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CLINICAL STUDY

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High neutrophil-to-lymphocyte ratio as a cost-effective marker of acute kidney injury and in-hospital mortality after cardiac surgery: a case-control study

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ABSTRACT

Background: Inflammation is one of the important pathophysiological characteristics of acute kidney injury (AKI) after cardiac surgery. The aim was to explore the relationship between preoperative neutrophil-to-lymphocyte ratio (NLR), a simple and cost-effective maker of inflammatory response, and AKI after cardiac surgery. Furthermore, whether the NLR affected in-hospital mortality was also investigated.

Methods: The electronic medical records of patients from January 1, 2006 to December 31, 2018 undergoing cardiac surgery were utilized. The interest outcome was AKI, defined as the criteria of Kidney Disease Improving Global Outcomes (KDIGO), and other outcomes were severe AKI (KDIGO stage ≥2) and in-hospital mortality. Logistic regression was utilized to assess the association of preoperative NLR with outcomes while adjust for potential confounders.

Results: Totally, 23,638 patients were included. The incidence of AKI was 27.6%. The NLR was significantly greater in patients with AKI compared to those without. As the nonlinear relationship between NLR and AKI indicated by restricted cubic spline, NLR was analyzed as a categorical variable with the cutoff value of five. Multivariate analysis demonstrated that NLR > 5 was significantly associated with an increased risk of AKI, with an odds ratio of 5.046 (95% confidence interval, 4.589 to 5.548), when compared to patients with NLR ≤ 5. Furthermore, high NLR was also an independent risk factor for severe AKI and in-hospital mortality.

Conclusions: A higher preoperative NLR was increased the risk of AKI, severe AKI, and in-hospital mortality after cardiac surgery, which may be helpful for stratifying patients to develop individualized treatment.

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Cardiac surgery; acute kidney injury; neutrophil-to-lymphocyte ratio; risk factor

Introduction

Acute kidney injury (AKI) frequently occurs as a complication after cardiac surgery, with the prevalence varied from 2% to 50% depending on different populations and diagnostic criteria [1]. AKI, even mild and transient, is related with increased risk of development of chronic kidney disease and mortality in the long term [2]. Currently, early identification of high-risk groups of AKI is particularly important due to limited effective treatment for AKI.

Inflammation is one of the most noted and crucial pathogenesis of AKI after cardiac surgery [3]. As a simple utilization and inexpensive maker of the inflammatory-related response, neutrophil-to-lymphocyte ratio (NLR) can be calculated directly from complete blood count of the patients [4]. NLR might be a novel predictor for AKI in septic patients [5]. However, limited by small sample sizes, disease heterogeneity, or including some patients with autoimmune diseases or infections who may have a significant impact on the NLR measurements in previous reports [6–9], the relationship between preoperative NLR and AKI after cardiac surgery

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remains unclear. Thus, we aimed to further evaluate the association between preoperative NLR and AKI after cardiac surgery, and also hypothesized that NLR would be associated with the severity of AKI and in-hospital mortality.

Materials and methods

Study design and population

A retrospective study received approval from the Ethics Committee of our Hospital (No. GDREC2018416H) was conducted and adhered to the ethical guidelines outlined in the Declaration of Helsinki. Due to the retrospective, the committee approved the anonymous analysis of the data without requiring participants' informed consent.

This was an unmatched case-control study. The data for all adult patients accepted cardiac surgery with cardiopulmonary bypass at our hospital (tertiary teaching hospital) from January 1, 2006 to December 31, 2018 were analyzed. We excluded the following patients: renal replacement therapy prior to cardiac surgery; history of unilateral nephrectomy; cardiac transplantation; preoperative critical state; emergency surgery; no serum creatinine values were available within 7 days after surgery; preoperative NLR were not obtained; the length of hospital stay after the procedure was less than or equal to 24 h; acute infective endocarditis or the accuracy of NLR measurement may be altered by conditions such as autoimmune diseases, receiving immunosuppressants, or immunodeficiency diseases. If two or more surgeries were performed, only the data of the first surgery were analyzed. Preoperative critical state was defined as the criteria of European System for Cardiac Operative Risk Evaluation II [10].

The sample size was determined using PASS software version 2021. As previously stated, the expected odds ratio of AKI was 1.45 [6]. Considering a presumed 5% prevalence of high NLR exposure in the control group [7], a type I error rate of 0.05, and a desired power of 0.9, with an estimated incidence of AKI post-cardiac surgery at approximately 22.3%, the calculated minimum sample size required was 8570.

