Signa Vitae

ORIGINAL RESEARCH

Early predictors of acute kidney injury after Cardiac Surgery

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Abstract

Background: Acute kidney injury (AKI) represents a significant postoperative complication affecting approximately 50% of cardiac surgery patients, with early detection and intervention being crucial for improved outcomes. **Methods**: We evaluated early biomarkers of cardiac surgery-associated AKI (CSA-AKI) in 60 patients undergoing elective cardiac procedures requiring extracorporeal circulation, including coronary artery bypass grafting and/or valve replacement surgery. Exclusion criteria encompassed preoperative sepsis, existing renal replacement therapy, advanced age (>80 years), emergency surgical intervention, established chronic renal or hepatic dysfunction, and malignancy. The investigation protocol included sequential measurement of serum neutrophil gelatinase-associated lipocalin (NGAL), neutrophil-lymphocyte ratio (NLR), blood urea nitrogen (BUN), and creatinine at preoperative baseline and at 6th and 24th hours postoperatively. Serum creatinine and BUN were reassessed at 48 hours after surgery. All serum specimens were preserved at -20 °C pending laboratory analysis of NGAL and standard hematological parameters. **Results**: Upon application of Kidney Disease: Improving Global Outcomes (KDIGO) criteria, twenty participants (33.3%) developed CSA-AKI. Comparative analysis revealed significant elevations in both NLR and NGAL at 6th and 24th hours postoperatively relative to preoperative baseline values ($p < 0.05$) in both AKI and non-AKI cohorts. However, the temporal progression pattern of these biomarkers demonstrated parallel trajectories across both groups ($p > 0.05$). **Conclusions**: Our findings suggest that systematic evaluation of serum NGAL and NLR concentrations at preoperative baseline and at 6 and 24 hours following cardiac surgery may facilitate expeditious identification of patients developing AKI, potentially enabling earlier therapeutic intervention.

Keywords

Acute kidney injury; Cardiac surgery; Neutrophil gelatinase-associated lipocalin; Neutrophil-lymphocyte ratio; Creatinine; Urea

1. Introduction

Acute kidney injury (AKI) represents a significant perioperative complication affecting approximately 50% of patients following cardiac surgery, which underscores the critical need for timely diagnosis and prompt management through therapeutic intervention [1, 2]. A significant challenge in contemporary clinical practice is the identification of sensitive biomarkers capable of diagnosing AKI secondary to cardiac surgery—commonly referred to as CSA-AKI—before the characteristic elevation of serum creatinine levels as they generally become apparent no earlier than 48 hours after the surgical procedure.

A range of perioperative variables—such as anesthetic depth and modality, pump flow parameters, hemodilution, or dilution of the blood, as well as arterial pressure regulation—may significantly impact tissue oxygenation profiles in both cerebral and renal tissues during extracorporeal circulation. Besides cardiopulmonary bypass (CPB). tends to induce robust activation of inflammatory cascades via complement system stimulation, leukocyte activation, coagulation pathway perturbation, and proinflammatory cytokine release [3–5].

Emerging clinical and experimental investigations have established that inflammatory processes initiated during ischemia-reperfusion events correlate strongly with subsequent AKI development within the broader context of systemic inflammatory response. A cardinal histopathological feature of AKI is renal tubular epithelial cell death, which involves diverse cellular demise mechanisms like necrosis, pyroptosis, and apoptosis, recognized as crucial in the context of pathogenesis. On top of that, growing evidence highlights the contribution of both endothelial dysfunction and endothelial cell damage to the pathogenic mechanisms of

acute kidney injury [6–8].

The neutrophil-to-lymphocyte ratio (NLR) provides an integrated perspective on immune status; neutrophils within this ratio typically signify ongoing inflammatory activity, whereas lymphocytes could be seen to indicate the status of immunoregulatory function. This hematological parameter has been linked to diverse cardiovascular diseases and the clinical course of patients following cardiac surgical procedures. As a readily accessible surrogate for the systemic inflammatory response, the NLR is both cost-effective and easily derived from a routine complete blood count with differential analysis [9].

In contemporary clinical settings, AKI diagnosis predominantly involves detecting sharp elevations in serum creatinine (SCr) concentration along with diminished urinary output—both parameters perceived as inadequate diagnostic indicators. The interpretation of SCr can also be complicated by numerous variables like biological sex, ethnicity, age, variations in the shape and size of the human body, dietary patterns, comorbidities such as diabetes and hepatic dysfunction, pharmacological agents, and laboratory methodological variations, collectively limiting its diagnostic precision for acute kidney injury [10]. Most importantly, it should be noted that tubular damage occurs prior to marked elevations in SCr levels; nonetheless clinical reliance on SCr and estimated glomerular filtration rate (eGFR) to assess kidney function frequently hinders implementation of timely therapeutic interventions. Serum creatinine also shows inadequate sensitivity for AKI detection in a timely manner and offers limited capacity to discriminate between diverse etiologies of renal injury. Besides, its utility as a biomarker is further compromised by lagging kinetics in reflecting functional kidney changes, confounding effects of perioperative fluid administration, and reduced creatinine generation in critically ill patients [11].

In the immediate aftermath of events causing direct kidney damage (nephrotoxic insults), such as the renal ischemia frequently associated with cardiopulmonary bypass procedures, renal tubular epithelial cells rapidly increase their synthesis and subsequent secretion of neutrophil gelatinase-associated lipocalin (NGAL). This prompt cellular response leads to a swift release of NGAL into circulation. Consequently, concentrations of NGAL in the serum escalate sharply, typically becoming measurable within a narrow timeframe of 2 to 6 hours following the initial renal insult. The ability to detect this early surge in NGAL is particularly significant because it coincides with a critical therapeutic window. During this period, acute kidney injury may still be highly responsive to interventions, offering a crucial opportunity to potentially mitigate the severity of the injury or even reverse its progression [12, 13].

The present investigation was designed to evaluate the potential clinical application of serum NGAL concentrations and NLR as early predictive biomarkers for the development of postoperative acute kidney injury among individuals that underwent elective cardiac surgical procedures.

