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Article

Value of Serum Retinol-Binding Protein, Lipoprotein A and Inflammatory Nutritional Indexes and their Interactions in Predicting Acute Kidney Injury after Coronary Angiography

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Abstract

Background: Contrast-induced acute kidney injury (CI-AKI) is a serious condition that can arise after undergoing coronary angiography (CAG). This complication is primarily caused by the toxic impact of contrast agents on the kidneys, along with oxidative stress and inflammatory responses. Identifying reliable biomarkers for early prediction remains essential due to the limited accuracy of existing clinical risk scores. **Methods**: This retrospective case-control study included 365 patients undergoing CAG between December 2021 and December 2023. Patients were categorized into non-AKI (n = 320) and AKI (n = 45) groups based on post-procedural renal function. Biomarkers including serum retinol-binding protein (RBP), lipoprotein A (Lp(a)), interleukin-6 (IL-6), and nutritional markers were measured. Baseline demographics, lipid profiles, and procedure details were recorded. **Results**: Baseline characteristics revealed no significant differences between groups in terms of age, BMI, gender, and prevalence of hypertension or diabetes mellitus. Notably, RBP (41.83 $\pm$ 10.22 mg/L vs. 32.45 $\pm$ 8.76 mg/L, $p < 0.001$), Lp(a) (42.35 $\pm$ 13.87 mg/dL vs. 35.76 $\pm$ 11.54 mg/dL, $p < 0.001$), and IL-6 (6.23 $\pm$ 2.14 pg/mL vs. 4.87 $\pm$ 1.59 pg/mL, $p < 0.001$) levels were significantly higher in the AKI group. Total protein levels were significantly lower in the AKI group (6.88 $\pm$ 0.62 g/dL vs. 7.12 $\pm$ 0.54 g/dL, $p = 0.006$). Multivariate logistic regression identified RBP (OR 1.118, 95% CI 1.072–1.166, $p < 0.001$), Lp(a) (OR 1.047, 95% CI 1.014–1.080, $p = 0.005$), and IL-6 (OR 1.710, 95% CI 1.355–2.157, $p < 0.001$) as independent predictors of AKI, while higher total protein levels were protective (OR 0.497, 95% CI 0.257–0.960, $p = 0.037$). **Conclusion**: Serum RBP, Lp(a), IL-6, and total protein levels are valuable biomarkers for predicting CI-AKI after CAG. Elevated RBP, Lp(a), and IL-6 indicate higher risk, while higher total protein suggests protective effects.

Keywords

contrast-induced acute kidney injury; coronary angiography; retinol-binding protein; lipoprotein A; interleukin-6; nutritional markers

Introduction

Acute kidney injury subsequent to contrast administration during coronary angiography, known as CI-AKI, significantly impacts patient outcomes, both immediately and over time [1–3]. CI-AKI typically exhibits severe renal impairment post administration of iodinated contrast media, posing formidable challenges in both cardiac intervention and diagnostic imaging [4–6]. Despite advances in preventive strategies, the incidence of CI-AKI persists at concerning levels, underlining the need for early identification and intervention in at-risk populations.

The development of CI-AKI involves several interrelated factors. These include the direct toxic effects of contrast agents on renal tissues, reduced oxygen availability in the medulla, increased oxidative stress, cell death in the tubular structures, and inflammatory processes [7,8]. Among these, inflammation has been increasingly recognized as a critical mediator, bridging various pathophysiological pathways involved in renal injury after contrast exposure. Identifying reliable biomarkers to predict CI-AKI is thus vital, as current clinical risk scores remain suboptimal in accurately stratifying patients pre-procedure.

Recent studies have pinpointed several promising biomarkers that correlate with the risk of CI-AKI, including serum retinol-binding protein (RBP), lipoprotein A (Lp(a)), and specific inflammatory and nutritional markers such as interleukin-6 (IL-6) and total protein levels [9–11]. RBP, a carrier for retinol (vitamin A), plays a significant role in renal physiology and pathology. Elevated serum RBP levels have been reported in conditions of proximal tubular dysfunction, which is a pertinent mechanism in CI-AKI [12–14]. Given that RBP levels can be modulated by inflamma-

tory states, oxidative stress, and renal handling of contrast agents, its potential as a CI-AKI biomarker warrants further exploration.

Lp(a) is another molecule of interest, known for its structural similarity to plasminogen and its role in cardiovascular diseases. Elevated Lp(a) levels may contribute to renal microvascular thrombosis and a pro-inflammatory state, exacerbating renal injury in the context of CAG-induced stress [15,16]. However, the exact role of Lp(a) in CI-AKI pathogenesis remains to be clarified, particularly in conjunction with other risk factors and biomarkers.

Inflammatory markers like IL-6 have solidified their role in predicting adverse renal outcomes. IL-6 is not only a systemic inflammatory cytokine but also implicates localized renal inflammation, which can be triggered or amplified by contrast media administration. Elevated levels of IL-6 may reflect a pre-existing pro-inflammatory state, which predisposes the kidneys to further injury upon exposure to nephrotoxic agents [17–19]. It is essential to integrate IL-6 assessment in predictive models for CI-AKI to enhance the accuracy and reliability of risk stratification.

