Kidney Medicine

Platelet-to-Lymphocyte Ratio and In-Hospital Mortality in Patients With AKI Receiving Continuous Kidney Replacement Therapy: A Retrospective Observational Cohort Study

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Rationale & Objective: The platelet-to-lymphocyte ratio (PLR) is a marker of inflammation and a predictor of mortality in a variety of diseases. However, the effectiveness of PLR as a predictor of mortality in patients with severe acute kidney injury (AKI) is uncertain. We evaluated the association between the PLR and mortality in critically ill patients with severe AKI who underwent continuous kidney replacement therapy (CKRT).

Study Design: Retrospective cohort study.

Setting & Participants: A total of 1,044 patients who underwent CKRT in a single center, from February 2017 to March 2021.

Exposures: PLR

Outcomes: In-hospital mortality.

Analytical Approach: The study patients were classified into quintiles according to the PLR values. A Cox proportional hazards model was used to investigate the association between PLR and mortality.

Results: The PLR value was associated with in-hospital mortality in a nonlinear manner, showing a higher mortality at both ends of the PLR. The Kaplan-Meier curve revealed the highest mortality with the first and fifth quintiles, whereas the lowest mortality occurred with the third quintile. Compared with the third quintile, the first (adjusted HR, 1.94; 95% CI, 1.44-2.62; $P < 0.001$) and fifth (adjusted HR, 1.60; 95% CI, 1.18-2.18; $P = 0.002$) quintiles of the PLR group had a significantly higher in-hospital mortality rate. The first and fifth quintiles showed a consistently increased risk of 30- and 90-day mortality rates compared with those of the third quintile. In the subgroup analysis, the lower and higher PLR values were predictors of in-hospital mortality in patients with older age, of female sex, and with hypertension, diabetes, and higher Sequential Organ Failure Assessment score.

Limitations: There may be bias owing to the single-center retrospective nature of this study. We only had PLR values at the time of initiation of CKRT.

Conclusions: Both the lower and higher PLR values were independent predictors of in-hospital mortality in critically ill patients with severe AKI who underwent CKRT.

Visual Abstract included

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Acute kidney injury (AKI), which presents more frequently in the intensive care unit (ICU) patients, is associated with poor outcomes.[1-4] Several publications have shown that the higher the AKI stage, the worse the outcome.[2,4,5] In the ICU setting, continuous kidney replacement therapy (CKRT) is performed for patients who develop severe AKI requiring dialysis.[2] The requirement of CKRT implies that a patient has deteriorating medical conditions, such as hemodynamic instability and severe AKI. Given the poor outcomes of patients requiring CKRT, several studies have explored the prognostic factors and identified the novel biomarkers of AKI.[5-8] However, patient heterogeneity in clinical studies makes it difficult to obtain consistent results. In addition, most biomarkers are neither readily available in clinical practice nor cost effective.[9]

The platelet-to-lymphocyte ratio (PLR) is a systemic inflammatory index that can be calculated easily. PLR has been demonstrated to be a prognostic factor in diseases such as cancer and myocardial infarction.[10-12] Several studies have also shown that PLR is associated with the occurrence of contrast-induced nephropathy in patients with ST-segment elevation myocardial infarction.[13,14]

However, studies on the role of PLR in patients with severe AKI are limited, particularly in critically ill patients. We analyzed observational cohort data to elucidate the role of PLR as a prognostic marker in critically ill patients with severe AKI who underwent CKRT.

METHODS

Study Patients and Data Collection

This retrospective cohort study was conducted at Kyungpook National University Hospital between February 2017 and March 2021. Patients aged 19 years or older who underwent CKRT were included in the study, whereas those who had previously undergone maintenance dialysis were excluded. Demographic characteristics and medical data, such as comorbidities and clinical information, were collected. Laboratory results at the time of CKRT initiation, such as complete blood count, creatinine, blood urea nitrogen (BUN), albumin, arterial pH, sodium, and

PLAIN-LANGUAGE SUMMARY

The platelet-to-lymphocyte ratio (PLR) is a marker of inflammation and has a role in predicting mortality in several diseases. This study evaluated the association between the PLR and mortality in critically ill patients with severe acute kidney injury. We found that both the lower and higher PLR groups showed a significantly higher in-hospital mortality rates. In addition, poor prognosis of the lower and higher PLR groups was associated with increased severity of acute illness and inflammation. These results suggest that PLR represents a complex medical condition and could be a readily available marker of mortality in patients with severe acute kidney injury.

potassium levels, were obtained from the electronic medical records from the Kyungpook National University Hospital. The PLR was calculated as the ratio of platelets count to lymphocytes count. The Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and Charlson Comorbidity Index (CCI) were used to estimate the patient severity. This study was approved by the Institutional Review Board (IRB) committee of Kyungpook National University Hospital (2021-07-068) and performed in accordance with the principles of the 2013 Declaration of Helsinki. The requirement for informed consent was waived by the IRB because all patient information was anonymized.

Study Outcomes

The primary outcome of this study was in-hospital mortality. The in-hospital mortality rate was also compared using a subgroup analysis. The secondary outcomes were 30- and 90-day mortality rates.

CKRT Protocol

In our hospital, CKRT is performed when azotemia, volume overload, electrolyte imbalance, metabolic abnormality, oliguria, and other indications occur, as deemed necessary by the responsible nephrologists. The details of the CKRT protocol at our hospital have been described previously.[15]

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or median (interquartile range [IQR]), whereas categorical variables are expressed as numbers (percentages). A restricted cubic spline regression model was used to explore the association between PLR as a continuous variable and in-hospital mortality. Because there was a nonlinear association between PLR and in-hospital mortality (Fig 1), patients were divided into quintiles according to their PLR values. An analysis of variance was performed to evaluate the differences between baseline characteristics and in-hospital information by quintiles. The cumulative survival according to the PLR quintiles was analyzed using the Kaplan-Meier method and compared using the log-rank test. A multivariable Cox regression analysis was used to adjust for confounding variables. We selected age, sex, and variables with $P < 0.10$ in the unadjusted analysis as adjustment factors. Hazard ratios (HRs) and 95% confidence intervals (CIs) were measured from the Cox proportional hazards regression model. Subgroup analyses were performed to assess differences according to the baseline characteristics. A logistic regression analysis was used to identify the association between PLR quintiles and clinical phenotypes such as severity of acute illness and degree of inflammation. A $P < 0.05$ indicated statistical significance. Statistical analyses were performed using the SAS for Windows, version 9.4 (SAS Institute Inc) and R (R Foundation for Statistical Computing; www.r-project.org).

