The predictive value of red blood cell distribution width and platelet-to-lymphocyte ratio for acute kidney injury in critically ill patients

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Research Article

Keywords: Acute kidney injury, critically ill patients, red blood cell distribution width, platelet, lymphocyte

Posted Date: November 10th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1006561/v1>

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Abstract

Background

Red blood cell distribution width (RDW) and the platelet-to-lymphocyte ratio (PLR) are associated with different types of prognoses in critically ill patients. But, the value of RDW and PLR in predicting the occurrence of acute kidney injury (AKI) in critically ill patients are unknown. The purpose of the study was to explore the associations of RDW and PLR with AKI incidence.

Methods

Among 1500 adult patients in the intensive care unit (ICU) between January 2016 and December 2019 were enrolled, we examined the associations of baseline RDW and PLR with the risk of AKI development using logistical analysis. In addition, we explored the value of RDW and PLR in predicting in-hospital mortality.

Results

The study participants included 951 men and 549 women, aged 60.1 ± 16.14 years. The subjects had a mean RDW of $14.65 \pm 2.14\%$ and a mean PLR of 188.16 ± 129.2 . Overall, 615 (41%) patients were diagnosed with AKI. There were remarkable differences in RDW and the PLR between the AKI and non-AKI groups ($P < 0.001$). After adjustment, the association of RDW with AKI development risk strengthened (OR: 1.28, 95% CI: 1.19-1.36). Moreover, we divided the groups into two subgroups each; the high-RDW ($\geq 14.045\%$) group had a high risk of developing AKI (OR=5.189, 95% CI: 4.088-6.588), while the high-PLR (≥ 172.067) group had a risk of developing AKI (OR=9.11, 95% CI: 7.09-11.71). The areas under the receiver operating characteristic curves (AUCs) for the prediction of AKI incidence based on RDW and PLR were 0.780 (95% CI: 0.755-0.804) and 0.728 (95% CI: 0.702-0.754) (all $P < 0.001$), with cut-off values of 14.045 and 172.067, respectively. Moreover, a higher RDW was associated with a higher rate of hospital mortality (OR: 2.907, 2.190-3.858), and the risk of in-hospital mortality related to PLR was 1.534 (95% CI: 1.179-1.995). The AUC for in-hospital mortality based on RDW was 0.663 (95% CI: 0.628-0.698), while the AUC for in-hospital mortality based on the PLR was 0.552 (0.514-0.589).

Conclusions

A higher RDW related to a higher risk of the occurrence of AKI and in-hospital mortality in ICU. The PLR also showed predictive value for the occurrence of AKI but did not show any clear prediction value of in-hospital mortality.

Introduction

Acute kidney injury (AKI) is a frequent and serious clinical condition in intensive care unit (ICU) patients, with an incidence of 20-70%¹⁻³. It is associated with increased mortality (approximately 40%) and a high financial burden and even affects long-term mortality³⁻⁵. In recent decades, research has suggested that early detection of AKI would be beneficial in predicting the prognosis of and providing more effective care for patients with AKI^{6,7}. Unfortunately, the clinical prediction of AKI progression remains a challenge. Several novel serum and urinary kidney injury biomarkers that can be detected to provide an early diagnosis of AKI have been discovered; however, most of these biomarkers require well-controlled conditions and are applicable in only restricted populations. Therefore, they are not widely used currently^{2,5}.

Inflammation and the immune response play important roles in the pathogenesis of AKI^{8,9}. Increasing evidence suggests that the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), which are based on complete blood cell counts, are inflammation-associated parameters and are predictors of the development of AKI¹⁰⁻¹². Clinically, red blood cell distribution width (RDW) is an indicator of anaemia, but previous studies have revealed that it is correlated with the outcome of AKI¹³⁻¹⁴. Zhu et al¹⁴ and Wang et al¹⁵ reported the predictive value of RDW in mortality: a higher RDW related to a higher risk of mortality. However, Elhosseiny et al¹⁶ demonstrated that RDW was not correlated with the occurrence of contrast-induced AKI in patients with acute coronary syndrome. However, little attention was taken to the role of RDW in the prediction of AKI in ICU. Therefore, we considered the correlation with RDW and the occurrence of AKI in critically ill patients to elucidate the predictive value of RDW for early diagnosis in AKI patients. In addition, we explored the relationship of RDW and PLR with in-hospital mortality.