Nutritional status, often reflected in serum total protein levels, has historically been underappreciated in the context of CI-AKI. Malnutrition and hypoalbuminemia may undermine the kidney's resilience against noxious stimuli by impairing the antioxidant defenses and increasing susceptibility to oxidative and inflammatory damage. Hypoalbuminemia can decrease the binding capacity for circulating toxins and free radicals, thus heightening the renal injury risk. Evaluating nutritional markers provides a holistic insight into the patient's overall health status and potential vulnerability to CI-AKI.

Given the multifactorial nature of CI-AKI, it is logical to consider that interactions among various biomarkers might offer a more accurate and comprehensive prediction model than single biomarkers alone. For instance, the interplay between oxidative stress (as indicated by RBP), inflammatory state (IL-6), and nutritional status (total protein) can create a synergistic effect, amplifying the risk of renal injury. Understanding these interactions could pave the way for more nuanced risk assessment tools and, consequently, more effective preventive strategies tailored to individual patient profiles.

The present study assesses the predictive role of serum RBP, Lp(a), IL-6, and total protein, along with their associations, in predicting CI-AKI post CAG. By systematically assessing these biomarkers and their combined impact, we intend to enhance the early identification of patients at high risk for CI-AKI and inform the development of targeted interventions. This study, conducted on a well-defined cohort, offers insights into the potential mechanistic pathways of CI-AKI and underscores the importance of a multi-biomarker approach in enhancing predictive accuracy.

Materials and Methods

Case Selection

A retrospective case-control study involving 365 hospitalised individuals who underwent CAG treatment within the period between December 2021 and December 2023 was conducted. The participants were categorized into two groups according to the development of CI-AKI post-procedure, namely the non-AKI group consisting of 320 individuals and the AKI group comprising 45 individuals. Patient demographics, including general information, serum RBP levels, lipoprotein(a) levels, lipid profiles, inflammatory markers, nutritional markers, renal function parameters, and details related to contrast agents and surgical procedures, were systematically collected.

This retrospective study exclusively utilized de-identified patient data, eliminating the potential for any impact on patient care or harm. Consequently, informed consent was waived. Both waiver and study were approved by the hospital's IRB and Ethics Committee, ensuring adherence to retrospective research directives.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Individuals of any gender, under 80 years of age, with normal cognitive function, capable of cooperating with various treatments and examinations; (2) The patient meets the Kidney Disease: Improving Global Outcomes (KDIGO) criteria for AKI, defined as an increase in serum creatinine of $\geq$0.3 mg/dL ($\geq$26.5 μmol/L) within 48 hours, or an increase in serum creatinine to 1.5 times the baseline, known or suspected to have occurred within the last 7 days [7]; (3) Absence of pre-existing renal disease and no use of nephrotoxic drugs, with iodixanol, a non-ionic isotonic contrast agent, being used during the procedure; (4) Utilization of the right radial artery for puncture.

Exclusion criteria: (1) Severe heart failure sufferers, measuring a left ventricular ejection fraction (LVEF) of $\leq$30%, manifesting an acute myocardial infarction, or facing serious heart valve disorders; (2) Individuals with pre-existing kidney disease or those taking nephrotoxic medications; (3) Exposure to contrast agents or allergies to contrast agents within two weeks prior to CAG surgery; (4) Patients who die during the CAG procedure or within 48 hours post-procedure; (5) Pregnant and lactating women; (6) Patients with end-stage renal disease or those undergoing dialysis treatment.

Blood Testing

Collect 3 mL of fasting venous blood from the patient for subsequent laboratory analyses. Utilize our cutting-edge blood cell Analyzer (Beckman Coulter, Inc., Brea, CA, USA) to ascertain white blood cell counts. Prior

to assessment, thoroughly vortex the blood sample at optimal speed of 3000 rpm for 5 full minutes to extract serum. Subsequently, employ our advanced automated biochemical analyzer (Beckman Coulter, Inc., Brea, CA, USA) in conjunction with the relevant reagent kit to measure key biochemical indicators such as RBP, vitamin A, transthyretin, zinc albumin, lipoprotein(a), total cholesterol, Low-Density Lipoprotein (LDL) cholesterol, High-Density Lipoprotein (HDL) cholesterol, triglycerides, C-reactive protein, IL-6, Tumor Necrosis Factor-α (TNF-α), fibrinogen, prealbumin, transferrin, total protein, hemoglobin, lymphocyte count, serum creatinine, blood urea nitrogen, and cystatin C. All blood samples were collected preoperatively and at 48 hours postoperatively.

Urine Examination

Urine samples will be collected from eligible patients then processed via microalbuminuria analyzer (Beckman Coulter, Brea, CA, USA), employing accompanying reagent kit for albumin-to-creatinine analysis. Urine samples were collected preoperatively and at 48 hours postoperatively.

Mehran Risk Score

The Mehran Risk Score (MRS) serves as a predictive tool designed to assess the likelihood of developing contrast-induced nephropathy (CIN) after the use of intravascular contrast mediums, which are frequently employed in CAG and various vascular imaging techniques. The MRS takes into account multiple clinical variables to evaluate the patient's risk level. The total score ranges from 0 to 74 points. Based on their scores, patients are categorized into different risk groups, allowing clinicians to implement appropriate preventive measures [20]. Risk stratification delineates three strata: low risk (0–5 points), medium risk (6–10 points) and elevated risk (11 points or more). Additionally, the Cronbach's alpha of the Mehran Risk Score exceeds 0.8, signifying robust internal consistency. Mehran Risk Scores were calculated preoperatively.

