.60)	152.69 (98.00)	0.014
Platelets during CRRT, ^a x 10 ⁹ /L, mean (SD)	122.19 (86.74)	131.93 (88.62)	113.60 (84.19)	< 0.001
% Drop in platelets during CRRT, ^b x 10 ⁹ /L, mean (SD)	14.02 (47.52)	10.06 (50.57)	17.52 (44.39)	0.003
% Drop in platelets during CRRT, ^{b, c} SD groups, n (%)				0.019
< -1 SD (< -33.49%)	164 (11.6)	90 (13.6)	74 (9.8)	
± 1 SD (-33.49–61.54%)	1111 (78.6)	517 (78.3)	594 (78.9)	
> 1 SD (> 61.54%)	131 (9.3)	52 (7.9)	79 (10.5)	
WBC before CRRT, ^a x 10 ⁹ /L, mean (SD)	14.46 (12.41)	13.99 (10.91)	14.85 (13.55)	0.199
WBC during CRRT, ^a x 10 ⁹ /L, mean (SD)	16.71 (11.20)	15.27 (10.92)	17.93 (11.29)	< 0.001
% Rise in WBC during CRRT, ^d x 10 ⁹ /L, mean (SD)	38.15 (97.30)	30.31 (94.80)	44.83 (98.95)	0.005
% Rise in WBC during CRRT, ^{c, d} SD groups, n (%)				< 0.001
< -1 SDs (< -59.15%)	26 (1.8)	11 (1.7)	15 (2.0)	
± 1 SD (-59.15–135.45%)	1259 (89.1)	594 (90.0)	665 (88.3)	
> 1 SDs (> 135.45%)	110 (7.8)	37 (5.6)	73 (9.7)	

Table 1. Baseline and clinical characteristics of the study cohort. Footnote: SD: standard deviation; UK: University of Kentucky; UTSW: University of Texas Southwestern, SOFA: sequential organ failure assessment, ICU: intensive care unit, CRRT: Continuous renal replacement therapy, LOS: length of stay. ^a Mean of platelets and mean of WBCs was calculated by averaging data from 7 days before or 7 days after CRRT initiation. ^b % drop in platelets = (mean of platelets before CRRT - mean of platelets after CRRT) / (mean of platelets before CRRT) * 100%. A positive value indicated a drop in platelets after CRRT initiation; a negative value indicated a rise in platelets after CRRT initiation. Seven patients had missing platelet data either before or after CRRT and were not included in the analysis. ^c 7 patients (1 survived and 6 died) had no data of platelet/WBC counts before or after CRRT. ^d % rise in WBCs = (mean of WBCs after CRRT - mean of WBCs before CRRT) / (mean of WBCs before CRRT) * 100%. A positive value indicated a rise in WBCs after CRRT initiation; a negative value indicated a drop in platelets after CRRT initiation. Eighteen patients had missing WBC data either before or after CRRT and were not included in the analysis.

(10% in those who survived versus 17.5% in patients who died, $p=0.003$). The mean WBC count increased by 38.2% from pre-CRRT to during CRRT in the whole cohort (30.3% in those who survived versus 44.8% in patients who died, $p=0.005$) (Table 1). Similar findings were observed in patient subgroups stratified by study location (e--Table 1).

Adjusted models demonstrated a significant association between platelet drop from before to during CRRT and hospital mortality (Table 2). Patients with > 1 SD (62%) drop in platelets from before to during CRRT had an 82% increased risk of hospital mortality (adjusted odds ratio [aOR] 1.82, 95% confidence interval [CI] 1.06 to 3.13, $p=0.031$). Every drop of 10% in platelets from before to during CRRT increased the adjusted odds of hospital mortality by 3% (aOR 1.03, CI 1.004–1.06, $p<0.05$) (Table 2).

Adjusted models showed no independent association between > 1 SD rise in WBCs from before to during CRRT and hospital mortality (aOR 1.55, 95% CI 0.66 to 3.76, $p=0.162$) (Table 3).

