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Advancing Early Detection of PCI-Related Renal Injury Based on Novel Biomarkers in Patients with Acute Coronary Syndrome

Objective — To evaluate the predictive value of novel biomarkers for early detection of renal function injury following percutaneous coronary intervention (PCI) in patients with acute coronary syndrome.

Material and methods — A prospective observational study was conducted, enrolling 326 patients with acute coronary syndrome who underwent PCI at Zhangjiakou First Hospital from January to December 2024. Patients were divided into acute kidney injury (AKI) group (n=52) and non-AKI group (n=274) based on whether AKI occurred within 48 h post-PCI. Blood samples were collected at pre-PCI baseline and at 2, 6, 12, and 24 h post-procedure to measure traditional renal markers (serum creatinine, blood urea nitrogen, estimated glomerular filtration rate, Cystatin C) and novel biomarkers (neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule-1 [KIM-1], interleukin-18 [IL-18], tissue inhibitor of metalloproteinases-2 [TIMP2], insulin-like growth factor-binding protein 7 [IGFBP7], liver-type fatty acid-binding protein [L-FABP], receptor-interacting protein kinase 3 [RIPK3], and N-acetyl-β-D-glucosaminidase [NAG]). Receiver operating characteristic (ROC) curves were used to assess the predictive value of biomarkers. Multivariate logistic regression analysis was performed to identify independent predictors of AKI.

Results — AKI occurred in 52 (16%) patients. Traditional markers showed no difference between groups within 12 h post-PCI, with differences emerging only at 24 h (p<0.001). Novel biomarkers demonstrated inter-group differences at 24 h (p<0.001), with TIMP2, IGFBP7, L-FABP, RIPK3, and NAG showing elevated concentrations in the AKI group as early as 2 h post-PCI (all p<0.001). The novel biomarker combination demonstrated superior predictive performance (AUC 0.89, 95% CI 0.84–0.94) compared to traditional markers (AUC 0.71, 95% CI 0.65–0.77, p<0.001), with NGAL showing the highest individual predictive value (AUC 0.85, 95% CI 0.79–0.91). Multivariate analysis revealed that elevated NGAL >150 ng/ml at 2 h post-PCI was the strongest independent predictor of AKI (OR 3.8, 95% CI 2.1–6.9, p<0.001). The AKI group had longer hospital stays (8.5±3.2 days vs 5.2±2.1 days), higher rates of major adverse cardiac events (18.5% vs 7.3%), and increased 30-day mortality (5.8% vs 1.5%) compared to the non-AKI group (all p<0.01).

Conclusion — Novel renal injury biomarkers, particularly NGAL, KIM-1, IL-18, along with TIMP2, IGFBP7, L-FABP, RIPK3, and NAG, provide superior early detection of post-PCI AKI compared to traditional markers, with abnormal elevation detectable as early as 2 h post-procedure. Elevated NGAL at 2 h post-PCI emerged as the strongest independent predictor of AKI occurrence. Integration of novel biomarker monitoring into routine post-PCI care would facilitate early identification of high-risk patients and timely implementation of renoprotective strategies.

Keywords — Acute coronary syndrome; percutaneous coronary intervention; acute kidney injury; biomarkers; neutrophil gelatinase-associated lipocalin; early detection

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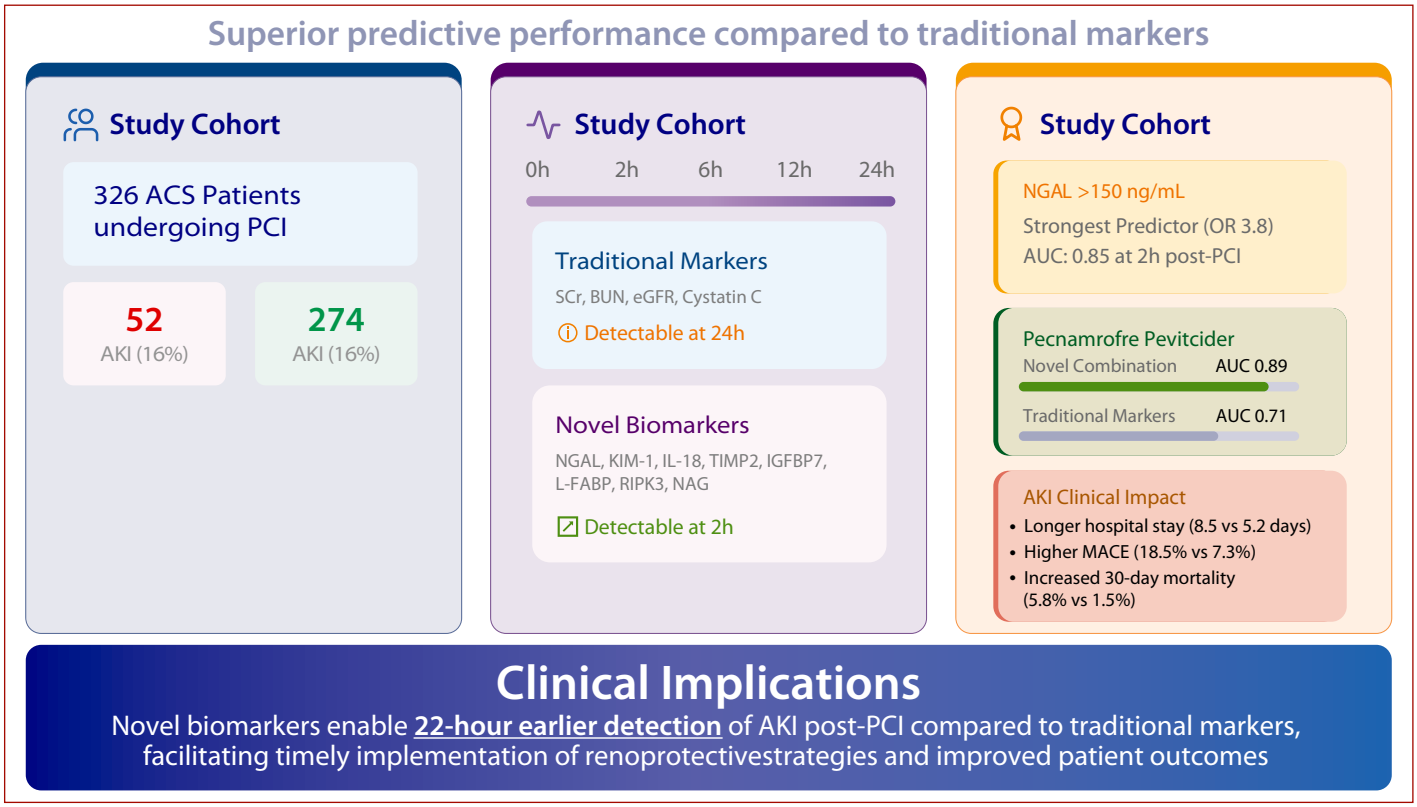
Introduction

