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Association Between Neutrophil-to-Lymphocyte Ratio and Acute Kidney Injury After Cardiac Surgery: A Multicenter Observational Study

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ABSTRACT

Introduction: Cardiac surgery-associated acute kidney injury (CSA-AKI) is a frequent complication that increases morbidity, mortality, and resource use. The neutrophil-to-lymphocyte ratio (NLR), derived from a routine complete blood count, is an inexpensive marker of systemic inflammation that may aid early risk stratification. We evaluated the association between perioperative NLR and CSA-AKI in a multicenter cohort of adults undergoing cardiac surgery.

Methods: We conducted a multicenter observational cohort study reported in accordance with the STROBE statement across five cardiac surgery centers in Indonesia. Adults (≥18 years) who underwent cardiac surgery with available complete blood count differentials and perioperative creatinine and urine output monitoring were included. NLR was measured preoperatively, at intensive care unit (ICU) arrival, and on postoperative day 1. The primary outcome was AKI within 7 days, as defined by the KDIGO criteria. Associations were estimated using multivariable mixed-effects logistic regression with a random intercept for the center, prespecified confounder adjustment, restricted cubic splines for non-linearity, propensity score analyses, and multiple imputation.

Results: We analyzed data of 2, 847 patients; CSA-AKI occurred in 24.1% (n=686), of whom 32.4% met KDIGO stages 2–3. Higher perioperative NLR was independently associated with CSA-AKI (adjusted odds ratio 1.71, 95% CI 1.48–1.97 per 1 SD of log-NLR), with consistent estimates across all three measurement windows and in propensity-score analyses. Model discrimination yielded an area under the curve of 0.79 (95% CI 0.77–0.81).

Conclusion: Elevated perioperative NLR was independently associated with CSA-AKI. As a low-cost, routinely available biomarker, NLR may support early identification of high-risk patients pending prospective validation.

Keywords

Neutrophil-to-Lymphocyte Ratio, Acute Kidney Injury, Cardiac Surgery, KDIGO, Inflammation, Risk Stratification

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INTRODUCTION

Cardiac surgery-associated acute kidney injury (CSA-AKI) is among the most common complications after cardiac surgery, with a reported incidence that has remained persistently in the range of approximately 20–

30% despite decades of preventive research [1-4]. Even mild, transient elevations in serum creatinine after cardiac surgery are associated with prolonged hospitalization, greater resource use, progression to chronic kidney disease, and increased short- and long-term mortality [5,6]. The persistence of this burden underscores the continuing need for simple, scalable tools that identify high-risk patients early enough to guide protective strategies.

The pathophysiology of CSA-AKI is multifactorial and includes renal hypoperfusion, ischemia–reperfusion injury, hemolysis with free-iron release, oxidative stress, and a pronounced systemic inflammatory response triggered by surgical trauma and cardiopulmonary bypass (CPB) [5]. Inflammation occupies a central position in this cascade, with activation of innate immunity and dysregulated leukocyte trafficking contributing to renal tubular injury. This mechanistic background motivates interest in inflammation-related biomarkers that are inexpensive and widely available. The neutrophil-to-lymphocyte ratio (NLR), calculated from the absolute neutrophil and lymphocyte counts of a routine complete blood count (CBC) with differential, is an integrative marker of the balance between innate (neutrophil-driven) and adaptive (lymphocyte-mediated) immune responses to physiological stress [7]. The NLR requires no additional sampling or cost beyond standard perioperative laboratory testing, making it operationally attractive across diverse healthcare settings, including resource-limited environments. Prior single-center studies have reported associations between elevated perioperative NLR and CSA-AKI, and a systematic review and meta-analysis has summarized the prognostic signals across cohorts, although heterogeneity in NLR timing, thresholds, AKI definitions, and risk of bias remains a recognized limitation of the existing literature [8].

