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Research Article

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Predictive Value of Combined Lipoprotein(a) and hs-CRP for Contrast-Induced Acute Kidney Injury After PCI in Elderly Patients With Acute Coronary Syndrome

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Background: Notwithstanding the evolution of safer contrast media and optimized hydration protocols, renal injury persists as a frequent sequela in the clinical management of acute coronary syndromes. This enduring risk stems inherently from the obligatory exposure to iodinated agents required to perform life-saving PCI.

Objective: To evaluate whether pre-procedural high-sensitivity C-reactive protein (hs-CRP) combined with lipoprotein(a) [Lp(a)] improves prediction of CI-AKI after PCI in elderly patients with ACS.

Methods: This retrospective study included 1,321 elderly ACS patients (age ≥60 years) treated with PCI from 2020 to 2024. The cohort was split into training and

validation sets (7:3). Following the definition of CI-AKI based on established criteria, data collection encompassed baseline laboratory and clinical parameters obtained 24 hours pre-procedure. Candidate variables were identified via LASSO regression and subsequently entered into a multivariable logistic model. These analyses culminated in the development of a risk-prediction nomogram using R software. Performance evaluation involved plotting ROC curves and estimating AUC values. Crucially, the assessment prioritized verifying if the dual addition of Lp(a) and hs-CRP improved prognostic accuracy relative to their standalone counterparts.

Results: Diuretic use, smoking, blood urea nitrogen (BUN), hemoglobin A1c (HbA1c), Lp(a), and hs-CRP were independently associated with CI-AKI after PCI. The combined biomarker model (hs-CRP + Lp(a)) achieved an AUC of 0.857 (95% CI 0.831–0.883), with 70.2% sensitivity and 77.2% specificity, outperforming either biomarker alone.

Conclusion: Hs-CRP and Lp(a) were independent predictors of CI-AKI in elderly ACS patients undergoing PCI. Their combination improved risk discrimination and may aid pre-procedural risk stratification and targeted prevention.

Keywords: Lipoprotein(a), high-sensitivity C-Reactive Protein, elderly patients, acute coronary syndrome, contrast-induced acute kidney injury

Introduction

Despite safer contrast media and optimized hydration protocols, renal injury remains common in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI).[1] This risk arises from necessary exposure to iodinated contrast agents, which is associated with prolonged hospitalization and adverse

long-term outcomes.[2] Because established clinical risk scores are often impractical to calculate during time-critical emergencies,[3] there is a pressing need for accessible, pre-procedural biomarkers to improve early risk stratification in this vulnerable population.[4]

The development of CI-AKI is complex, involving multiple pathophysiological pathways.[5] Previous studies have shown that high lipoprotein(a) [Lp(a)] levels are associated with cardiovascular and CI-AKI risk,[6,7] and that elevated high-sensitivity C-reactive protein (hs-CRP) is an independent predictor of adverse outcomes.[8] However, they are predominantly evaluated in isolation. Mechanistically, Lp(a) contributes to vascular inflammation and thrombosis, whereas hs-CRP reflects systemic inflammation. It remains unknown whether combining Lp(a) with hs-CRP offers new predictive insight beyond known predictors. Furthermore, this combination has not been adequately studied before in elderly ACS patients, a cohort with unique physiological responses and heightened baseline inflammation.[9]

Materials and Methods

Study Population

In this single-center retrospective cohort study, clinical data were obtained from consecutive patients undergoing PCI in the coronary care unit of the Affiliated Hospital of Xuzhou Medical University from 2020 to 2024. A total of 1,321 elderly patients with ACS (age ≥60 years) met the eligibility criteria. Patients were randomly divided into a training cohort (n=925, 70%) and a validation cohort (n=396, 30%), a standard ratio chosen to balance adequate model development with reliable internal validation.

Eligibility criteria

Inclusion criteria:

- Age ≥60 years.
- A diagnosis of ACS, including STEMI, NSTEMI, or unstable angina, based on symptoms, ECG findings, and cardiac biomarkers (troponin) as applicable.[10]
- PCI performed during the index hospitalization.
- Complete clinical records available.

Exclusion criteria:

- Missing pre-or post-procedural renal function data (including serum creatinine).
- Severe valvular heart disease requiring surgical intervention.
- Active systemic infection.
- History of malignancy.
- Severe hepatic dysfunction.

Patient selection flow is shown in Figure 1.

Definition

CI-AKI was determined by observing a post-procedural creatinine increment of ≥0.3 mg/dL or a ≥ 50 % rise from baseline within a 3-day window, provided that confounding renal insults were ruled out.[11]

Regarding hematological status, patients were classified as anemic if hemoglobin concentrations were found to be <130 g/L (men) or <120 g/L (non-pregnant women).[12]

The likelihood of developing nephropathy was assessed using the standard 2004 Mehran risk score. This algorithm allocates specific points to predictive factors: hemodynamic instability (hypotension, IABP use) and heart failure carry 5 points

each, followed by age >75 years (4 points), and metabolic/hematologic factors like diabetes and anemia (3 points each). Additionally, contrast dosage adds 1 point for every 100 mL administered. Pre-existing renal impairment is weighted between 2 and 6 points based on eGFR or fixed at 4 points for elevated serum creatinine (>1.5 mg/dL). Final risk stratification is defined as follows: ≤5 (low), 6–10 (moderate), 11–15 (high), and ≥16 (very high).

The Mehran 2 (2021) pre-procedural risk score (Model 1) was calculated using baseline variables only. The score assigns points for ACS (4), heart failure or impaired ejection fraction (3–5), chronic kidney disease stage (2–6 by eGFR), diabetes (2), anemia (2), and age ≥75 years (2). Patients were categorized as low (0–2), moderate (3–7), high (8–11), and very high (≥12) risk.

Data collection

Data for the present study were retrieved from the electronic medical record (EMR) system of our institution. Demographic characteristics and clinical covariates encompassed age, sex, smoking status, and comorbid medical conditions. Pre-procedural laboratory tests performed within 24 hours prior to PCI (with timing as close to the index procedure as feasible) included white blood cell count, red blood cell count, hemoglobin, platelets, total bilirubin, albumin, fasting glucose, serum creatinine, hs-CRP, Lp(a), as well as other routine biochemical parameters. Variables with a missing data rate exceeding 30% were excluded from the final analysis. For the remaining missing data points, multiple imputation by chained equations (MICE) was employed for imputation.

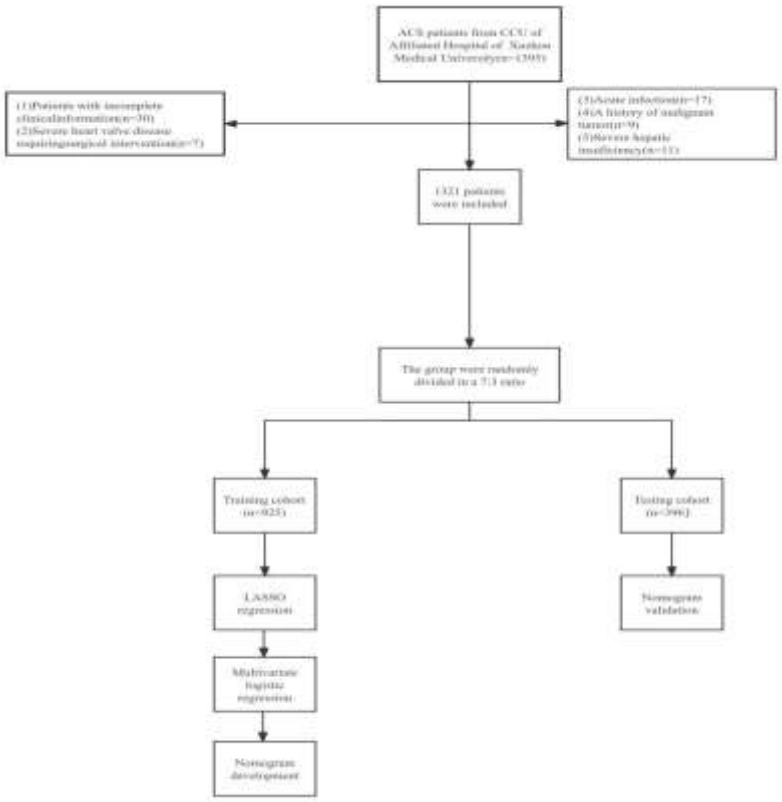


Figure 1 The flowchart summarizes patient selection and analyses for elderly ACS patients undergoing PCI.