Percutaneous coronary intervention (PCI) has become the primary revascularization strategy for patients with acute coronary syndrome (ACS). However, post-procedural acute kidney injury (AKI) remains an important clinical challenge, affecting approximately 10–25% of patients undergoing PCI. This complication is associated with prolonged hospital stays, increased healthcare costs, and elevated short- and long-term mortality [1–4]. While PCI techniques and technology have significantly advanced over the past decades, procedure-related complications remain a concern in clinical practice. In addition

Central illustration. Novel Biomarkers for Early Detection of Renal Injury Post-PCI



to AKI, other major complications include periprocedural myocardial infarction, coronary artery dissection, stent thrombosis, and access site complications. Among these complications, AKI stands out due to its frequent occurrence and significant impact on patient prognosis. The use of contrast agents during PCI, combined with potential atheroembolic events, hemodynamic instability, and oxidative stress, all contribute to the development of post-procedural renal injury [5–7].

The pathophysiology of contrast-induced AKI involves multiple mechanisms, including direct tubular toxicity, oxidative stress, and renal medullary hypoxia. Pre-existing risk factors such as diabetes mellitus, chronic kidney disease (CKD), advanced age, and hemodynamic instability can significantly increase the likelihood of developing renal function impairment after PCI. Despite the implementation of various preventive strategies, including optimal hydration protocols and minimizing contrast agent volume, the incidence of post-PCI AKI remains high. This highlights the critical need for better risk stratification and early detection methods to improve patient outcomes [8–11].

Traditional renal function markers, particularly serum creatinine, have significant limitations in the early detection of AKI. Serum creatinine typically does not rise until 24–48 h after initial renal injury, leading to delayed diagnosis and intervention. Furthermore, creatinine concentrations may be influenced by various factors such as age, muscle mass, and hydration status, and may mask early renal injury.

In recent years, there has been growing interest in novel biomarkers that enable early detection of renal injury [12]. These include neutrophil gelatinase-associated lipocalin (NGAL), a protein expressed in renal tubules that rapidly increases after renal injury; kidney injury molecule-1 (KIM-1), a transmembrane protein upregulated in proximal tubular cells following injury [13, 14]; and interleukin-18 (IL-18), a proinflammatory cytokine that serves as an early indicator of tubular damage [15, 16].

Early identification of patients at risk for AKI may allow for timely implementation of preventive strategies and modification of treatment approaches. This could potentially improve patient outcomes by enabling targeted interventions before significant renal damage occurs. However, the clinical utility of these novel biomarkers in the specific context of renal function injury following PCI in ACS patients remains to be fully established.

Therefore, this study aimed to evaluate the predictive value of these novel biomarkers, both individually and in combination, for early detection of renal function injury following PCI in ACS patients. We hypothesized that these markers would demonstrate superior early predictive capability compared to traditional renal function markers, potentially enabling earlier intervention and improved patient outcomes.

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Material and methods

Study Population and Design

This prospective observational study included 326 consecutive ACS patients undergoing PCI at Zhangjiakou First Hospital from January to December 2024.

All patients met the following *inclusion criteria*:

1) age 18 yrs or older;
2) confirmed diagnosis of ACS (including ST-elevation myocardial infarction [STEMI] or non-ST-elevation myocardial infarction [NSTEMI]);
3) unstable angina requiring PCI;
4) written informed consent.

To ensure data quality and minimize confounding factors, we *excluded patients*:

1) with pre-existing end-stage renal disease requiring dialysis;
2) with cardiogenic shock (defined as systolic blood pressure <90 mmHg for >30 min despite adequate fluid resuscitation, or requiring inotropic/vasopressor support, or mechanical circulatory support);
3) requiring emergency PCI;
4) with severe hepatic dysfunction.

Patient Grouping and AKI Definition

Patients were divided into two groups based on the occurrence of AKI within 48 h post-PCI according to criteria of the Kidney Disease: Improving Global Outcomes Organization. AKI was defined as an increase in serum creatinine ≥0.3 mg/dl within 48 h or an increase ≥1.5 times baseline within 7 days post-procedure. This classification produced AKI and non-AKI groups for comparative analysis.

Interventional Procedures

All PCI procedures were performed by experienced interventional cardiologists following standardized clinical protocols. Prior to intervention, patients received standard dual antiplatelet therapy. To minimize contrast-induced renal injury, we exclusively used low-osmolar contrast agents, with careful monitoring and recording of the total contrast volume administered. Preventive measures included standardized hydration protocols with normal saline (1 ml/kg/h) administered 12 h before and after the procedure [17–19]. Technical aspects of the intervention, including arterial access site selection, stent type selection, and other procedural characteristics, were determined by the operating physician based on individual patient characteristics and clinical requirements.

Clinical Assessment and Monitoring

Comprehensive baseline characteristics were recorded for all patients. These included:

1. Demographic features: age, gender, and body mass index (BMI);
2. Cardiovascular risk factors: diabetes mellitus (defined as fasting plasma glucose ≥126 mg/dl, HbA1c ≥6.5%, or use of antidiabetic medications), hypertension (defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medications), chronic kidney disease (defined as eGFR <60 ml/min/1.73 m^2 for >3 mos or evidence of kidney damage), smoking history (current or former smoker), family history of cardiovascular disease (defined as first-degree relative with coronary artery disease, myocardial infarction, or sudden cardiac death before age 55 in males or 65 in females), and hyperlipidemia (defined as total cholesterol ≥240 mg/dl, LDL cholesterol ≥160 mg/dl, or use of lipid-lowering medications);
3. Laboratory parameters: serum creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI equation, Cystatin C, hemoglobin, platelet count, and white blood cell count;
4. Biochemical markers: homocysteine (Hcy), uric acid (UA), secreted frizzled-related protein 5 (SFRP5), C-reactive protein (CRP), and N-terminal pro-brain natriuretic peptide (NT-proBNP);
5. Clinical parameters: ACS type (STEMI, NSTEMI, or unstable angina), left ventricular ejection fraction (LVEF) classification (≥50%, 40–49%, or <40% measured by echocardiography using the modified Simpson's method), symptom onset to PCI time (<6 h, 6–12 h, or >12 h), and pre-admission medications.

