Journal of Cardiology 74 (2019) 109–115

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

# Association of intensive care unit admission and mortality in patients with acute myocardial infarction

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ARTICLE INFO

*Article history:*
Received 2 October 2018
Received in revised form 25 December 2018
Accepted 15 January 2019
Available online 14 February 2019

*Keywords:*
Acute myocardial infarction
Intensive care unit
Mortality

ABSTRACT

*Background:* An admission to the intensive care unit (ICU) after developing acute myocardial infarction (AMI) has been the standard of care and is recommended by professional societies. However, evidence that justifies its use, such as a reduction in mortality, has never been shown despite the associated financial burden. This study aimed to investigate the association between ICU admission and a reduction in 30-day mortality in patients who developed AMI.
*Methods:* The multicenter retrospective cohort study was conducted using data from an administrative database between 2014 and 2016 in Japan. Patients with AMI as the primary diagnosis in the Diagnosis Procedure Combination database were included. Exposure was ICU admission, which was defined by an ICU management code in the claims record. Comparison was those without an ICU management code. The primary outcome was 30-day mortality. An association between ICU admission and a 30-day mortality was tested using a logistic regression model with random effects.
*Results:* Of 18,745 patients [mean (standard deviation) age, 69 (13) years; 74% male] identified, 11,538 (62%) were admitted to ICUs and 7207 (38%) were admitted to non-ICUs. Among patients admitted to ICUs, 575 patients (5%) died within 30 days of admission, while 429 patients (6%) died in the non-ICU group. The association between ICU admission and mortality was confirmed both in unadjusted analysis [odds ratio (OR), 0.75; 95% confidence interval (CI), 0.64–0.89; $p = 0.001$] and adjusted analysis (OR, 0.70; 95% CI, 0.54–0.90; $p = 0.01$).
*Conclusions:* ICU admission was associated with lower 30-day mortality in patients who developed AMI.
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## Introduction

Mortality due to acute myocardial infarction (AMI) has been declining in past decades [1]. Admission to the intensive care unit (ICU) after developing AMI has been widely accepted as a standard practice and is thought to play a major role in improving outcomes. On the other hand, ICU stays represent a substantial financial burden [2]. In addition, evidence that justifies its use, such as a reduction in mortality, has never been shown in the contemporary revascularization era.

No randomized controlled trials have been conducted to investigate the mortality benefit of ICU admission in patients with AMI. There are several observational studies with conflicting results [3–12]. The clinical guidelines in the USA recommend admission to a coronary care unit under specific conditions for non-ST-elevation acute coronary syndromes, and the use of an ICU is not mentioned for those with ST-elevation myocardial infarction (STEMI) [13,14]. The clinical guidelines of the European Society of Cardiology and the Japanese Circulation Society recommend that patients suffering from AMI be admitted to the ICU [15–18], although supporting evidence is lacking thus far.

Among the major limitations of the previous studies are small sample sizes, a limited number of study sites, or lack of clinically

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https://doi.org/10.1016/j.jjcc.2019.01.007
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important covariates to adjust which may lead to biased or less generalizable results. In fact, even the largest prospective cohort study consisted of only 479 patients at a single center [3]. A large-scale multi-center study with sufficient clinical information for adjustment is warranted to draw a more robust conclusion. Since it is difficult to conduct a randomized controlled trial due to the fact that an admission to the ICU after AMI is recommended by clinical guidelines and has become the standard of care, a large-scale observational study is warranted to better understand the benefit of ICU admission among patients with AMI.

Thus, the present study aimed to investigate the association between ICU admission and 30-day mortality in patients with AMI, using the Japanese Diagnosis Procedure Combination (DPC) database. The hypothesis tested in this study was that ICU admission is associated with a reduction in 30-day mortality.

