Impact of Acute Kidney Injury on Clinical Outcomes after ST Elevation Acute Myocardial Infarction

Min Jee Kim,1 Hong Sang Choi,1 Seul Hyun Oh,1 Hyung Chul Lee,1 Chang Seong Kim,1 Joon Seok Choi,1 Jeong Woo Park,1 Eun Hui Bae,1 Seong Kwon Ma,1 Nam Ho Kim,1 Myung Ho Jeong,1,2 and Soo Wan Kim1,2

1Department of Internal Medicine, 2Heart Research Center, Chonnam National University Medical School, Gwangju, Korea.

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Corresponding author: Dr. Soo Wan Kim, Department of Internal Medicine, Chonnam National University Medical School, 8 Hak-dong, Dong-gu, Gwangju 501-757, Korea.
Tel: 82-62-220-6271, Fax: 82-62-225-8578
E-mail: skimw@chonnam.ac.kr

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Purpose: This study aimed to compare the incidence and clinical significance of transient versus persistent acute kidney injury (AKI) on acute ST elevation myocardial infarction (STEMI).

Materials and Methods: The study was a retrospective cohort of 855 patients with STEMI. AKI was defined as an increase of ≥0.3 mg/dL in creatinine level at any point during hospital stay. The study population was classified into 5 groups: 1) patients without AKI; 2) patients with mild AKI that was resolved by discharge (creatinine change less than 0.5 mg/dL compared with admission creatinine during hospital stay, transient mild AKI); 3) patients with mild AKI that did not resolve by discharge (persistent mild AKI); 4) patients with moderate/severe AKI that was resolved by discharge (creatinine change more than 0.5 mg/dL compared with admission creatinine, transient moderate/severe AKI); 5) patients with moderate/severe AKI that did not resolve by discharge (persistent moderate/severe AKI).

We investigated 1-year all-cause mortality after hospital discharge for the primary outcome of the study. The relation between AKI and 1-year mortality after STEMI was analyzed.

Results: AKI occurred in 74 (8.7%) patients during hospital stay. Adjusted hazard ratio for mortality was 3.139 (95% CI 0.764 to 12.897, p=0.113) in patients with transient, mild AKI, and 8.885 (95% CI 2.710 to 29.128, p<0.001) in patients with transient, moderate/severe AKI compared to patients without AKI. Persistent moderate/severe AKI was also independent predictor of 1 year mortality (hazard ratio, 5.885; 95% CI 1.079 to 32.101, p=0.041).

Conclusion: Transient and persistent moderate/severe AKI during acute myocardial infarction is strongly related to 1-year all cause mortality after STEMI.

Key Words: Acute kidney injury, myocardial infarction, mortality

INTRODUCTION

Acute kidney injury (AKI) is a common complication in hospitalized patients, especially in high risk patients such as those hospitalized with acute myocardial infarction (AMI), congestive heart failure, sepsis, and those undergoing cardiac surgery.1-6 Recent studies suggest that in patients with AMI, AKI is associated with poor outcomes and independently predicts increasing in-hospital and long-term mortality.7-9
Previous investigations principally emphasized the relationship between baseline indicators of renal function and outcome. However, renal function during the acute phase of AMI may change rapidly and AKI can be resolved by discharge. In such patients, it is thought that AKI is not associated with high risk long-term follow up. By contrast, AKI after AMI can be partly or completely irreversible in some patients, resulting in profound impact on cardiovascular outcomes. Few studies have examined the association between exacerbation of renal function and adverse clinical outcomes in patients with acute coronary syndrome. Furthermore, the prognostic value of transient versus persistent AKI for acute ST elevation myocardial infarction (STEMI) is unknown in Korea. Therefore, the present study aimed to compare the incidence and clinical significance of transient versus persistent AKI on acute STEMI.