Two experienced interventional cardiologists independently assessed the coronary angiograms of all patients. They calculated the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score, with disagreements resolved through discussion. The SYNTAX score was calculated according to standard algorithms, thus evaluating the complexity of coronary lesions, including factors such as lesion location, extent, and severity.

During the PCI procedure, all procedural characteristics, including the selected access site (radial or femoral artery), number and type of stents implanted (drug-eluting stent or bare metal stent), total contrast volume, procedure duration, and any complications occurring during or immediately after the procedure, were carefully recorded.

For assessment of renal function and injury, blood samples were collected at five time points: pre-PCI (baseline) and at 2, 6, 12, and 24 h post-procedure. Each sample was analyzed for traditional renal markers (serum creatinine, blood urea nitrogen [BUN], estimated glomerular filtration rate [eGFR], and Cystatin C) and for novel biomarkers (neutrophil gelatinase-associated lipocalin [NGAL]

and kidney injury molecule-1 [KIM-1]). To comprehensively evaluate the early detection capability of various renal injury biomarkers and validate the superiority of novel markers, we additionally measured a panel of emerging biomarkers: tissue inhibitor of metalloproteinases-2 (TIMP2), insulin-like growth factor-binding protein 7 (IGFBP7), liver-type fatty acid-binding protein (L-FABP), receptor-interacting protein kinase 3 (RIPK3), and N-acetyl-β-D-glucosaminidase (NAG). These additional markers reflect different pathophysiological mechanisms of renal injury: TIMP2 and IGFBP7 are cell cycle arrest markers indicating renal stress, L-FABP reflects proximal tubular injury, RIPK3 is associated with necroptosis pathways, and NAG is a lysosomal enzyme released during tubular damage.

Serum creatinine and BUN were measured using standard enzymatic methods on an automated biochemistry analyzer (Roche Cobas c702, Basel, Switzerland). Cystatin C was quantified by particle-enhanced turbidimetric immunoassay. NGAL was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (BioPorto Diagnostics, Hellerup, Denmark) with a detection range of 10–10,000 ng/ml. KIM-1 concentrations were determined using quantitative sandwich ELISA kits (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's protocols. TIMP2 and IGFBP7 were measured using the NephroCheck® Test (Astute Medical, San Diego, CA, USA), a fluorescence immunoassay platform. L-FABP was quantified using a commercially available ELISA kit (CMIC Holdings Co., Ltd., Tokyo, Japan) with a detection range of 1–1,000 ng/ml. RIPK3 was measured using a human RIPK3 ELISA kit (MyBioSource, San Diego, CA, USA). NAG activity was determined by a colorimetric assay using a commercial kit (Diazyme Laboratories, Poway, CA, USA) and normalized to urinary creatinine concentration (U/Cr). All biomarker assays were performed in duplicate, and the intra-assay and inter-assay coefficients of variation were <5% and <10%, respectively.

The primary study endpoint was defined as the incidence of AKI within 48 h post-PCI. Secondary endpoints included hospital length of stay, major adverse cardiac events (MACE), 30-day mortality, renal replacement therapy requirements, and in-hospital complications.

Renal replacement therapy was defined as the requirement for intermittent hemodialysis due to severe AKI with complications including hyperkalemia (serum potassium >6.5 mmol/l), severe metabolic acidosis (pH <7.2), fluid overload refractory to diuretics, or uremic symptoms. The decision to initiate hemodialysis was made by the attending nephrologist.

MACE was defined as a composite of cardiovascular death, recurrent myocardial infarction, stroke, or urgent revascularization. All patients were followed for 30 days post-discharge, with clinical events, renal function parameters, and cardiovascular outcomes recorded through direct follow-up or telephone interview.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]) depending on their distribution and compared using Student's t-tests or Mann-Whitney U tests, as appropriate. Categorical variables were expressed as numbers (percentages) and compared using chi-square tests or Fisher's exact tests. Receiver operating characteristic (ROC) curves were used to evaluate the predictive value of biomarkers for AKI. Sensitivity and specificity were calculated by ROC curve analysis, and optimal cutoff values were determined using the Youden index (sensitivity + specificity-1). The threshold that maximized the Youden index was selected as the optimal cutoff point. Logistic regression was performed to identify independent predictors of AKI. Variables with $p<0.10$ in univariate analysis were included in multivariate analysis. These results were expressed as odds ratio (OR) with (95% confidence interval (CI)). For all analyses, $p<0.05$ was considered statistically significant.

Results

Baseline Characteristics

This study included 326 ACS patients, of whom 52 (16%) developed AKI within 48 h post-PCI. Patients in the AKI group had a significantly higher burden of cardiovascular risk factors, including significantly higher prevalence of diabetes mellitus, hypertension, and CKD compared to the non-AKI group. Regarding coronary lesion complexity, the AKI group had significantly higher SYNTAX scores than the non-AKI group [28.5 (IQR: 22.0–35.0) vs 21.0 (IQR: 16.0–27.5), $p<0.001$], indicating that patients who developed AKI had more complex coronary lesions. The AKI group had significantly impaired baseline renal function, manifested by higher serum creatinine concentrations (1.2 ± 0.3 vs 1.0 ± 0.2 mg/dl, $p<0.001$) and lower eGFR (58.5 ± 12.8 vs 74.2 ± 15.6 ml/min/1.73 m^2, $p<0.001$). Regarding inflammatory markers, the AKI group had significantly elevated C-reactive protein (CRP) concentrations (15.8 ± 8.2 vs 8.6 ± 5.4 mg/l, $p<0.001$), and N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations were also significantly higher (2850 ± 1260 vs 1680 ± 890 pg/ml, $p<0.001$), suggesting

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Table 1. Baseline characteristics of the patients