Predictor	Drop-in-platelet SD groups		Drop-in-platelet percent change	
	Odd ratio (95% CI)	P-value	Odd ratio (95% CI)	P-value
Age	1.016 (1.007, 1.025)	< 0.01	1.015 (1.006, 1.024)	< 0.01
Charlson Comorbidity Index	1.066 (1.014, 1.122)	0.013	1.065 (1.013, 1.120)	0.014
Baseline serum creatinine	0.876 (0.802, 0.952)	< 0.01	0.879 (0.805, 0.955)	< 0.01
SOFA at ICU admission	1.067 (1.034, 1.101)	< 0.01	1.066 (1.033, 1.100)	< 0.01
SOFA at CRRT initiation	1.047 (1.017, 1.077)	< 0.01	1.047 (1.018, 1.078)	< 0.01
Drop in platelets ^a during CRRT by SD groups ^b				
± 1 SD (61.54% to -33.49%)	1.241 (0.839, 1.840)	0.281	-	-
> 1 SD (> 61.54%)	1.815 (1.061, 3.129)	0.031	-	-
Drop in platelets during CRRT by 10%	-	-	1.031 (1.004, 1.059)	0.0273

Table 2. Regression models of drop-in-platelets from pre- to during CRRT and hospital mortality. CI: confidence interval, SOFA: sequential organ failure assessment, ICU: intensive care unit, CRRT: Continuous renal replacement therapy, SD: standard deviation. ^a % Drop in platelets = (mean of platelets before CRRT - mean of platelets after CRRT)/(mean of platelets before CRRT)*100%. A positive value indicated a drop in platelets after CRRT initiation; a negative value indicated a rise in platelets after CRRT initiation. ^b Reference group was selected using the SD group with the lowest mortality rate after CRRT initiation.

Predictor	Rise-in-WBC SD groups		Rise-in-WBC percent change	
	Odd ratio (95% CI)	P-value	Odd ratio (95% CI)	P-value
Age	1.015 (1.006, 1.024)	< 0.01	1.015 (1.006, 1.024)	< 0.01
Charlson Comorbidity Index	1.063 (1.011, 1.119)	0.017	1.062 (1.010, 1.117)	0.019
Baseline serum creatinine	0.873 (0.799, 0.949)	< 0.01	0.871 (0.797, 0.947)	< 0.01
SOFA at ICU admission	1.068 (1.036, 1.102)	< 0.01	1.068 (1.036, 1.102)	< 0.01
SOFA at CRRT initiation	1.043 (1.014, 1.073)	< 0.01	1.04 (1.015, 1.074)	< 0.01
Rise in WBCs ^a during CRRT by SD groups ^b				
< 1 SD (-59.15%)	1.546 (0.655, 3.764)	0.323		
> 1 SD (135.45%)	1.408 (0.878, 2.297)	0.162		
Rise in WBCs during CRRT, by 10%			1.001 (0.999, 1.002)	0.455

Table 3. Regression models of rise-in-WBCs from pre- to during CRRT and hospital mortality. CI: confidence interval; SOFA: sequential organ failure assessment, ICU: intensive care unit, WBC: white blood cell, CRRT: Continuous renal replacement therapy, SD: standard deviation. ^a Change was calculated by the difference between the mean after CRRT minus before CRRT; a negative value indicated a drop in platelet/WBC count after CRRT initiation while a positive value indicated an increase in platelet/WBC counts after CRRT initiation. ^b Reference group was selected using the SD group with the lowest mortality rate after CRRT initiation.

Figure 2 represents the adjusted odds for mortality according to the changes in platelets and WBCs from before to during CRRT, stratified by SD groups.

While adjusting for the covariates used in the multivariable models, an interaction analysis revealed a statistically significant four-way interaction between four continuous variables ($p < 0.001$), i.e., platelet and WBC counts before CRRT, drop in platelets during CRRT, and rise in WBCs during CRRT. Due to the challenging nature of interpreting multi-way continuous variable interactions, we first categorized each continuous variables by < 1 SD, within 1 SD, or > 1 SD. The most frequently identified subgroups based on platelet and WBC changes from pre-CRRT to during CRRT also had the highest odds of hospital mortality in this cohort. This multi-pronged assessment identified four independent high-risk clinical subgroups: (1) Pre-CRRT low platelet count that remained low during CRRT (while pre-CRRT WBC count and rise in WBC count during CRRT is within 1 SD), (2) Pre-CRRT normal platelet count with a drop of > 1 SD during CRRT (while pre-CRRT WBC count and rise in WBC count during CRRT is within 1 SD), (3) Pre-CRRT elevated WBC count that remained high during CRRT (while pre-CRRT platelet count and drop in platelet count during CRRT is within 1 SD), and (4) Normal or elevated pre-CRRT WBC count that increased to > 1 SD during CRRT (while pre-CRRT platelet count and drop in platelet count during CRRT is within 1 SD) (Table 4). Supplemental e-Figs. 1 and e and 2 provide a graphic visualization of the patterns of WBCs and platelets for these four groups. Supplemental e-Figs. 3 and e and 4 describe density of measurements of platelets and WBC pre- and during CRRT.