Statistical Method

Data metrics are represented by means $\pm$ standard deviations or medians plus interquartile ranges, contingent upon normal data distribution. Categorical variables exhibit as frequencies and percentages. Unpaired *t*-tests assessed differences in continuous variables between groups. Multivariate logistic regression examined odds ratios (ORs) and 95% confidence intervals (CIs) of these variables. Statistical significance was set at $p < 0.05$. Data evaluation used Statistical Package for Social Sciences version 19 (SPSS Inc., Chicago, IL, USA) and R software package version 3.0.2 (Free Software Foundation, Inc., Boston, MA, USA).

Results

Baseline Characteristics

In our population of 365 patients, including 320 without contrast-induced AKI and 45 diagnosed with AKI post-CAG, various baseline factors were scrutinized (Table 1). Interestingly, no significant differences existed in these factors between the AKI and non-AKI cohorts.

Serum RBP

Evaluating serum RBP concentration and associated variables revealed a substantial increase in patients with AKI (41.83 $\pm$ 10.22 mg/L) when compared to those unaffected by AKI (32.45 $\pm$ 8.76 mg/L), displaying extreme significance ($p < 0.001$) (Fig. 1). Meanwhile, nostatistically significant variances existed for any other parameters studied. Serum vitamin A levelswere comparable at 52.32 $\pm$ 12.65 µg/dL in both groups and likewise for transthyretin levels at 25.58 $\pm$ 4.32 mg/dL vs. 24.84 $\pm$ 3.87 mg/dL (p = 0.277). Total zinc content was more abundant at 82.43 $\pm$ 15.76 µg/dL in the non-AKI group than 78.92 $\pm$ 14.53 µg/dL in the AKI group (p = 0.159). Albumin levels also remained consistent at 4.02 $\pm$ 0.38 g/dL in the non-AKI group and 3.96 $\pm$ 0.42 g/dL in the AKI group (p = 0.271). Thus, among these variables, only serum RBP exhibited a statistically significant disparity between the groups.

Lp(a) and Lipid Profile

In evaluating Lp(a) levels and lipid profiles among the study participants, we discovered elevated Lp(a) levels in the AKI group (42.35 $\pm$ 13.87 mg/dL) relative to the non-AKI group (35.76 $\pm$ 11.54 mg/dL), exhibiting profound statistical significance ($p < 0.001$; Fig. 2). Lipid profile parameters remained unremarkably consistent. Total cholesterol was 193.45 $\pm$ 38.92 mg/dL in AKI patients and 186.32 $\pm$ 35.67 mg/dL in controls (p = 0.215). Likewise, LDL cholesterol was 124.87 $\pm$ 31.23 mg/dL in AKI individuals and 117.45 $\pm$ 28.76 mg/dL in controls (p = 0.11). HDL cholesterol was 45.78 $\pm$ 10.98 mg/dL in AKI sufferers and 48.65 $\pm$ 12.34 mg/dL in non-AKI counterparts (p = 0.14). Triglycerides averaged 158.54 $\pm$ 52.36 mg/dL in AKI patients and 146.87 $\pm$ 47.43 mg/dL in controls (p = 0.128). Thus, apart from Lp(a), no other lipid profile parameters demonstrated statistically significant differences between the groups.

Inflammatory Markers

IL-6 concentrations were significantly elevated in AKI patients (6.23 $\pm$ 2.14 pg/mL) versus non-AKI patients (4.87 $\pm$ 1.59 pg/mL), exhibiting a highly significant disparity ($p < 0.001$; Fig. 3). No other inflammatory mark-

Table 1. Participant baseline profile.

Characteristic	Non-AKI (n = 320)	AKI (n = 45)	t/χ^2	p
Age (years)	62.85 ± 10.24	64.72 ± 9.86	0.032	0.248
Male gender (%)	65.3 (209)	71.1 (32)	0.871	0.858
BMI (kg/m^2)	23.42 ± 3.78	23.95 ± 4.12	3.325	0.384
Hypertension (%)	58.4 (197)	75.6 (30)	0.665	0.068
Diabetes mellitus (%)	28.1 (163)	44.4 (20)	1.156	0.415
SYNTAX Score	22.35 ± 5.67	23.82 ± 6.12	1.614	0.107

Note: AKI, acute kidney injury; BMI, body mass index; SYNTAX Score, Synergy Between PCI with Taxus and Cardiac Surgery score.

Table 2. Nutritional markers.

