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ORIGINAL ARTICLE
Coronary artery disease

Resources for cardiovascular healthcare associated with 30-day mortality in acute myocardial infarction with cardiogenic shock

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Aims Although primary percutaneous coronary intervention (PCI) and mechanical circulatory support (MCS), such as extracorporeal membrane oxygenation (ECMO) or intra-aortic balloon pumping (IABP), have been widely used for acute myocardial infarction (AMI) patients with cardiogenic shock (AMICS), their in-hospital mortality remains high. This study aimed to investigate the association of cardiovascular healthcare resources with 30-day mortality in AMICS.

Methods and results This was an observational study using a Japanese nationwide administrative data (JROAD-DPC) of 260 543 AMI patients between April 2012 and March 2018. Of these, 45 836 AMICS patients were divided into three categories based on MCS use: with MCS (ECMO with/without IABP), IABP only, or without MCS. Certified hospital density and number of board-certified cardiologists were used as a metric of cardiovascular healthcare resources. We estimated the association of MCS use, cardiovascular healthcare resources, and 30-day mortality. The 30-day mortality was 71.2% for the MCS, 23.9% for IABP only, and 37.8% for the group without MCS. The propensity score-matched and inverse probability-weighted Cox frailty models showed that primary PCI was associated with a low risk for mortality. Higher hospital density and larger number of cardiologists in the responsible hospitals were associated with a lower risk for mortality.

Conclusion Although the 30-day mortality remained extremely high in AMICS, indication of primary PCI and improvement in providing cardiovascular healthcare resources associated with the short-term prognosis of AMICS.

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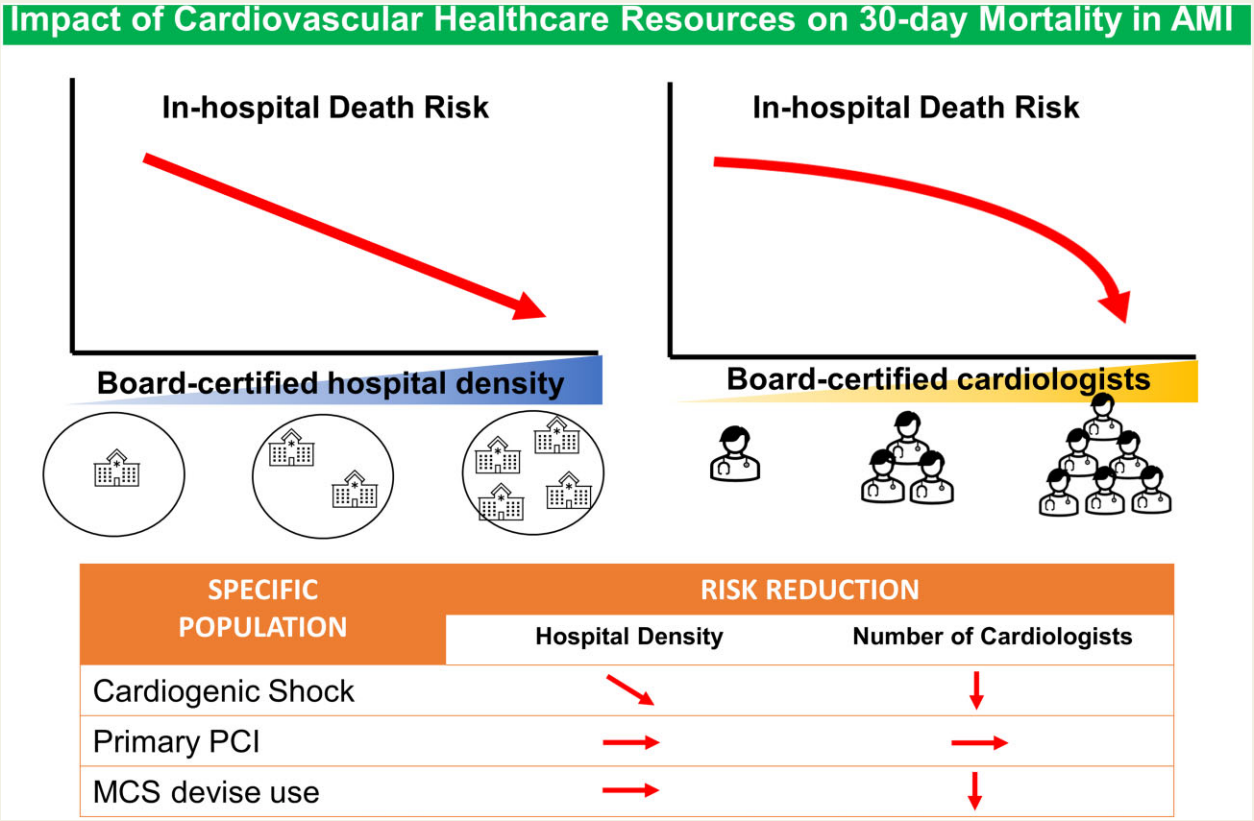
Graphical Abstract



Keywords Acute myocardial infarction • Cardiogenic shock • Primary PCI • Cardiovascular healthcare resources

Introduction

The short-term prognosis of acute myocardial infarction (AMI) has been improved using optimal medical therapies such as antithrombotic therapy and early revascularization, particularly indicative of primary percutaneous coronary intervention (PCI). However, among them, 6.9–15.2% are critically ill patients with AMI complicated by cardiogenic shock (CS),[1–4] and their in-hospital mortality rate is as high as 39–45%,[3–5] which makes it the leading cause of mortality in AMI patients. In addition, accumulating evidence suggests increased trends in incidence rates of CS,[1,4,6] particularly in the older than in the younger population.[4] In a super-ageing society, such as that of Japan, the incidence rate of AMI has increased significantly with ageing.[7] Therefore, as the incidence rate of older patients with AMI complicated by CS increases in countries with an ageing population, measures must be taken to improve the survival rate of those patients.

To improve the survival rate of patients with AMI complicated by CS, mechanical circulatory support (MCS) devices such as extracorporeal membrane oxygenation (ECMO), a catheter-based micro-axial flow pump, Impella (Abiomed, Danvers, MA, USA), or intra-aortic balloon pumping (IABP) have been widely used[8–10]; however, the short-term mortality rate remains high, leaving room for intervention for improving survival.

It is crucial to consider the medical healthcare provision system for implementing measures for the improvement of survival. Several previous studies have reported that a larger number of cardiologists per hospital was associated with a lower risk of in-hospital mortality in AMI patients.[11,12] However, owing to limited cardiology-related resources, it would be challenging to have catheter laboratories and numerous cardiologists in all hospitals. It would be ideal to strike a balance between the increasing demand for cardiologists and curbing the growing burden of cardiovascular disease worldwide.[13] Thus, implementing appropriate cardiovascular healthcare, such as easy access to hospitals or sufficient cardiovascular workforce, should be clarified. This study aimed to investigate the association between cardiovascular healthcare resources (i.e. density of cardiovascular hospitals in a local

area and the number of cardiologists per hospital) and the 30-day mortality in patients with AMI complicated by CS.