RESULTS

Baseline Characteristics

A total of 1,044 patients who underwent CKRT in the ICU were included and divided into quintiles based on the PLR values. The mean age of the patients was 65.3 years, and 63.1% were men. The mean and median PLR values were 241.3 and 150.6 (83.0-281.6), respectively. In addition, the PLR quintiles 1–5 values ranged from <71.4; 71.4 ≤ PLR < 122.3; 122.3 ≤ PLR < 184.4; 184.4 ≤ PLR < 325.7; and ≥325.7, respectively. The first quintile group showed decreased platelet counts and increased lymphocyte counts. In the fifth quintile group, the number of lymphocytes decreased and platelet counts were at normal levels. Distributions of PLR, platelet counts, and lymphocyte counts are provided in Figure S1. Detailed baseline characteristics according to the PLR quintiles are indicated in Table 1. No significant differences in CCI or other comorbidities were observed among the quintiles. However, age and body weight during ICU admission differed among the quintiles ($P = 0.01$ and $P = 0.02$, respectively). Notably, the SOFA and APACHE II scores showed significant differences across the quintiles, and both scores were highest in the first quintile (all $P < 0.01$). The etiology of AKI differed according to the PLR quintiles, and septic AKI occurred most frequently in the fifth quintile (56.9%). Laboratory findings—such as white blood cell, lymphocyte, and platelet counts; hemoglobin, albumin, BUN, and creatinine levels; and arterial pH—differed significantly among the PLR quintiles.

In-Hospital Mortality Outcomes

Among patients treated using CKRT, 651 (62.4%) died during the follow-up period. The mean length of hospital stay was 26.1 days (range, 5–32 days). Patients were admitted to the ICU for an average of 12.5 days and

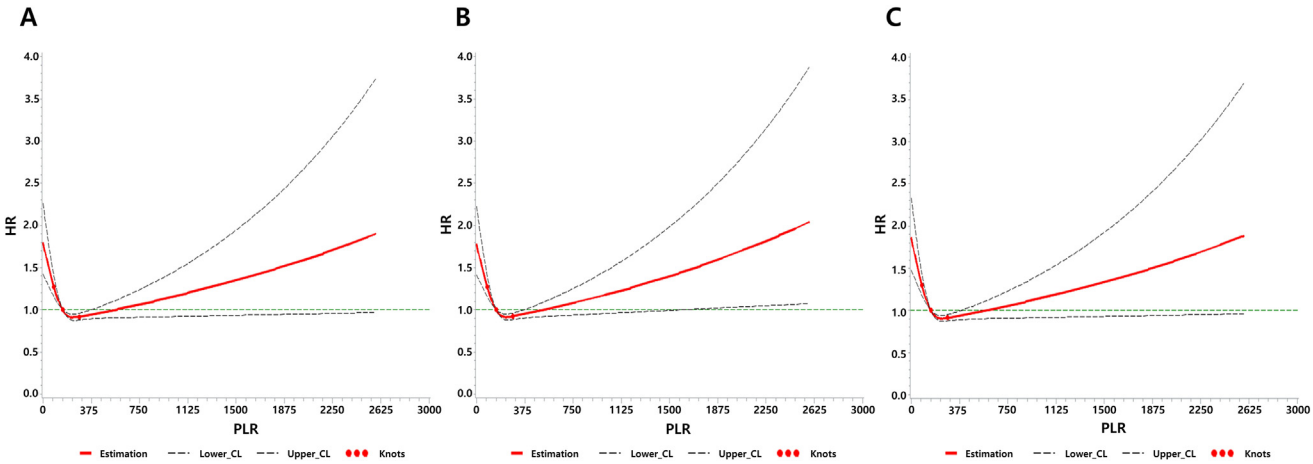

Figure 1. Association between PLR and mortality hazard ratio by restricted cubic spline regression models. The associations between 30-day mortality and PLR (A), 90-day mortality and PLR (B), and in-hospital mortality and PLR (C) show U-shaped patterns. HRs for mortality, where the reference value for PLR was 151.0. The dashed lines indicate 95% confidence intervals. Abbreviations: HR, hazard ratio; PLR, platelet-to-lymphocyte ratio.

received CKRT treatment for ~4.3 days. Overall, PLR as the independent variable and in-hospital mortality rate showed a U-shaped relationship in the cubic spline regression model (Fig 1). In-hospital mortality and other in-hospital information according to the PLR quintiles are presented in Table 2. In brief, we observed significantly higher in-hospital mortality rates in the first (157 [75.5%]) and fifth (148 [70.8%]) quintile groups than those in the third quintile group (93 [44.5%]), which had the lowest mortality. Furthermore, the 30- and 90-day mortality rates showed a significant increase at both ends of the quintiles (Table 2). The ratio of patients who received mechanical ventilation and were prescribed vasopressors differed significantly by quintiles, with the highest and lowest rates in the first and fifth quintiles, respectively (both $P < 0.05$).

Association Between PLR and Mortality

Kaplan-Meier curves showed a significant difference in the cumulative survival according to PLR quintiles (Fig 2). The first and fifth quintiles showed the highest mortality, whereas the third quintile showed the lowest mortality. Similar differences were observed in the 30- and 90-day mortality rates (all $P < 0.05$) (Fig 2). In model 4, after adjusting for various factors, including age, sex, comorbidities, and severity indicators, compared with the third quintile of PLR (reference group), the lowest (adjusted HR [aHR], 1.94; 95% CI, 1.44-2.62; $P < 0.001$) and highest (aHR, 1.60; 95% CI, 1.18-2.18; $P = 0.002$) quintiles showed significantly greater in-hospital mortality rates (Table 3). Figure 3 shows the aHRs of the 30-day (quintile 1: aHR, 1.93; 95% CI, 1.43-2.61; $P < 0.001$; quintile 5: aHR, 1.63; 95% CI, 1.20-2.22; $P = 0.002$), 90-day (quintile 1: aHR, 1.97; 95% CI, 1.47-2.65; $P < 0.001$; quintile 5: aHR, 1.70; 95% CI, 1.26-2.30; $P < 0.001$), and in-hospital mortality rates for model 4, showing U-shaped aHRs across the PLR quintiles. Table S1 presents the detailed results of the Cox regression analysis for 30- and 90-day mortality rates across the PLR quintiles. However, there were no significant associations between the in-hospital mortality rate and platelet and lymphocyte quintiles, respectively (Tables S2 and S3, respectively).