## Methods

### *Study design and database*

The study design is a retrospective cohort study with data collected from an administrative database. The administrative database used in this study is the DPC database. DPC is a payment system, launched by the Japanese Ministry of Health, Labor, and Welfare in 2002, in which provider reimbursement is calculated based on a per-diem fee according to the diagnosis category of inpatients [19]. It contains patients' clinical information and claims data on diagnosis, procedures, and medications during hospitalization. DPC data are collected from 78% of all acute care beds in Japan as of the end of March 2016 [20]. The DPC data used in this study were provided by Medical Data Vision Co. Ltd (MDV; Tokyo, Japan) which covered approximately 16 million patients from 275 hospitals by the end of September 2016 [21]. DPC data provided by MDV have been widely used for research purposes [22,23]. The DPC database was the only database used and was not linked to any other databases. The first author (RM) has full access to all the data in the study and takes responsibility for its integrity and the data analysis. The study protocol was approved by the institutional review board of Kyoto University, and individual informed consent was waived due to the anonymous nature of the data (R0977).

### *Patients*

All patients with AMI as the primary diagnosis at hospitalization between April 01, 2014 and March 31, 2016, were identified. AMI was defined as an international classification of diseases, 10th revision (ICD-10) of "I210", "I211", "I212", "I213", "I214", or "I219" (eTable 1). The positive predictive value for identifying myocardial infarction in DPC data is 92.3%, and the negative predictive value is 96.4% [24]. Patients in whom demographic, clinical, diagnostic, or procedural information intended to collect was missing were excluded from the sample. The analysis was limited to the first hospitalization for patients with multiple hospitalizations within the study period.

### *Exposure and control*

The exposure was ICU admission, defined as the presence of an ICU management code in the claims record (eTable 1). The control group included those without the above-mentioned codes, which was a mixture of patients in high care units (HCU), and cardiology/general wards. The characteristics of ICUs and HCUs in Japan are shown in eTable 2.

### *Outcomes*

The primary outcome was 30-day mortality, defined as death within 30 days from the time of admission. Outpatient data were used to confirm survival of patients who were discharged alive before day 30. For patients whose outcome was not confirmed, a multiple imputation method was used to impute missing outcome. The secondary outcome was the length of hospital stay in days. Both outcomes were collected and measured from DPC clinical information (eTable 1).

### *Covariates*

Covariates were selected to adjust for and represent patient characteristics, information on hospital presentation, therapeutic interventions, and hospital characteristics. Covariates for patient characteristics were age, sex, Charlson comorbidity index, smoking status, hypertension, diabetes mellitus, dyslipidemia, renal failure, previous myocardial infarction, STEMI, anterior myocardial infarction, and Killip class [25,26]. Covariates for information on hospital presentation were referral from other institutions, ambulance use, and off-hour admission [27]. Covariates for therapeutic interventions were percutaneous coronary intervention (PCI), fibrinolytic, coronary artery bypass grafting, intravenous catecholamine, intra-aortic balloon pump, percutaneous cardiopulmonary support, and ventilator use [28]. Covariates for hospital characteristics were number of beds, annual AMI volume, annual PCI volume, door-to-balloon time, cardiologist training center, proportions of essential drug prescription, and unique hospital identifier [28–35]. These covariates were selected either because they were shown to be associated with mortality from previous studies or deemed important from the clinical standpoint. Details of the above codes are shown in eTable 1.

### *Statistical analyses*

A logistic regression model with random effects was used to evaluate an association between ICU admission and 30-day mortality. A linear regression model with random effect was used to assess the length of hospital stay. In the analyses, the following patient characteristics, information on hospital presentation, therapeutic interventions, and hospital characteristics were adjusted for: age, sex, Charlson comorbidity index, smoking status, hypertension, diabetes mellitus, dyslipidemia, renal failure, previous myocardial infarction, STEMI, anterior myocardial infarction, Killip class, referral, ambulance use, off-hour admission, PCI, door-to-balloon time, fibrinolytic, coronary artery bypass grafting, intravenous catecholamine, intra-aortic balloon pump, percutaneous cardiopulmonary support, ventilator, number of beds, annual AMI volume, annual PCI volume, cardiologist training center, proportions of essential drug prescription. A unique hospital identifier was included as a random effect in the logistic and linear regression models to account for heterogeneity across hospitals.