Methods

Study design, setting, and study population

This retrospective, observational study was performed using a nationwide Japanese administrative case-mix Diagnostic Procedure Combination (DPC), from the Japanese Registry Of All cardiac and vascular Disease (JROAD)-DPC.[14–18] In brief, the JROAD-DPC database contains DPC-based payment health insurance claims data on hospitalization due to cardiovascular diseases collected from 1040 Japanese Circulation Society (JCS)-certified hospitals between April 2012 and March 2018. Using the International Classification of Disease, 10th Revision (ICD-10) codes of I21.0, I21.1, I21.2, I21.3, I21.4, and I21.9 for AMI hospitalization recorded as 'the main diagnosis', 'the admission precipitating diagnosis', or 'the most resource-consuming diagnosis' in the DPC claims data, 260 543 AMI patients aged ≥20 years were identified. ICD-10 codes for AMI were validated in the JROAD-DPC database, as previously described.[19] Of these patients, 28 350 were excluded due to the missing value of the Killip classification. The remaining participants were divided into two groups based on the Society for Cardiovascular Angiography and Interventions (SCAI) stages of CS.[20] The CS equivalent to the SCAI C/D/E group were defined as Killip III that met at least one of the following criteria: (i) MCS use or (ii) intravenous administration of catecholamines on admission, or Killip IV, whereas others were defined as non-CS equivalent to SCAI A/B group. The CS group was further divided into three categories based on MCS use: with MCS (ECMO with/without IABP), IABP only, or without MCS. The baseline participant information and variables were extracted from the JROAD-DPC database, and the details are shown in the Supplementary material online, *Methods*.

Outcome

The primary outcome was the 30-day all-cause mortality. The secondary outcome was the 7-day mortality and in-hospital mortality. The date of survival discharge was used as the date of censor in cases where no information about survival or death of the patients after discharge was available.

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and its amendments. The ethics committees at Miyazaki Prefectural Nobeoka Hospital (No. 20200721-1), Kawasaki Medical School (No. 3928), and Kumamoto University Hospital (No. 2095) approved the study protocol. The study was exempted from the requirement for individual informed consent owing to the opt-out policy, i.e. participants were notified of their participation in this study through the website (https://nobeoka-kenbyo.jp/sinryoka/junkankika/ 03 July 2021) and could refuse the use of their information from the database.

Statistical analysis

Data were presented as the median and interquartile range (IQR) for continuous variables, and number (percentage) for categorical variables. To estimate the hazard ratios and 95% confidence intervals (95% CIs) for associated factors of all-cause mortality, a Cox frailty model was used with random effects to account for institution-related variation.[21] The following variables were used as adjusted factors in the multivariable analysis to perform group comparison for MCS use: (i) Model 1 included age category, sex, total score of the Barthel index at admission, Killip classification, comorbidities (as mentioned above), cardiac arrest at admission, and hospital characteristics [hospital with ≥500 beds, number of board-certified cardiologists (BCC), hospital with coronary care unit, hospital with cardiac surgery, regional ageing rate, and JCS-certificated hospital density], (ii) Model 2 included age category, sex, total score of the Barthel index at admission, Killip classification, cardiac arrest at admission, and hospital characteristics, and (iii) Model 3 included age category, sex, total score of the Barthel index at admission, Killip classification, comorbidities, and cardiac arrest at admission.

To estimate the effect of primary PCI on 30-day mortality in AMI patients with CS, propensity score matching was performed to reduce the effect of known possible confounders. Of 45 836 patients with CS group, 2294 were excluded from receiving coronary artery bypass grafting; finally, 43 542 patients were included in this analysis. The predicted probability of receiving primary PCI was calculated by applying a logistic regression model using all clinically relevant variables such as age, sex, activities of daily living, Killip classification, comorbidities, cardiac arrest at admission, MCS use, and hospital characteristics. One primary PCI group participant was matched with one participant in the non-primary PCI group using nearest-neighbour matching within a caliper width of 0.2 standard deviation without replacement. A comparison of the baseline characteristics between the primary PCI group and the non-primary PCI group in the matched cohort was performed using the absolute standardized mean difference, whereby an absolute standardized difference >0.10 represented meaningful imbalance. In addition, to confirm the results' robustness, inverse probability of treatment weighting (IPTW) with the same predicted probability used in the propensity score matching was performed as sensitivity analysis for the same outcome.

To estimate the association between cardiovascular healthcare resources and the outcome, a Cox frailty model with random effects to account for institution-related variation was applied. Hazard ratios and 95% CIs for risk of 30-day mortality were calculated with reference to a group of ≤2 BCC in the first quartile of hospital density. A two-sided *P*-value of <0.05 was considered significant. All statistical analyses were conducted using SAS9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Between April 2012 and March 2018, 45 836 (19.7%; age, median 74, IQR 65–82) patients with CS and 186 357 (80.3%; age, median 70, IQR 60–79) without CS were admitted at JCS-certified hospitals (*Figure 1*). The proportion of CS patients did not seem to change significantly annually; however, older female patients had a higher proportion of CS (Supplementary material online, *Figure S1*). The proportion of CS patients among AMI patients tended to be lower in the higher board-certified hospital density or with a larger number of BCCs than in the lower board-certified hospital density or with a smaller number of BCCs (Supplementary material online, *Figure S1*). Of the CS patients, 4437 (9.7%) received MCS (ECMO with/without IABP), 16 119 (35.2%) received IABP only, and 25 280 (55.2%) did not receive MCS. Although the proportion of MCS use did not seem to change significantly annually, younger male patients had a higher proportion of MCS use (*Figure 2*). The proportion of MCS use among AMI patients complicated by CS tended to be higher in the higher board-certified hospital density or with a larger number of BCCs than in the lower board-certified hospital density or with a smaller number of BCCs (*Figure 2*). In regard to clinical characteristics (*Table 1*), MCS patients tended to

