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Early prediction of acute kidney injury in patients with acute myocardial injury☆,☆☆

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Abstract

Introduction: Previous studies have revealed that acute myocardial infarction (AMI) with acute kidney injury (AKI), about 17%, is strongly related to long-term mortality and heart failure. The dynamic changes in renal function during AMI are strongly related to long-term mortality and heart failure.

Objectives: Our study used clinical parameters and AKI biomarkers including neutrophil gelatinase–associated lipocalin, interleukin (IL)-6, IL-18, and cystatin C to evaluate prognostic relevance of AKI in the setting of AMI.

Methods: This prospective study was conducted from November 2009 to January 2011 and enrolled sequential 96 patients with catheter-proven AMI; it was approved by the institutional review board of Chang Gung Memorial Hospital, Taiwan (institutional review board no. 99-0140B) and conformed to the tenets of the Declaration of Helsinki. The definition of *AKI* is the elevation of serum creatinine of more than 0.3 mg/dL within 48 hours.

Results: Our results show that the incidence of AKI after AMI is 17.7% (17 patients). The following could be statistically related to AKI after AMI: age (P = .012), cardiac functions (Killip stage and echocardiogram; P = .003 each), Thrombolysis in Myocardial Infarction (TIMI) flow grade (P < .001), stenting (P < .001), neutrophil gelatinase–associated lipocalin (P = .005), IL-6 (P = .01), IL-18 (P = .002), and cystatin C (P = .002) in serum. The TIMI flow grade and serum cystatin C were shown to be important predictors by using multivariate analysis. Both TIMI flow lower than grade 2 and serum cystatin C of more than 1364 mg/L could be used to predict AKI (both overall correctness, 0.78). Moreover, IL-6 in serum is also associated with the major cardiovascular events after AMI (P = .02), as demonstrated in our study.

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Conclusion: In conclusion, the worse TIMI flow and high plasma cystatin C can be used to predict AKI after AMI. Moreover, IL-6 can also be used as a 30-day major cardiovascular event indicator after AMI. A larger prospective and longitudinal study should follow the relationship between AKI predictors after AMI.

1. Background

Acute kidney injury (AKI) is a common complication of acute myocardial infarction (AMI) [1-7]. It is thought to be secondary to unstable hemodynamic status or contrast [4,8]. The dynamic changes in renal function during AMI are strongly related to long-term mortality and heart failure [4]. The risk factors for developing AKI after AMI include being elderly, having congestive heart failure, and insufficient use of low-molecular-weight heparins and β-blockers as well as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins [7]. Although serum creatinine is traditionally used for the diagnosis of AKI, it is an insensitive and unreliable biomarker during acute changes in kidney function. Recently, however, there have been discoveries of some early renal damage biomarkers such as neutrophil gelatinase–associated lipocalin (NGAL) [9], interleukin-18 (IL-18) [10], interleukin-6 (IL-6) [11], and cystatin C (CysC) [12].

Neutrophil gelatinase–associated lipocalin can be used to predict early biomarkers for acute renal injury in children undergoing cardiopulmonary bypass [9]. Urine IL-18 is also a predictive biomarker for AKI in the same group of patients [10]. However, elevation of urinary IL-18 is not associated with AKI after adult cardiac surgery and, rather, represents a nonspecific marker of cardiopulmonary bypass–associated systemic inflammation [13]. Interleukin 6 is another proinflammatory cytokine, as both urine and serum IL-6 increased in children undergoing cardiac surgery and can, thus, act as early predictors of AKI [14,15]. Cystatin C is a 13-kd endogenous cysteine proteinase inhibitor that is produced by nucleated cells at a constant rate [16]. Cystatin C detects early changes in glomerular filtration rate in patients with heart valve replacement [12]. These novel biomarkers potentially allow timely intervention in high-risk patients at a point when damage is still reversible [9,10,14,15]. To the best of our knowledge, there are no studies using these early renal injury biomarkers to detect AKI in AMI [2,17]. We applied these biomarkers to prospectively investigate the clinical and prognostic relevance between AKI and AMI.