Marker	Non-AKI (n = 320)	AKI (n = 45)	t	p
Prealbumin (mg/dL)	26.76 ± 5.43	25.32 ± 4.87	1.683	0.093
Transferrin (mg/dL)	246.43 ± 45.76	234.87 ± 41.23	1.604	0.110
Total Protein (g/dL)	7.12 ± 0.54	6.88 ± 0.62	2.751	0.006
Hemoglobin (g/dL)	13.27 ± 1.65	12.94 ± 1.87	1.217	0.224
Lymphocyte Count ($\times 10^9$/L)	2.12 ± 0.70	1.96 ± 0.65	1.478	0.140

ers demonstrated significant differences between groups. Mean CRP levels were 7.13 ± 2.02 mg/L for AKI patients and 6.64 ± 2.07 mg/L for non-AKI patients (p = 0.139). TNF-α levels were 3.11 ± 1.04 pg/mL in AKI patients and 2.95 ± 0.61 pg/mL in non-AKI patients (p = 0.314). Fibrinogen levels were 387.54 ± 89.76 mg/dL in AKI patients and 368.76 ± 75.43 mg/dL in non-AKI patients (p = 0.128). Moreover, WBC counts were 9.15 ± 2.43 × 10^9/L in AKI patients and 8.62 ± 1.87 × 10^9/L in non-AKI patients (p = 0.164). Therefore, among the analyzed inflammatory markers, only IL-6 levels exhibited a statistically significant elevation in the AKI group.

Nutritional Markers

Nutritional analysis revealed stark differences in total protein concentration: participants with AKI displayed a markedly reduced level of 6.88 ± 0.62 g/dL, drastically contrasting with the normal range of 7.12 ± 0.54 g/dL (p = 0.006; Table 2). However, prealbumin, transferrin, hemoglobin, and lymphocyte counts exhibited no significant variations between the two groups. Specifically, prealbumin levels were 25.32 ± 4.87 mg/dL for AKI patients and 26.76 ± 5.43 mg/dL for controls (p = 0.093); transferrin levels were 234.87 ± 41.23 mg/dL for AKI patients and 246.43 ± 45.76 mg/dL for controls (p = 0.11); hemoglobin levels were 12.94 ± 1.87 g/dL for AKI patients and 13.27 ± 1.65 g/dL for controls (p = 0.224); and lymphocyte counts were 1.96 ± 0.65 × 10^9/L for AKI patients and 2.12 ± 0.70 × 10^9/L for controls (p = 0.14). Consequently, only total protein levels demonstrated a significant disparity between AKI and control groups, highlighting its potential as an early indicator of kidney injury.

Renal Function Parameters

Mean serum creatinine for AKI patients was 1.22 ± 0.38 mg/dL versus 1.18 ± 0.23 mg/dL for non-AKI subjects (p = 0.585). eGFR equalled 64.76 ± 12.43 mL/min/1.73 m^2 vs. 68.54 ± 15.87 mL/min/1.73 m^2 (p = 0.126), respectively. BUN levels were 25.32 ± 6.65 mg/dL and 24.76 ± 5.43 mg/dL (p = 0.529), while cystatin C was 1.02 ± 0.35 mg/L and 0.97 ± 0.21 mg/L (p = 0.398). Urine albumin-to-creatinine ratio was 106.65 ± 32.43 mg/g and 98.54 ± 29.76 mg/g (p = 0.092), respectively. Thus, no significant differences were observed in any renal function parameter between the two groups (Table 3).

Contrast Media and Procedure-Related Factors

Mean contrast medium quantity trended higher for AKI patients (154.76 ± 42.34 mL) relative to non-AKI individuals (142.45 ± 45.76 mL; p = 0.089). Procedure time spanned 52.32 ± 18.76 minutes in both groups (p = 0.223). Fluoroscopy duration was comparable at 11.43 ± 4.87 minutes for AKI patients and 10.65 ± 3.21 minutes for non-AKI subjects (p = 0.306). Stent usage was 1.76 ± 0.58 for AKI patients and 1.62 ± 0.47 for non-AKI patients (p = 0.058). Lastly, the MRS, a measure of CIN risk, was 9.37 ± 3.04 for AKI patients and 8.63 ± 2.76 for non-AKI patients (p = 0.097). Therefore, no significant disparities were observed in contrast medium or procedural variables between the two groups (Table 4).

Multivariate Logistic Regression Analysis

Univariate approach pinpointed key factors affecting AKI using logistic regression analysis. RBP was a significant predictor, with a coefficient of 0.111 ($p < 0.001$),