Characteristic	AKI Group (n=52)	Non-AKI Group (n=274)	p Value
Demographic Characteristics			
Age (y)	64.1±10.5	63.4±10.1	0.68
Gender (M/F)	32/20	148/126	0.75
Body mass index (BMI, kg/m²)	26.7±4.3	26.3±4.0	0.54
Cardiovascular Risk Factors			
Diabetes mellitus	45.2 (23/52)	32.1 (88/274)	<0.01
Hypertension	68.5 (36/52)	54.7 (154/274)	<0.01
Chronic kidney disease	28.8 (15/52)	15.3 (42/274)	<0.001
Smoking history	40.4 (21/52)	28.8 (79/274)	0.049
Family history of cardiovascular disease	32.7 (17/52)	18.6 (51/274)	0.012
Hyperlipidemia	36.5 (19/52)	23.7 (65/274)	0.023
Baseline Laboratory Parameters			
Serum creatinine (mg/dl)	1.2±0.3	1.0±0.2	<0.001
Estimated GFR (ml/min/1.73m²)	58.5±12.8	74.2±15.6	<0.001
Blood urea nitrogen (mg/dl)	18.3±6.2	14.8±4.5	<0.001
Hemoglobin (g/dl)	11.8±1.9	13.2±1.6	<0.001
Platelet count (×10³/μl)	215±68	242±72	0.018
White blood cell count (×10³/μl)	11.2±3.8	9.8±3.2	0.024
Biochemical Markers			
Hcy (μmol/l)	14.2±3.5	12.1±3.0	<0.001
UA (μmol/l)	350±90	315±75	0.003
SFRP5 (ng/l)	180±45	205±50	<0.001
CRP (mg/l)	15.8±8.2	8.6±5.4	<0.001
NT-proBNP (pg/ml)	2850±1260	1680±890	<0.001
SYNTAX score (points)	28.5 (22.0–35.0)	21.0 (16.0–27.5)	<0.001
ACS Type			**0.032**
STEMI	30 (57.7)	128 (46.7)	–
NSTEMI	16 (30.8)	98 (35.8)	–
Unstable angina	6 (11.5)	48 (17.5)	
Symptom onset to PCI (time)			**0.041**
<6 h	28 (53.8)	118 (43.1)	–
6–12 h	15 (28.8)	86 (31.4)	–
>12 h	9 (17.4)	70 (25.5)	–
LVEF Classification			**0.007**
≥50%	18 (34.6)	142 (51.8)	–
40–49%	22 (42.3)	98 (35.8)	–
<40%	12 (23.1)	34 (12.4)	–
Pre-admission Medications			
Aspirin	26 (50.0)	145 (52.9)	0.72
Clopidogrel	18 (34.6)	98 (35.8)	0.88
Statins	22 (42.3)	128 (46.7)	0.58
Beta-blockers	19 (36.5)	118 (43.1)	0.42
ACE inhibitors/ARB	25 (48.1)	142 (51.8)	0.65
Proton pump inhibitors	15 (28.8)	68 (24.8)	0.56
Insulin/ hypoglycemic agents	23 (44.2)	88 (32.1)	0.11
Diuretics	16 (30.8)	52 (19.0)	0.048

Data are mean ± SD, percentage (ratio), or n (percentage). M, male; F, female; BMI, body mass index; GFR, glomerular filtration rate; Hcy, homocysteine; UA, uric acid; SFRP5, secreted frizzled-related protein 5; CRP, C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

more severe cardiac dysfunction. Regarding ACS type distribution, the proportion of STEMI patients was higher in the AKI group compared to the non-AKI group (57.7% vs 46.7%, p=0.18). Also, among STEMI patients, the proportion of patients with symptom onset <6 h after PCI was also higher (53.8% vs 43.1%, p=0.22) for STEMI patients. The proportion of patients with LVEF <40% was significantly increased in the AKI group (23.1% vs 12.4%, p=0.007), reflecting more severe cardiac dysfunction. There were no significant differences between the two groups in age, gender, and most pre-admission medications, but the AKI group had higher diuretic use (30.8% vs 19.0%, p=0.048), which may reflect differences in baseline cardiac functional status (Table 1).

Procedural Characteristics

Compared to the non-AKI group, patients in the AKI group received significantly higher contrast volumes (245±65 vs 198±52 ml, p<0.001), had longer procedure durations (68±22 vs 52±18 min, p<0.01), and had more stents implanted (2.1±0.8 vs 1.7±0.6, p<0.05). Access site selection and stent type distributions were similar between the two groups (p>0.05). The percentage of radial access and use of drug-eluting stents did not differ between the groups. Notably, the AKI group had higher pre-procedural creatinine concentrations (1.2±0.3 vs 1.0±0.2 mg/dl, p<0.001). Periprocedural complications were also more frequent in the AKI group, including post-procedural fluid overload (30.8% vs 15.7%, p=0.002), intraprocedural hypotension (28.8% vs 12.4%, p=0.004), and post-procedural vasopressor support requirements (23.1% vs 8.0%, p<0.001). These findings suggest that the patients who developed AKI had more complex procedures, higher contrast exposure, and experienced more periprocedural complications (Table 2).

Table 2. Procedural characteristics

Characteristic	AKI Group (n=52)	Non-AKI Group (n=274)	p Value
Contrast volume (ml)	245 ± 65	198 ± 52	<0.001
Procedure duration (min)	68 ± 22	52 ± 18	<0.01
Number of stents implanted	2.1 ± 0.8	1.7 ± 0.6	<0.05
Access Site Selection			**>0.05**
Radial artery	30 (57.7)	150 (54.7)	
Femoral artery	22 (42.3)	124 (45.3)	
Stent type			>0.05
Drug-eluting stent	45 (86.5)	235 (85.8)	
Bare metal stent	7 (13.5)	39 (14.2)	
Other Characteristics			
Pre-procedural creatinine (mg/dl)	1.2 ± 0.3	1.0 ± 0.2	<0.001
Post-procedural fluid overload	30.8 (16/52)	15.7 (43/274)	0.002
Intraprocedural hypotension	28.8 (15/52)	12.4 (34/274)	0.004
Post-procedural vasopressor use	23.1 (12/52)	8.0 (22/274)	<0.001

Data are mean ± SD, percentage (ratio), or n (percentage).

