Renal Dysfunction on Admission, Worsening Renal Function, and Severity of Acute Kidney Injury Predict 2-Year Mortality in Patients With Acute Myocardial Infarction

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Background: Recent studies have proven that initial renal dysfunction and worsening renal function during hospitalization can predict the clinical outcome of patients with acute myocardial infarction (AMI). There is limited study regarding acute kidney injury (AKI) by the RIFLE classification (Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal failure) to assess the outcome of AMI survivors.

Methods and Results: During a mean follow-up period of 635.3±204.9 days, the 2-year mortality rate was 10.6% in 613 AMI patients who survived to discharge. Adjusted Cox regression analysis revealed that left ventricular dysfunction (<40%) [hazard ratio (HR), 2.83; 95% confidence interval (CI), 1.11–7.20; P=0.029], estimated glomerular filtration rate <60 ml·min⁻¹·1.73 m⁻² on admission (HR, 4.01; 95% CI, 1.51–10.62; P=0.005), and AKI severity by RIFLE classification during first week after hospitalization (Injury: HR, 8.11; 95% CI, 2.53–26.05; P=0.001; Failure: HR, 19.28; 95% CI, 2.24–166.26; P=0.007) were independent predictors of 2-year mortality.

Conclusions: Independent of initial renal dysfunction on admission, the AKI severity by RIFLE classification may be useful in establishing the hospital discharge risk score for predicting long-term mortality in AMI patients who survive to discharge.

Key Words: Acute kidney injury; Acute myocardial infarction; Long-term outcome; RIFLE
including 48 patients who died during hospitalization and 26 patients who underwent dialysis, or kidney transplantation therapy for chronic kidney disease before admission. Among the remaining 613 patients, patients who survived an AMI event were included in the study. The demographic and clinical characteristics of the patients were recorded on admission. Information regarding the laboratory and pharmacological data and interventional therapy was obtained from the hospital’s computer database. This was an observational study, and the patient up to 3 months before admission) of selected patients were retrieved from the hospital’s computer database. For patients with no previous serum creatinine record, baseline creatinine levels were calculated by using the MDRD equation.22 The maximum RIFLE classification was determined by comparing the highest serum creatinine during hospitalization with the baseline creatinine level. Patients who met the RIFLE criteria were classified as the AKI group, and those who did not were classified as the non-AKI group. Patients in the AKI group were further classified into RIFLE-R (Risk, 150% increase in creatinine), RIFLE-I (Injury, 200% increase in creatinine), and RIFLE-F (Failure, 300% increase in creatinine) groups according to the maximal serum creatinine value obtained during the first 7 days after hospitalization. This study aimed to evaluate the effect of AKI severity by the RIFLE classification on long-term outcomes of AMI patients who survived to discharge. The patients who finally reached the level of either loss or end-stage renal disease were initially included in the the RIFLE-R, I or F groups.

AMI was defined as the occurrence of 2 or more of the following: chest pain, ischemic ECG change, and elevated cardiac marker. It was further classified as ST-elevation MI (STEMI) or non-STEMI (NSTEMI) according to the ECG findings. STEMI was defined as ST-segment elevation >1 mm in 2 contiguous leads. Elevated cardiac marker was defined as peak cardiac troponin I level >3-fold the upper limit of normal within 72 h after admission.

### Table 1. Demographic and Clinical Characteristics of Patients

|                        | Survivor (n=548) | Non-survivor (n=65) | P value |
|------------------------|------------------|---------------------|---------|
| **Age (years)**        | 62.1±13.5        | 74.4±11.2           | <0.001  |
| **Women [n (%)]**      | 109 (19.9)       | 24 (37.5)           | 0.002   |
| **Hypertension [n (%)]** | 307 (56.0)     | 46 (70.8)           | 0.024   |
| **Diabetes [n (%)]**   | 168 (30.8)       | 32 (49.2)           | 0.003   |
| **Smoking [n (%)]**    | 291 (53.1)       | 27 (41.5)           | 0.088   |
| **Hypercholesterolemia [n (%)]** | 178 (32.8) | 17 (26.6)           | 0.396   |
| **Previous history of MI [n (%)]** | 61 (11.1)   | 16 (24.6)           | 0.005   |
| **Peak cTn-I levels (μg/L)** | 15.7±39.1   | 11.5±19.5           | 0.411   |
| **LVEF (%)**           | 55.1±15.7        | 48.9±17.9           | 0.003   |
| **eGFR on admission (ml·min⁻¹·1.73m⁻²)** | 70.8±26.1     | 39.9±26.4           | <0.001  |
| **WRF during hospitalization [n (%)]** | 42 (7.7)     | 14 (21.5)           | 0.001   |
| **Killip class ≥3 [n (%)]** | 54 (9.8)     | 19 (29.7)           | <0.001  |
| **CAD 2- or 3-vessel/total coronary angiography number (%)** | 228/442 (51.6) | 13/22 (59.1) | 0.521   |
| **STEMI [n (%)]**      | 287 (52.3)       | 20 (31.3)           | 0.001   |