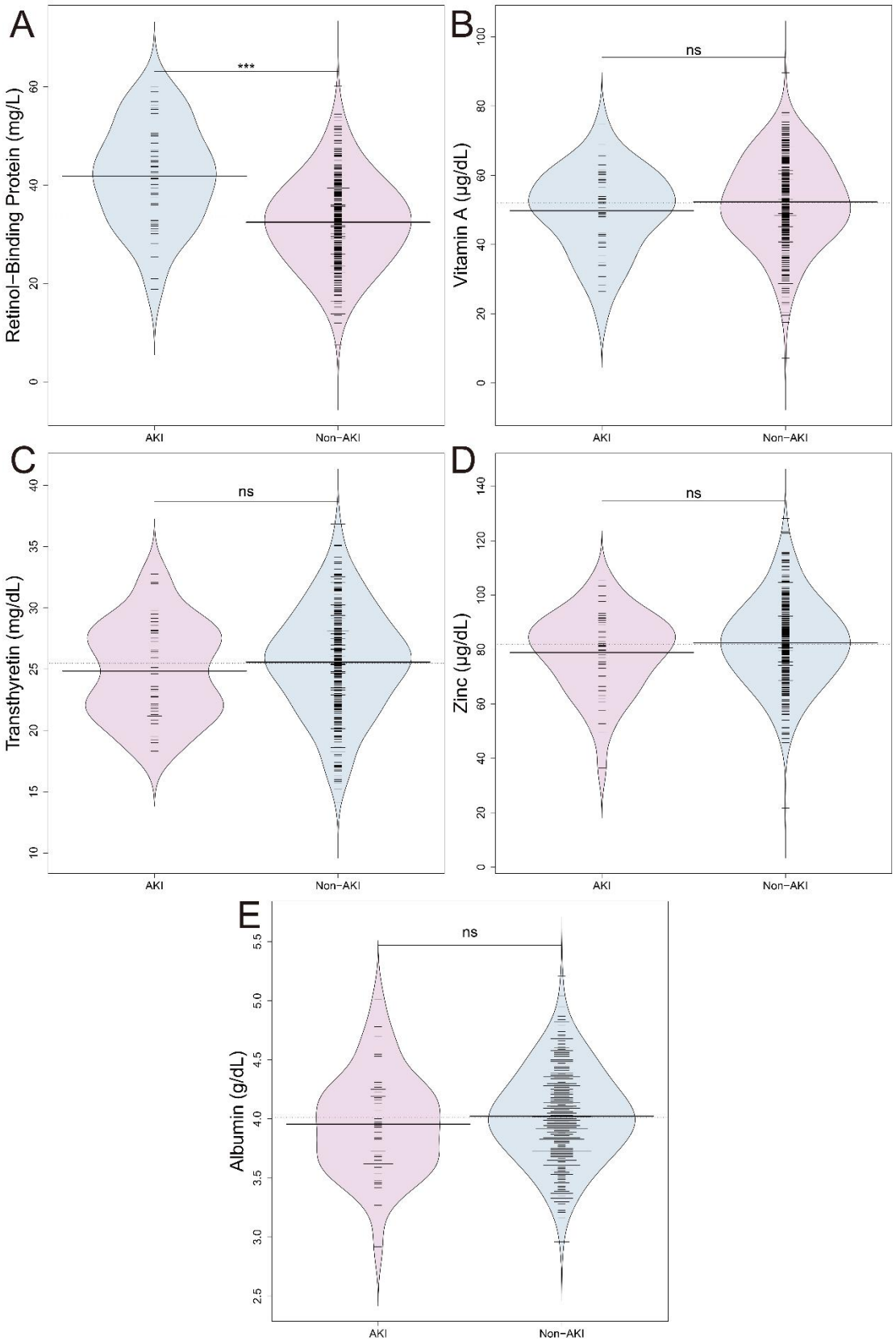

Fig. 1. Serum RBP levels and related parameters. Serum concentrations of (A) retinol-binding protein (RBP), (B) vitamin A, (C) transthyretin, (D) zinc, and (E) albumin in patients with and without acute kidney injury (AKI). Data are presented as mean ± standard deviation. ***$p < 0.001$, ns: not significant.