Two methodological gaps are particularly relevant. First, many studies are single-center and may not generalize across surgical case-mix and perioperative practice. Second, the optimal timing of NLR measurement (preoperative versus early postoperative) and its incremental value over established clinical risk factors are not firmly established [9]. Therefore, we conducted a multicenter observational cohort study to evaluate the association between perioperative NLR—measured preoperatively, at intensive care unit (ICU) arrival, and on postoperative day 1—and CSA-AKI defined according to KDIGO criteria, with prespecified confounder adjustment, appropriate handling of center-level clustering, and propensity-score and sensitivity analyses to probe robustness.

METHOD

Study design and setting

We conducted a multicenter observational cohort study to evaluate the association between perioperative NLR and CSA-AKI. The study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. Participating centers provided adult cardiac surgery services and were able to extract perioperative laboratory data and urine output records for at least the first 7 postoperative days using a shared data dictionary and standardized quality-control procedures. Five centers contributed data over the study period from January 2022 to December 2024.

Ethics and Oversight

The study was approved by the institutional review board/ethics committee of each participating center ([IRB names/IDs]). For retrospective data collection, informed consent was [waived/obtained] in accordance with local regulations. For prospective enrollment, written informed consent was obtained from the participants or their legally authorized representatives. All procedures adhered to the principles of the Declaration of Helsinki.

Participants

We included adult patients (age ≥18 years) who underwent cardiac surgery ([CABG, valve, combined, and/or aortic surgery]) with or without CPB. Eligible patients had at least one preoperative serum creatinine value, postoperative creatinine monitoring sufficient for AKI ascertainment, and a CBC with differential at the prespecified measurement window(s) required to compute the NLR. We excluded patients with pre-existing maintenance kidney replacement therapy or prior kidney transplantation, missing or implausible preoperative

creatinine levels precluding baseline definition, and AKI at baseline. Patients with active hematologic malignancies or immunosuppressive therapy expected to markedly distort the leukocyte differential were also excluded. Surgery for active endocarditis was performed according to a prespecified rule. Consecutive eligible patients were enrolled to minimize selection bias.

Baseline Creatinine Definition

Because the baseline creatinine reference materially affects the KDIGO classification, we prespecified a primary definition with sensitivity analyses. The primary baseline was the most recent stable outpatient serum creatinine measured 7–365 days before surgery when available; otherwise, the preoperative value obtained within 24 hours before incision was used. Sensitivity analyses applied the lowest preoperative value within 7 days, and where no prior value existed, a back-calculated estimate assuming a baseline eGFR of 75 mL/min/1.73 m² (clearly labeled and tested separately).

Exposure: Neutrophil-to-Lymphocyte Ratio

NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count from a CBC with a differential count. Three measurement windows were prespecified: preoperative NLR (CBC within 6–24 h before surgery), ICU-arrival NLR (first CBC within 0–2 h of ICU arrival), and postoperative day 1 (POD1) NLR (CBC obtained 6–24 h after ICU arrival). In the primary analysis, NLR was modeled as a continuous variable (log-transformed to reduce skew) with nonlinearity assessed using restricted cubic splines. Secondary analyses used prespecified quartiles and literature-informed thresholds for propensity score analyses.

Outcome: Acute Kidney Injury

The primary outcome was postoperative AKI within 7 days, defined by KDIGO criteria using serum creatinine and, where available, urine output: an increase in serum creatinine ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours, or an increase to ≥1.5 times baseline known or presumed within the prior 7 days, or urine output <0.5 mL/kg/h for 6 hours. AKI severity was staged 1–3 according to KDIGO. Secondary outcomes included KDIGO stage 2–3 AKI and the need for kidney replacement therapy.

Covariates and Prespecified Confounders

Confounders were prespecified from clinical knowledge and established CSA-AKI risk models, including demographics (age, sex, body mass index), baseline kidney function (baseline creatinine/eGFR, chronic kidney disease), comorbidities (diabetes mellitus, hypertension, heart failure, peripheral vascular, and chronic lung disease), cardiac status (left ventricular ejection fraction, urgent/emergent surgery), and operative variables (procedure type, CPB and aortic cross-clamp time, and intraoperative transfusion). Variables on the causal pathway (e.g., early postoperative vasopressor requirement) were treated as potential mediators and examined separately to avoid over-adjustment.

