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Early diagnosis of acute kidney injury in aged patients undergoing percutaneous coronary intervention*#

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In aged patients, acute kidney injury (AKI) is a common clinical complication after percutaneous coronary intervention (PCI), highlighting the need for timely and certain diagnosis of this disease. A single centre, nested case-control study was conducted, which assessed the usefulness of urinary liver-type fatty acid-binding protein (uL-FABP), neutrophil gelatinase-associated lipocalin (uNGAL), and kidney injury molecule-1 (uKIM-1) for early detection of AKI. One hundred and thirty-two patients at or over 60 years old undergoing PCI were included. Serum creatinine (SCr) was measured before PCI, 24 and 48 h after PCI; uL-FABP, uNGAL, and uKIM-1 were measured before PCI, 6, 24, and 48 h after PCI. We identified 16 AKI patients and selected 32 control patients matched by admission time (<1 week), age (±5 years), and gender. In the receiver operating characteristic (ROC) curve analysis, the areas under the curve (AUCs) for the relative measurements of uL-FABP, uNGAL, and uKIM-1 were 0.809, 0.867, and 0.512 at 6 h after PCI, and 0.888, 0.840, and 0.676 at 24 h after PCI, respectively. AUC for the combination of uL-FABP and uNGAL was 0.899 at 6 h after PCI, and 0.917 at 24 h after PCI. Thus, measurement of uL-FABP and uNGAL levels at 6 and 24 h after PCI may be useful in detecting AKI in aged patients. Measurement of uKIM-1 levels provides inferior predictive power for early diagnosis of AKI.

AKI is a recognized complication of PCI, accounting for 11% of hospital-acquired renal insufficiency (Nash et al., 2002). This complication is associated with prolonged hospitalization, long-term mortality, and development of end stage renal disease (James et al., 2013).

Biomarkers are used effectively in the diagnosis of AKI, with the assay of SCr being the gold standard. On the other hand, McCullough and Sandberg (2003) reported that SCr typically peaks at 3–5 d postcontrast from the baseline. Also a single 24-h determination of SCr would have missed 58.2% of contrast-induced nephropathy patients who were detected by the 48-h determination, which really underlines the need for identifying reliable biomarkers to facilitate early determination of AKI (Reddan et al., 2009).

Furthermore, SCr is a marker reflective of renal function change, and is not specific for tissue injury. Recent research efforts have identified several new potential biomarker proteins, which derive from the injured renal tubule cells of patients with AKI; these new compounds might detect AKI at early stages (Schrezenmeier et al., 2017). Currently, uL-FABP, uNGAL, and uKIM-1 are three of the most promising biomarkers (Luo et al., 2013; Torregrosa et al., 2015). However, it remains unknown whether changes in these three biomarkers could predict early AKI in aged patients subject to PCI. Thus, we performed a

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prospective trial to evaluate the diagnostic performance of these novel biomarkers.

A total of 132 in-hospital patients at Ningbo No. 2 Hospital, Medical School of Ningbo University, Ningbo, China, were eligible for enrollment during the period between July 2015 and August 2016 (Table 1). AKI was identified with an elevation from the preoperative value in SCr level of 0.3 mg/dl (26.5 μmol/L) within 48 h after the procedure (Stacul et al., 2011). In our study, 16 patients developed AKI. Controls (n=32) were selected from the remainder. They were individually matched to cases by admission time (<1 week), age (±5 years), and gender. This study was approved by the Ethics Committee of Ningbo No. 2 Hospital (PJ-NBEY-KY-2015-020-01). We registered this study at the Chinese Clinical Trial Registry (ChiCTR-IPD-17010596).

Detailed materials, methods, and declarations are described in Data S1.

Table 1 Background of total patients in this study

Parameter	Value
N	132
Age (year)	74.42±7.40
Female	42 (31.8%)
Body mass index (kg/m^2)	23.58±3.28
Diabetes mellitus	40 (30.3%)
Hypertension	96 (72.7%)
Diseased vessels (branch)	
Average	2.20
1	31
2	44
3	57
ACEI	32 (24.2%)
ARB	56 (42.4%)
Diuretics	58 (43.9%)
Statin	132 (100.0%)
eGFR (ml/(min·1.73 m^2))	77.22±21.05
Hemoglobin (g/L)	126.89±16.71
C-reactive protein (mg/L)	3.26 (1.51–9.79)
Albumin (g/L)	38.54±4.79
Uric acid (μmol/L)	352.12±103.35
Total cholesterol (mmol/L)	4.01±1.06
LDL (mmol/L)	2.20±0.84
Triglycerides (mmol/L)	1.29 (0.93–1.72)
NT-proBNP (pg/ml)	682 (348–2332)
LVEF (%)	62.03±8.17
Contrast medium (ml)	169.00 (148.25–193.00)

Data are presented as number, the mean±standard deviation (SD), number (percentage) of patients, or medians with interquartile ranges (25%–75%). *N*, total number of patients; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction

There was a significantly higher level of N-terminal pro-brain natriuretic peptide (NT-proBNP) in the AKI group (P=0.01; Table 2).