We conducted sensitivity analyses using a shorter 3-day window to assess whether early changes in platelet and WBC counts after CRRT initiation could help identify high-risk patients. Although trends remained similar,

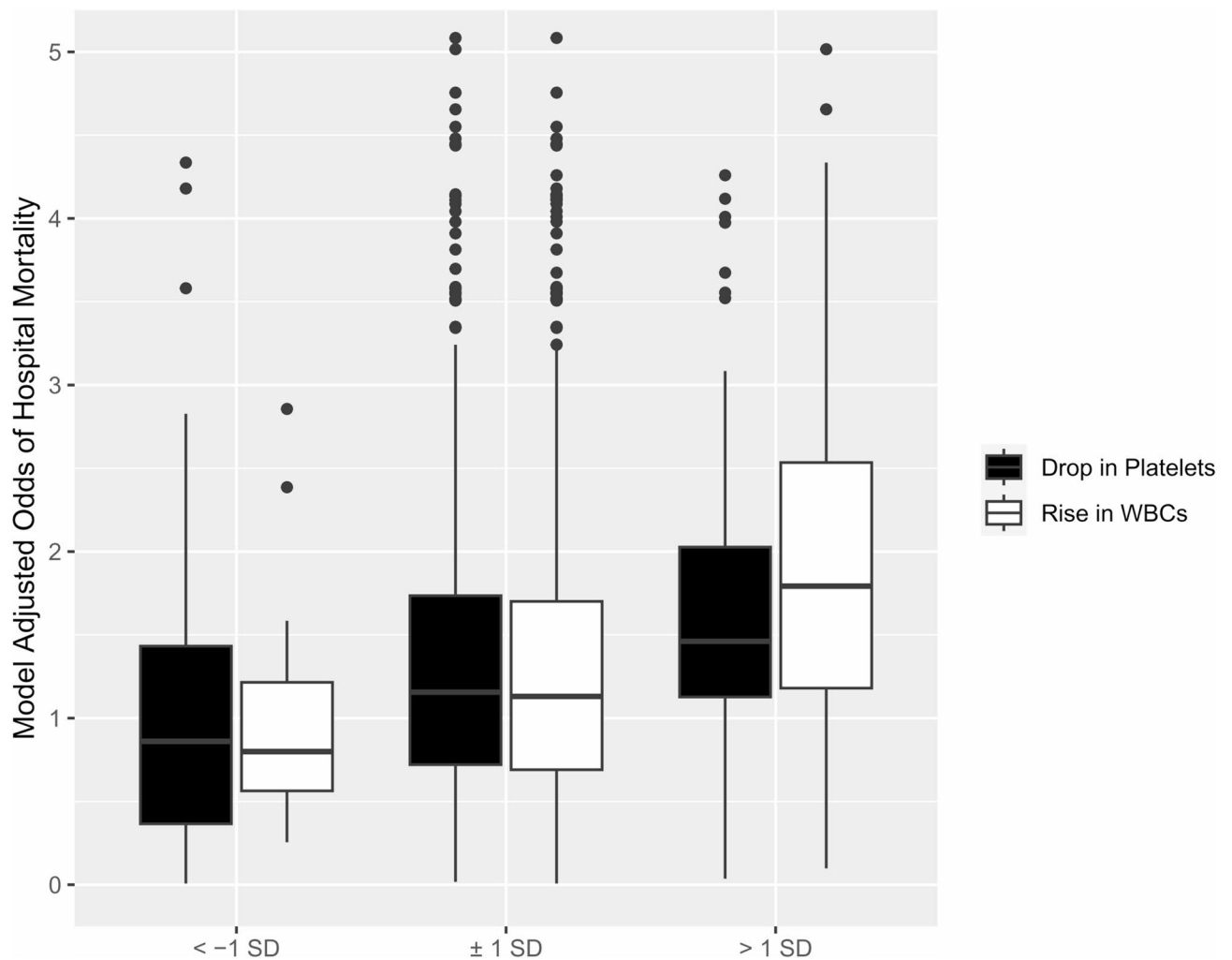


Fig. 2. Change in platelets and WBC from pre-CRRT to during CRRT and in-hospital mortality. SD: Standard Deviation groups were stratified based on change in platelets/WBC after CRRT initiation = $(\text{mean of platelets/WBC after CRRT} - \text{mean of platelets/WBC before CRRT}) / (\text{mean of platelets/WBC before CRRT})$. A positive value indicated a rise in platelets/WBC after CRRT initiation; a negative value indicated a drop in platelets/WBC after CRRT initiation. The figure describes adjusted odds for mortality with patients with a platelet count and WBC change after CRRT initiation, stratifying by changing in platelets/ WBC after CRRT initiation SD groups. The middle lines of the boxes represent the median odds of mortality from adjusted models. Odds of mortality were adjusted for age, Charlson Comorbidity Index, baseline serum creatinine, SOFA score at ICU admission, and SOFA score at CRRT initiation.

the associations were weaker and not statistically significant. In a separate sensitivity analysis including patients with COVID-19, the associations also remained directionally consistent but not statistically significant. These patients were excluded from the primary analysis because COVID-19 is known to cause distinct immune and hematologic abnormalities, including thrombocytopenia, which could confound the relationship between platelet or WBC changes and hospital mortality²⁹.

Discussion

