Clinica Chimica Acta 490 (2019) 207–213

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Neutrophil-lymphocyte ratio is associated with all-cause mortality among critically ill patients with acute kidney injury

Lai Lai Fan[a], Yi Jun Wang[a], Cun Jin Nan[a], Ying He Chen[a,*], Hong Xia Su[b,*]

[a] Department of Urology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, China
[b] Department of Nursing, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, China

ARTICLE INFO

Keywords:
Neutrophil-lymphocyte ratio
Acute kidney injury
Intensive care unit
Mortality
NLR
AKI
ICU

ABSTRACT

Background: Inflammation plays a critical role in the development of acute kidney injury (AKI). Neutrophil-lymphocyte ratio (NLR) is a biomarker of systemic inflammation used to predict the prognostic outcome of several diseases. We conducted a retrospective cohort study to investigate if NLR can be used as a biomarker to predict the mortality of AKI.

Methods and results: Records of critically ill patients with AKI were extracted from the Medical Information Mart for Intensive Care Database III version 1.3 (MIMIC-III v1.3). The primary outcome was 30-day mortality and the two secondary outcomes were in hospital and 90-day mortality. We used the Cox proportional hazards models to assess the association between different categories of NLR and outcomes. This analysis included data for 13,678 eligible subjects, with a total of 2,588 30-day, 2,224 in-hospital and 3,545 90-day deaths during the follow-up period. For 30-day mortality, an increased risk of mortality was associated with a higher level of NLR. The HR (95% confidence interval [CI]) of upper tertile (NLR > 12.14) was 1.37 (1.17-1.60) in a multivariate model when compared with that of the lower tertile (NLR < 5.55). In the quintile analysis, we confirmed the upward trend with HR (95% CI) of the fifth quintile (NLR > 17.4) of 1.35 (1.08, 1.69) in a multivariate model compared to the first quintile (NLR < 3.82). A similar tendency was observed for 90-day mortality. In the analysis of in-hospital mortality, the HR of fifth quintile (NLR > 17.4) showed a slight decrease.

Conclusions: Our analysis indicates that a higher level of NLR is associated with increased risk of 30-day and 90-day mortality in AKI patients. The similar upward trend is not detected in analysis of in-hospital mortality.

1. Introduction

Acute kidney injury (AKI) presents a high risk of death in critically ill patients [1–3]. Overall in-hospital mortality of AKI in developed countries is about 20%, and can be 50% in the intensive care unit (ICU) patients [4,5]. Renal replacement therapy (RRT) is the only definitive treatment for the complications of AKI, but is costly and not widely available in resource-poor settings [6,7]. Early prediction and avoidance of the development of established AKI will be useful to identify patients at high risk of a poor prognosis and assess the need for RRT.

The pathogenesis of AKI is characterized by endothelial dysfunction, hemodynamic alterations, tubular injury, and intrarenal inflammation. Inflammation plays a key role in the pathophysiology of AKI [8,9]. Recent studies attribute promising prognostic and predictive values to various potential inflammatory biomarkers in AKI [10–14]. The neutrophil-lymphocyte ratio (NLR) is an easily determinable potential inflammatory biomarker that is associated with increased risk of AKI after cardiovascular surgery [11,14] and predictive of poor outcome in a variety of diseases, such as cardiovascular disease, solid tumors, liver failure, and postoperative infection [15–17]. Therefore, we hypothesized that NLR may affect the prognosis of AKI. However, to our knowledge, there has been no examination between mortality and NLR in patients with AKI. Therefore, we conducted a retrospective cohort study to investigate whether the NLR is predictive of the mortality of AKI.

2. Methods

2.1. Data source

The Medical Information Mart for Intensive Care Database III ver 1.3 (MIMIC-III v1.3) is a freely accessible critical care database, including information related to 53,423 distinct hospital admissions for adult patients (aged ≥16 y) at Beth Israel Deaconess Medical Center

* Corresponding authors.
E-mail address: chenyinghe1965@163.com (Y.H. Chen).

https://doi.org/10.1016/j.cca.2018.09.014
Received 21 April 2018; Received in revised form 3 September 2018; Accepted 6 September 2018
Available online 07 September 2018
0009-8981/

between 2001 and 2012. The median age of the included adult patients is 65.8 years, the median length of an ICU stay for these patients is 2.1 days, and a mean of 4579 charted observations and 380 laboratory measurements are available for each hospital admission [18]. The dates of patient death corresponding to these records were recorded in-hospital or were obtained from the Social Security Death Index (SSDI) records for out-of-hospital mortality. If the information included in the hospital data differed from the government record, then the hospital data was assumed to be more accurate. Patients who left the US (and subsequently died) after receiving treatment may not have their date of death recorded in the archives. The original establishment and use of the database was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. To apply for permission to access the database, researchers completed the National Institutes of Health's web-based course, Protecting Human Research Participants (certification number 26881639).

2.2. Population selection criteria

A total of 38,597 distinct adult patients and 49,785 hospital admissions were recorded in the MIMIC-III database. Only patients diagnosed with AKI were considered. Of these patients, we included in our analysis patients who were older than 18 at first admission and who had an in-hospital stay of at least 2 days. Patients were excluded from our study if (1) a patient was also diagnosed with hematologic neoplasms, (2) a patient's record was missing > 1% of the required data, or (3) a patient with baseline data values that exceeded the mean ± 3 times the standard deviation (SD).

The diagnosis of AKI was according to the classification of Kidney Disease: Improving Global Outcomes (KDIGO) [19]. These guidelines specify an increase in serum creatinine (SCr) of at least 0.3 mg/dl (≥ 26.4 μmol/l) within 48 hours; SCr increases of at least 50% (1.5-fold from baseline) within the prior 7 days; and urine output that is < 0.5 ml/kg/h per 6 h. Of patients with a diagnosis of AKI, they can be further classified into stages. Stage 1 is defined as an increase in SCr of at least 0.3 mg/dl (≥ 26.4 μmol/l), or an increase of at least 150% to 200% (1.5- to 2-fold) from the baseline, or urine output < 0.5 ml/kg/h per 6 h. Stage 2 is defined as an increase in SCr to a level > 200% of the baseline or urine output < 0.5 ml/kg/h per 12 h. Stage 3 is defined as an increase in SCr to > 300% (> 3-fold) or the baseline value (or SCr of ≥ 4.0 mg/dl [≥ 354 μmol/l] with an acute increase of at least 0.5 mg/dl [44 μmol/l]), or urine output that is < 0.3 ml/kg/h for 24 h, or anuria for 12 h [20].

2.3. Date extraction

Data extraction was performed by using structure query language (SQL) [21]. The data of demographic parameters, clinical parameters, laboratory parameters, and scoring systems were extracted from Beth Israel Deaconess Medical Center. The baseline characteristics used were those recorded within 24 h of ICU admission, and complete blood count was used to calculate NLR.

