Impact of Acute Kidney Injury on In-Hospital Outcomes of Patients With Acute Myocardial Infarction

— Results From the Japanese Registry of Acute Myocardial Infarction Diagnosed by Universal Definition (J-MINUET) Substudy —

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Background: Acute kidney injury (AKI) is associated with poor outcome after acute myocardial infarction (AMI), but whether hemodynamic status at presentation influences this prognostic significance is unknown.

Methods and Results: A total of 2,798 AMI patients admitted within 48 h after symptom onset and who underwent urgent coronary angiography were enrolled in the present study. AKI was defined as an increase in serum creatinine ≥ 0.3 mg/dL or $\geq 50\%$ within 48 h during hospitalization. Patients were classified into 3 groups according to Killip class on admission: Killip 1, $n=2,164$; Killip 2–3, $n=366$; and Killip 4, $n=268$. AKI occurred more frequently with increasing Killip class (Killip 1, 2–3, and 4: 6.3%, 15.3%, and 31.3%, respectively; $P<0.001$). AKI was associated with increased in-hospital mortality, regardless of Killip class (non-AKI and AKI patients: 1.1% vs. 6.6% in Killip 1; 5.2% vs. 35.7% in Killip 2–3, and 28.8% vs. 45.2% in Killip 4, $P<0.01$ for all). On multivariate analysis, the adjusted OR of AKI for in-hospital mortality in Killip 1, Killip 2–3, and Killip 4 were 3.79 (95% CI: 1.54–9.33, $P=0.004$), 5.35 (95% CI: 2.67–10.7, $P<0.001$), and 1.48 (95% CI: 0.94–2.35, $P=0.093$), respectively.

Conclusions: In AMI patients undergoing urgent coronary angiography, AKI was significantly associated with increased in-hospital mortality in Killip 1 as well as Killip 2–3 at presentation, but not in Killip 4.

Key Words: Myocardial infarction; Prognosis; Renal function

During the past decades, mortality after acute myocardial infarction (AMI) has dramatically decreased owing to the development and widespread use of primary percutaneous coronary intervention (PCI), including stent implantation.^{1,2} Further decreases in mortality, however, have not been achieved.³ The identi-

fication of high-risk patients likely to benefit from more aggressive strategies is needed.

A growing number of studies have shown that acute kidney injury (AKI) is strongly related to increased morbidity and mortality after AMI.^{4–8} Although possible mechanisms for worsening of renal function during hospi-

Received October 28, 2016; revised manuscript received December 7, 2016; accepted December 31, 2016; released online February 9, 2017 Time for primary review: 23 days

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Table 1. Baseline Characteristics

	Non-AKI (n=2,522)	AKI (n=276)	P value
Age (years)	68 (59–77)	72 (64–81)	<0.001
Male	1,922 (76.2)	215 (77.9)	0.531
Hypertension	1,639 (65.4)	197 (71.6)	0.039
Diabetes	687 (27.6)	114 (42.5)	<0.001
Previous MI	272 (10.8)	36 (13.1)	0.250
STEMI	1,808 (71.7)	200 (72.5)	0.786
SBP (mmHg)	138 (118–160)	134 (107–158)	0.005
HR (beats/min)	76 (64–89)	86 (70–104)	<0.001
Killip class			<0.001
Class 1	2,028 (80.4)	136 (49.3)	
Class 2–3	310 (12.3)	56 (20.3)	
Class 4	184 (7.3)	84 (30.4)	
Anemia	608 (24.1)	138 (50.0)	<0.001
SCr (mg/dL)	0.82 (0.68–1.02)	1.40 (1.01–2.22)	<0.001
CKD	895 (35.5)	222 (80.4)	<0.001
Multivessel disease	1,043 (41.5)	171 (62.0)	<0.001
Primary PCI	2,323 (92.1)	242 (87.7)	0.011
IABP	382 (15.2)	120 (44.1)	<0.001
Max CK (IU/L)	1,487 (552–3,162)	2,384 (1,011–5,176)	<0.001

Data given as median (IQR) or n (%). AKI, acute kidney injury; CK, creatinine kinase; CKD, chronic kidney disease; HR, heart rate; IABP, intra-aortic balloon pumping; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SCr, serum creatine; STEMI, ST-segment elevation myocardial infarction.