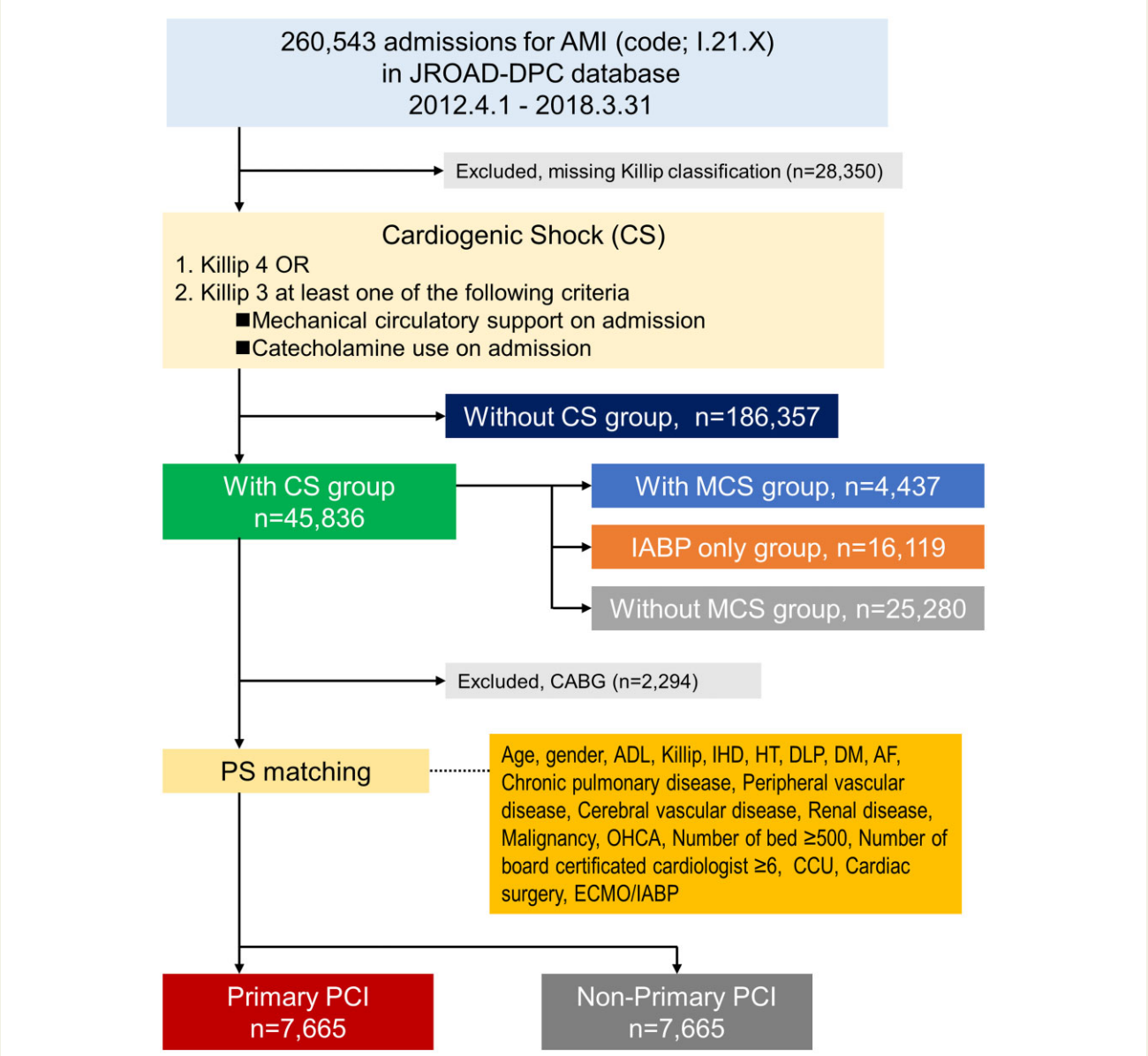


Figure 1 Study flow chart. This chart shows the enrolment criteria and the flow of acute myocardial infarction patients complicated by cardiogenic shock who were divided into three groups according to the mechanical circulatory support use on admission. ADL, activities daily of living; AF, atrial fibrillation; AMI, acute myocardial infarction; CABG, coronary artery bypass graft surgery; CCU, coronary care unit; CS, cardiogenic shock; DLP, dyslipidaemia; DM, diabetes mellitus; DPC, Diagnosis Procedure Combination; ECMO, extracorporeal membrane oxygenation; HT, hypertension; IABP, intra-aortic balloon pumping; IHD, ischaemic heart disease; JROAD, Japanese Registry Of All cardiac and vascular Disease; MCS, mechanical circulatory support; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; PS, propensity score.

be younger and male and were less likely to have coronary risk factors, such as hypertension, dyslipidaemia, and diabetes mellitus. In addition, those patients tended to present anterior myocardial infarction and cardiac arrest at admission were more likely to receive primary PCI, have higher rate of achieving door-to-balloon time within 90 min, and were treated in a hospital with larger number of beds and BCC. Conversely, patients without MCS tended to be older and female and were less likely to have coronary angiography and revascularization than patients with MCS or IABP only.

Mechanical circulatory support and in-hospital mortality

During the study period, the 30-day mortality rate was 36.1% in AMI patients with CS, among whom 3160 (71.2%) patients with MCS, 3852 (23.9%) with IABP only, and 9552 (37.8%) without MCS were reported for in-hospital mortality within 30 days. *Figure 2* shows the difference in the 30-day mortality between patients with and without MCS stratified by sex, age, board-certified hospital density, and

