International Immunopharmacology 70 (2019) 372–377

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Relation of neutrophil-to-lymphocyte ratio to acute kidney injury in patients with sepsis and septic shock: A retrospective study

Xi Bu, Lian Zhang, Peina Chen, Xiaoyan Wu*

Department of Nephrology, Zhongnan Hospital of Wuhan University, Wuhan, China

ARTICLE INFO

Keywords:
Neutrophil-to-lymphocyte ratio
Acute kidney injury
Sepsis
Septic shock
Intensive care unit

ABSTRACT

Background: The purpose of this study was to determine the association of the neutrophil-to-lymphocyte ratio (NLR) measured at the time of admission to intensive unit (ICU) with acute kidney injury (AKI) in patients with sepsis and septic shock. In addition, we investigated whether the NLR affects in-hospital mortality in septic AKI patients.

Methods: In this retrospective study, a total of 222 adult patients with sepsis and septic shock were included, who were admitted to the ICU of Zhongnan Hospital of Wuhan University from January 2015 to December 2017. Sepsis and septic shock were diagnosed based on sepsis-3 consensus. AKI was diagnosed according to the KDIGO-AKI criteria. The primary outcome of the study was septic AKI. The secondary endpoint was in-hospital mortality of patients with septic AKI.

Results: 132 patients (59.46%) had AKI, and 64 (28.83%) died, of whom 55 (41.67%) in the AKI group and 9 (10.00%) in the non-AKI group. The NLR of the AKI group was significantly higher than that of the non-AKI group, and there was a statistically significant difference between the two groups ($P < 0.001$). Multivariate logistic regression analysis suggested that the NLR was independent predictors of septic AKI (OR = 1.047, 95% CI: 1.005–1.091, $P = 0.026$). The ROC curve showed that the AUC of the NLR for predicting septic AKI was 0.656 (95% CI 0.584–0.728, $P < 0.001$) and the cutoff value was 17.11 (sensitivity, 62.1%; specificity, 68.9%). However, no correlation was found between the NLR and in-hospital mortality in septic AKI patients.

Conclusion: NLR, a laboratory variable that is simple, widely available and inexpensive, was associated with the development of septic AKI and may be potential for risk stratification of septic AKI.

1. Introduction

Acute kidney injury (AKI) is a common and serious complication in critically ill patients with an incidence of 16% to 67% [1], with mortality of > 50% [2], depending on the definition of AKI. As we know, the main causes of AKI are sepsis and septic shock. Septic AKI has high morbidity and mortality, leading to delay hospital stays and increase costs [1], and it is related to adverse outcomes such as chronic kidney disease and end-stage renal failure [3].

The detection of early AKI would be beneficial to provide more-effective care for patients with sepsis. Serum creatinine is the traditional indicator for the diagnosis of AKI, but increase at the relatively late stages of renal injury. Although several novel urinary biomarkers have been studied for early AKI, most of them are too expensive to carry out well in clinical practice. Thus, early identification for the development of septic AKI remains challenging.

The neutrophil-to-lymphocyte ratio (NLR), calculated from complete blood count, is a surrogate marker for the systemic inflammatory response that is widely available and inexpensive. Elevated NLR was confirmed to have prognostic value in a variety of diseases, such as cardiovascular disease [4,5], sepsis [6,7], cancer [8] and unselected critical illness [9]. Inflammation is known to play a significant role in the physiopathology of septic AKI [10,11]. In the field of nephrology, the NLR was shown to be associated with kidney function [12,13] and served as a useful biomarker for adverse prognosis of patients with chronic kidney disease (CKD) [14] and undergoing peritoneal dialysis and hemodialysis [15,16]. Nevertheless, limited study demonstrated the diagnostic value of the NLR for early AKI [17,18], and we know so little about the clinical value in septic AKI patients.

Therefore, in this study, we aimed to determine the correlation between NLR and AKI in patients with sepsis and septic shock. Furthermore, we hypothesized that the NLR would also be associated with in-hospital mortality in septic AKI patients.

* Corresponding author at: Department of Nephrology, Zhongnan Hospital of Wuhan University, No.169 Donghu Road, Wuhan 430071, China.
E-mail address: wuxiaoyan2k6@163.com (X. Wu).

https://doi.org/10.1016/j.intimp.2019.02.043
Received 6 September 2018; Received in revised form 13 February 2019; Accepted 25 February 2019
Available online 07 March 2019
1567-5769/

Table 1
Baseline clinical and laboratory for AKI and non-AKI groups, survivors and non-survivors groups.