Our study demonstrated that in critically ill adults with AKI requiring CRRT, a drop in platelets after CRRT initiation was independently associated with hospital mortality. We also showed that the combination of a drop in platelets and an increase in WBC from pre-CRRT to during CRRT could assist with identification of high-risk groups. Our study is unique as it evaluated the relationship between mortality and changes in platelets and WBCs over an extended period (up to 7 days before and after CRRT initiation) in critically ill patients with AKI requiring CRRT. The evaluation of change in platelet and leukocyte counts up to 7 days of CRRT was determined as the mean time on CRRT in this multicenter cohort was 7.6 days.

During CRRT, a drop in platelets can occur due to platelet activation and consumption caused by activation of the coagulation system and contact with extracorporeal surfaces. Additionally, the hemofilter may contribute to either destruction or retention of platelets during passage, which appeared attenuated by higher blood flows³⁰. Thrombocytopenia, commonly defined as a platelet count below $150 \times 10^9/\text{L}$, increases the risk of bleeding and

Phenotype ^a	Pre-CRRT mean platelet count (x10 ⁹ /L)	Drop in platelets during CRRT	Pre-CRRT mean WBC count (x10 ⁹ /L)	Rise in WBC during CRRT	Observed odds of hospital mortality ^b	Model adjusted odds (25–75%) of hospital mortality ^c
1 (n = 71)	< 55 (< 1 SD)	-34 to 62% (within 1 SD)	2.1 to 27 (within 1 SD)	-59 to 135% (within 1 SD)	1.22	1.42 (1.07, 1.85)
2 (n = 63)	55 to 263 (within 1 SD)	> 62% (> 1 SD)	2.1 to 27 (within 1 SD)	-59 to 135% (within 1 SD)	1.74	1.61 (1.14, 2.17)
3 (n = 37)	55 to 263 (within 1 SD)	-34 to 62% (within 1 SD)	> 27 (> 1 SD)	-59 to 135% (within 1 SD)	2.08	1.88 (1.13, 3.35)
4 (n = 41)	55 to 263 (within 1 SD)	-34 to 62% (within 1 SD)	2.1 to 27 (within 1 SD)	> 135% (> 1 SD)	2.15	1.73 (1.22, 2.15)