Data *collection* and *variables* definitions

Data of each enrolled patient was extracted from electronic medical record system of our hospital. We reviewed the variables of patients based on clinical judgment and previous literature [3]. Demographic characteristics, comorbidities, history of surgery, left ventricular ejection fraction (LVEF), baseline estimated glomerular filtration rate (eGFR), records of medication administration within a week prior to surgery, surgical procedure and preoperative laboratory tests were reviewed. We also analyzed intraoperative variables, such as red blood cell (RBC) transfusion, cardiopulmonary bypass (CPB) time, intra-aortic balloon pump (IABP), and early postoperative variables (duration of mechanical ventilation, IABP, sepsis, RBC transfusion and resurgery). Preoperative laboratory tests were extracted the latest laboratory results before surgery after admission. NLR was calculated as the ratio of absolute neutrophil count to lymphocyte count. A baseline serum creatinine level was used to calculate the baseline eGFR using the Chronic Kidney Disease-Epidemiology Collaboration formula [11]. The baseline serum creatinine level was determined as the lowest recorded creatinine level within a period of up to three months prior to hospital admission. In cases where the creatinine value before admission was not available, the lowest recorded value of serum creatinine observed during the patient's hospitalization prior to surgery was used. Early postoperative variables were recorded within 48 h after surgery. Sepsis was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [12].

Outcomes

The interest outcome was AKI, defined according to the criteria of Kidney Disease Improving Global Outcomes (KDIGO), which was an increase in serum creatinine levels by at least 0.3 mg/dL with 48 h after surgery or an increase of 50% from baseline within 7 days post-surgery [13]. The staging of AKI was also classified according to the KDIGO criteria. Baseline serum creatinine definition was detailed in section of data collection and variables definitions. Other outcomes of interest were severe AKI (KDIGO stage $\geq$ 2) and in-hospital mortality.

Statistical analysis

Data cleaning and quality control were conducted before data analysis. Outliers were identified by boxplot and clinical judgment. To minimize the effect of extreme values, continuous variables (LVEF, eGFR, CPB time, and NLR) were trimmed at the 1st and 99th percentiles. For handling missing data, we employed multiple imputations using chained equations, iterated 30 times, and consolidated according to the rules of Rubin [14]. Continuous variables were shown as mean ± standard deviation or median (interquartile distance), and compared with T-test or Mann-Whitney U test. Categorical variables were described by frequency (percentage), and compared with using Chi-square test or Fisher exact probability method.

Potential nonlinear relationship between preoperative NLR and the risk of AKI was analyzed using restricted cubic spline. Then, NLR was analyzed as a categorical variable. The optimal cutoff value for NLR calucated using Youden index was five. Logistic regression was used to evaluate the association of preoperative NLR with AKI while adjust for potential confounders with three modles. Modle 1 was only adjusted for age and male. Modle 2 was additionally adjusted for comorbidities. Model 3 was fully adjusted for all covariates included age, male, comorbidities, LVEF, eGFR, history of transfusion, recent contrast media exposure, preoperative drugs use, procedures, laboratory findings (hemoglobin, platelet, magnesemia < 0.8 mmol/L, uric acid), intraoperative variables (CPB time, RBC transfusion, IABP) and postoperative variables (duration of mechanical ventilation, IABP, resurgery, spesis, RBC transfusion). The relationships between NLR and other outcomes were also analyzed by using logistic regression.

To test the stability of the results, several sensitivity analyses were performed. NLR was analyzed as a continuous variable instead of a dichotomous variable for outcomes in logistic regression analysis. In addition, propensity-score matching analysis was used to balance possible baseline confounders between patients with NLR above 5 and patients with NLR less or equal 5. By using calipers with width of 0.05 of the standard deviation of the logit of the propensity-score, the propensity-scores of the two groups were matched one-to-one. Standardized differences were used to validate covariate balances after matching. A standardized difference of more than 10% was considered imbalanced after propensity-score matching [15]. The outcomes between the two groups were analyzed using Chi-square test or Fisher exact probability method. Finally, the main analysis was assessed only in participants with complete data (no missing data for all variables).

All analyses were computed using R software (version 4.2.1; https://www.r-project.org). The p-value of <0.05 was definded as statistical significance.

Results

Baseline characteristics

Totally, 29,328 adult patients with cardiac surgery were screened. After excluding 5,690 patients, the remaining 23,638 patients were ultimately enrolled, as shown in Figure 1. Only six variables with missing data, the proportion of missing data in variables ranged from 2.2% to 25.7%. The number of missing data were shown in Table S1. Among patients, 11,424 (48.3%) were males and the median age was 50.0 (38.0, 60.0) years. The incidence of AKI was 27.6% ($n = 6525$). Similarly, that of in hospital mortality was observed to be 0.80% ($n = 189$). The basal characteristics of patients were shown in Table 1.