Characteristic	AKI (n = 132)	non-AKI (n = 90)	P value	Non-survivors (n = 55)	Survivors(n = 77)	P value
Age, years	65.70 ± 16.92	63.54 ± 17.46	0.358	73.09 ± 12.40	60.43 ± 17.80	< 0.001
Gender, male, n (%)	74 (56.06)	49 (54.44)	0.812	36(65.45)	38(49.35)	0.066
Hypertension, n (%)	47 (35.61)	22 (24.44)	0.078	22(40.00)	25(32.47)	0.373
Diabetes, n (%)	36 (27.27)	16 (17.78)	0.101	16(29.09)	20(25.97)	0.692
Chronic kidney disease, n (%)	12 (9.09)	4 (4.44)	0.189	6(10.91)	6(7.79)	0.539
Characteristics on admission						
Mean arterial pressure, mmHg	73.93 ± 16.68	84.09 ± 16.81	< 0.001	72.95 ± 17.58	74.63 ± 16.09	0.571
Serum creatinine, μmol/L	80.00 (69.48, 89.70)	68.95 (57.15, 79.43)	< 0.001	82.00(71.00, 88.00)	78.00(68.00, 90.00)	0.248
eGFR, $mL{\cdot}min^{-1}{\cdot}(1.73m^2)^{-1}$	81.71 ± 26.02	100.11 ± 27.66	< 0.001	75.13 ± 19.34	86.42 ± 29.11	0.008
WBC count, $\times 10^9$/L	14.30 (8.86, 21.49)	9.59 (6.97, 13.58)	< 0.001	12.99(6.74, 17.35)	15.09(10.27, 24.51)	0.035
NLR	20.43 (11.61, 36.23)	12.94 (8.54, 21.64)	< 0.001	17.75(10.86, 24.09)	25.38(12.59, 41.29)	0.018
Hemoglobin, g/L	104.23 ± 25.22	107.60 ± 26.00	0.335	106.66 ± 26.88	102.50 ± 23.98	0.352
Platelet count, $\times 10^9$/L	92.00 (40.50, 166.50)	115.00 (63.75, 174.00)	0.068	106.00(51.00, 172.00)	77.00(36.50, 146.50)	0.245
Serum lactate, mmol/L	3.00 (2.00, 5.30)	1.90 (1.20, 3.40)	0.001	3.80(2.15, 7.25)	2.80(1.70, 4.60)	0.009
Procalcitonin, ng/mL	42.36 (6.17, 106.96)	6.66 (1.74, 20.74)	< 0.001	40.28(5.22, 82.70)	44.79(8.37, 116.99)	0.228
hs-CRP, mg/L	110.10(52.22, 198.05)	118.37(75.27, 161.65)	0.972	80.60(33.47, 194.43)	143.60(65.24, 199.40)	0.187
Uric acid, μmol/L	376.30(295.18, 503.03)	204.30(157.63, 284.63)	< 0.001	439.10(294.80, 518.60)	364.00(295.30, 471.40)	0.277
BUN, μmol/L	13.54 (9.66, 20.78)	6.42 (4.69, 9.06)	< 0.001	16.90(10.87, 25.80)	11.60(9.12, 17.40)	0.009
Serum albumin, ng/L	25.86 ± 5.42	29.12 ± 6.61	< 0.001	25.19 ± 5.55	26.34 ± 5.31	0.231
Na, mmol/L	137.13 ± 7.56	136.45 ± 7.30	0.518	138.55 ± 8.81	136.15 ± 6.46	0.079
K, mmol/L	3.99 ± 0.90	3.83 ± 0.64	0.133	4.17 ± 0.96	3.87 ± 0.83	0.070
APACHE II score	23.42 ± 7.66	12.57 ± 6.01	< 0.001	26.73 ± 8.12	21.05 ± 6.39	< 0.001
Intervention						
Renal repalcement therapy, n (%)	43 (32.57)	0	–	25(45.45)	18(23.38)	0.008
Mechanical ventilation, n (%)	74 (56.06)	16 (17.78)	< 0.001	48(87.27)	28(36.36)	< 0.001
Vasopressors, n (%)	109 (82.57)	33 (36.67)	< 0.001	53(96.36)	56(72.72)	< 0.001
Outcome						
In-hospital mortality, n (%)	55 (41.67)	9 (10.00)	< 0.001	–	–	–
Length of ICU stay, days	4.00 (2.25, 8.00)	2.00 (1.00, 4.00)	< 0.001	4.00(2.00, 10.00)	4.00(3.00,7.50)	0.829
Length of hospital stay, days	12.50 (7.25, 21.00)	14.50 (9.00, 23.25)	0.144	8.00(3.00, 16.00)	16.00(10.00, 23.00)	< 0.001
SOFA score	11.00 (8.00, 15.75)	4 (3.00, 6.00)	< 0.001	15.00(12.00, 17.00)	9.00(6.00, 13.00)	< 0.001

eGFR: estimated glomerular filtration rate; WBC: white blood cell count; NLR: neutrophil to lymphocyte ratio; hs-CRP: high sensitivity C-reactive protein; BUN: blood urea nitrogen; APACHE: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; ICU: intensive care unit.