Methods

1.1 | Patient cohort

The study population comprised all patients who attended to the ICU in the First Affiliated Hospital of the University of South China between 1st January 2016 and 31st December 2019. AKI diagnosis was based on the classification of the Kidney Disease: Improving Global Outcomes (KDIGO).¹⁷ The lowest value of serum creatinine (Scr) detected in the emergency clinic or general ward before admission to the ICU was considered the baseline creatinine value. When this value could not be obtained, the Modification of Diet in Renal Disease (MDRD) calculation was performed, assuming that the normal glomerular filtration rate (GFR) was $75 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$.¹⁸ Patients were excluded if they had received a diagnosis of chronic renal insufficiency; had undergone kidney transplantation; were younger than 18 years of age; were readmitted to the ICU; were admitted to the ICU for less than 24 hours; had undergone dialysis within 1 month before admission or were undergoing dialysis when admitted to the ICU; or had no renal function or routine blood test data within 2 days after admission to the ICU.

1.2 | Data Extraction

Patient demographic, complete blood count, blood biochemistry, inflammatory marker, Acute Physiology and Chronic Health Evaluation II (APACHE II) score and primary disease data were recorded for each patient. The baseline characteristic within 24 hours of ICU admissions and complete blood count data were recorded also. The PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. The development of AKI was used as the primary endpoint in the study, and all-cause hospital mortality was the secondary endpoint.

1.3 | Statistical Analysis

Complete statistical analysis was conducted with SPSS 16 software (Chicago, IL, USA). Two tailed $p < 0.05$ signified statistical significance for all the analyses. In case of continuous data, variables were given as medians with interquartile range and categorical variables were shown as frequency counts (%). Comparisons between groups were computed with the test of chi-square. The association of RDW with other variables was assessed with Spearman's correlation analysis. Multivariable logical regression was used to examine the associations of RDW and the PLR with the development of AKI and hospital mortality. To determine the diagnostic ability of RDW and PLR for AKI occurrence and in-hospital mortality, we generated receiver operating characteristic (ROC) curves. Cut-off values with sensitivity and specificity of variables were determined by Youden index.

Results

2.1 | Subject characteristics

After reviewing the records of 2435 eligible subjects who were attended to the ICU of the First Affiliated Hospital of the University of South China from 1 January 2016 to 31 December 2019. The final cohort comprised 1500 critically ill patients in the analysis (Fig 1). The subject characteristics of critically ill patients are presented in Table 1. Most patients were men (63.4%); 615 patients (41%) were classified in the AKI group, and 885 patients (59%) were allocated to the non-AKI group. The number of patients with stage 1 AKI was 159 (25.9%), with stage 2 AKI was 184 (29.9%) and with stage 3 AKI was 272 (44.2%).

The AKI group with a remarkably higher RDW than non-AKI group. Compared with non-AKI patients, the number of older people was larger and the prevalence rates of hypertension, diabetes mellitus, and coronary artery disease were higher in the AKI patients. The AKI patients had remarkably higher PLRs, cystatin C (CystC), Scr, blood urea nitrogen (BUN), C-reactive protein (CRP), and procalcitonin (PCT) levels and APACHE II scores than the non-AKI group. However, haemoglobin was lower in AKI group. Notably, no statistical differences was observed between the AKI group and non-AKI group in the prevalence of chronic obstructive pulmonary disease (COPD) or albumin level and white blood cells (WBC) (Table 1).