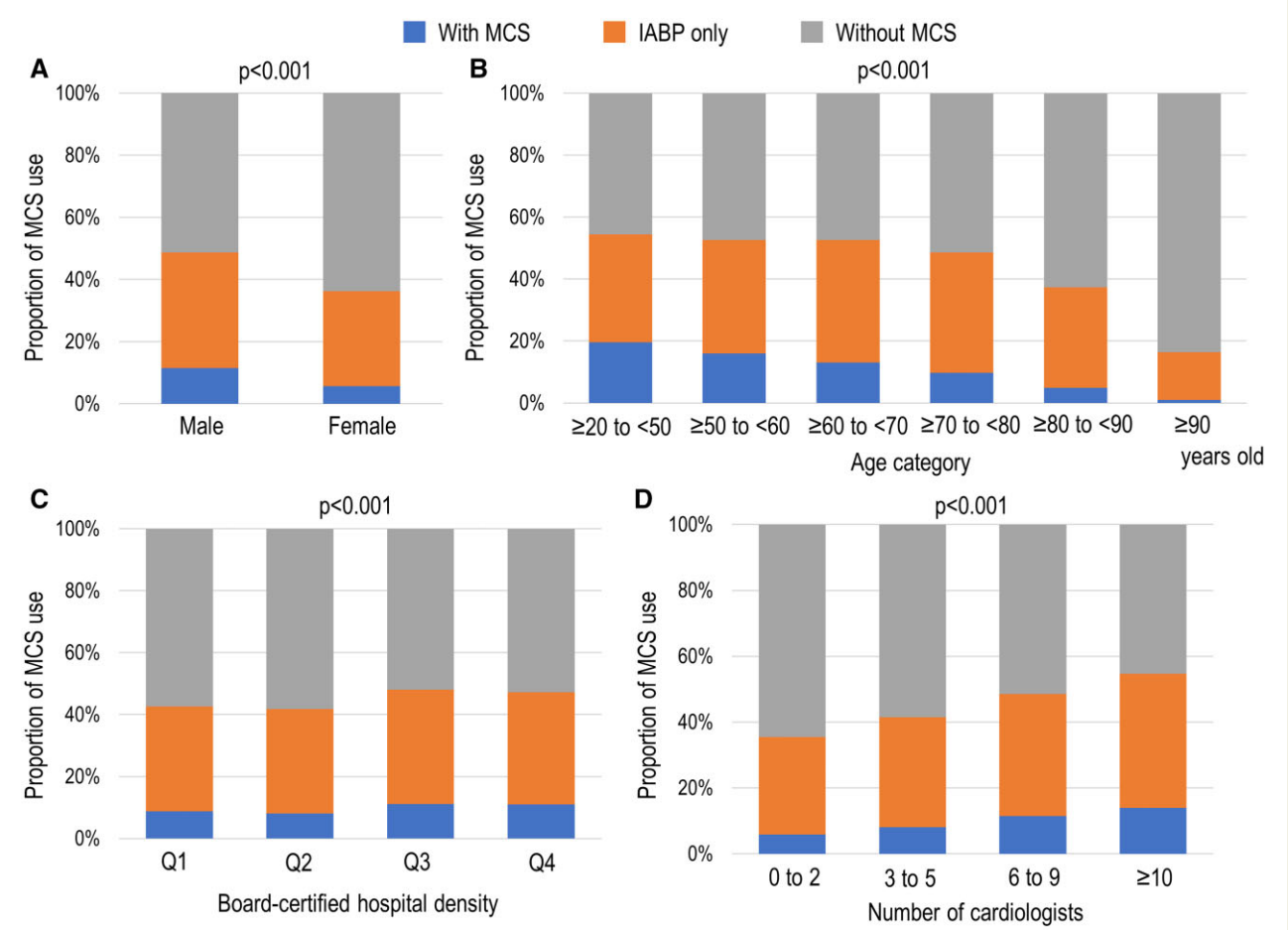


Figure 2 Proportion of mechanical circulatory support use in patients with acute myocardial infarction complicated by cardiogenic shock. This bar graph shows the proportion of mechanical circulatory support use on admission in patients with acute myocardial infarction complicated by cardiogenic shock stratified by (*A*) sex, (*B*) age category, (*C*) board-certified hospital density, and (*D*) number of cardiologists. IABP, intra-aortic balloon pumping; MCS, mechanical circulatory support.

number of BCCs. Sex difference in 30-day mortality was not observed in patients with MCS ($P = 0.158$), but the 30-day mortality was significantly lower in male patients with IABP only or without MCS than in female patients ($P < 0.001$, $P < 0.001$, respectively). In addition, the 30-day mortality tended to be lower in the higher hospital density group than in the lower group, and a similar tendency was observed in the number of BCCs (*Figure 3*). The univariate Cox frailty model showed that the patients with and without MCS were significantly associated with 30-day mortality compared with those with IABP only (*Table 2*). Furthermore, multivariable models identified that patients with and without MCS were significantly associated with a high risk of 30-day mortality compared with those with IABP only. In the stratified analysis of revascularization, patients with MCS were associated with a high risk of 30-day mortality, in consistence with the results of the entire population. On the contrary, revascularization patients without MCS were associated with a low risk of 30-day mortality, whereas patients without revascularization were associated with a high risk of 30-day mortality (*Table 2*).

After performing propensity score matching for the entire population, 7665 matched pairs of patients were identified. No significant difference was found in clinically relevant variables between patients with and without primary PCI (Supplementary material online, *Table S1*). Propensity score-matched Cox frailty model showed that primary PCI was significantly associated with a low risk of 30-day mortality, 7-day mortality, and in-hospital mortality (*Table 3*). Consistently, IPTW analysis confirmed the robustness of the association between primary PCI and a low risk of 30-day, 7-day, and in-hospital mortality in AMI patients with CS. The 30-day mortality was lower in patients with primary PCI than in those without primary PCI in any age category (Supplementary material online, *Figure S2*).

Cardiovascular healthcare resources and in-hospital mortality

Baseline characteristics according to the board-certified hospital density are shown in *Table 4*. Cardiovascular healthcare resources were assessed by investigating the association of JCS-certified

Table 1 Baseline characteristics according to the mechanical circulatory support use on admission in AMI patients with cardiogenic shock