Subgroup Analysis

We divided the patients into subgroups according to age, sex, body mass index, comorbidities (hypertension and diabetes), SOFA, and APACHE II scores. The first and fifth quintiles showed significant associations with increased in-hospital mortality in most subgroups, including those with older age, of female sex, and with hypertension, diabetes, and higher SOFA score (Table 4).

Associations Between PLR and Severity Score and Inflammation

To identify the clinical phenotypes according to the PLR quintiles, logistic regression analyses for higher severity score (median APACHE II score of 26 or higher) and septic AKI were performed. The first quintile was significantly associated with a higher APACHE II score (adjusted odds ratio [aOR], 1.78; 95% CI, 1.00-3.17; $P = 0.04$) (Table S4), whereas the fifth quintile was significantly associated with septic AKI (aOR, 3.52; 95% CI, 2.11-5.85; $P < 0.001$) (Table S5).

DISCUSSION

This study evaluated PLR as a prognostic factor by investigating the mortality according to the PLR quintiles in critically ill patients with AKI who underwent CKRT. The prognostic value of PLR was ascertained by our results, showing no differences in mortality rate according to the platelet and lymphocyte counts. The in-hospital mortality

Table 1. Baseline Characteristics

	Quintile 1 (n = 208)	Quintile 2 (n = 210)	Quintile 3 (n = 209)	Quintile 4 (n = 208)	Quintile 5 (n = 209)	*P*
PLR	37.4 ± 18.8	96.6 ± 14.3	151.7 ± 17.7	245.3 ± 41.3	675.5 ± 392.3	<0.001
Age, y	62.5 ± 16.0	65.7 ± 15.7	64.1 ± 17.3	67.1 ± 14.5	66.9 ± 15.2	0.01
Sex, male	138 (66.4)	135 (64.3)	129 (61.7)	128 (61.5)	129 (61.7)	0.80
ICU admission body weight, kg	64.5 ± 13.3	62.9 ± 12.0	61.9 ± 12.3	62.5 ± 12.9	60.3 ± 11.5	0.02
ICU admission BMI, kg/m	23.5 ± 4.3	23.4 ± 3.9	23.9 ± 11.4	23.3 ± 4.5	22.8 ± 3.5	0.58
CCI	3.9 ± 2.4	4.0 ± 2.2	4.2 ± 2.4	4.5 ± 2.5	4.4 ± 2.4	0.06
Causes of AKI						<0.001
Septic	77 (37.0)	65 (31.0)	65 (31.1)	68 (32.7)	119 (56.9)	
Ischemic	101 (48.6)	113 (53.8)	111 (53.1)	112 (53.8)	62 (29.7)	
Postoperative	13 (6.3)	12 (5.7)	15 (7.2)	10 (4.8)	8 (3.8)	
Nephrotoxic	9 (4.3)	10 (4.8)	10 (4.8)	8 (3.8)	12 (5.7)	
Others	8 (3.8)	10 (4.8)	8 (3.8)	10 (4.8)	8 (3.8)	
Comorbidities						
Hypertension	59 (29.8)	63 (32.1)	65 (35.3)	80 (42.8)	75 (38.7)	0.06
Diabetes	58 (27.9)	59 (28.1)	56 (26.9)	66 (31.7)	53 (25.3)	0.68
Congestive heart failure	10 (4.8)	21 (10.0)	19 (9.1)	24 (11.5)	14 (6.7)	0.10
Cerebrovascular accident	16 (7.7)	21 (10.0)	19 (9.1)	19 (9.1)	18 (8.6)	0.95
Malignancy	15 (7.2)	13 (6.2)	10 (4.8)	17 (8.1)	27 (12.9)	0.10
SOFA	14.1 ± 5.0	12.7 ± 4.7	12.2 ± 4.6	11.8 ± 4.4	11.7 ± 4.6	<0.001
APACHE II	27.6 ± 8.5	25.9 ± 7.9	24.7 ± 8.1	24.4 ± 7.3	25.6 ± 8.1	0.001
Laboratory findings						
White blood cell, $\times 10^3/\mu L$	20.2 ± 11.3	12.7 ± 7.9	11.9 ± 7.3	12.4 ± 7.9	11.5 ± 8.9	<0.001
Neutrophil, $\times 10^3/\mu L$	10.9 ± 9.0	10.7 ± 7.4	10.2 ± 6.8	11.0 ± 7.4	10.5 ± 8.4	0.88
Lymphocyte, $\times 10^3/\mu L$	4.2 ± 1.3	1.3 ± 0.9	1.0 ± 0.6	0.7 ± 0.4	0.4 ± 0.3	<0.001
Platelet, $\times 10^3/\mu L$	81.6 ± 84.4	128.0 ± 82.9	146.9 ± 82.0	169.1 ± 93.3	203.4 ± 145.2	<0.001
Hemoglobin, g/dL	10.1 ± 3.3	10.5 ± 2.9	10.5 ± 2.8	10.7 ± 2.4	10.0 ± 2.5	0.04
Sodium, mEq/L	138.1 ± 8.7	139.2 ± 7.7	138.3 ± 7.8	137.7 ± 7.6	137.3 ± 8.1	0.14
Potassium, mEq/L	4.9 ± 1.2	4.7 ± 1.1	4.9 ± 1.2	4.8 ± 1.0	4.8 ± 1.1	0.27
Albumin, g/dL	2.8 ± 0.7	3.0 ± 0.7	3.0 ± 0.7	3.1 ± 0.6	2.8 ± 0.7	< 0.001
BUN, mg/dL	53.1 ± 36.1	54.4 ± 31.0	63.7 ± 40.0	58.6 ± 33.2	65.0 ± 37.0	< 0.001
Creatinine, g/dL	3.4 ± 3.0	3.3 ± 2.0	4.1 ± 3.3	3.9 3.2	4.0 ± 3.1	0.01
Arterial, pH	7.23 ± 0.15	7.26 ± 0.16	7.27 ± 0.23	7.28 ± 0.12	7.28 ± 0.12	0.01

Note: Data are presented as mean ± standard deviation or number (%).
Abbreviations: PLR, platelet-to-lymphocyte ratio; ICU, intensive care unit; BMI, body mass index; CCI, Charlson Comorbidity Index; AKI, acute kidney injury; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; BUN, blood urea nitrogen.

rate was the lowest in the third quintile of PLR and significantly higher in the first and fifth quintiles. We also observed a U-shaped correlation between the in-hospital mortality rate and PLR quintiles, with similar results for 30- and 90-day mortality patterns across the PLR quintiles. This is the first study to demonstrate PLR as a predictor of mortality in critically ill patients who underwent CKRT.

