The Efficacy of Acute Myocardial Infarction Intensive Care Unit Management with a Collaborative Intensivists and Cardiologists in Japan: A Retrospective Observational Study

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Abstract:
Objective Dedicated intensive care unit (ICU) physician staffing is associated with a reduction in ICU mortality rates in general medical and surgical ICUs. However, limited data are available on the role of intensivists in ICU for cardiac disease, especially in Japan. This study investigated the association of collaborative intensivists and cardiologist care with clinical outcomes in patients with acute myocardial infarction (AMI) admitted to the ICU.

Methods This study analyzed 106 patients admitted to the ICU at Nara Prefecture General Medical Center in Nara, Japan, from April 2017 to April 2019. Eligible patients were divided into either the high-intensity ICU management group (n=51) or the low-intensity ICU management group (n=55). The primary outcome of in-hospital mortality was compared in the two groups.

Results The high-intensity ICU group was found to be associated with a lower mortality rate in a multivariate analysis than the low-intensity group [7.8% vs. 16.4%; odds ratio (OR): 0.07; 95% confidence interval (CI): 0.01-0.54; p=0.01]. There were no significant differences in the length of either the ICU stay or hospital stay or the hospital costs between the two groups. A subgroup analysis revealed that the in-hospital mortality rate was lower in the high-intensity ICU group than in the low-intensity ICU group among patients with Killip class IV (16.7% vs. 34.6%; OR, 0.08; 95% CI, 0.01-0.67; p=0.02).

Conclusion The presence of dedicated intensivists in high-intensity ICU collaborating with cardiologists might reduce in-hospital mortality in patients with Killip class IV AMI who require critical care.

Key words: acute myocardial infarction, intensivists, cardiologists, collaborative management

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Introduction

Acute myocardial infarction (AMI) due to sudden coronary artery occlusion or spasm is one of the most life-threatening diseases in the world. Although early reperfusion therapy as percutaneous coronary intervention (PCI) is important, systemic management is even more important in severe patients with cardiogenic shock and respiratory failure treated with several mechanical devices such as non-invasive positive pressure ventilation (NPPV), mechanical ventilation (MV), intra-aorta balloon pumping (IABP) or veno-arterial extracorporeal membrane oxygenation (VA-ECMO).

High-intensity intensive care unit (ICU) physician staffing, which is defined as the presence of a dedicated ICU and mandatory intensivist consultation, has been implemented in several general medical and surgical ICUs in an effort to improve clinical outcomes in patients with critical illnesses (1, 2). Furthermore, the efficacy of the high-intensity ICU in neuro intensivist-managed care for severe
neurological diseases has been reported (3, 4). High-intensity ICU staffing was associated with a significant decrease in ICU mortality rates in several critical illnesses (1-4). The presence of a cardiac intensivist has been shown to reduce cardiac ICU mortality (5), and collaboration between intensivists and cardiologists or cardiointensivists has improved the cardiac ICU outcomes (6).

However, no data are available on the role of high-intensity ICU staffing by intensivists in the management of AMI in Japan.

The present study evaluated the efficacy of collaborative management care between intensivists and cardiologists on clinical outcomes for patients with AMI admitted to the ICU.

Materials and Methods

Study design and setting

This single-center retrospective observational study consisted of adult patients who were hospitalized with a confirmed diagnosis of AMI, including ST-segment elevated myocardial infarction (STEMI) and non-ST-segment elevated myocardial infarction (NSTEMI), between April 1, 2017, and May 31, 2019, at Nara Prefecture General Medical Center in Japan.

Nara Prefecture General Medical Center was renewed and relocated in May 2018 and changed its operation from the low-intensity ICU (eight beds) to the high-intensity ICU (eight beds) with dedicated intensivist physician staffing. Intensivists in the high-intensity ICU functioned mainly as the primary attending physician for all patients in the ICU, including managing inotropes or vasopressors and mechanical devices, such as IABP, VA-ECMO, NPPV, and MV. Mechanical support was decided mainly by the cardiologist before admission to the ICU; when such support was deemed necessary after admission to the ICU, the decision was made in consultation between the intensivist and cardiologist.