	With MCS *n* = 4437 (9.7)	IABP only *n* = 16 119 (35.2)	Without MCS *n* = 25 280 (55.2)	*P*-value
Age, median (IQR)	67 (58–75)	73 (64–80)	77 (66–85)	<0.001
Males, *n* (%)	3633 (81.9)	11 823 (73.4)	16 284 (64.4)	<0.001
Body mass index, kg/m^2, median (IQR)	23.9 (21.6–26.3)	23.2 (20.9–25.6)	22.7 (20.3–25.2)	<0.001
Missing, *n* (%)	1098 (24.7)	2036 (12.6)	5896 (23.3)	
In-hospital days, median (IQR)	5 (2–24)	20 (12–32)	12 (2–21)	<0.001
Emergency admission, *n* (%)	4390 (99.1)	15 991 (99.3)	24 840 (98.4)	<0.001
Missing, *n* (%)	8 (0.2)	17 (0.1)	31 (0.1)	
Ambulance use, *n* (%)	3896 (88.0)	13 032 (80.9)	19 728 (78.1)	<0.001
Missing, *n* (%)	8 (0.2)	9 (0.1)	22 (0.1)	
Smoker, *n* (%)	1632 (36.8)	6566 (40.7)	8379 (33.1)	<0.001
Missing, *n* (%)	1262 (28.4)	2711 (16.8)	5630 (22.3)	
Site of myocardial infarction				
Anterior, *n* (%)	2372 (53.5)	8449 (52.4)	8767 (34.7)	<0.001
Inferior, *n* (%)	855 (19.3)	4441 (27.6)	7958 (31.5)	<0.001
Lateral and other, *n* (%)	288 (6.5)	1280 (7.9)	2000 (7.9)	0.003
Unknown, *n* (%)	950 (21.4)	2162 (13.4)	6791 (26.9)	<0.001
Door to balloon time within 90 min, *n* (%)	2489 (74.0)	8002 (68.3)	7967 (43.6)	<0.001
Full score Barthel Index at admission, *n* (%)	353 (8.0)	2351 (14.6)	3720 (14.7)	<0.001
Previous ischaemic heart disease, *n* (%)	56 (1.3)	628 (3.9)	833 (3.3)	<0.001
Hypertension, *n* (%)	914 (20.6)	7185 (44.6)	10 669 (42.2)	<0.001
Dyslipidaemia, *n* (%)	610 (13.8)	6019 (37.3)	8748 (34.6)	<0.001
Diabetes mellitus, *n* (%)	860 (19.4)	5099 (31.6)	5915 (23.4)	<0.001
Atrial fibrillation, *n* (%)	137 (3.1)	890 (5.5)	735 (2.9)	<0.001
Chronic pulmonary disease, *n* (%)	40 (0.9)	291 (1.8)	605 (2.4)	<0.001
Peripheral vascular disease, *n* (%)	177 (4.0)	559 (3.5)	970 (3.8)	0.094
Cerebrovascular disease, *n* (%)	164 (3.7)	859 (5.3)	1718 (6.8)	<0.001
Renal disease, *n* (%)	294 (6.6)	1273 (7.9)	1867 (7.4)	0.011
Malignancy, *n* (%)	57 (1.3)	429 (2.7)	937 (3.7)	<0.001
Cardiac arrest at admission, *n* (%)	2614 (58.9)	2366 (14.7)	5541 (21.9)	<0.001
Procedure, *n* (%)				
Overall CAG	4143 (93.4)	15 667 (97.2)	17 637 (69.8)	<0.001
Revascularization	3991 (90.0)	15 219 (94.4)	16 744 (66.2)	<0.001
PCI	3893 (87.7)	13 974 (86.7)	16 427 (65.0)	<0.001
primary PCI	3880 (87.5)	13 769 (85.4)	15 103 (59.7)	<0.001
CABG	168 (3.8)	1686 (10.5)	440 (1.7)	<0.001
Hospital teaching status, *n* (%)				<0.001
A	4285 (96.6)	15 258 (94.7)	22 893 (90.6)	
B	147 (3.3)	761 (4.7)	1987 (7.9)	
C	5 (0.1)	100 (0.6)	400 (1.6)	
Hospital with the number of hospital beds ≥500, *n* (%)	2564 (57.8)	8078 (50.1)	11 066 (43.8)	<0.001
Number of BCC per hospital, *n* (%)				<0.001
0 to 2	368 (8.3)	1851 (11.5)	4038 (16.0)	
3 to 5	1535 (34.6)	6418 (39.8)	11 187 (44.3)	
6 to 9	1368 (30.8)	4423 (27.4)	6144 (24.3)	
≥10	1158 (26.1)	3389 (21.0)	3761 (14.9)	
Unknown	8 (0.2)	38 (0.2)	150 (0.6)	
Hospital with CCU, *n* (%)	4311 (97.2)	15 367 (95.3)	23 045 (91.2)	<0.001
Hospital with cardiac surgery, *n* (%)	3952 (89.1)	13 224 (82.0)	18 666 (73.8)	<0.001

Continued

Table I *Continued*

	With MCS *n* = 4437 (9.7)	IABP only *n* = 16 119 (35.2)	Without MCS *n* = 25 280 (55.2)	*P*-value
Regional ageing rate, *n* (%)				<0.001
Q1	1297 (29.2)	4604 (28.6)	6789 (26.9)	
Q2	1174 (26.5)	3922 (24.4)	6159 (24.4)	
Q3	942 (21.2)	3478 (21.6)	5699 (22.6)	
Q4	1023 (23.1)	4103 (25.5)	6599 (26.1)	
Board-certified hospital density, *n* (%)				<0.001
Q1	1000 (22.5)	3828 (23.8)	6517 (25.8)	
Q2	954 (21.5)	4019 (24.9)	6932 (27.5)	
Q3	1419 (32.0)	4747 (29.5)	6676 (26.4)	
Q4	1063 (24.0)	3513 (21.8)	5121 (20.3)	

The variable for door-to-balloon time within 90 min was calculated using available data from April 2014.
AMI, acute myocardial infarction; BCC, board-certified cardiologists; CABG, coronary artery bypass graft surgery; CAG, coronary angiography; CCU, coronary care unit; IABP, intra-aortic balloon pump; IQR, interquartile range; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention.