In addition to the main analyses, several pre-specified subgroup analyses were performed. First, age was stratified into six categories (younger than 40, 40–49, 50–59, 60–69, 70–79, and 80 years and above) and interactions were tested to evaluate the age-groups which would benefit from ICU admission. Second, to account for the different disease severities, subgroup analysis according to Killip class stratified into five categories (1, 2, 3, 4, and unknown) was performed. Third, patients with STEMI were compared with non-STEMI. Fourth, to evaluate the influence of PCI, an analysis was conducted in groups with and without PCI. Interactions between ICU admission and each subgroup category on 30-day mortality in the logistic and linear regression models were tested.

The following sensitivity analyses were performed to evaluate the robustness of findings in the main analysis. First, HCUs were included in the exposure group, and a comparison was made between ICU/HCU and general/cardiology wards. Second, patients with Killip class specified in the DPC clinical data were identified as a new AMI population. Third, an analysis was limited to hospitals with an ICU. Fourth, covariates related to therapeutic interventions which might have occurred after ICU admission were eliminated from an adjustment. Fifth, an analysis was limited to patients in Killip class one to three.

All tests were two-sided, and a $p$-value of less than 0.05 was considered significant. All data management and analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA).

## Results

### *Patient and hospital characteristics*

A total of 28,743 DPC hospitalization records with AMI as the primary diagnosis were identified from April 01, 2014 to March 31, 2016. Among them, 9998 records (35%) were excluded (9388 re-admissions and 610 with missing data). The final sample included 18,745 patients admitted to 249 hospitals (Fig. 1). Among these patients, 11,538 patients (62%) were admitted to ICUs, and 7207 patients (38%) were admitted to non-ICUs. The mean age of patients was 69 years and 74% were male.

The demographics of patients were similar in the two groups except for ambulance use, off-hour admission, and several therapeutic interventions such as the use of catecholamine, PCI, and mechanical circulatory support which were more frequent in the ICU group (Table 1). On the other hand, the heterogeneity of the hospitals in two groups was evident. Large-scale academic hospitals with more cases of AMI and PCI were more frequent in the ICU group, while middle-size private hospitals with lower case volumes were seen in the non-ICU group. Essential drugs, such as aspirins and statins that are viewed as hospitals' quality indicators, were more often prescribed in the ICU group. In addition, HCU accounted for 41 (28%) of non-ICU hospitals (Table 2).

### *Primary and secondary outcomes*

Among patients admitted to the ICU, 575 patients (5%) died within 30 days of admission [the median and interquartile range (IQR) of time to death were 7 and 3–14 days], while 429 patients (6%) died in the non-ICU group (the median and IQR of time to death was 6 and 3–13 days) (Fig. 1). The median length of hospital stay for the ICU group was 14 days (IQR, 10–20) while that in the non-ICU group was 13 days (IQR, 9–20).

In univariate analysis, ICU admission was associated with a reduction in 30-day mortality [odds ratio (OR), 0.75; 95% confidence interval (CI), 0.64–0.89; $p = 0.001$]. Multivariate regression analysis also showed that ICU admission was significantly associated with a reduction in 30-day mortality (OR, 0.70; 95% CI, 0.54–0.90; $p = 0.01$) (Table 3). ICU admission was significantly associated with a prolonged length of hospital stay in univariate analysis (1.64 days; 95% CI, 0.97–2.32; $p < 0.001$). However, the association was no longer observed after adjustment with multivariate analysis (0.31 days; 95% CI, −0.54 to 1.15; $p = 0.48$) (Table 3).