Table 1. Subject characteristics

Variables	ALL (n=1500)	Patients with AKI (n=615)	Patients without AKI (n=885)	p-value
Male (%)	951(63.4%)	404(42.5%)	547(57.5%)	0.125
Age (years)	60.1±16.14	63.27±16.89	58.91±16.73	<0.001*
Comorbidities				
Hypertension	486(32.4%)	223(36.3%)	263(29.7%)	0.008*
Diabetes mellitus	225(14.9%)	127(20.7%)	96(10.8%)	<0.001*
Coronary artery disease	263(17.5%)	144(23.4%)	119(13.4%)	<0.001*
COPD	135(9%)	48(7.8%)	87(9.8%)	0.178
Laboratory index at ICU admission				
Baseline Scr (umol/L)	100.64±9.8	127.34±14.73	82.09±19.25	<0.001*
BUN (mmol/L)	10.97±9.25	16.58±10.99	7.07±4.91	<0.001*
Albumin (g/l)	33.45±6.91	32.16±4.79	34.35±6.85	0.364
Triglycerides (mmol/l)	1.15(0.79,1.72)	1.23(0.87,1.24)	1.09(0.75,1.66)	0.002*
PCT (ng/ml)	0.52(0.17,3.88)	1.86(0.31,16)	0.26(0.14,1.4)	<0.001*
WBC count/mm ³	11.77(8.26,17.0)	12.23(8.46,12.23)	11.59(8.11,16.28)	0.786
Haemoglobin (g/dl)	104.98±29.75	103.06±20.81	106.31±29.65	0.038*
CystC	1.38(0.89,2.72)	2.75(1.86,4.6)	1.01(0.75,1.41)	<0.001*
CRP	37.22(8.28,95.24)	55.78(17.02,131.59)	25.47(4.6,76.08)	<0.001*
APACHE II score	16.50±7.32	19.09±7.42	16.69±6.7	<0.001*
RDW	14.65±2.14	15.72±2.30	13.91±1.37	<0.001*
PLR	188.16±129.2	277.3±133.5	153.1±111.3	<0.001*

AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; Scr, serum creatinine; BUN, blood urea nitrogen; PCT, procalcitonin; WBC, white Blood Cell; CystC, cystatin C; CRP, C-reactive protein; APACHE II, Acute Physiology and Chronic Health Evaluation II; RDW, red cell distribution width, PLR, platelet-to-lymphocyte ratio.

2.2 The association of RDW with other parameters

RDW and PLR were positively associated with CRP, PCT, ferritin and CystC levels ($P<0.05$) and negatively associated with albumin and haemoglobin levels. There was no correlation between RDW and WBC count. The PLR was positively associated with RDW and PCT, CRP and CystC levels ($P<0.05$), and no correlation was observed between PLR and albumin, haemoglobin or triglyceride level or WBC count (Table 2).

Table2.Bivariate correlation analyses of baseline RDW/PLR and laboratory indicators

Variable	RDW (r)	<i>P</i> value	PLR (r)	<i>P</i> value
RDW (%)	1	-	0.182	0.000
PCT	0.161	0.000	0.122	0.000
CRP	0.108	0.001	0.102	0.000
WBC count	-0.04	0.09	0.000	0.999
PLR	0.182	0.000	1	-
Haemoglobin (g/l)	-0.297	0.000	-0.021	0.406
Albumin (g/l)	-0.229	0.000	-0.044	0.086
Triglycerides (mmol/l)	0.081	0.004	0	0.983
CystC	0.370	0.000	0.317	0.000

RDW, red blood cell distribution width; PLR, platelet-to-lymphocyte ratio; PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cell; CystC, cystatin C.

2.3 RDW /PLR and the development of AKI

After multi-variable adjustment, the risk of the occurrence of AKI in critically ill patients with an elevated RDW and PLR was 1.381 (95% CI:1.300-1.467) and 1.008 (95% CI: 1.007-1.009), respectively. We further divided the patients into four subgroups: RDW-low (RDW<14.045), RDW-high (≥ 14.045), PLR-low (PLR <172.067) and PLR-high (PLR (≥ 172.067)). Patients within the RDW-high group had a 5.189-fold higher risk of developing AKI than those in the RDW-low group (OR=5.189, 95% CI: 4.088-6.588) (Table 3), and those in the PLR-high group had a 9.109-fold higher risk of developing AKI t (OR= 9.109, 95% CI:7.089-11.705)han those in the PLR-low group. Moreover, CystC, CRP, PCT and triglyceride levels and the APACHE II score were identified as potential risk factors for the development of AKI.