Table 4. Identified clinical subphenotypes with high odds for hospital mortality based on patterns of platelets and WBCs from pre-CRRT to during CRRT. ^a Phenotype (1) Pre-CRRT low platelet count that remained low during CRRT (while pre-CRRT WBC count and rise in WBC count during CRRT is within 1 SD), phenotype (2) Pre-CRRT normal platelet count with a drop of > 1 SD during CRRT (while pre-CRRT WBC count and rise in WBC count during CRRT is within 1 SD), phenotype (3) Pre-CRRT elevated WBC count that remained high during CRRT (while pre-CRRT platelet count and drop in platelet count during CRRT is within 1 SD), and phenotype (4) Normal or elevated pre-CRRT WBC count that increased to > 1 SD during CRRT (while pre-CRRT platelet count and drop in platelet count during CRRT is within 1 SD). ^b Odds of mortality were calculated ratios of the proportion of expired patients/proportion of survived patients. ^c Odds of mortality were adjusted for age, Charlson Comorbidity Index, baseline serum creatinine, SOFA score at ICU admission, and SOFA score at CRRT initiation.

can indicate inflammation, poor tissue integrity, and impaired immune response^{16,27,31}. A drop in platelet count before or during CRRT has also been associated with an increased risk of secondary infection²⁰. In our analysis, patients with severely low pre-CRRT platelet count (< 55 × 10⁹/L), which remained low during CRRT (± 1 SD), had an increased adjusted odds of hospital mortality by 40%. Similarly, in patients with relatively normal platelet count (> 55 × 10⁹/L), a drop in platelets > 62% (> 1 SD) during CRRT increased the adjusted odds of hospital mortality by 60% (Table 4, e-Figure 1).

We conducted sensitivity analyses using a shorter 3-day window, instead of the 7-day period used in the primary analysis, to evaluate whether early changes in platelet and WBC counts after CRRT initiation could help identify high-risk patients. In clinical practice, prognosis may already be evident after seven days of CRRT, making later changes less useful for early risk classification. Additionally, some patients in our cohort received CRRT for only a few days, introducing variability. Although the results from the 3-day window showed similar directional trends, the associations were weaker and not statistically significant, suggesting that the longer 7-day window may better capture meaningful changes in platelet and WBC counts during CRRT.

Previous studies have found that a drop in platelet count after CRRT initiation was associated with mortality at various time points^{14,15,17,21}. A decrease in platelet count (mean decrease of 33% from pre-CRRT baseline) within 48 h following CRRT initiation was independently associated with increased 60-day mortality (OR = 1.51, 95% CI = 1.12–2.02)¹⁷. Another study showed increased 90-day mortality in patients with ≥ 50% drop in platelet count from the first measurement at CRRT start to within three days of CRRT initiation (59.0% vs. 35.0%, *p* = 0.012)¹⁴. One similar study found that a decline of ≥ 60% in platelets from the first measurement from CRRT start to within four days of CRRT initiation was independently associated with 90-day mortality (hazard ratio = 1.93, 95% CI = 1.23–3.05)²¹. While the association between platelet drop after CRRT initiation and mortality has been consistently established, using measurements in an extended period pre-CRRT and during CRRT is unique to our study.

Instead of relying on a single reference measurement and the lowest value following 2–4 days of CRRT^{14,17,21}, we utilized multiple measurements of platelets and WBCs up to 7 days before (mean [SD], 4.0 [2.4] days) and 7 days after (mean [SD], 6.1 [1.4] days) CRRT initiation to calculate the drop in platelets. This strategy offers several advantages: it captures overall trends, reduces the influence of isolated outlier values, and accommodates variability in the timing and frequency of lab draws, which is common in critically ill populations. However, this approach also has limitations. Averaging measurements over a longer period may dilute sharp, clinically significant changes—such as an abrupt drop in platelet count—that the nadir method is designed to capture. As a result, the sensitivity of our model to detect short-term but important prognostic changes may be reduced. By contrast, nadir or peak-based methods may be more responsive to rapid shifts but are also more vulnerable to measurement timing and outlier influence. Our findings suggest that the 7-day averaging approach provides a more stable and comprehensive picture of platelet and WBC dynamics, but future studies could explore combining both approaches to optimize clinical prediction and subgroup identification.