Statistical Analysis

All analyses were performed using R (v4.5.1). Continuous variables were assessed for normality. As all continuous variables were found to be non-normally distributed, they are presented as medians (interquartile ranges) and compared using the Mann-Whitney U test. Categorical variables are presented as counts (percentages) and compared using the chi-square test.Missing data were addressed using multiple imputation to minimize bias. To construct the prediction model, a combined data-driven and clinically guided strategy was employed. Potential predictors were first screened via LASSO regression (glmnet package), with the optimal penalty parameter determined by 10-fold cross-validation. Subsequently, the variables

identified by LASSO, alongside essential clinical confounders, were incorporated into a multivariable logistic regression model (glm) to isolate independent predictors of CI-AKI. The final model coefficients were translated into a risk-prediction nomogram using the rms package. For performance assessment, receiver operating characteristic (ROC) curves were generated via the pROC package. Calibration was validated using the Hosmer‑Lemeshow test (ResourceSelection package) and calibration curves (rms package). Finally, net clinical benefit was gauged via decision curve analysis (dca.R). Subgroup analyses were pre-specified across 7 clinical variables: age, sex, diabetes, chronic kidney disease, prior heart failure, anemia, and contrast volume. To properly assess effect modification on CI-AKI risk, interaction terms were incorporated into the full multivariable models rather than running separate stratified models. Given the risk of type I error from multiple testing, these interactions are interpreted cautiously as exploratory.

Results

Basic Information Comparison

There were statistically significant differences in smoking, Hypotension,female distribution, Contrast agent dosage,Contrast agent,Killip Classification,left ventricular ejection fraction, SBP,Aspirin and diuretic between the two groups ($P < 0.05$). No statistically significant differences were observed in other indicators ($P > 0.05$), as detailed in.Table 1

Comparison of Preoperative Laboratory Data

The preoperative levels of Serum uric acid, Serum creatinine, LDH, CKMB, hsTnT, TC,Hemoglobin,LDL-C,HDL-C,TBIL,FPG,hs-CRP,Neutrophil,Lymphocyte,RBC,M

ehran2 score,and Mehran score,showed statistically significant differences between the two groups ($P<0.05$), while the remaining indicators showed no significant differences ($P > 0.05$), with detailed results presented in Table 2.

Table 1 The Comparison of Basic Information Between the Two Groups of Patients

	CI-AKI (n=218)	Non-CI-AKI (n=707)	P
Female (n%)	71(32.6)	150(21.2)	<0.001
Hypertension (n%)	102(45.9)	321(45.4)	0.720
Hypotension (n%)	12(5.5)	19(2.7)	0.043
Diabetes (n%)	63(28.9)	180(25.5)	0.313
CKD (n%)	9(4.1)	18(2.5)	0.225
IABP(n%)	24(11.0)	63(8.9)	0.353
Contrast agent dosage>100mL (n%)	46(21.1)	96(13.6)	0.002
Contrast agent (n%)			<0.001
Ioversol	71(32.6)	150(21.2)	
Iodixanol	147(67.4)	557(78.8)	
Killip>II(n%)	31(14.2)	53(7.5)	0.009
Smoke(n%)	84(38.5)	128(18.1)	< 0.001
Heart rate (times/min)	82.00[72.00,91.00]	80.00[72.00,90.00]	0.176
Anemia(n%)	20(9.2)	30(4.2)	0.179
History of Heart Failure(n%)	21(9.6)	46(6.5)	0.257
LVEF (%)	51.00[46.00,53.00]	51.00[48.00,56.00]	<0.001
SBP(mmHg)	120.00[108.00,139.00]	126.00[113.00,140.00]	0.021
DBP(mmHg)	70.00[60.00,80.00]	78.00[70.00,87.00]	0.164
Aspirin (n%)	213(97.7)	702(99.7)	0.048
Clopidogrel/Ticagrelor (n%)	214(98.2)	694(98.2)	0.997
Beta-blocker (n%)	182(83.5)	601(85.0)	0.586
ACEI/ARB (n%)	113(51.8)	363(51.3)	0.899
CCB (n%)	74(33.9)	203(28.7)	0.140
Diuretic (n%)	151(69.3)	345(48.8)	<0.001
Statin (n%)	216(99.1)	701(99.2)	0.924
Heparin (n%)	165(75.7)	540(76.4)	0.834

Abbreviations:LVEF, left ventricular ejection fraction; SBP,systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; ARNI, angiotensin receptor neprilysin inhibitor.HFrEF,Heart failure with reduced ejection fraction HFrEF. CKD, chronic kidney disease.IABP,Intra-Aortic Balloon Pump

Table 2 The Comparison of Laboratory Information Between the Two Groups of Patients

	CI-AKI (n=218)	Non-CI-AKI (n=707)	P
BUN(mmol/L)	5.83[4.71,7.16]	5.67[4.74,6.95]	0.421
Serum uric acid(μmol/L)	291.00[227.00,339.00]	313.00[257.00,380.00]	<0.001
Serum creatinine(μmol/L)	65.00[55.00,76.50]	57.00[47.00,68.00]	<0.001
eGFR [mL/(min·1.73m²)]	110.38[88.60,129.93]	123.56[95.55,152.38]	0.297
Cys C(mg/L)	0.90[0.69,1.31]	0.89[0.68,1.19]	0.567
LDH (U/L)	572.50[373.00,949.00]	490.00[298.50,721.00]	<0.001
CKMB (ng/mL)	44.34[9.59,127.40]	18.08[3.66,89.14]	<0.001
hsTnT (ng/L)	638.70[102.40,2022.00]	279.30[38.28,1554.00]	<0.001
NTproBNP (pg/mL)	573.50[208.00,1748.00]	405.00[105.50,1579.50]	0.002
TC(mmol/L)	4.35[3.72,5.22]	4.22[3.63,4.89]	0.035
TG(mmol/L)	1.30[0.91,1.87]	1.26[0.88,1.85]	0.212
LDL-C(mmol/L)	2.83[2.18,3.53]	2.62[2.10,3.21]	0.010
HDL-C(mmol/L)	0.94[0.81,1.12]	1.03[0.84,1.23]	0.003
DBIL(μmol/L)	5.62[4.30,7.80]	5.20[4.00,6.80]	0.010
TBIL(μmol/L)	15.00[10.00,21.00]	13.00[10.00,18.00]	0.048
PAB(mg/L)	0.21[0.17,0.25]	0.21[0.17,0.25]	0.732
Albumin(g/L)	38.10[35.45,40.70]	38.20[35.80,41.20]	0.023
AT3(%)	86.00[78.00,93.60]	87.00[79.00,94.90]	0.255
HbA1c (%)	6.50[5.60,7.50]	6.00[5.10,6.60]	0.382
FPG(mmol/L)	6.46[5.39,8.82]	5.93[5.18,7.67]	<0.001
Sd-LDL(mmol/L)	0.80[0.51,1.20]	0.74[0.51,1.09]	0.340
hs-CRP(mg/L)	3.40[1.60,14.90]	2.90[0.80,8.60]	<0.001
Leukocyte(10^9/L)	10.10[8.40,12.20]	9.90[8.00,12.05]	0.387
Neutrophil(10^9/L)	8.30[6.48,10.33]	7.56[5.62,9.85]	0.002
Lymphocyte(10^9/L)	1.15[0.80,1.60]	1.40[1.00,2.05]	<0.001
RBC(10^9/L)	4.55[4.05,4.93]	4.60[4.21,5.00]	0.041
Hemoglobin(g/L)	138.00[123.00,149.00]	141.00[129.00,153.00]	0.008
Platelet(10^9/L)	202.00[174.00,239.00]	209.00[177.00,251.00]	0.110
Platelet distribution width(%)	15.00[11.40,16.30]	13.80[11.30,16.20]	0.272