Table 3. Univariate and multivariate logical regression analysis for the prevalence of AKI

Variable	Unadjusted		Adjusted	
	OR (95%CI)	P value	OR (95%CI)	P value
RDW (%)	1.381(1.30-1.47)	0.000	1.28(1.19-1.36)	0.000
RDW-low (<14.045%)	1 (reference)		1 (reference)	
RDW-high ($\geq$ 14.045%)	5.23(4.17-6.56)	0.000	5.19(4.09-6.59)	0.000
PCT	1.03(1.02-1.04)	0.000	1.03(1.02-1.13)	0.000
CRP	1.01(1.00-1.02)	0.000	1.01(1.00-1.02)	0.000
WBC count	1.00(0.99-1.01)	0.705	1.00(0.99,1.01)	0.383
CystC	2.95(2.58-3.37)	0.000	2.86(2.50-3.27)	0.000
Albumin (g/l)	0.95(0.94-0.97)	0.000	0.98(0.97-1.00)	0.101
Haemoglobin	1.00(0.98-1.00)	0.038	1.00(0.99,1.01)	0.494
PLR	1.01(1.00-1.02)	0.000	1.01(1.00-1.02)	0.000
PLR-low (<172.067)	1 (reference)	0.000	1 (reference)	0.000
PLR-high ($\geq$ 172.067)	9.30(7.31-11.82)	0.000	9.11(7.09-11.71)	0.000
Triglycerides (mmol/l)	1.09(1.03-1.16)	0.000	1.10(1.03-1.17)	0.004
APACHE II score	1.09(1.075,1.109)	0.000	1.07(1.05-1.09)	0.000

Adjusted by sex, age, hypertension, diabetes mellitus, coronary artery disease, COPD, baseline Scr and BUN. AKI, acute kidney injury; BUN, blood urea nitrogen; PCT, procalcitonin; CystC, cystatin C; CRP, C-reactive protein; RDW, red blood cell distribution width; APACHE II, Acute Physiology and Chronic Health Evaluation II; PLR, platelet-to-lymphocyte ratio.

2.4 RDW and PLR predicted the occurrence of AKI

The ROC curve was used to assess the discriminative ability of RDW in predicting AKI in ICU compared with other inflammation index parameters (including the PLR, CRP, PCT and CystC). The AUC for AKI development based on RDW was 0.728 (95% CI: 0.702-0.754), and the optimal cut-off value was 14.045; with the sensitivity was 73.3%, and the specificity was 65.5%, which were higher than those for PCT, CRP and the APACHE II score (Fig 2a, Table 4). The AUC for AKI development based on the PLR was 0.780 (95% CI: 0.755-0.804), with a cut-off value of 172.067 (sensitivity: 77.1%, specificity: 73.4%). However, CystC was associated with the highest AUC, at 0.821 (95% CI: 0.800-0.843) (Fig 2b, Table 4).

2.5 Risk of in-hospital mortality predicted by multi-variable logical regression

After adjustment for male, age, diabetes mellitus, hypertension, COPD, coronary artery disease, baseline Scr and BUN, the adjusted ORs for in-hospital mortality based on RDW was 1.202 (1.136-1.271); there

was no relationship between the PLR and in-hospital mortality. Therefore, we divided the patients into two subgroups for each parameter: RDW-low and RDW-high and PLR-low and PLR-high. The adjusted ORs for in-hospital mortality in the RDW-high group were 2.907 and 1.534, respectively. The adjusted ORs for in-hospital mortality based on WBC count, CystC, and the APACHE II score were 1.016, 1.128 and 1.095, respectively ($P<0.05$). However, albumin, haemoglobin and triglycerides unrelated to mortality($P>0.05$). (Table5)