Zheng et al[16] demonstrated the predictive value of PLR on mortality in critically ill patients with mild-to-moderate AKI. They reported an increased risk of 90-day mortality in the lower and higher PLR groups compared with the reference median PLR group, and the results were similar when patients were divided into quintiles of PLR.[16] The patients in our study had a higher SOFA score than those in the previous study, and all experienced severe AKI that required CKRT, which indicated high severity. Nevertheless, the PLR was an independent predictor of mortality, and both low and high PLR quintiles were associated with poor prognosis. Therefore, the PLR can be an effective predictor of mortality in critically ill patients with AKI irrespective of the degree of AKI.

The value of PLR as a prognostic marker has been demonstrated in several studies. As PLR is considered a systemic inflammatory indicator, previous studies have mainly focused on cancer, autoimmune disease, and cardiovascular disease.[17-23] In addition, PLR contributes to predicting the prognosis in acute inflammatory episodes because PLR increases along with other inflammatory

Table 2. In-Hospital Information of PLR Quintile Groups

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*
30-d mortality	150 (72.1)	120 (57.1)	90 (43.1)	112 (53.9)	136 (65.1)	<0.001
90-d mortality	155 (74.5)	129 (61.4)	92 (44.0)	114 (54.8)	137 (65.6)	<0.001
In-hospital mortality	157 (75.5)	132 (62.9)	93 (44.5)	121 (58.2)	148 (70.8)	<0.001
CKRT duration, d	4.0 ± 4.1	4.8 ± 4.8	4.3 ± 5.0	4.3 ± 3.7	4.2 ± 3.6	0.34
ICU duration, d	10.5 ± 17.0	12.8 ± 14.7	13.4 ± 19.2	13.4 ± 22.2	12.5 ± 28.9	0.65
ICU admission to CKRT initiation, d	2.7 ± 4.6	2.9 ± 5.3	2.7 ± 4.1	3.1 ± 11.5	2.8 ± 4.3	0.96
Length of hospital stay, d	24.1 ± 37.6	24.5 ± 33.1	27.5 ± 32.8	27.3 ± 47.5	27.1 ± 37.1	0.81
Need for mechanical ventilation	134 (64.4)	134 (63.8)	118 (56.5)	121 (58.7)	98 (47.1)	0.002
Vasopressor requirements	175 (84.1)	157 (74.8)	163 (78.0)	151 (73.3)	149 (71.6)	0.02
Prescribed target clearance, mL/kg/h	35.8 ± 9.3	35.5 ± 9.9	35.7 ± 10.2	36.0 ± 8.7	35.5 ± 9.4	0.99

Note: Data are presented as mean ± standard deviation or number (%).
Abbreviations: CKRT, continuous kidney replacement therapy; ICU, intensive care unit; PLR, platelet-to-lymphocyte ratio.

indicators, such as C-reactive protein and procalcitonin levels, and predicts patient mortality in sepsis.[24] Recent studies have reported that PLR is independently associated with all-cause mortality in patients with kidney failure treated with either hemodialysis or peritoneal dialysis.[25,26] Patients with kidney failure are continuously exposed to chronic inflammation, and PLR positively correlates with inflammatory markers such as C-reactive protein. Therefore, a high PLR might indicate an increased inflammatory state and could be a predictor of mortality in patients with kidney failure. In this study, sepsis was the major etiology of AKI in the fifth quintile group. In addition, the fifth quintile group showed a significant increased risk of septic AKI. Despite the relatively low severity of organ failure, the high mortality in the fifth quintile could be explained by the association between increased PLR and severe inflammation.

In addition, the high mortality in the highest PLR quintile group may also be associated with the patients' baseline characteristics. The highest quintile group tended to be older, have lower body weight and albumin levels, and have more comorbidities with malignancy. Frailty could not be assessed in this study because of the severity of illness; however, the higher PLR group seemed to have high frailty, considering their age and nutritional parameters. Patients receiving maintenance hemodialysis showed a positive correlation between frailty and PLR, with increased mortality in the frailty group.[27] The high PLR might be associated with these different baseline characteristics, presumed to be present before hospitalization, and explain the increased mortality in the fifth quintile regardless of the severity of illness. Patients with cancer also showed higher PLR values than the healthy population, and increased PLR is a well-known predictive marker associated with poor patient outcomes.[17-20,28,29]

However, both high and low PLRs were associated with a poor prognosis in our study. The relationship between a low PLR and poor prognosis is not well understood; however, a low PLR was a consistent predictor of poor prognosis in our study after adjusting for various factors. Although it was difficult to clarify the causal relationship in this study, we suggest an interpretation based on