MATERIALS AND METHODS

Study population
This study was a retrospective cohort of consecutive 855 patients (62±13 years, men 75.2%) who were admitted to Chonnam National University Hospital and whose discharge diagnosis was acute STEMI by ACC criteria. Between October 2005 and June 2008, a total of 921 patients presenting with acute STEMI were enrolled. To investigate the effects of AKI on the long term mortality, we excluded 66 patients who died during the hospital stay, and enrolled remaining 855 patients who were discharged from hospital in stable condition. On the other hand, to investigate the effects of AKI on the acute events, we analyzed in-hospital deaths separately to compare acute mortality according to AKI categories.

Definition of AKI
The cutoffs for AKI were based on absolute creatinine changes during hospitalization. AKI was defined as an increase of ≥0.3 mg/dL in creatinine level at any point during hospital stay. The severity of AKI was subdivided on evidence of AKI for acute ST elevation myocardial infarction (STEMI) or the day before discharge. The abbreviated Modification of Diet in Renal Disease formula was used to estimate glomerular filtration rate (GFR) in milliliters per minute per 1.73 m² from creatinine level.

Assessment of renal function
Laboratory data, including serum creatinine, was collected before coronary angiography on admission. Venous blood samples were obtained at 24, 48 and 72 hr thereafter. Pre-discharge creatinine was measured on the day of discharge or the day before discharge. The abbreviated Modification of Diet in Renal Disease formula was used to estimate glomerular filtration rate (GFR) in milliliters per minute per 1.73 m² from creatinine level.

Study endpoint
The primary endpoint was 1 year all cause mortality. After hospital discharge, clinical endpoint information was acquired by contacting each patient individually and reviewing hospital course if the patient had been re-hospitalized.

Statistical assessment
Continuous variables are demonstrated as either means (±SD) or medians, and categorical variables as numbers and percentages. We compared baseline characteristics of the groups using analysis of variance (ANOVA) for continuous variables and by the χ² statistic for categorical variables. Using Kaplan Meier method, event-free survival was estimated and curves were compared with log-rank test. To determine the relation between AKI categories and inhospital mortality, univariate and multivariate logistic regression analyses were examined. Univariate and multivariate Cox proportional hazards analyses were used to assess the relationship between AKI categories and 1-year mortality after adjustments to the variables. Analyses were adjusted for age, gender, heart rate on admission, Killip class II-IV, estimated glomerular filtration rate, left ventricular ejection fraction, and medication (aspirin, beta blocker, angiotensin converting enzyme ACE inhibitors, and statin). A p value less than 0.05 was deemed as significant. Statistical analysis was done with the Statisti-
Mortality of AKI in STEMI

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RESULTS

Baseline characteristics

Eight hundred fifty five patients were included in the present study (patients without AKI: n=781, 91.3%, patients with AKI; n=74, 8.7%). During the hospital course, mild AKI occurred in 38 (4.4%) patients and moderate/severe AKI in 36 (4.2%). Mild AKI was transient in 28 (73.7%) patients, and moderate/severe AKI was transient in 22 (61.1%) patients. Table 1 and 2 list baseline clinical characteristics of patients based on AKI categories. More severe AKI during the hospital course was associated with older age, higher Killip class and heart failure (ejection fraction <45%). Patients with AKI had higher creatinine level at baseline, higher

Table 1. Baseline Clinical Characteristics

|                      | No AKI (n=781) | Mild AKI                   | Moderate/Severe AKI        | p value |
|----------------------|----------------|---------------------------|---------------------------|---------|
|                      | Transient (n=28) | Persistent (n=10)         | Transient (n=22)          | Persistent (n=14) |
| Age (yrs)            | 61±13          | 68±12                     | 65±14                     | 71±7    | 65±14 | <0.001 |
| Male gender (%)      | 588 (75.3)     | 18 (64.3)                 | 10 (100)                  | 15 (68.2) | 12 (85.7) | 0.165 |
| Hypertension (%)     | 343 (43.9)     | 16 (57.1)                 | 5 (50)                    | 14 (63.6)  | 7 (50) | 0.252 |
| Smoking (%)          | 529 (67.7)     | 17 (64.3)                 | 10 (100)                  | 13 (59.1)  | 8 (57.1) | 0.146 |
| Diabetes (%)         | 195 (25.0)     | 7 (25)                    | 5 (50)                    | 8 (36.4)   | 5 (35.7) | 0.252 |
| CAD History (%)      | 58 (7.4)       | 4 (14.3)                  | 3 (30)                    | 3 (13.6)   | 2 (14.3) | 0.043 |
| Killip class II-IV (%)| 128 (16.4)    | 12 (42.9)                 | 3 (30)                    | 11 (50)    | 5 (35.7) | <0.001 |
| SBP (mmHg)           | 131±30         | 138±33                    | 124±22                    | 120±41     | 91±55 | 0.100 |
| HR (beats/min)       | 75±17          | 88±18                     | 78±14                     | 72±29      | 75±18 | 0.003 |
| EF (%)               | 55±12          | 53±15                     | 53±11                     | 46±12      | 41±15 | <0.001 |
| Hospital length (days)| 9±8            | 14±10                     | 10±4                      | 22±18      | 25±39 | <0.001 |