Table 5 The predictive indicators of in-hospital mortality

Variable	Unadjusted		Adjusted	
	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>
RDW (%)	1.224(1.160-1.292)	0.000	1.202(1.136-1.271)	0.000
RDW-low (<14.045%)	1 (reference)	0.000	1 (reference)	0.000
RDW-high ($\geq$ 14.045%)	3.023(2.888-3.994)	0.000	2.907(2.190-3.858)	0.000
PLR	1.001(1.000-1.002)	0.056	1.000(0.999-1.001)	0.529
PLR-low (<170.067)	1 (reference)	0.000	1 (reference)	0.000
PLR-high ($\geq$ 170.067)	1.629(1.258-2.109)	0.000	1.534(1.179-1.995)	0.000
WBC count	1.014(1.000-1.029)	0.051	1.016(1.002-1.031)	0.026
CystC	1.183(1.111-1.260)	0.000	1.128(1.047-1.214)	0.001
Albumin (g/L)	0.983(0.965-1.002)	0.076	0.992(0.972-1.012)	0.417
Haemoglobin	0.997(0.993-1.001)	0.166	0.998(0.994-1.003)	0.447
Triglycerides (mmol/L)	1.014(0.961-1.069)	0.614	1.023(0.967-1.082)	0.426
APACHE II score	1.103(1.083-1.123)	0.000	1.095 (1.074-1.116)	0.000
Baseline Scr (umol/L)	1.005(1.002-1.007)	0.001		
BUN (mmol/L)	1.029(1.016-1.042)	0.000		

Adjusted for male, age, hypertension, diabetes mellitus, coronary artery disease, COPD, baseline Scr, and BUN. AKI, acute kidney injury; PCT, procalcitonin; CystC, cystatin C; CRP, C-reactive protein; APACHEII, Acute Physiology and Chronic Health Evaluation II; RDW, red cell distribution width;PLR, platelet-to-lymphocyte ratio.

The prognostic cut-off value for RDW identified by the ROC curve followed by Youden's test was 14.45 (AUC 0.663; 95% CI, 0.628–0.698). The AUC for AKI based on CystC was 0.614 (95% CI:0.575-0.653), with a sensitivity of 61.6% and a specificity of 57.6%. The APACHE II score was associated with the highest

AUC: 0.706 (95% CI:0.673-0.738). PLR, CRP and PCT did not show a clear ability to predict in-hospital mortality considering a cut-off value of 0.5 (Table 6).

Discussion

In this respective study, we observed that a high RDW ($RDW \geq 14.045$) and a high PLR ($PLR \geq 172.067$) were independent predictor for the occurrence of AKI in ICU patients. Furthermore, we found that patients with high-RDW denoted 2.9 fold risk of hospital mortality than those in the RDW-low group, but the PLR did not show a clear predictive value of in-hospital mortality (AUC:0.552). The results suggested that RDW and PLR, two parameters that are easy and inexpensive to detect, may be valuable in predicting the development of AKI.

The high incidence of AKI has caused substantial social and economic burdens worldwide, and early diagnosis and intervention are important. In recent decades, many studies on potential biomarkers of AKI, including CystC and kidney injury molecule-1 (KIM-1), have been conducted by clinicians and researchers, with the goal of improving early diagnosis of AKI¹⁹⁻²⁰; however, few studies have been conducted in the clinic because these biomarkers are expensive and difficult to examine. Some studies have explored the value of some inflammatory factors, such as NLR and PLR, in prediction of the development and prognosis of AKI¹⁰⁻¹². RDW is a parameter detected in routine blood tests; however, the association between RDW and the occurrence of AKI in ICU patients is still unclear.

The study indicated that RDW shown clear predictive value of the occurrence of AKI, RDW and the PLR outperformed CystC in the prediction of AKI. This finding supports the significance of RDW and PLR as indictors of AKI²¹⁻²². We compared the predictive value of RDW with those of other inflammatory factors and found that a high RDW and high PLR were better predictors of AKI than CRP, PCT, and WBC count. This result is similar to those of studies conducted by Elhosseiny et al¹⁶ and Fatih Akin et al²³. Yanfei Shen et al²⁴ suggested that the PLR related to increased risk of mortality in sepsis patients. However, contrary to their study result, in the current study, the PLR did not show a clear ability to predict in-hospital mortality in the study. This may be because the population comprised critically ill patients, the elevated PLR was due to inflammation, and inflammation was not the only primary reason for in-hospital mortality.