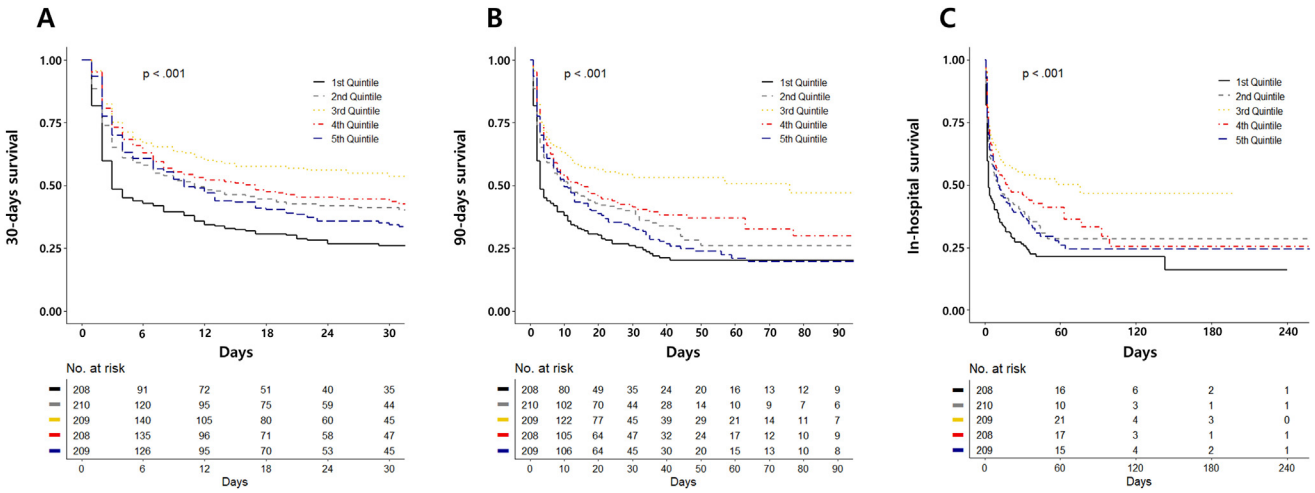

Figure 2. Kaplan-Meier curves for mortality by PLR quintiles. (A) 30-day mortality, (B) 90-day mortality, (C) and in-hospital mortality are significantly different according to the PLR quintiles (all $P < 0.001$). Abbreviation: PLR, platelet-to-lymphocyte ratio.

Table 3. Cox Regression Analyses for In-hospital Mortality in PLR Quintile Groups

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P*	aHR (95% CI)	*P*	aHR (95% CI)	*P*	aHR (95% CI)	*P*
Quintile 1	2.19 (1.69-2.83)	<0.001	2.34 (1.78-3.09)	<0.001	2.26 (1.70-3.00)	<0.001	1.94 (1.44-2.62)	<0.001
Quintile 2	1.55 (1.19-2.03)	0.001	1.50 (1.13-1.99)	0.01	1.46 (1.09-1.95)	0.01	1.42 (1.05-1.94)	0.02
Quintile 3	Reference		Reference		Reference		Reference	
Quintile 4	1.29 (0.98-1.70)	0.07	1.28 (0.95-1.72)	0.10	1.26 (0.93-1.70)	0.16	1.28 (0.93-1.75)	0.13
Quintile 5	1.57 (1.20-2.04)	<0.001	1.62 (1.22-2.14)	<0.001	1.57 (1.17-2.10)	0.003	1.60 (1.18-2.18)	0.002

Note: Model 1: unadjusted; model 2: adjusted for age, sex, and BMI; model 3: adjusted for age, sex, BMI, CCI, hypertension, and malignancy; and model 4: adjusted for age, sex, BMI, CCI, hypertension, malignancy, SOFA score, APACHE II score, mechanical ventilator use, and vasopressor use.
Abbreviations: PLR, platelet-to-lymphocyte ratio; HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; BMI, body mass index, CCI, Charlson Comorbidity Index; SOFA Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II.

thrombocytopenia, because a low PLR results from low platelet counts. Thrombocytopenia is a coagulation disorder frequently encountered in patients admitted to the ICU.[30] The common causes of thrombocytopenia in the ICU population include sepsis, disseminated intravascular coagulation, and major trauma.[31] Unsurprisingly, a low platelet count reflects the severity of disease and worsens the outcomes in patients with AKI.[32-34] Moreover, our results supported our hypothesis by showing that the first quintile group had an increased risk of higher APACHE II scores among the other quintile groups. Hence, the higher mortality in the low PLR group might be associated with the highest severity of illness.

Although the predictive role of the PLR in various diseases has been demonstrated, the underlying mechanism remains unknown. Recent studies have focused on the bidirectional relationship between AKI and inflammation.[35,36] Noninfectious causes can promote inflammation during AKI.[37] Conversely, AKI can also affect the immune system by interfering with cytokine clearance and causing immune cell dysfunction.[35,38] Various immune cells and mediators are involved in AKI pathophysiology. Platelets and lymphocytes, which are components of the PLR index, may play important roles in this pathophysiologic mechanism. First, platelets play an important role in hemostasis and inflammation. Once the endothelial cell damage occurs, platelets are activated, releasing various cytokines and chemokines. In experimental studies, markers appearing in activated platelets, such as P-selectin, thromboxane A2, CC-chemokine ligand 5, and platelet factor 4, have been reported in the AKI model.[39] Second, lymphocytes are components of adaptive immunity, whereas T cells are emerging mediators involved in the development and recovery of AKI.[36,40,41] Further studies are required to determine the specific roles of platelets and lymphocytes in AKI.

We demonstrated that the PLR index is an easily measurable and cost-effective marker for predicting mortality in patients with severe AKI who underwent CKRT. However, some limitations of our study need to be considered. First, owing to the retrospective nature of this study, there may have been unmeasured confounding factors such as any medications that could affect in platelet and lymphocyte counts. Our study did not exclude solid organ transplant recipients (n = 34), and their use of immunosuppressants may affect the PLR. However, we

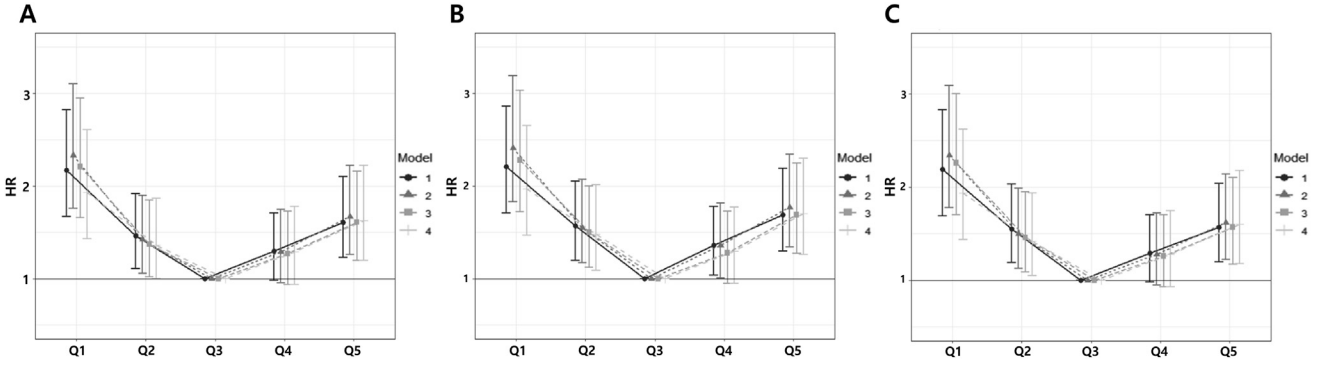

Figure 3. HRs and 95% CIs for mortality among PLR quintile groups by Cox proportional hazards models. The HRs and 95% CIs for (A) 30-day mortality, (B) 90-day mortality, and (C) in-hospital mortality are significantly higher in the first and fifth quintiles than those in the third quintile. Model 1 was unadjusted. Model 2 was adjusted for age, sex, and BMI. Model 3 was adjusted for age, sex, BMI, CCI, hypertension, and malignancy status. Model 4 was adjusted for age, sex, BMI, CCI, hypertension, malignancy, SOFA and APACHE II scores, mechanical ventilator use, and vasopressor use. Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; PLR, platelet-to-lymphocyte ratio; SOFA, Sequential Organ Failure Assessment.