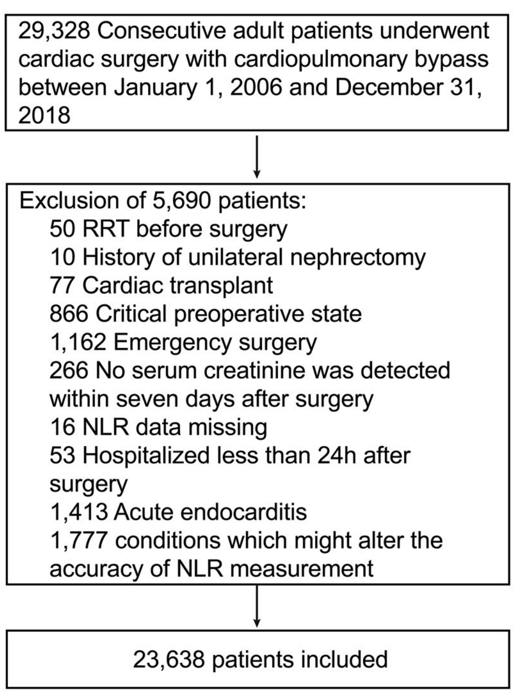

Figure 1. Flow chart for selection of participants. NLR; neutrophil-to-lymphocyte ratio; RRT: renal replacement therapy

NLR and outcomes

The median preoperative NLR in patients with AKI was greater than that in patients without AKI (Figure 2). The restricted cubic spline curve indicated a nonlinear relationship between the AKI risk and NLR, *P* value for nonlinear trend less than 0.001 (Figure 3). Then, NLR was analyzed as a categorical variable. The optimal cutoff value for NLR calucated using Youden index was five. Compared with patients with NLR ≤5, patients with NLR >5 tend to be older, male, lower eGFR, higher incidence of comorbidities, such as hypertension, and prolonged ventilation, detailed in Table 1.

Univariate analysis indicated that NLR >5 was associated with increased AKI risk (unadjusted OR equal 6.016, 95%CI 5.585, 6.480). The basal characteristics of subjects grouped by the occurrence of AKI were presented in Table S2. Apart from NLR, several potential confounders, such as eGFR, hypertension, were related with AKI. Adjusting for confounding factors in different models revealed the same relationships between NLR and AKI. After adjusting for fully potential confounders, compared with reference, patients with NLR >5 was independently associated with a high risk of AKI (adjusted OR equal 5.046, 95%CI 4.589, 5.548). Furthermore, we also explored the relationships between NLR and other clinical outcomes in logistic regression. NLR >5 was also an independent risk factor for severe AKI and in-hospital mortality, were presented in Table 2.

Sensitivity analyses

To confirm the main results, several sensitivity analyses were carried out. Firstly, a higher NLR analyzed as a continuous variable remained as an independent risk factor for AKI and other clinical outcomes in logistic regression, Table S3. Secondly, patients with NLR ≤5 and those with NLR >5 were matched using propensity score analyses. A total of 3514 pairs of matched patients were obtained using propensity score matching. Patient characteristics before and after propensity score matching were shown in Table S4. As shown in Figure 4, the dot plot indicated the standardized differences for each factor before and after propensity score matching. The standardized mean differences for each factor were less than 0.1 after propensity matching. Confounding factors after matching were balanced between two groups. In the matched patients, the rate of AKI was lower in patients with NLR ≤5 than that in patients with NLR >5 (35.3% vs 60.4%, $p < 0.001$). Compared with patients with NLR ≤5, a greater percentage of other clinical outcomes, including severe AKI and in-hospital mortality, were found in patients with NLR

Table 1. Clinical characteristics of patients.