Sample Size Considerations

The sample size was guided by the events-per-variable (EPV) principle for logistic regression: $N \approx (EPV \times k)/p$, where k is the number of effective parameters and p the event proportion. Assuming a CSA-AKI incidence of 24% and approximately 22 effective parameters with a target EPV of 15, the final analytic sample of 2,847 patients provided excellent statistical power and stability for a well-adjusted multivariable model with non-linearity terms; power for a threshold-based exposure was cross-checked using established logistic-regression methods.

Statistical Analysis

Continuous variables are summarized as mean (SD) or median (IQR), and categorical variables as counts (percentages). Baseline characteristics across NLR categories were compared using standardized mean differences (SMD) rather than p-values. The primary estimand was the adjusted association between NLR and CSA-AKI, expressed as an odds ratio (OR) with 95% CI, estimated with a mixed-effects logistic regression

including a random intercept for center and prespecified confounders, with log(NLR) modeled using restricted cubic splines.

Robustness was examined through propensity-score analyses defining "high NLR" by a prespecified threshold, using inverse probability of treatment weighting and nearest-neighbor matching with covariate balance assessed by SMD. Missing data were handled by multiple imputation by chained equations ($m \geq 20$), pooled using Rubin's rules. Model performance was assessed by discrimination (area under the ROC curve) and calibration (calibration plot and slope). Additional sensitivity analyses used a creatinine-only KDIGO definition and alternative baseline-creatinine definitions. A two-sided α of 0.05 defined statistical significance. Analyses were performed in R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Among 3,156 patients screened, 309 were excluded (mainly for missing baseline creatinine or NLR data), leaving 2,847 patients in the analytic cohort (Figure 1). The median age was 65 years (IQR 57–72) and 33.8% were female. Using the KDIGO criteria, postoperative AKI occurred in 24.1% (n=686), of whom 32.4% (n=222) met KDIGO stages 2–3 and 4.8% (n=33) required kidney replacement therapy. Baseline characteristics across preoperative NLR quartiles are presented in Table 1.

Table 1. Baseline characteristics of the study cohort, stratified by preoperative NLR quartile

Characteristic	Q1 (lowest)	Q2	Q3	Q4 (highest)	SMD
Age, years, mean (SD)	62.4 (9.8)	64.1 (10.2)	65.8 (10.5)	67.9 (11.1)	0.21
Female sex, n (%)	248 (34.8)	239 (33.6)	241 (33.9)	234 (32.9)	0.04
Body mass index, kg/m², mean (SD)	24.8 (3.9)	25.1 (4.1)	25.4 (4.3)	25.9 (4.6)	0.18
Baseline eGFR, mL/min/1.73 m²	78.2 (18.4)	74.5 (19.1)	71.3 (20.2)	67.8 (22.5)	0.29
Diabetes mellitus, n (%)	142 (19.9)	168 (23.6)	195 (27.4)	231 (32.5)	0.25
Hypertension, n (%)	412 (57.8)	428 (60.1)	451 (63.4)	478 (67.2)	0.19
LVEF <50%, n (%)	98 (13.7)	112 (15.7)	134 (18.8)	167 (23.5)	0.22
CPB time, min, median (IQR)	92 (68–118)	98 (72–125)	105 (78–138)	118 (85–152)	0.31
Emergent surgery, n (%)	45 (6.3)	58 (8.1)	71 (10.0)	89 (12.5)	0.18

Note: Between-group balance across quartiles is summarized using standardized mean differences (SMD) rather than p-values. SD, standard deviation; IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass.