Demographic parameters included age, gender, and ethnicity. Clinical parameters included heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), respiratory rate (RR), temperature, percutaneous oxygen saturation (SPO_2), NLR, vasoactive drug, death, renal function, and multiple comorbidities. Laboratory parameters included anion gap, serum lactate, serum bicarbonate, serum chloride, serum potassium, serum sodium, serum glucose, hematocrit, hemoglobin, platelet count, white blood cell (WBC) count, and lymphocytes count. Scoring systems of severity-of-illness included the Sequential Organ Failure Assessment (SOFA) [22] and Glasgow Coma Scale (GCS) [23], and both scores were calculated for each patient. The SOFA score is calculated as the sum of points allocated from the assessment of the respiratory, cardiac, hepatic, renal, hematologic and central nervous systems [24]. The GCS assessment tool describes the level of consciousness, and includes separate responses of eye opening, verbal, and motor responses [25]. All scores were calculated using physiological measurements and clinical information according to published recommendations and accepted formulae.

The date of the patient's admission was used as the initial date of treatment for follow-up. The termination of follow-up was the time of death. The primary outcome of our study was 30-day mortality and the two secondary outcomes were in-hospital mortality and 90-day mortality.

2.4. Statistical analysis and modeling strategy

The baseline characteristics of all patients were stratified by NLR tertiles. Continuous variables were presented as the mean ± SD or medians and interquartile range (IQR). Categorical data were summarized as frequencies and percentages. Categorical variables were compared using χ^2 test [26] or Fisher's exact test [27] as appropriate. The Kruskal Wallis test [28] was used to test for differences in continuous variables between different categories of NLR. We used Cox proportional hazards models [29] to assess the association between different categories of NLR and outcomes. Potential multicollinearity between covariates was quantified by calculation of the variance inflation factor (VIF), which provided an index of how much the variance of an estimated regression coefficient is increased due to collinearity [30]. A VIF value bigger than 5 was considered evidence of multicollinearity. Results were presented as hazard ratios (HRs) with confidence intervals (CIs). To determine whether the NLR was independently associated with endpoints, we selected these confounders based on their associations with the outcomes or a change in effect estimate of more than 10% [31].

Three models for each outcome on the basis of NLR were constructed in tertiles and quintiles. There was no confounder adjustment in the non-adjusted model. The variables included in the two multivariate models are listed in Table 1. We conducted stratification analyses to examine whether the effect of the NLR differed across various subgroups classified by AKI stage, RRT, congestive heart failure (CHF), atrial fibrillation (AF), chronic renal disease, chronic liver disease, chronic obstructive pulmonary disease (COPD), coronary heart disease (CAD), stroke, malignancy, acute respiratory distress syndrome (ARDS), pneumonia, and use of vasoactive drugs. All probability values were 2-sided, a $p < 0.05$ was considered statistically significant, and R ver 3.42 (http://www.R-project.org) was used for all statistical analyses.

3. Results

3.1. Subject characteristics

Of the 38,597 patient records reviewed, patient records of 13,678 eligible subjects from Beth Israel Deaconess Medical Center were initially extracted from the MIMIC-III database. The subjects included 7,601 men and 6,077 women with a mean age of 65.8 y. The overall mean (SD) NLR was 12.7 (16.6). Selected characteristic and hematologic laboratory data across NLR tertiles are listed in Table 1. Most participants (71.5%) included in our analysis were white. Participants with higher NLR were more likely to be elderly, female, white and report a history of COPD, malignancy, ARDS, pneumonia, or vasoactive drug use. These patients also had higher heart rate, RR, serum glucose, BUN, platelet count, WBC count, and lower blood pressure, hemoglobin, and lymphocytes. Participants with higher NLR were more likely to be diagnosed at a higher stage of AKI and have received RRT than those with lower NLR. Additionally, participants with higher NLR had a higher SOFA score and a lower GCS score.

3.2. Association between NLR and mortality

A total of 2,588 30-day, 2,224 in-hospital and 3,545 90-day death

Table 1
Baseline characteristics of the study population.