2. Materials and methods

The current prospective investigation was undertaken at the University of Health Sciences, Antalya Training and Research Hospital, Turkey. The study cohort comprised patients scheduled for elective cardiac surgery at our institution between 20 January 2024 and 20 August 2024. Ethical approval was granted by the Institutional Ethics Committee of Health Science University Antalya Training and Research Hospital (Reference No. 2023-336, 18/27). The research was performed in accordance with the principles outlined in the Declaration of Helsinki, and all participants in the study cohort provided a written informed consent prior to their respective surgical procedures.

We evaluated several potential biomarkers for AKI in 60 patients (61.6% male, 38.4% female) undergoing pump-assisted surgical procedures, such as valve replacement and/or coronary artery bypass grafting, necessitating extracorporeal circulation. Specifically, serum concentrations of urea, NGAL, NLR, and creatinine were assessed preoperatively and at 6- and 24-hours post-surgery. Additionally, serum BUN and creatinine levels were re-evaluated 48 hours postoperatively. Arterial blood gas analyses were conducted to determine lactate and bicarbonate (HCO_3^-) levels preoperatively and 24 hours after surgery. Exclusion criteria included preoperative sepsis, receipt of renal replacement therapy, requirement for emergency surgery, age exceeding 80, and a prior diagnosis of chronic renal or hepatic insufficiency or malignancy. Initially, 72 patients undergoing cardiac surgery were screened; 12 were subsequently excluded based on these criteria, resulting in a final study population of 60 patients. The final analytical cohort included all 60 enrolled patients. Complete serum NGAL and NLR data were available for the entire study population. This provided adequate statistical power for the primary endpoints.

Postoperative CSA-AKI was identified in 20 patients based on the 2020 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. The specific criterion for this diagnosis was a rise in serum creatinine of 0.3 mg/dL or more (equivalent to ≥ 26.5 μmol/L) within 48-hour period [14]. These individuals were designated as the AKI group. The remaining 40 patients, not meeting these criteria, constituted the non-AKI group. Based on this criteria, postoperative AKI developed in 20 patients (33.3%) and patients were categorized into an AKI group (N = 20) and a non-AKI group (N = 40).

Demographic and preoperative data included age, gender, smoking status, ejection fraction, presence of hypertension or diabetes mellitus, and routine hematological and biochemical parameters. Key operative data recorded encompassed anesthesia duration, aortic cross-clamp time, duration of cardiopulmonary bypass, the specific surgical procedure performed, and the number of grafts. Immediately following the operation, all patients were transferred intubated to the intensive care unit (ICU). Extubation was performed once patients exhibited spontaneous breathing and achieved normalization of orientation and cooperation, provided their hemodynamic and respiratory functions were stable. Postoperative data, including routine blood parameters and lengths of hospital and ICU stay, were also documented.

2.1 Anesthesia technique

All participants received a standardized anesthesia protocol. Premedication consisted of midazolam (0.1 mg/kg), after which radial artery cannulation was performed to enable continuous hemodynamic monitoring throughout the surgical procedure. Following a 3-minute period of oxygen administration by mask, intravenous anesthetic induction was achieved with midazolam (0.2 mg/kg) and vecuronium (0.1 mg/kg), complemented by an initial infusion of remifentanil (2 μg/kg). Endotracheal intubation was then carried out, and mechanical ventilation commenced. Subsequently, anesthesia was maintained using intravenous infusions of remifentanil (1 μg/kg/min) and propofol (2 mg/kg/h). Throughout the operation, patients' physiological states were closely observed, with anesthetic dosages adjusted according to clinical requirements. A central venous catheter was placed in the right internal jugular vein. A probe was placed in the esophagus for body temperature measurement.

2.2 Operative technique

Surgical interventions were performed on all study participants through a midline chest incision (median sternotomy) while under complete sedation and analgesia. Following systemic heparinization (300 IU per kilogram of body weight), extracorporeal circulation was initiated via cannulation of the ascending aorta and venous vasculature. Hemostatic monitoring ensured that activated clotting time remained consistently elevated beyond 450 seconds throughout the operative period. The surgical team employed standardized extracorporeal circulation equipment and adhered to established perioperative management protocols across all cases. Myocardial preservation was achieved through delivery of hyperkalemic, cooled blood-based cardioplegic solution administered in an antegrade fashion. Thermal regulation during these cardiac interventions involved moderate body cooling to core temperatures ranging between 28–30 degrees Celsius. The perfusion specialists maintained strict physiological parameters during bypass, including extracorporeal perfusion rates of 2.2–2.5 liters per minute per square meter of body surface area, arterial pressure values consistently ranging from 50–80 millimeters of mercury, and blood concentration metrics showing hematocrit percentages carefully managed between 20–25% to optimize oxygen-carrying capacity.

2.3 Biochemical analysis

Following a minimum 8-hour fasting interval, peripheral venous blood specimens were obtained and subjected to ambient temperature coagulation for a minimum duration of 30 minutes. Subsequent centrifugation at 4000 revolutions per minute (RPM) for 10 minutes facilitated serum separation. The resultant supernatant was harvested and maintained at $-20\,^{\circ}$C pending analysis of neutrophil gelatinase-associated lipocalin (NGAL) and standard hematological parameters. For specimens requiring extended preservation exceeding a month, ultra-low temperature storage at $-80\,^{\circ}$C was implemented until biochemical assessment. Prior to analytical procedures, all samples underwent controlled equilibration to ambient laboratory temperature.

Quantitative determination of NGAL concentrations was accomplished through solid-phase enzyme-linked immunosorbent assay methodology utilizing a commercially available immunoassay system (BT LAB, catalog No: designation E1719Hu, Jiaxing, Zhejiang, China). According to manufacturer specifications, this analytical platform demonstrates a quantification range spanning 5–600 nanograms per milliliter with a lower limit of detection established at 2.01 nanograms per milliliter. Calibration was performed using a seven-point standard curve encompassing concentrations from 20 to 640 nanograms per milliliter (ng/mL). The neutrophil-to-lymphocyte ratio (NLR) was derived through division of absolute neutrophil count by absolute lymphocyte count obtained from differential leukocyte analysis, consistent with previously established methodological approaches in the scientific literature [15].