Variables	Total (*n* = 23638)	NLR< =5 (*n* = 19916)	NLR > 5 (*n* = 3722)	*P*-value
Age, years	50.0 (38.0,60.0)	50.0 (37.0,59.0)	54.0 (43.0,63.0)	<0.001
Age, years				<0.001
Age <60	17593 (74.4%)	15188 (76.3%)	2405 (64.6%)	
60 ≤ Age <75	5789 (24.5%)	4559 (22.9%)	1230 (33.0%)	
Age ≥75	256 (1.1%)	169 (0.8%)	87 (2.3%)	
Male	11424 (48.3%)	9279 (46.6%)	2145 (57.6%)	<0.001
LVEF, %				<0.001
LVEF ≤40%	738 (3.1%)	522 (2.6%)	216 (5.8%)	
40% <LVEF ≤60%	5768 (24.4%)	4691 (23.6%)	1077 (28.9%)	
LVEF >60%	17132 (72.5%)	14703 (73.8%)	2429 (65.3%)	
eGFR, ml/min/1.73m^2	88.1 (69.1,104.1)	90.8 (73.1,105.9)	68.8 (44.0,91.0)	<0.001
eGFR, ml/min/1.73m^2				<0.001
15 < eGFR <30	663 (2.8%)	238 (1.2%)	425 (11.4%)	
30 ≤ eGFR <45	1132 (4.8%)	600 (3.0%)	532 (14.3%)	
45 ≤ eGFR <60	2047 (8.7%)	1456 (7.3%)	591 (15.9%)	
60 ≤ eGFR <90	8610 (36.4%)	7414 (37.2%)	1196 (32.1%)	
eGFR ≥90	11186 (47.3%)	10208 (51.3%)	978 (26.3%)	
Comorbidities				
Hypertension	5157 (21.8%)	4002 (20.1%)	1155 (31.0%)	<0.001
Diabetes mellitus	1351 (5.7%)	1022 (5.1%)	329 (8.8%)	<0.001
Coronary heart disease	2751 (11.6%)	2052 (10.3%)	699 (18.8%)	<0.001
PCI history	288 (1.2%)	210 (1.1%)	78 (2.1%)	<0.001
COPD	337 (1.4%)	249 (1.3%)	88 (2.4%)	<0.001
Previous cardiac surgery	683 (2.9%)	540 (2.7%)	143 (3.8%)	<0.001
Cerebrovascular disease	1035 (4.4%)	817 (4.1%)	218 (5.9%)	<0.001
Peripheral vascular disease	113 (0.5%)	78 (0.4%)	35 (0.9%)	<0.001
Atrial fibrillation	6674 (28.2%)	5656 (28.4%)	1018 (27.4%)	0.20
History of transfusion	56 (0.2%)	41 (0.2%)	15 (0.4%)	0.04
Recent contrast media exposure	5429 (23.0%)	4676 (23.5%)	753 (20.2%)	<0.001
Preoperative drugs use				
Renin-angiotensin system inhibitors	8045 (34.0%)	6401 (32.1%)	1644 (44.2%)	<0.001
NSAID	3203 (13.6%)	2512 (12.6%)	691 (18.6%)	<0.001
Stain	3313 (14.0%)	2588 (13.0%)	725 (19.5%)	<0.001
Proton pump inhibitors	10305 (43.6%)	8405 (42.2%)	1900 (51.0%)	<0.001
Procedure				<0.001
CABG	1303 (5.5%)	996 (5.0%)	307 (8.2%)	
Valve	14598 (61.8%)	12444 (62.5%)	2154 (57.9%)	
Aortic	1744 (7.4%)	1201 (6.0%)	543 (14.6%)	
CHD	4795 (20.3%)	4365 (21.9%)	430 (11.6%)	
CABG + valve	844 (3.6%)	602 (3.0%)	242 (6.5%)	
Others	354 (1.5%)	308 (1.5%)	46 (1.2%)	
Laboratory Findings				
Baseline serum creatinine, μmol/L	79.0 (65.0,96.3)	77.0 (64.0,92.0)	96.3 (76.0,140.8)	<0.001
Hemoglobin, g/L	136.0 (124.7,145.6)	137.0 (126.0,147.0)	130.2 (115.3,137.8)	<0.001
Platelet (×10^9/L)	200.0 (162.6,236.8)	199.0 (163.6,237.4)	207.3 (157.0,230.3)	0.39
Neutrophil count (×10^9/L)	3.8 (3.0,5.0)	3.6 (2.8,4.4)	6.9 (4.9,10.8)	<0.001
Lymphocyte count (×10^9/L)	2.0 (1.5,2.5)	2.1 (1.7,2.6)	0.9 (0.7,1.2)	<0.001
Magnesium < 0.8 mmol/L	18750 (79.3%)	15744 (79.1%)	3006 (80.8%)	0.02
Uric acid, μmol/L	409.0 (329.0,458.0)	399.3 (325.0,457.0)	430.7 (367.0,465.0)	<0.001
Intraoperative variables				
CPB time	126.8 (110.0,126.8)	114.0 (110.0,126.8)	126.8 (126.8,130.0)	<0.001
RBC transfusion,Units	0.0 (0.0,4.0)	0.0 (0.0,4.0)	2.0 (0.0,6.0)	<0.001
IABP	184 (0.8%)	121 (0.6%)	63 (1.7%)	<0.001
Postoperative variables				
Duration of mechanical ventilation,h	9.0 (3.0,20.0)	9.0 (3.0,19.0)	10.5 (1.0,25.0)	<0.001
IABP	409 (1.7%)	255 (1.3%)	154 (4.1%)	<0.001
Resurgery	794 (3.4%)	609 (3.1%)	185 (5.0%)	<0.001
Sepsis	98 (0.4%)	46 (0.2%)	52 (1.4%)	<0.001
RBC transfusion, U	0.0 (0.0,1.0)	0.0 (0.0,0.0)	0.0 (0.0,3.0)	<0.001
Outcomes				
AKI	6525 (27.6%)	4224 (21.2%)	2301 (61.8%)	<0.001
AKI stage				<0.001
1	4393 (18.6%)	2942 (14.8%)	1451 (39.0%)	
2	1454 (6.2%)	938 (4.7%)	516 (13.9%)	
3	678 (2.9%)	344 (1.7%)	334 (9.0%)	
Severe AKI	2132(9.0%)	1282(6.4%)	850(22.8%)	<0.001
Inhospital mortality	189 (0.8%)	108 (0.5%)	81 (2.2%)	<0.001

Values are median (interquartile range) or n (%).