	All	Neutrophil–lymphocyte ratio			P-value
		< 5.55	5.55-12.14	> 12.14	
NLR	12.7 ± 16.6	3.3 ± 1.4	8.4 ± 1.9	26.5 ± 23.0	< 0.001
N	13678	4558	4558	4562	
Age	65.8 ± 17.3	64.6 ± 17.6	66.0 ± 17.3	66.8 ± 17.0	< 0.001
Gender, n (%)					0.029
Female	6077 (44.4)	2003 (43.9)	1976 (43.4)	2098 (46.0)	
Male	7601 (55.6)	2555 (56.1)	2582 (56.6)	2464 (54.0)	
Ethnicity, n (%)					< 0.001
White	9773 (71.5)	3095 (67.9)	3248 (71.3)	3430 (75.2)	
Black	1423 (10.4)	675 (14.8)	431 (9.5)	317 (6.9)	
Other	2482 (18.1)	788 (17.3)	879 (19.3)	815 (17.9)	
Vital signs					
Heart rate, beats/min	86.9 ± 16.7	85.0 ± 17.2	86.6 ± 16.1	89.2 ± 16.6	< 0.001
SBP, mmHg	118.5 ± 17.5	119.5 ± 18.0	119.1 ± 17.4	116.9 ± 17.0	< 0.001
DBP, mmHg	60.4 ± 11.1	61.5 ± 11.4	60.5 ± 11.3	59.3 ± 10.6	< 0.001
MBP, mmHg	77.5 ± 11.5	78.4 ± 11.6	77.8 ± 11.6	76.4 ± 11.1	< 0.001
RR, beats/minute	19.6 ± 4.2	19.0 ± 4.0	19.6 ± 4.2	20.2 ± 4.4	< 0.001
Temperature, ˚C	36.8 ± 0.7	36.8 ± 0.7	36.9 ± 0.7	36.9 ± 0.7	< 0.001
SPO_2, %	97.0 ± 2.5	97.1 ± 2.7	97.1 ± 2.3	96.9 ± 2.6	0.002
Laboratory parameters					
Anion gap, mmol/l	17.7 ± 5.4	17.2 ± 5.3	17.6 ± 5.3	18.3 ± 5.5	< 0.001
Serum lactate, mmol/l	3.3 ± 2.9	3.4 ± 3.3	3.1 ± 2.7	3.3 ± 2.8	< 0.001
Serum bicarbonate, mmol/l	24.7 ± 4.7	25.1 ± 4.4	24.8 ± 4.7	24.1 ± 4.9	< 0.001
Serum potassium, mmol/l	4.8 ± 1.0	4.8 ± 1.1	4.8 ± 1.0	4.8 ± 1.0	0.006
Serum chloride, mmol/l	107.3 ± 6.9	107.5 ± 6.6	107.1 ± 7.0	107.2 ± 7.2	0.009
Serum sodium, mmol/l	140.5 ± 5.3	140.7 ± 5.0	140.6 ± 5.5	140.3 ± 5.5	0.002
Serum glucose, mg/dl	198.6 ± 129.8	192.9 ± 127.5	197.1 ± 132.7	205.7 ± 128.8	< 0.001
Hematocrit, %	36.0 ± 6.1	36.2 ± 6.3	35.8 ± 6.1	35.9 ± 6.0	0.007
Hemoglobin, g/dl	12.0 ± 2.2	12.1 ± 2.2	11.9 ± 2.1	11.9 ± 2.1	< 0.001
Platelet count, 10^9/l	255.6 ± 131.9	242.6 ± 121.9	257.2 ± 130.3	267.1 ± 141.5	< 0.001
WBC count, 10^9/l	14.9 ± 11.5	12.2 ± 14.8	14.1 ± 7.2	18.4 ± 10.3	< 0.001
Lymphocytes count, 10^9/l	12.8 ± 10.8	23.9 ± 11.7	10.2 ± 2.1	4.3 ± 1.8	< 0.001
Renal function					
AKI stage, n (%)					< 0.001
1	3579 (26.2)	1324 (29.0)	1225 (26.9)	1030 (22.6)	
2	2148 (15.7)	643 (14.1)	759 (16.7)	746 (16.4)	
3	7951 (58.1)	2591 (56.8)	2574 (56.5)	2786 (61.1)	
RRT, n (%)	1216 (8.9)	370 (8.1)	407 (8.9)	439 (9.6)	0.041
SCr, mg/dl	2.0 ± 2.0	2.0 ± 2.3	2.0 ± 1.9	2.0 ± 1.9	0.108
BUN, mg/dl	36.4 ± 27.0	33.0 ± 25.3	36.5 ± 26.6	39.7 ± 28.5	< 0.001
Comorbidities, n (%)					
Endocarditis	22 (0.2)	5 (0.1)	9 (0.2)	8 (0.2)	0.554
CHF	2601 (19.0)	789 (17.3)	951 (20.9)	861 (18.9)	< 0.001
AF	3822 (27.9)	1132 (24.8)	1357 (29.8)	1333 (29.2)	< 0.001
Chronic renal disease	2468 (18.0)	835 (18.3)	830 (18.2)	803 (17.6)	0.631
Chronic liver disease	1016 (7.4)	341 (7.5)	368 (8.1)	307 (6.7)	0.049
COPD	402 (2.9)	104 (2.3)	115 (2.5)	183 (4.0)	< 0.001
CAD	3352 (24.5)	1211 (26.6)	1148 (25.2)	993 (21.8)	< 0.001
Stroke	1305 (9.5)	468 (10.3)	466 (10.2)	371 (8.1)	< 0.001
Malignancy	2442 (17.9)	845 (18.5)	703 (15.4)	894 (19.6)	< 0.001
ARDS	297 (2.2)	73 (1.6)	99 (2.2)	125 (2.7)	< 0.001
Pneumonia	4134 (30.2)	1081 (23.7)	1376 (30.2)	1677 (36.8)	< 0.001
Vasoactive drug, n (%)	4901 (35.8)	1491 (32.7)	1511 (33.2)	1899 (41.6)	< 0.001
Death, n (%)					
In-hospital	2224 (16.3)	555 (12.2)	692 (15.2)	977 (21.4)	< 0.001
30-day	2588 (18.9)	643 (14.1)	825 (18.1)	1120 (24.6)	< 0.001
90-day	3545 (25.9)	924 (20.3)	1131 (24.8)	1490 (32.7)	< 0.001
Score systems, mean (Q1-Q3)					
SOFA	5.0 (2.0–7.0)	4.7 (2.0–6.0)	4.9 (2.0–7.0)	5.5 (3.0–7.0)	< 0.001
GCS	13.6 (14.0–15.0)	13.7 (14.0–15.0)	13.6 (14.0–15.0)	13.5 (14.0–15.0)	< 0.001

NLR: neutrophil–lymphocyte ratio; N: number; ICU: intensive care unit; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; RR: respiratory rate; SPO_2: percutaneous oxygen saturation; WBC: white blood cell; AKI: Acute renal injury; RRT: renal replacement therapy; SCr: Serum creatinine; BUN: blood urea nitrogen; CHF: congestive heart failure; AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; CAD: coronary heart disease; ARDS: acute respiratory distress syndrome; SOFA: Sequential Organ Failure Assessment; GCS: Glasgow Coma Scale.
Normally distributed data are presented as the mean ± SD, non-normally distributed data are presented as median (IQR) and categorical variables are presented as n (%).

occurred during the follow-up period. For 30-day mortality, we detected that a higher level of NLR was associated with increased risk of mortality. The HR (95% CI) of the upper tertile (NLR > 12.14) was 1.83 (1.66-2.02) when compared with the reference of lower tertile (NLR < 5.55). When adjusted for age, gender and ethnicity in model 1, there was still an increasing trend, and the HR (95% CI) of upper tertile (NLR > 12.14) was 1.75 (1.59-1.93) when compared with the reference. With further adjustment for important confounders in model II,

Table 2
HRs (95% CIs) for mortality across groups of neutrophil–lymphocyte ratio.