Figure 1. Incidence of acute kidney injury (AKI) according to Killip class on admission.

talization for AMI are multifactorial and complex,^{9,10} hemodynamic instability such as cardiogenic shock has been shown to be strongly related to the occurrence of AKI.^{6,11} AKI might reflect renal impairment secondary to hypoperfusion associated with hemodynamic instability. The poor outcomes of AKI patients may be explained at least in part by the confounding effects of hemodynamic instability. Whether AKI can be used as a prognostic factor to identify high-risk AMI patients who present with cardiogenic shock is unknown. On the other hand, in the current interventional era, mortality in AMI patients who present with Killip class 1 without hemodynamic instability is very low, as compared with those who present with Killip class 2 or higher.^{12–14} Whether AKI negatively affects

clinical outcome even in AMI patients with Killip class 1 has yet to be investigated. The aim of this study was therefore to elucidate the relationship between AKI and hemodynamic status, as estimated by Killip class at presentation, in a recent large prospective multicenter study of AMI patients, and to assess the effects of this relationship on in-hospital outcome.

Methods

The present patients were selected from the Japanese registry of acute Myocardial Infarction diagnosed by Universal dEfiniTion (J-MINUET), a prospective observational multicenter study. A total of 3,283 consecutive patients admitted within 48 h after onset of AMI to 28 Japanese medical institutions were enrolled between July 2012 and March 2014. The design, inclusion criteria, and results of the J-MINUET study have been previously reported.¹⁵ Briefly, AMI was diagnosed using the new universal definition, in which cardiac troponin is the preferred biomarker of myocardial injury.¹⁶ ST-segment elevation AMI was diagnosed in the presence of new ST elevation at the J point in at least 2 contiguous leads ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2–3, or ≥ 0.1 mV in another 2 contiguous leads.^{17,18} This study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committee of each participating institution.

In the J-MINUET study, urgent coronary angiography was performed in 3,053 patients within 48 h after hospital admission. Among these patients, 255 were excluded from the study for one or more of the following reasons: hemodialysis (n=199), missing data related to Killip class on admission (n=18), or missing or unavailable serum creatinine (SCr; n=48) during hospitalization. Therefore, the

Table 2. In-Hospital Outcomes

	Non-AKI (n=2,522)	AKI (n=276)	P value
Mortality	91 (3.6)	67 (24.3)	<0.001
MACE	355 (14.1)	137 (49.6)	<0.001
Cardiac failure	273 (11.0)	118 (43.5)	<0.001
VT/VF	77 (3.1)	29 (10.7)	<0.001
Bleeding	45 (1.8)	23 (8.5)	<0.001

Data given as n (%). AKI, acute kidney injury; MACE, major adverse cardiac events; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 3. Independent Predictors of In-Hospital Mortality

	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (per 1 year)	1.04 (1.03–1.06)	<0.001	1.04 (1.02–1.05)	<0.001
Male	1.39 (0.98–1.96)	0.065		
Hypertension	0.78 (0.55–1.10)	0.149		
Diabetes	1.20 (0.84–1.72)	0.307		
Previous MI	1.17 (0.70–1.97)	0.552		
STEMI	1.90 (1.27–2.85)	0.002		
SBP (per 1 mmHg)	0.97 (0.96–0.98)	<0.001		
HR (per 1 beat/min)	1.02 (1.01–1.03)	<0.001		
Killip class				
Class 1	Ref.		Ref.	
Class 2–3	7.89 (4.75–13.1)	<0.001	5.00 (2.97–8.42)	<0.001
Class 4	46.4 (29.8–72.3)	<0.001	19.0 (11.5–31.4)	<0.001
Anemia	1.77 (1.27–2.47)	0.001		
CKD	7.75 (5.03–11.9)	<0.001		
Multivessel disease	2.10 (1.50–2.94)	<0.001		
Primary PCI	2.30 (1.01–5.21)	0.046		
IABP	5.53 (3.98–7.68)	<0.001	1.40 (0.98–2.00)	0.065
Log Max CK	2.46 (2.05–2.95)	<0.001	1.55 (1.29–1.86)	<0.001
AKI	7.76 (5.58–10.8)	<0.001	2.36 (1.66–3.37)	<0.001

Abbreviations as in Table 1.

final study group consisted of 2,798 patients.