AKI, acute kidney injury; SBP, systolic blood pressure; CAD, coronary arterial disease; EF, ejection fraction; HR, heart rate.

Table 2. Baseline Kidney Function, Medical History and Major Adverse Cardiac Event

|                      | No AKI (n=781) | Mild AKI                   | Moderate/Severe AKI        | p value |
|----------------------|----------------|---------------------------|---------------------------|---------|
|                      | Transient (n=28) | Persistent (n=10)         | Transient (n=22)          | Persistent (n=14) |
| Kidney function      |                |                           |                           |         |
| Serum Cr (mg/dL)     | 1.07±0.98      | 1.02±0.35                 | 1.3±1.67                  | 1.38±0.53 | 2.39±1.91 | <0.001 |
| Estimated GFR (mL/min/m²)* | 82.6±24.4 | 77.2±25.0               | 121.4±90.1               | 58.0±24.2 | 80.6±136.6 | <0.001 |
| Peak Cr (mg/dL)      | 0.98±0.52      | 1.35±0.36                 | 1.64±1.66                 | 2.32±0.65 | 3.75±2.69 | <0.001 |
| Medications (%)      |                |                           |                           |         |
| Aspirin              | 761 (97.4)     | 26 (92.9)                 | 9 (90)                    | 22 (100) | 14 (100) | 0.267 |
| Beta blocker         | 638 (81.7)     | 22 (78.6)                 | 8 (80)                    | 14 (63.6)  | 10 (71.4) | 0.241 |
| Statin               | 674 (86.3)     | 26 (92.9)                 | 6 (70)                    | 16 (72.7)  | 10 (71.4) | 0.027 |
| ACE inhibitor/ARB    | 706 (90.4)     | 27 (96.4)                 | 7 (80)                    | 14 (63.6)  | 12 (85.7) | <0.001 |
| Major adverse cardiac event (%) |          |                           |                           |         |
| MACE                  | 106 (13.6)     | 3 (10.7)                  | 2 (20)                    | 7 (31.8)  | 5 (14.3) | 0.021 |
| Cardiac death        | 9 (1.2)        | 0 (0)                     | 1 (10)                    | 5 (22.7)  | 2 (14.3) | <0.001 |
| All-cause death      | 16 (2.0)       | 1 (3.6)                   | 1 (10)                    | 6 (27.3)  | 2 (14.3) | <0.001 |
| Re-PCI               | 80 (10.2)      | 1 (3.6)                   | 1 (10)                    | 1 (4.5)   | 1 (7.1) | 0.698 |
| CABG                 | 2 (0.3)        | 0 (0)                     | 0 (0)                     | 0 (0)     | 0 (0) | 0.996 |
| Treatment strategy   |                |                           |                           |         |
| Primary PCI          | 536 (68.6)     | 21 (75)                   | 7 (70)                    | 17 (77.3) | 10 (71.4) | 0.867 |
| Thrombolysis         | 114 (14.6)     | 2 (7.2)                   | 0 (0)                     | 0 (0)     | 1 (7.1) | 0.064 |
| Conservative treatment | 67 (8.6)  | 1 (3.6)                   | 1 (10)                    | 4 (18.2)  | 3 (21.4) | 0.128 |

AKI, acute kidney injury; GFR, Glomerular filtration rate; Cr, creatinine; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

*On the basis of abbreviated MDRD (Modification of Diet in Renal Disease) study equation.
peak creatinine during the hospital course, present with lower ejection fraction compared with the patients without AKI. Use of statin, angiotensin converting enzyme inhibitors or angiotensin receptor blockers was less frequent in more severe AKI. However, estimated GFR was the lowest in the group with transient moderate/severe AKI.