Early Performance Comparison of Biomarkers

Baseline and serial measurements of traditional renal function markers and novel biomarkers were obtained to evaluate their early detection capability for post-PCI AKI. Baseline values were similar between the AKI and non-AKI groups for most biomarkers, indicating comparable pre-procedural renal status. Serum creatinine concentrations showed no significant change in either group during the first 12 h post-PCI (p>0.05). A significant elevation was detected at 24 h only in the AKI group (p<0.001). Similar patterns were observed for BUN and eGFR, demonstrating the delayed response of the traditional markers. In contrast to the traditional markers, the novel biomarkers exhibited different trends between groups in the early post-PCI period. Although Cystatin C, NGAL, and KIM-1 did not reach statistical significance at 0–12 h (though showing trends toward elevation compared to baseline), they all showed significant differences at 24 h (p<0.001), suggesting their potential value as early warning indicators. Table 3 presents the detailed temporal changes of all biomarkers with baseline comparisons, where † symbol denotes values showing no significant change from baseline (p>0.05).

Dynamic Changes in Additional Emerging Biomarkers

To further validate the early detection capability of the novel biomarkers and to explore alternative predictive indicators beyond the primary biomarkers (NGAL, KIM-1, IL-18), we examined the temporal profile of five additional emerging biomarkers that reflect diverse pathophysiological pathways of renal injury. The biomarker concentrations at three time points (2, 6, and 24 h) post-PCI were compared between the AKI group and non-AKI group. All five biomarkers (tissue inhibitor of metalloproteinases-2 [TIMP2], insulin-like growth factor-binding protein 7 [IGFBP7], liver-type fatty acid-binding protein [L-FABP], receptor-interacting protein kinase 3 [RIPK3], and N-acetyl-β-D-glucosaminidase [NAG]) showed significantly higher concentrations in the AKI group compared to the non-AKI group at all time points (all p<0.001). For example, TIMP2 concentrations in the AKI group increased from 30±10 ng/ml at 2 h to 60±20 ng/ml at 24 h (a 100% increase), while in the non-AKI group, they increased from 15±5 ng/ml to 25±10 ng/ml (a 67% increase). Similarly, IGFBP7 demonstrated progressive elevation from 25±8 ng/ml at 2 h to 45±15 ng/ml at 24 h (an 80% increase) in the AKI group, compared to 12±4 ng/ml to

Table 3. Early performance comparison of traditional renal function markers and novel biomarkers

Time Point	Biomarker	AKI Group (n=52)	Non-AKI Group (n=274)	p Value
Pre-PCI (Baseline)	Serum creatinine (mg/dl)	1.2±0.3	1.0±0.2	<0.001
	BUN (mg/dl)	18.3±6.2	14.8±4.5	<0.001
	eGFR (ml/min/1.73 m²)	58.5±12.8	74.2±15.6	<0.001
	Cystatin C (mg/l)	0.98±0.18	0.91±0.12	>0.05
	NGAL (ng/ml)	75±25	70±20	>0.05
	KIM-1 (ng/ml)	28±12	25±10	>0.05
Traditional Markers				
0–12 h post-PCI	Serum creatinine (mg/dl)	1.2±0.3†	1.0±0.2†	>0.05
	BUN (mg/dl)	15±5†	14±4†	>0.05
	eGFR (ml/min/1.73 m²)	60±15†	65±10†	>0.05
24 h post-PCI	Serum creatinine (mg/dl)	1.5±0.4	1.0±0.2†	<0.001
	BUN (mg/dl)	20±6	14±4†	<0.001
	eGFR (ml/min/1.73 m²)	45±10	65±10†	<0.001
Novel Biomarkers				
0–12 h post-PCI	Cystatin C (mg/l)	1.0±0.2†	0.9±0.1†	>0.05
	NGAL (ng/ml)	120±40	80±30	>0.05
	KIM-1 (ng/ml)	50±20	30±10	>0.05
24 h post-PCI	Cystatin C (mg/l)	1.2±0.3	0.9±0.1†	<0.001
	NGAL (ng/ml)	200±50	85±35	<0.001
	KIM-1 (ng/ml)	80±30	35±15	<0.001

Data are mean±SD. † indicates no significant change from baseline value (p>0.05 compared to pre-PCI baseline within the same group). BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1; AKI, acute kidney injury; PCI, percutaneous coronary intervention.

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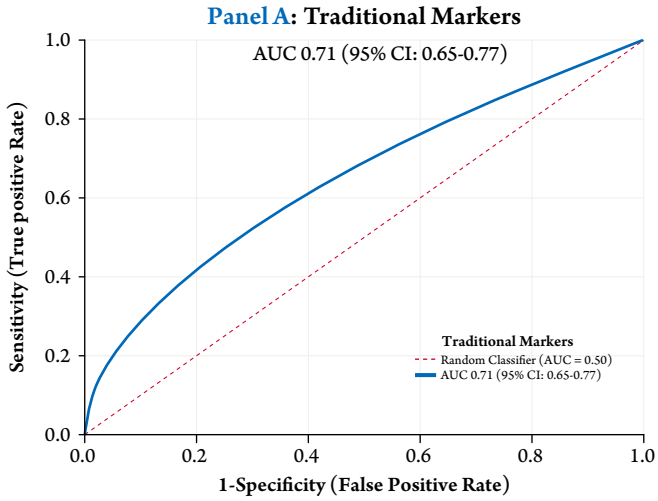
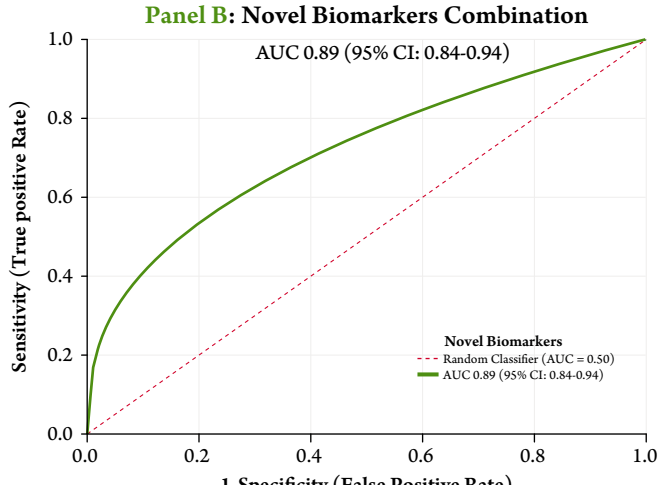
Figure 1. Receiver operating characteristic (ROC) curves comparing the predictive value of different biomarker approaches for post-PCI acute kidney injury



Panel A: Traditional markers combination (serum creatinine, BUN, eGFR, and Cystatin C) showing moderate predictive performance with AUC 0.71 (95% CI 0.65–0.77).