AKI: acute kidney injury; CABG: coronary artery bypass grafting; CHD: congenital heart disease; COPD: chronic obstructive pulmonary disease; CPB: cardiopulmonary bypass; eGFR: estimated glomerular filtration rate; IABP: intra-aortic balloon pump; LVEF: left ventricular ejection fraction; NLR: neutrophil-to-lymphocyte ratio; NSAID: non-steroidal anti-inflammatory drugs; PCI: percutaneous coronary intervention; RBC: red blood cell.

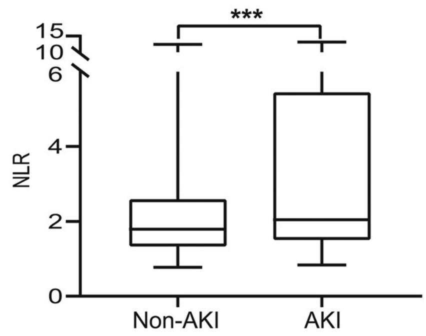

Figure 2. Boxplot of the preoperative NLR level in patients with AKI or not. AKI: acute kidney injury; NLR: neutrophil-to-lymphocyte ratio

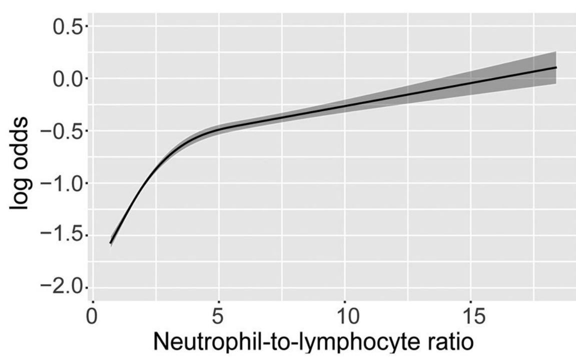

Figure 3. Nonlinear relationship between preoperative NLR and the risk of AKI after cardiac surgery using restricted cubic spline. *P* value for nonlinear trend less than 0.001. AKI: acute kidney injury; NLR: neutrophil-to-lymphocyte ratio

>5 (Table 3). Finally, the main analysis was carried out only in participants with complete data ($n=14482$). Baseline characteristics and outcomes of patients were shown in Table S5. Similarly, those stratifed by NLR in complete data were also indicated in Table S5. Compared with patients with NLR≤ 5, patients with NLR > 5 tend to be a high incidence of AKI, severe AKI, and in-hospital mortality. After adjusting for confounding factors, their effects did not change in complete data (Table S6).

Table 2. Association of preoperative NLR above five with AKI after cardiac surgery and in-hospital mortality.

Variables	Odds ratio (95% CI)	*P*-value
AKI		
Unadjusted	6.016 (5.585,6.480)	<0.001
Model 1	5.617 (5.192,6.077)	<0.001
Model 2	5.514 (5.094,5.969)	<0.001
Model 3	5.046 (4.589,5.548)	<0.001
AKI stage (none AKI as the reference)		
AKI stage 1		
Unadjusted	5.446 (5.012,5.918)	<0.001
Model 1	5.088 (4.665,5.551)	<0.001
Model 2	5.037 (4.615,5.497)	<0.001
Model 3	4.809 (4.355,5.310)	<0.001
AKI stage 2		
Unadjusted	6.075 (5.386,6.852)	<0.001
Model 1	5.739 (5.072,6.493)	<0.001
Model 2	5.624 (4.967,6.368)	<0.001
Model 3	5.471 (4.758,6.292)	<0.001
AKI stage 3		
Unadjusted	10.722 (9.136, 12.583)	<0.001
Model 1	9.868 (8.385,11.613)	<0.001
Model 2	9.325 (7.913,10.989)	<0.001
Model 3	6.753 (5.544,8.225)	<0.001
Severe AKI		
Unadjusted	4.302 (3.911,4.731)	<0.001
Model 1	3.724 (3.378,4.106)	<0.001
Model 2	3.582 (3.246,3.952)	<0.001
Model 3	2.628 (2.334,2.960)	<0.001
In-hospital mortality		
Unadjusted	4.080 (3.052,5.454)	<0.001
Model 1	3.834 (2.854,5.152)	<0.001
Model 2	3.584 (2.660,4.830)	<0.001
Model 3	1.836 (1.277,2.640)	0.001

NLR ≤5 was used as the reference.
Logistic regression: model 1 was adjusted for age and male; model 2 was adjusted for age, male and comorbidities; model 3 was adjusted for age, male, comorbidities, LVEF (LVEF >60%, 40%< LVEF ≤60%, LVEF ≤40%), eGFR, history of transfusion, recent contrast media exposure, preoperative drugs use, Procedure, laboratory findings (hemoglobin, platelet, magnesium< 0.8 mmol/L, uric acid), intraoperative variables and postoperative variables in Table 1.
AKI: acute kidney injury; CI: confidence interval; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NLR: neutrophil-to-lymphocyte ratio; RBC: red blood cell.