The low-intensity ICU comprised five cardiologists who were board-certified members of the Japanese Circulation Society and one senior resident. The high-intensity ICU, conversely, comprised six members, including two emergency physicians who were board-certified members of the Japanese Association for Acute Medicine; one intensivist who was a board-certified member of the Japanese Association for Acute Medicine and the Japanese Society of Intensive Care Medicine; one intensivist who was a board-certified member of the Japanese Association for Acute Medicine and the Japanese Society of Anesthesiologist; one cardiac intensivist who was a board-certified member of the Japanese Association for Acute Medicine; the Japanese Society of Intensive Care Medicine, and the Japan Society of Anesthesiologists; one cardiac intensivist who was a board-certified member of the Japanese Circulation Society and the Japanese Society of Intensive Care Medicine; and one senior resident.

The high-intensity ICU staff were assigned to the ICU all day in order to attend to and manage the patients, while low-intensity ICU staff were assigned only during the day-time by the cardiologist in charge.

All data were collected retrospectively by reviewing medical records.

Study participants and inclusion criteria

We included all patients of ≥18 years old who were diagnosed with AMI. We enrolled 183 consecutive patients admitted to the hospital at Nara Prefecture General Medical Center in Nara, Japan, from April 1, 2017, to May 31, 2019. However, April 2018 was excluded because of limited medical care due to preparations for the hospital relocation. The criteria for admission to the ICU were all patients with a diagnosis of AMI. However, if the ICU beds were full or the cardiologist made the decision based on a patient’s general condition, palliative care was to be provided, and patients were admitted to the high care unit or the general ward.

Among these patients, 77 (including 38 patients admitted between April 1, 2017, and March 31, 2018, and 39 patients admitted between May 1, 2018, and April 30, 2019) who were not admitted to the ICU were excluded, and the remaining 106 patients were analyzed in this study. No patients admitted to ICU were withdrawn from treatment during the period of this study. Patients were classified into 1 of 2 study periods depending on their admission date, as follows: low-intensity ICU (cardiologist-managed ICU) group of the 55 patients admitted between April 1, 2017, and March 31, 2018; and high-intensity ICU (cardiologist-and-intensivist-managed ICU) group of the 51 patients admitted between May 1, 2018, and April 30, 2019 (Figure).

Data sampling

The following data were collected: age, sex, medical history, Killip classification, STEMI, NSTEMI, door to balloon time, infarct-related artery, final Thrombolysis In Myocardial Infarction (TIMI) flow grade, Global Registries of Acute Coronary Events (GRACE) Acute Coronary Syndrome (ACS) score, treatment modality (PCI, IABP, VA-ECMO, NPPV, MV), in-hospital mortality, length of ICU stay, length of hospital stay, and hospital costs.

Outcome measures

The primary outcome was in-hospital mortality. The secondary outcome was the length of ICU stay, length of hospital stay, and hospital costs.

Statistical analyses

All baseline characteristics, including clinical variables, laboratory parameters, and radiological data, were compared between patients in the low-intensity ICU and those in the high-intensity ICU. The distribution of each variable was compared between the two groups (low- and high-intensity ICU). Continuous variables are expressed as the median with the interquartile range (IQR) for normally distributed and non-normally distributed variables, respectively, whereas categorical variables are expressed as the frequency and percentage. Univariate analyses were conducted by using...
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Mann-Whitney U tests or Fisher exact tests, depending on variables. The multivariable logistic regression model used variables with p<0.20 in univariable analyses as clinically significant or having potential associations. Multivariable logistic regression analyses were conducted to explore the prognostic factors among the age, sex, NPPV, MV, and IABP in AMI patients overall as well as in the subcategories of Killip class (I-IV).

All statistical analyses were performed with EZR (Jichi Medical University Saitama Medical Center, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. A two-sided p value less than 0.05 was considered statistically significant.