	Non-adjusted			Model I[a]			Model II[b]		
	HR (95% CI)	P value	P trend	HR (95% CI)	P value	P trend	HR (95% CI)	P value	P trend
30-day mortality									
Tertiles			< 0.0001			< 0.0001			0.0001
< 5.55	1.0			1.0			1.0		
5.55–12.14	1.31 (1.18, 1.45)	< 0.0001		1.26 (1.13, 1.40)	< 0.0001		1.17 (1.03, 1.34)	0.0181	
> 12.14	1.83 (1.66, 2.02)	< 0.0001		1.75 (1.59, 1.93)	< 0.0001		1.37 (1.17, 1.60)	0.0001	
Quintiles			< 0.0001			< 0.0001			0.0008
< 3.82	1.0			1.0			1.0		
3.82–6.57	1.00 (0.87, 1.15)	NS		0.96 (0.83, 1.10)	NS		0.97 (0.82, 1.16)	NS	
6.57–10.36	1.34 (1.18, 1.53)	< 0.0001		1.27 (1.11, 1.45)	0.0004		1.15 (0.95, 1.39)	NS	
10.36–17.4	1.59 (1.40, 1.80)	< 0.0001		1.49 (1.31, 1.70)	< 0.0001		1.30 (1.06, 1.59)	0.0124	
> 17.4	1.93 (1.71, 2.19)	< 0.0001		1.84 (1.62, 2.08)	< 0.0001		1.35 (1.08, 1.69)	0.0080	
In-hospital mortality									
Tertiles			< 0.0001			< 0.0001			< 0.0001
< 5.55	1.0			1.0			1.0		
5.55–12.14	1.27 (1.14, 1.42)	< 0.0001		1.22 (1.09, 1.37)	0.0004		1.23 (1.05, 1.45)	0.0112	
> 12.14	1.85 (1.66, 2.05)	< 0.0001		1.77 (1.60, 1.97)	< 0.0001		1.49 (1.24, 1.79)	< 0.0001	
Quintiles			< 0.0001			< 0.0001			0.0008
< 3.82	1.0			1.0			1.0		
3.82–6.57	0.93 (0.80, 1.08)	NS		0.89(0.77, 1.04)	NS		1.04 (0.84, 1.28)	NS	
6.57–10.36	1.28 (1.11, 1.48)	0.0006		1.22 (1.06, 1.40)	0.0066		1.23 (0.98, 1.54)	NS	
10.36–17.4	1.55 (1.35, 1.78)	< 0.0001		1.47 (1.28, 1.69)	< 0.0001		1.51 (1.19, 1.92)	0.0008	
> 17.4	1.90 (1.67, 2.17)	< 0.0001		1.81 (1.59, 2.07)	< 0.0001		1.48 (1.14, 1.93)	0.0030	
90-day mortality									
Tertiles			< 0.0001			< 0.0001			< 0.0001
< 5.55	1.0			1.0			1.0		
5.55–12.14	1.26 (1.16, 1.38)	< 0.0001		1.21 (1.11, 1.32)	< 0.0001		1.10 (0.99, 1.24)	NS	
> 12.14	1.74 (1.60, 1.89)	< 0.0001		1.67 (1.53, 1.81)	< 0.0001		1.32 (1.16, 1.51)	< 0.0001	
Quintiles			< 0.0001			< 0.0001			< 0.0001
< 3.82	1.0			1.0			1.0		
3.82–6.57	1.07 (0.95, 1.20)	NS		1.03 (0.91, 1.16)	NS		1.05 (0.91, 1.22)	NS	
6.57–10.36	1.33 (1.19, 1.49)	< 0.0001		1.26 (1.13, 1.42)	< 0.0001		1.17 (0.99, 1.37)	NS	
10.36–17.4	1.54 (1.38, 1.72)	< 0.0001		1.45 (1.30, 1.62)	< 0.0001		1.32 (1.11, 1.57)	0.0020	
> 17.4	1.91 (1.72, 2.13)	< 0.0001		1.83 (1.64, 2.03)	< 0.0001		1.44 (1.19, 1.74)	0.0002	

[a] Adjusted for age; gender; ethnicity.
[b] Adjusted for age; gender; ethnicity; heart rate; systolic blood pressure; diastolic blood pressure; respiratory rate; percutaneous oxygen saturation; serum bicarbonate; serum potassium; serum sodium; serum glucose; Serum creatinine; blood urea nitrogen; hemoglobin; white blood cells count; lymphocytes count, renal replacement therapy; congestive heart failure; chronic liver disease; stroke; pneumonia; vasoactive agent; Sequential Organ Failure Assessment; Glasgow Coma Scale.

the increased trend was still significant with the HR (95% CI) of upper tertile (NLR > 12.14) of 1.37 (1.17-1.60). The HR values of the three models were all significant compared to the lower tertile (NLR < 5.55). By quintile analysis, we further confirmed the upward trend with the HR (95% CI) of the fifth quintile (NLR > 17.4) of 1.35 (1.08, 1.69) in model II. However, the HR of second quintile (NLR = 3.82-6.57) and third quintile (NLR = 6.57-10.36) in model II were not significant compared to the first quintile (NLR < 3.82). A similar tendency was observed for 90-day mortality (P trend < 0.0001 in model II). In the analysis of in-hospital mortality, we detected the same upward trend by tertile analysis, however, the HR of the fifth quintile (NLR > 17.4) of in-hospital mortality showed a slight decrease (P trend = 0.0008 in model II). The results are presented in Table 2.

3.3. Subgroup analyses

In the subgroup analyses of 30-day mortality, AKI patients with CAD [middle tertile: HR 1.57 (95% CI 1.26-1.96); upper tertile: HR 2.35 (95% CI 1.90-2.91); p = 0.0029] had a higher risk of mortality, AKI patients with malignancy [middle tertile: HR 1.05 (95% CI 0.86-1.28); upper tertile: HR 1.47 (95% CI 1.23-1.76); p = 0.0351], pneumonia [middle tertile: HR 0.94 (95% CI 0.79-1.12); upper tertile: HR 1.35 (95% CI 1.15-1.57); p = 0.0007], and vasoactive drug use [middle tertile: HR 1.13 (95% CI 0.98-1.30); upper tertile: HR 1.37 (95% CI 1.21-1.56); p = 0.0009] had a lower risk of mortality. In the subgroup analyses of in-hospital mortality, AKI patients with CAD [middle tertile: HR 1.39 (95% CI 1.08, 1.78); upper tertile: HR 2.34 (95% CI 1.85, 2.95); p = 0.0103] had a higher risk of mortality, AKI patients with malignancy [middle tertile: HR 0.97 (95% CI 0.77, 1.21); upper tertile: HR 1.50 (95% CI 1.23, 1.82); p = 0.0281], pneumonia [middle tertile: HR 0.89 (95% CI 0.74, 1.06); upper tertile: HR 1.28 (95% CI 1.09, 1.51); p < 0.0001], vasoactive drug use [middle tertile: HR 1.13 (95% CI 0.99, 1.30); upper tertile: HR 1.36 (95% CI 1.19, 1.54); p < 0.0001], and patients that received RRT [middle tertile: HR 1.20 (95% CI 0.91, 1.58); upper tertile: HR 1.35 (95% CI 1.03, 1.76); p = 0.0362] had a lower risk of mortality. Similar results were observed for 90-day mortality in the CAD subgroup [middle tertile: HR 1.60 (95% CI 1.33-1.93); upper tertile: HR 2.34 (95% CI 1.96-2.80); p < 0.0001], malignancy [middle tertile: HR 1.06 (95% CI 0.90-1.25); upper tertile: HR 1.45 (95% CI 1.25-1.67); p = 0.0305] and pneumonia [middle tertile: HR 0.93 (95% CI 0.80-1.07); upper tertile: HR 1.27 (95% CI 1.11-1.45); p = 0.0001]. Other subgroups did not exhibit statistically significant correlations. The results are presented in Table 3.

4. Discussion

In this study, we examined the ability of NLR to predict mortality in a cohort of AKI patients admitted to the ICU. The main finding of our analysis is the association of a higher level of NLR with increased risk of 30-day and 90-day mortality after adjusting for the important confounders.

The NLR is a combination of neutrophil and lymphocyte counts that serves as a readily available biomarker of systemic inflammation that was shown to predict the prognostic outcome of patients. Leithead et al.

Table 3
Subgroup analysis of the associations between mortality and the neutrophil–lymphocyte ratio.