2. Methods

2.1. Patient population

In this retrospective study, we reviewed the electronic medical records of consecutive adult patients with a first episode of sepsis and septic shock in critical care unit (ICU) of Zhongnan Hospital of Wuhan University from January 2015 to December 2017. This study protocol was approved by the Ethics Committee of Zhongnan Hospital of Wuhan University.

The inclusion criteria included patients with age ≥ 18 years, hospitalization in the ICU for at least 24 h and complete clinical data. The exclusion criteria were as follows: (1) renal replacement therapy has been used at the beginning of the study; (2) a history of renal transplantation; (3) patients with secondary infection who have been in ICU for many days; (4) women during pregnancy and lactation (5) exposure to radiocontrast or nephrotoxic drugs at least one week before entering the ICU; (6) patients with acute cardiovascular and cerebrovascular events, malignant tumors, and severe hematological diseases; (7) other comorbidities that cause lymphopenia, such as malignant tumors, malnutrition, HIV infection, autoimmune diseases, immunosuppressive drugs, cytotoxic agents.

2.2. Definitions

Sepsis and septic shock was defined according to the third international consensus definitions for sepsis and septic shock (Sepsis-3) [19]. Sepsis was identified as an acute change in sequential organ failure assessment (SOFA) score ≥ 2 points after infection. Septic shock was diagnosed when patients with persistent hypotension required vasopressors to maintain mean arterial pressure ≥ 65 mmHg and had a serum lactate level > 2 mmol/L even if a sufficient volume resuscitation is performed. Patients with an estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m^2 before admission were defined as CKD. The CKD-EPI equation was used to calculate eGFR from baseline serum creatinine (SCr) levels [20]. The baseline SCr was obtained within 6 months before admission. If the baseline SCr is not available, the lowest SCr entered into the ICU was used.

AKI was defined by KDIGO criteria [21] as an increase in SCr to ≥1.5 times baseline within the prior 7 days, or SCr 0.3 mg/dL within 48 h. AKI severity was stratified based on KDIGO criteria. In patients with AKI survival, we defined renal function recovery as a SCr value below 150% of baseline and no need for renal replacement therapy at discharge.

2.3. Data collection and outcome measurements

Demographic, clinical, biochemical data and acute physiology and chronic health evaluation (APACHE) II score were collected for all eligible patients in this study immediately after admission to the ICU. The NLR was calculated from the whole blood count via dividing absolute count of neutrophil by absolute count of lymphocyte. The changes in kidney function during hospitalization were recorded. Adverse events occurred during hospitalization were recorded, including invasive mechanical ventilation, renal replacement therapy, vasopressors, length of stay and the worst SOFA score. The primary outcome of the study was septic AKI. The secondary endpoint was in-hospital mortality of patients with septic AKI.

2.4. Statistical analysis

SPSS software version 20.0 was used to perform statistical analysis. Normally or near normally distributed variables were presented as means ± SD and compared using Student's t-test, analysis of variance.

Non-normally distributed continuous data were presented as medians with interquartile ranges and compared using Mann-Whitney *U* test. Categorical data were presented as proportions and compared using Fisher's exact test or chi-square test where appropriate. Spearman correlation coefficients were used to assess the relationships between NLR and other clinical variables. The relationships of the septic AKI and in-hospital mortality with NLR were determined by univariate and forward stepwise multivariate logistic regression analysis. Age, gender, comorbidities, and variables with $P < 0.05$ in univariate analysis were entered into the multivariate model. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. The receiver operating characteristic (ROC) curve was used to analyze the predictive power of NLR for septic AKI and to obtain NLR cutoff values to maximize sensitivity and specificity. All tests of data were two-tailed and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

Table 1 lists the demographics and characteristics of the AKI and non-AKI groups as well as survivors and non-survivors groups. A total of 222 adult patients were ultimately enrolled in this study, including 123 males (55.41%) and 99 females (44.59%), with an average age of 64.83 ± 17.13 years.

The most common infection foci were intra-abdomen (52.70%). Respiratory tract (20.72%) and urinary tract (15.32%) were the next most common infection foci. According to the KDIGO criteria, patients were divided into two groups, including the AKI group and the non-AKI group. 132 patients (59.46%) were assigned to the AKI group (32 patients in stage 1 AKI, 43 patients in stage 2 AKI, and 57 patients in stage 3 AKI). 90 patients (40.54%) were allocated to the non-AKI group. There were no significant differences in age, gender, and comorbidities between the two groups ($P > 0.05$).