Estimated glomerular filtration rate (eGFR) was calculated from creatinine concentration using the modified glomerular filtration rate estimating equation for Japanese patients with chronic kidney disease (CKD): $eGFR (mL/min/1.73 m^2) = 194 \times SCr^{-1.094} \times age^{-0.287} (\times 0.739 \text{ if female})$.¹⁹ CKD was defined as eGFR on admission $<60 mL/min/1.73 m^2$.²⁰ AKI was defined as an increase in SCr by $\geq 0.3 mg/dL$ or $\geq 50\%$ within 48 h during hospitalization.²¹ Anemia was defined using the World Health Organization diagnostic criteria (hemoglobin $<13.0 g/dL$ in men, $<12.0 g/dL$ in women).²²

Clinical events were collected at the time of discharge. The primary endpoint was in-hospital mortality. The secondary endpoint was major adverse cardiac events (MACE), defined as a composite of all-cause death, cardiac failure, ventricular tachycardia or ventricular fibrillation (or both), and bleeding during hospitalization. Cardiac failure was defined as congestive heart failure or cardiogenic shock (or both) that required treatment.

Statistical Analysis

Continuous variables are presented as median (IQR). Differences between continuous variables were analyzed

using Mann-Whitney U-test. Categorical data are expressed as percentages and were compared using the chi-squared test or Fisher's exact test. Differences were considered statistically significant at $P < 0.05$. Univariate and multivariate analyses were performed to identify predictors of in-hospital mortality and MACE. Stepwise selection for multivariable logistic regression with $P \leq 0.1$ for backward elimination was used to select the best predictive model. Odds ratios (OR) and 95% CI were calculated. Missing values were imputed with the use of a multivariate normal model and the chained equations approach.²³ The multiple imputation method has been described previously.²⁴ Statistical analysis was performed with SPSS version 19.0 (SPSS, Chicago, IL, USA) and STATA, version 12 (StataCorp LP, College Station, TX, USA).

Results

Patient Characteristics

AKI occurred in 276 patients (9.9%). Clinical patient characteristics according to presence of AKI are listed in Table 1. Patients with AKI were older, more likely to have a previous history of hypertension and diabetes mellitus, presented with a lower systolic blood pressure and a more

	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (per 1 year)	1.02 (1.01–1.02)	<0.001		
Male	0.97 (0.78–1.19)	0.740		
Hypertension	1.03 (0.85–1.26)	0.761		
Diabetes	1.21 (0.99–1.47)	0.060		
Previous MI	1.35 (1.03–1.78)	0.030		
STEMI	1.87 (1.50–2.34)	<0.001	1.10 (0.87–1.40)	0.427
SBP (per 1 mmHg)	0.98 (0.98–0.98)	<0.001		
HR (per 1 beat/min)	1.02 (1.01–1.02)	<0.001		
Killip class				
Class 1	Ref.		Ref.	
Class 2–3	4.44 (3.50–5.62)	<0.001	2.96 (2.31–3.81)	<0.001
Class 4	16.6 (13.4–20.5)	<0.001	6.99 (5.37–9.11)	<0.001
Anemia	1.52 (1.26–1.83)	<0.001		
CKD	3.56 (2.93–4.32)	<0.001	1.76 (1.41–2.19)	<0.001
Multivessel disease	1.92 (1.59–2.31)	<0.001		
Primary PCI	1.00 (0.73–1.37)	0.992		
IABP	4.63 (3.86–5.56)	<0.001	1.68 (1.37–2.05)	<0.001
Log Max CK	1.80 (1.65–1.98)	<0.001	1.27 (1.16–1.40)	<0.001
AKI	4.02 (3.28–4.92)	<0.001	1.43 (1.15–1.78)	0.001

Abbreviations as in Tables 1,2.