Although the predictive value of RDW for AKI in ICU patients has been revealed, the underlying mechanisms are still unknown. Inflammation and renal ischaemia-reperfusion are major primary causes of AKI. RDW is usually a parameter associated with anaemia, but some studies have demonstrated that RDW can also be a surrogate biomarker of inflammation²⁵⁻²⁶. It has been reported that an elevated RDW value increases the risk of progression of cardiovascular diseases, potentially leading to a decrease in renal blood flow and reduced renal artery pressure, which could cause prerenal AKI¹⁵⁻¹⁶. An increasing amount of evidence has demonstrated that poor nutritional status and inflammatory cytokines directly influence iron status, decrease erythropoietin production and enhancing erythropoietin resistance¹⁵⁻¹⁶. Lin Pei Jia et al demonstrated that systemic inflammatory response syndrome (SIRS) values were

increased in the high-RDW group in a large-sample study in critically ill patients²⁹. Our study also suggested that RDW was positively associated with CRP and PCT and negatively associated with low haemoglobin. Therefore, RDW is related to prognosis, partly because of the role of inflammation and poor nutritional status.

Although RDW was remarkably negatively related to haemoglobin and albumin levels, RDW showed a good ability to predict the development of AKI and in-hospital mortality according to the ROC analysis. In the current study, both RDW and the PLR were correlated with other inflammatory markers, and RDW was also associated with the PLR ($r = 0.182$, $P=0.000$) which contracted to the results of the study conducted by Jiefu Zhu²⁵; therefore, we did not combined the two parameters.

In addition to the intrinsic limitations of all retrospective designs, other aspects of this study were subject to certain limitations, which should be acknowledged. First, our study was a retrospective observational study which conducted in a single centre, and control confounders and selective bias were difficult to control. However, patients with a hospital stay less than 48 hours and patients with less than two blood tests were excluded to avoid selection bias caused by other factors. Therefore, the results of this study can still represent the epidemiological characteristics of AKI in the ICU. Second, we defined AKI based solely on the change in the Scr level because diuretics could affect urine output, so the actual incidence of AKI may be higher than the result. Finally, the study investigated only short-term prognosis and did not analyse long-term prognosis; the latter will require the long-term follow-up of patients with AKI.

Conclusions

In summary, our study supports the independent predictive and prognostic power of high RDW in critically ill AKI patients. A high PLR also provides valuable information for the early diagnosis of AKI but is not predictive of in-hospital mortality.

Abbreviations

RDW:Red blood cell distribution width (RDW); PLR:Platelet-to-lymphocyte ratio;AKI:Acute kidney injury; ICU:intensive care unit;AUC: Areas under the receiver operating characteristic curve;Scr: Serum creatine; COPD, Chronic obstructive pulmonary disease; APACHE II:Acute Physiology and Chronic Health Evaluation II;MDRD:Modification of Diet in Renal Disease; KDIGO:Kidney Disease: Improving Global Outcomes; NLR: Neutrophil-to-lymphocyte ratio; KIM-1:Kidney injury molecule-1; ROC:receiver operating characteristic.BUN:Blood urea nitrogen; PCT:Procalcitonin; WBC:White Blood Cell; GFR: Glomerular filtration rate; CystC, cystatin C; CRP: C-reactive protein

Declarations

Acknowledgement

We thank the state of the ICU of the first affiliated Hospital of South China University for invaluable help in data collection.

Funding Source

This study was supported from grants of Hunan Provincial Health Commission Technology Foundation (202103050110,202103052372), and Hunan Provincial Science Technology Foundation (2020JJ4550).

Availability of data and materials

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

Conflict of interest

None

Ethics Statement

The study was in accordance with the ethical principles of the Declaration of Helsinki and approved by the ethics committee of the first affiliated hospital of South China (certification number 20201211LL012). And the study has been granted an exemption from requiring informed consent by the ethics committee of the first affiliated hospital of South China .

Consent for publication

Not applicable.

Author Contribution

YT and FJ were involved in the draft the manuscript ,conceptualized and design.JL, JX,JF,WX and YT obtained all patients data. LZwas involved in the interpretation of data and revising the manuscript critically for important intellectual content.BY was involved in funding acquisition and resource.All authors gave final approval of the version to be published.

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Tables

Due to technical limitations, Tables 4 and 6 are only available as a download in the Supplemental Files section.

Figures

Figure 1

Flowchart of participant screening. ICU, intensive care unit, Scr, serum creatinine.

Figure 2

ROC curves for the prediction of AKI development based on various parameters. ROC, receiver operating characteristic; AKI, acute kidney injury; RDW, red blood cell distribution width; PLR, platelet-to-lymphocyte ratio.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table4and6.docx](#)