2. Materials and methods

2.1. Patient selection

This prospective study was conducted from November 2009 to January 2011 and enrolled sequential 96 patients with catheter-proven AMI; it was approved by the institutional review board of Chang Gung Memorial Hospital, Taiwan (institutional review board no. 99-0140B) and conformed to the tenets of the Declaration of Helsinki. All patients gave informed consent. Among these patients, 69 patients had ST-elevation AMI, and the remainders had non–ST-elevation AMI. Inclusion criteria were patients with AMI receiving percutaneous coronary intervention (PCI). Exclusion criteria were patients with chronic kidney disease requiring dialysis or with previous kidney transplantation. The end points were the 30-day major cardiovascular events (MACEs) [18] and mortality. The MACEs include myocardial infarction (MI), heart failure, PCI, coronary artery bypass grafting, malignant dysrhythmia, cardiac shock, thrombolysis, or implantable cardiac defibrillator.

Table 1 Baseline clinical characteristics of the study patients (N = 96)

Parameter	Value
Age (y)	63 ± 13
Man, n (%)	87 (90.6)
Body mass index (kg/m^2)	25.5 ± 3.74
Smokers, n (%)	62 (64.6)
Diabetes mellitus, n (%)	45 (46.9)
Hypertension, n (%)	56 (58.3)
History of CAD, n (%)	33 (34.4)
Congestive heart failure history, n (%)	11 (12.5)
Day 1 creatinine (mg/dL)	1.42 ± 0.2
Day 3 creatinine (mg/dL)	1.43 ± 0.3
AKI, n (%)	17 (17.7)
Killip class	2 ± 1
LVEF (%)	54 ± 14
Mean blood pressure (mm Hg)	90 ± 27
White blood count (/μL)	11 209 ± 4119
Serum NGAL (μg/L)	155.6 ± 146.5
Urine NGAL (μg/L)	59.1 ± 191.8
Serum IL-6 (pg/dL)	25.4 ± 48.2
Urine IL-6 (pg/dL)	7.8 ± 11.8
Serum CysC (mg/L)	1299.5 ± 816.7
Urine CysC (mg/L)	551.1 ± 2702.3
Serum IL-18 (pg/dL)	420.4 ± 192.3
Urine IL-18 (pg/dL)	62.1 ± 62.5
Mortality in 30 d, n (%)	3 (3.10)
MACE in 30 d, n (%)	6 (6.30)
Arrhythmia after AMI, n (%)	10 (10.50)

CAD indicates coronary artery disease; LVEF, left ventricular ejection fraction.

2.2. Sampling and quantifying serum and urinary CysC, NGAL, IL-6, and IL-18

Blood and urine sample for NGAL, CysC, IL-6, and IL-18 were taken on the first day of AMI after PCI. Serum creatinine was measured on the first and third days. All samples were centrifuged at 1500 rpm for 5 minutes, and then stored at −80°C until assay. Serum and urinary CysC, IL-6, and NGAL were measured in duplicate by a single enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota). Serum and urinary IL-18 were measured in duplicate by a single enzyme-linked immunosorbent assay (Medical and Biologic Laboratories, Nagoya, Japan) according to the manufacturer's instructions.

The definition of *AKI*, following the new definition for AKI proposed by the AKI Network [19], is an increase in the level of serum creatinine of more than 0.3 mg/dL within 48 hours.

2.3. Statistical analysis

The SPSS program version 18.0 was used for data analysis (SPSS, Chicago, Illinois). Descriptive statistics were expressed as mean ± SE. The Student *t* test was applied to compare the means of continuous variables and normally distributed data. Categorical data were tested using the χ^2 test. A *P* value less than .05 was considered significant.

Discrimination was assessed using the area under a receiver operating characteristic curve (AUROC). Areas under 2 AUROC curves were compared by a nonparametric approach. The analysis for AUROC was also conducted to estimate the cutoff values, sensitivity, specificity, and overall correctness. Finally, cutoff points were calculated by determining the best Youden index.