During CRRT, alterations in WBC counts may occur due to several underlying factors, including inflammatory response, infections, activation of blood components during the CRRT process, medications, and pre-existing medical conditions^{13,32}. Both leukopenia and leukocytosis are associated with AKI^{13,33} and mortality risk in critically ill patients¹³. Additionally, lymphopenia is linked to mortality and AKI risk in ICU patients with sepsis¹³. Our study found a non-significant association between the rise of WBCs from pre- to during CRRT and hospital mortality (Table 3). Although we did not include information regarding subtypes of WBCs, we identified that patients with severely elevated pre-CRRT WBCs (> 26.86 × 10⁹/L), which remained

high during CRRT (± 1 SD), had an increased adjusted odds of hospital mortality by 88%. Similarly, in patients with relatively normal pre-CRRT WBCs (2.05 to $26.86 \times 10^9/L$), a rise in WBCs during CRRT $> 135.45\%$ (> 1 SD) increased the adjusted odds of hospital mortality by 73% (Table 4 and e-Figure 2).

Some limitations of this study should be noted. First, this observational study is subject to selection and indication biases related to study populations and CRRT practices specific to the two academic study sites. Second, the study lacked key baseline ICU-level clinical details—such as admission source, primary diagnosis, and use of additional critical care interventions (e.g., vasopressors)—because these variables were not routinely or consistently documented in the electronic health record systems across the two participating hospitals during the study period. This limitation reduces our ability to fully characterize cohort heterogeneity and adjust for potential confounders related to illness severity and ICU context. Although we accounted for several relevant factors, including demographics, comorbidities, and illness acuity in our multivariable models, residual confounding from unmeasured variables may still be present. Third, we did not have information regarding potential causes for changes in platelets or WBCs, such as heparin-induced thrombocytopenia, infections, specific anticoagulation use for CRRT, blood product transfusions, or administration of steroids or other immunosuppressive medications. Therefore, this study cannot establish a causal relationship between platelet and WBC changes from pre-CRRT to during CRRT and mortality. Additionally, we did not include baseline platelet and WBC counts in the multivariable model, despite their known prognostic value, because our primary focus was on percentage change, which better captures dynamic trends during CRRT. Including both baseline values and their corresponding change measures could introduce multicollinearity due to their mathematical dependency; therefore, we prioritized the change variables to preserve model stability and interpretability. Finally, the utilized platelet and WBC exploratory cutoffs, determined based on SDs, are not intended to serve as clinical cutoffs. Rather, their purpose is to inform future research to assess the specificity and utility of these cutoffs in clinical sub-phenotyping.

Our study has several strengths that needs to be highlighted. First, we used a large sample of adult patients from two large academic institutions. Second, we carefully evaluated the change in platelet and WBC counts from pre- to during CRRT utilizing multiple measures up to 7 days before CRRT initiation and up to 7 days during CRRT. This differentiates our study from prior studies that used single time points subject to day-to-day laboratory and clinical variation. Third, we used multivariable regression and interaction terms to identify high-risk subgroups of patients with increased adjusted odds of mortality based on pre-CRRT and change during CRRT of platelet and WBC counts. This reflects a step towards more precise use of dynamic data for clinical sub-phenotyping, although further validation is needed.

Conclusions

In conclusion, a drop in platelets from up to 7 days before to 7 days after CRRT initiation was independently associated with hospital mortality in critically ill adults with AKI requiring CRRT. The dynamic monitoring of platelets and leukocyte counts during CRRT in reference to pre-CRRT levels could assist with identification of high-risk groups. Further, the functional aspect of platelets and leukocytes in patients exposed to CRRT should be investigated.

Data availability

Data utilized in this study is available upon reasonable request via contact with the corresponding author.

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Author contributions

JWL and JAN conceived the study design. JWL, LJJ and VOS managed data extraction, transformation, and quality control. JWL performed statistical analyses. LNB, CGB, ACO, and JAN drafted the manuscript. OWM, RDT, AJT and JAN provided resources for the conduction of the study. All authors revised the manuscript, incorporated feedback, and approved the final version.

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Declarations

Ethics approval and consent to participate

The study was approved by the University of Kentucky and the University of Texas Southwestern Institutional Review Boards (IRBs 43159 and STU112015-069, respectively). A waiver of informed consent was obtained given the retrospective nature of the investigation.

Consent for publication

This manuscript has not been published elsewhere and is not under consideration by any other journal. All authors have approved the manuscript and agree with its submission to *Journal of Intensive Care*.

Competing interests

The authors declare no competing interests.

Additional information

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