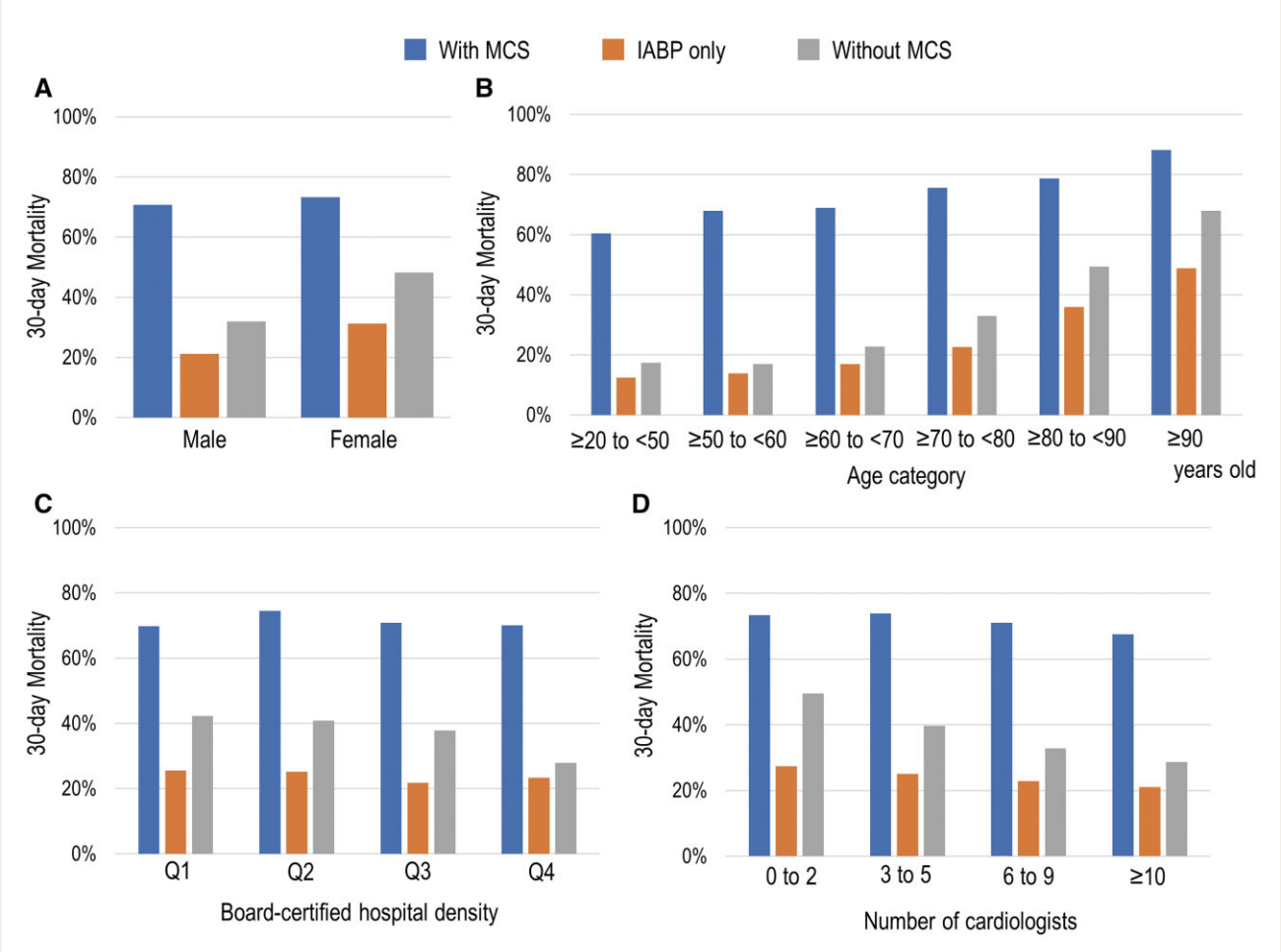


Figure 3 Thirty-day mortality in patients with acute myocardial infarction complicated by cardiogenic shock. This bar graph shows the difference in 30-day mortality rate between patients with mechanical circulatory support, intra-aortic balloon pumping only, and without mechanical circulatory support stratified by (*A*) sex, (*B*) age category, (*C*) board-certified hospital density, and (*D*) number of cardiologists. IABP, intra-aortic balloon pumping; MCS, mechanical circulatory support.

Table 2 Univariate and multivariable Cox frailty models for risk of 30-day mortality in AMI patients with and without mechanical circulatory support

	Univariate		Multivariable					
			Model 1		Model 2		Model 3	
	HR, 95% CI	*P*-value	HR, 95% CI	*P*-value	HR, 95% CI	*P*-value	HR, 95% CI	*P*-value
IABP only	Ref		Ref		Ref		Ref	
Without MCS	1.83 (1.76–1.90)	<0.001	1.04 (1.00–1.09)	0.078	1.03 (0.96–1.05)	0.907	1.05 (1.00–1.09)	0.033
With MCS	3.87 (3.68–4.06)	<0.001	2.66 (2.53–2.80)	<0.001	3.45 (3.28–3.63)	<0.001	2.63 (2.50–2.77)	<0.001
With revascularization								
IABP only	Ref		Ref		Ref		Ref	
Without MCS	0.67 (0.63–0.71)	<0.001	0.72 (0.68–0.76)	<0.001	0.65 (0.62–0.69)	<0.001	0.73 (0.69–0.77)	<0.001
With MCS	4.16 (3.95–4.39)	<0.001	3.24 (3.06–3.42)	<0.001	4.32 (4.08–4.56)	<0.001	3.19 (3.01–3.37)	<0.001
Without revascularization								
IABP only	Ref		Ref		Ref		Ref	
Without MCS	3.01 (2.61–3.48)	<0.001	2.67 (2.30–3.09)	<0.001	2.78 (2.40–3.22)	<0.001	2.77 (2.40–3.21)	<0.001
With MCS	2.86 (2.37–3.45)	<0.001	2.38 (1.97–2.88)	<0.001	2.57 (2.13–3.10)	<0.001	2.37 (1.96–2.86)	<0.001

In Model 1, HRs and 95% CIs were adjusted for age category, sex, total score of the Barthel index at admission, Killip classification, comorbidities (previous ischaemic heart disease, hypertension, dyslipidaemia, diabetes mellitus, atrial fibrillation, chronic pulmonary disease, peripheral vascular disease, cerebrovascular disease, renal disease, and malignancy), cardiac arrest at admission, revascularization (PCI and CABG), and hospital characteristics (hospital with ≥500 beds, number of BCCs, hospital with CCU, hospital with cardiac surgery, regional ageing rate, and board-certificated hospital density). In Model 2, HRs and 95% CIs were adjusted for age category, sex, total score of the Barthel index at admission, Killip classification, cardiac arrest at admission, revascularization (PCI and CABG), and hospital characteristics (hospital with ≥500 beds, number of BCCs, hospital with CCU, hospital with cardiac surgery, regional ageing rate, and board-certificated hospital density). In Model 3, HRs and 95% CIs were adjusted for age category, sex, total score of the Barthel index at admission, Killip classification, comorbidities (previous ischaemic heart disease, hypertension, dyslipidaemia, diabetes mellitus, atrial fibrillation, chronic pulmonary disease, peripheral vascular disease, cerebrovascular disease, renal disease, and malignancy), cardiac arrest at admission, and revascularization (PCI and CABG).
BCC, board-certified cardiologists; CABG, coronary artery bypass graft surgery; CCU, coronary care unit; CI, confidence interval; HR, hazard ratio; IABP, intra-aortic balloon pump; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention.

Table 3 Propensity score-matched and inverse probability of treatment-weighted Cox frailty model for the risk of 30-day mortality in AMI patients with and without primary PCI

	Propensity score matching			IPTW		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Total death	0.39	0.37–0.41	<0.001	0.45	0.44–0.46	<0.001
30-day mortality	0.37	0.35–0.39	<0.001	0.44	0.43–0.45	<0.001
7-day mortality	0.35	0.33–0.37	<0.001	0.41	0.40–0.42	<0.001

AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; PCI, percutaneous coronary intervention.

hospital density and the number of BCCs with 30-day mortality. Univariate and multivariable Cox frailty models showed that the fourth quartile of hospital density was associated with a low risk of 30-day mortality compared with the first quartile, and ≥10 BCCs per hospital was associated with a low risk of 30-day mortality compared with ≤2 BCCs per hospital (*Table 5*). As shown in *Figure 4*, the multivariable model revealed that a higher hospital density and larger number of BCCs in the responsible hospital were associated with a lower risk for mortality in the patients with CS. *Figure 5* shows the 30-day mortality risk of patients with CS stratified by MCS use. In patients with MCS, the 30-day mortality risk was significantly lower in ≥10 BCCs in the first, third, and fourth quartiles than in ≤2 BCCs in the first quartile of hospital density, whereas no significant difference was found in the 30-day mortality risk in patients with IABP only. In patients with primary PCI, the multivariable model showed that almost comparable risk of 30-day mortality in any hospital density and number of BCCs (Supplementary material online, *Figure S3*). The sex difference in 30-day mortality risk is shown in Supplementary material online, *Figure S4*, indicating a similar tendency in the association of cardiovascular healthcare resources with 30-day mortality.