The NLR, SCr, white blood cell (WBC) count, serum lactate, procalcitonin, uric acid, blood urea nitrogen (BUN), APACHE II score were significantly higher in the AKI group compared with the non-AKI group ($P < 0.05$). Mean arterial pressure (MAP), eGFR, serum albumin were lower in the AKI group than in the non-AKI group ($P < 0.05$). There were no significant difference in hemoglobin, platelet count, hypersensitive C-reactive protein (hs-CRP), serum sodium and potassium between the two groups ($P > 0.05$).

64 patients (28.83%) died, of whom 55 (41.67%) in the AKI group and 9 (10.00%) in the non-AKI group. AKI patients required more invasive mechanical ventilation, renal replacement therapy and vasopressors than non-AKI patients ($P < 0.001$). Compared with non-AKI patients, AKI patients had a worse prognosis, with higher in-hospital mortality, and longer ICU stay ($P < 0.001$). As expected, the SOFA score in the AKI group was significantly higher than that in the non-AKI group ($P < 0.001$).

In patients with septic AKI, age, serum lactate, BUN, APACHE II score, use of invasive mechanical ventilation, need for renal replacement therapy, requirement of vasopressors and SOFA score were significantly higher in survivors than non-survivors ($P < 0.05$); eGFR, WBC, the NLR and length of hospital stay were lower in survivors than non-survivors ($P < 0.05$).

3.2. Dynamic changes of the NLR during renal function recovery in patients with septic AKI

Among the 77 patients with AKI survival, 60 patients recovered from renal injury before discharge and 17 patients failed to recover. The dynamic changes of the NLR measured at four different time points (at ICU admission, AKI diagnosis, highest SCr after admission, discharge) are shown in Fig. 1. In patients with or without renal function recovery, the NLR were no significant difference between at ICU admission, AKI diagnosis, and highest SCr ($P > 0.05$). At the time of discharge, the NLR of patients with renal function recovery was significantly decreased ($P < 0.05$), while the NLR was not significantly changed in unrecovered patients ($P > 0.05$).

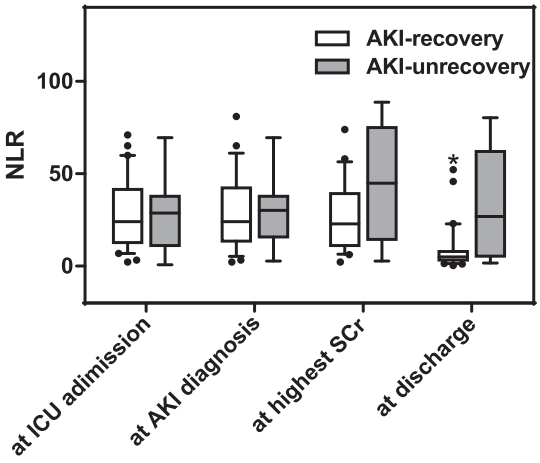

Fig. 1. Dynamic changes of the NLR measured at the time of ICU admission, AKI diagnosis, the highest SCr after admission, and hospital discharge in patients with renal function recovery and unrecovered. * $P < 0.05$, compared with at the time of ICU admission. Data were presented as box plots (median with inter quartile range) with 5th and 95th percentile as whiskers.

3.3. Correlations between the NLR and clinical variables

The correlations between NLR and clinical variables are shown in Table 2 using the Spearman correlation coefficient. There was a significant positive correlation between the NLR and WBC counts ($r = 0.517$, $P < 0.001$), procalcitonin ($r = 0.218$, $P = 0.002$) and length of ICU stay ($r = 0.155$, $P = 0.021$). Moreover, the NLR was negatively correlated with eGFR ($r = -0.014$, $P = 0.035$). However, we did not get a correlation between NLR and age, gender, hemoglobin, albumin and hs-CRP in our study.

3.4. The NLR as a predictor for the primary outcome

The results of the NLR as a predictor of septic AKI are presented in Table 3 by logistic regression analysis. The NLR was related to the development of septic AKI in univariate analysis (unadjusted OR = 1.044, 95% CI 1.021–1.067, $P < 0.001$). It was further confirmed in the multivariate model that the NLR was an independent predictor of septic AKI (OR = 1.047, 95% CI 1.005–1.091, $P = 0.026$), adjusted for age, gender, comorbidities, MAP, eGFR, WBC count, procalcitonin, serum lactate, uric acid, serum albumin, BUN and APACHE II score.

Table 2
Correlations between the NLR and clinical parameters.

Variables	*r*	*P* value
Age	−0.021	0.751
Male	−0.107	0.111
WBC count	0.517	< 0.001
Procalcitonin	0.218	0.002
High sensitivity C-reactive protein	0.090	0.420
eGFR	−0.141	0.035
Hemoglobin	−0.014	0.833
Serum albumin	−0.112	0.097
Length of ICU stay	0.155	0.021
Length of hospital stay	−0.028	0.683

Table 3
Independent predictors of septic AKI by univariate and multivariate logistic regression analysis.