	NLR of 30-day mortality					NLR of in-hospital mortality					NLR of 90-day mortality				
	N	< 5.55	5.55–12.14	> 12.14	P for interaction	N	< 5.55	5.55–12.14	> 12.14	P for interaction	N	< 5.55	5.55–12.14	> 12.14	P for interaction
AKI stage					NS					NS					NS
1	3579	1.0	1.27 (1.03, 1.58)	1.81 (1.47, 2.23)		3579	1.0	1.18 (0.93, 1.49)	1.74 (1.38, 2.18)		3579	1.0	1.30 (1.09, 1.56)	1.83 (1.54, 2.18)	
2	2148	1.0	1.29 (0.99, 1.69)	1.45 (1.11, 1.88)		2148	1.0	1.17 (0.88, 1.55)	1.44 (1.10, 1.88)		2148	1.0	1.16 (0.93, 1.45)	1.31 (1.06, 1.63)	
3	7951	1.0	1.24 (1.09, 1.41)	1.77 (1.57, 2.00)		7951	1.0	1.25 (1.08, 1.44)	1.83 (1.60, 2.09)		7951	1.0	1.18 (1.05, 1.32)	1.67 (1.51, 1.85)	
RRT					NS					0.0362					0.0418
No	12462	1.0	1.26 (1.12, 1.40)	1.78 (1.61, 1.98)		12462	1.0	1.21 (1.07, 1.37)	1.81 (1.62, 2.03)		12462	1.0	1.20 (1.09, 1.32)	1.69 (1.55, 1.85)	
Yes	1216	1.0	1.20 (0.91, 1.59)	1.37 (1.05, 1.79)		1216	1.0	1.20 (0.91, 1.58)	1.35 (1.03, 1.76)		1216	1.0	1.22 (0.97, 1.55)	1.33 (1.06, 1.68)	
CHF					NS					NS					NS
No	11077	1.0	1.33 (1.18, 1.49)	1.78 (1.60, 1.98)		11077	1.0	1.31 (1.16, 1.48)	1.83 (1.63, 2.05)		11077	1.0	1.26 (1.14, 1.39)	1.68 (1.53, 1.84)	
Yes	2601	1.0	1.06 (0.82, 1.37)	1.64 (1.29, 2.08)		2601	1.0	0.94 (0.71, 1.24)	1.52 (1.17, 1.98)		2601	1.0	1.09 (0.90, 1.33)	1.61 (1.33, 1.95)	
AF					NS					NS					NS
No	9856	1.0	1.26 (1.11, 1.43)	1.74 (1.54, 1.96)		9856	1.0	1.24 (1.08, 1.43)	1.84 (1.62, 2.09)		9856	1.0	1.21 (1.08, 1.34)	1.68 (1.52, 1.87)	
Yes	3822	1.0	1.24 (1.04, 1.49)	1.77 (1.50, 2.10)		3822	1.0	1.16 (0.96, 1.40)	1.64 (1.37, 1.96)		3822	1.0	1.20 (1.04, 1.39)	1.62 (1.41, 1.86)	
Choric renal disease					NS					NS					NS
No	11210	1.0	1.24 (1.10, 1.39)	1.72 (1.55, 1.92)		11210	1.0	1.16 (1.02, 1.31)	1.71 (1.53, 1.92)		11210	1.0	1.18 (1.07, 1.30)	1.65 (1.50, 1.80)	
Yes	2468	1.0	1.32 (1.04, 1.67)	1.87 (1.49, 2.34)		2468	1.0	1.54 (1.17, 2.01)	2.08 (1.61, 2.69)		2468	1.0	1.32 (1.09, 1.59)	1.74 (1.45, 2.09)	
Choric liver disease					NS					NS					NS
No	12662	1.0	1.21 (1.09, 1.36)	1.74 (1.57, 1.93)		12662	1.0	1.18 (1.04, 1.33)	1.77 (1.58, 1.98)		12662	1.0	1.18 (1.08, 1.30)	1.67 (1.53, 1.83)	
Yes	1016	1.0	1.52 (1.14, 2.02)	1.99 (1.49, 2.64)		1016	1.0	1.46 (1.08, 1.96)	1.96 (1.46, 2.63)		1016	1.0	1.39 (1.09, 1.78)	1.75 (1.36, 2.24)	
COPD					NS					NS					NS
No	13276	1.0	1.27 (1.15, 1.42)	1.77 (1.60, 1.95)		13276	1.0	1.23 (1.10, 1.38)	1.78 (1.61, 1.99)		13276	1.0	1.23 (1.12, 1.34)	1.68 (1.55, 1.83)	
Yes	402	1.0	0.75 (0.39, 1.45)	1.26 (0.73, 2.18)		402	1.0	0.86 (0.40, 1.84)	1.41 (0.74, 2.68)		402	1.0	0.73 (0.43, 1.23)	1.18 (0.76, 1.83)	
CAD					0.0029					0.0103					< 0.0001
No	10326	1.0	1.17 (1.04, 1.31)	1.56 (1.40, 1.75)		10326	1.0	1.16 (1.03, 1.32)	1.60 (1.42, 1.79)		10326	1.0	1.10 (1.00, 1.21)	1.46 (1.33, 1.61)	
Yes	3352	1.0	1.57 (1.26, 1.96)	2.35 (1.90, 2.91)		3352	1.0	1.39 (1.08, 1.78)	2.34 (1.85, 2.95)		3352	1.0	1.60 (1.33, 1.93)	2.34 (1.96, 2.80)	
Stroke					NS					NS					NS
N	12373	1.0	1.26 (1.12, 1.41)	1.82 (1.64, 2.03)		12373	1.0	1.24 (1.10, 1.40)	1.86 (1.66, 2.09)		12373	1.0	1.21 (1.10, 1.33)	1.71 (1.57, 1.87)	
Yes	1305	1.0	1.30 (1.01, 1.68)	1.56 (1.21, 2.02)		1305	1.0	1.17 (0.89, 1.53)	1.51 (1.16, 1.97)		1305	1.0	1.25 (1.00, 1.56)	1.53 (1.22, 1.92)	
Malignancy					0.0351					0.0281					0.0305
No	11236	1.0	1.38 (1.22, 1.56)	1.87 (1.66, 2.10)		11236	1.0	1.35 (1.19, 1.54)	1.89 (1.67, 2.14)		11236	1.0	1.32 (1.19, 1.47)	1.76 (1.59, 1.95)	
Yes	2442	1.0	1.05 (0.86, 1.28)	1.47 (1.23, 1.76)		2442	1.0	0.97 (0.77, 1.21)	1.50 (1.23, 1.82)		2442	1.0	1.06 (0.90, 1.25)	1.45 (1.25, 1.67)	
ARDS					NS					NS					NS
No	13381	1.0	1.26 (1.13, 1.40)	1.77 (1.60, 1.95)		13381	1.0	1.22 (1.09, 1.36)	1.79 (1.61, 1.99)		13381	1.0	1.22 (1.11, 1.33)	1.68 (1.55, 1.83)	
Yes	297	1.0	1.12 (0.62, 2.02)	1.07 (0.61, 1.87)		297	1.0	1.26 (0.66, 2.40)	1.08 (0.58, 2.03)		297	1.0	0.99 (0.59, 1.65)	0.99 (0.61, 1.59)	
Pneumonia					0.0007					< 0.0001					0.0001
No	9544	1.0	1.40 (1.23, 1.59)	1.85 (1.63, 2.10)		9544	1.0	1.39 (1.21, 1.61)	1.94 (1.69, 2.23)		9544	1.0	1.33 (1.19, 1.48)	1.75 (1.58, 1.95)	
Yes	4134	1.0	0.94 (0.79, 1.12)	1.35 (1.15, 1.57)		4134	1.0	0.89 (0.74, 1.06)	1.28 (1.09, 1.51)		4134	1.0	0.93 (0.80, 1.07)	1.27 (1.11, 1.45)	
Vasoactive drug					0.0009					< 0.0001					0.0575
No	8777	1.0	1.45 (1.24, 1.70)	2.03 (1.74, 2.37)		8777	1.0	1.40 (1.16, 1.69)	2.17 (1.81, 2.60)		8777	1.0	1.27 (1.12, 1.43)	1.76 (1.56, 1.98)	
Yes	4901	1.0	1.13 (0.98, 1.30)	1.37 (1.21, 1.56)		4901	1.0	1.13 (0.99, 1.30)	1.36 (1.19, 1.54)		4901	1.0	1.16 (1.02, 1.31)	1.41 (1.26, 1.58)	