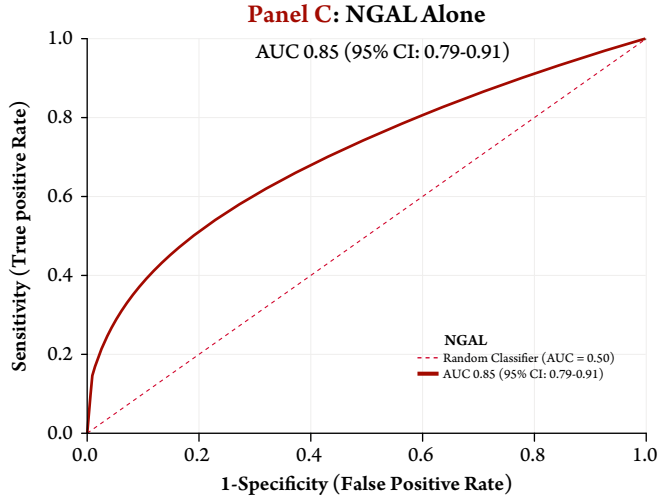


Panel B: Novel biomarkers combination (NGAL, KIM-1, and IL-18) demonstrating superior predictive performance with AUC 0.89 (95% CI 0.84-0.94).

Table 4. Dynamic changes in additional emerging biomarkers

Time post-PCI	Biomarker	AKI Group (n=52)	Non-AKI Group (n=274)	p Value
2 h	TIMP2 (ng/ml)	30±10	15±5	<0.001
	IGFBP7 (ng/ml)	25±8	12±4	<0.001
	L-FABP (ng/ml)	70±20	40±15	<0.001
	RIPK3 (ng/ml)	45±15	20±8	<0.001
	NAG (U/Cr)	40±10	25±7	<0.001
6 h	TIMP2 (ng/ml)	45±15	20±8	<0.001
	IGFBP7 (ng/ml)	35±12	18±6	<0.001
	L-FABP (ng/ml)	100±30	50±20	<0.001
	RIPK3 (ng/ml)	60±20	25±10	<0.001
	NAG (U/Cr)	50±12	30±9	<0.001
24 h	TIMP2 (ng/ml)	60±20	25±10	<0.001
	IGFBP7 (ng/ml)	45±15	20±8	<0.001
	L-FABP (ng/ml)	120±35	60±20	<0.001
	RIPK3 (ng/ml)	70±25	30±12	<0.001
	NAG (U/Cr)	60±15	35±10	<0.001

Data are mean±SD. TIMP2, tissue inhibitor of metalloproteinases-2; IGFBP7, insulin-like growth factor-binding protein 7; L-FABP, liver-type fatty acid-binding protein; RIPK3, receptor-interacting protein kinase 3; NAG, N-acetyl-β-D-glucosaminidase; U/Cr, units per gram creatinine; AKI, acute kidney injury; PCI, percutaneous coronary intervention.



Panel C: NGAL as an individual marker showing high predictive value with AUC 0.85 (95% CI 0.79–0.91). All biomarker measurements were obtained at 24 h post-PCI. The combination of novel biomarkers (Panel B) demonstrated significantly better discriminative ability compared to traditional markers (Panel A) (p<0.001).

20±8 ng/ml (a 67% increase) in the non-AKI group. L-FABP showed the largest absolute differences between groups, reaching 120±35 ng/ml in the AKI group at 24 h compared to 60±20 ng/ml in the non-AKI group (a 71% increase from 2 h baseline and a 50% increase from 2 h baseline, respectively). RIPK3, a marker of necroptosis, increased from 45±15 ng/ml to 70±25 ng/ml (a 56% increase) in the AKI group, while also demonstrating elevation in the non-AKI group (from 20±8 ng/ml to 30±12 ng/ml, a 50% increase). NAG activity, normalized to urinary creatinine, rose from 40±10 U/Cr at 2 h to 60±15 U/Cr at 24 h (a 50% increase) in the AKI group, which was significantly higher than the non-AKI group (25±7 U/Cr to 35±10 U/Cr, a 40% increase) (Table 4).

The consistent elevation of these biomarkers in the AKI group, detectable as early as 2 h post-PCI, indicates their potential value as early predictive indicators for AKI development following PCI. These findings complement our primary biomarker analysis (NGAL, KIM-1, IL-18) and provide a more comprehensive understanding of the diverse molecular mechanisms underlying early renal injury. The simul-

Table 5. Multivariate analysis of independent predictors for post-PCI AKI

Predictor	Odds Ratio (OR)	95% Confidence Interval (CI)	p Value
Elevated NGAL at 2 h post-PCI (>150 ng/ml)	3.8	2.1–6.9	<0.001
Diabetes mellitus	2.1	1.4–3.2	<0.01
Contrast volume >200 ml	2.5	1.6–3.9	<0.001
Elevated CRP	3.6	2.2–6.0	<0.001
Elevated BUN	2.8	1.8–4.5	<0.001
Low Hb	2.3	1.5–3.6	<0.001
Elevated Hcy	2.4	1.6–3.7	<0.001

Data are presented as odds ratios with 95% confidence intervals. AKI, acute kidney injury; PCI, percutaneous coronary intervention; NGAL, neutrophil gelatinase-associated lipocalin; CRP, C-reactive protein; BUN, blood urea nitrogen; Hb, hemoglobin; Hcy, homocysteine; OR, odds ratio; CI, confidence interval.

taneous elevation of markers representing different injury pathways (tubular damage, cell cycle arrest, necroptosis, and lysosomal enzyme release) suggests a multi-faceted injury process in post-PCI AKI.

Predictive Value Analysis

ROC curve analysis demonstrated that the combination of novel biomarkers had superior predictive performance compared to traditional markers (AUC 0.89, 95% CI 0.84–0.94 vs AUC 0.71, 95% CI 0.65–0.77, p<0.001). The novel biomarkers combination included NGAL, KIM-1, and IL-18, which were measured at 24 h post-PCI and analyzed together using a composite score derived from their individual predictive values. Traditional markers comprised serum creatinine, BUN, eGFR, and Cystatin C measured at 24 h post-PCI. NGAL alone showed the highest individual predictive value (AUC 0.85, 95% CI 0.79–0.91, Figure 1).