Discussion

Based on clinical data from 23,638 patients with cardiac surgery, we found that a higher preoperative NLR was increased the risk of AKI after cardiac surgery. Alternately, increased preoperative NLR was also independently related with the development of severe AKI and in-hospital mortality. For patients with a higher preoperative NLR, such as NLR greater than 5, the intensity of clinical management should be escalated to mitigate the incidence of AKI after cardiac surgery and improve the prognosis. Our findings may help clinicians risk stratify patients to improve AKI screening and personalized management to optimize the effective use of available resources and improve prognosis.

A meta-analysis consisted of 320,086 patients with cardiac surgery, the pooled incidence of AKI was 22.3% [1]. Similar to previous reports, the prevalence of AKI was 27.6% in our study. However, the in-hospital mortality of 0.8% in present study was slightly lower than that reported in previous reports, which shown the in-hospital mortality of 1% to 3% [16,17]. This phenomenon may be attributed to several reasons. First, patients with preoperative critical conditions or patients underwent emergency surgery were excluded in present study. As is well known, preoperative critical condition and emergency surgery were independent risk factors for in-hospital mortality. Additionally, in the current study, the prevalence of comorbidities, such as hypertension and diabetes, were found to be lower than in previous studies involving Western populations. These comorbidities serve as independent risk factors for in-hospital mortality. Finally, due to the influence of Confucian culture and folk customs, some patients nearing the end of their lives choose passed away at home rather than hospital.

NLR, obtained from blood routine testing which was the most common test for patients, was the ratio of neutrophil to lymphocyte. Since it was not easily influenced by dehydration or edema, NLR might be more stable as a ratio than