	CI-AKI (n=218)	Non-CI-AKI (n=707)	P
Lipoprotein(a) (mg/L)	237.00[142.00,376.00]	220.00[143.00,363.50]	0.399
Mehran score	3.00[0.00,6.00]	3.00[0.00,5.00]	<0.001
Mehran2 score	5.00[4.00,6.00]	4.00[4.00,6.00]	<0.001

Abbreviations: BUN,blood urea nitrogen;eGFR, estimated Glomerular Filtration Rate; CK, Creatine Kinase; CK-MB, Creatine Kinase-Muscle/Brain; NTproBNP, N-terminal pro-B-type natriuretic peptide; Cys C, Cystatin C;TC,total cholesterol;TG,Triglyceride;LDH, lactate dehydrogenase;LDL-C, low-density lipoprotein cholesterol;HDL-C,high-density lipoprotein cholesterol;DBIL,DirectBilirubin;TBIL,total bilirubin;PAB,Prealbumin;HbA1c,Hemoglobin A1c; FPG, fasting plasma glucose;Sd-LDL, small and dense low-density lipoprotein; hs-CRP, highly sensitiveC-reactive protein; RBC, red blood cell.Lp(a),Lipoprotein(a)

LASSO Clinical Feature Selection

A total of 56 candidate variables were incorporated into the LASSO model, designating CI-AKI as the dependent outcome. Using 10-fold cross-validation, the optimal penalty parameter (lambda.1se) was 0.01479716. Six predictors were retained: smoking, hs-CRP, HbA1c, diuretic use, BUN, and Lp(a) (Figure 2A and 2B).

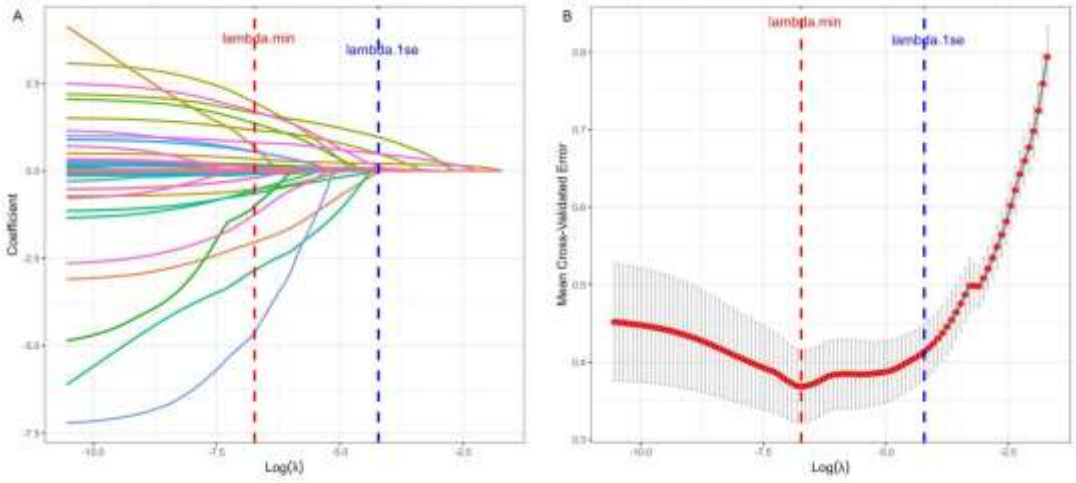


Figure 2 This is LASSO regression. (A)This graph shows the coefficient curve of the independent variable. (B)This graph shows the selection of the optimal independent variable by LASSO regression and 10-fold cross-validation.

Non-linear associations of hs-CRP and Lp(a) with CI-AKI

To characterize the dose-response curve, multivariable restricted cubic splines were employed. Our analysis unveiled a curvilinear association linking the biomarkers to the development of CI-AKI, a pattern that persisted even after controlling for potential clinical confounders. For hs-CRP, a clinically relevant threshold emerged at 3.1 mg/L: values below this concentration demonstrated neutral renal effects, whereas concentrations exceeding this threshold were associated with progressively elevated odds of CI-AKI (Figure 3). Lp(a) exhibited a more complex trajectory—risk remained negligible below 215 mg/L, rose steeply to a peak odds ratio at 436 mg/L (suggesting

maximal renal vulnerability within this range), and subsequently attenuated at higher concentrations (Figure 4).

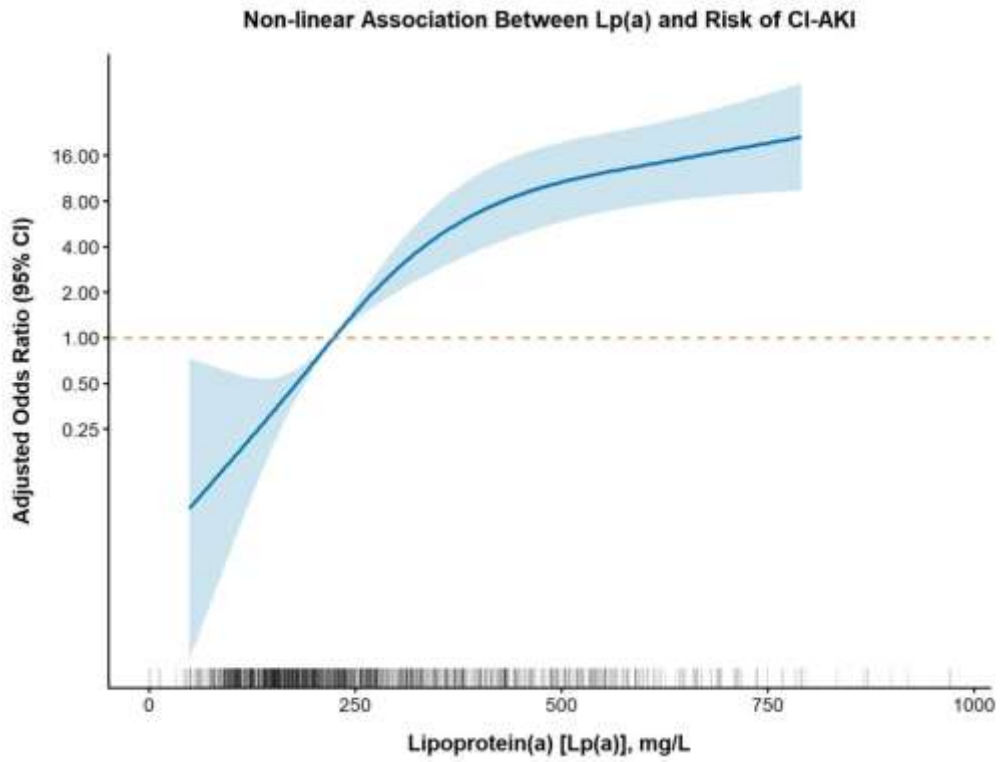


Figure 3 Nonlinear associations between Lp(a) concentration and the prevalence of CI-AKI.