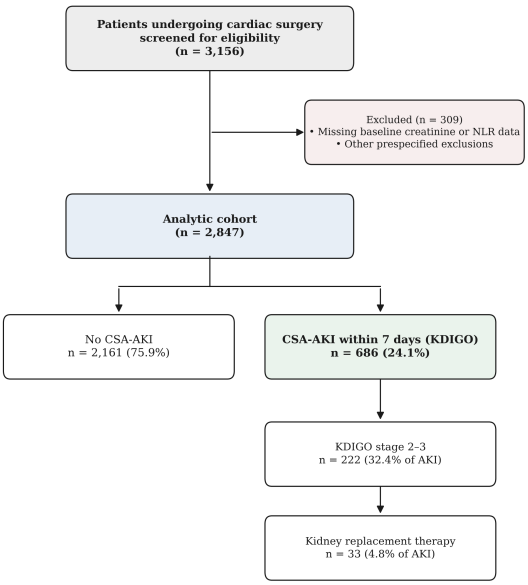

Figure 1. Participant flow diagram (STROBE) showing screening, exclusions, the final analytic cohort (n = 2,847), and distribution of cardiac surgery–associated acute kidney injury (CSA-AKI) by KDIGO stage and need for kidney replacement therapy.

In the primary multivariate mixed-effects logistic regression adjusting for prespecified confounders and center-level clustering, higher preoperative log(NLR) was independently associated with CSA-AKI (adjusted OR 1.71, 95% CI 1.48–1.97 per 1 SD increase). Comparable associations were observed for ICU-arrival NLR (adjusted OR 1.84, 95% CI 1.59–2.13) and postoperative day 1 NLR (adjusted OR 1.62, 95% CI 1.40–1.88; Table 2).

Table 2. Adjusted association between perioperative NLR and cardiac surgery-associated AKI (multivariable mixed-effects logistic regression).

Exposure (per 1 SD of log-NLR)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
Preoperative NLR	1.92 (1.68–2.19)	1.71 (1.48–1.97)	<0.001
ICU-arrival NLR	2.05 (1.79–2.35)	1.84 (1.59–2.13)	<0.001
Postoperative day 1 NLR	1.78 (1.55–2.04)	1.62 (1.40–1.88)	<0.001

Note: Models were adjusted for prespecified confounders (age, sex, body mass index, baseline eGFR, diabetes, hypertension, LVEF, procedure type, CPB and cross-clamp time, transfusion, and emergent status) with a random intercept for the center. OR: odds ratio; CI: confidence interval; SD: standard deviation; NLR: neutrophil-to-lymphocyte ratio; ICU: intensive care unit.

The adjusted model demonstrated an area under the ROC curve of 0.79 (95% CI 0.77–0.81; Figure 2). Calibration plots showed close agreement between the predicted and observed AKI risk, with a calibration slope of 0.95 (Figure 3).

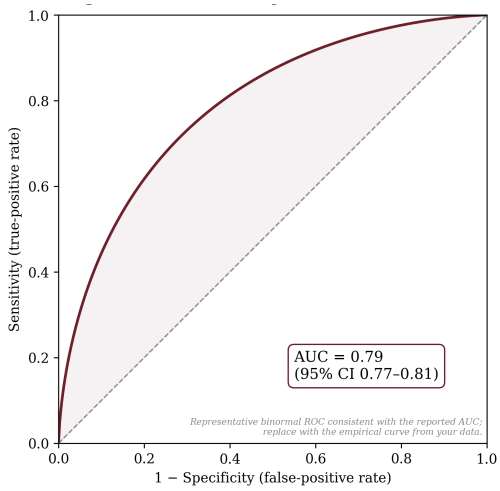

Figure 2. Receiver operating characteristic (ROC) curve for the adjusted model predicting CSA-AKI (AUC = 0.79, 95% CI: 0.77–0.81). The curve shown is a representative binormal ROC consistent with the reported AUC and should be replaced with the empirical ROC generated from the study data.