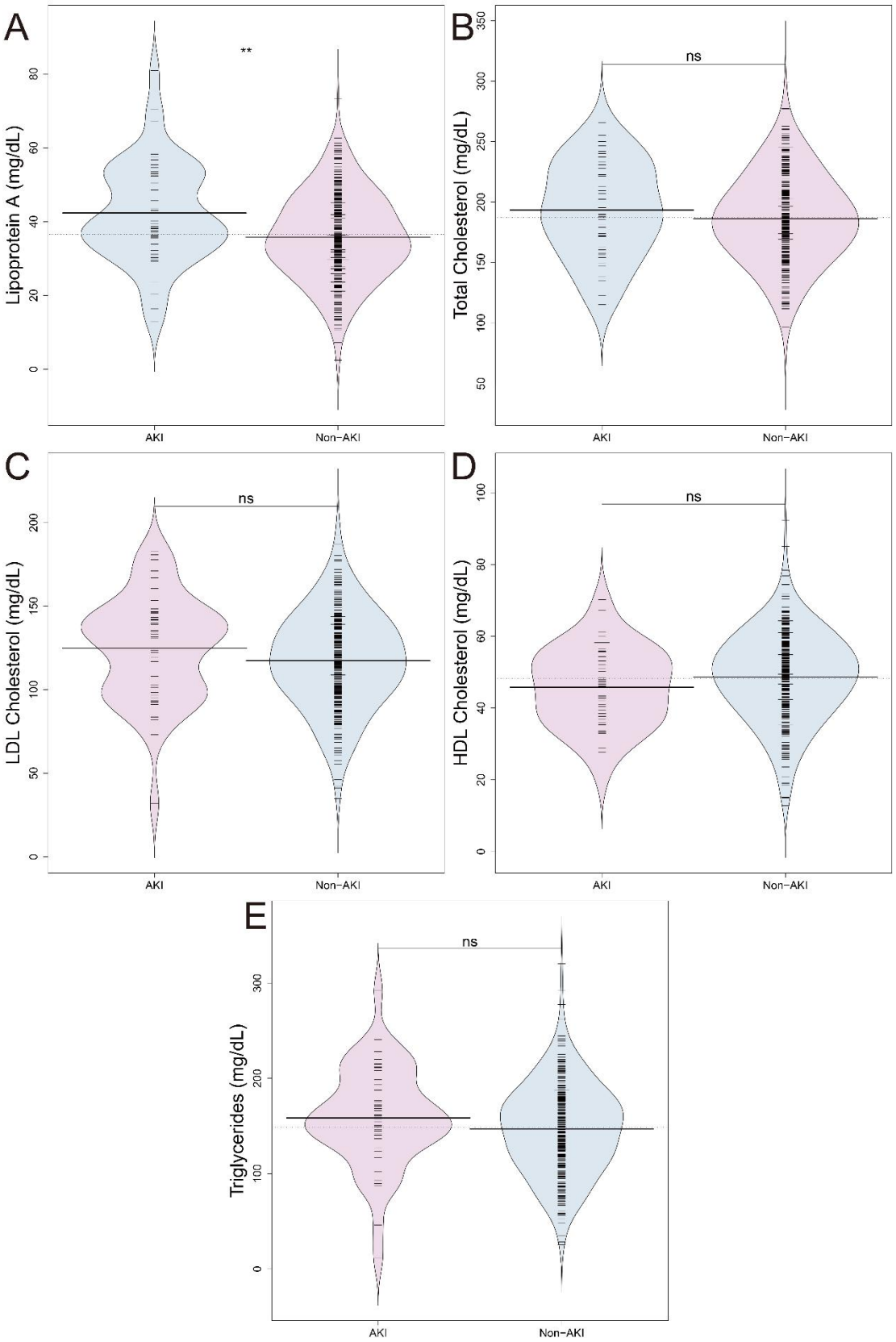

Fig. 2. Lp(a) and lipid profile. Note: Serum concentrations of (A) lipoprotein A [Lp(a)]; (B) Total cholesterol; (C) LDL cholesterol; (D) HDL cholesterol; (E) Triglycerides in patients with and without acute kidney injury (AKI). LDL, low density lipoprotein; HDL, high density lipoprotein. Statistical significance is indicated as follows: $^{**}p < 0.001$, ns: not statistically significant.