Relation of AKI and inhospital mortality
A total of 66 (7.2%) deaths occurred in hospital, with 25 (37.9%) deaths occurring in patients with acute kidney injury. Univariate logistic regression showed that persistent moderate/severe AKI was associated with a statistically significant increase of inhospital mortality. However, after adjustment for other risk variables, there was no association with AKI categories and in hospital mortality.

Relation of AKI and 1 year mortality
The median duration of follow-up after hospital discharge was 358 days. Of the 855 patients who survived their index hospitalization, a total of 25 (2.9%) deaths occurred during the follow-up period. Fig. 1 illustrates Kaplan-Meier survival in patients with AKI groups during follow-up. The Kaplan-Meier survival curves for the AKI groups showed significant differences of 1-year mortality after hospital discharge statistically. In each of the AKI groups, persistent moderate/severe AKI group showed lower probability of event-free survival compared with the other groups. Also, during the follow-up period, probability of death increased with increasing degrees of AKI.

The results of a multivariable cox proportional hazards model adjusting for other clinical variables of mortality are shown in Table 3 and 4. After adjustments for other risk variables including baseline estimated GFR and other clinical variables, there was no differences in 1-year mortality risk between transient mild AKI group and group without AKI. On the other hand, transient moderate/severe AKI was associated with an adjusted hazard ratio of 8.885 compared with the transient mild AKI group. Use of statin, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers was less frequent in more severe AKI. However, estimated GFR was the lowest in the group with transient moderate/severe AKI.

Table 3. Unadjusted and Adjusted Logistic Regression Model for Inhospital Mortality According to Acute Kidney Injury Categories

| AKI Category          | Unadjusted OR (95% CI) | p value | Adjusted OR (95% CI) | p value |
|-----------------------|------------------------|---------|----------------------|---------|
| Normal                | 0.186                  |         | 0.323 (0.021-3.578)  | 0.323   |
| Transient mild AKI    | 0.77 (0.102-5.818)     | <0.001  | 0.273 (0.021-3.578)  | 0.323   |
| Persistent mild AKI   | 2.156 (0.269-17.299)   | 0.470   | 12.445 (0.847-182.901) | 0.066 |
| Transient moderate/severe AKI | 1.96 (0.444-8.657) | 0.375 | 0.368 (0.038-3.595) | 0.390 |
| Persistent moderate/severe AKI | 32.333 (15.208-68.745) | <0.001 | 2.087 (0.430-10.121) | 0.361 |

AKI, acute kidney injury; CI, confidence interval.

Table 4. Unadjusted and Adjusted Logistic Regression and Cox Proportional Hazards Model for Mortality According to Acute Kidney Injury Categories*

| AKI Category          | No AKI | Mild AKI | Moderate/Severe AKI |
|-----------------------|--------|---------|---------------------|
|                       | Transient | Persistent | Transient | Persistent |
| Inhospital mortality  | <0.001 | 0.800  | 0.470 | 0.375 | <0.001 |
| 1-yr mortality        | 0.186 | 0.323  | 0.066 | 0.390 | 0.361 |

AKI, acute kidney injury; CI, confidence interval.

*The final model adjusted for age, gender, estimated glomerular filtration rate, history of hypertension, diabetes, smoking, previous myocardial infarction, Killip class, heart rate and blood pressure on admission, medical therapy (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers) and left ventricular ejection fraction.
pared with group without AKI. Patients with persistent moderate/severe AKI had the highest all-cause of mortality compared with other groups (hazard ratio, 5.885; 95% CI 1.079 to 32.101, \( p = 0.046 \)).