Abbreviations: Lpa, Lipoprotein(a); CI-AKI, contrast-induced acute kidney injury

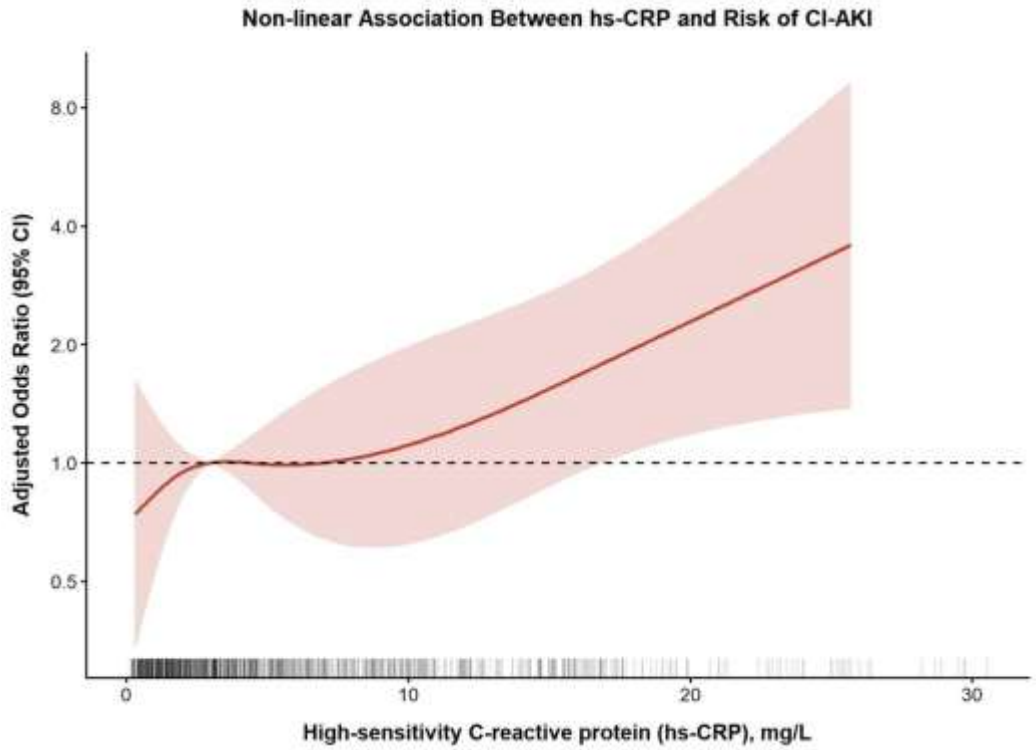


Figure 4 Nonlinear associations between hsCRP concentration and the prevalence of CI-AKI.

Abbreviations: hsCRP, high-sensitivity C-reactive protein; CI-AKI, contrast-induced acute kidney injury

Independent predictors of CI-AKI

The six variables selected by LASSO were entered into a multivariable logistic regression model (Table 3). Smoking was associated with higher odds of CI-AKI (adjusted OR 1.88, 95% CI 1.03–3.43; P=0.039), and diuretic use showed a strong association (adjusted OR 5.11, 95% CI 2.77–9.45; P<0.001). HbA1c was also associated with CI-AKI (adjusted OR 1.07; P=0.028). For spline-modeled predictors, BUN, hs-CRP, and Lp(a) demonstrated significant overall associations with evidence of non-linearity (P for non-linearity <0.001). Multivariable analyses identified all six variables as independent determinants of CI-AKI in elderly ACS patients after PCI.

Table 3 Multivariate Logistic Regression Analysis of CI-AKI Incidence

Predictor	Modeling	Adjusted OR (95% CI)	P (overall)	P (non-linear)
Smoke (yes vs no)	Linear	1.88 (1.03, 3.43)	0.039	
HbA1c (per 1%)	Linear	1.07 (1.05, 1.28)	0.028	
Diuretic (yes vs no)	Linear	5.11 (2.77, 9.45)	<0.001	
BUN	RCS (4 knots)	2.24 (1.65, 3.69)	<0.001	<0.001
hs-CRP	RCS (4 knots)	3.16 (2.08, 6.07)	<0.001	<0.001
Lp(a)	RCS (4 knots)	5.65 (3.45, 9.25)	<0.001	<0.001

Added Table Note:

For continuous variables modeled with restricted cubic splines (BUN, hs-CRP, and Lp(a)), the Adjusted Odds Ratios represent the risk comparison between the 75th and 25th percentiles (interquartile range).

Abbreviations: BUN,blood urea nitrogen;HbA1c,Hemoglobin A1c;hs-CRP, highly sensitiveC-reactive protein;Lp(a),Lipoprotein(a).

Predictive value of hs-CRP and Lp(a)

In ROC analyses, Lp(a) demonstrated an AUC of 0.742 (95% CI, 0.703–0.782; P<0.001), and hs-CRP exhibited an AUC of 0.695 (95% CI, 0.653–0.738; P<0.001). The combined model incorporating hs-CRP and Lp(a) showed improved discrimination, with an AUC of 0.857 (95% CI, 0.831–0.883; P<0.001), a sensitivity of 70.2%, and a specificity of 77.2% (Figure 5).

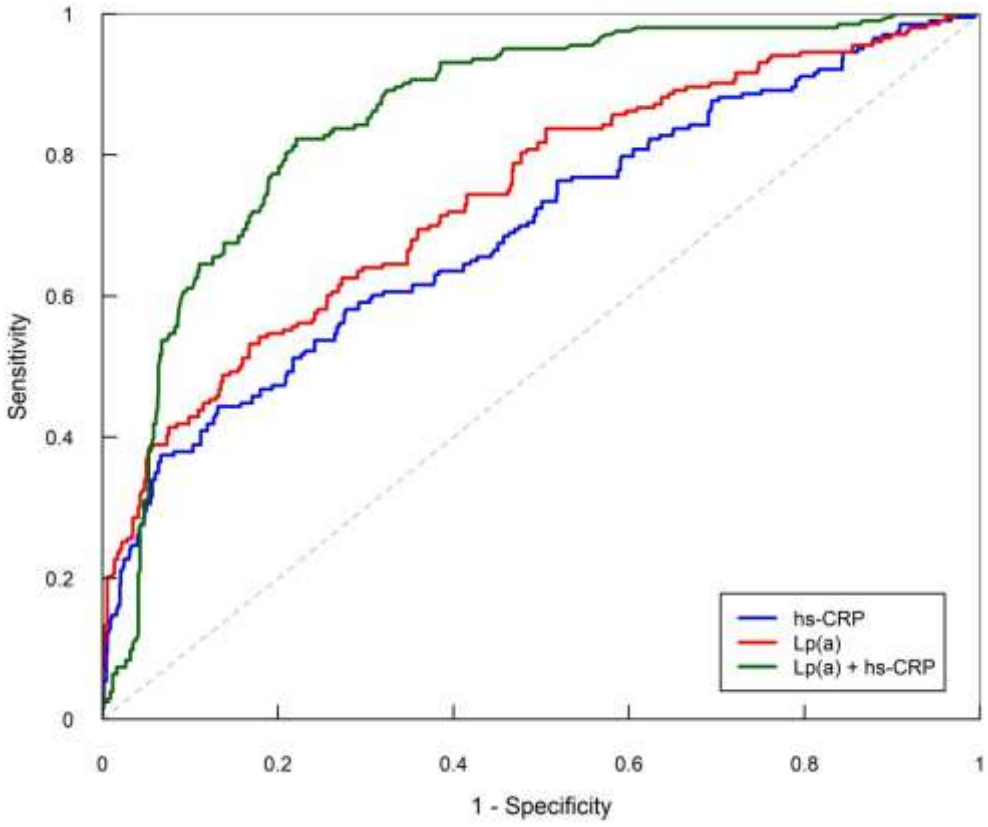


Figure 5 ROC curve of CI-AKI predicted by Lp(a), hsCRP and combined index.