3. Results

Duration the study period, a total of 96 patients with AMI were enrolled (mean age 63 + 13 years old), including 87 (90%) men and 9 (10%) women (Table 1). Basically, the patients were in high-risk groups, such as smoking (64.6%), diabetes (46.9%), hypertension (58.3%), and history of coronary artery disease (34.4%) and heart failure (12.5). The 30-day mortality after AMI was 3.1% and MACEs [18]

Table 2 Clinical characteristics between AKI and non-AKI

	Non-AK I (n = 79)	AKI (n = 17)	*P*
Age (y)	61 ± 12	70 ± 8	.02*
DM, n (%)	34 (43)	11 (65)	.11
Hypertension, n (%)	43 (54)	13 (76)	.12
Body mass index (kg/m^2)	25.6 ± 3.9	25.2 ± 2.8	.723
Mean BP (mm Hg)	91 ± 26	89 ± 2	.853
Killip class	2 ± 1	3 ± 1	.006*
LVEF (%)	55.8 ± 11.7	43.5 ± 17.1	.013*
Aspirin	96%	82%	.06
Clopidogrel	100%	88%	.03*
ACEi/ARB	86%	58%	.016*
β-Block	87%	76%	.213
Statin	94%	76%	.031*
Troponin I (*μ*g/L)	13.2 ± 6.3	25.2 ± 13.8	.246
CK-MB (U/L)	194 ± 182	271 ± 154	.64
Contrast volume (mL)	161 ± 54	206 ± 61	.012*
PCI time (min)	52 ± 13	62 ± 17	.068
TIMI flow grade	3 ± 1	2 ± 1	.004*
Stenting, n (%)	74 (93%)	8 (47%)	<.001
White blood count (/*μ*L)	10 669 ± 3248	13 776 ± 5784	.047*
Serum NGAL (*μ*g/L)	132.6 ± 109.8	300.1 ± 220.2	.015*
Urine NGAL (*μ*g/L)	18.1 ± 22.8	198.7 ± 373.7	1.07
Serum IL-6 (pg/dL)	17.6 ± 19.6	71.2 ± 92.9	.035*
Urine IL-6 (pg/dL)	4.6 ± 5.0	14.2 ± 14.1	.33
Serum CysC (mg/L)	1064.8 ± 323.0	2418.7 ± 1356.4	.03*
Urine CysC (mg/L)	745.54 ± 3591.6	425.5 ± 692.6	.634
Serum IL-18 (pg/dL)	386.3 ± 161.2	586.3 ± 200.9	.03*
Urine IL-18 (pg/dL)	54.6 ± 30.1	96.2 ± 126.6	.283
Death in 30 d, n (%)	0 (0%)	3 (17.6%)	<.001*
MACE in 30 d, n (%)	1 (1%)	5 (29.4%)	.001*

ACEi/ARB indicates angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; CK-MB, creatine kinase MB; DM, diabetes mellitus; LVEF, left ventricular ejection fraction *$P < .05$.

Table 3 Discrimination of the biomarkers by univariate and multivariate analyses to predict AKI

Parameter	β Coefficient	SE	Odd ratio (95% CI)	*P*
Univariate logistic regression				
Age	0.063	0.025	1.065 (1.014-1.119)	.012
Killip class	0.702	0.235	2.018 (1.272-3.200)	.003
Ejection fraction	−0.069	0.023	0.933 (0.892-0.976)	.003
TIMI flow grade	−1.179	0.03	0.308 (0.171-0.553)	<.001
Contrast volume	−0.017	0.007	0.983 (0.970-0.977)	.019
Stenting	−3.090	0.878	0.046 (0.008-0.254)	<.001
Serum NGAL	0.007	0.005	1.007 (1.002-1.012)	.005
Serum IL-6	0.029	0.011	1.030 (1.008-1.053)	.011
Serum CysC	0.03	0.01	1.003 (1.001-1.005)	.002
Serum IL-18	0.005	0.02	1.005 (1.002-1.009)	.002
Multivariate logistic regression				
TIMI flow grade	−1.211	0.452	0.298 (0.123-0.722)	.007
Serum CysC	0.003	0.001	1.003 (1.001-1.006)	.008

CI indicates confidence interval.

6.3%. Moreover, there were 17 patients (17.7%) with AKI after AMI.