Table 6. Clinical outcomes

Outcome	AKI Group (n=52)	Non-AKI Group (n=274)	p Value
Hospital length of stay (days)	8.5±3.2	5.2±2.1	<0.001
Major adverse cardiac events	18.5 (9/52)	7.3 (20/274)	<0.001
30-day mortality	5.8 (3/52)	1.5 (4/274)	<0.01
Temporary hemodialysis	7.7 (4/52)	0 (0/274)	<0.05
Post-operative infection rate	21.2 (11/52)	8.4 (23/274)	<0.01
Intensive care unit stay (days)	6.0±2.5	3.0±1.5	<0.001
Acute respiratory distress syndrome (ARDS)	15.4 (8/52)	3.3 (9/274)	<0.001
Pulmonary infection	38.5 (20/52)	15.3 (42/274)	<0.001
Hemodynamic instability	19.2 (10/52)	5.1 (14/274)	<0.001
Post-operative delirium	13.5 (7/52)	3.7 (10/274)	<0.01

Data are mean ± SD or percentage (ratio). AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; MACE, major adverse cardiac events.

Multivariate Analysis of Independent Predictors for Post-PCI AKI

After adjusting for confounding factors, elevated NGAL at 2 h post-PCI (>150 ng/ml) remained an independent predictor of AKI (OR 3.8, 95% CI 2.1–6.9, p<0.001). Other independent predictors included diabetes mellitus, contrast volume >200 ml, SYNTAX score >25, elevated CRP, elevated BUN, low hemoglobin, and elevated Hcy (Table 5).

Clinical Outcomes

The AKI group experienced longer hospital stays (8.5±3.2 days vs 5.2±2.1 days, p<0.001), higher rates of MACE (18.5% vs 7.3%, p<0.001), and increased 30-day mortality (5.8% vs 1.5%, p<0.01). Four patients (7.7%) in the AKI group required temporary hemodialysis, while no patients in the non-AKI group required such intervention (Table 6). All patients receiving renal replacement therapy underwent intermittent hemodialysis, with a median of 3 sessions (range 2–5) until recovery of renal function.

Discussion

This prospective observational study systematically evaluated the clinical utility of novel biomarkers for early detection of AKI following PCI in ACS patients. Our findings demonstrate that novel renal injury biomarkers, particularly NGAL, KIM-1, and IL-18, along with TIMP2, IGFBP7, L-FABP, RIPK3, and NAG, provide superior early detection of post-PCI AKI compared to traditional markers, with abnormal elevation detectable as early as 2 h post-procedure. The incidence of AKI in our cohort was 16%, which aligns with reported rates in contemporary literature [20]. Importantly, elevated NGAL >150 ng/ml at 2 h post-PCI emerged as the strongest independent predictor of AKI occurrence (OR 3.8, 95% CI 2.1–6.9, p<0.001), highlighting its potential as a critical early warning indicator for clinical decision-making.

Traditional renal function markers, particularly serum creatinine, have well-documented limitations in early AKI detection [21]. Creatinine concentrations typically remain stable for 24–48 h following renal injury, reflecting its dependence on glomerular filtration rate changes rather than direct tubular damage. Our results confirm these limitations, as serum creatinine, BUN, and eGFR showed no significant inter-group differences during the first 12 h post-PCI, with detectable changes emerging only at 24 h. This delayed re-

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sponse creates a critical therapeutic window during which renal injury progresses unchecked [12]. Furthermore, creatinine is influenced by multiple non-renal factors including age, muscle mass, hydration status, and medication use, potentially masking early injury signals in vulnerable populations [22]. These inherent limitations underscore the urgent need for more sensitive and specific biomarkers that can identify renal injury during its earliest, potentially reversible stages.

The superior performance of novel biomarkers in our study reflects their direct relationship to specific pathophysiological mechanisms of renal injury. NGAL, a 25-kDa protein belonging to the lipocalin superfamily, is rapidly upregulated in renal tubular epithelial cells following ischemic, toxic, or inflammatory injury [23]. Unlike creatinine, which reflects overall filtration capacity, NGAL directly indicates tubular stress and damage, explaining its early elevation in our AKI cohort. Recent systematic reviews have confirmed NGAL's robust diagnostic performance across diverse clinical settings, with pooled sensitivity and specificity exceeding 80% for early AKI detection [24].

KIM-1, a type 1 transmembrane glycoprotein, is minimally expressed in normal kidneys but dramatically upregulated in proximal tubular cells following injury. Its ectodomain is shed into urine, making it an accessible biomarker for tubular damage assessment [25]. Studies in cardiac surgery populations have demonstrated KIM-1's predictive value for AKI 12–24 h before creatinine elevation, consistent with our findings. The complementary nature of NGAL and KIM-1 – reflecting different aspects of tubular injury – may explain why their combination enhanced predictive performance in our analysis.

IL-18, a proinflammatory cytokine of the IL-1 superfamily, plays a crucial role in ischemia-reperfusion injury through activation of innate immune responses and promotion of tubular cell apoptosis [26]. Elevated urinary IL-18 has been associated with AKI severity and adverse outcomes in various clinical contexts, including cardiac surgery and critical illness. Our finding that IL-18 contributed to the superior performance of the novel biomarker combination aligns with evidence that inflammatory mediators provide complementary prognostic information to tubular injury markers.

The additional biomarkers examined in our study – TIMP2, IGFBP7, L-FABP, RIPK3, and NAG – reflect diverse pathophysiological pathways of renal injury. TIMP2 and IGFBP7 are cell cycle arrest markers that indicate renal stress before overt injury occurs, providing a unique "pre-injury" signal [27]. Their combination, marketed as the NephroCheck® test, has received regulatory approval for AKI risk stratification in critically ill patients. L-FABP, highly expressed in proximal tubules, is released during ischemic and oxidative injury, serving as an early indicator of tubular dysfunction [28]. RIPK3, a key mediator of regulated necrosis (necroptosis), reflects programmed cell death pathways distinct from apoptosis, offering insights into injury mechanisms [29]. NAG, a lysosomal enzyme abundant in proximal tubular cells, has been studied for decades as a marker of tubular damage but has gained renewed interest in combination biomarker panels [30]. The consistent elevation of all these markers in our AKI group as early as 2 h post-PCI, across multiple mechanistic pathways, supports the concept that post-PCI AKI involves multi-faceted injury processes requiring comprehensive biomarker assessment.