	Univariate analysis		Multivariate analysis	
	OR(95%CI)	*P*	OR (95%CI)	*P*
Age	1.007 (0.992–1.023)	0.356		
Male (versus female)	1.068 (0.623–1.830)	0.812		
Hypertension	1.709 (0.940–3.109)	0.079		
Chronic kidney disease	2.150 (0.671–6.893)	0.198		
Diabetes	1.734 (0.894–3.364)	0.103		
mean arterial blood pressure	0.964 (0.948–0.981)	< 0.001		
eGFR	0.975 (0.964–0.986)	< 0.001		
NLR	1.044 (1.021–1.067)	< 0.001	1.047 (1.005–1.091)	0.026
WBC count	1.092 (1.048–1.138)	< 0.001		
Procalcitonin	1.025 (1.013–1.038)	< 0.001	1.013 (1.001–1.026)	0.037
Serum lactate	1.381 (1.114–1.712)	0.003		
BUN	1.218 (1.138–1.303)	< 0.001		
Uric acid	1.012 (1.008–1.015)	< 0.001	1.009 (1.004–1.014)	< 0.001
Serum albumin	0.912 (0.870–0.957)	< 0.001		
APACHE II score	1.264 (1.189–1.343)	< 0.001	1.185 (1.089–1.290)	< 0.001

3.5. The NLR as a predictor for secondary outcome

For in-hospital mortality in patients with septic AKI, age, gender, comorbidities, eGFR, serum lactate, BUN, APACHE II score, renal replacement therapy, mechanical ventilation, vasopressors, SOFA score were added in the multivariate logistic regression model in Table 4. However, no correlation was found between the NLR and in-hospital mortality in septic AKI patients.

3.6. Performance of the NLR as a predictor of septic AKI by ROC curve analysis

Fig. 2 shows ROC curves plotted using independent predictor of septic AKI. The AUC of the NLR, uric acid, APACHE II score, and procalcitonin for septic AKI were 0.656 (95% CI 0.584–0.728, $P < 0.001$), 0.834(95%CI 0.782–0.886, $P < 0.001$), 0.871 (95% CI 0.823–0.920, $P < 0.001$), and 0.731(95%CI 0.661–0.801, $P < 0.001$). The ROC analysis yielded a cut-off value of 17.11 for the NLR to predict septic AKI with 62.1% sensitivity and 68.9% specificity.

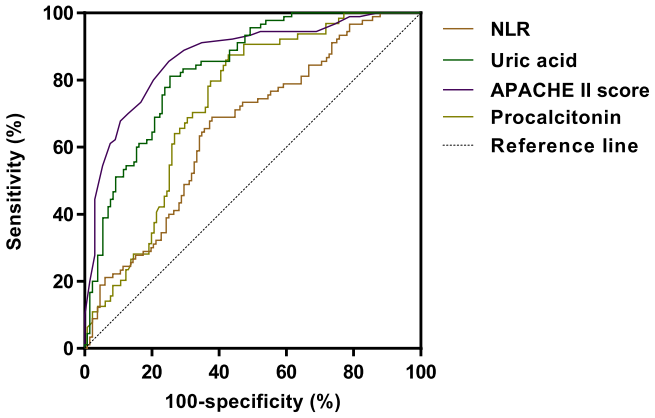

Fig. 2. ROC curves for NLR, uric acid, APACHE II score, and procalcitonin NLR had a modest power for predicting septic AKI as suggested by AUC of 0.656(95%CI0.584–0.728), $P < 0.001$.

4. Discussion

Our retrospective study revealed that the initial NLR measured at ICU admission was associated with the development of AKI in patients with sepsis and septic shock, after adjustment for other clinical and laboratory variables. When the cutoff value of the NLR was 17.11, the sensitivity of identifying AKI was 62.1% and the specificity was 68.9%.

The NLR is an indicator of the patient's response to inflammatory injury, primarily based on physiological connections between neutrophils and lymphocytes with systemic inflammation and stress. Sepsis triggers the systemic cytokine-chemokine response that results in extensive activation and dysfunction of the immune system, which can manifest neutrophilia and lymphopenia [22]. Neutrophils are the key

Table 4
Independent predictors of in-hospital mortality in patients with septic AKI by univariate and multivariate logistic regression analysis.