Univariate analysis identified 10 of the 29 variables as valuable for AKI prediction (Tables 2 and 3). Patients with AKI were older ($P = .02$); had a worse hemodynamic status such as severer Killip class ($P = .003$); had poor cardiac function ($P = .003$); had a worse coronary flow (Thrombolysis in Myocardial Infarction [TIMI] grade, $P < .001$); had more contrast volume ($P = .02$) but less stenting implantation after PCI ($P < .001$); and had higher mortality ($P < .001$) and MACE ($P = .001$). The novel biomarkers, including white blood cell ($P = .0047$), serum NGAL ($P = .015$), IL-6 ($P = .035$), CysC ($P = .03$), and IL-18 ($P = .03$), were statistically higher in the AKI group (Table 3). Multivariate analysis showed worse TIMI flow grade ($P = .007$) and plasma CysC ($P = .008$), which were the most important factors (Table 3). The AUROC indicated that worse TIMI flow grade less than 2 ($P = .005$) and higher serum CysC ($P < .001$) significantly raised the incidence of AKI (Table 4). The best predictive cutoff of AKI in AMI, in our study, were the TIMI flow grade less than 2 and higher serum CysC above 1364 mg/L (Table 5).

The univariate analysis indicated that TIMI flow grade ($P = .003$), stenting ($P = .002$), contrast volume serum ($P = .02$), NGAL ($P = .005$), IL-6 ($P = .0018$), CysC ($P = .002$), IL-18 ($P = .045$), and AKI ($P = .006$) were related to the higher 30-day MACE rate after AMI. Multivariate analysis identified that only IL-6 independently predicted 30-day MACE in AMI, as demonstrated in our study (Table 6).

4. Discussion

Acute kidney injury is defined as an increase of at least 50% mg/dL or at least 0.3 mg/dL in the serum creatinine level as stated in the AKI Network criteria that require the rise in the creatinine level to occur within 48 hours [20,21]. Because of the possibility of hemodilution associated with cardiopulmonary bypass, we anticipated an early postoperative decline in the creatinine concentration in some patients and a delay in achieving the AKI Network threshold required for the diagnosis of AKI. Our rate of AKI after AMI was 17.7%, which is statistically associated with elderly patients, cardiac dysfunction, coronary flow, contrast volume, stenting, and elevated biomarkers, especially CysC. Our findings (Tables 2-5) are also compatible with a very recent study in which the condition of patients with ST-elevation AMI was complicated by worsening Killip class, age greater than 75 years, and worsening left ventricular function; these were also determined to be independent predictors of AKI [2]. In fact, systolic dysfunction often accompanied about one third of the 107 362 patients in a study [22] who had renal dysfunction in the Acute Decompensated Heart Failure

Table 4 Two AUROCs were compared by a nonparametric approach demonstrating that serum CysC and TIMI flow were good predictors of AKI in patients with AMI

	AUROC	SE	95% CI	*P*
TIMI flow grade	0.718	0.081	0.599	.005
Serum Cys	0.864	0.056	0.754	<.001

CI indicates confidence interval.

Table 5 Predictors of AKI after MI and cutoff values

	Cutoff point	Sensitive	Specificity	Youden index	Overall correctness
TIMI flow grade	2	0.962	0.471	0.433	0.716
Serum CysC	1364	0.692	0.859	0.511	0.775

Table 6 Novel biomarkers predicting major adverse cardiac events within 30 days

Variable	β Coefficient	SE	Odds ratio	95% Confidence interval	*P*
Univariate logistic regression					
TIMI flow grade	−1.006	0.039	0.366	0.188-0.710	.003
Stenting	−3.183	1.020	0.041	0.006-0.306	.002
Contrast volume	−0.51	0.021	0.950	0.912-0.990	.015
AKI	3.152	1.158	23.385	2.419-226.098	.006
Serum NGAL	0.007	0.02	1.007	1.002-1.012	.005
Serum IL-6	0.035	0.015	2.036	1.006-1.067	.018
Serum CysC	0.001	<0.001	1.001	1.001-1.002	.002
Serum IL-18	0.005	0.002	1.005	1.000-1.010	.045
Multivariate logistic regression					
Serum IL-6	0.035	0.015	1.035	1.006-1.066	.02

National Registry. Early detection of AKI implies that the early treatment can improve the prognosis [2,5-7,10,23]. There are more sensitive biomarkers including NGAL, IL-6, IL-18, and CysC that detect early acute renal injury [1,4,9,10,13,14].