Figure 2. (A) In-hospital mortality and (B) major adverse cardiac events (MACE) according to the presence or absence of acute kidney injury (AKI) stratified by Killip class on admission.

rapid heart rate, and more frequently had anemia and CKD than those without AKI. **Figure 1** shows the incidence of AKI development according to the Killip class on admission. The proportion of patients with AKI increased in parallel to an increase in Killip class. Patients with AKI more frequently had multivessel disease, less frequently underwent primary PCI, and more frequently underwent intra-aortic balloon pumping. Infarct size as estimated using maximum creatine kinase was larger in patients with AKI. **Table 2** lists in-hospital outcome according to presence of AKI. The rates of both in-hospital mortality and MACE were higher in the AKI patients.

Predictors of In-Hospital Outcome

Tables 3,4 list the univariate and multivariate predictors of

in-hospital mortality and MACE. Killip class 2 or higher and AKI were significant independent predictors of both in-hospital mortality and MACE (P-values of the interaction between Killip class and AKI: P<0.001 and P<0.001, respectively).

AKI and In-hospital Outcome Stratified by Killip Class on Admission

Figure 2A shows the in-hospital mortality in the presence or absence of AKI stratified by Killip class on admission. In patients with Killip class 1 and Killip class 2–3, in-hospital mortality in the presence of AKI was 6-fold and 7-fold higher than in the absence of AKI, respectively, while there was a smaller relative increase in in-hospital mortality in AKI patients for Killip class 4. **Figure 2B** shows

the rates of MACE in the presence or absence of AKI stratified by Killip class on admission. In patients with Killip class 1 or Killip class 2–3, the rates of MACE were significantly higher in the AKI patients than in those without AKI. In patients with Killip class 4, however, the rate of MACE in the AKI patients tended to be higher than in patients without AKI, but the difference did not reach statistical significance. **Table 5** lists the multivariate adjusted OR of AKI for in-hospital mortality and MACE according to Killip class on admission. AKI was a significant predictor of both in-hospital mortality and MACE in Killip class 1 as well as in Killip class 2–3, but not in Killip class 4.

Discussion

In this substudy of the J-MINUET study, evaluating 2,798 AMI patients who underwent urgent coronary angiography, the prevalence of AKI was 9.9%, similar to that in previous studies of AMI patients.^{6,25} The present analysis supports the association of AKI with poor short-term cardiovascular outcome, including mortality, as reported previously.^{6–8,25} In the present study, the prevalence of AKI increased in a stepwise fashion with increasing Killip class on admission, and there was a close link between the development of AKI and poor in-hospital outcome regardless of Killip class. Of note, on multivariate analysis AKI maintained its negative prognostic impact on in-hospital clinical outcomes in patients who presented with Killip class 1, as well as Killip class 2–3, but not in those with Killip class 4. To the best of our knowledge, this is the first report to show the differential impact of AKI on in-hospital clinical outcome after AMI by Killip class at presentation in the current troponin era. The present findings highlight the importance of the interaction between AKI and Killip class on admission in early risk stratification of AMI patients.

In the current era of primary PCI for AMI, AMI patients who are in Killip class 1 at presentation are generally recognized to have excellent outcomes.¹² In the present study, primary PCI was performed in 2,565 patients (91.7%), and the in-hospital mortality in Killip class 1 was very low (1.4%). AKI had a significant adverse impact on in-hospital outcome, including mortality, even in low-risk patients with Killip class 1. This suggests that confounding by hemodynamic instability, which has been shown to be strongly related to the development of AKI after AMI,^{6,11,26} does not completely explain the poor outcomes of AMI patients in whom AKI develops. The interpretation of higher rates of in-hospital mortality and MACE after the development of AKI, however, is challenging because of pre-existing clinical variables related to both AKI development and adverse outcomes. Consistent with previous studies,^{4–6,8} patients with AKI were older and had higher rates of hypertension, diabetes mellitus, anemia, CKD, and more severe coronary artery disease, as indicated by the higher prevalence of multivessel disease. These high-risk profiles more likely explain the poor outcomes in patients with AKI. The contribution of AKI to poor outcome, however, continued to be significant even after adjustment for baseline characteristics. In addition to contrast-induced nephropathy,^{4,5} links between renal dysfunction and oxidative stress, inflammation, altered cytokine levels, platelet activation, and hypercoagulable or thromboresistant state have been confirmed, and these