Table 4. Subgroup Analyses for In-Hospital Mortality in PLR Quintile Groups

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
	aHR (95% CI)	aHR (95% CI)	Reference	aHR (95% CI)	aHR (95% CI)
Age, y					
≤68.0	1.67 (1.10-2.54)[a]	1.39 (0.89-2.16)	1.00	1.28 (0.80-2.03)	1.50 (0.96-2.34)
>68.0	2.43 (1.59-3.73)[c]	1.54 (1.01-2.35)[a]	1.00	1.29 (0.84-2.00)	1.85 (1.22-2.80)[b]
Sex					
Male	1.54 (0.95-2.50)	1.23 (0.76-2.00)	1.00	1.17 (0.71-1.94)	1.69 (1.05-2.72)[a]
Female	2.08 (1.41-3.07)[c]	1.65 (1.11-2.46)[a]	1.00	1.32 (0.88-1.99)	1.69 (1.14-2.50)[b]
BMI, kg/m^2					
≤22.9	2.04 (1.33-3.12)[b]	1.74 (1.14-2.64)[b]	1.00	1.38 (0.89-2.16)	1.64 (1.09-2.48)[a]
>22.9	2.02 (1.32-3.08)[b]	1.30 (0.83-2.03)	1.00	1.25 (0.80-1.96)	1.86 (1.19-2.90)[b]
Hypertension					
Yes	2.59 (1.52-4.42)[c]	1.57 (0.91–2.72)	1.00	1.60 (0.93–2.73)	2.39 (1.40–4.07)[b]
No	1.73 (1.21-2.48)[b]	1.37 (0.95–1.98)	1.00	1.12 (0.76–1.66)	1.39 (0.97–2.01)
DM					
Yes	2.45 (1.35-4.48)[b]	1.98 (1.08-3.62)[a]	1.00	1.91 (1.01-3.61)[a]	2.53 (1.37-4.68)[b]
No	1.70 (1.20-2.41)[b]	1.32 (0.92-1.88)	1.00	1.12 (0.78-1.61)	1.42 (1.00-2.01)[a]
SOFA					
≤13.0	1.59 (0.97-2.61)	1.60 (0.99-2.58)	1.00	1.00 (0.62-1.64)	1.73 (1.11-2.71)[a]
>13.0	2.16 (1.46-3.17)[c]	1.49 (1.00-2.22)	1.00	1.57 (1.03-2.39)[a]	1.62 (1.07-2.46)[a]
APACHE II					
≤26.0	1.74 (1.06-2.86)[a]	1.95 (1.23-3.08)[b]	1.00	1.48 (0.93-2.36)	1.69 (1.08-2.66)[a]
>26.0	1.99 (1.36-2.93)[c]	1.21 (0.80-1.83)	1.00	1.15 (0.74-1.77)	1.62 (1.08-2.44)[a]

Note: The statistical values are based on the multivariable Cox regression model 4 except for the variables corresponding to each subgroup.
Abbreviations: PLR, platelet-to-lymphocyte ratio; aHR, adjusted hazard ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II
[a]$P < 0.05$;
[b]$P < 0.01$;
[c]$P < 0.001$.

evaluated the association of PLR by adjusting for various variables in various models to minimize the effects of residual confounding factors. Second, we obtained PLR values at the time of initiation of CKRT; therefore, we could not assess the effect of serial changes of PLR in mortality. Third, the enrolled patients showed clinical heterogeneity, including the underlying disease or cause of AKI. Therefore, the number of patients was relatively small to contemplate variability in patient characteristics. Further large-scale, prospective, and longitudinal studies are required to validate the results of this study.

In summary, this is the first study to our knowledge to provide a prognostic analysis according to PLR values in patients with severe AKI who underwent CKRT in the ICU. We confirm a U-shaped relationship between PLR and mortality, underlining the need for special attention in these high-risk groups. Further studies are needed to validate the PLR index as a predictor of mortality and understand the mechanisms of the immune system involved.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Cox regression analyses for 30- and 90-day mortality rates in the PLR quintile groups.

Table S3: Cox regression analyses for in-hospital mortality in lymphocyte quintile groups.

Table S2: Cox regression analyses for in-hospital mortality in platelet quintile groups.

Figure S1: Distributions of PLR, platelet counts, and lymphocyte counts.

Table S4: Logistic regression analyses for higher APACHE II score in quintile groups.

Table S5: Logistic regression analyses for septic AKI in quintile groups.