\section*{Results}

Among the 106 patients included in this study, 55 were admitted to the low-intensity ICU and 51 to the high-intensity ICU. The baseline clinical characteristics, including the age, sex, and medical history (Table 1); cardiovascular state that led to ICU admission, including STEMI, NSTEMI, and in- and out-of-hospital cardiopulmonary arrest; Killip classification; door to balloon time; infarct-related artery; PCI; final TIMI flow grade; maximum creatine kinase (CK) and CK-MB levels; GRACE ACS score, and mechanical devices used (IABP, VA-ECMO, NPPV, MV), were not markedly different between the two groups (Table 2). In the univariate analysis, the primary outcome of in-hospital mortality in the high-intensity ICU group was not significantly better than in the low-intensity ICU group (7.8% vs. 16.4%, respectively, p=0.19) (Table 3). However, according to the multivariate logistic regression analysis after adjusting for the age, sex, door to balloon time, IABP, and NPPV, high-intensity ICU admission for patients with AMI was significantly associated with a reduced in-hospital mortality [odds ratio (OR): 0.07; 95% confidence interval (CI): 0.01-0.54; p=0.01; Table 3]. These results are explained by the subgroup analysis of the Killip classification described below.

The secondary outcomes of the length of ICU stay, length of hospital stay, and hospital costs were analyzed. High-intensity ICU admission was not significantly associated with the length of ICU stay or length of hospital stay [median (IQR), 3.0 (2.0-4.0) days vs. 2.0 (2.0-4.0) days, p=0.39; 15.0 (12.0-18.5) days vs. 16.0 (12.0-22.0) days, p=0.59, respectively; Table 2]. There were also no significant differences between the groups in total hospital costs [median (IQR) $22,307 ($17,055-$28,704) vs. $20,926 ($15,494-$27,923); p=0.41; Table 2].

We conducted a subgroup analysis by Killip classification. In the subgroup analysis of patients with Killip class I to III, high-intensity ICU admission was not significantly associated with in-hospital mortality reduction due to no hospital deaths being recorded in these classes in either group (Table 4). Although the proportion of patients with Killip class IV in the univariate analysis showed no significant differ-
Table 1. Baseline Clinical Characteristics of the Patients in the Low- and High-intensity ICU Groups.

|                        | High-intensity ICU (n=51) | Low-intensity ICU (n=55) | p value |
|------------------------|---------------------------|--------------------------|---------|
| Sex, men, n (%)        | 38 (74.5)                 | 40 (72.7)                | 1.00    |
| Age, median (IQR)      | 68 (60-78)                | 74 (66-81)               | 0.06    |
| Smoke, n (%)           | 31 (60.8)                 | 30 (54.5)                | 0.56    |
| BMI, mean (kg/m²)      | 24.3 (21.8-25.6)          | 23.1 (21.3-25.4)         | 0.64    |
| Diabetes mellitus, n (%) | 19 (37.3)              | 29 (47.3)                | 0.12    |
| Dyslipidemia, n (%)    | 38 (74.5)                 | 34 (61.8)                | 0.21    |
| COPD, n (%)            | 2 (3.9)                   | 2 (3.6)                  | 1.00    |
| Ischemic stroke, n (%) | 4 (7.8)                   | 8 (14.5)                 | 0.36    |
| Hypertension, n (%)    | 42 (82.4)                 | 43 (78.2)                | 0.63    |
| Coronary artery disease, n (%) | 13 (25.5)       | 12 (21.8)                | 0.82    |
| Chronic heart failure, n (%) | 4 (7.8)             | 6 (10.9)                 | 0.74    |
| Arrhythmia, n (%)      | 5 (9.8)                   | 6 (10.9)                 | 1.00    |
| Atrial fibrillation, n (%) | 3 (5.9)              | 3 (5.5)                  | 1.00    |
| Chronic kidney disease, n (%) | 22 (43.1)            | 18 (32.7)                | 0.32    |
| Hemodialysis, n (%)    | 3 (5.9)                   | 3 (5.5)                  | 1.00    |
| Hyperuricemia, n (%)   | 9 (17.6)                  | 10 (18.2)                | 1.00    |