2.4 Statistical analysis

Statistical evaluation of the data collected was performed on IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA). Categorical variables were reported as relative frequencies (percentages), whereas continuous variables were summarized as central tendency (means) with standard deviations. Comparative analyses between the AKI and non-AKI groups were conducted through either the Student's t-test (for normally distributed data) or the Mann-Whitney U test (if parametric assumptions were not fulfilled) was employed. Similar statistical methodology was applied when comparing subgroups stratified by NGAL elevation status at the 24-hour postoperative timepoint. Repeated measures analysis of variance (ANOVA) was performed to assess time-dependent changes in the measured parameters. Receiver Operating Characteristic (ROC) analysis was performed to measure the diagnostic value of NGAL and NLR, and Area Under Curve (AUC) values were calculated. Logistic regression analysis was conducted to analyze variables that determine AKI development (NGAL and NLR), adjusting for age, cardiopulmonary bypass duration, and the presence of diabetes mellitus. For all statistical analyses, a p-value < 0.05 was established as the threshold for significance.

Based on pre-study projected values, the required sample size was calculated as at least 11 patients per group. The study groups consisted of 20 and 40 patients. Power values were recalculated at study completion based on the obtained NGAL and NLR values and found to be 0.905 and 0.968, respectively.

3. Results

This prospective single-center study encompassed 60 adult patients undergoing cardiac surgery. The cohort included 37 males (61.6%), and the mean age was 62.05 ± 9.15 years. Regarding surgical procedures, 31 patients (51.6%) underwent coronary artery bypass grafting (CABG), 22 (36.6%) underwent valvular surgery, and 7 (11.6%) had combined valvular and CABG procedures. Prevalent comorbidities among the participants included systemic arterial hypertension in 34 patients (56.6%), diabetes mellitus in 29 patients (48.3%), and

current smoking status in 20 patients (33.3%).

Detailed patient characteristics are presented in Tables 1 and 2. Comparative analysis revealed no statistically significant differences between study groups regarding demographic characteristics, preoperative cardiovascular function, or perioperative variables. In particular, patient age distribution, left ventricular ejection fraction measurements, aortic cross-clamp duration, total cardiopulmonary bypass time, anesthetic exposure intervals, procedural duration, and postoperative hospitalization length demonstrated comparable values across cohorts. None of the study participants developed renal dysfunction requiring renal replacement therapy during the observation period.

Patients who developed AKI were significantly older (67.10 ± 5.35 years) compared to those with no AKI (59.53 ± 9.65 years; $p = 0.002$). The AKI group had a significantly longer ICU stay (2.30 ± 1.30 days $vs.$ 1.40 ± 0.59 days, respectively; $p = 0.007$).

Further stratification of baseline characteristics by AKI status (detailed in supplementary tables, referenced as Tables 1 and 2 descriptions) revealed that within the AKI group, 50% were male, 35% were current smokers, 65% had diabetes mellitus, and 70% had arterial hypertension. In the non-AKI group, 67.5% were male, 32.5% were current smokers, 40% had diabetes mellitus, and 50.0% had arterial hypertension. No significant differences were found between the two groups for these particular variables.

Preoperative and postoperative values of other clinical parameters, including hemoglobin, hematocrit, NLR, lactate, and HCO_3^-, are presented in Table 3. These baseline and sequentially measured values were generally similar between the two groups at the specified time points, apart from the changes detailed below.

Temporal changes in blood urea nitrogen (BUN), creatinine, and NGAL levels are detailed in Table 4. Notably, BUN and creatinine levels at the postoperative 6th and 48th hours exhibited differences between the AKI and non-AKI groups. The time-dependent changes for BUN, creatinine, NGAL, NLR, lactate, and HCO_3^- levels, analyzed via Repeated Measures ANOVA, are illustrated in Figs. 1,2,3,4,5,6.

TABLE 1. Demographics and clinical data for the study cohort.

Variables	AKI Group (N = 20)	Non-AKI Group (N = 40)	$p*$
Age (yr)	67.10 ± 5.35	59.53 ± 9.65	0.002
Ejection Fraction	55.50 ± 7.93	55.00 ± 9.54	0.841
Aortic cross-clamp time (min)	84.60 ± 29.81	74.23 ± 35.08	0.262
Duration of CPB (min)	126.20 ± 38.39	107.42 ± 50.76	0.151
Hospitalization length (d)	7.40 ± 3.88	5.95 ± 1.45	0.262**
ICU stay (d)	2.30 ± 1.30	1.40 ± 0.59	0.007**
Surgery time (min)	233.25 ± 49.48	207.75 ± 51.30	0.071
Anesthesia time (min)	257.75 ± 52.83	235.75 ± 51.50	0.127

*Note. Values are presented as mean ± standard deviation. *Group comparisons were conducted via Student's t-test; **The Mann-Whitney U test was used for hospitalization length and ICU stay. AKI: acute kidney injury; CPB: cardiopulmonary bypass; ICU: intensive care unit.*

TABLE 2. Demographics and clinical data for the study cohort.

Variables	AKI Group n = 20 (%)	Non-AKI Group n = 40 (%)	$p*$
Males, n (%)	10 (50.0)	27 (67.5)	0.188
Current smoker, n (%)	7 (35.0)	13 (32.5)	0.846
Diabetes Mellitus, n (%)	13 (65.0)	16 (40.0)	0.068
Arterial Hypertension, n (%)	14 (70.0)	20 (50.0)	0.141
Procedure, (n)			
CABG	11	20	
(4 arterial grafts)	(3)	(3)	
(3 arterial grafts)	(5)	(7)	
(2 arterial grafts)	(3)	(10)	
Valvular procedures	6	16	
Valvular + CABG	3	4	

*Note. Values are presented as n (%). *Statistical comparisons were performed via the chi-square (χ^2) test. The granular data on arterial grafts within CABG procedures was excluded from the table for clarity and is best described in the main text. AKI: acute kidney injury; CABG: coronary artery bypass graft.*

