Circulation Reports
Circ Rep 2021; 3: 249–255
doi:10.1253/circrep.CR-21-0017

ORIGINAL ARTICLE
Ischemic Heart Disease

Out-of-Hospital Cardiac Arrest Does Not Affect Post-Discharge Survival in Patients With Acute Myocardial Infarction

Takeyuki Kubota, MD; Kimiaki Komukai, MD; Satoru Miyanaga, MD; Keisuke Shirasaki, MD; Yoshitsugu Oki, MD; Ritsu Yoshida, MD; Keisuke Fukushima, MD; Takahito Kamba, MD; Toraaki Okuyama, MD; Tomoki Maehara, MD; Michihiro Yoshimura, MD

Background: Acute myocardial infarction (AMI) patients complicated by out-of-hospital cardiac arrest (OHCA) show poor in-hospital outcomes. However, the post-discharge outcomes of survivors of OHCA have not been well studied.

Methods and Results: Data for patients admitted to The Jikei University Kashiwa Hospital with AMI between April 2012 and March 2020 were examined retrospectively. The Jikei University Kashiwa Hospital is a tertiary emergency medical facility, so the frequency of OHCA in this hospital is higher than in an ordinary AMI population. Of 803 patients, 92 (11.5%) were complicated by OHCA. Of the 92 OHCA patients, 37 died in hospital, compared with 45 of 711 non-OHCA patients who died in hospital (P<0.001). OHCA was more frequent in men than in women. The estimated glomerular filtration rate was lower in those with than without OHCA. Long-term mortality was evaluated in patients discharged alive and followed-up at an outpatient clinic (n=635; median follow-up period 607 days). The long-term post-discharge mortality was comparable between AMI patients with and without OHCA.

Conclusions: The post-discharge mortality of AMI patients with OHCA was comparable that of patients without OHCA.

Key Words: Acute coronary syndrome; Mortality; Resuscitation

In recent decades there has been a marked decrease in the in-hospital mortality for acute myocardial infarction (AMI).[1] This is due to: (1) early reperfusion therapy, such as primary percutaneous coronary intervention (PCI); (2) intensive care in the coronary care unit; and (3) improvements in medical therapy. However, the in-hospital mortality of AMI complicated by out-of-hospital cardiac arrest (OHCA) remains high.[1]

Cardiac arrest sometimes occurs after typical chest pain or other chest symptoms and can be the first manifestation of AMI.[2] In cases where it is the first manifestation of AMI, cardiac arrest occurs outside the hospital. Approximately 60% of deaths among AMI patients occur outside the hospital.[3]

Many studies have examined the in-hospital outcomes of AMI patients with OHCA. However, relatively little is known about the post-discharge survival of such patients.

The purpose of the present study was to compare the in-hospital and post-discharge mortality of AMI patients with and without OHCA.

Methods

The study protocol complies with the Declaration of Helsinki and was approved by the Ethics Committee of The Jikei University School of Medicine (32-113[10189]) and the Clinical Research Committee of The Jikei University Kashiwa Hospital. The opportunity to opt-out of the study was announced on the website because written informed consent was not obtained from individual patients.

Patients with AMI who had been admitted to The Jikei University Kashiwa Hospital between April 2012 and March 2020 were included. Furthermore, data were reviewed for those AMI patients who were discharged alive and then followed-up at the outpatient clinic.

Emergency medical services (EMS) take OHCA patients

Received February 15, 2021; accepted February 15, 2021; J-STAGE Advance Publication released online March 20, 2021 Time for primary review: 1 day

Division of Cardiology, The Jikei University Kashiwa Hospital, Kashiwa (T. Kubota, K.K., S.M., K.S., Y.O., R.Y., K.F., T. Kamba, T.O., T.M.); Division of Cardiology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo (M.Y.), Japan

M.Y. is a member of *Circulation Reports*' Editorial Team.