For both groups, the patients displayed significant increases in SCr from baseline at the 48 h time point (P<0.01 for AKI group, P<0.05 for non-AKI group). The SCr did not significantly change at the 24 h time point in the two groups, but the relative SCr levels at 24 h after PCI were significantly higher in patients with AKI (P<0.01; Table 3).

Compared to baseline levels, patients with AKI showed a significant increase in uL-FABP and uNGAL at 6, 24, and 48 h after PCI, but uKIM-1 levels were significantly increased only at 48 h after PCI. Patients without AKI displayed statistically insignificant changes in uNGAL and uKIM-1 from baseline at 6, 24, and 48 h after PCI, but significant increases in uL-FABP from baseline at 6, 24, and 48 h after PCI (Table 3). At 6 and 24 h after PCI, there were significant differences in the relative measurements of uL-FABP and uNGAL between patients developing AKI and those without AKI. However, the relative measurement of uKIM-1 was able to discriminate between the two patient groups only at the 24 h time point (Table 3).

We performed ROC curve analysis to assess the ability of the biomarkers in predicting AKI. As early as 6 h after PCI, the AUCs of uL-FABP, uNGAL, and uKIM-1 were 0.809 (95% CI 0.669–0.908; P<0.001), 0.867 (95% CI 0.738–0.948; P<0.001), and 0.512 (95% CI 0.363–0.659; P=0.90), respectively (Fig. 1a). Based on the logistic model, combined predictors of uL-FABP and uNGAL were gained, with an AUC of 0.899 (95% CI 0.778–0.967; P<0.001).

At the 24 h time point after PCI, the AUCs of uL-FABP, uNGAL, and uKIM-1 were 0.888 (95% CI 0.763–0.960; P<0.001), 0.840 (95% CI 0.705–0.930; P<0.001), and 0.676 (95% CI 0.525–0.804; P=0.049), respectively (Fig. 1b). Combined predictors of uL-FABP and uNGAL were gained, with an AUC of 0.917 (95% CI 0.801–0.977; P<0.001).

In this study, we evaluated the usefulness of uL-FABP, uNGAL, and uKIM-1 determinations for the early (6 and 24 h following PCI) detection of AKI in a group of aged patients undergoing PCI. This prospective pilot study found that AKI occurred in 12.12% patients within 48 h after intervention. A relative increase in uL-FABP or uNGAL was useful for the diagnosis of AKI as early as 6 h after PCI.