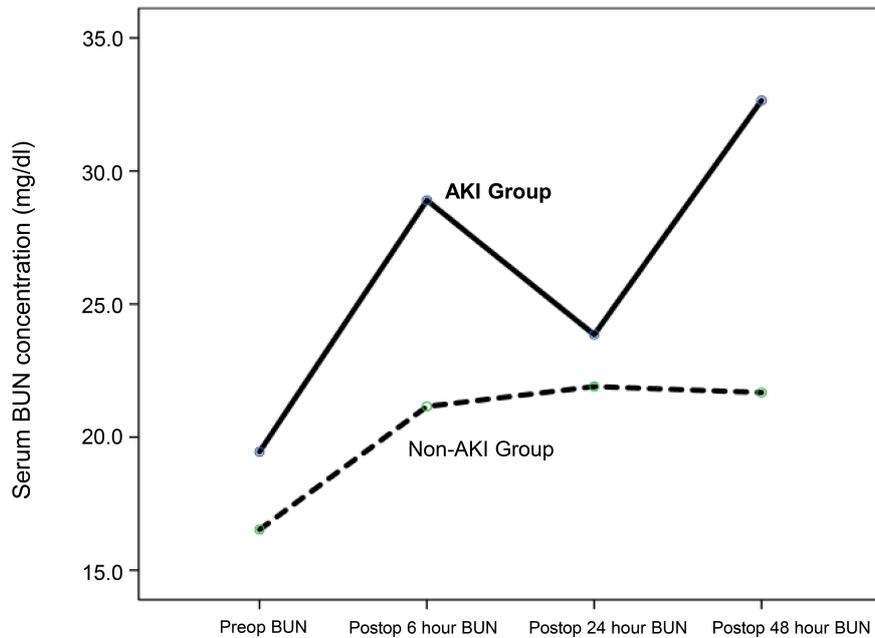**T A B L E 3. Comparison of clinical parameters: preoperative versus postoperative values.**

Variables	AKI Group (N = 20)	Non-AKI Group (N = 40)	$p*$
Hemoglobin (g/dL)			
Preoperative	13.14 ± 1.83	13.78 ± 1.33	0.138**
Postoperative 6 hour	8.87 ± 1.02	9.36 ± 1.12	0.112
Postoperative 24 hour	9.55 ± 0.72	9.72 ± 1.26	0.748**
Hematocrit (%)			
Preoperative	42.11 ± 12.07	49.92 ± 5.379	0.526
Postoperative 6 hour	27.01 ± 2.70	28.15 ± 3.40	0.197
Postoperative 24 hour	31.14 ± 11.78	28.94 ± 3.61	0.280
NLR			
Preoperative	3.96 ± 3.78	2.55 ± 1.68	0.071**
Postoperative 6 hour	11.12 ± 4.69	11.62 ± 7.38	0.783
Postoperative 24 hour	27.04 ± 12.11	23.31 ± 11.29	0.243
Lactate (mmol/L)			
Preoperative	1.03 ± 0.48	1.06 ± 0.42	0.821
Postoperative 24 hour	3.23 ± 2.00	2.43 ± 1.47	0.083
HCO_3^- (mmol/L)			
Preoperative	24.86 ± 2.73	24.84 ± 2.00	0.968
Postoperative 24 hour	25.39 ± 2.59	24.31 ± 2.46	0.123

*Note. Values are presented as mean $\pm$ standard deviation. The p-values reflect the comparison between the AKI and Non-AKI groups at each specific time point. *Group comparisons were performed via Student's t-test. **The Mann-Whitney U test was used for preoperative hemoglobin, 24-hour postoperative hemoglobin, and preoperative NLR. A rounding correction was applied to the standard deviation for preoperative hematocrit in the Non-AKI group. AKI: acute kidney injury; NLR: neutrophil-to-lymphocyte ratio; HCO_3^-: bicarbonate.*
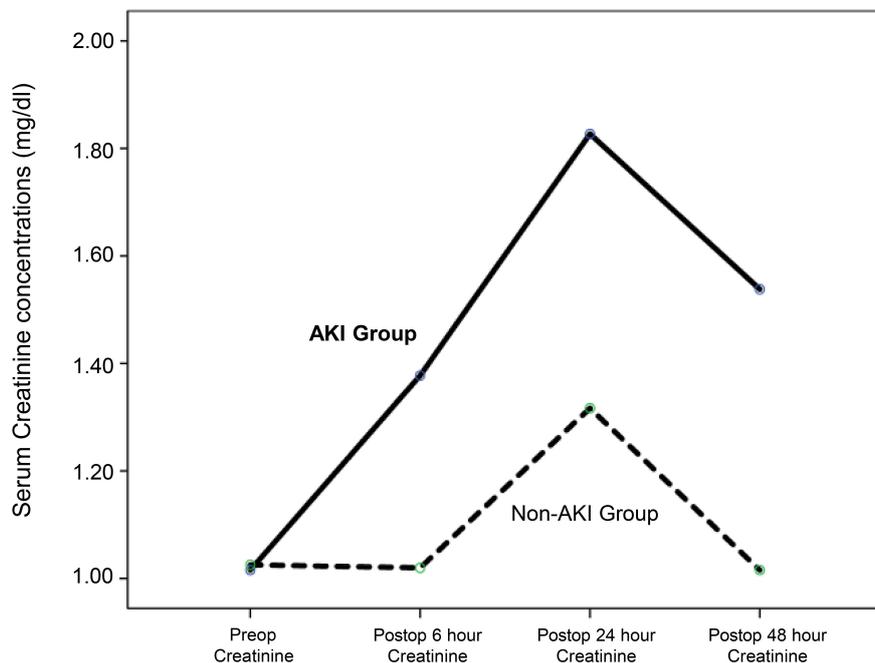
T A B L E 4. Temporal changes in BUN, creatinine, and NGAL levels.