NLR: neutrophil–lymphocyte ratio; N: number; AKI: Acute renal injury; RRT: renal replacement therapy; CHF: congestive heart failure; AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; CAD: coronary heart disease; ARDS: Acute Respiratory Distress Syndrome.
HRs were adjusted for age; gender; ethnicity.

[32] reported that NLR value > 5 was correlated with high mortality in patients waiting for liver transplantation. Another retrospective study reported by Biyik et al. [33] indicated that stable cirrhotic patients exhibiting NLR > 4.39 had a lower survival probability. Additionally, a higher NLR was associated with an increased mortality risk in patients receiving chemotherapy or undergoing resection of colorectal liver metastasis [34,35]. Templeton et al. [17] conducted a meta-analysis of one hundred studies to demonstrate that NLR > 4 was associated with an adverse overall survival in many solid tumors. Finally, Forget et al. [15] reported that an increased NLR was associated with more complications seven days after major abdominal surgery. However, no study has so far identified the mechanistic relationship of NLR and outcome, and most studies explain poor outcomes as being related to inflammation.

The association of NLR with mortality may be explained by the inflammatory process associated with AKI. Ischemia reperfusion injury and inflammation have been suggested to play critical roles in AKI development [36–38]. Acute ischemic insult can activated endothelial renal cells that express adhesion molecules, thus facilitating adhesion of inflammatory blood cells [39]. Neutrophil and lymphocyte are known to be a potential surrogate marker of inflammation [40]. The level of neutrophils increase with the systemic inflammatory response, and lymphocyte count is inversely correlated with inflammation, resulting in higher NLR [41]. Severe inflammation with high neutrophils may cause shock and sepsis and contribute to the mortality. In sepsis-induced AKI, the pathophysiological mechanisms are not yet fully defined, and have been recently attributed to immunologic and inflammatory mechanisms [42]. The severe inflammation with high neutrophils caused by sepsis could induce multi-organ failure (MOF), and AKI patients admitted to the ICU with sepsis exhibited a further increase in mortality rate [43]. Taken together, high neutrophils could result in a high NLR in patients with AKI and could lead to high mortality. Although severe inflammation is associated with high mortality in AKI patients, other factors appeared to contribute to poor outcomes.

The subgroup analysis of 30-day mortality, in-hospital mortality and 90-day mortality revealed that AKI patients with CAD had a higher risk of mortality, and this risk was higher for higher NLR. Several studies reported an association of higher NLR with increased risk of CAD and mortality [44–46]. Interestingly, we found that AKI patients with malignancy or pneumonia had a lower risk of mortality, the risk was higher for higher NLR. Cancer patients of IUC are typically older, more likely to be admitted after surgery, more commonly suffered from sepsis, with a higher incidence of nephrotoxicity induced by targeted therapies, and one study [47] reported that these patients have the highest hospital mortality rate. One analysis [48] summarized 15 studies and showed that the mortality of AKI cancer patients was higher than that of non-AKI cancer patients. This study that examined the AKI aspect lacked a comparison with subjects without cancer. Given the important role of inflammation in the pathophysiology of AKI, we speculated that low mortality might be related to the immunosuppression of tumors. Regulatory T cells and tumor-associated macrophages are significant components of the microenvironment of solid tumors that inhibit the inflammatory response [49–51], and play an important role in the protection of AKI [52,53], this result should be further verified. However, higher NLR has been reported to be associated with increased risk of morbidity and mortality in several cancers [17,54–56]. The risk of AKI is higher following pneumonia [57,58], and recent studies reported that AKI patients with pneumonia exhibited higher immune response and a worse prognosis [58,59], although this should be further verified. Our analysis also revealed that AKI Patients who used vasoactive drugs had significantly lower risks of 30-day mortality and in-hospital mortality, and AKI Patients who received RRT had significantly lower risks of in-hospital mortality, with an even higher risk associated with higher NLR. However, a previous analysis found that the use of vasoactive drugs and RRT were risk factors of in-hospital death among critically ill patients with AKI [60,61]. Clearly, additional research into the relationships between RRT, vasoactive drug use and NLR is required.

Our study was the first study to investigate if NLR can be used as a biomarker to predict the mortality of critically ill patients with AKI. This study included a large number of participants, improving the reliability of the results. Limitations of this study should also be acknowledged. First, our study was a retrospective observational study with the inherent biases of this type of analysis. Second, the NLR was determined only upon admission to the ICU, at the same time, we lost some samples, the selection bias cannot be ignored. Third, we could not obtain some essential data such as income, insurance status, residence (rural or urban) and education which related to social support, which might relevant to mortality. Fourth, owing to lack of related data, we did not assess the modification of sepsis and shock, which might predict higher mortality among patients with AKI. Finally, the single measure of NLR does not fully reflect the extent of inflammation, and the simultaneous measurement of other inflammatory mediators would allow more comprehensive analysis. Such limitations limit the generalizability of the results.

5. Conclusions

Our analysis indicates that a higher level of NLR is associated with increased risk of 30-day and 90-day mortality in AKI patients. The similar upward trend is not detected in analysis of in-hospital mortality. Our findings need to be further confirmed by other studies, especially for large prospective studies.

Acknowledgements

We thank the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University for supporting the work of our study.