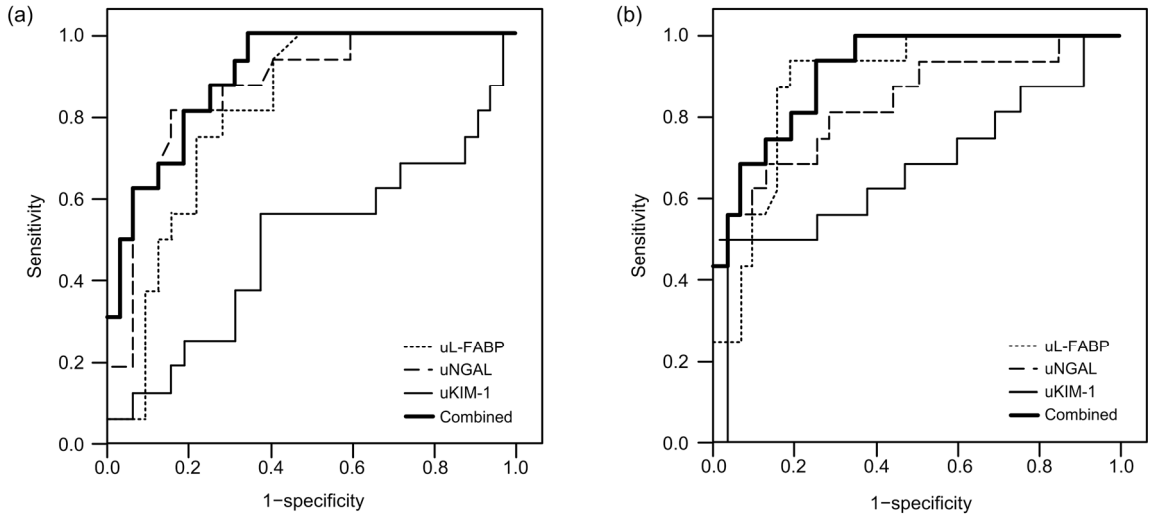

Fig. 1 ROC curves for the different markers analyzed for early detection of AKI

(a) A relative measurement at 6 h after PCI (AUC for uL-FABP: 0.809; AUC for uNGAL: 0.867; AUC for uKIM-1: 0.512; AUC for combined predictors: 0.899). (b) A relative measurement at 24 h after PCI (AUC for uL-FABP: 0.888; AUC for uNGAL: 0.840; AUC for uKIM-1: 0.676; AUC for combined predictors: 0.917). uL-FABP: urinary liver-type fatty acid-binding protein; uNGAL: urinary neutrophil gelatinase-associated lipocalin; uKIM-1: urinary kidney injury molecule-1; Combined: combined predictors of uL-FABP and uNGAL

Table 2 Background of AKI and non-AKI groups

Parameter	Patients with AKI	Patients without AKI	*P*-value
N	16	32	
Age (year)	75.06±8.31	74.34±6.08	0.74
Female	4 (25.0%)	8 (25.0%)	1.00
Body mass index (kg/m^2)	24.40±3.19	23.84±2.71	0.54
Diabetes mellitus	5 (31.3%)	10 (31.3%)	1.00
Hypertension	14 (87.5%)	23 (71.9%)	0.40
Diseased vessels (branch)			
Average	2.19	2.00	0.42
1	4	9	
2	5	14	
3	7	9	
ACEI	2 (12.5%)	10 (31.3%)	0.29
ARB	7 (43.8%)	16 (50.0%)	0.68
Diuretics	9 (56.3%)	16 (50.0%)	0.68
Statin	16 (100.0%)	32 (100.0%)	1.00
eGFR (ml/(min·1.73 m^2))	62.46 (51.01–92.35)	79.05 (66.43–95.12)	0.36
Hemoglobin (g/L)	121.5±12.71	124.69±18.45	0.54
C-reactive protein (mg/L)	7.57 (2.54–12.43)	3.59 (1.51–10.52)	0.26
Albumin (g/L)	36.44±4.24	38.31±4.13	0.15
Uric acid (μmol/L)	374.57±123.84	378.27±105.67	0.91
Total cholesterol (mmol/L)	3.66±0.65	3.96±0.95	0.26
LDL (mmol/L)	2.03±0.61	2.16±0.75	0.54
Triglycerides (mmol/L)	1.24 (1.02–1.67)	1.32 (1.02–1.71)	0.65
NT-proBNP (pg/ml)	3592 (496–6258)	562 (300–1889)	0.01
LVEF (%)	57.00 (53.25–66.50)	64.00 (59.00–68.00)	0.16
Contrast medium (ml)	203.5 (148.5–233.5)	170.5 (149.0–189.0)	0.16

Data are presented as number, the mean±standard deviation (SD), number (percentage) of patients, or medians with interquartile ranges (25%–75%). *N*, total number of patients; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; AKI: acute kidney injury