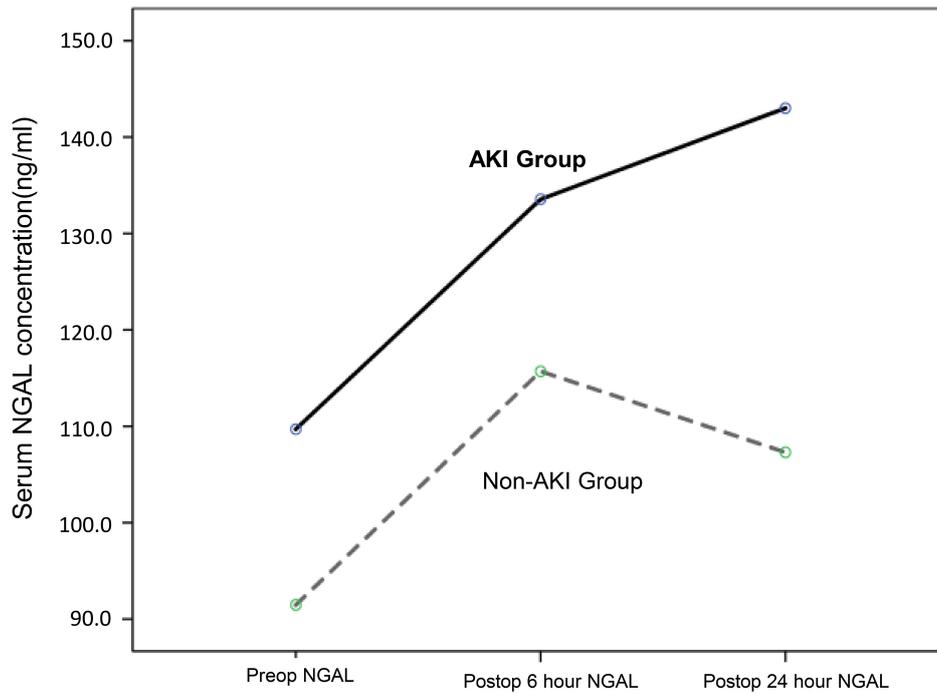| Variables	AKI Group (N = 20)	Non-AKI Group (N = 40)	$p*$
BUN (mg/dL)			
Preoperative	19.45 ± 6.00	16.52 ± 5.59	0.040
Postoperative 6 hour	28.90 ± 12.65	21.15 ± 7.01	0.048**
Postoperative 24 hour	23.85 ± 7.96	21.90 ± 9.80	0.444
Postoperative 48 hour	32.65 ± 10.26	21.67 ± 6.97	<0.001
Creatinine (mg/dL)			
Preoperative	1.02 ± 0.31	1.03 ± 0.25	0.896
Postoperative 6 hour	1.38 ± 0.53	1.01 ± 0.32	0.013**
Postoperative 24 hour	1.83 ± 2.02	1.31 ± 0.95	0.186
Postoperative 48 hour	1.54 ± 0.52	1.01 ± 0.23	<0.001**
NGAL (ng/mL)			
Preoperative	109.70 ± 93.34	91.47 ± 48.72	0.319
Postoperative 6 hour	133.56 ± 125.27	115.70 ± 73.42	0.489
Postoperative 24 hour	143.00 ± 126.26	107.30 ± 78.23	0.183

*Note. Values are presented as mean $\pm$ standard deviation. The p-values reflect the comparison between the AKI and Non-AKI groups at each specific time point. *Group comparisons were performed via Student's t-test; **The Mann-Whitney U test was used for 6-hour postoperative BUN, 6-hour postoperative creatinine, and 48-hour postoperative creatinine. AKI: acute kidney injury; BUN: blood urea nitrogen; NGAL: neutrophil gelatinase-associated lipocalin.*
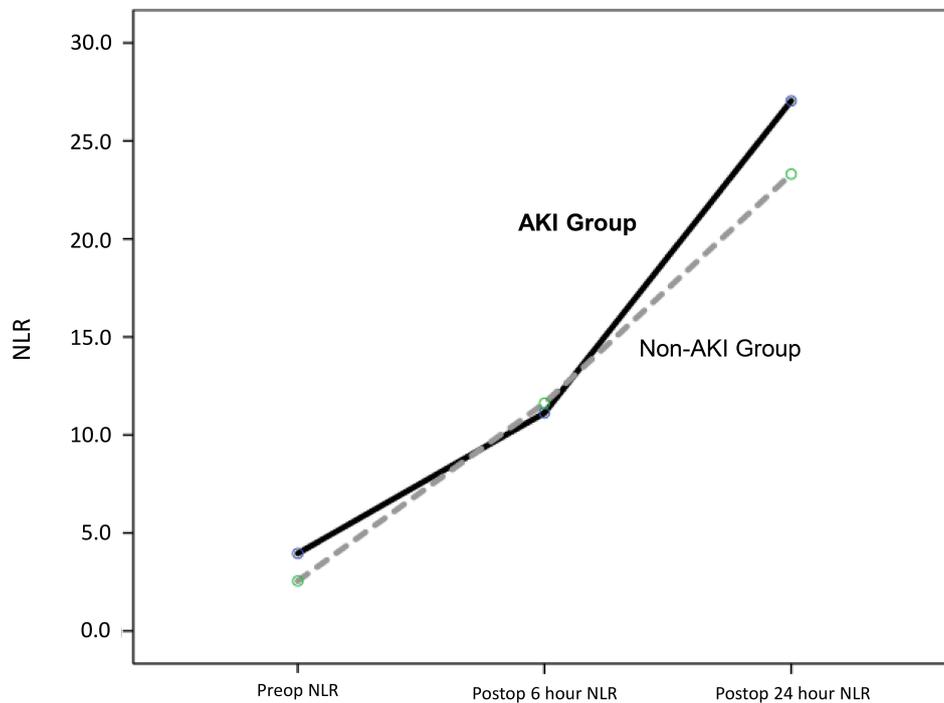
F I G U R E 1. Serum blood urea nitrogen (BUN) concentrations (mg/dL) at baseline (preoperative) and at 6, 24, and 48 hours following CPB, comparing AKI and non-AKI patient groups. Results from the Repeated Measures ANOVA indicated a significant difference between the groups ($p < 0.001$), a significant time-dependent change ($p = 0.001$), and a significant interaction effect ($p < 0.001$). Serum BUN values increased significantly from preoperative levels in both groups at 6, 24, and 48 hours postoperatively ($p < 0.05$ for all). The rate of this time-dependent increase was significantly faster in the group that developed AKI ($p < 0.05$). Serum BUN values were significantly higher in the AKI group at baseline (preoperatively) and at the postoperative 6th and 48th-hour marks ($p < 0.05$). AKI: acute kidney injury.
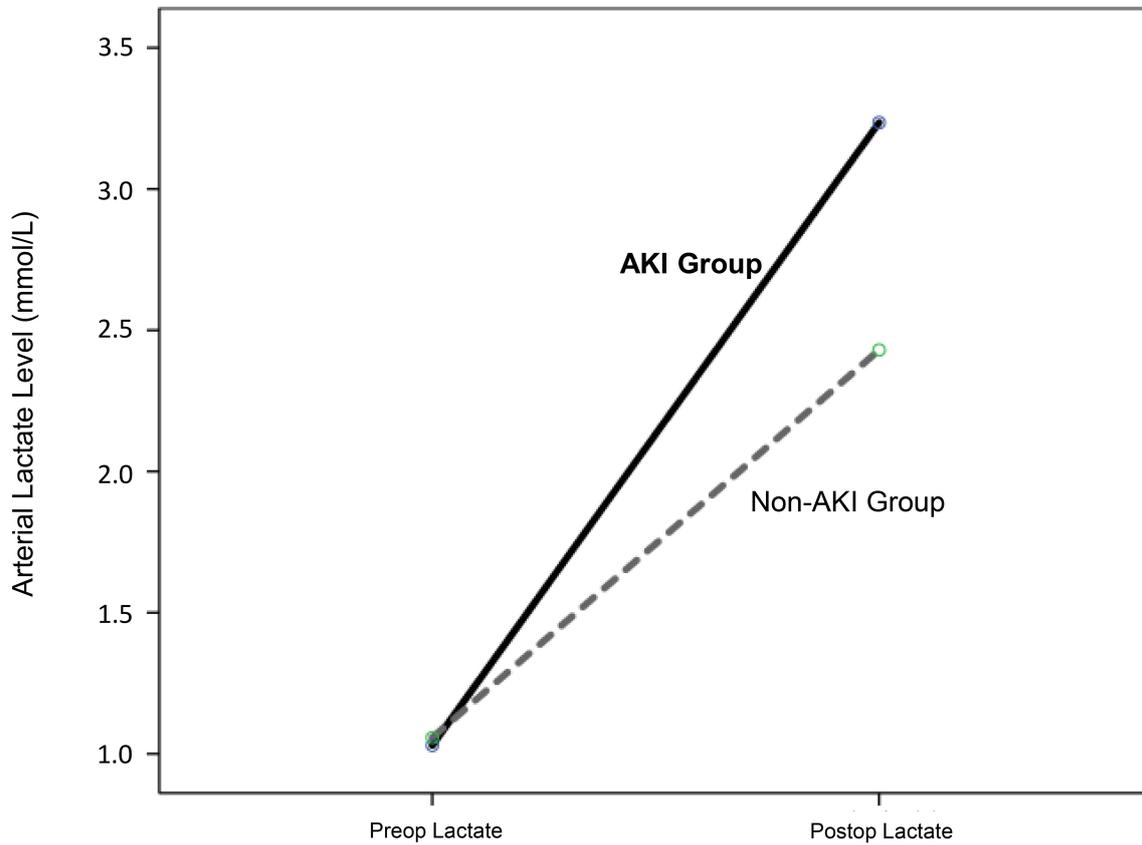