References

[1] N. Pannu, M. James, B. Hemmelgarn, S. Klarenbach, Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge, Clin. J. Am. Soc. Nephrol. 8 (2013) 194–202.
[2] S. Uchino, J.A. Kellum, R. Bellomo, G.S. Doig, H. Morimatsu, S. Morgera, M. Schetz, I. Tan, C. Bouman, E. Macedo, Acute renal failure in critically Ill patients, J. Am. Med. Assoc. 294 (2010) 813–818.
[3] X. Xu, S. Nie, Z. Liu, C. Chen, G. Xu, Y. Zha, J. Qian, B. Liu, S. Han, A. Xu, X. Xu, F.F. Hou, Epidemiology and clinical correlates of AKI in Chinese hospitalized adults, Clin. J. Am. Soc. Nephrol. 10 (2015) 1510–1518.
[4] Y. Fang, X. Ding, Y. Zhong, J. Zou, J. Teng, Y. Tang, J. Lin, P. Lin, Acute kidney injury in a chinese hospitalized population, Blood Purif. 30 (2010) 120–126.
[5] J.P. Lafrance, D.R. Miller, Acute kidney injury associates with increased long-term mortality, J. Am. Soc. Nephrol. 21 (2010) 345.
[6] R. Aviles-Gomez, V.H. Luquin-Arellano, G. Garcia-Garcia, M. Ibarra-Hernandez, G. Briseño-Renteria, Is renal replacement therapy for all possible in developing countries? Ethn. Dis. 16 (2006) 70–72.
[7] M. Ostermann, J. Cerda, The burden of acute kidney injury and related financial issues, Contrib. Nephrol. 193 (2018) 100–112.
[8] J.V. Bonventre, L. Yang, Cellular pathophysiology of ischemic acute kidney injury, J. Clin. Invest. 121 (2011) 4210–4221.
[9] M. Ostermann, K. Liu, Pathophysiology of AKI, Best Pract. Res. Clin. Anaesthesiol. 31 (2017) 305.
[10] R. Jeeha, D.L. Skinner, K.D. Vasconcellos, N.P. Magula, Serum procalcitonin levels predict acute kidney injury in critically ill patients, Nephrology (2017).
[11] W.H. Kim, Y.P. Ji, S.H. Ok, I.W. Shin, J.T. Sohn, Association between the neutrophil/lymphocyte ratio and acute kidney injury after cardiovascular surgery: a retrospective observational study, Medicine 94 (2015) e1867.
[12] C.F. Zheng, W.Y. Liu, F.F. Zeng, M.H. Zheng, H.Y. Shi, Y. Zhou, J.Y. Pan, Prognostic value of platelet-to-lymphocyte ratios among critically ill patients with acute kidney injury, Crit. Care 21 (2017) 238.
[13] H.J. Oh, J.T. Park, J.K. Kim, D.E. Yoo, S.J. Kim, S.H. Han, S.W. Kang, K.H. Choi, T.H. Yoo, Red blood cell distribution width is an independent predictor of mortality in acute kidney injury patients treated with continuous renal replacement therapy, Nephrol. Dial. Transplant. 27 (2012) 589–594.
[14] C.H. Koo, J.D. Eun, Y.S. Park, J. Bae, Y.J. Cho, W.H. Kim, J.H. Bahk, Neutrophil, lymphocyte, and platelet counts and acute kidney injury after cardiovascular surgery, J. Cardiothorac. Vasc. Anesth. 32 (2017) 212–222.
[15] P. Forget, V. Dinant, K.M. De, Is the neutrophil-to-lymphocyte ratio more correlated than C-reactive protein with postoperative complications after major abdominal