Table 3 Serial changes of serum and urinary markers

Parameter	Patients with AKI	Patients without AKI	*P*-value
SCr (μmol/L)			
Pre PCI	87.19±29.88	84.82±29.55	
24 h after PCI	110.33±38.94	87.90±27.28	
48 h after PCI	135.79±53.99**	90.02±29.74*	
A relative measurement at 24 h after PCI	1.30±0.26	1.07±0.19	0.001
uL-FABP (μg/g Cr)			
Pre PCI	1.92 (1.23–3.22)	3.93 (1.48–5.55)	
6 h after PCI	4.31 (2.22–6.75)**	4.62 (1.96–6.96)**	
24 h after PCI	6.64 (5.92–9.40)**	4.63 (2.22–8.19)**	
48 h after PCI	5.85 (2.75–8.65)**	4.78 (2.01–7.42)*	
A relative measurement at 6 h after PCI	1.95 (1.69–2.21)	1.18 (1.01–1.75)	0.001
A relative measurement at 24 h after PCI	3.13 (2.64–5.48)	1.39 (1.10–1.89)	<0.001
uNGAL (μg/g Cr)			
Pre PCI	25.20 (11.25–55.62)	59.69 (39.81–85.98)	
6 h after PCI	88.05 (45.22–248.75)**	56.32 (37.63–122.26)	
24 h after PCI	104.05 (50.08–162.82)**	60.69 (33.86–112.10)	
48 h after PCI	103.15 (40.83–178.27)**	61.86 (35.41–118.14)	
A relative measurement at 6 h after PCI	4.30 (2.02–4.93)	1.12 (0.66–1.80)	<0.001
A relative measurement at 24 h after PCI	3.22 (1.72–5.53)	1.09 (0.60–2.03)	<0.001
uKIM-1 (μg/g Cr)			
Pre PCI	1.24 (0.46–2.64)	1.10 (0.70–1.57)	
6 h after PCI	1.21 (0.50–2.66)	1.18 (0.66–1.57)	
24 h after PCI	1.72 (1.16–7.08)	1.21 (0.64–1.68)	
48 h after PCI	2.08 (1.18–7.74)*	1.07 (0.78–1.76)	
A relative measurement at 6 h after PCI	1.08 (0.71–1.53)	0.98 (0.81–1.47)	0.896
A relative measurement at 24 h after PCI	2.91 (0.86–7.13)	1.11 (0.75–1.53)	0.049

SCr: serum creatinine; Cr: creatinine; uL-FABP: urinary liver-type fatty acid-binding protein; uNGAL: urinary neutrophil gelatinase-associated lipocalin; uKIM-1: urinary kidney injury molecule-1; PCI: percutaneous coronary intervention; AKI: acute kidney injury. Data are presented as the mean±SD or medians with interquartile ranges (25%–75%). Values that are significantly different between pre- and post-PCI are indicated by * $P<0.05$, ** $P<0.01$

In the human kidney, L-FABP is expressed predominantly in the proximal tubules and plays a key role in fatty acid metabolism. L-FABP binds to lipid peroxidation products and is excreted from the cytoplasm of ischemic proximal tubule cells. Urinary excretion of L-FABP is elevated in kidney injury, reflecting tubulointerstitial damage (Kamijo et al., 2004). In our study, compared with the levels before PCI, uL-FABP levels were significantly higher at the 6 h time point in patients both who experienced AKI and who did not. However, the relative measurement was significantly higher in the AKI group. In a report by Torregrosa et al. (2015), uL-FABP has also been shown to increase significantly at 12 h after coronary angiography in patients without AKI. We think uL-FABP might reflect unrecognized tubular damage or nonspecific expression, and the relative measurement was probably more suitable for the diagnosis of AKI. In addition, uL-FABP has been reported as a promising indicator for the occurrence of AKI in patients undergoing cardiac surgery or coronary angiography (Katagiri et al., 2012; Manabe et al., 2012). Although these cohorts are heterogeneous because the enrolled patients had undergone different cardiac therapy, it can be concluded that uL-FABP is an early biomarker for AKI, and the relative measurement at 6 h after PCI could detect AKI with an AUC value of 0.809 in our report.

NGAL is normally reabsorbed by megalin-facilitated endocytosis in the proximal tubules. Once the proximal tubular damage occurs, uNGAL concentration will increase (Singer et al., 2013). Moreover, NGAL may be produced in the damaged renal tubules and participate in renal repair (Mishra et al., 2003).

In the research by Liebetrau et al. (2014), uNGAL at 24 h after contrast medium application is predictive of AKI in patients undergoing PCI, but the uNGAL levels before PCI were significantly higher in the AKI group and this may influence the subsequent uNGAL levels. In a meta-analysis, uNGAL appeared to be a promising biomarker of AKI within 6 h after cardiac surgery, especially in neonates/children (Zhou et al., 2016). In our study, uNGAL increased significantly at 6 h after PCI in aged patients with AKI, and remained at high levels at the 24 and 48 h time points. However, it changed little in those who did not experience AKI. Furthermore, the AUCs of uNGAL relative measurement were 0.867 at the 6 h time point and 0.840 at the 24 h time point in this report.