ARTICLE INFORMATION

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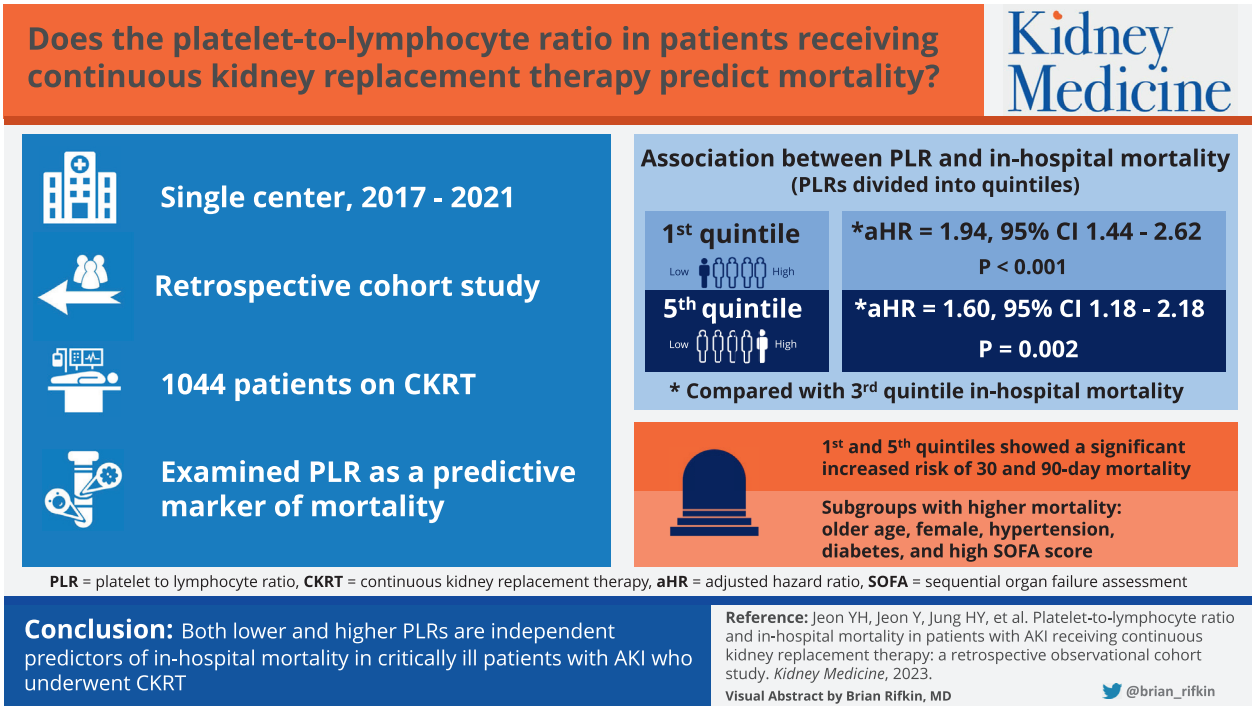
REFERENCES

1. Bouchard J, Acharya A, Cerda J, et al. A prospective international multicenter study of AKI in the intensive care unit. *Clin J Am Soc Nephrol*. 2015;10(8):1324-1331. doi:10.2215/CJN.04360514
2. Hoste EA, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med*. 2015;41(8):1411-1423. doi:10.1007/s00134-015-3934-7
3. Søvik S, Isachsen MS, Nordhuus KM, et al. Acute kidney injury in trauma patients admitted to the ICU: a systematic review and meta-analysis. *Intensive Care Med*. 2019;45(4):407-419. doi:10.1007/s00134-019-05535-y
4. Susantitaphong P, Cruz DN, Cerda J, et al. World incidence of AKI: a meta-analysis. *Clin J Am Soc Nephrol*. 2013;8(9):1482-1493. doi:10.2215/CJN.00710113
5. Xu X, Nie S, Liu Z, et al. Epidemiology and clinical correlates of AKI in Chinese hospitalized adults. *Clin J Am Soc Nephrol*. 2015;10(9):1510-1518. doi:10.2215/CJN.02140215
6. Nie S, Feng Z, Tang L, et al. Risk factor analysis for AKI including laboratory indicators: a nationwide multicenter study of hospitalized patients. *Kidney Blood Press Res*. 2017;42(5):761-773. doi:10.1159/000484234
7. Wu L, Hu Y, Yuan B, et al. Which risk predictors are more likely to indicate severe AKI in hospitalized patients? *Int J Med Inform*. 2020;143:104270. doi:10.1016/j.ijmedinf.2020.104270
8. Bhatraju PK, Zelnick LR, Katz R, et al. A prediction model for severe aki in critically ill adults that incorporates clinical and biomarker data. *Clin J Am Soc Nephrol*. 2019;14(4):506-514. doi:10.2215/CJN.04100318
9. Oh DJ. A long journey for acute kidney injury biomarkers. *Ren Fail*. 2020;42(1):154-165. doi:10.1080/0886022X.2020.1721300
10. Smith RA, Bosonnet L, Raraty M, et al. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. *Am J Surg*. 2009;197(4):466-472. doi:10.1016/j.amjsurg.2007.12.057
11. Proctor MJ, Morrison DS, Talwar D, et al. A comparison of inflammation-based prognostic scores in patients with cancer. A glasgow inflammation outcome study. *Eur J Cancer*. 2011;47(17):2633-2641. doi:10.1016/j.ejca.2011.03.028
12. Azab B, Shah N, Akerman M, McGinn JT Jr. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. *J Thromb Thrombolysis*. 2012;34(3):326-334. doi:10.1007/s11239-012-0718-6
13. Hudzik B, Szkodziński J, Korzonek-Szlacheta I, et al. Platelet-to-lymphocyte ratio predicts contrast-induced acute kidney injury in diabetic patients with ST-elevation myocardial infarction. *Biomark Med*. 2017;11(10):847-856. doi:10.2217/bmm-2017-0120
14. Sun XP, Li J, Zhu WW, et al. Platelet to lymphocyte ratio predicts contrast-induced nephropathy in patients with st-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Angiology*. 2018;69(1):71-78. doi:10.1177/0003319717707410
15. Jung HY, Jeon Y, Jeon S, Lim JH, Kim YL. Superiority of simplified acute physiologic score ii compared with acute physiologic and chronic health evaluation ii and sequential organ failure assessment scores for predicting 48-hour mortality in patients receiving continuous kidney replacement therapy. *Nephron*. 2022;146(4):369-376. doi:10.1159/000521495
16. Zheng CF, Liu WY, Zeng FF, et al. Prognostic value of platelet-to-lymphocyte ratios among critically ill patients with acute kidney injury. *Crit Care*. 2017;21(1):238. doi:10.1186/s13054-017-1821-z
17. Li B, Zhou P, Liu Y, et al. Platelet-to-lymphocyte ratio in advanced cancer: review and meta-analysis. *Clin Chim Acta*. 2018;483:48-56. doi:10.1016/j.cca.2018.04.023
18. Ma JY, Ke LC, Liu Q. The pretreatment platelet-to-lymphocyte ratio predicts clinical outcomes in patients with cervical cancer: a meta-analysis. *Med (Baltim)*. 2018;97(43):e12897. doi:10.1097/MD.0000000000012897
19. Zhang M, Huang XZ, Song YX, Gao P, Sun JX, Wang ZN. High platelet-to-lymphocyte ratio predicts poor prognosis and clinicopathological characteristics in patients with breast cancer: a meta-analysis. *BioMed Res Int*. 2017;2017:9503025. doi:10.1155/2017/9503025
20. Hu G, Liu Q, Ma JY, Liu CY. Prognostic significance of platelet-to-lymphocyte ratio in cholangiocarcinoma: a meta-analysis. *BioMed Res Int*. 2018;2018:7375169. doi:10.1155/2018/7375169
21. Erre GL, Paliogiannis P, Castagna F, et al. Meta-analysis of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio in rheumatoid arthritis. *Eur J Clin Invest*. 2019;49(1):e13037. doi:10.1111/eci.13037
22. Qin B, Ma N, Tang Q, et al. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. *Mod Rheumatol*. 2016;26(3):372-376. doi:10.3109/14397595.2015.1091136
23. Kurtul A, Ornek E. Platelet to lymphocyte ratio in cardiovascular diseases: a systematic review. *Angiology*. 2019;70(9):802-818. doi:10.1177/0003319719845186
24. Tian T, Wei B, Wang J. Study of C-reactive protein, procalcitonin, and immunocyte ratios in 194 patients with sepsis. *BMC Emerg Med*. 2021;21(1):81. doi:10.1186/s12873-021-00477-5
25. Yaprak M, Turan MN, Dayanan R, et al. Platelet-to-lymphocyte ratio predicts mortality better than neutrophil-to-lymphocyte ratio in hemodialysis patients. *Int Urol Nephrol*. 2016;48(8):1343-1348. doi:10.1007/s11255-016-1301-4
26. Liu S, Yang M, Zhao Q, Zhang L, Chen Q, Wang Y. Platelet-to-lymphocyte ratio is associated with the mortality in peritoneal dialysis patients. *Iran J Kidney Dis*. 2021;15(3):206-212.
27. Wang J, Huang L, Xu M, Yang L, Deng X, Li B. Study on the clinical implications of NLR and PLR for diagnosing frailty in