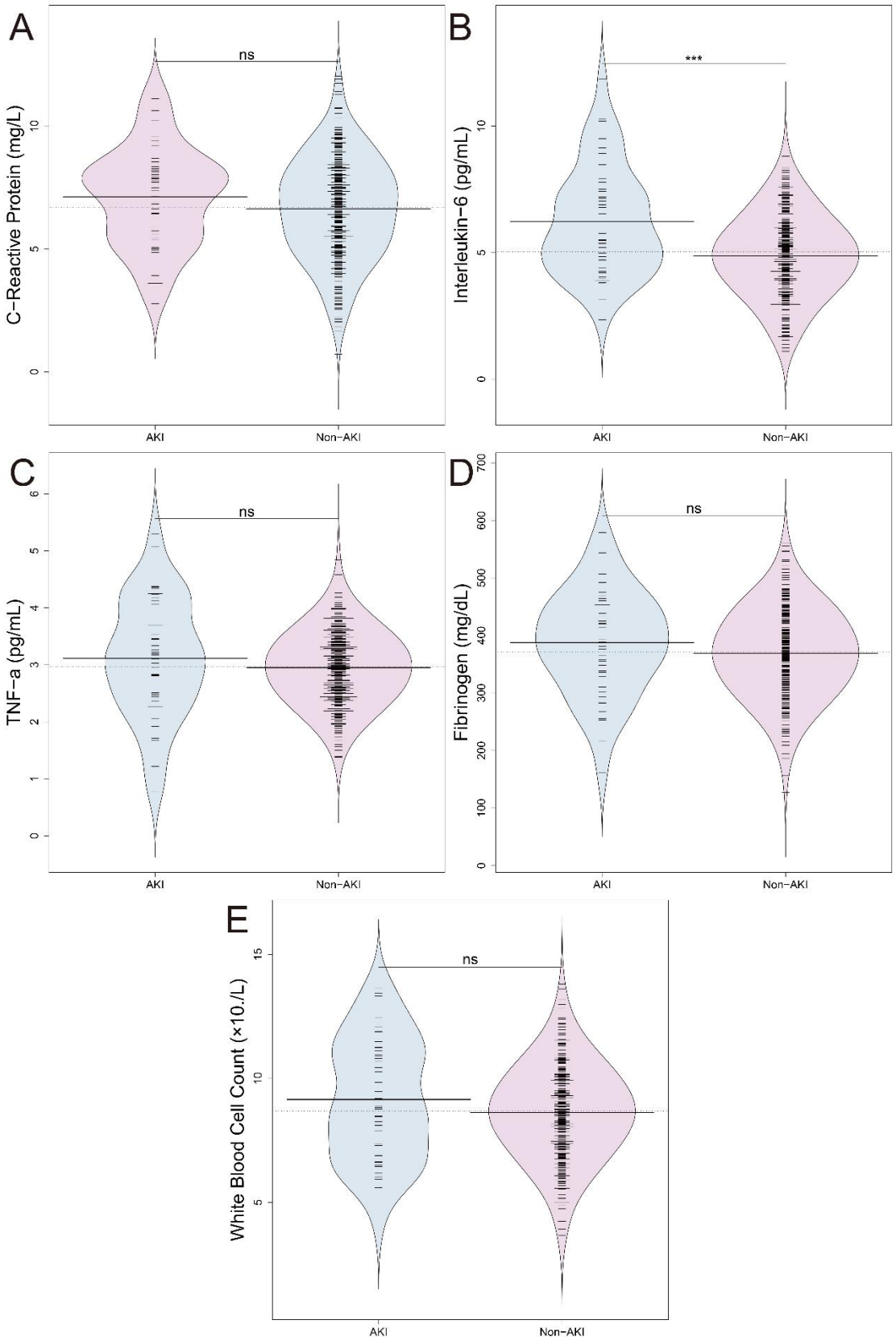

Fig. 3. Inflammatory markers. Note: TNF, tumor necrosis factor. (A) CRP (C-reactive protein); (B) IL-6 (Interleukin-6); (C) TNF-α (Tumor necrosis factor-alpha); (D) Fibrinogen; (E) WBC (White blood cell count). ***$p < 0.001$ (indicates a statistically significant difference). ns: not significant ($p > 0.05$).

Table 3. Renal function parameters.

Parameter	Non-AKI (n = 320)	AKI (n = 45)	*t*	*p*
Serum Creatinine (mg/dL)	1.18 ± 0.23	1.22 ± 0.38	0.549	0.585
eGFR (mL/min/1.73 m^2)	68.54 ± 15.87	64.76 ± 12.43	1.533	0.126
Blood Urea Nitrogen (mg/dL)	24.76 ± 5.43	25.32 ± 6.65	0.629	0.529
Cystatin C (mg/L)	0.97 ± 0.21	1.02 ± 0.35	0.853	0.398
Urine Albumin-to-Creatinine Ratio (mg/g)	98.54 ± 29.76	106.65 ± 32.43	1.692	0.092

Note: eGFR, estimated Glomerular Filtration Rate; AKI, Acute Kidney Injury

Table 4. Contrast media and procedure-related factors.

Factor	Non-AKI (n = 320)	AKI (n = 45)	*t*	*p*
Contrast Media Volume (mL)	142.45 ± 45.76	154.76 ± 42.34	1.704	0.089
Procedure Duration (min)	48.76 ± 12.54	52.32 ± 18.76	1.234	0.223
Fluoroscopy Time (min)	10.65 ± 3.21	11.43 ± 4.87	1.035	0.306
Number of Stents	1.62 ± 0.47	1.76 ± 0.58	1.901	0.058
Mehran Risk Score	8.63 ± 2.76	9.37 ± 3.04	1.662	0.097

an OR of 1.118, and a 95% CI of 1.072 to 1.166. Lp(a) also emerged as a significant predictor, with a coefficient of 0.046 ($p = 0.005$), an OR of 1.047, and a 95% CI of 1.014 to 1.080. IL-6 was strongly predictive of AKI, with a coefficient of 0.536 ($p < 0.001$), an OR of 1.710, and a 95% CI of 1.355 to 2.157. Conversely, total protein levels were inversely associated with AKI, shown by a coefficient of –0.700 ($p = 0.037$), an OR of 0.497, and a 95% CI of 0.257 to 0.960 (Table 5). These findings highlight that higher levels of RBP, Lp(a), and IL-6 are associated with increased risk of AKI, while higher total protein levels are protective against AKI.

Discussion

This case-control analysis explored the predictive power of serum RBP, Lp(a) and inflammatory/nutritional indicators for CI-AKI after CAG. RBP, which serves as a carrier for retinol (vitamin A), exhibited a significant association with CI-AKI in our study cohort. Increased RBP correlated with heightened risk of post-CAG AKI occurrence. The underlying mechanism may be related to the dual role of RBP in renal physiology and pathology. RBP is primarily filtered in the glomeruli and reabsorbed in the proximal tubules [21,22]. Under pathological conditions, such as oxidative stress or inflammation induced by contrast agents, proximal tubular cells might be damaged, leading to impaired reabsorption and subsequent elevation of RBP in the serum. This elevated RBP could act as a marker of early tubular dysfunction, reflecting subclinical kidney injury before it becomes clinically evident. Additionally, RBP is known to induce pro-inflammatory cytokines, which might further exaggerate renal injury via inflammatory pathways, creating a vicious cycle that predisposes patients to CI-AKI [23,24].

Lp(a) — a lipid marker significantly linked to CI-AKI — portends heightened cardiopathy risk. Elevated Lp(a) levels were found to be higher in our AKI group, suggesting that lipoprotein levels might aggravate renal injury. The pathophysiology of Lp(a) in CI-AKI can be attributed to its structural similarities with plasminogen, which impair fibrinolysis and promote thrombosis. This pro-thrombotic state can exacerbate renal microcirculation, leading to ischemia and hypoxia within the kidney, thereby increasing susceptibility to AKI [25,26]. Furthermore, Lp(a) carries oxidized phospholipids, which can induce oxidative stress and atherosclerosis, both of which may contribute to renal endothelial dysfunction and subsequent AKI following contrast media exposure.