Mailing address: Kimiaki Komukai, MD, Division of Cardiology, The Jikei University Kashiwa Hospital, 163-1 Kashiwa-shita, Kashiwa 277-8567, Japan. E-mail: komu@jikei.ac.jp

ISSN-2434-0790

Table 1. Characteristics of AMI Patients With and Without OHCA

	With OHCA	Without OHCA	P value
No. patients	92	711	
Age (years)	67.0±13.2	69.0±12.5	NS
Male sex	87 (94.6)	546 (76.8)	<0.001
BMI (kg/m^2)	23.6±5.1 [79]	24.0±4.0 [684]	NS
Cardiogenic shock	53 (60.2) [88]	89 (12.6) [709]	<0.001
STEMI	47 (56.0) [84]	493 (72.9) [676]	0.002
Emergency CAG	89 (96.7)	694 (97.6)	NS
Culprit LAD	47 (59.5) [79]	307 (45.6) [673]	0.023
Vessel disease (no. vessels)	1.9±0.8 [89]	1.7±0.8 [703]	NS
Maximum CK (IU/L)	4,610±5,240	2,400±2,440	<0.001
Diabetes	31 (37.8) [82]	307 (43.5) [705]	NS
Hypertension	42 (56.0) [75]	476 (67.6) [704]	NS
Dyslipidemia	46 (52.9) [87]	407 (57.6) [706]	NS
eGFR (mL/min/1.73 m^2)	47.9±19.6	61.0±24.1	<0.001
In-hospital death	37 (40.2)	45 (6.3)	<0.001

Unless indicated otherwise, data are given as the mean±SD or as n (%). Numbers in [ ] show the sample number when some cases were missed. AMI, acute myocardial infarction; BMI, body mass index; CAG, coronary angiography; CK, creatine kinase; eGFR, estimated glomerular filtration rate; LAD, left descending coronary artery; OHCA, out-of-hospital cardiac arrest; STEMI, ST-elevation myocardial infarction.

Table 2. Characteristics of AMI Patients With and Without OHCA Enrolled in the Follow-up Study

	With OHCA	Without OHCA	P value
No. patients	39	596	
Age (years)	65.0±12.3	67.6±12.0	NS
Male sex	37 (94.9)	465 (78.0)	0.013
BMI (kg/m^2)	24.3±3.7	24.2±3.9 [592]	NS
Cardiogenic shock	10 (26.3) [38]	48 (8.1) [594]	0.001
STEMI	20 (55.6) [36]	421 (73.2) [575]	0.033
Emergency CAG	39 (100)	588 (98.7)	NS
Culprit LAD	22 (59.5) [37]	267 (46.5) [574]	NS
Vessel disease (no. vessels)	1.7±0.8	1.7±0.8 [594]	NS
Maximum CK (IU/L)	3,730±3,820	2,300±2,180	0.027
Diabetes	15 (38.5)	260 (43.8) [593]	NS
Hypertension	27 (69.2)	403 (67.8) [594]	NS
Dyslipidemia	23 (59.0)	357 (60.0) [595]	NS
eGFR (mL/min/1.73 m^2)	58.6±14.9	63.1±22.9	NS

Unless indicated otherwise, data are given as the mean±SD or as n (%). Numbers in [ ] show the sample number when some cases were missed. Abbreviations as in Table 1.

to The Jikei University Kashiwa Hospital following a tertiary hot-line call to the emergency department (ED). When the ED doctors judge that the OHCA is likely of cardiac origin, they immediately call a cardiologist. The ED doctors sometimes call cardiologists before a patient's arrival depending on the details of the call received from the EMS. If there is no obvious extracardiac cause of the OHCA, regardless of electrocardiogram (ECG) findings, coronary angiography (CAG) is generally performed at The Jikei University Kashiwa Hospital.

The diagnosis of AMI was determined based on international guidelines;[4] however, creatine kinase (CK) was used as a biomarker of cardiac injury (2-fold higher than the normal upper limit).[5] The diagnosis was further confirmed taking the following into consideration: a rapid increase or decrease in cardiac injury markers and symptoms, as well as ECG , CAG, physical examination, ultrasound echocardiography, chest X-ray, and computed tomography findings, laboratory tests, and follow-up examinations in an outpatient clinic.[6] AMI was also categorized as ST-elevation myocardial infarction (STEMI) or non-ST segment elevation myocardial infarction (NSTEMI).

Patients were divided into 2 groups, namely those with and without OHCA. The age, sex, and other laboratory findings of the 2 groups were compared. Patients discharged alive and followed-up at the outpatient clinic were reviewed for a long-term follow-up study. In all, 635 patients met the selection criteria and were enrolled in the study. The duration of follow-up (post-discharge) ranged from 6 to 3,036 days (median 607 days). The primary endpoint was all-cause mortality.