F I G U R E 2. Serum creatinine concentrations (mg/dL) at baseline (preoperative) and at 6, 24, and 48 hours following CPB, comparing AKI and non-AKI patient groups. The Repeated Measures ANOVA showed a significant difference in serum creatinine between the groups ($p = 0.014$) and a significant time-dependent change ($p = 0.011$). However, the interaction effect was not significant ($p = 0.134$). Serum creatinine values increased significantly in both groups at 6, 24, and 48 hours postoperatively compared to preoperative levels ($p < 0.05$). The time-dependent increase was parallel between the AKI and non-AKI groups ($p > 0.05$). In patients who developed AKI, serum creatinine levels at the postoperative 6th and 48th hours were significantly higher compared to those in the non-AKI group ($p < 0.05$). AKI: acute kidney injury.
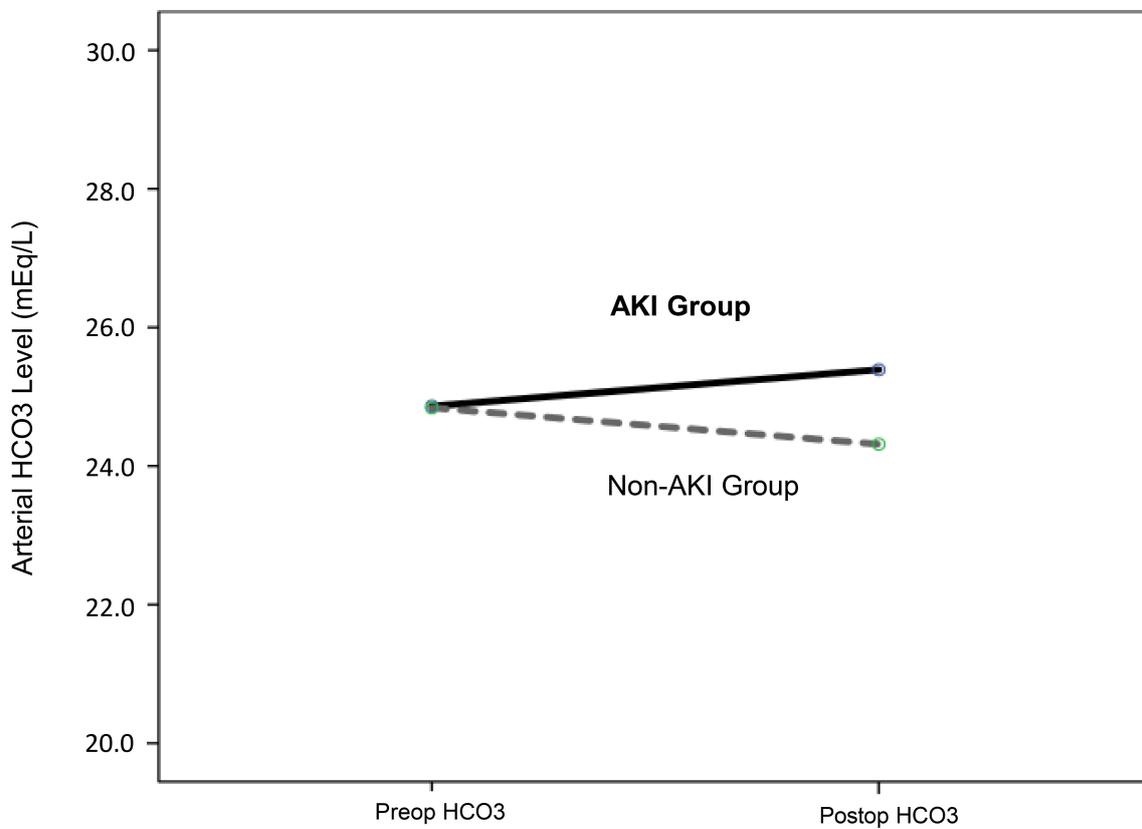
F I G U R E 3. Serum NGAL concentrations (ng/mL) at baseline (preoperative) and at 6 and 24 hours following CPB, comparing AKI and non-AKI patient groups. For serum NGAL, the Repeated Measures ANOVA indicated no significant difference between the groups ($p = 0.265$). There was a significant time-dependent change ($p = 0.010$), but the interaction effect was not significant ($p = 0.533$). Serum NGAL values increased significantly in both groups at 6 and 24 hours postoperatively compared to preoperative values ($p < 0.05$). However, this time-dependent increase occurred in parallel in both groups ($p > 0.05$), and NGAL values were similar between the groups at each measured time point ($p > 0.05$). AKI: acute kidney injury; NGAL: neutrophil gelatinase-associated lipocalin.