BMI: body mass index, COPD: chronic obstructive pulmonary disease, IQR: interquartile range, ICU: intensive care unit

ence between the two groups (16.7% vs. 34.6% respectively, p=0.15; Table 4), a multivariate logistic regression analysis with adjusting for the age, sex, door to balloon time, IABP, and NPPV revealed that high-intensity ICU management reduced in-hospital mortality (OR, 0.08; 95% CI, 0.01-0.67; p =0.02; Table 5).

Discussion

This study is the first report to evaluate the efficacy of intensivists’ and cardiologists’ collaborative intervention for patients with AMI in Japan. In the current study, high-intensity ICU admission did not improve the clinical outcome of in-hospital mortality in AMI patients overall; however, in a subgroup analysis, improvements were observed in AMI patients with Killip class IV. The difference in mortality was not statistically significant, but the lack of p<0.05 may be due to sampling size.

There was no notable effect of intensivists’ intervention on in-hospital mortality in patients with Killip class III or lower, the ICU stay, or the hospital stay. Several reasons have been proposed for the difference in mortality in Killip class IV. First, we considered the differences in the quality of multiple device management, including MV, IABP, and VA-ECMO; however, there were no significant differences in the 28-day MV-free days, 28-day IABP free-days, and 28-day VA-ECMO free-days between the groups (Table 2). The only difference was seen in the ratio of MV to NPPV, which suggested that cardiologists were characterized by a higher rate of NPPV, while intensivists were characterized by a higher rate of MV management (Table 2). This might suggest that for Killip class IV patients in cardiogenic shock with hypoxia or disturbance of consciousness, MV management may have been more effective than NPPV for providing appropriate respiratory management.

Patients with cardiogenic shock are often hemodynamically unstable after catheterization and require continuous management. In critically ill patients, both circulatory and respiratory conditions should be treated simultaneously, as they are closely related interactions. Intensivists might be more familiar with MV management than cardiologists. For instance, MV settings, such as positive end-expiratory pressure settings, to improve pulmonary congestion, or lung recruitment maneuvers or sucking with bronchoscopy for phlegm collected in the trachea may have been more intensively implemented than cardiologists. Interestingly, there have been few reports on the frequency of NPPV or MV usage among patients with Killip class IV.

The second proposed reason is that the selection and dosage of inotropes, vasopressors, sedatives, and analgesics may have affected the mortality. Although there were potential confounding factors in these treatments, we did not investigate these detailed differences in the present study. The third proposed reason is that intensivists, who serve in the ICU all day, may have good familiarity with multiple-device management and be able to respond quickly to changes in vital signs, physical findings, adjustment of multiple drugs, MV, and ECMO settings. Therefore, high-intensity ICUs supposed that the early detection of critical complications followed by appropriate intervention contributed to a better outcome. The fourth proposed reason is that there may have been some differences in the characteristics of patients after post-ICU admission between the two groups that could not be demonstrated by the Killip classification. We evaluated the GRACE ACS risk score, final TIMI flow grade, CK, and CK-MB level in addition to Killip classification; however,
Table 2. The Comparison of the Outcomes among Patients in the Low- and High-intensity ICU Groups.