ACEI, angiotensin-converting enzyme inhibitors; AKI, acute kidney injury; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass graft; CAD, coronary artery disease; cTn-I, cardiac troponin-I; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; RIFLE, Risk, Injury, Failure, Loss, and End-stage kidney disease; STEMI, ST-elevation MI.
Statistical Analysis
Continuous variables are represented as mean±standard deviation, while categorical variables are expressed as frequencies and group percentages. The statistical normality was assessed using the Kolmogorov-Smirnov test. The $χ^2$ test was used to compare categorical variables. The ANOVA and the t-tests were used for variables with normal distributions, and the Mann-Whitney U test was used for other data.

The 2-year event-free survival curves were estimated by Kaplan-Meier method and compared by log-rank test. Incidence of death (deaths per 10,000 person-days) was calculated for each category. Univariate- and multivariate-adjusted hazard ratios (HR) were obtained by using the Cox regression analysis, with adjustment for multiple covariates that were potentially associated with patient survival. Multivariate binary logistic regression analysis was used to find out which patient group’s renal function would worsen during the first 7 days after hospitalization. A P value less than 0.05 was considered statistically significant, and analysis was performed with the statistical software package (SPSS 17.0; Chicago, IL, USA) for Windows.

Results
Comparison of Demographic and Clinical Characteristics of 2-Year Survivors and Non-Survivors (Table 1)
There were no significant differences between the patients in the survivor and non-survivor groups for smoking, hypercholesterolemia, 2- or 3-vessel coronary artery disease, peak cardiac troponin I levels, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker therapy, and coronary artery bypass graft therapy. More patients in the non-survivor group were elderly women with diabetes mellitus, hypertension, previous MI history, impaired left ventricular ejection fraction (LVEF <40%), NSTEMI and Killip class ≥3, as well as patients who had not received aspirin therapy, β-blocker therapy, or interventional therapy, and patients with eGFR <60 ml·min$^{-1}$·1.73 m$^{-2}$ on admission, WRF, and severe RIFLE classification during hospitalization. The reasons for patients not undergoing percutaneous coronary intervention (PCI) in the non-survivor group were NSTEMI with low TIMI risk score (28 patients), multiple comorbidities (12 patients) and disinclination to undergo coronary angiography (9 patients).

Comparison of Baseline Clinical and Biochemical Characteristics on Admission Based on the RIFLE Classification (Table 2)
We further analyzed the baseline clinical and biochemical characteristics based on the RIFLE classification. There were no significant differences between the 4 groups of patients for sex, diabetes mellitus, previous history of MI, mean blood pressure on admission, white blood count, high-density lipoprotein, triglyceride, PCI and coronary bypass therapy. AMI patients with severe AKI were older with hypertension, advanced Killip class, higher cardiac troponin I level, and impaired heart and kidney function on admission. In addition, the levels of inflammatory markers on admission, including high-sensitivity C-reactive protein (hs-CRP) and uric acid, were significantly higher in patients with AKI by the RIFLE classification.

Independent Predictors of 2-Year All-Cause Mortality
In the univariate analysis for survival, age >65 years, female sex, diabetes mellitus, hypertension, previous history of MI, cardiac troponin I ≥3-fold the upper limit of normal, Killip class ≥3, LVEF <40%, NSTEMI, hyperuricemia, eGFR <60 ml·min$^{-1}$·1.73 m$^{-2}$ on admission, WRF during the first week after hospitalization, RIFLE classification, and no administration of aspirin or β-blocker, or PCI were major predictors of survival (Table 3). Risk factors other than the RIFLE classification were adjusted in Cox regression model 1, and eGFR <60 ml·min$^{-1}$·1.73 m$^{-2}$ on admission [HR, 5.58; 95% confidence interval (CI), 1.93–16.2; P=0.003] and WRF during hospitalization (HR, 3.99; 95% CI, 1.46–10.9; P=0.021) were found to be independent predictors of 2-year mortality. All the risk factors were adjusted in Cox regression model 2, and LVEF