maintenance hemodialysis patients and their correlations with patient prognosis. *J Healthc Eng*. 2022;2022:1267200. doi:10.1155/2022/1267200
28. Zhu X, Song H, Chen Y, Han F, Wang Q, Cui Y. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in blood to distinguish lung cancer patients from healthy subjects. *Dis Markers*. 2020;2020:8844698. doi:10.1155/2020/8844698
29. Prodromidou A, Andreakos P, Kazakos C, Vlachos DE, Perrea D, Pergialiotis V. The diagnostic efficacy of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in ovarian cancer. *Inflamm Res*. 2017;66(6):467-475. doi:10.1007/s00011-017-1026-6
30. Thachil J, Warkentin TE. How do we approach thrombocytopenia in critically ill patients? *Br J Haematol*. 2017;177(1):27-38. doi:10.1111/bjh.14482
31. Zarychanski R, Houston DS. Assessing thrombocytopenia in the intensive care unit: the past, present, and future. *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):660-666. doi:10.1182/asheducation-2017.1.660
32. Guru PK, Singh TD, Akhoundi A, Kashani KB. Association of thrombocytopenia and mortality in critically ill patients on continuous renal replacement therapy. *Nephron*. 2016;133(3):175-182. doi:10.1159/000447543
33. Pan L, Mo M, Huang A, et al. Coagulation parameters may predict clinical outcomes in patients with septic acute kidney injury. *Clin Nephrol*. 2021;96(5):253-262. doi:10.5414/CN110459
34. Gameiro J, Lopes JA. Complete blood count in acute kidney injury prediction: a narrative review. *Ann Intensive Care*. 2019;9(1):87. doi:10.1186/s13613-019-0561-4
35. Singbartl K, Formeck CL, Kellum JA. Kidney-immune system crosstalk in AKI. *Semin Nephrol*. 2019;39(1):96-106. doi:10.1016/j.semnephrol.2018.10.007
36. Dellepiane S, Leventhal JS, Cravedi P. T cells and acute kidney injury: a two-way relationship. *Front Immunol*. 2020;11:1546. doi:10.3389/fimmu.2020.01546
37. Sharfuddin AA, Molitoris BA. Pathophysiology of ischemic acute kidney injury. *Nat Rev Nephrol*. 2011;7(4):189-200. doi:10.1038/nrneph.2011.16
38. Andres-Hernando A, Dursun B, Altmann C, et al. Cytokine production increases and cytokine clearance decreases in mice with bilateral nephrectomy. *Nephrol Dial Transplant*. 2012;27(12):4339-4347. doi:10.1093/ndt/gfs256
39. Jansen MPB, Florquin S, Roelofs JJTH. The role of platelets in acute kidney injury. *Nat Rev Nephrol*. 2018;14(7):457-471. doi:10.1038/s41581-018-0015-5
40. Fathabad SG, Kurzhagen JT, Sadasivam M, et al. T lymphocytes in acute kidney injury and repair. *Semin Nephrol*. 2020;40(2):114-125. doi:10.1016/j.semnephrol.2020.01.003
41. Cao C, Yao Y, Zeng R. Lymphocytes: versatile participants in acute kidney injury and progression to chronic kidney disease. *Front Physiol*. 2021;12:729084. doi:10.3389/fphys.2021.729084


Does the platelet-to-lymphocyte ratio in patients receiving continuous kidney replacement therapy predict mortality?
Kidney Medicine
Single center, 2017 - 2021
Retrospective cohort study
1044 patients on CKRT
Examined PLR as a predictive marker of mortality
Association between PLR and in-hospital mortality
(PLRs divided into quintiles)
1st quintile
Low High
*aHR = 1.94, 95% CI 1.44 - 2.62
P < 0.001
5th quintile
Low High
*aHR = 1.60, 95% CI 1.18 - 2.18
P = 0.002
* Compared with 3rd quintile in-hospital mortality
1st and 5th quintiles showed a significant increased risk of 30 and 90-day mortality
Subgroups with higher mortality: older age, female, hypertension, diabetes, and high SOFA score
PLR = platelet to lymphocyte ratio, CKRT = continuous kidney replacement therapy, aHR = adjusted hazard ratio, SOFA = sequential organ failure assessment
Conclusion: Both lower and higher PLRs are independent predictors of in-hospital mortality in critically ill patients with AKI who underwent CKRT
Reference: Jeon YH, Jeon Y, Jung HY, et al. Platelet-to-lymphocyte ratio and in-hospital mortality in patients with AKI receiving continuous kidney replacement therapy: a retrospective observational cohort study. Kidney Medicine, 2023.
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