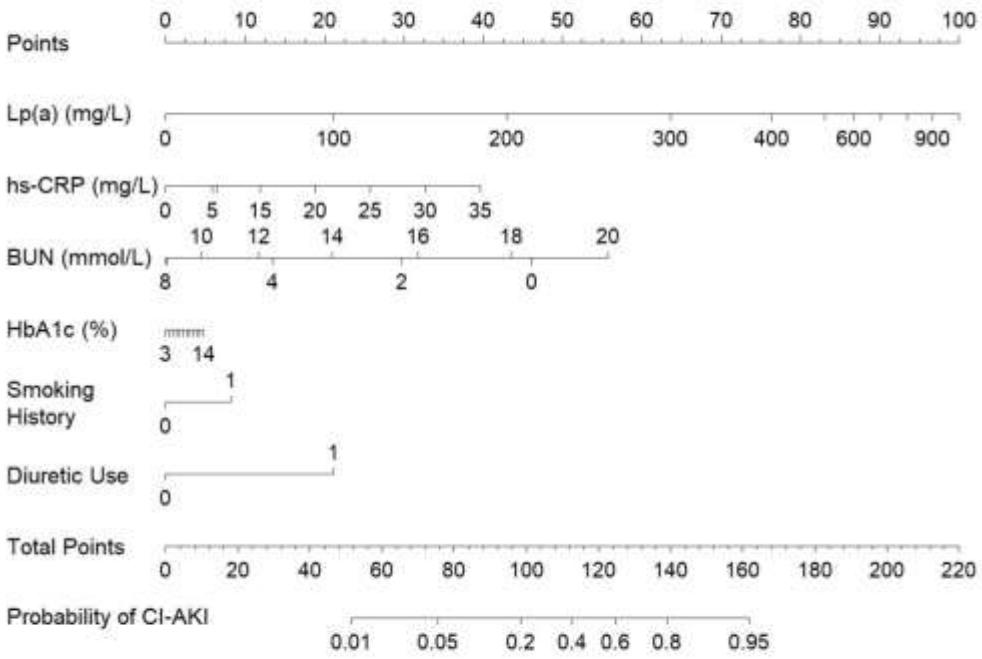
Abbreviations:Lp(a),Lipoprotein(a); hsCRP, high-sensitivity C-reactive protein.

Nomogram development and validation

A nomogram incorporating the six predictors was constructed (Figure 6). In the training cohort, the model showed strong discrimination (AUC 0.834, 95% CI 0.796–0.872), with sensitivity of 85.3% and specificity of 75.4% (Figure 7A). The Hosmer–Lemeshow test suggested good fit (χ^2=7.8954; P=0.5169), and bootstrap validation (1,000 resamples) demonstrated good agreement between predicted and observed risks (Figure 8A).

In the validation cohort, 54 of 396 patients (13.63%) developed CI-AKI. The model retained good discrimination (AUC 0.833, 95% CI 0.776–0.891; Figure 7B) and calibration (Hosmer–Lemeshow χ^2=4.728; P=0.739; Figure 8B). To facilitate bedside use, an interactive R Shiny calculator featuring an English interface (Figure 9) was developed and is freely accessible at https://zhangxishen.shinyapps.io/ciaki-predictor/, with the source code provided in the Supplementary Materials.

Figure 6 This is a nomogram of CI-AKI in ACS elderly patients after PCI.



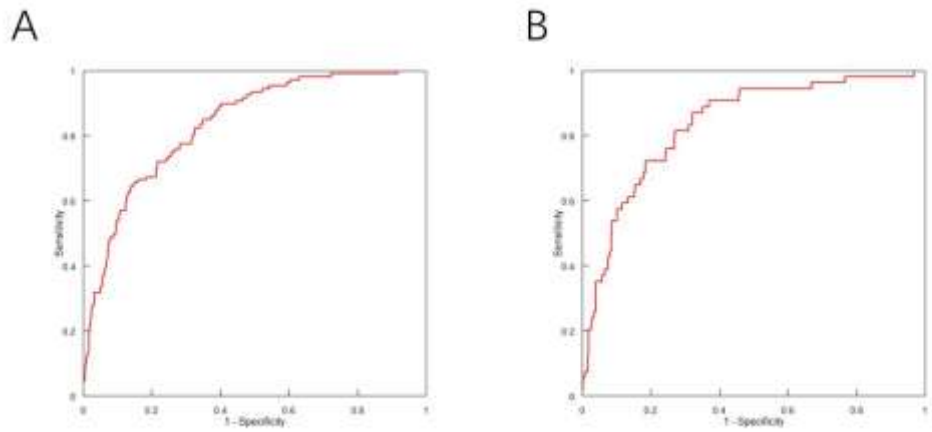


Figure 7 These two graphs are ROC curves. (A)This graph shows ROC curves for predicting CI-AKI in ACS elderly patients in training group. (B)This graph shows ROC curves for predicting CI-AKI in ACS elderly patients in validation group

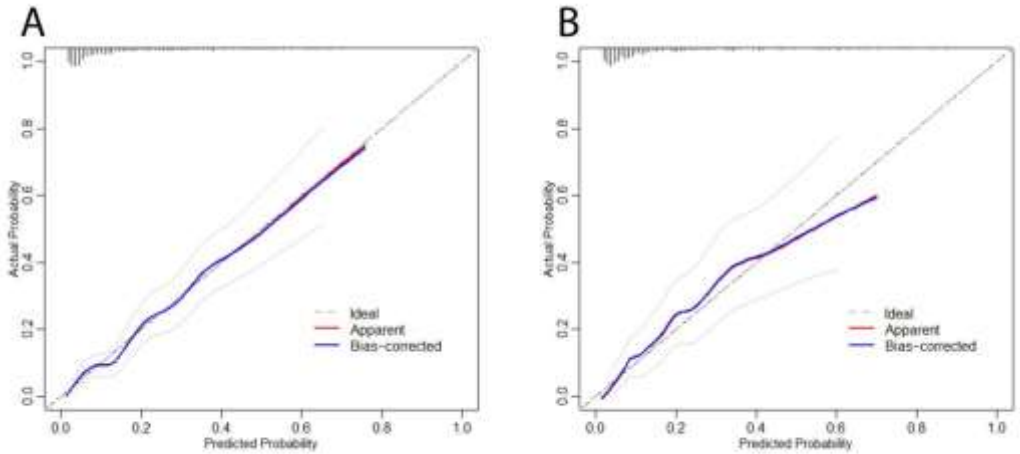


Figure 8 These two graphs are calibration curves. (A)This graph shows the calibration curve of CI-AKI in ACS elderly patients after PCI in training group. (B)This graph shows the calibration curve of CI-AKI in ACS elderly patients after PCI in validation group

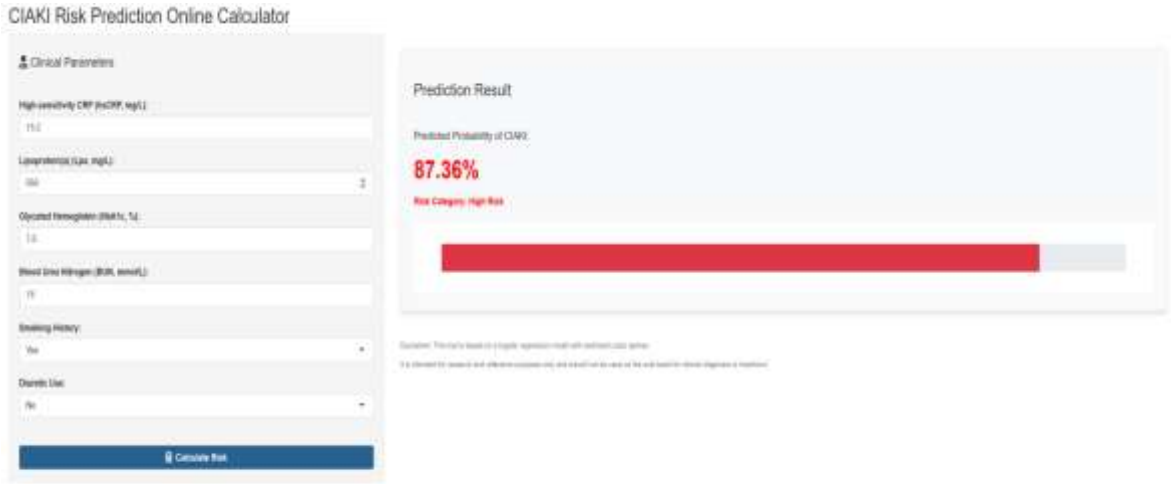


Figure 9 The online dynamic nomogram to predict CI-AKI After PCI in elderly patients with ACS.