### *Subgroup and sensitivity analyses*

No significant interactions were observed in any of the pre-specified subgroups. After re-stratifying patients into four age-groups (<60, 60–69, 70–79, and ≥80 years), so that the number of patients in each group is balanced and the model became stable, the mortality benefit increased as the patients got older (Fig. 2). ICU admission was associated with a reduction in mortality in patients in Killip class four and those with STEMI (Fig. 2). No difference was observed in the subgroup with and without PCI (Fig. 2).

Association of ICU admission and a reduction in 30-day mortality was confirmed with statistical significance in the first to third sensitivity analyses, where (1) HCU was included in the ICU

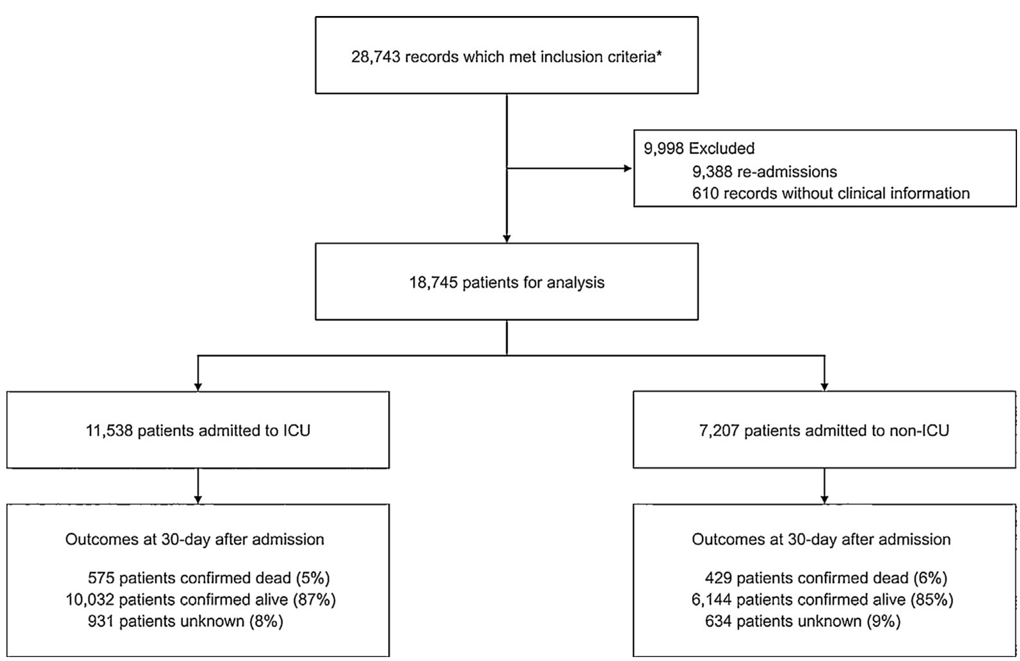


**Fig. 1.** Patient selection. *Inpatient records with a primary diagnosis of acute myocardial infarction (ICD10 code: I210, I211, I212, I213, I214, I219) admitted between April 1, 2014 and March 31, 2016. ICD10, International Classification of Diseases, 10th Revision; ICU, intensive care unit.