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or a relevant history. Dyslipidemia was defined as serum total

Table 3. Prescriptions at Discharge for Patients With and Without OHCA Enrolled in the Follow-up Study

	With OHCA	Without OHCA	P value
No. patients	39	596	
ACEIs/ARBs	31 (79.5)	436 (73.2)	NS
β-blockers	33 (84.6)	457 (76.7)	NS
Calcium antagonists	10 (24.9)	148 (24.8)	NS
MRA	16 (41.0)	183 (30.7)	NS
Loop diuretics	18 (46.2)	161 (27.0)	0.012
Statins	32 (82.1)	510 (85.6)	NS

Unless indicated otherwise, data shown (%). ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; MRA, mineralocorticoid receptor antagonist; OHCA, out-of-hospital cardiac arrest.

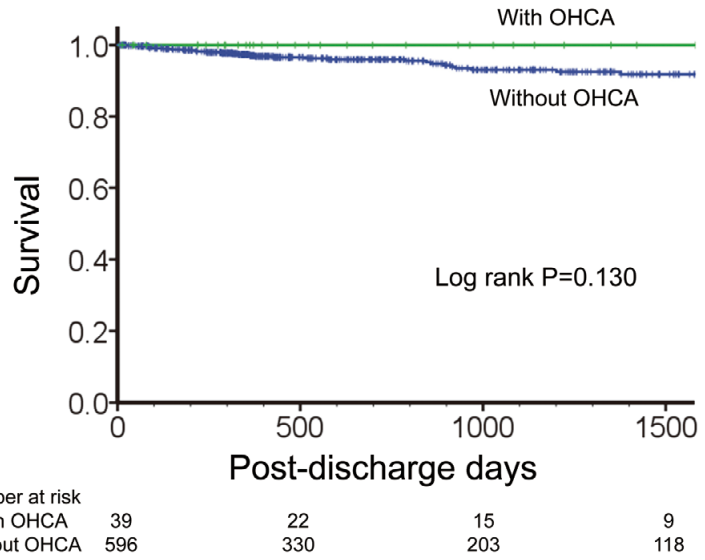

Figure 1. Kaplan-Meier survival curves of acute myocardial infarction patients with and without out-of-hospital cardiac arrest (OHCA) enrolled in the follow-up study.

cholesterol ≥220 mg/dL, serum high-density lipoprotein-cholesterol ≤40 mg/dL, serum triglyceride ≥150 mg/dL, or a treatment history.[7,8] Diabetes was defined as a previous diagnosis of diabetes or HbA1c ≥6.5%.[9,10] All measurements, including echocardiography, were taken on the day of admission. The estimated glomerular filtration rate (eGFR; mL/min/1.73 m^2) was calculated using the Modification of Diet in Renal Disease equation[11] coefficient modified for Japanese patients, as follows:[12]

$$eGFR = 194 \times Cr^{-1.094} \times age^{-0.287}$$

where Cr is serum creatinine. For female patients, the eGFR was multiplied by a correction factor of 0.739. Cardiogenic shock was defined as a sustained episode of systolic blood pressure <90 mmHg secondary to cardiac dysfunction and/or the requirement for inotropic or vasopressor agents[13] and was evaluated on arrival at hospital.

For AMI patients with OHCA, in addition to the above variables, the presence of a witness, bystander cardiopulmonary resuscitation (CPR), shockable/non-shockable rhythm, the use of a public automated external defibrillator (AED), the rate of return of spontaneous circulation (ROSC) before hospital arrival, and the use of extracorporeal CPR (ECPR) were examined. For all arrhythmias, ROSC was defined as restoration of a spontaneous perfusion rhythm.[14] Shockable rhythms were defined as ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT), whereas non-shockable rhythms were defined as asystole and pulseless electrical activity (PEA).

Continuous variables are expressed as the mean±SD and were compared using t-tests. Categorical variables are expressed as numbers and percentages and were compared using Chi-squared tests. Cumulative survival curves were constructed with the Kaplan-Meier method and compared using the log-rank test.

Results

The characteristics of AMI patients with and without OHCA are presented in **Table 1**. Patients with OHCA were more likely to be male and have a lower eGFR than those without OHCA. The prevalence of diabetes, hypertension, and dyslipidemia did not differ according to the presence of OHCA. NSTEMI and complication of cardiogenic shock were more frequent and the culprit lesion more likely to be the left anterior descending coronary artery in patients with than without OHCA. Maximum CK levels, which reflect myocardial damage, were higher in patients with than without OHCA.