	Univariate analysis		Multivariate analysis	
	OR(95%CI)	*P*	OR(95%CI)	*P*
Age	1.056 (1.028–1.085)	< 0.001	1.056 (1.021–1.093)	0.002
Male (versus female)	1.956 (0.953–3.967)	0.068		
Hypertension	1.387 (0.675–2.849)	0.374		
Chronic kidney disease	1.449 (0.441–4.757)	0.541		
Diabetes	1.169 (0.540–2.534)	0.692		
eGFR	0.981 (0.966–0.997)	0.018		
NLR	0.991 (0.974–1.009)	0.325		
WBC count	0.963 (0.928–1.000)	0.053		
Serum lactate	1.259 (1.075–1.474)	0.004		
BUN	1.045 (1.008–1.082)	0.016		
APACHE II score	1.118 (1.057–1.183)	< 0.001		
SOFA score	1.343 (1.205–1.497)	< 0.001	1.296 (1.146–1.466)	< 0.001
Renal replacement therapy	2.731 (1.292–5.774)	0.009		
Mechanical ventilation	8.944 (3.815–20.969)	< 0.001		
Vasopressors	9.937 (2.221–44.459)	0.003		

cell type of the innate immune system, responding rapidly to microbial infections and dramatically increasing the number of cytokines. Activation of the severe and uncontrolled innate immune system can lead to tissue damage and even death. On the other hand, lymphocytes play a key role in the regulation of appropriate inflammatory responses. The release of various anti-inflammatory cytokines induces immunosuppression and apoptosis in a large number of lymphocytes [23]. Lymphopenia is an important feature of immunosuppression induced by sepsis [24]. The NLR, therefore, is considered to be a subtle and sensitive predictor of inflammation due to subtle changes in its numerator and denominator. In general, the level of NLR can reflect the severity of the systemic inflammatory.

It has been shown that septic AKI occurs in the setting of microcirculatory dysfunction, inflammation, bioenergetics, and tubular cell adaptation to cellular stress [10,11]. Inflammation plays an increasingly critical role in the physiopathology of AKI. In addition, inflammatory markers, such as interleukin-6, interleukin-10 and procalcitonin, were found to be strongly related to septic AKI [25,26], further indicating the important role of systemic inflammatory in this process. In the current study, procalcitonin was significantly correlated with the NLR, both of which were independent risk factors for septic AKI.

The association between the NLR and septic AKI development can be attributed to the role of inflammation in the pathogenesis of AKI. The role of a variety of cells such as neutrophils and lymphocytes in the development of AKI has been partially confirmed. Neutrophil infiltration was detected in mouse kidneys and biopsy samples from patients with early AKI [27], and renal damage was alleviated by inhibiting neutrophil infiltration or activity in rats [28]. In the mouse model, T cells induce renal tissue damage early in the injury, which then promotes tubular regeneration during the recovery phase, and B cells are activated and differentiated during the injury phase and restrict tubular regeneration during the recovery phase [27]. However, further experimental studies are needed to elucidate the underlying mechanisms of the NLR in the pathogenesis of septic AKI.

To the best of our knowledge, the study by Yilmaz et al. [18] was the only study in the literature to determine the association between NLR and septic AKI. The study, including 118 cases of severe sepsis, demonstrated that the NLR measured at ICU admission could be used to predict the development of AKI and the cutoff value of the NLR was 10.15 with a sensitivity of 90.2% and a specificity of 92.9%. In our research, we confirmed and expanded the results of previous surveys. They only investigated patients with severe sepsis, but our study included patients with sepsis and septic shock. Our sample size was larger and therefore more reflective of the risk of septic AKI. We also investigated the utility of initial NLR for in-hospital mortality in patients with septic AKI. In addition to differences in inclusion and exclusion criteria, demographic differences could explain the modest difference in NLR cut-off value. Azab et al. [29] found the differences in the NLR among different ethnic groups.

The relationship between NLR and kidney function was also studied. Solak et al. [13] reported that the NLR significantly increased as CKD worsened. Kocyigit et al. [14] suggested that the NLR may predict the progression rate of stage 4 chronic kidney disease to dialysis in 105 patients with stage 4 CKD. Consistent with the Tonyali et al. [12], we found a negative correlation between NLR and eGFR. Similarly, we observed that the NLR was associated with renal function in septic AKI, and the NLR was significantly reduced when renal function was recovered.

Current studies reported that the NLR was able to stratify the adverse outcome in patients with sepsis or septic shock. Riche et al. [7] revealed an relationship between the NLR with early and late death for patients with septic shock. The study conducted by Huang et al. [6] demonstrated that the initial NLR measured at emergency department admission was an independent risk factor for predicting 28-day mortality in patients with severe sepsis or septic shock. In addition, the NLR was related to kidney function and the development of septic AKI and was also identified as a predictor of all-cause mortality in patients undergoing hemodialysis or peritoneal dialysis [15,16]. In our study, we investigated the association between NLR and in-hospital mortality in septic AKI patients, and the NLR was positively associated with the length of ICU stay, suggesting that NLR may be associated with poor prognosis. However, there was no association between the NLR and in-hospital mortality in patients with septic AKI by multivariate logistic regression analysis.