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### Table 2. Comparison of Baseline Clinical and Biochemical Characteristics on Admission Based on RIFLE Classification

| Characteristic                        | Non-AKI (n=534) | RIFLE-R (n=38) | RIFLE-I (n=23) | RIFLE-F (n=20) | P value |
|---------------------------------------|-----------------|---------------|----------------|---------------|---------|
| Age (years)                           | 62.1±19.7       | 72.6±10.8     | 72.7±9.9       | 71.4±13.2     | <0.001  |
| Women [n (%)]                         | 109 (20.4)      | 8 (22.2)      | 9 (39.1)       | 7 (35.0)      | 0.056   |
| Hypertension [n (%)]                  | 294 (55.0)      | 28 (77.8)     | 18 (78.3)      | 13 (65.0)     | 0.001   |
| Diabetes [n (%)]                      | 171 (32.0)      | 13 (36.1)     | 10 (43.4)      | 6 (30.0)      | 0.442   |
| Smoking [n (%)]                       | 287 (53.7)      | 18 (50.0)     | 5 (21.7)       | 8 (40.0)      | 0.021   |
| Previous history of MI [n (%)]        | 68 (12.7)       | 3 (8.3)       | 3 (13.0)       | 3 (15.0)      | 0.87    |
| Killip class >1 [n (%)]               | 116 (21.7)      | 16 (44.4)     | 10 (43.5)      | 15 (75.0)     | <0.001  |
| LVEF (%)                              | 55.3±15.9       | 52.6±16.1     | 45.5±14.4      | 45.5±17.0     | 0.001   |
| Peak cTn-I (ratio of the upper limit of normal) | 34.3±81.6 | 54.5±158.8 | 94.6±186.4 | 41.2±72.6 | 0.017 |
| Cholesterol (mg/dl)                   | 186.6±44.4      | 164.2±45.1    | 163.3±26.9     | 178.4±74.1    | 0.003   |
| HDL (mg/dl)                           | 40.1±10.0       | 37.1±11.1     | 37.3±7.7       | 37.1±12.4     | 0.132   |
| Triglyceride (mg/dl)                  | 161.3±113.6     | 133.9±64.6    | 120.4±44.4     | 167.0±134.5   | 0.173   |
| Mean blood pressure (mmHg)            | 100.4±21.6      | 92.2±29.0     | 98.2±21.1      | 92.1±20.0     | 0.07    |
| WBC (1,000/μl)                        | 10.6±4.9        | 10.6±3.8      | 11.4±4.8       | 12.9±6.5      | 0.18    |
| hs-CRP (mg/L)                         | 34.8±43.9       | 39.5±45.7     | 114.8±117.2    | 94.2±83.5     | <0.001  |
| Uric acid (mg/dl)                     | 6.3±1.9         | 8±2.9         | 8.1±2.7        | 7.0±1.9       | <0.001  |
| eGFR on admission (ml·min$^{-1}$·1.73 m$^{-2}$) | 72.6±25.3 | 37±15.8 | 39±17.9 | 18±16.2 | <0.001 |
| PCI therapy [n (%)]                   | 323 (60.5)      | 21 (58.3)     | 15 (65.2)      | 10 (50.0)     | 0.758   |
| CABG therapy [n (%)]                  | 26 (4.9)        | 3 (8.3)       | 3 (13.0)       | 0 (0.0)       | 0.553   |

HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cells. Other abbreviations as in Table 1.

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<40% (HR, 2.83; 95% CI, 1.11–7.20; P=0.029), eGFR <60 ml·min⁻¹·1.73 m⁻² on admission (HR, 4.01; 95% CI, 1.51–10.62; P=0.005), and RIFLE classification during hospitalization (Injury: HR, 8.11; 95% CI, 2.53–26.05; P=0.001; Failure: HR, 19.28; 95% CI, 2.24–166.26; P=0.007) were found to be independent predictors of 2-year mortality (Table 4).

### 2-Year Follow-up Prognosis
During 389,457 person-days of follow-up (mean, 635.3±204.9 days), 65 patients (10.6%) died. The 2-year incidence of death