F I G U R E 4. Neutrophil-Lymphocyte Ratio (NLR) levels at baseline (preoperative) and at 6 and 24 hours following CPB, comparing AKI and non-AKI patient groups (NLR = neutrophil count/lymphocyte count). AKI: acute kidney injury.

F I G U R E 5. Arterial Lactate levels (mmol/L) in arterial blood gas at preoperative and postoperative 24th hour in AKI and non-AKI patient groups. AKI: acute kidney injury.

F I G U R E 6. Arterial bicarbonate (HCO_3^-) levels (mEq/L) in arterial blood gas at preoperative and postoperative 24 hours in AKI and non-AKI patient groups. AKI: acute kidney injury.

ROC analysis showed that preoperative, postoperative 6-hour, and postoperative 24-hour NGAL values had AUC values of 0.514, 0.529, and 0.591 for AKI diagnosis, respectively. Logistic regression analysis found no significant effect of preoperative NGAL, postoperative 6-hour NGAL, or postoperative 24-hour NGAL on AKI development after adjusting for age and cardiopulmonary bypass duration ($p = 0.407$, $p = 0.455$, and $p = 0.352$, respectively).

The Repeated Measures ANOVA for NLR revealed no significant difference between the groups ($p = 0.304$). A significant time-dependent change was observed ($p < 0.001$), while the interaction effect was not significant ($p = 0.289$). The NLR increased significantly in both groups at 6 and 24 hours postoperatively compared to preoperative values ($p < 0.05$). This time-dependent increase was parallel in both groups ($p > 0.05$). In patients who developed AKI, the NLR was similar to that of the non-AKI group at each time period ($p > 0.05$) (Fig. 4).

ROC analysis showed that preoperative, postoperative 6-hour, and postoperative 24-hour neutrophil-lymphocyte ratio values had AUC values of 0.644, 0.551, and 0.569 for AKI diagnosis, respectively. Logistic regression analysis found no significant effect of preoperative NLR, postoperative 6-hour NLR, or postoperative 24-hour NLR on AKI development after adjusting for age and cardiopulmonary bypass duration ($p = 0.394$, $p = 0.307$, and $p = 0.510$, respectively).

For arterial lactate levels, the Repeated Measures ANOVA showed no significant difference between the groups ($p = 0.123$). There was a significant change over time ($p < 0.001$), but the interaction effect was not significant ($p = 0.066$). Lactate levels increased significantly postoperatively compared to preoperative levels in both groups ($p < 0.05$). This time-dependent increase was parallel in both groups ($p > 0.05$). In patients who developed AKI, lactate levels were similar to those in the non-AKI group at each time point ($p > 0.05$) (Fig. 5).

The Repeated Measures ANOVA for arterial blood gas HCO_3^- levels indicated no significant difference between groups ($p = 0.192$), no significant time-dependent change ($p = 0.999$), and no significant interaction effect ($p = 0.302$) (Fig. 6). HCO_3^- levels did not change significantly postoperatively compared to preoperative values in either group ($p > 0.05$), and any temporal changes were parallel between the groups ($p > 0.05$). HCO_3^- levels in the AKI group were similar to the non-AKI group at each time point ($p > 0.05$).

4. Discussion

Acute kidney injury (AKI) represents a frequent and serious postoperative complication in patients receiving cardiac surgical procedures requiring extracorporeal circulation, substantially increasing mortality risk and adverse clinical outcomes. The underlying pathophysiological mechanisms precipitating renal dysfunction in this clinical context demonstrate some complexity with multiple contributory pathways. Critical etiological factors encompass ischemia-reperfusion injury sequelae, transient periods of compromised cardiac performance with consequent reduced renal perfusion, alterations in ren-

ovascular tone favoring vasoconstriction, physiological perturbations associated with deliberate hypothermia during cardiopulmonary bypass (CPB) followed by subsequent thermal normalization, and activation of systemic proinflammatory cascades directly attributable to blood-circuit interface interactions. These inflammatory processes subsequently facilitate renal parenchymal inflammation and microvascular coagulation abnormalities, potentially culminating in CPB-related renal embolic events [8, 13]. Epidemiological investigations consistently demonstrate that post-cardiac surgery AKI correlates significantly with elevated mortality indices, increased incidence of major postoperative complications, and extended hospitalization requirements, which underscores the clinical imperative for early detection strategies.

Neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a promising biomarker. Research indicates that NGAL levels are elevated in patients with various cardiovascular diseases [16, 17]. Of particular note, an increase in NGAL often precedes elevations in traditional renal markers like serum creatinine. In certain clinical scenarios, augmented NGAL levels have demonstrated utility in predicting the need for renal replacement therapy following severe kidney injury. Increased concentrations of NGAL in both urine and plasma have been specifically reported in patients who received heart-related surgical interventions [18–21]. In our study, however, this promise was not realized, as NGAL failed to significantly differentiate between patients who developed AKI and those who did not.