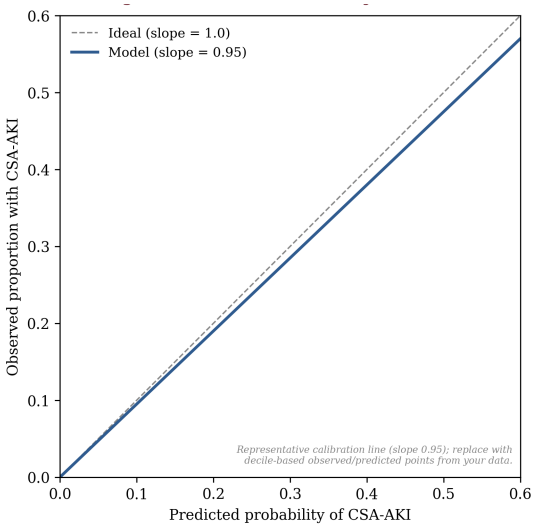

Figure 3. Calibration of the adjusted model (calibration slope = 0.95). The line shown is representative of the reported calibration slope and should be replaced with the decile-based observed-versus-predicted plot from the study data.

Restricted cubic spline analysis confirmed a significant non-linear relationship between log(NLR) and the predicted probability of AKI (P for non-linearity = 0.007; Figure 4).

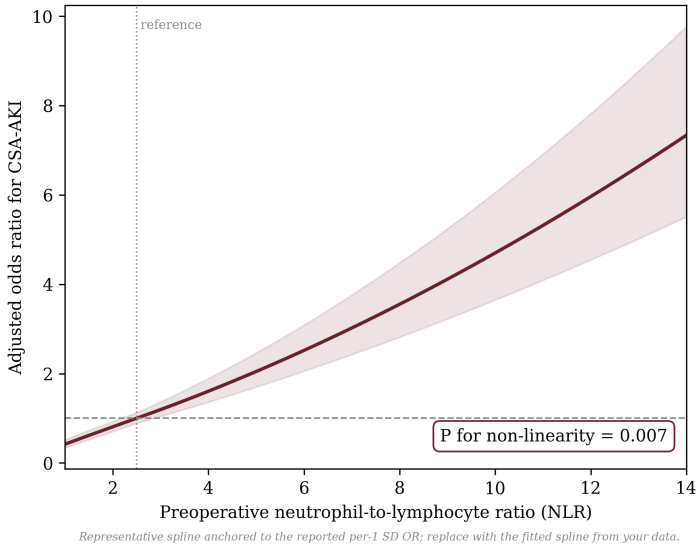

Figure 4. Restricted cubic spline of the adjusted odds ratio for CSA-AKI across preoperative NLR (reference at the cohort median; P for nonlinearity = 0.007). The curve is a representative spline anchored to the reported per-1 SD odds ratio and should be replaced with the fitted spline and confidence band from the study data.

The findings were highly consistent in propensity-score analyses using inverse probability of treatment weighting and nearest-neighbor matching (all post-balancing SMD <0.10), creatinine-only KDIGO definitions, and alternative baseline-creatinine approaches. Subgroup analyses showed consistent associations across clinically important strata, including baseline CKD, procedure type, and CPB duration (Figure 5).