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**Table 3.** Univariate Cox Regression Analysis for 2-Year Mortality Following Discharge From Hospital

| HR       | 95% CI          | P value |
|----------|-----------------|---------|
| Age ≥65 years | 4.89 | 2.65–8.95 | <0.001 |
| Female sex | 2.4  | 1.46–3.95 | 0.001 |
| Diabetes mellitus | 2.04 | 1.25–3.32 | 0.004 |
| Hypertension | 1.90 | 1.11–3.24 | 0.019 |
| Smoking | 0.64 | 0.39–1.05 | 0.077 |
| Hypercholesterolemia | 0.78 | 0.45–1.36 | 0.385 |
| Previous history of MI | 2.45 | 1.39–4.31 | 0.002 |
| cTn-I >3-fold the upper limit of normal | 2.89 | 1.77–4.71 | <0.001 |
| Hyperuricemia | 2.35 | 1.32–4.19 | 0.004 |
| hs-CRP >3 mg/L | 0.72 | 0.43–1.19 | 0.203 |
| eGFR <60 ml·min⁻¹·1.73 m⁻² on admission | 9.24 | 4.83–17.67 | <0.001 |
| WRF during hospitalization | 2.87 | 2.59–5.19 | <0.001 |
| CAD 2- or 3-vessel disease | 1.34 | 0.57–3.13 | 0.503 |
| Killip class ≥3 | 3.69 | 2.16–6.30 | <0.001 |
| LVEF <40% | 2.77 | 1.68–4.57 | <0.001 |
| NSTEMI (compare with STEMI) | 2.36 | 1.39–4.00 | 0.001 |
| RIFLE during hospitalization | 1.00 | – | – |
| Risk | 2.66 | 1.19–5.93 | 0.017 |
| Injury | 3.72 | 1.58–8.77 | 0.003 |
| Failure | 11.39 | 5.96–21.78 | <0.001 |
| No aspirin therapy | 4.10 | 2.42–6.94 | <0.001 |
| No β-blocker therapy | 2.72 | 1.65–4.48 | <0.001 |
| No ACEI/ARB therapy | 1.42 | 0.86–2.32 | 0.171 |
| No PCI therapy | 5.27 | 2.99–9.26 | <0.001 |
| No CABG therapy | 0.8 | 0.29–2.21 | 0.672 |

CI, confidence interval; HR, hazard ratio; NSTEMI, non-STEMI; WRF, worsening renal function. Other abbreviations as in Table 1.

**Table 4.** Multivariate Cox Regression Analysis Models for 2-Year Mortality Following Discharge From Hospital

| HR       | 95% CI          | P value |
|----------|-----------------|---------|
| Model 1  | eGFR <60 ml·min⁻¹·1.73 m⁻² | 5.58 | 2.25–13.85 | <0.001 |
|          | WRF | 3.99 | 1.46–10.92 | 0.007 |
| Model 2  | eGFR <60 ml·min⁻¹·1.73 m⁻² | 4.01 | 1.51–10.62 | 0.005 |
|          | LVEF <40% | 2.83 | 1.11–7.20 | 0.029 |
|          | RIFLE classification | 0.001 |
|          | No AKI | 1.00 | – | – |
|          | Risk | 1.48 | 0.32–6.90 | 0.620 |
|          | Injury | 8.11 | 2.53–26.05 | 0.001 |
|          | Failure | 19.28 | 2.24–166.26 | 0.007 |

Model 1: adjusted covariates were age ≥65 years, sex, diabetes mellitus, hypertension, smoking, hypercholesterolemia, previous MI history, cardiac troponin I >3-fold the upper limit of normal, STEMI or NSTEMI, hs-CRP >3 mg/L, hyperuricemia, eGFR <60 ml·min⁻¹·1.73 m⁻² on admission, WRF during hospitalization, multiple CAD, Killip grade, LVEF <40%, aspirin, β-blocker, ACEI/ARB, PCI, and CABG therapy in the multivariate Cox regression model.

Model 2: adjusted for all the covariates in model 1 + RIFLE classification during hospitalization in the Cox regression analysis.

Abbreviations as in Tables 1, 3.
per 10,000 person-days of follow-up was 1.16 in non-AKI patients, 3.13 in RIFLE-R patients, 4.41 in RIFLE-I patients, and 14.44 in RIFLE-F patients (Table 5). The Kaplan-Meier survival plot and log-rank test showed that all-cause mortality during the 2-year follow-up period was proportional to the severity of AKI that was determined using the RIFLE classification during hospitalization (Figure).

### Multivariate Analysis of Predictors of AKI During First 7 Days After Hospitalization

The baseline clinical and biochemical characteristics including age, sex, hypertension, diabetes mellitus, smoking, impaired LVEF, Killip class, cardiac troponin I >3-fold of the upper limit of normal, mean blood pressure, serum lipid profile levels, white blood count, hs-CRP, uric acid level and receiving reperfusion therapies, which were possible predictors for developing AKI by RIFLE classification, were adjusted in the multivariate logistic regression analysis. The eGFR on admission per 1 ml·min⁻¹·1.73 m⁻² decrease (odds ratio (OR), 1.07; 95% CI, 1.04–1.09; P<0.001) and hs-CRP per 1 mg/L increase (OR, 1.01; 95% CI, 1.01–1.02; P=0.045) were independent predictors of AKI by the RIFLE classification (Table 6).