**Table 1**
Patient characteristics by admission to the ICU vs non-ICU.

| Characteristics | Patients, no. (%) | |
|---|---|---|
| | ICU | Non-ICU |
| Patients, no. | 11,538 | 7207 |
| Male | 8693 (75) | 5131 (71) |
| Age, mean (SD), years | 69 (13) | 70 (13) |
| <40 | 166 (1) | 91 (1) |
| 40–49 | 919 (8) | 483 (7) |
| 50–59 | 1667 (14) | 906 (13) |
| 60–69 | 3057 (27) | 1742 (24) |
| 70–79 | 3119 (27) | 1988 (28) |
| ≥80 | 2610 (23) | 1997 (28) |
| CCI, median (IQR) | 3 (2, 4) | 3 (2, 4) |
| Smoking history | 7165 (62) | 3982 (55) |
| HT | 8481 (74) | 5223 (73) |
| DM | 4170 (36) | 2439 (34) |
| DL | 8178 (71) | 4778 (66) |
| RF | 796 (7) | 534 (7) |
| OMI | 1360 (12) | 866 (12) |
| STEMI | 9848 (85) | 5539 (77) |
| Anterior MI | 4647 (40) | 2684 (37) |
| Killip | | |
| 1 | 5367 (47) | 3292 (46) |
| 2 | 3102 (27) | 2095 (29) |
| 3 | 1053 (9) | 677 (9) |
| 4 | 1614 (14) | 902 (13) |
| Unknown | 402 (3) | 241 (3) |
| Referral | 4627 (40) | 2901 (40) |
| Ambulance | 8060 (70) | 4249 (59) |
| Off-hour admission | 5668 (49) | 2576 (36) |
| PCI | 10,272 (89) | 5578 (77) |
| D2B time < 90 min | 6696 (58) | 2898 (40) |
| Fibrinolytic | 47 (0.4) | 24 (0.3) |
| CABG | 330 (3) | 24 (0.3) |
| IABP | 2141 (19) | 595 (8) |
| PCPS | 339 (3) | 70 (1) |
| Ventilator | 2018 (17) | 705 (10) |
| Catecholamine | 3590 (31) | 1518 (21) |

CABG, coronary artery bypass graft; CCI, Charlson comorbidity index; DL, dyslipidemia; DM, diabetes mellitus; D2B, door to balloon; HT, hypertension; IABP, intra-aortic balloon pump; ICU, intensive care unit; IQR, interquartile range; MI, myocardial infarction; OMI, old myocardial infarction; PCI, percutaneous coronary intervention; PCPS, percutaneous cardio-pulmonary support; RF, renal failure; SD, standard deviation; STEMI, ST-elevation myocardial infarction.

**Table 2**
Hospital characteristics with and without ICU.

| Characteristics | Hospitals, no. (%) | |
|---|---|---|
| | ICU | Non-ICU |
| Hospitals, no. | 106 | 143 |
| Beds | | |
| <200 | 3 (3) | 39 (27) |
| 200–499 | 60 (57) | 96 (67) |
| ≥500 | 43 (41) | 8 (6) |
| Nurse to patient ratio | | |
| 1:7 | 102 (96) | 110 (77) |
| 1:10 | 4 (4) | 33 (23) |
| Highest level of care | | |
| ICU | 106 (100) | 0 (0) |
| HCU | 0 (0) | 41 (28) |
| General ward | 0 (0) | 102 (71) |
| Management | | |
| University | 9 (8) | 1 (0.7) |
| Public | 24 (23) | 30 (21) |
| Semi-public | 48 (45) | 49 (34) |
| Private | 25 (24) | 63 (44) |
| Teaching hospital | 104 (98) | 109 (76) |
| Emergency hospital | 106 (100) | 141 (99) |
| Cardiologist training center | 98 (92) | 56 (39) |
| CV surgery center | 78 (74) | 33 (23) |
| AMI annual case volume | | |
| <60 | 9 (9) | 83 (58) |
| 60–179 | 47 (45) | 53 (37) |
| ≥180 | 50 (47) | 7 (5) |
| PCI annual case volume | | |
| <10 | 15 (14) | 101 (70) |
| 10–59 | 68 (64) | 35 (24) |
| ≥60 | 23 (22) | 7 (5) |
| Medication (average %) | | |
| Aspirin | 93 | 74 |
| Statin | 81 | 52 |
| Beta-blocker | 66 | 40 |
| ACE-I/ARB | 70 | 46 |

ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin 2 receptor blocker; AMI, acute myocardial infarction; CV, cardiovascular; HCU, high care unit; ICU, intensive care unit; PCI, percutaneous coronary intervention.

group, (2) Killip class was used as a different definition to identify the AMI population, (3) analysis was limited to hospitals with an ICU (Fig. 2, eTables 3–5). The fourth sensitivity analysis with adjustment excluding covariates after hospital admission did not reach statistical significance, although the result was in accordance with that of the main analysis (Fig. 2, eTable 6). In the fifth sensitivity analysis with patients limited to Killip class one to three, an association with ICU admission and mortality was no longer observed (Fig. 2, eTable 6).