Decision Curve Analysis and Clinical Impact Curve

Decision curve analysis was used to assess clinical utility in the training and validation cohorts. For risk thresholds exceeding roughly 0.4 in the training dataset, our model demonstrated a distinct advantage in standardized net benefit compared to the "treat-none" strategy; at lower thresholds, it performed worse than the treat-all strategy (Figure 10A). In the validation cohort, the model showed higher standardized net benefit than both default strategies across a broad range of thresholds (~0.1–0.6), suggesting potential value for guiding targeted preventive interventions (Figure 10B). The clinical impact curve (Figure 11) depicts the expected number of individuals classified as high risk and the corresponding number of true positives per 1,000 patients at different thresholds.

When compared with the Mehran and Mehran 2 scores (Figure 12), the nomogram showed superior discrimination (AUC 0.834, 95% CI 0.796–0.872) versus the Mehran score (AUC 0.663, 95% CI 0.614–0.712) and the Mehran 2 score (AUC 0.728, 95%

CI 0.684–0.771). DeLong tests indicated that the differences were statistically significant (Z=3.083; P=0.002).

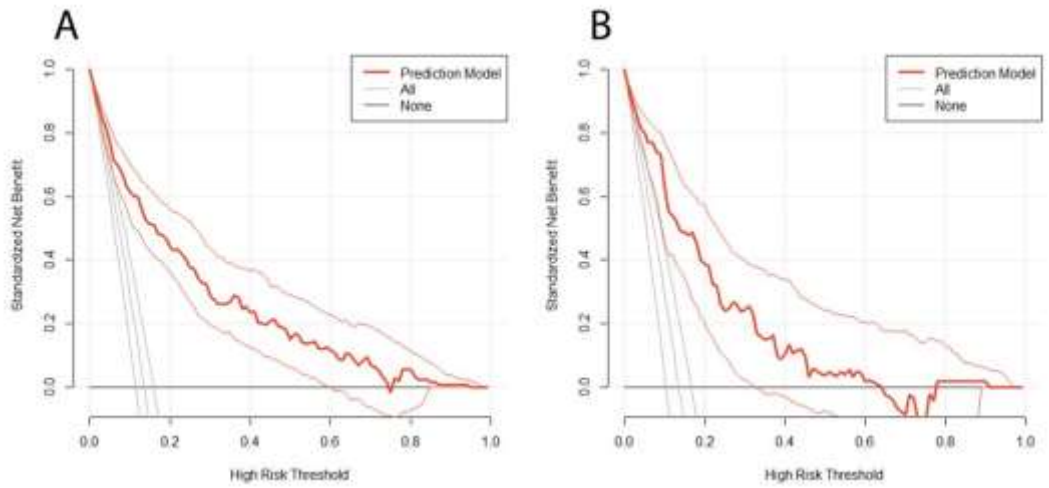


Figure 10 These two graphs are DCA curves. (A)This graph shows the DCA curve of CI-AKI in ACS patients after PCI in training group. (B)This graph shows the DCA curve of CI-AKI in ACS patients after PCI in validation group.Thin lines/shaded areas indicate the 95% confidence intervals (bootstrap, n = 1,000).

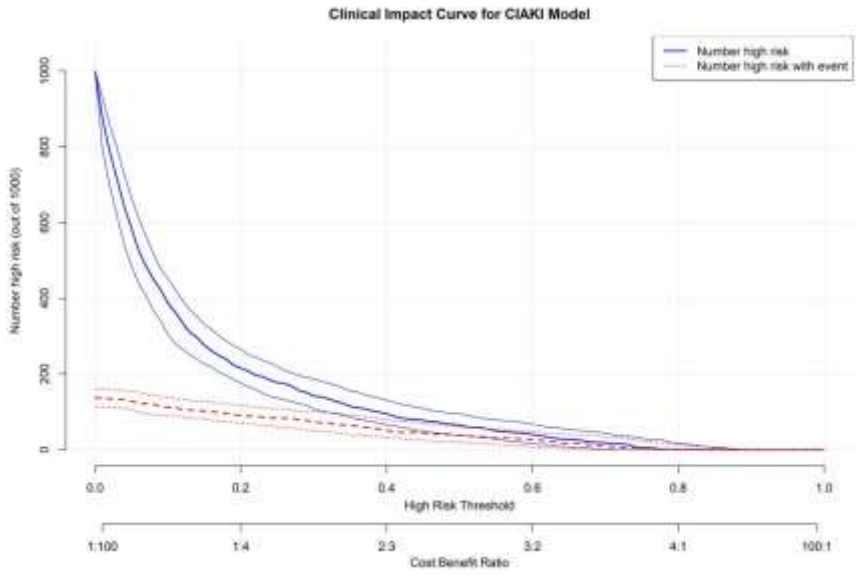


Figure 11 This is a CIC curve of CI-AKI in ACS patients after PCI.Thin lines indicate the 95% confidence intervals (bootstrap, n = 1,000).

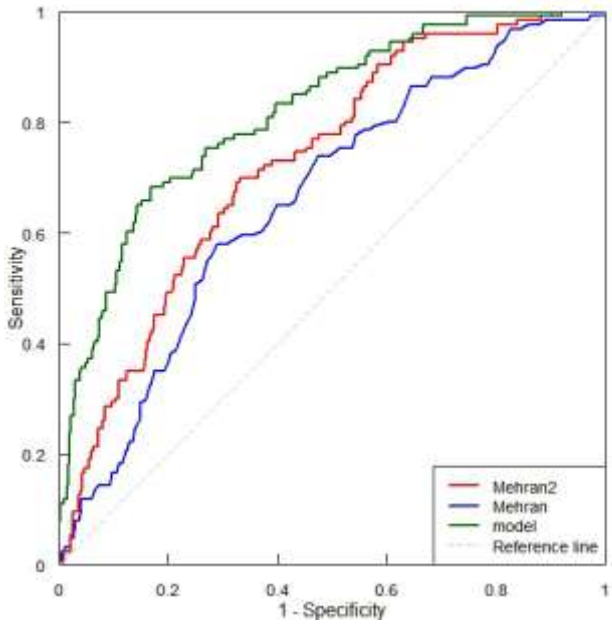


Figure 12 Comparison of ROC Curves Between Predicative CI-AKI Models

Subgroup analyse

In the pre-specified subgroup analyses (Figure 13), the associations of elevated hs-CRP and Lp(a) with increased CI-AKI risk were largely consistent across the evaluated strata. When testing for interactions within the multivariable models, the strength of the hs-CRP association was significantly modified by sex (P for interaction = 0.036). For Lp(a), significant interactions were observed for contrast volume (>100 mL; P for interaction = 0.043) and the presence of anemia (P for interaction = 0.039). Other subgroups, including diabetes, CKD, and prior heart failure, did not significantly modify these predictive effects. However, considering the multiple comparisons performed, these significant interactions are interpreted cautiously as exploratory signals rather than definitive conclusions.