In terms of inflammatory markers, our study identified IL-6 as a strong predictor of CI-AKI. IL-6 is a cytokine involved in the acute phase response and is known for its role in modulating immune responses and inflammation. Elevated IL-6 levels can enhance the inflammatory milieu within the kidneys, promoting leukocyte infiltration, endothelial activation, and further release of other pro-inflammatory cytokines. Augmented inflammation may instigate amplified vascular leakage, tubule cell demise and necrosis [27–29]. The association between IL-6 and CI-AKI underscores the significance of inflammation in the pathogenesis of CIN. It suggests that patients with elevated IL-6 are in a state of heightened systemic inflammation, predisposing them to renal damage upon exposure to contrast agents.

Oppositely, total protein concentrations exhibited negative correlation with CI-AKI susceptibility. Lower total protein levels might reflect poor nutritional status or underlying chronic inflammation, both of which can have deleterious effects on kidney function. Malnutrition and hypoalbuminemia, often reflected in low total protein levels, can compromise the antioxidant defense system, making renal tissues more vulnerable to oxidative damage caused by con-

Table 5. Multivariate logistic regression analysis of AKI.

Parameter	Coefficient	Std Error	Wald Stat	*p*	OR	OR_CI_Lower	OR_CI_Upper
Retinol-Binding Protein (mg/L)	0.111	0.021	5.214	<0.001	1.118	1.072	1.166
Lipoprotein A (mg/dL)	0.046	0.016	2.809	0.005	1.047	1.014	1.080
Interleukin-6 (pg/mL)	0.536	0.119	4.516	<0.001	1.710	1.355	2.157
Total Protein (g/dL)	–0.700	0.336	–2.081	0.037	0.497	0.257	0.960

trast agents [30]. Moreover, albumin has been shown to have a role in binding and neutralizing toxic substances, including free radicals and inflammatory mediators. Therefore, adequate nutritional status, indicated by higher total protein levels, might protect against the development of CI-AKI by enhancing the body's resilience to oxidative and inflammatory insults.

The findings of our study also suggest a multifactorial interaction among these biomarkers in the development of CI-AKI. The simultaneous elevation of RBP, Lp(a), and IL-6 points towards a complex interplay between oxidative stress, inflammation, and lipid metabolism in the pathogenesis of CI-AKI. Contrast agents can trigger oxidative stress through two main mechanisms: by directly producing reactive oxygen species (ROS) or indirectly by causing hypoxia due to vasoconstriction. This oxidative stress can disrupt cellular homeostasis, leading to apoptosis and necrosis of renal tubular cells. In tandem, the inflammatory response, characterized by elevated IL-6, exacerbates the damage by promoting further ROS production and recruiting immune cells to the site of injury. Lp(a), through its pro-thrombotic and oxidative properties, adds another layer of complexity to this pathogenic model by impairing renal microcirculation and contributing to the ischemic injury. Together, these factors create an environment in which the kidneys are highly susceptible to damage following contrast exposure [31–33].

Our study also offers implications for clinical practice. Utilizing these markers to identify individuals at heightened risk of CI-AKI facilitates personalized prevention maneuvers, including pre-procedural hydration, implementation of low- or iso-osmolar contrast media, and restriction of contrast dose. Additionally, interventions aimed at modulating these biomarkers, like anti-inflammatory treatments or nutritional optimization, might offer therapeutic benefits in reducing the incidence of CI-AKI. For instance, agents targeting IL-6 or strategies aimed at reducing oxidative stress might prove beneficial in high-risk patients.

Recognizing the limitations of this study is crucial. As a retrospective analysis, it is inherently limited by potential biases in data collection and patient selection. Additionally, this observational study refrains from asserting causal connections, necessitating confirmation through prospective, randomized controlled trials. Furthermore, the study did not include external validation in an independent cohort, which is essential for confirming the general applicability of the identified biomarkers. While we accounted for several known risk factors for CI-AKI, other potential confounders related to contrast agent use, procedural details, or comorbidities were not extensively discussed. It should also be noted that the degree of acute renal dysfunction experienced by patients post-coronary angiography was not stratified and graded, limiting our ability to fully characterize the severity of renal injury. Lastly, although the study identified biomarkers associated with CI-AKI, the underlying mechanisms linking these biomarkers to AKI were not thoroughly explored. Understanding the pathophysiological basis would provide deeper insights into the roles of these biomarkers.

Conclusion

In summary, our study highlights the significant predictive value of serum RBP, Lp(a), IL-6, and total protein levels in assessing the risk of CI-AKI following CAG. These biomarkers reflect different pathological mechanisms-tubular dysfunction, pro-thrombotic state, systemic inflammation, and nutritional status-that converge to increase the likelihood of renal injury upon contrast exposure. Understanding these interactions not only enhances our comprehension of CI-AKI pathogenesis but also underscores the potential for biomarker-driven preventive and therapeutic strategies in clinical practice. Future research should focus on validating these findings and exploring targeted interventions that might mitigate the risk of CI-AKI in vulnerable populations.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Author Contributions

GM: Developed and planned the study, performed experiments, and interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions. XF: Participated in collecting, assessing, and interpreting the data. Made significant contributions to date interpretation and manuscript preparation. The manuscript

has neither been previously published nor is under consideration by any other journal. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

This study was approved by The Affiliated Taizhou People's Hospital of Nanjing Medical University (KY2024-127-01). Informed consent was waived by the Taizhou People's Hospital's IRB and Ethics Committee.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

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