## Discussion

The present study investigated the association between ICU admission and 30-day mortality in patients who developed AMI using data from the DPC database. The result showed that patients admitted to the ICU had significantly lower 30-day mortality than those who did not. The length of hospital stay was not prolonged for those admitted to the ICU.

### *Benefit of ICU*

The results of the present study suggest that there may be a mortality benefit from admission to ICU in AMI patients on average. However, subgroup and sensitivity analyses identified subsets of patients who are likely to gain the most benefit from intensive care and those who would not. For patients with STEMI, ICU admission may have been advantageous because the incidence of ventricular arrhythmia was reported to be higher in those with STEMI compared to those with non-STEMI even in the revascularization era [36]. In the subgroup analysis, an association of ICU admission and mortality was distinct in the Killip class four, but it was no longer present when the analysis was limited to those in Killip class one to three in the sensitivity analysis (Fig. 2). As reported in the previous study, this suggests that there may be no additional benefit from intensive care for stable patients [37]. There seems to be a clear trend in favor of ICU as the age increased (Fig. 2). The results of the present study suggest that benefit of ICU was mainly experienced by patients with complications in the higher age group.

**Table 3**
Association of ICU admission on 30-day Mortality and length of hospital stay.

| | OR | 95% CI | *p*-Value |
|---|---|---|---|
| 30-Day mortality | | | |
| Unadjusted regression | 0.75 | 0.64–0.89 | 0.001 |
| Adjusted regression | 0.70 | 0.54–0.90 | 0.01 |
| Length of hospital stay (days) | | | |
| Unadjusted regression | 1.64 | 0.97–2.32 | <0.001 |
| Adjusted regression | 0.31 | −0.54 to 1.15 | 0.48 |

CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

| | Patients, No. ICU | non-ICU | OR | 95% CI | p value |
|---|---|---|---|---|---|
| Original analysis | 11538 | 7207 | 0.70 | 0.54 to 0.90 | 0.01 |
| Subgroup analyses | | | | | |
| Age group, years | | | | | |
| <60 | 2752 | 1480 | 0.58 | 0.19 to 1.84 | N/A |
| 60-69 | 3057 | 1742 | 0.91 | 0.38 to 2.19 | 0.85 |
| 70-79 | 3119 | 1988 | 0.78 | 0.49 to 1.26 | 0.88 |
| ≥80 | 2610 | 1997 | 0.70 | 0.50 to 0.98 | 0.82 |
| Disease severity, Killip class | | | | | |
| 1 | 5367 | 3292 | 0.61 | 0.32 to 1.17 | N/A |
| 2 | 3102 | 2095 | 0.82 | 0.46 to 1.44 | 0.23 |
| 3 | 1053 | 677 | 1.05 | 0.60 to 1.84 | 0.66 |
| 4 | 1614 | 902 | 0.72 | 0.52 to 0.99 | 0.54 |
| unknown | 402 | 241 | 0.28 | 0.08 to 0.98 | 0.28 |
| AMI type | | | | | |
| STEMI | 9848 | 5539 | 0.72 | 0.52 to 0.98 | 0.36 |
| NSTEMI | 1690 | 1668 | 0.64 | 0.39 to 1.07 | N/A |
| PCI | | | | | |
| performed | 10272 | 5578 | 0.83 | 0.57 to 1.19 | 0.17 |
| not performed | 1266 | 1629 | 0.75 | 0.52 to 1.07 | N/A |
| Sensitivity analysis | | | | | |
| ICU&HCU vs wards | 13698 | 5047 | 0.62 | 0.48 to 0.80 | <0.001 |
| different AMI definition | 15065 | 14069 | 0.67 | 0.52 to 0.88 | 0.004 |
| limited to hospitals with ICUs | 11537 | 2582 | 0.65 | 0.48 to 0.88 | 0.01 |
| limited covariates | 11538 | 7207 | 0.81 | 0.64 to 1.01 | 0.06 |
| limited to Killip 1,2,3 | 9522 | 6064 | 0.76 | 0.53 to 1.09 | 0.14 |