Table 2 presents the characteristics of the patients

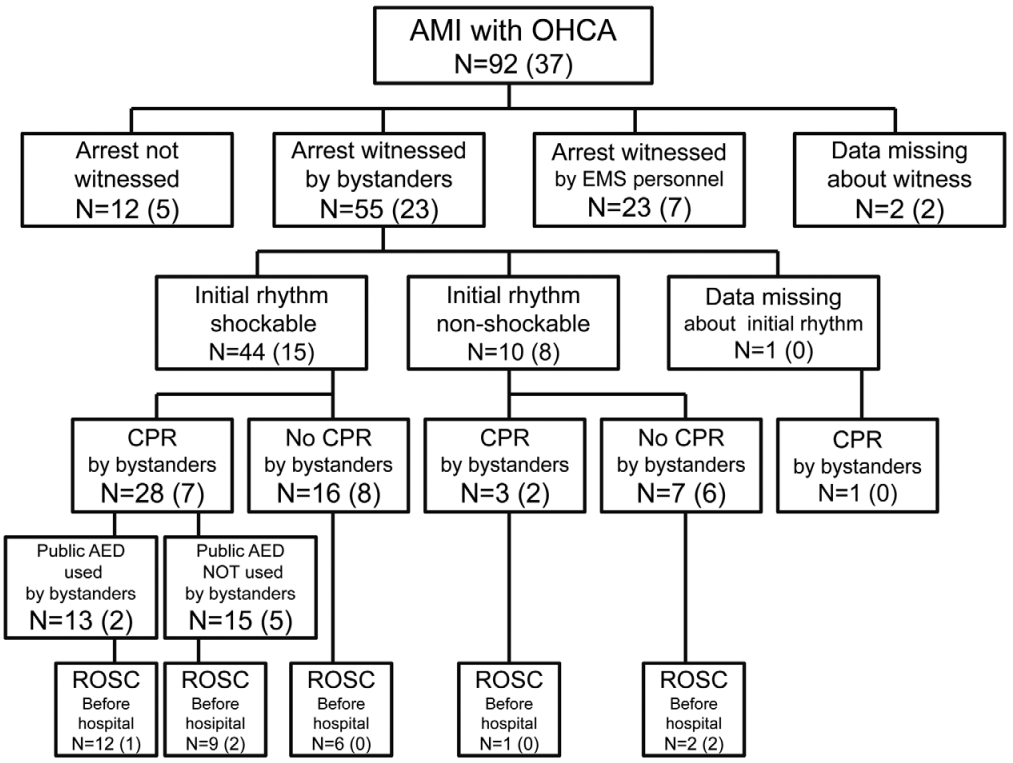

Figure 2. Prehospital care of acute myocardial infarction (AMI) patients with out-of-hospital cardiac arrest (OHCA). Numbers in parentheses indicate the number of patients who died in hospital. AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ROSC, return of spontaneous circulation.

enrolled in the follow-up study, and **Table 3** summarizes their prescriptions at discharge. The rate of prescriptions was not markedly different between AMI patients with and without OHCA, except for diuretics. **Figure 1** shows a Kaplan-Meier curve for survival according to the presence or absence of OHCA. The survival of AMI patients was comparable between those with and without OHCA.

Prehospital care for AMI patients with OHCA is shown in **Figure 2**. The characteristics of AMI patients with OHCA according to in-hospital death or survival are presented in **Table 4**. The rate of initial shockable rhythm was higher and the rate of cardiogenic shock lower among in-hospital survivors than among those who died. Conversely, the rate of ROSC before hospital arrival was higher among in-hospital survivors than among those who died. Body mass index (BMI) was higher and renal function better among in-hospital survivors. Among patients with a shockable initial rhythm and in whom CPR was performed by a bystander (n=28), a public AED was used in 13 patients, 11 of whom were discharged alive (**Figure 2**). ECPR was performed in 15 patients; however, only 2 of these patients were discharged alive.

Discussion

CAG in OHCA Patients

In OHCA patients, the diagnosis of ACS without CAG is complex.[15] In a Japanese registry, among all patients with OHCA, a cardiac origin was determined in 55% of cases.[16] After excluding external etiologies (18% from Kitamura et al[17]), which is not difficult, the proportion of cases with a cardiac origin increased further. A cardiac origin accounted for more than 85% of cases with a shockable initial rhythm.[18] A coronary lesion was present in 58% of OHCA patients without obvious extracardiac cause of arrest and without ST elevation.[19] The predictive value of an ECG for coronary stenosis is poor, and clinical data are lacking in the case of OHCA.[19–21] Thus, emergency CAG followed by PCI is recommended under the current guidelines, even for OHCA without ST elevation.[22] In the present study, 89 of 92 OHCA patients with AMI underwent emergent CAG, and the diagnosis of AMI was sometimes obtained after CAG.