Discussion

The major findings of this retrospective, observational study, which used a nationwide Japanese administrative claims database, JROAD-DPC, were as follows: (i) the subject population with AMI included 19.7% of the patients complicated by CS, in whom there were 9.7%

Table 4 Baseline characteristics according to the board-certified hospital density in AMI patients with cardiogenic shock

	Board-certified hospital density				*P*-value
	Q1, *n* = 11 345 (24.8)	Q2, *n* = 11 905 (26.0)	Q3, *n* = 12 842 (28.1)	Q4, *n* = 9697 (21.2)	
Age, median (IQR)	74 (65–83)	75 (65–83)	74 (65–82)	73 (65–82)	<0.001
Males, *n* (%)	7736 (68.2)	8162 (68.6)	8881 (69.2)	6930 (71.5)	<0.001
Body mass index, kg/m^2, median (IQR)	23.2 (20.8–25.7)	22.8 (20.5–25.2)	22.9 (20.7–25.4)	23.0 (20.7–25.4)	<0.001
Missing, *n* (%)	2644 (23.3)	2668 (22.4)	2125 (16.6)	1581 (16.3)	
In-hospital days, median (IQR)	15 (3–26)	15 (2–25)	15 (4–25)	15 (6–26)	<0.001
Emergency admission, *n* (%)	11 217 (98.9)	11 754 (99.0)	12 686 (98.8)	9517 (98.4)	0.002
Missing, *n* (%)	3 (0.03)	26 (0.2)	1 (0.01)	26 (0.3)	
Ambulance use, *n* (%)	9244 (81.5)	9503 (79.9)	10 199 (79.4)	7679 (79.4)	<0.001
Missing, *n* (%)	2 (0.02)	13 (0.1)	1 (0.01)	23 (0.2)	
Smoker, *n* (%)	4085 (36.0)	4198 (35.3)	4735 (36.9)	3549 (36.6)	<0.001
Missing, *n* (%)	2610 (23.0)	2595 (21.8)	2476 (19.3)	1916 (19.8)	
Site of myocardial infarction					
Anterior, *n* (%)	4764 (42.0)	5051 (42.4)	5663 (44.1)	4096 (42.2)	0.003
Inferior, *n* (%)	3246 (28.6)	3411 (28.7)	3693 (28.8)	2891 (29.8)	0.182
Lateral and other, *n* (%)	848 (7.5)	939 (7.9)	996 (7.8)	784 (8.1)	0.404
Unknown, *n* (%)	2596 (22.9)	2473 (20.8)	2671 (20.8)	2144(22.1)	<0.001
Door to balloon time within 90 min, *n* (%)	4462 (53.6)	4570 (53.5)	5284 (57.0)	4119 (57.5)	<0.001
Full score Barthel Index at admission, *n* (%)	1321 (11.6)	1421 (11.9)	1984 (15.5)	1692 (17.5)	<0.001
Previous ischaemic heart disease, *n* (%)	377 (3.3)	321 (2.7)	400 (3.1)	419 (4.3)	<0.001
Hypertension, *n* (%)	4830 (42.6)	4512 (37.9)	5074 (39.5)	4329 (44.6)	<0.001
Dyslipidaemia, *n* (%)	3706 (32.7)	3770 (31.7)	4300 (33.5)	3591 (37.0)	<0.001
Diabetes mellitus, *n* (%)	3049 (26.9)	3005 (25.2)	3283 (25.6)	2527 (26.1)	0.027
Atrial fibrillation, *n* (%)	446 (3.9)	441 (3.7)	478 (3.7)	394 (4.1)	0.451
Chronic pulmonary disease, *n* (%)	233 (2.1)	233 (2.0)	256 (2.0)	211 (2.2)	0.693
Peripheral vascular disease, *n* (%)	438 (3.9)	455 (3.8)	411 (3.2)	401 (4.1)	0.002
Cerebrovascular disease, *n* (%)	819 (7.2)	701 (5.9)	723 (5.6)	496 (5.1)	<0.001
Renal disease, *n* (%)	865 (7.6)	815 (6.9)	999 (7.8)	752 (7.8)	0.019
Malignancy, *n* (%)	343 (3.0)	368 (3.1)	353 (2.8)	356 (3.7)	0.001
Cardiac arrest at admission, *n* (%)	2758 (24.3)	2941 (24.7)	2904 (22.6)	1900 (19.6)	<0.001
Procedure, *n* (%)					
Overall CAG	8913 (78.6)	9360 (78.6)	10 662 (83.0)	8480 (87.5)	<0.001
Revascularization	8548 (75.4)	8984 (75.5)	10 232 (79.7)	8158 (84.1)	<0.001
PCI	8175 (72.1)	8578 (72.1)	9756 (76.0)	7753 (80.0)	<0.001
Primary PCI	7800 (68.8)	8219 (69.0)	9316 (72.5)	7387 (76.2)	<0.001
CABG	535 (4.7)	555 (4.7)	639 (5.0)	565 (5.8)	<0.001
Hospital teaching status, *n* (%)					<0.001
A	10 258 (90.4)	11 005 (92.4)	11 833 (92.1)	9320 (96.1)	
B	875 (7.7)	739 (6.2)	894 (7.0)	360 (3.7)	
C	212 (1.9)	161 (1.4)	115 (0.9)	17 (0.2)	
Hospital with the number of hospital beds ≥500, *n* (%)	5091 (44.9)	5722 (48.1)	6276 (48.9)	4619 (47.6)	<0.001
Number of BCC per hospital, *n* (%)					<0.001
0 to 2	2137 (18.8)	1701 (14.3)	1535 (12.0)	846 (8.7)	
3 to 5	5204 (45.9)	5648 (47.4)	5113 (39.8)	3166 (32.7)	
6 to 9	2273 (20.0)	2718 (22.8)	3615 (28.2)	3329 (34.3)	
≥10	1724 (15.2)	1816 (15.3)	2579 (20.1)	2189 (22.6)	
Unknown	7 (0.1)	22 (0.2)	0 (0)	167 (1.7)	

Continued

Table 4 *Continued*

	Board-certified hospital density				*P*-value
	Q1, *n* = 11 345 (24.8)	Q2, *n* = 11 905 (26.0)	Q3, *n* = 12 842 (28.1)	Q4, *n* = 9697 (21.2)	
Hospital with CCU, *n* (%)	10 293 (90.7)	11 141 (93.6)	11 915 (92.8)	9344 (96.4)	<0.001
Hospital with cardiac surgery, *n* (%)	9097 (80.2)	9014 (75.7)	9612 (74.9)	8111 (83.6)	<0.001
Regional ageing rate, *n* (%)					<0.001
Q1	0 (0)	557 (4.7)	6054 (47.1)	6079 (62.7)	
Q2	2429 (21.4)	1604 (13.5)	4416 (34.4)	2806 (28.9)	
Q3	1732 (15.3)	5689 (47.8)	1886 (14.7)	812 (8.4)	
Q4	7184 (63.3)	4055 (34.1)	486 (3.8)	0 (0)	

AMI, acute myocardial infarction; BCC, board-certified cardiologists; CABG, coronary artery bypass graft surgery; CAG, coronary angiography; CCU, coronary care unit; IQR, interquartile range; PCI, percutaneous coronary intervention.