surgery? Peer J. 3 (2015) e713.
[16] N. Moreau, X. Wittebole, Y. Fleury, P. Forget, P.F. Laterre, C.Z. Diego, Neutrophil-to-lymphocyte ratio predicts death in acute-on-chronic liver failure patients admitted to the intensive care unit: A retrospective cohort study, Shock 1 (2017).
[17] A.J. Templeton, M.G. Mcnamara, B. Šeruga, F.E. Verabadillo, P. Aneja, A. Ocaña, R. Leibowitzamit, G. Sonpavde, J.J. Knox, B. Tran, Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis, J. Natl. Cancer Inst. 106 (2014) dju124.
[18] A.E. Johnson, T.J. Pollard, L. Shen, L.W. Lehman, M. Feng, M. Ghassemi, B. Moody, P. Szolovits, L.A. Celi, R.G. Mark, MIMIC-III, a freely accessible critical care database, Sci. Data 3 (2016) 160035.
[19] G. Eknoyan, N. Lameire, R. Barsoum, K.U. Eckardt, A. Levin, N. Levin, F. Locatelli, A. MacLeod, R. Vanholder, R. Walker, H. Wang, The burden of kidney disease: improving global outcomes, Kidney Int. 66 (2004) 1310–1314.
[20] R.L. Mehta, J.A. Kellum, S.V. Shah, B.A. Molitoris, C. Ronco, D.G. Warnock, A. Levin, A.A. Lastname, Acute kidney injury network: Report of an initiative to improve outcomes in acute kidney injury, (2007).
[21] Askoolum A. Structured query language. System building with APL+ Win. 447-77.
[22] J.L. Vincent, R. Moreno, J. Takala, S. Willatts, A. De Mendonca, H. Bruining, C.K. Reinhart, P.M. Suter, L.G. Thijs, The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure, On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine, Intensive Care Med. 22 1996, pp. 707–710.
[23] G. Teasdale, G. Murray, L. Parker, B. Jennett, Adding up the Glasgow coma score, Acta Neurochir. Suppl. (Wien). 28 (1979) 13–16.
[24] J.-L. Vincent, A. De Mendonça, F. Cantraine, R. Moreno, J. Takala, P.M. Suter, C.L. Sprung, F. Colardyn, S. Blecher, Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study, Crit. Care Med. 26 (1998) 1793–1800.
[25] C. Jones, Glasgow coma scale, LWW, 1979.
[26] R.J. Tallarida, R.B. Murray, Chi-square test, Manual of Pharmacologic Calculations, Springer, 1987, pp. 140–142.
[27] G.J. Upton, Fisher's exact test, J. R. Stat. Soc. Ser. A (Stat. Soc.) (1992) 395–402.
[28] P.E. McKight, J. Najab, Kruskal-Wallis test, Corsini Encyclopedia of Psychology, 2010.
[29] D.Y. Lin, L.-J. Wei, The robust inference for the Cox proportional hazards model, J. Am. Stat. Assoc. 84 (1989) 1074–1078.
[30] E.R. Mansfield, B.P. Helms, Detecting multicollinearity, Am. Stat. 36 (1982) 158–160.
[31] V.W. Jaddoe, L.L. de Jonge, A. Hofman, O.H. Franco, E.A. Steegers, R. Gaillard, First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study, BMJ 348 (2014) g14.
[32] J.A. Leithead, N. Rajoriya, B.K. Gunson, J.W. Ferguson, Neutrophil-to-lymphocyte ratio predicts mortality in patients listed for liver transplantation, Liver Int. 35 (2015) 502–509.
[33] M. Biyik, R. Ucar, Y. Solak, G. Gungor, I. Polat, A. Gaipov, O.O. Cakir, H. Ataseven, A. Demir, S. Turk, H. Polat, Blood neutrophil-to-lymphocyte ratio independently predicts survival in patients with liver cirrhosis, Eur. J. Gastroenterol. Hepatol. 25 (2013) 435–441.
[34] K.J. Halazun, A. Aldoori, H.Z. Malik, A. Al-Mukhtar, K.R. Prasad, G.J. Toogood, J.P.A. Lodge, Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases, Eur. J. Surg. Oncol. J. Eur. Soc. Surg. Oncol. Br. Assoc. Surg. Oncol. 34 (2008) 55–60.
[35] Y. Kishi, S. Kopetz, Y.S. Chun, M. Palavecino, E.K. Abdalla, J.N. Vauthey, Blood neutrophil-to-lymphocyte ratio predicts survival in patients with colorectal liver metastases treated with systemic chemotherapy, Ann. Surg. Oncol. 16 (2009) 614–622.
[36] J.V. Bonventre, A. Zuk, Ischemic acute renal failure: an inflammatory disease? Kidney Int. 66 (2004) 480–485.
[37] A.A. Sharfuddin, B.A. Molitoris, Pathophysiology of ischemic acute kidney injury, Nat. Rev. Nephrol. 7 (2011) 189–200.
[38] C. Hu, Y. Sheng, Z. Qian, Current understanding of inflammatory responses in acute kidney injury, Curr. Gene Ther. 17 (2017) 405–410.
[39] C. Rotunno, D. Paparella, G. Scrascia, P. Guida, L.D.L.T. Schinosa, Anti-inflammatory strategies to reduce acute kidney injury in cardiac surgery patients: a meta-analysis of randomized controlled trials, Artif. Organs 38 (2014) 101–112.
[40] P.H. Gibson, B.L. Croal, B.H. Cuthbertson, G.R. Small, A.I. Ifezulike, G. Gibson, R.R. Jeffrey, K.G. Buchan, H. Elshafei, G.S. Hillis, Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting, Am. Heart J. 154 (2007) 995–1002.
[41] S.R. Ommen, R.J. Gibbons, D.O. Hodge, S.P. Thomson, Usefulness of the lymphocyte concentration as a prognostic marker in coronary artery disease, Am. J. Cardiol. 79 (1997) 812–814.
[42] 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 (2017) 351–359.
[43] N.H. Lameire, A. Bagga, D. Cruz, M.J. De, Z. Endre, J.A. Kellum, K.D. Liu, R.L. Mehta, N. Pannu, B.W. Van, Acute kidney injury: an increasing global concern, Lancet 382 (2013) 170–179.
[44] N. Shah, V. Parikh, N. Patel, N. Patel, A. Badheka, A. Deshmukh, A. Rathod, J. Lafferty, Neutrophil lymphocyte ratio significantly improves the Framingham risk score in prediction of coronary heart disease mortality: insights from the National Health and Nutrition Examination Survey-III, Int. J. Cardiol. 171 (2014) 390–397.
[45] C. Yu, M. Chen, Z. Chen, G. Lu, Predictive and prognostic value of admission neutrophil-to-lymphocyte ratio in patients with CHD, Herz 41 (2016) 605–613.
[46] G.Y. Zhang, M. Chen, Z.M. Yu, X.D. Wang, Z.Q. Wang, Relation between neutrophil-to-lymphocyte ratio and severity of coronary artery stenosis, Genet. Mol. Res. 13 (2014) 9382–9389.
[47] F.S. Taccone, A.A. Artigas, C.L. Sprung, R. Moreno, Y. Sakr, J.L. Vincent, Characteristics and outcomes of cancer patients in European ICUs, Crit. Care 13 (2009) R15.
[48] N. Lameire, R. Vanholder, W. Van Biesen, D. Benoit, Acute kidney injury in critically ill cancer patients: an update, Crit. Care 20 (2016) 209.
[49] T. Fujimura, Y. Kambayashi, Y. Fujisawa, T. Hidaka, S. Aiba, Tumor-associated macrophages: therapeutic targets for skin cancer, Front. Oncol. 8 (2018) 3.
[50] Y. Ning, K. Shen, Q. Wu, X. Sun, Y. Bai, Y. Xie, J. Pan, C. Qi, Tumor exosomes block dendritic cells maturation to decrease the T cell immune response, Immunol. Lett. 199 (2018) 36–43.
[51] W. Ou, R. Thapa, L. Jiang, Z. Soe, M. Gautam, J. Chang, J. Jeong, S. Ku, H. Choi, C. Yong, J. Kim, Regulatory T cell-targeted hybrid nanoparticles combined with immuno-checkpoint blockage for cancer immunotherapy, J. Control. Release 281 (2018) 84–96.
[52] G.R. Kinsey, R. Sharma, L. Huang, L. Li, A.L. Vergis, H. Ye, S.-T. Ju, M.D. Okusa, Regulatory T cells suppress innate immunity in kidney ischemia-reperfusion injury, J. Am. Soc. Nephrol. 20 (2009) 1744–1753.
[53] V.P. Persy, A. Verhulst, D.K. Ysebaert, K.E. De Greef, M.E. De Broe, Reduced postischemic macrophage infiltration and interstitial fibrosis in osteopontin knockout mice, Kidney Int. 63 (2003) 543–553.
[54] N.S. Demirci, G.U. Erdem, Prognostic role of the neutrophil-to-lymphocyte ratio (NLR) in patients with operable ampullary carcinoma, Bosn J. Basic Med. Sci. 18 (2017) 268–274.
[55] M. DZ, R. Karamert, H. Tutar, M. Sahin, A. Turkcan, M. Yilmaz, Diagnostic role of neutrophil-lymphocyte ratio in oral cavity cancers, Niger. J. Clin. Pract. 21 (2018) 49–53.
[56] T. Mochizuki, T. Kawahara, D. Takamoto, K. Makiyama, Y. Hattori, J.I. Teranishi, Y. Miyoshi, Y. Yumura, M. Yao, H. Uemura, The neutrophil-to-lymphocyte ratio (NLR) predicts adrenocortical carcinoma and is correlated with the prognosis, BMC Urol. 17 (2017) 49.
[57] T.Y. Lin, Y.G. Chen, C.L. Lin, C.H. Kao, Increased risk of acute kidney injury following Pneumococcal Pneumonia: A Nationwide Cohort Study, PLoS One 11 (2016) e0158501.
[58] R. Murugan, V. Karajala-Subramanyam, M. Lee, S. Yende, L. Kong, M. Carter, D.C. Angus, J.A. Kellum, Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival, Kidney Int. 77 (2010) 527–535.
[59] L.S. Chawla, R.L. Amdur, C. Faselis, P. Li, P.L. Kimmel, C.E. Palant, Impact of acute kidney injury in patients hospitalized with pneumonia, Crit. Care Med. 45 (2017) 600–606.
[60] P.G. Metnitz, C.G. Krenn, H. Steltzer, T. Lang, J. Ploder, K. Lenz, J.R. Le Gall, W. Druml, Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients, Crit. Care Med. 30 (2002) 2051–2058.
[61] G.B. Silva Junior, F. Daher Ede, R.M. Mota, F.A. Menezes, Risk factors for death among critically ill patients with acute renal failure, Sao Paulo Med. J. 124 (2006) 257–263.