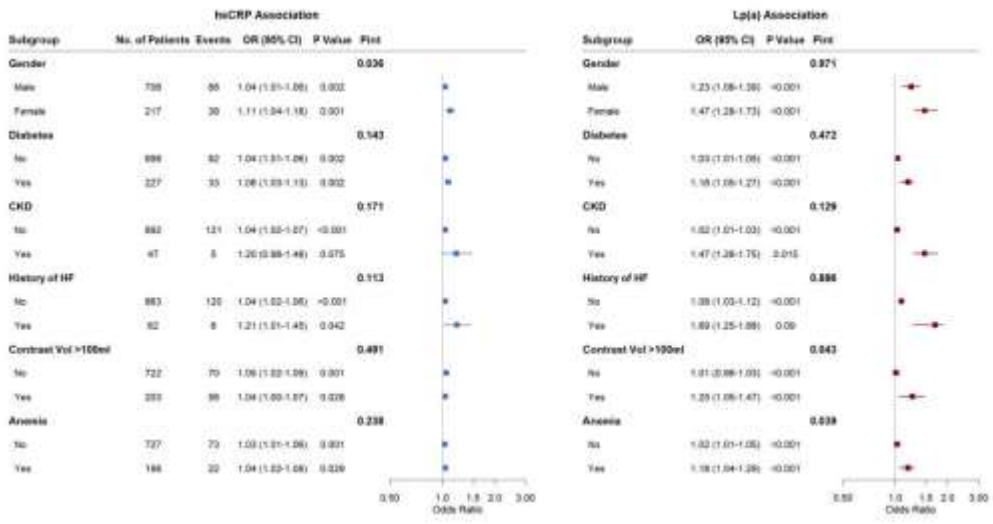


Figure 13 Subgroup analyses of hsCRP and Lp(a) in relation to CI-AKI

Discussion

In elderly patients with ACS undergoing PCI, we found that smoking, diuretic use, BUN, HbA1c, hs-CRP, and Lp(a) were independently associated with CI-AKI. A nomogram incorporating these variables showed good discrimination and calibration in both cohorts. Importantly, the superior performance of the combined hs-CRP and Lp(a) model should not be interpreted as implying biomarker specificity or causality. Rather, these two markers may capture complementary dimensions of vulnerability that are incompletely represented by conventional clinical variables, including acute inflammatory activation, endothelial dysfunction, prothrombotic tendency, and pre-existing vascular injury. This interpretation is broadly consistent with the emerging view that inflammation- and lipid-related biomarkers may add incremental value to risk assessment, but are unlikely to replace established clinical risk models when used in isolation.[13,14]

Inflammation is biologically plausible in the pathogenesis of CI-AKI. Following PCI, renal injury may result not only from direct contrast toxicity but also from medullary hypoxia, oxidative stress, endothelial dysfunction, and amplification of inflammatory cascades. Prior studies have shown that conventional inflammatory indices, including the WBC count and its differential subpopulations, are associated with CI-AKI risk.[15] Specifically, neutrophils may aggravate tubular injury through reactive oxygen species and proteolytic enzymes, whereas lymphopenia may reflect stress-related neurohumoral activation and impaired immune regulation. In a previous emergency PCI cohort, both the WBC count and, to a greater extent, the neutrophil count were independent predictors of CI-AKI.[16] Compared with single-cell inflammatory indices, composite or complementary biomarkers may better reflect the balance between inflammatory activation and host response, which may explain their improved predictive performance in several cardiovascular settings.[17]

Within this framework, hs-CRP is of particular interest because it is a sensitive marker of systemic inflammation and has been associated with AKI across cardiovascular populations.[18] Elevated hs-CRP before PCI may identify patients with heightened inflammatory tone, endothelial dysfunction, and increased susceptibility to oxidative and microvascular injury after contrast exposure.[19,20] In our study, hs-CRP $\geqslant$ 4.2 mg/L was associated with a significantly higher risk of CI-AKI, supporting the view that inflammatory priming may lower the threshold for kidney injury in elderly ACS patients. However, this finding should be interpreted cautiously. In ACS, especially in myocardial infarction, hs-CRP is not kidney-specific and may simply reflect infarct-related inflammation, tissue injury, or overall hemodynamic stress

rather than renal inflammation per se. Accordingly, hs-CRP may be better viewed as a marker of global acute-phase vulnerability than as a specific indicator of impending contrast nephrotoxicity.[21]

Lp(a) may provide complementary information of a different kind. As an LDL-like particle covalently bound to apolipoprotein(a), Lp(a) has proatherogenic, proinflammatory, and antifibrinolytic properties.[22] Unlike hs-CRP, which is strongly influenced by the acute clinical state, Lp(a) is largely genetically determined and remains relatively stable over the life course, making it an attractive marker of chronic vascular susceptibility.[23] Elevated Lp(a) has recognized value in cardiovascular risk stratification, and its biological effects — including promotion of endothelial dysfunction, oxidized phospholipid – mediated inflammation, thrombosis, and impaired fibrinolysis — make its association with renal ischemic vulnerability biologically plausible.[24,25] In our cohort, the risk of CI-AKI increased significantly when Lp(a) exceeded 215 mg/L, with evidence of a non-linear relationship at higher concentrations. Nevertheless, Lp(a) should not be interpreted as a direct marker of acute tubular injury. More plausibly, it may reflect the chronic vascular and microcirculatory substrate on which an ACS event, procedural stress, and contrast exposure interact to precipitate kidney injury.

A more critical issue concerns the definition and interpretation of the study endpoint. In ACS, particularly in patients with myocardial infarction, serum creatinine measured during the early phase of hospitalization may not represent true steady-state renal function. Reduced cardiac output, renal hypoperfusion, venous congestion, neurohumoral activation, and other acute cardiorenal perturbations may all contribute

to transient creatinine elevation independent of contrast exposure. Therefore, baseline eGFR calculated from admission creatinine may misclassify actual renal reserve, and part of the post-procedural creatinine rise may reflect the evolving ACS itself rather than contrast toxicity alone.[26] This is particularly relevant in elderly patients, in whom reduced renal reserve, frailty, and lower muscle mass may further complicate interpretation of creatinine-based estimates.

Related to this, our study adopted a relatively sensitive creatinine-based definition (serum creatinine increase $\geqslant$ 0.3 mg/dL), which may detect earlier and milder kidney injury than older definitions used in many previous CI-AKI studies, such as an absolute increase > 0.5 mg/dL or a relative increase > 25% within 2 – 3 days.[27] While this approach is consistent with contemporary AKI frameworks, it may also increase the likelihood of capturing transient or multifactorial creatinine fluctuations in the acute ACS setting. This definitional difference may partly explain variation in reported incidence rates and predictor performance across studies and should be considered when comparing our findings with earlier literature. Sensitivity analyses using alternative definitions would further strengthen the robustness and interpretability of the results.

From a clinical perspective, the combined assessment of hs-CRP and Lp(a) may help identify a subgroup of elderly ACS patients in whom acute inflammatory activation and chronic vascular/prothrombotic susceptibility coexist. Such patients may warrant more intensive preventive strategies, including optimized hemodynamic management, adequate hydration when feasible, strict minimization of contrast volume, and closer post-procedural renal surveillance. At the same time, our findings should be regarded

primarily as hypothesis-generating for risk stratification rather than proof that either biomarker is specifically involved in contrast-induced renal injury. Prospective studies are needed to determine whether integrating these biomarkers into routine clinical workflows improves decision-making, calibration across different AKI definitions, and ultimately patient outcomes.

Limitations

This study is subject to certain limitations. Given the retrospective, single-center design relying on electronic records (2020–2024), inherent selection bias exists, potentially restricting generalizability across different clinical workflows. While the model underwent random splitting and bootstrap internal validation, the lack of external validation warrants caution and necessitates future independent verification. Additionally, data constraints necessitated the exclusion of urine output criteria, limiting CI-AKI diagnosis to serum creatinine fluctuations within a 72-hour window. As a result, detection of some cases may have been compromised, and delayed kidney injury remained unassessed. Lastly, the measurement of biomarkers solely within the 24-hour pre-PCI window precluded the capture of all peri-procedural variables; therefore, residual confounding remains a possibility, and the associations observed are indicative of prediction rather than causality.

Conclusion

In this single-center retrospective study, the combined pre-procedural assessment of Lp(a) and hs-CRP improved risk prediction for CI-AKI in elderly patients with ACS. While elevated levels of both markers indicate heightened systemic inflammation and thrombotic risk, this predictive association does not justify immediate clinical action. Therefore, these biomarkers should currently serve as supplementary tools for early

risk stratification rather than definitive triggers for targeted interventions. Future prospective studies with external validation are needed to evaluate whether biomarker-guided strategies can tangibly improve clinical outcomes.

Ethic Approval

The study was approved by the Ethics Committee of The Affiliated Hospital of Xuzhou Medical University (ethics approval number: XYFY-2025-KL348-01) and informed consent was obtained from all participants. Our study was conducted in accordance with the Declaration of Helsinki.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest/Competing interests: The authors declare that they have no conflicts of interest.