Our multivariate analysis identified several independent predictors of post-PCI AKI beyond novel biomarkers. Diabetes mellitus (OR 2.1) emerged as a significant risk factor, consistent with extensive literature demonstrating that diabetic nephropathy increases susceptibility to contrast-induced injury through endothelial dysfunction, oxidative stress, and impaired vasodilatory responses [31]. The association between contrast volume >200 ml (OR 2.5) and AKI reflects dose-dependent toxicity mechanisms, including direct tubular epithelial cell damage, renal vasoconstriction, and medullary hypoxia. Contemporary practice emphasizes contrast minimization strategies, though our results suggest that even with modern preventive measures, volume remains a critical modifiable risk factor.

Elevated CRP (OR 3.6) and the high SYNTAX scores observed in our AKI group (median 28.5 vs 21.0) highlight the interplay between systemic inflammation, atherosclerotic burden, and renal injury susceptibility. Complex coronary lesions necessitate prolonged procedures, higher contrast volumes, and potentially greater hemodynamic instability – all contributing to AKI risk [32]. The independent predictive value of elevated homocysteine (OR 2.4) aligns with emerging evidence linking hyperhomocysteinemia to endothelial dysfunction and increased oxidative stress, potentially sensitizing kidneys to contrast-mediated injury. Low hemoglobin (OR 2.3) likely reflects both pre-existing comorbidity burden and reduced oxygen-carrying capacity, exacerbating renal medullary hypoxia during contrast exposure [33].

The clinical consequences of post-PCI AKI in our cohort were substantial and align with established literature. Patients developing AKI experienced significantly longer hospital stays (8.5±3.2 vs 5.2±2.1 days), higher MACE rates (18.5% vs 7.3%), and increased 30-day mortality (5.8% vs 1.5%). These findings underscore that post-PCI AKI is not merely a laboratory abnormality but a serious complication with profound implications for patient outcomes and healthcare resource utilization [34]. The 7.7% rate of temporary hemodialysis requirement in our AKI

group, while relatively low, represents the most severe end of the injury spectrum and carries particularly poor prognosis.

The superior predictive performance of the novel biomarker combination (AUC 0.89) compared to traditional markers (AUC 0.71) has important clinical implications. Early identification of high-risk patients could enable timely implementation of renoprotective strategies, including aggressive hydration, hemodynamic optimization, avoidance of nephrotoxic agents, and closer monitoring. Furthermore, the 2-hour detectability of biomarker elevation creates an actionable timeframe for intervention, potentially before irreversible injury occurs. The individual performance of NGAL (AUC 0.85) suggests that even single-biomarker monitoring could significantly improve upon current standard-of-care approaches.

Translating these research findings into routine clinical practice requires consideration of practical implementation challenges. Point-of-care testing platforms for NGAL and other novel biomarkers are increasingly available, potentially enabling rapid bedside assessment [35]. However, cost-effectiveness analyses, standardization of cutoff values across diverse populations, and integration into clinical decision algorithms remain important considerations. Our finding that NGAL >150 ng/ml at 2 h post-PCI independently predicts AKI provides a specific, actionable threshold that could guide clinical decision-making, though external validation in diverse populations is warranted.

The comprehensive biomarker panel examined in our study – spanning tubular injury markers (NGAL, KIM-1, L-FABP, NAG), inflammatory mediators (IL-18), cell cycle arrest markers (TIMP2, IGFBP7), and necroptosis indicators (RIPK3) – reflects the growing recognition that AKI is a heterogeneous syndrome requiring multi-marker approaches for optimal risk stratification [36]. While measuring all biomarkers may not be practical in routine care, strategic selection based on local resources, patient risk profiles, and procedural characteristics could optimize clinical utility. For high-risk procedures or patients, comprehensive biomarker monitoring may be justified by the potential to prevent severe AKI and its associated morbidity.

Several limitations merit consideration. First, as a single-center study, our findings require external validation in diverse populations and practice settings before widespread adoption. Regional variations in patient characteristics, procedural practices, and post-procedural care may influence biomarker performance. Second, while our sample size was adequate for primary objectives, larger studies would enable more detailed subgroup analyses and assessment of rare outcomes. Third, we did not evaluate long-term outcomes beyond 30 days, limiting assessment of chronic kidney disease progression or late cardiovascular events. Fourth, the observational design prevents definitive causal inferences about relationships between biomarkers and outcomes. Fifth, we did not assess urinary biomarker concentrations, which may provide complementary information to serum measurements for certain markers. Finally, cost-effectiveness analyses were beyond our scope but represent important considerations for clinical implementation.

Future research should focus on several key areas. Multicenter prospective studies with standardized protocols would establish generalizability and enable derivation and validation of clinical decision rules incorporating novel biomarkers. Randomized controlled trials evaluating biomarker-guided interventions versus standard care would provide definitive evidence regarding clinical utility and impact on patient outcomes [37]. Investigation of biomarker kinetics in specific subgroups – including patients with pre-existing CKD, diabetes, or heart failure – could enable personalized risk assessment. Development and validation of point-of-care testing platforms would facilitate practical implementation. Finally, economic analyses evaluating cost-effectiveness of routine novel biomarker monitoring in post-PCI care would inform resource allocation decisions and reimbursement policies.

Conclusion

This study demonstrates that novel renal injury biomarkers, particularly NGAL, KIM-1, IL-18, TIMP2, IGFBP7, L-FABP, RIPK3, and NAG, provide superior early detection of post-PCI AKI in ACS patients compared to traditional markers, with abnormal elevation detectable as early as 2 h post-procedure. Elevated NGAL >150 ng/ml at 2 h post-PCI emerged as the strongest independent predictor of AKI occurrence. The substantial clinical consequences of post-PCI AKI – including prolonged hospitalization, increased MACE rates, and elevated mortality – underscore the importance of early detection and intervention. Integration of novel biomarker monitoring into routine post-PCI care protocols would facilitate early identification of high-risk patients and enable timely implementation of renoprotective strategies, potentially improving outcomes in this vulnerable population. While practical implementation challenges remain, the compelling evidence for superior diagnostic performance supports continued development and validation of these biomarkers for clinical use.

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