A recent prospective randomized study, namely the Coronary Angiography after Cardiac Arrest (COACT) trial, showed that among ROSC patients after OHCA without signs of STEMI, immediate CAG is not better than delayed CAG.[23] However, as pointed out in an Editorial in the same issue of that journal,[24] acute unstable lesions were found in <20% of cases.[23] The results would be affected by the rate of acute coronary lesions in the study population. Thus, immediate CAG should not be denied; however, the clinical evaluation of patients (to predict the probability of an acute lesion before CAG) is also important.

Prehospital Care and In-Hospital Mortality in OHCA Patients

Patients with OHCA suffer more complications, such as

Table 4. Comparison Between AMI Patients With and Without OHCA Who Died in Hospital or Survived to Discharge

	Died in hospital	Survived to discharge	P value
No. patients	37	55	
Age (years)	68.2±12.0	66.1±14.0	NS
Male sex	35 (94.6)	52 (94.5)	NS
BMI (kg/m^2)	21.8±7.0 [26]	24.4±3.6 [53]	0.033
Initial shockable rhythm	21 (60.0) [35]	44 (84.6) [52]	0.013
ROSC before hospital arrival	8 (21.6)	37 (74.0) [50]	<0.001
Cardiogenic shock	33 (89.2)	20 (39.2) [51]	<0.001
STEMI	19 (59.4) [32]	28 (53.8) [52]	NS
Emergency CAG	34 (91.9)	55 (100)	NS
Culprit LAD	16 (59.3) [27]	31 (588) [52]	NS
Vessel disease (no. vessels)	2.0±0.9 [34]	1.7±0.8	NS
Maximum CK (IU/L)	5,700±6,700	3,870±3,870	NS
Diabetes	14 (48.3) [29]	17 (32.1) [53]	NS
Hypertension	10 (45.5) [22]	32 (60.4) [53]	NS
Dyslipidemia	15 (45.5) [33]	31 (57.4) [54]	NS
eGFR (mL/min/1.73 m^2)	40.2±18.4	53.0±18.8	0.002

Unless indicated otherwise, data are given as the mean±SD or as n (%). Numbers in [ ] show the sample number when some cases were missed. ROSC, return of spontaneous circulation. Other abbreviations as in Table 1.

cardiogenic shock, heart failure, cardiac arrest, cerebrovascular events, major bleeding, multiple organ failure, and sepsis, than those without OHCA.[1,13] Furthermore, CPR frequently induces intrathoracic injuries.[25,26] Therefore, the in-hospital mortality is much higher in AMI patients with than without OHCA.

In-hospital mortality depends on the study population.[15,27] The relatively high in-hospital mortality in the present study was due to the severe condition of patients in the present population; the rate of cardiogenic shock was 60%. Some patients had ongoing CPR at admission. In such cases, PCI was performed with CPR and sometimes with percutaneous cardiopulmonary support (PCPS). Almalla et al[28] reported that patients who underwent CAG with ongoing CPR showed an extremely poor in-hospital prognosis, even though ROSC was achieved in a large proportion of patients. In the present study population, ECPR was performed in 15 patients, but only 2 of those patients were discharged alive. The Study of Advanced Life Support for Ventricular Fibrillation with Extracorporeal Circulation in Japan (SAVE-J) trial showed that ECPR was better than conventional CPR in patients with VF/pulseless VT but not in those with PEA/asystole.[29] In the present study, 2 of 6 patients with VF/pulseless VT survived, but all 9 PEA/asystole patients died in hospital. EPCR may not be indicated for patients with PEA/asystole.