### Discussion

The main finding of this study is that AKI by the RIFLE classification, as used in other critical diseases, is an independent predictor of 2-year mortality in AMI patients. The overall 2-year all-cause mortality rate in this investigation was 10.6%, which is in agreement with the findings of previous reports. Many clinical risk factors and treatments, which showed significant differences in the survivor and non-survivor groups in this study, have been reported to affect the outcomes of AMI.
patients. In addition, these clinical variables also have been proved to be AKI predictors in cardiovascular patients. In the present study, by adjusting the baseline risk factors, inflammatory markers, severity of AMI and treatment in the multivariate analysis, initial eGFR and hs-CRP level on admission were independent predictors for AKI occurrence during the first week of an AMI patient’s hospitalization. This finding agrees with previous studies and prompts clinicians to pay more attention to those patients with initial renal dysfunction and greater inflammatory status in order to avoid further kidney injury. Adjusting these risk factors, treatment and the 3 types of assessment of renal function (ie, initial renal dysfunction on admission, WRF and RIFLE classification) in the multivariate Cox regression model, only initial renal dysfunction, RIFLE classification, and impaired LVEF were found to be independent predictors for 2-year mortality.

AKI is defined as a sudden deterioration of kidney function, which presents as an increase in serum creatinine levels or a decrease in urine output. In high-risk patients, such as those hospitalized for AMI, congestive heart failure, sepsis, and those who have undergone cardiac surgery, the incidence of AKI is high, ranging from 10% to 25%. Many clinical trials have shown that decreased renal function is an independent predictor of adverse outcomes in AMI patients. However, the limitation of those clinical trials is that only the initial renal function levels were used. AMI and its complications, such as hypotension or shock-related kidney hypoperfusion, may be partly responsible for impaired initial renal function on admission. However, patients with chronic renal disease before admission can also present with decreased initial renal function. Therefore, unless the baseline renal function data are considered, initial renal function levels cannot represent the effect of AKI.

AKI can occur not only during the initial period but also during the course of hospitalization (ie, WRF). WRF during hospitalization can predict clinical outcomes in acute heart failure patients. However, few studies have evaluated the effect of WRF in the AMI population. Our study results agree that WRF is an independent predictor for 2-year mortality after adjusting for multiple risk factors except the RIFLE classification (model 1). However, when the RIFLE classification was included in the multivariate Cox analysis (model 2), initial renal dysfunction, RIFLE classification, and impaired LVEF were found to be independent predictors.

WRF was determined by comparing the worst renal function outcomes during hospitalization with the initial renal function levels. However, the RIFLE classification compares the worst outcomes of renal function during hospitalization with the baseline renal function levels. As we have previously mentioned, the initial renal function on admission may be affected by the disease course of AMI, thereby leading to underestimation of the severity of WRF. This may explain why RIFLE during hospitalization was more significant than WRF in predicting the 2-year mortality in AMI patients after adjusting all the risk factors. Moreover, with an increase in the RIFLE severity grade, the HR and incidence of deaths per 10,000 person-days also increased.

The mechanism of AKI by RIFLE classification resulting in worsening prognosis is very complex. It has been shown that a large percentage of AKI patients will not have an improvement in their renal function and, moreover, they will suffer from chronic kidney disease or require permanent renal replacement therapy. The incidence of progressive to chronic kidney disease was proportional to AKI severity by RIFLE classification. In addition, AKI will directly contribute to
tant organ dysfunction through the mechanism of oxidative stress, immunity and inflammation. This means AKI severity by RIFLE classification represents not only kidney damage but also imbalance between the kidney and other organ systems. Therefore, AKI by RIFLE classification, rather than initial renal function and impaired LVEF, has a greater effect on mortality.

The hospital discharge risk score is a useful tool for assessing the long-term outcomes of AMI patients at the time of discharge. The initial renal dysfunction is used in this risk score system. Our findings indicated that AKI by RIFLE classification, in addition to initial renal dysfunction, may be considered as involved in the establishment of a new hospital discharge risk score to predict long-term outcomes in AMI patients who survive to discharge.

Study Limitations
The observational study has some limitations. First, using recorded serum creatinine levels rather than other methods as the baseline reference in the RIFLE classification can improve the accuracy of AKI. However, previous records of the serum creatinine levels of only 310 patients were available in our database. Second, the volume of contrast used in diagnostic angiography and PCI therapy was not available in all cases, so the effect of contrast volume on renal impairment was not included in the analysis.

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Disclosures
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