An emerging inflammatory indicator gaining substantial recognition across diverse surgical disciplines—including cardiovascular interventions—is the ratio between neutrophil and lymphocyte counts (NLR) [22, 23]. Researchers propose that the correlation between elevated NLR values and subsequent kidney dysfunction may stem from underlying subclinical activation of stress-responsive immune mechanisms and inflammatory pathways. For instance, a large retrospective study by Hu P *et al.* [24], involving approximately 24,000 cardiac surgery patients, found that 27.6% developed AKI. This study identified heightened preoperative NLR proportions as a factor significantly correlated with increased mortality and severe renal impairment risk [24]. The process of CPB itself significantly activates immunological responses, prompting widespread release of inflammatory mediators including various interleukins, chemotactic proteins, and other proinflammatory molecules, thereby amplifying AKI risk. Supporting this, Parlar *et al.* [25] demonstrated that post-surgical NLR independently predicted kidney injury following coronary artery bypass grafting. Their findings further revealed significantly increased incidence of postoperative renal dysfunction across multiple assessment timepoints specifically among patients exhibiting elevated preoperative NLR. Despite this potential, our data did not show a significant predictive capacity for NLR, as its levels rose similarly in both the AKI and non-AKI groups.

In a retrospective study by Jiang *et al.* [26], AKI occurred in 53.4% of their 734 patients, and those who developed AKI had significantly longer hospital stays. Similarly, our prospective study observed AKI in 33.3% of patients, who also

experienced significantly prolonged ICU stays, aligning with the broader literature on the impact of AKI.

While some studies, like that of Joseph Wheatley *et al.* [27], suggest an elevated preoperative NLR could possess predictive capacity, our findings indicate a more complex picture. Although both NGAL and NLR levels did rise significantly from their baseline values postoperatively in all patients, this appears to reflect a generalized systemic response to surgery rather than a specific signal of incipient renal injury. The critical finding from our analysis was the lack of a statistically significant difference in these biomarker levels between the AKI and non-AKI groups at any time point. This might imply that in our cohort, the inflammatory and injury response measured by NLR and NGAL was not specific enough to discriminate between those who would and would not develop AKI.

The meta-analysis by Sharrod-Cole *et al.* [28], which included 3131 patients across 16 distinct investigations, examined plasma NGAL (pNGAL) sampled 4–8 hours following cardiopulmonary bypass. Their analysis revealed superior diagnostic performance for AKI identification at this temporal interval compared with earlier or later assessment timepoints within their defined study population. However, substantial heterogeneity in combined sensitivity and specificity predictions, evidenced through wide prediction regions and confidence intervals, led the investigators to conclude that the definitive diagnostic utility of plasma NGAL in this specific clinical context remains incompletely established [28]. Our study's results, which demonstrated poor diagnostic performance with AUC values for NGAL peaking at only 0.591, strongly support this conclusion of heterogeneity and underscore the challenge in applying these biomarkers universally.

Epidemiological evaluations examining cardiac surgery-associated acute kidney injury consistently demonstrate associations with prolonged hospitalization requirements, extended mechanical ventilatory support duration, and significantly increased mortality rates [29]. Although findings can be variable, some research suggests that biomarkers hold enhanced predictive capability for acute renal dysfunction after cardiac surgery and facilitates earlier detection through rapid appearance in plasma within hours following initial kidney insult, thus demonstrating superior sensitivity compared with traditional monitoring parameters including serum creatinine fluctuations and urinary output quantification. For example, in their prospective clinical investigation, Adisurya *et al.* [30] observed that cardiac surgery patients who maintained normal renal function postoperatively demonstrated paradoxically elevated NGAL concentrations accompanied by reduced plasma interleukin-9 levels, leading them to conclude that neither biomarker, as assessed in their study, could reliably predict AKI incidence [30]. In our investigation, both serum NGAL and NLR demonstrated statistically significant elevations from preoperative baseline at both 6 and 24 hours postoperatively across all study participants ($p < 0.05$). However, temporal analysis revealed that the trajectory and magnitude of these biomarker elevations followed parallel patterns between patients who subsequently developed AKI and those who maintained normal renal function ($p > 0.05$). Furthermore, comparative analysis between cohorts

at corresponding time intervals indicated no statistically significant differences in absolute NGAL and NLR values between AKI and non-AKI groups ($p > 0.05$).

Our findings concerning lactate levels exhibited significant postoperative increases compared with preoperative measurements across both study cohorts ($p < 0.05$). While the temporal pattern of lactate elevation was comparable between groups ($p > 0.05$), patients who developed AKI demonstrated significantly prolonged ICU requirements, suggesting potential clinical implications despite similar biomarker kinetics. This observation is partially consistent with the work of Govender *et al.* [31], who found that intraoperative elevations in blood lactate concentration represent a valuable dynamic predictor for both intensive care unit length of stay and subsequent development of acute kidney injury in a large cohort of 779 patients undergoing elective cardiac interventions.

5. Conclusions

In this study, while postoperative elevations in NGAL and NLR were observed in all patients, a statistically significant difference in their absolute levels between the AKI and non-AKI groups was not found. However, we noted a pattern of persistently elevated NGAL levels in patients who subsequently developed AKI.

These findings should be considered preliminary. While the observed trajectory of NGAL may be of interest, this study does not provide sufficient evidence to advocate for its use as a standalone diagnostic or prognostic marker in this setting. Our results underscore that further, large-scale prospective studies are essential to rigorously evaluate whether the temporal dynamics of these biomarkers have any true clinical utility and cost-effectiveness in the early detection or risk stratification of cardiac surgery-associated AKI. Until such evidence is available, proposing changes to current clinical monitoring protocols would be premature.

6. Limitations of the study

A primary constraint of this research lies in its relatively modest cohort size (N = 60). To establish with greater certainty, the prognostic utility of serum NGAL and neutrophil-to-lymphocyte ratio, whether as standalone indicators or integrated within a comprehensive biomarker panel for early AKI detection post-cardiac surgery, more extensive multicenter prospective investigations are essential. Such expanded clinical trials would additionally facilitate thorough examination of optimal biomarker assessment intervals and potential confounding variables that may influence interpretation of results. Also, validation across diverse patient populations would strengthen the generalizability of our findings within broader clinical contexts.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

ZAAO, LD, GO and SK—designed the research study; analyzed the data; wrote the manuscript. ZAAO, AB, FM and BA—performed the research. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was granted by the Institutional Ethics Committee of Health Science University Antalya Training and Research Hospital (Reference No. 2023-336, 18/27). The research was performed in accordance with the principles outlined in the Declaration of Helsinki, and all participants in the study cohort provided a written informed consent prior to their respective surgical procedures.

ACKNOWLEDGMENT

Not applicable.

CONFLICT OF INTEREST

The authors affirm that this research was executed without any commercial affiliations or financial arrangements that might constitute a perceived or actual conflict of interest.

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