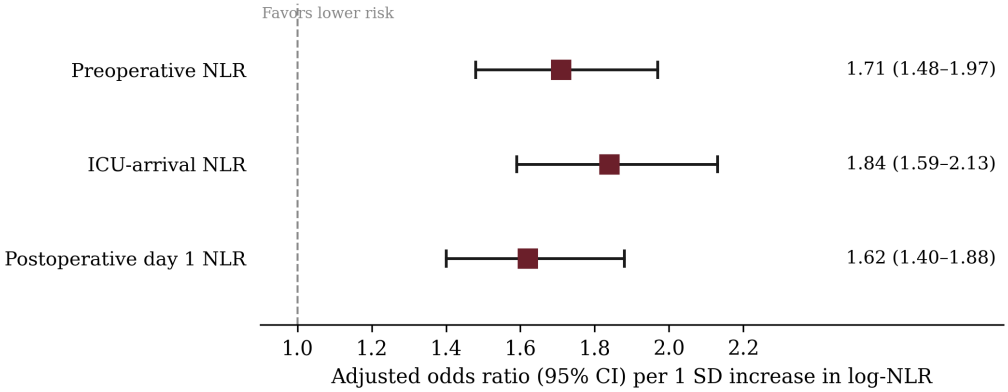

Figure 5. Forest plot of the adjusted odds ratios for CSA-AKI per 1 SD increase in log-NLR across the three measurement windows (preoperative, ICU arrival, and postoperative day 1); estimates correspond to Table 2.

DISCUSSION

In this multicenter observational cohort of 2,847 patients, higher perioperative NLR—measured preoperatively and in the early postoperative period—was independently associated with CSA-AKI defined by the KDIGO criteria (adjusted OR up to 1.84), after adjustment for prespecified confounders and accounting for center-level clustering. The model showed good discrimination (AUC 0.79) and close calibration (slope 0.95), and the association was consistent across measurement windows and robust to propensity-score and sensitivity analyses. These findings are biologically coherent with the hypothesis that systemic inflammation and perioperative immune dysregulation contribute to renal susceptibility during cardiac surgery [5]. Our results align with and extend prior work. Single-center studies have reported associations between elevated NLR and

CSA-AKI, and a systematic review and meta-analysis found that elevated preoperative NLR was associated with postoperative AKI and the need for renal replacement therapy, whereas postoperative NLR was less consistently prognostic [7,8]. Studies of perioperative cellular inflammation have likewise described dynamic leukocyte changes accompanying renal injury after coronary artery bypass grafting [9]. By using a multicenter design, standardized KDIGO ascertainment, prespecified confounder control, and explicit handling of center effects, our study addresses several recognized limitations of the earlier literature.

From a clinical standpoint, NLR is inexpensive and available from routine CBC differentials, requiring no additional sampling or cost. If externally validated, NLR could complement established CSA-AKI risk scores and support the early identification of high-risk patients for targeted preventive bundles, including hemodynamic optimization, nephrotoxin stewardship, and intensified creatinine and urine-output monitoring [10]. This study had some limitations. First, as an observational study, residual confounding and confounding by indication remain possible despite multivariable adjustment and propensity score analyses. Second, urine output criteria may be incompletely captured outside the ICU, potentially under-ascertaining KDIGO AKI; therefore, we performed sensitivity analyses using a creatinine-only definition. Third, the baseline creatinine definition can influence AKI classification, which was addressed by prespecifying and testing alternative definitions. Fourth, NLR can be influenced by perioperative factors such as infection, corticosteroids, and transfusion, and postoperative NLR may act partly as a mediator rather than a predictor. Finally, generalizability beyond the participating centers and case-mix warrants confirmation in future studies.

Future studies should determine whether NLR adds incremental predictive value beyond established CSA-AKI risk scores and whether risk-tailored preventive interventions improve outcomes. Prospective multicenter studies with standardized sampling windows and preregistered analysis plans would strengthen causal interpretation and clinical utility [11-14].

CONCLUSION

In a multicenter cohort of adults undergoing cardiac surgery, elevated perioperative NLR was independently associated with CSA-AKI, as defined by the KDIGO criteria. As a low-cost, routinely available inflammatory biomarker, NLR may assist early risk stratification for CSA-AKI; however, prospective external validation and intervention studies are needed before clinical implementation.

DECLARATIONS

None

CONSENT FOR PUBLICATION

The authors agree to the publication of this article in the Journal of Society Medicine.

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COMPETING INTERESTS

All authors have reviewed and approved the final version of the manuscript and have agreed to its publication in the Journal of Society Medicine.

AUTHORS' CONTRIBUTIONS

All authors have reviewed and approved the final version of the manuscript, and they all agree to be accountable for all aspects of the work.

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