KIM-1 is a transmembrane tubular protein that is induced after kidney injury, and the US Food and Drug Administration approved KIM-1 as a biomarker for preclinical trials (Dieterle et al., 2010). Urinary KIM-1 is the ectodomain of KIM-1, and reflects tissue KIM-1; it is a non-invasive biomarker associated with inflammation and renal proximal tubular damage (van Timmeren et al., 2007). A systematic review had reported that uKIM-1 was a specific predictor for early AKI in patients undergoing cardiopulmonary bypass surgery (Shao et al., 2014). In addition, uKIM-1 has also been shown to be a moderately useful predictor for AKI 12 h after coronary angiography (AUC=0.713) and 24 h after PCI (AUC=0.850) (Luo et al., 2013; Torregrosa et al., 2015). In this study, compared to the non-AKI group, the relative measurement of uKIM-1 was significantly higher at 24 h after intervention, showing relatively low predictive power for early diagnosis of AKI (AUC=0.676, P= 0.049). However, uKIM-1 levels significantly increased only at the 48 h time point, and in a report by Parikh et al. (2013), uKIM-1 peaked 2 d after cardiac surgery and remained elevated for several days. A variety of reasons might explain the differences: definitions of AKI adopted in the individual studies varied, and age, population settings, and time of urine collections may also contribute to the heterogeneity in results.

Because of the differential expression of urinary biomarkers, combining these biomarkers may enhance their own predictive value, and it might be a reasonable strategy to combine the markers with different sensitivity and specificity (Katagiri et al., 2012). Luo et al. (2013) described the advantages of combining the biomarker levels (uKIM-1, uNGAL, and urinary interleukin-18 (uIL-18)) to improve their performance, but we considered that the biomarker levels were probably unsuitable for patients with abnormal baseline levels. In our study, we combined the relative levels and found that combinations of uL-FABP and uNGAL at the 6 and 24 h time points were able to increase the AUC for AKI up to 0.899 and 0.917, respectively. However, optimal combinations of urinary biomarkers still need further investigation.

Several limitations might affect the results obtained in our study. First, we studied aged patients at a single hospital. Evaluation should be conducted at multicenter hospitals to confirm the findings. Second, patients with AKI had relatively low estimated glomerular filtration rate and left ventricular ejection fraction on admission, and were more likely to receive higher contrast medium volume during the operation. These factors had been shown to be independent predictors of AKI (Andò et al., 2014, 2015). Our study population is small and therefore in a larger population it is likely that the differences would be significant between the AKI and non-AKI groups. Third, although we recruited a relatively homogeneous cohort, there was a significant difference in NT-proBNP between the two groups, and NT-proBNP is associated with heart failure and poor renal function. In addition, owing to the possible fundamental expression, uL-FABP and uNGAL baseline levels in AKI patients were lower than those in patients without AKI. Based on this condition, a relative increase in urinary biomarker seems better than the level for the assessment of biomarker performance. Finally, AKI was diagnosed using only SCr. Another criterion based on urine output was not used, and therefore renal injury might be underestimated. Also this definition may not reflect tubular injury, so it might appear inaccurate for evaluation of the diagnostic performance of urinary biomarkers. Stricter criteria to diagnose AKI still require further studies.

Urinary L-FABP and NGAL are predictive of AKI in aged patients at 6 and 24 h after PCI, and a combination of urinary biomarkers (including uL-FABP and uNGAL) shows better predictive capacity. However, uKIM-1 provides inferior predictive power for early diagnosis of AKI.

Compliance with ethics guidelines

Hong-hua YE, Gen SHEN, Qun LUO, Fang-fang ZHOU, Xiao-ling XIE, Chun-yan WANG, and Li-na HAN declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for which identifying information is included in this article.

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List of electronic supplementary materials

Data S1 Materials, methods, and declarations

中文概要

题　目：老年患者经皮冠状动脉介入术后急性肾损伤的早期诊断的研究

目　的：探索老年患者尿液中肝型脂肪酸结合蛋白（L-FABP）、中性粒细胞明胶酶相关脂质运载蛋白（NGAL）及肾损伤分子 1（KIM-1）三种新型肾损伤标志物对经皮冠状动脉介入（PCI）术后急性肾损伤（AKI）的早期预测作用。

创新点：本研究主要评估 PCI 术后肾损伤标志物的上升倍数对 AKI 早期诊断的价值，对基线标志物水平不同的患者而言，具有一定意义。

方　法：采用巢式病例对照研究的方法来比较 PCI 术后 AKI 患者和对照组患者围手术期肾损伤标志物的变化。

结　论：老年患者 PCI 术后 6 小时尿 L-FABP 和 NGAL 的上升倍数对 AKI 具有一定的预测价值。二者联合检验预测价值更高。而尿 KIM-1 的早期预测价值较低。

关键词：肝型脂肪酸结合蛋白；中性粒细胞明胶酶相关脂质运载蛋白；肾损伤分子 1；经皮冠状动脉介入术；急性肾损伤