|                     | High-intensity ICU (n=51) | Low-intensity ICU (n=55) | p value |
|---------------------|---------------------------|--------------------------|---------|
| STEMI, n (%)        | 46 (90.2)                 | 48 (87.3)                | 0.76    |
| NSTEMI, n (%)       | 5 (9.8)                   | 7 (12.7)                 | 0.76    |
| Out-of-hospital CPA, n (%) | 9 (17.6)             | 5 (9.1)                  | 0.25    |
| In-hospital CPA, n (%) | 5 (9.8)               | 4 (7.3)                  | 0.74    |
| Killip classification |                           |                          |         |
| Class I, n (%)      | 15 (29.4)                 | 17 (30.9)                | 1.00    |
| Class II, n (%)     | 4 (7.8)                   | 5 (9.1)                  | 1.00    |
| Class III, n (%)    | 8 (15.7)                  | 7 (12.7)                 | 0.78    |
| Class IV, n (%)     | 24 (47.1)                 | 26 (47.3)                | 1.00    |
| Door to balloon time (min), median (IQR) | 101 (79-166)            | 86 (64-137)              | 0.07    |
| Infarct-related artery |                        |                          |         |
| Left anterior descending coronary artery, n (%) | 21 (41.2)             | 28 (50.9)                | 0.34    |
| Right coronary artery, n (%)            | 25 (49)                  | 20 (36.4)                | 0.24    |
| Circumflex artery, n (%)                  | 6 (11.8)                 | 6 (10.9)                 | 1.00    |
| Other, n (%)                          | 0 (0)                    | 1 (1.8)                  | 1.00    |
| PCI, n (%)                            | 44 (86.3)                | 50 (90.9)                | 0.55    |
| Final TIMI flow grade |                        |                          |         |
| Grade 0, n (%)         | 1 (2.0)                  | 2 (3.6)                  | 1.00    |
| Grade 1, n (%)         | 3 (5.9)                  | 2 (3.6)                  | 0.67    |
| Grade 2, n (%)         | 9 (17.6)                 | 6 (10.9)                 | 0.41    |
| Grade 3, n (%)         | 45 (89.1)                | 38 (74.5)                | 0.48    |
| Maximum CK level (U/L), median (IQR) | 2,064 (850-3,625)       | 2,264 (1,005-5,260)      | 0.24    |
| Maximum CK-MB level (U/L), median (IQR) | 180 (77-363)            | 229 (103-455)            | 0.46    |
| GRACE ACS score, median (IQR) | 163 (123-207)         | 165 (139-203)            | 0.73    |
| GRACE ACS score in Killip class I, median (IQR) | 110 (96-147)          | 133 (113-149)            | 0.43    |
| GRACE ACS score in Killip class II, median (IQR) | 117 (107-123)        | 137 (130-149)            | 0.26    |
| GRACE ACS score in Killip class III, median (IQR) | 152 (146-184)        | 163 (161-181)            | 0.60    |
| GRACE ACS score in Killip class IV, median (IQR) | 207 (185-215)        | 204 (183-222)            | 0.98    |
| IABP, n (%)                     | 18 (35.5)                | 12 (21.8)                | 0.14    |
| VA-ECMO, n (%)                 | 4 (7.8)                  | 4 (7.3)                  | 1.00    |
| NPPV, n (%)                   | 2 (3.9)                  | 9 (16.4)                 | 0.05    |
| MV, n (%)                     | 14 (27.5)                | 9 (16.4)                 | 0.24    |
| 28-day MV-free days, median (IQR) | 24 (22-26)              | 23 (18-24)               | 0.9     |
| 28-day IABP free-days, median (IQR) | 25 (24-26)              | 25 (24-26)               | 0.51    |
| 28-day VA-ECMO free-days, median (IQR) | 24 (23-25)              | 25 (24-26)               | 0.45    |
| In-hospital mortality, n (%)     | 4 (7.8)                  | 9 (16.4)                 | 0.14    |
| Length of ICU stays, median (IQR) | 3 (2-4)                  | 2 (2-4)                  | 0.39    |
| Length of hospital stays, median (IQR) | 15 (12-19)              | 16 (12-22)               | 0.59    |
| Hospital costs ($), median (IQR) | 22,307 (17,055-28,704) | 20,926 (15,494-27,923)   | 0.41    |

CPA: cardiopulmonary arrest, IQR: interquartile range, TIMI: Thrombolysis In Myocardial Infarction, GRACE: Global Registries of Acute Coronary Events, ICU: intensive care unit

Table 3. Results of a Multivariate Logistic Regression Analysis of the In-hospital Mortality.