Ethics approval: The study protocol was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (Approval No. XYFY2022-KL122-01). The study was conducted in accordance with the Declaration of Helsinki.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Availability of data and material: The datasets generated and analyzed during the current study are not publicly available due to strict ethical restrictions and hospital privacy regulations regarding patient confidentiality.

Code availability: The custom R code utilized for the statistical analysis and nomogram construction in this study is proprietary and not publicly available.

Clinical trial number: not applicable.

References

1. Wang Z, Yang S, Li C, et al. Development and validation of an AMR-based predictive model for post-PCI contrast-induced nephropathy in patients with acute ST-segment elevation myocardial infarction. *Front Cardiovasc Med*. 2025;12:1552762. doi:10.3389/fcvm.2025.1552762

2. Li Y, Wang J. Contrast-induced acute kidney injury: a review of definition, pathogenesis, risk factors, prevention and treatment. *BMC Nephrol*. Apr 22 2024;25(1):140. doi:10.1186/s12882-024-03570-6

3. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol*. Oct 6 2004;44(7):1393-9. doi:10.1016/j.jacc.2004.06.068

4. Lee PH, Huang SM, Tsai YC, Wang YT, Chew FY. Biomarkers in Contrast-Induced Nephropathy: Advances in Early Detection, Risk Assessment, and Prevention Strategies. *Int J Mol Sci*. Mar 21 2025;26(7)doi:10.3390/ijms26072869

5. Hoogeveen RC, Ballantyne CM. Residual Cardiovascular Risk at Low LDL: Remnants, Lipoprotein(a), and Inflammation. *Clin Chem*. Jan 8 2021;67(1):143-153. doi:10.1093/clinchem/hvaa252

6. Lambert G, Chemello K, Gallo A. Lipoprotein(a): More Than Just a Biomarker of Myocardial Fibrosis. *J Am Coll Cardiol*. Dec 12 2023;82(24):2292-2295. doi:10.1016/j.jacc.2023.10.019

7. Berman AN, Biery DW, Besser SA, et al. Lipoprotein(a) and Major Adverse Cardiovascular Events in Patients With or Without Baseline Atherosclerotic Cardiovascular Disease. *J Am Coll Cardiol*. Mar 5 2024;83(9):873-886. doi:10.1016/j.jacc.2023.12.031

8. Fröbert O, Stone GW, Larsen AI, et al. Relationships of hsCRP to High-Risk Vulnerable Plaque After NSTEMI: Insights From the PROSPECT II Trial. *JACC Cardiovasc Interv*. May 26 2025;18(10):1217-1228. doi:10.1016/j.jcin.2025.01.440

9. Krzyżak D, Basiak M, Dec A, Hachuła M, Okopień B. The Crucial Question About Contrast-Induced Nephropathy (CIN): Should It Affect Clinical Practice? *Pharmaceuticals (Basel)*. Mar 28 2025;18(4)doi:10.3390/ph18040485

10. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. Oct 12 2023;44(38):3720-3826. doi:10.1093/eurheartj/ehad191

11. Shah A, Stouffer GA. Do Novel Antidiabetic Therapies Reduce the Risk of Contrast-Associated Acute Kidney Injury? *Am J Cardiol*. Jul 1 2025;246:86-87. doi:10.1016/j.amjcard.2025.01.027

12. Zheng Y, Liu X, He Y, et al. Prevalence and morphological subtype distributions of anaemia in a Chinese rural population: the Henan Rural Cohort study. *Public Health Nutr*. Jun 2023;26(6):1254-1263. doi:10.1017/s1368980023000319

13. Antonopoulos AS, Angelopoulos A, Papanikolaou P, et al. Biomarkers of Vascular Inflammation for Cardiovascular Risk Prognostication: A Meta-Analysis. *JACC Cardiovasc Imaging*. Mar 2022;15(3):460-471. doi:10.1016/j.jcmg.2021.09.014

14. Mahapatro A, Nobakht S, Mukesh S, et al. Evaluating biomarkers for contrast-induced nephropathy following coronary interventions: an umbrella review on meta-analyses. *Eur J Med Res*. Apr 1 2024;29(1):210. doi:10.1186/s40001-024-01782-y

15. Yildiz SS, Cetinkal G, Kalendar E, et al. Inflammatory Biomarkers Predicting Contrast-Induced Acute Kidney Injury in Elderly Patients with ST-Segment Elevation Myocardial Infarction. *Diagnostics (Basel)*. May 8 2025;15(10)doi:10.3390/diagnostics15101191

16. Yuan Y, Qiu H, Hu X, et al. Predictive value of inflammatory factors on contrast-induced acute kidney injury in patients who underwent an emergency percutaneous coronary intervention. *Clin Cardiol*. Sep 2017;40(9):719-725. doi:10.1002/clc.22722

17. Qin P, Ho FK, Celis-Morales CA, Pell JP. Association between systemic inflammation biomarkers and incident cardiovascular disease in 423,701 individuals: evidence from the UK biobank cohort. *Cardiovasc Diabetol*. Apr 15 2025;24(1):162. doi:10.1186/s12933-025-02721-9

18. Mensah GA, Arnold N, Prabhu SD, Ridker PM, Welty FK. Inflammation and Cardiovascular Disease: 2025 ACC Scientific Statement: A Report of the American College of Cardiology. *J Am Coll Cardiol*. Sep 29 2025;doi:10.1016/j.jacc.2025.08.047

19. Zhang Z, Liu P, Yang L, et al. Association between the High-Sensitivity C-Reactive Protein/Albumin Ratio and New-Onset Chronic Kidney Disease in Chinese Individuals. *Nephron*. 2024;148(3):160-170. doi:10.1159/000534034

20. Santas E, Villar S, Palau P, et al. High-sensitivity C-reactive protein and risk of clinical outcomes in patients with acute heart failure. *Sci Rep*. Sep 17 2024;14(1):21672. doi:10.1038/s41598-024-72137-0

21. Liu Y, Tan N, Zhou YL, et al. High-sensitivity C-reactive protein predicts contrast-induced nephropathy after primary percutaneous coronary intervention. *J Nephrol*. May-Jun 2012;25(3):332-40. doi:10.5301/jn.5000007

22. Wong ND, Fan W, Hu X, et al. Lipoprotein(a) and Long-Term Cardiovascular Risk in a Multi-Ethnic Pooled Prospective Cohort. *J Am Coll Cardiol*. Apr 23 2024;83(16):1511-1525. doi:10.1016/j.jacc.2024.02.031

23. Bhatia HS, Wandel S, Willeit P, et al. Independence of Lipoprotein(a) and Low-Density Lipoprotein Cholesterol-Mediated Cardiovascular Risk: A Participant-Level Meta-Analysis. *Circulation*. Jan 28 2025;151(4):312-321. doi:10.1161/circulationaha.124.069556

24. Szarek M, Reijnders E, Jukema JW, et al. Relating Lipoprotein(a) Concentrations to Cardiovascular Event Risk After Acute Coronary Syndrome: A Comparison of 3 Tests. *Circulation*. Jan 16 2024;149(3):192-203. doi:10.1161/circulationaha.123.066398

25. Tsioulos G, Kounatidis D, Vallianou NG, et al. Lipoprotein(a) and Atherosclerotic Cardiovascular Disease: Where Do We Stand? *Int J Mol Sci*. Mar 21 2024;25(6)doi:10.3390/ijms25063537

26. Brankovic M, Kardys I, van den Berg V, et al; BIOMArCS Investigators. Evolution of renal function and predictive value of serial renal assessments among patients with acute coronary syndrome: BIOMArCS study. Int J Cardiol. 2020;299:12-19. doi:10.1016/j.ijcard.2019.07.052

27. Mehran R, Dangas GD, Weisbord SD. Contrast-associated acute kidney injury. N Engl J Med. 2019;380(22):2146-2155. doi:10.1056/NEJMra1805256