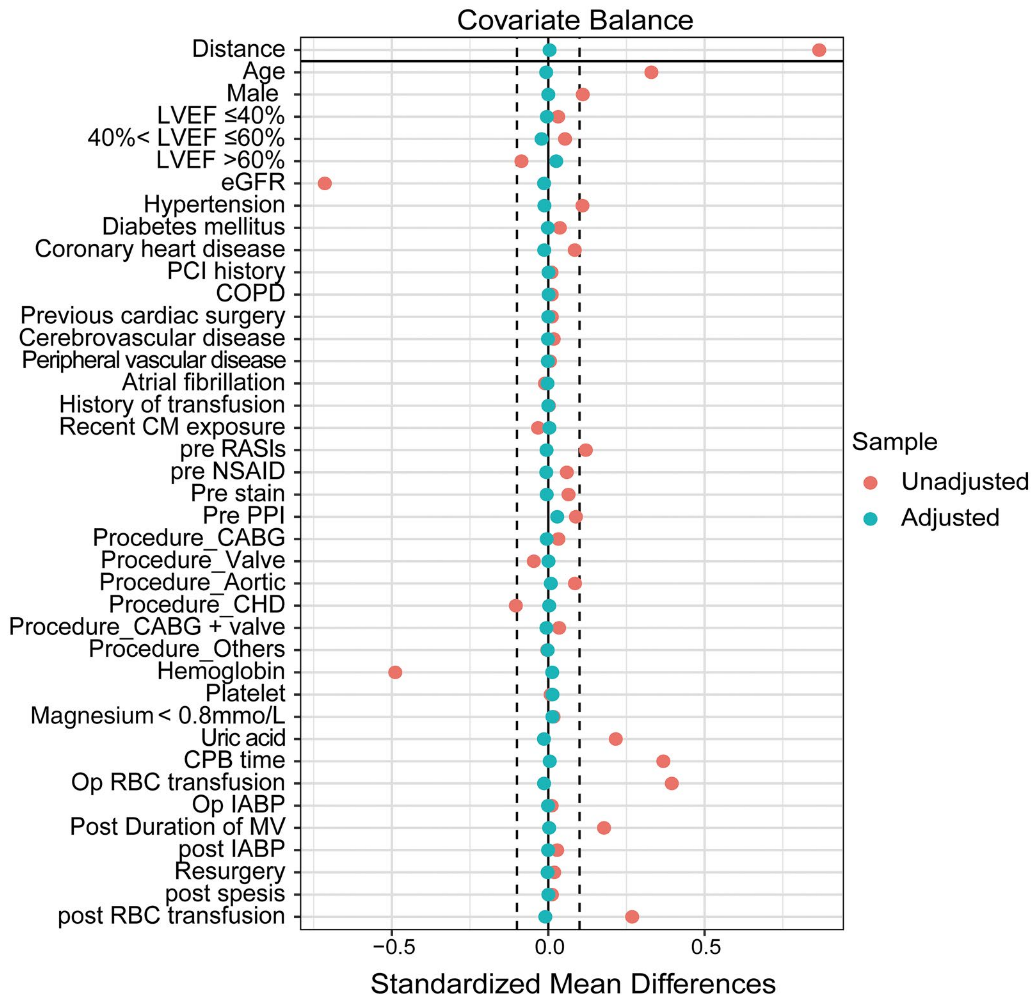

Figure 4. Standardized differences in variables were analyzed between patients exhibiting a NLR exceeding five and those with an NLR of five or less. Differences prior to matching were represented by red circles, while post-matching differences were indicated by green circles. The application of propensity score matching served to effectively minimize discrepancies in baseline characteristics between the two cohorts. CABG: coronary artery bypass grafting; CHD: congenital heart disease; CM: contrast media; COPD: chronic obstructive pulmonary disease; CPB: cardiopulmonary bypass; eGFR: estimated glomerular filtration rate; IABP: intra-aortic balloon pump; LVEF: left ventricular ejection fraction; MV: mechanical ventilation; NSAID: non-steroidal anti-inflammatory drugs; PCI: percutaneous coronary intervention; PPI: proton pump inhibitors; RASIs: renin-angiotensin system inhibitors; RBC: red blood cell.

Table 3. Outcomes after propensity score matching.

Outcomes	Total (*n* = 7028)	NLR< =5 (*n* = 3514)	NLR > 5 (*n* = 3514)	*P*-value
AKI	3363 (47.9%)	1239 (35.3%)	2124 (60.4%)	<0.001
AKI stage				<0.001
1	2190 (31.2%)	816 (23.2%)	1374 (39.1%)	
2	749 (10.7%)	269 (7.7%)	480 (13.7%)	
3	424 (6.0%)	154 (4.4%)	270 (7.7%)	
Severe AKI	1173 (16.7%)	423 (12.0%)	750 (21.3%)	<0.001
Inhospital mortality	122 (1.7%)	55 (1.6%)	67 (1.9%)	0.32

AKI: acute kidney injury.

individual blood parameters such as neutrophil. NLR, combined both innate immunity and acquired immunity, was an accurate indicator of evaluating the inflammatory state of the body. NLR was associated with disease progression, severity and mortality in critically ill [5]. However, the relationship between NLR before cardiac surgery and postoperative AKI and prognosis remain unclear. A meta-analysis based on low quality evidence and consisted of ten studies with 7,760 patients indicated preoperative NLR increased the risk of AKI [6], while in another study of 906 cardiac surgery patients without infectious endocarditis indicated the preoperative NLR was not correlated with AKI [8]. Kim et al. reported the incidence of AKI after cardiac surgey was 28.1% which was a slightly higher than that in our study and also found preoperative NLR could not predict AKI [9]. A another study consisted of 3, 249 patients with valve surgery shown a high NLR was associated with a higher risk of AKI in univariate analysis. Unfortunately, the relationship between NLR and AKI after adjusting for confounding factors was unavailable [7]. Hence, we enrolled 23,638 patients with cardiac surgery to explore the relationship between NLR and AKI. We found a higher preoperative NLR might increase the risk of postoperative AKI.

The potential pathophysiological mechanisms underlying the relationship between NLR and AKI after cardiac surgery may be attributable to the following aspects. Firstly, inflammation is one of the proposed mechanisms of the postoperative AKI. NLR, represented the proportion between the innate immune response and the adaptive immune response, has recently been demonstrated to be a stronger marker of inflammation than either the absolute neutrophil count or the absolute lymphocyte count alone [18]. A high NLR was marked by reduced lymphocytes and elevated neutrophils. A low lymphocyte count indicates a decline in health status and may contribute to the dysregulation of the immune response during cardiac surgery. Neutrophils promote inflammation and stimulate the release of inflammatory mediators, such as, oxygen free radicals, myeloperoxidase, and elastase. The adhesion of neutrophils to endothelial cells and erythrocytes may lead to capillary congestion, potentially impairing oxygen delivery to organ systems such as the kidney. The activation of neutrophils may elevate serum levels of arachidonic acid metabolites, thereby reducing the response to vasodilation and causing vasoconstriction. These reactions have the potential to induce endothelial dysfunction or heightened vascular permeability, which may result in renal ischemia and elevate the risk of renal injury [19]. Additionally, an increase in NLR might indicate a potentially deleterious inflammatory state before surgery. During cardiac surgery, particularly with the use of cardiopulmonary bypass, blood interacts with non-biological surfaces, activating the complement system and coagulation pathways, thereby exacerbating the preexisting inflammatory state and worsening kidney injury [3,20]. Finally, consistent with prior reports [21], patients exhibiting elevated preoperative NLR demonstrated a greater prevalence of comorbid conditions, including hypertension or diabetes, which were recognized risk factors for AKI.