Neutrophil gelatinase–associated lipocalin is an excellent early biomarker for ischemic renal injury [9]. It is a siderophore-binding lipocalin involved in nephrotoxic and ischemic injury [24], and it is a 25-kd glycoprotein also found in granules of human neutrophil [25]. In our study, serum NGAL level can accurately serve as an early detector of AKI ($P = .015$) on the first day of AMI. The cutoff value of NGAL in this study was 148 mg/dL (sensitivity, 0.857; specificity, 0.766; overall correctness, 0.74; Youden index, 0.623). The mean (SD) receiver operating characteristic curve was 0.830 ± 0.053. A reduced renal blood flow after reduced cardiac output is one reason for the elevation of NGAL concentrations after MI [26]. Neutrophil gelatinase–associated lipocalin is not only an AKI marker but also an inflammation marker. Recently, research revealed that NGAL may also be involved in cell survival, inflammation, and matrix degradation in osteoarthritis [27]. The experiment demonstrated that the hypoxic stress simulating AMI, the NGAL 24p3 messenger RNA, is increased [28]. However, there are 2 major factors that interact with NGAL in our patients with AMI. First, the amount of contrast medium and the procedure time of PCI [1,8,29] can aggravate renal function. Second, the hemodynamic status of a patient with AMI can be related to the incidence of AKI [29].

Other inflammation-related markers such as serum white blood count, IL-6 IL-18, and CysC were also statistically elevated in patients with AMI and AKI (Table 3). Atherosclerosis is an inflammatory disease [30], and active inflammation is evident in the accumulation of macrophages at sites of plaque rupture [31]. Basal neutrophil counts and IL-6 can be predictors of infarct size [11,32], and IL-6 can predict in-hospital and 30-day mortality as well as in-hospital clinical events, as demonstrated in our study [33] (Table 6).

Interleukin 18 is another proinflammatory cytokine, and it is produced by renal tubular cells and macrophages [10]. Plasma IL-18 concentrations are increased in patients with acute coronary syndromes and correlate with the severity of myocardial dysfunction [15]. Although our result showed that IL-18 was associated with AKI after AMI (Table 3), it is not a strong prognosis predictor in this AMI group.

Cystatin C is a better new marker of renal function than creatinine [12,34]. CysC can also be a good prognostic indicator of recurrent cardiovascular events in patients with acute coronary syndrome [34-37]. Our study demonstrated that patients older than 62 years, serum CysC above 1364 mg/L, and ejection fraction lower than 42.5% are among the best predictors of AKI after multivariate logistic regression with 77% correctness (Table 4 and 5).

Neutrophil gelatinase–associated lipocalin is related to the detection and extent of coronary artery disease [38]. Interleukin-18 may be a useful biomarker of the clinical manifestations of metabolic syndrome and arterial damage [10,39,40]. Cystatin C has been shown also to be associated with renal dysfunction, the severity of metabolic syndrome, arterial stiffness, and weight change in obese patients [41], but not with coronary artery or abdominal aortic calcium [42]. In the future, it will be interesting to further elucidate the roles of plasma NGAL, IL-18, and CysC in vascular compliance.

Our study has some limitations. First, the sample size is still relatively small, and all samples were coming from a single institute. Second, all our enrolled patients received coronary angiography. In the clinical practice, some patients with chronic kidney disease did not receive reperfusion therapy because of concerns regarding elevated risks for developing contrast nephropathy [1]. In other words, our study possibly excludes some high risks for AKI after MI. Third, the onset time of AMI could vary between patients. Fourth, the definition of AKI we used is not all well accepted yet. Finally, we did not follow up renal function and all biomarkers daily to show continuous changes. In established AKI, serum creatinine poorly differentiates prerenal from intrinsic AKI. The median concentration of Kidney injury molecule-1, CysC, and IL-18 was significantly greater in prerenal AKI, but not urinary NGAL. This confounds analysis in 2 directions, giving more power to prerenal markers and reducing the power of non–prerenal markers [43,44].

In conclusion, advanced age, impaired systolic function and coronary flow, contrast volume and stenting, and severity of the AMI are clinical factors relating to AKI, and plasma NGAL, IL-6, IL-18, and CysC can be used to predict AKI. Worse TIMI flow grade and high CysC are in the highest-risk group for AKI. Moreover, IL-6 can also be used as a 30-day MACE indicator after AMI. A larger prospective and longitudinal study should follow the relationship between AKI predictors after AMI.

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