OHCA induces global ischemia in addition to the culprit area, as well as systemic malperfusion. After ROSC, ischemia in the non-culprit area can be restored. A delay in CPR in OHCA patients is an important predictor of in-hospital mortality.[30] The ROSC rate from VF decreases with increasing collapse to shock time.[31] In the present retrospective study, the precise interval between arrest and ROSC could not be determined. When the collapse to initial ECG time is short, the rate of shockable rhythms is high.[32] The predicted rate of shockable rhythms at arrest is approximately 60%.[32] The rate of shockable rhythm decays in a time-dependent manner,[32] as VF tends to convert in non-shockable rhythms over time.[33] Thus, initial shockable rhythms indicate a shorter time after arrest. The bystander CPR rate plays a critical role in improving survival[30] because bystander CPR can maintain a shockable rhythm for approximately 27 min.[32] Bystander CPR also aids in cerebrovascular circulation. However, not all patients with a shockable rhythm can achieve ROSC with conventional CPR;[31] resistance to CPR appears to be related to continuous myocardial ischemia.[31] OHCA in AMI patients is primarily due to sustained myocardial ischemia or reperfusion arrhythmia. In cases of reperfusion arrhythmia, early CPR can improve the prognosis. However, in cases of sustained myocardial ischemia, CPR may not be effective if the area of ischemia is large.

In the present study population, the rate of arrest witnessed by EMS personnel was 25%, which is much higher than that reported by Nagao et al[18] (<10%). In contrast with idiopathic arrhythmia, OHCA due to AMI is sometimes preceded by chest pain. In these cases, OHCA may occur after the arrival of the EMS.

The use of public AED increases each year, and was 16.5% in Japan in 2013.[16] Moreover, public AED can be beneficial even when ROSC is not achieved before the arrival of the EMS.[34] In the present study, an AED was used in 13 of 28 witnessed arrests with shockable rhythms and resuscitation was performed by a bystander. This rate is quite good because AEDs are located in public settings and two-thirds of arrests occurred at home.[16]

In the present study, decreased renal function was associated with a poor in-hospital prognosis in AMI with OHCA. Furthermore, renal dysfunction increased the rate of OHCA complication and long-term mortality in AMI patients. Renal function affects almost all cardiovascular diseases, including heart failure[7] and MI. Thus, preserving renal function in daily life is very important for preventing cardiovascular events.

Post-Discharge Mortality

The present study showed that the post-discharge mortality is not markedly different between AMI patients with

and without OHCA. Lettieri et al[33] and Kvakkestad et al[27] also showed comparable prognoses between AMI patients with and without OHCA complication. However, Samanta et al[35] showed that the presence of OHCA was associated with a higher long-term mortality rate in STEMI patients who underwent PCI/coronary artery bypass grafting (mean follow-up 18.6 months) than in the absence of OHCA. These discrepant results may be due to differences in the patient populations.

Two studies including a relatively large number of patients have been conducted. Fordyce et al[13] showed in aged AMI patients that the long-term prognosis was comparable between those with and without OHCA when patients were discharged alive (with OHCA, n=641; without OHCA, n=54,219). Dawson et al[36] showed in STEMI patients who underwent PCI that the long-term prognosis of those with OHCA was comparable to that in those without OHCA when they survived for the first 30 days after the onset (with OHCA, n=666; without OHCA, n=10,923).

The risk of death occurs early during hospitalization, and this risk decays over time.[13] In the present study, 40% of deaths occurred within 2 days, and 65% occurred within 7 days after the onset in patients with OHCA. Efforts should be made to improve short-term outcomes by optimization of post-ROSC care.[27]

Study Limitations

Several limitations of this study should be considered. First, this was a retrospective and not a prospective study. However, prospective studies have a strong selection bias for patient inclusion. This study included all patients admitted to The Jikei University Kashiwa Hospital with AMI. Therefore, the selection bias for patient inclusion by investigators was minimized. Second, this hospital is a tertiary emergency center; AMI patients without shock are taken to all PCI hospitals in Kashiwa city almost equally, whereas those with shock are taken to The Jikei University Kashiwa Hospital selectively. Thus, the findings of the present study may not be able to be generalized to other hospitals. Third, the sample size in this study was relatively small. Even so, the results were clear and compelling.

Conclusions

The post-discharge mortality of AMI patients was comparable between those with OHCA and without OHCA. Efforts should be made to discharge such patients alive.

Acknowledgment

The authors thank Brian Quinn, Japan Medical Communication, for reading the manuscript.

Sources of Funding

This study did not receive any specific funding.

Disclosures

M.Y. is a member of *Circulation Reports*' Editorial Team. The remaining authors have no conflicts of interest to declare.

IRB Information

This study was approved by the Ethics Committee of The Jikei University School of Medicine (32-113[10189]).

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