|                        | Univariate analysis |                        | Multivariate analysis |                        |
|------------------------|---------------------|------------------------|-----------------------|------------------------|
|                        | OR      | 95% CI | p value | OR      | 95% CI | p value |
| High-intensity ICU     | 0.44    | 0.13-1.5 | 0.19      | 0.07    | 0.01-0.54 | 0.01   |
| Age median, (IQR)      | 1.0     | 0.97-1.1 | 0.34      | 0.96    | 0.89-1.0 | 0.30   |
| Sex men, n (%)         | 0.25    | 0.08-0.83 | 0.02      | 0.13    | 0.02-0.68 | 0.02   |
| Door to balloon time, median (min) | 1.0     | 0.99-1.0 | 0.07      | 1.01    | 1.00-1.02 | 0.02   |
| IABP, n (%)            | 7.7     | 2.2-27 | <0.01     | 29      | 4.5-186 | <0.01   |
| NPPV, n (%)            | 1.7     | 0.32-8.9 | 0.53      | 0.22    | 0.02-2.1 | 0.19   |

IQR: interquartile range
there were no significant differences between the two groups (Table 2). This current study also compared the length of hospital stay and hospital costs between the two groups. An increased survival would likely increase the length of stay and hospital costs. Therefore, the lack of a decrease in either the length of hospital stay or hospital costs with the intensivist model is reasonable, as long as the mortality improved.

Although literature demonstrating the efficacy of critical care for cardiac disease patients is limited to studies conducted in only a few faculties (5, 6), the reduction in cardiac ICU mortality rates associated with a high-intensity setting may be related to the multidisciplinary approach to the treatment of ECMO in patients with refractory cardiogenic shock (7, 8). The American Heart Association suggested that high-intensity management led by a cardiac intensivist or co-directorship with a non-intensivist cardiologist and a general intensivist was the optimal organizational structure in a level 1 cardiac ICU, which can manage all types of cardiovascular disease and comorbidities and has all forms of monitoring capabilities and advanced therapeutic technologies, including ventricular assist devices (9). There are few accredited dual training pathways in cardiovascular and critical care medicine in the United States (10) and Japan. The organization of cardiac disease care is quite different between the United States and Japan. Cardiac intensivists need to be trained in emergency medicine, internal medicine, anesthesiology, cardiology, and cardiovascular surgery. In Japan, an official board certification system for cardiac intensivists has not yet been developed. In the future, it will be important to be a trained cardiac intensivist as well as to engage in collaborative management between intensivists and cardiologists. Given the present results, high-intensity ICU staffing for AMI with Killip class IV may be the most feasible staffing model.

Finally, we should not emphasize the significant difference in mortality for Killip class IV in the sample size of this study; however, it should be noted that intervention by intensivists showed non-inferior outcomes with regard to in-hospital mortality compared to cardiologists’ management of AMI in the ICU.

Several limitations associated with the present study warrant mention. First, it was retrospectively conducted in a single center, which introduces a potential selection bias. Furthermore, uncontrolled confounding factors may exist. Second, changes in medications, procedures, relocated facilities, and ICU experience may have contributed to the improved outcomes in the postintervention group. These confounders may be the mediators/effects of the intensivist model. Third, we were unable to follow patients concerning their outcomes after discharge. Fourth, we cannot exclude the possibility that changes in the patient population influenced the outcomes. For example, comorbidities were not examined in the current study. Finally, the sample size in this study was small.

**Conclusion**

The presence of dedicated intensivists in a high-intensity ICU collaborating with cardiologists might reduce in-hospital mortality in AMI patients with Killip class IV who require critical care. This study suggests that a system wherein intensivists and cardiologists collaborate has a favorable impact on the quality of care for severe AMI, and
its implementation in the Japanese medical system may be effective. However, further prospective studies in a larger study population with a multicenter setting will be necessary to clarify the relationship between intensivists in a high-intensity ICU along with cardiologists and mortality in cardiac disease.

The authors state that they have no Conflict of Interest (COI).

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