Table 5. Multivariate Adjusted OR of AKI for In-Hospital Outcome According to Killip Class on Admission

	OR (95% CI)	P value
Mortality		
Killip class 1	3.79 (1.54–9.33)	0.004
Killip class 2–3	5.35 (2.67–10.7)	<0.001
Killip class 4	1.48 (0.94–2.35)	0.093
MACE		
Killip class 1	1.93 (1.25–3.00)	0.003
Killip class 2–3	1.64 (1.08–2.49)	0.021
Killip class 4	1.10 (0.80–1.50)	0.569

Abbreviations as in Table 2.

factors are more likely to increase the risk of adverse events after AMI.^{9,10,27} Regardless of causality, the present findings highlight the importance of AKI as a predictor of adverse outcomes in patients with Killip class 1 on presentation, as well as those with Killip class 2–3. Thus, close monitoring of SCr during hospitalization is important for identifying high-risk patients, and the targeting of patients with AKI for more careful and aggressive treatment may potentially improve short-term survival after AMI in patients with Killip class 1–3 on presentation.

Another important finding was that AKI was not a significant independent predictor of in-hospital adverse outcome, including mortality, in patients with Killip class 4 at presentation. Mortality in AMI patients with cardiogenic shock remains very high, even in the current interventional era for AMI.²⁸ In the present study, in-hospital mortality in the Killip class 4 group reached 34.0%, and AKI commonly developed in this subgroup of patients (prevalence, 31.3%) and was closely linked to adverse outcomes; nonetheless, the significant adverse effects of AKI on in-hospital outcome were not evident after multivariate adjustment. Although the reason why AKI did not predict adverse outcome in the Killip class 4 group remains unclear, several factors may account for the results. First, baseline SCr may already reflect impairment associated with acute hemodynamic instability in this particular clinical setting, and we may have thus potentially underestimated the true incidence of AKI development. Second, because the number of patients who presented with Killip 4 was relatively small, the subgroup analysis might have been underpowered; J-MINUET, however, was a prospective multicenter study in which a relatively large number of consecutive patients were enrolled. Therefore, the present findings can be generalized to AMI patients in a real-world clinical setting. Further prospective studies in a larger number of patients, however, are needed to verify the present results.

The present study had several important limitations. First, multivariate analysis was performed, but there were many differences in baseline clinical characteristics between the patients with and without AKI. We therefore cannot rule out the possibility of unassessed confounding factors. Second, AKI was defined solely on the basis of an increase in SCr within 48 h during hospitalization. Because SCr often changes during the acute phase in AMI patients,⁷ we might not have estimated the true incidence of AKI development. The present definition of AKI is widely used and was strongly associated with clinical outcome in the present study, as well as in previous studies,^{6,21,25} but it might be, at least in part, arbitrary. Third, we did not have

data on the course of AKI (whether AKI resolved or persisted) and the need for hemodialysis or renal replacement therapy during or after the index hospitalization, which have significant prognostic implications.⁸ Fourth, the sample size for stratified analysis in Killip class 4 might have been too small to show an association between AKI and in-hospital mortality, although there was a marginally significant association on multivariate analysis. Finally, the volume of contrast agent used during coronary angiography and PCI was not available in this study. Higher contrast volume has been reported to be associated with higher rates of contrast-induced AKI and in-hospital death in AMI patients undergoing primary PCI.²⁹ Minimizing contrast volume may help to prevent AKI and improve clinical outcome in AMI patients. Because of the limited ability to study this issue, further studies are required to determine the risk factors for AKI, and whether the prevention of AKI can help to improve clinical outcome after AMI.

Conclusions

In AMI patients, the development of AKI during hospitalization had a significant adverse impact on in-hospital clinical outcome in patients in Killip class 1, as well in Killip class 2–3 on admission, but not in Killip class 4.

Acknowledgments

This study was supported by the Intramural Research Fund, grant number 23-4-5, for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center. The authors thank all the enrolled patients, participating cardiologists, medical and other staff who have contributed to this study. The J-MINUET investigators are listed in Appendix.

Disclosures / Conflict of Interests

None.

Grants

This study was supported by the Intramural Research Fund, grant number 23-4-5, for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center.

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