Our study has several limitations. First, it is a single-center retrospective study with single ethnicity population. It was difficult to control for bias and confounders, despite conduction of multivariate analysis. Whether these results can be extended to other ethnic groups remains to be seen. Second, we simply analyzed circulating neutrophil and lymphocyte counts and failed to classify lymphocyte subsets. Third, lack of tracking of dynamic changes in the NLR and failed to compare NLR with recently developed renal injury markers such as neutrophil gelatinase-associated lipocalin, kidney injury factor-1 and cystatin C. Finally, diagnosing AKI was based only on elevated SCr, while the role of urine output was ignored. Patients with oliguria who received diuretics can affect the diagnosis of AKI.

5. Conclusion

Our study suggests that the initial NLR measured at ICU admission was an independent predictor of patients with septic AKI. The NLR, a laboratory variable that is simple, widely available and inexpensive, may be potential for risk stratification of septic AKI.

Acknowledgement

We thank the staff of the ICU of Zhongnan Hospital of Wuhan University for assisting with data collection. This work was supported by National Natural Science Foundation of China (No. 81170679).

Disclosure statement

The authors have no conflicts of interest to declare.

References

[1] R. Alobaidi, R.K. Basu, S.L. Goldstein, S.M. Bagshaw, Sepsis-associated acute kidney injury, Semin. Nephrol. 35 (1) (2015) 2–11.
[2] R. Bellomo, J.A. Kellum, C. Ronco, Acute kidney injury, Lancet 380 (9843) (2012) 756–766.
[3] S.L. Goldstein, B.L. Jaber, S. Faubel, L.S. Chawla, A.S. Nephrology, AKI transition of care: a potential opportunity to detect and prevent CKD, Clin. J. Am. Soc. Nephrol. 8(3) (2013) 476–483.
[4] E. Durmus, T. Kivrak, F. Gerin, M. Sunbul, I. Sari, O. Erdogan, Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are predictors of heart failure, Arq. Bras. Cardiol. 105(6) (2015) 606-13.
[5] H. Wada, T. Dohi, K. Miyauchi, J. Shitara, H. Endo, S. Doi, H. Konishi, R. Naito, S. Tsuboi, M. Ogita, T. Kasai, A. Hassan, S. Okazaki, K. Isoda, S. Suwa, H. Daida, Pre-procedural neutrophil-to-lymphocyte ratio and long-term cardiac outcomes after percutaneous coronary intervention for stable coronary artery disease, Atherosclerosis 265 (2017) 35–40.
[6] S.Y. Hwang, T.G. Shin, I.J. Jo, K. Jeon, G.Y. Suh, T.R. Lee, H. Yoon, W.C. Cha, M.S. Sim, Neutrophil-to-lymphocyte ratio as a prognostic marker in critically-ill septic patients, Am. J. Emerg. Med. 35 (2) (2017) 234–239.
[7] F. Riche, E. Gayat, R. Barthelemy, M. Le Dorze, J. Mateo, D. Payen, Reversal of neutrophil-to-lymphocyte count ratio in early versus late death from septic shock, Crit. Care 19 (2015) 439.
[8] H. Yodying, A. Matsuda, M. Miyashita, S. Matsumoto, N. Sakurazawa, M. Yamada, E. Uchida, Prognostic significance of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in oncologic outcomes of esophageal cancer: a systematic review and meta-analysis, Ann. Surg. Oncol. 23 (2) (2016) 646–654.
[9] J.D. Salciccioli, D.C. Marshall, M.A. Pimentel, M.D. Santos, T. Pollard, L.A. Celi, J. Shalhoub, The association between the neutrophil-to-lymphocyte ratio and mortality in critical illness: an observational cohort study, Crit. Care 19 (2015) 13.
[10] F. Fani, G. Regolisti, M. Delsante, V. Cantaluppi, G. Castellano, L. Gesualdo, G. Villa, E. Fiaccadori, Recent advances in the pathogenetic mechanisms of sepsis-associated acute kidney injury, J. Nephrol. 31 (3) (2018) 351–359.
[11] A. Zarbock, H. Gomez, J.A. Kellum, Sepsis-induced acute kidney injury revisited:

pathophysiology, prevention and future therapies, Curr. Opin. Crit. Care 20 (6) (2014) 588–595.
[12] S. Tonyali, C. Ceylan, S. Yahsi, M.S. Karakan, Does neutrophil to lymphocyte ratio demonstrate deterioration in renal function? Ren. Fail. 40 (1) (2018) 209–212.
[13] Y. Solak, M.I. Yilmaz, A. Sonmez, M. Saglam, E. Cakir, H.U. Unal, M. Gok, K. Caglar, Y. Oguz, M. Yenicesu, M. Karaman, S.A. Ay, A. Gaipov, S. Turk, A. Vural, J.J. Carrero, Neutrophil to lymphocyte ratio independently predicts cardiovascular events in patients with chronic kidney disease, Clin. Exp. Nephrol. 17 (4) (2013) 532–540.
[14] I. Kocyigit, E. Eroglu, A. Unal, M.H. Sipahioglu, B. Tokgoz, O. Oymak, C. Utas, Role of neutrophil/lymphocyte ratio in prediction of disease progression in patients with stage-4 chronic kidney disease, J. Nephrol. 26 (2) (2013) 358–365.
[15] X. An, H.P. Mao, X. Wei, J.H. Chen, X. Yang, Z.B. Li, X.Q. Yu, Z.J. Li, Elevated neutrophil to lymphocyte ratio predicts overall and cardiovascular mortality in maintenance peritoneal dialysis patients, Int. Urol. Nephrol. 44 (5) (2012) 1521–1528.
[16] H. Li, X. Lu, R. Xiong, S. Wang, High neutrophil-to-lymphocyte ratio predicts cardiovascular mortality in chronic hemodialysis patients, Mediat. Inflamm. 2017 (2017) 9327136.
[17] M. Abu Alfeilat, I. Slotki, L. Shavit, Single emergency room measurement of neutrophil/lymphocyte ratio for early detection of acute kidney injury (AKI), Intern. Emerg. Med. 13 (5) (2018) 717–725.
[18] H. Yilmaz, M. Cakmak, O. Inan, T. Darcin, A. Akcay, Can neutrophil-lymphocyte ratio be independent risk factor for predicting acute kidney injury in patients with severe sepsis? Ren. Fail. 37 (2) (2015) 225–229.
[19] M. Singer, C.S. Deutschman, C.W. Seymour, M. Shankar-Hari, D. Annane, M. Bauer, R. Bellomo, G.R. Bernard, J.D. Chiche, C.M. Coopersmith, R.S. Hotchkiss, M.M. Levy, J.C. Marshall, G.S. Martin, S.M. Opal, G.D. Rubenfeld, T. van der Poll, J.L. Vincent, D.C. Angus, The third international consensus definitions for sepsis and septic shock (Sepsis-3), JAMA 315(8) (2016) 801–10.
[20] A.S. Levey, L.A. Stevens, C.H. Schmid, Y.L. Zhang, A.F. Castro, 3rd, H.I. Feldman, J. W. Kusek, P. Eggers, F. Van Lente, T. Greene, J. Coresh, E.P.I. Ckd, A new equation to estimate glomerular filtration rate, Ann. Intern. Med. 150(9) (2009) 604–12.
[21] A. Khwaja, KDIGO clinical practice guidelines for acute kidney injury, Nephron. Clin. Pract. 120(4) (2012) c179–84.
[22] D.S. Heffernan, S.F. Monaghan, R.K. Thakkar, J.T. Machan, W.G. Cioffi, A. Ayala, Failure to normalize lymphopenia following trauma is associated with increased mortality, independent of the leukocytosis pattern, Crit. Care 16 (1) (2012) R12.
[23] N.K. Patil, J.K. Bohannon, E.R. Sherwood, Immunotherapy: a promising approach to reverse sepsis-induced immunosuppression, Pharmacol. Res. 111 (2016) 688–702.
[24] A.M. Drewry, N. Samra, L.P. Skrupky, B.M. Fuller, S.M. Compton, R.S. Hotchkiss, Persistent lymphopenia after diagnosis of sepsis predicts mortality, Shock 42 (5) (2014) 383–391.
[25] D. Payen, A.C. Lukaszewicz, M. Legrand, E. Gayat, V. Faivre, B. Megarbane, E. Azoulay, F. Fieux, D. Charron, P. Loiseau, M. Busson, A multicentre study of acute kidney injury in severe sepsis and septic shock: association with inflammatory phenotype and HLA genotype, PLoS One 7 (6) (2012) e35838.
[26] M. Araujo, S.Q. Doi, C.E. Palant, E.S. Nylen, K.L. Becker, Procalcitonin induced cytotoxicity and apoptosis in mesangial cells: implications for septic renal injury, Inflamm. Res. 62 (10) (2013) 887–894.
[27] H.R. Jang, H. Rabb, Immune cells in experimental acute kidney injury, Nat. Rev. Nephrol. 11 (2) (2015) 88–101.
[28] K.M. Rouschop, J.J. Roelofs, N. Claessen, P. da Costa Martins, J.J. Zwaginga, S.T. Pals, J.J. Weening, S. Florquin, Protection against renal ischemia reperfusion injury by CD44 disruption, J. Am. Soc. Nephrol. 16(7) (2005) 2034–43.
[29] B. Azab, M. Camacho-Rivera, E. Taioli, Average values and racial differences of neutrophil lymphocyte ratio among a nationally representative sample of United States subjects, PLoS One 9 (11) (2014) e112361.