**DISCUSSION**

In the present study, AKI occurred in 74 (8.7%) patients during hospital course with STEMI who survived their index hospitalization. After acute stage of myocardial infarction, improvement of renal function within the index hospitalization revealed 73.7% of patients in mild AKI and 61.1% of patients in moderate/severe AKI. Patients developing AKI have worse baseline renal function and are more likely to present higher peak serum creatinine level. Baseline estimated GFR was the lowest in transient moderate/severe AKI group and peak serum creatinine was the highest in persistent moderate/severe AKI group. More severe AKI group showed longer hospital lengths. It is thought that there were more combined complications in severe AKI. Furthermore, in patients with transient mild AKI and transient moderate/severe AKI, there was no association with prognostic significance of 1-year all cause mortality after STEMI. Especially in mild transient AKI group, outcome of the group was similar to that of patients without AKI. Although it did not completely exclude absolute impacts and many questions about the relationship between renal dysfunction and mortality after AMI, several studies suggested that increment of serum creatinine level during admission is a significant independent predictor of mortality, especially in the setting of decompensated heart failure8,18 and AMI.19 However, our result showed that transient mild AKI did not affect long-term mortality in STEMI. In patients with mild transient AKI and moderate/severe transient AKI, there was no association with prognostic significance of 1-year all cause mortality, suggesting that transient mild or moderate/severe AKI represent a reversible renal impairment and do not affect long term mortality if corrected.

To investigate the effects of AKI on the acute events, we analyzed inhospital deaths separately according to acute kidney injury categories, and found that AKI has no association with inhospital mortality after adjustment for clinical predictors of mortality among patients with STEMI. These findings suggest that impaired renal function after STEMI is an independent predictor of 1-year mortality, but not of inhospital mortality. These observations are different from other study.7 Differences may be attributed to different races, measurement methods of serum creatinine and enrolled size.

Previous investigators have demonstrated that baseline renal dysfunction or CKD is associated with poor outcomes during short and intermediate-term follow up after AMI20–24 or acute coronary syndromes.25–27 The present study showed transient and persistent moderate/severe AKI as a risk factor for all cause mortality after STEMI. This means that worsening renal dysfunction and baseline renal dysfunction specifically define a group at a very high risk for mortality and may reflect underlying mechanisms that adversely affect both cardiac and renal function.7

AKI is a complex multifactorial phenomenon, preconditioned by underlying renal dysfunction and modulated by multiple contributing factors.28 For example, neurohormonal factors,29 such as norepinephrine, rennin-angiotensin, vasopressin, and endothelin, may affect renal function and play a role in renal dysfunction, modulating post infarct left ventricular remodeling.30–32 Also, volume depletion, the use of contrast media,33 and medical treatment such as diuretics or angiotensin converting enzyme inhibitors or angiotensin receptor blocker may affect renal dysfunction in reversible manner. Even though these factors may affect renal function and the outcomes of AMI, there are few studies regarding the incidence and clinical impact of transient versus persistent AKI in patients with AMI. Therefore, understanding the impact of transient versus persistent AKI on acute mortality and long-term outcomes is expected to assist with guiding follow up care for patients with acute myocardial infarction after discharge.

There are several points to be considered. Other predictors of AKI, such as current pharmacologic and procedural interventions for therapy of AMI that may be helpful to the heart but affect renal dysfunction, need to be considered.9 Furthermore, it has to be considered other types of therapeutic managements that can be applied to these patients to decrease the risk of mortality after AKI. AKI occurrences in MI patients should be monitored for given the increased risk of long-term death. Patients with AKI should be carefully monitored after discharge for potential development of related complications. Our study has several limitations. Because of methodological limitations inherent in retrospective analyses, our data cannot include the volume of contrast. Therefore, we did not address the influence of contrast volume that was administered during percutaneous coronary intervention. In addition, patients with poorer general condition are more likely to have longer hospitalizations and,
hence, performed more frequent renal function studies including blood sampling, thus there has been the increasing probability of serum creatinine level change detection.

In conclusion, the present study shows that hemodynamic changes in renal function are common in AMI that is associated with long term mortality, especially in transient and persistent moderate/severe AKI.

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