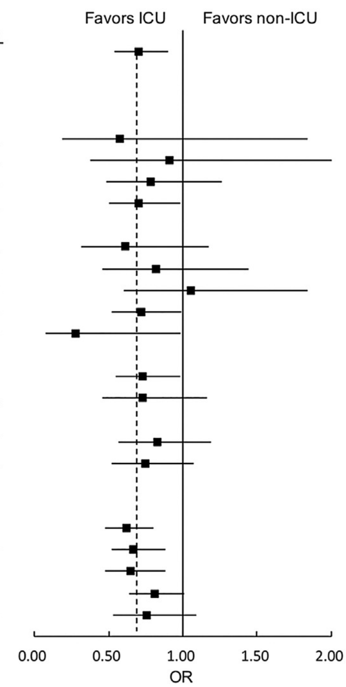


**Fig. 2.** Subgroup and sensitivity analyses for 30-day mortality in patients admitted to ICU vs non-ICU. The Forrest plot shows OR and CI in squares and lines for each category. CIs shown were calculated within each category and *p*-values for subgroup analyses represent tests for interaction. AMI, acute myocardial infarction; CI, confidence interval; HCU, high care unit; ICU, intensive care unit; NSTEMI, non-ST-elevation myocardial infarction; N/A, not applicable; OR, odds ratio; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

### *Comparison with previous studies*

Previous studies have shown mixed results on the effects of ICU stays on mortality [3–12], while the results of this study were in favor of ICU admission. The study result differs from that of some previous studies [4,5,10–12], probably due to four reasons. The first reason is the difference in the number of adjusted covariates. This study adjusted for patient characteristics, information on hospital presentation, therapeutic interventions, and hospital characteristics, and most of these covariates were shown to be associated with mortality in previous studies [25–35]. Some of the previous studies never adjusted for confounding variables, adjusted with very few, or missed important confounding variables such as Killip class. The second reason is the difference in the study setting. Previous studies [3,4,6–9] were conducted in a single or a few centers, which were mostly university hospitals. The present study consisted of a wide variety of acute-care hospitals from large university hospitals to middle-sized private hospitals. In addition, some studies were conducted in the 1990s and 2000s. The standard intervention in contemporary practice such as PCI was less often performed in previous studies, although acute-phase management and primary PCI have been shown to improve survival [38]. The third reason is that most of the studies with a large sample size [5,10,12] sought to answer a different question; they tried to investigate the difference in mortality based on groups of hospitals with different ICU utilization rates and not whether the patients were actually admitted to the ICU. The last reason is the difference in the target population. Because patients in cardiogenic shock or STEMI were excluded or not in the control group in some of the previous studies [5,11], more severely ill patients in the present study could have made the mortality benefit more distinct.