Preoperative NLR may be associated with poor prognosis after cardiac surgery. Recently, a retrospective study of 1,694 patients found that a higher preoperative NLR was associated with high 30-day mortality following cardiac surgery [22]. Similar to previous reported, the present study shown that for preoperative NLR above five, the risk of in-hospital mortality rose by 54% after adjusting for confounders.

For the significance of our work, we emphasize the following aspects. Firstly, The findings shown in present study may be helpful to make individualized and precision medicine decision. For patients with preoperative NLR exceeding five, monitoring might be strengthened during surgery, and treatment options optimized as soon as possible, such as adjustment of surgical methods and the choice of antibiotics. Futhermore, it may be beneficial to recruit patients at high-risk to assess the effects of interventions on kidney function in clinical studies. Finally, preoperative NLR may be considered to construct a risk prediction model for AKI or in-hospital mortality in patients with cardiac surgery in the future.

The present study has following strengths. First, to our knowledge, the sample size of present study was one of the largest collected so far, with 23,638 patients with cardiac surgery. Hence, the results might be robustness and reliability because data from sufficient number of subjects were available for analysis. In addition, previous studies explored the relationship between NLR and AKI did not specify whether patients with NLR values affected by some conditions, such as autoimmune diseases, were included or not. As suggested by some scholars, the present study tied to exclude these patients to reduce potential bias [6]. Finally, in order to improve the rigor of the results, a series of sensitivity analyses was conducted.

Naturally, there are some flaws. Firstly, the study was a single-center and retrospective study. Due to the nature of retrospective, the effect of dynamic NLR values on AKI and their effect on kidney function after discharge were not evaluated, which was also the direction of our future research. Additionally, there were some variables with missing values in present study. Missing data for some variables were unavoidable in most clinical studies, especially in retrospective studies. Patients with missing data were removed roughly, which may induce bias in the results. As recommended by previous studies, missing data were imputed using multiple imputations. To increase the stability of the results, the main analysis were conducted in the complete data and the results did not change fundamentally. Furthermore, several biomarkers might be simple markers of early phase of kidney dysfunction. However, the value of these biomarkers has yet to be investigated. In the absence of current alternatives to serum creatinine, diagnosis of AKI was still based on creatinine or urine volume [23]. To facilitate homogeneous description and better knowledge of AKI epidemiology worldwide, the KDIGO issued a clinical practice guideline that proposed a diagnostic criteria AKI based on variations in serum creatinine or urine volume, which was the most widely accepted international diagnostic criteria for AKI. Due to the retrospective nature of the present study, there was a large number of missing data for urine volume, which was susceptible to affected by fluid loading and by the use and dose of diuretics. Similar to previous studies, only the serum creatinine-based criterion of KDIGO was used for AKI diagnosis in present study. Finally, NLR may be a non-modifiable risk factor for AKI after cardiac surgery. Whether prophylactic use of antibiotics could reduce the incidence of AKI and improve prognosis remained unclear.

Conclusion

The present study provided insights into the value of preoperative NLR on AKI and in-hospital mortality in patients with cardiac surgery. A higher preoperative NLR was increased the risk of AKI, severe AKI, and in-hospital mortality after cardiac surgery It may be helpful for stratifying patients to develop individualized treatment and precision medicine. For patients at high risk, renal function monitoring and treatment options should be optimized to reduce postoperative AKI and improve prognosis in clinical practice.

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Authors' contributions

Penghua Hu, Huaban Liang, Yuanhan Chen, Xinling Liang, and Yanhua Wu were responsible for designing the study; Penghua Hu, Huaban Liang, Hong Chu, Zhi Zhao, Zhiming Mo, Li Song, Li Zhang, and Zhilian Li for collecting the data; Penghua Hu, Huaban Liang, Lei Fu, and Yiming Tao were in charge of statistical analysis. Penghua Hu and Huaban Liang drafted the manuscript; Shuangxin Liu, Zhiming Ye, Yuanhan Chen, Xinling Liang, and Yanhua Wu revised and commented the manuscript. Yanhua Wu supervised the whole project, provided valueable comments and obtained funding. Each author read and approved the final version of the manuscript.

Ethics approval

All procedures carried out in present study involving human subjects were complied with the ethical standards of the institutional and/or national research committee, as well as with the Helsinki Declaration of 1964 and its subsequent updates or equivalent ethical standards. The Institutional Ethics Committee of Guangdong Provincial People's Hospital granted approval for this study (No. GDREC2018416H).

Consent to participate

Patient consent was waived due to the retrospective nature of data analysis and complete anonymization.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare that they have no conflict of interest.

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Data availability statement

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

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