### *Limitations and strengths*

Several limitations of this study need to be mentioned. First, the difference in level of care provided in ICU and non-ICU group might not have been clearly differentiated. Some therapeutic interventions such as use of catecholamine and mechanical support were seen in the non-ICU group (Table 1), and HCUs are responsible for most of these interventions. Details on differences between ICUs and HCUs in Japan are described in eTable 2. The first sensitivity analysis was conducted by including HCUs in the ICU group to make a clearer distinction in the care provided. The results showed almost the same OR, assuring the robustness of the original finding (Fig. 2, eTable 3). Second, misclassification might have occurred in the selection of AMI patients. A validation study [24] of the DPC database for myocardial infarction demonstrated its sensitivity remaining as low as 52%. A second sensitivity analysis was performed to include patients who could have been missed due to low sensitivity by re-defining AMI as patients with Killip class specified in the DPC patient information. The results showed almost the same OR once again (Fig. 2, eTable 4). Third, whether the clinical benefit is achieved by the ICU admission itself or the performance of the hospitals with ICU is difficult to distinguish since ICU admission is likely when the hospitals themselves have ICUs. In order to distinguish the direct effect of ICU admission, actual ICU admission was used as an exposure instead of merely comparing hospitals with and without ICU or hospitals with different ICU admission rates. Hospital characteristics were adjusted for and each hospital was treated as a random effect in the model to account for heterogeneity among hospitals. In addition, a third sensitivity analysis was performed by limiting patients to only those who were admitted to hospitals with an ICU, and the result was the same as that of the original analysis (Fig. 2, eTable 5). Fourth, covariates related to therapeutic intervention were used for adjustment in the model. Although some interventions such as PCI and use of catecholamine are done prior to the decision to admit to an ICU, a fourth sensitivity analysis was performed by excluding covariates that might have occurred after hospital presentation from adjustment in the model. The result was clearly in accordance with that of the original analysis (Fig. 2, eTable 6). Fifth, the effect of unmeasured confounding must not be ignored. Unmeasurable covariates such as the preference of patients to receive aggressive care, emergency medical services' selection of hospital to transfer, and hospital norms have significant impact on outcomes. In addition, the proportion of cardiac ICUs among ICUs was unknown, and the specialty of the physicians working in the unit, cardiologist, intensivist, or both, was unknown as well. Since it is impossible to adjust for the unmeasured or unmeasurable confounding, the effect of the ICU admission should be taken conservatively. Sixth, the cause of death was unknown. There is no information about the cause of death in DPC data. Information about cardiac or non-cardiac death and their proportions in the ICU and non-ICU groups could have given an important implication in combination with staffing and specialty of physicians. At last, the difference in ICU bed availability, ICU requirements both in staffing and in structure [39], and patient population across countries should be taken into an account. PCIs have been performed in 85% of the whole population in this study, and the results are based on high proportion of PCI being performed. The regulations regarding ICUs may be different between countries. For example, ICU bed availability is 8 per 100,000 people in Japan, whereas it is 20–30 in the USA [40]. Disease prevalence and demographics of patients admitted to the ICU are reportedly different as well [41]. Thus, the generalizability of the findings in different settings is not fully guaranteed.

Although there were some limitations, this study is novel and has several strengths that previous studies could not achieve. This is the largest scale multi-center observational study, with important clinical information to adjust for patient and hospital characteristics. The population of this study reflects a whole array of AMI patients and contemporary practice in Japan.

Since some questions remain unanswered, future studies investigating how the ICU accounts for the mortality benefit and subsets of patients who might benefit the most from ICU admission are warranted.

## Conclusions

In patients who developed AMI, ICU admission was associated with a lower 30-day mortality.

## Funding

This research received no grant from any funding agency in the public, commercial or not-for-profit sectors.

## Conflict of interests

KK received honoraria from Astellas, Eisai, Abbie, Takeda Pharmaceutical Company Limited, Novartis KK, Santen, Bayer Yakuhin, Sanofi K.K., Kyowa Hakko Kirin, Otsuka Pharmaceutical; consult fees from Olympus and Kaken Pharmaceutical. There are no patents, products in development or marketed products to declare, relevant to those companies. Other authors declare that there is no conflict of interests.

## Acknowledgments

No information reported in the article has been presented in scientific meetings.

We would like to thank Editage (www.editage.jp) for English language editing.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.01.007.

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