Table 5 Univariate and multivariable Cox frailty models for the risk of 30-day mortality according to the characteristics of the admitting hospital

	Univariate		Multivariable			
			Model 1		Model 2	
	HR, 95% CI	*P*-value	HR, 95% CI	*P*-value	HR, 95% CI	*P*-value
Board-certified hospital density						
Q1	Ref		Ref		Ref	
Q2	0.97 (0.88–1.08)	0.564	0.90 (0.83–0.97)	0.005	0.95 (0.88–1.02)	0.181
Q3	0.92 (0.83–1.02)	0.104	0.87 (0.80–0.96)	0.003	0.92 (0.84–1.00)	0.061
Q4	0.70 (0.63–0.78)	<0.001	0.79 (0.71–0.87)	<0.001	0.81 (0.73–0.89)	<0.001
Number of BCC per hospital						
0 to 2	Ref		Ref		Ref	
3 to 5	0.81 (0.76–0.86)	<0.001	0.99 (0.93–1.07)	0.857	1.01 (0.94–1.08)	0.754
6 to 9	0.71 (0.66–0.77)	<0.001	0.94 (0.86–1.02)	0.110	0.93 (0.86–1.01)	0.098
≥10	0.60 (0.55–0.67)	<0.001	0.84 (0.76–0.93)	<0.001	0.84 (0.76–0.93)	<0.001

In Model 1, HRs and 95% CIs were adjusted for age category, sex, total score of the Barthel index at admission, Killip classification, comorbidities (previous ischaemic heart disease, hypertension, dyslipidaemia, diabetes mellitus, atrial fibrillation, chronic pulmonary disease, peripheral vascular disease, cerebrovascular disease, renal disease, and malignancy), cardiac arrest at admission, revascularization (PCI and CABG), and hospital characteristics (hospital with ≥500 beds, hospital with CCU, hospital with cardiac surgery, and regional ageing rate). In Model 2, HRs and 95% CIs were adjusted for age category, sex, total score of the Barthel index at admission, Killip classification, cardiac arrest at admission, revascularization (PCI and CABG), and hospital characteristics (hospital with ≥500 beds, hospital with CCU, hospital with cardiac surgery, and regional ageing rate).
BCC, board-certified cardiologists; CABG, coronary artery bypass graft surgery; CCU, coronary care unit; CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention.

MCS (ECMO with/without IABP) and 35.2% IABP-alone users; (ii) the 30-day mortality rate of AMI patients with CS was as high as 36.1%, of which the 30-day mortality rate of patients with MCS use was extremely high, at 71.2%; (iii) even in older patients with CS, primary PCI was significantly associated with a low risk of 30-day mortality; and (iv) a higher JCS-certified hospital density and larger number of BCCs were associated with a lower risk of 30-day mortality.

The prevalence of AMI patients complicated by CS in the present study (19.7%) was higher than that reported in previous studies.[1,4] In a prospective observational study, conducted from January 1995 to May 2004 at 775 US revascularization-capable hospitals, 8.6% of 293 633 enrolled patients with ST-elevation AMI (STEMI) were diagnosed with AMI complicated with CS.[1] Another study also showed that 7.9% of 1 990 486 patients with STEMI in the 2003–2010 Nationwide Inpatient Sample databases were diagnosed with CS, and the incidence rate of CS was higher in older patients than among non-older patients.[4] Considering a higher incidence of CS in older AMI patients, it may be possible that the higher prevalence of CS in the present study was due to a higher proportion of older patients. Another explanation for the difference in the incidence of CS could be the definition of CS used in various studies. In the present study, the SCAI shock classification,[20] which was validated in AMI patients enrolled in the National Cardiogenic Shock Initiative,[22] was used as the definition of CS. In this classification, patients who require intervention such as inotrope, pressor, or MCS due to reduced cardiac output and end-organ hypoperfusion were considered stage C, even

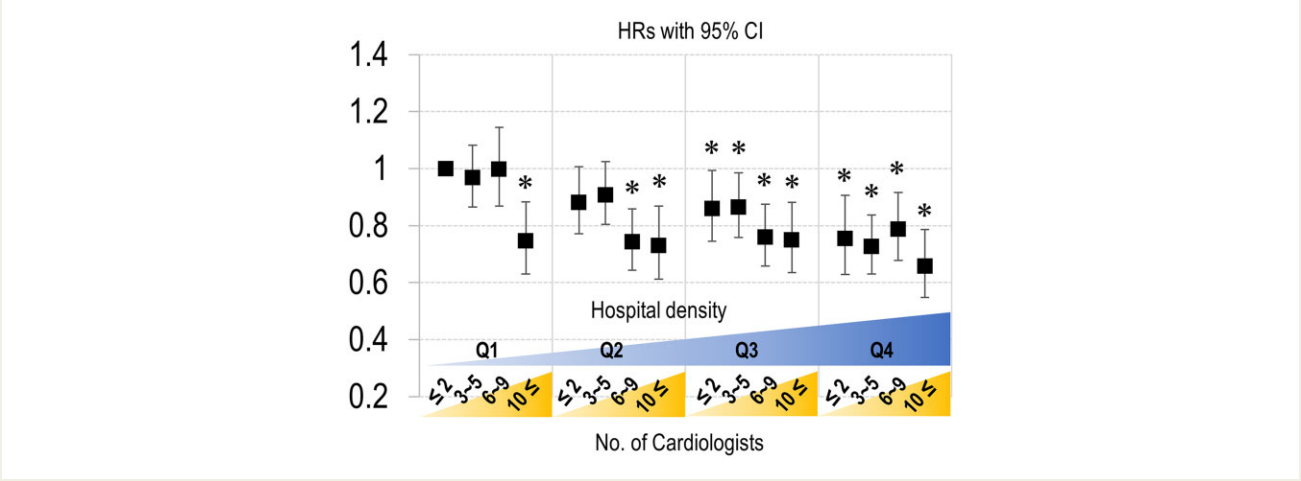


Figure 4 Thirty-day mortality risk of acute myocardial infarction patients with cardiogenic shock stratified by hospital density and number of cardiologists. Hazard ratios and 95% confidence intervals were adjusted for age category, sex, activities daily of living at admission, Killip classification, comorbidities (ischaemic heart disease, hypertension, dyslipidaemia, diabetes, atrial fibrillation, chronic pulmonary disease, peripheral artery disease, cerebrovascular disease, renal disease, or malignancy), cardiac arrest at admission, hospital with >500 beds, hospital with coronary care unit, hospital with cardiac surgery, regional ageing rate, and mechanical circulatory support (extracorporeal membrane oxygenation, intra-aortic balloon pumping). *P < 0.05. AMI, acute myocardial infarction; CI, confidence interval; CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; IABP, intra-aortic balloon pumping; MCS, mechanical circulatory support.

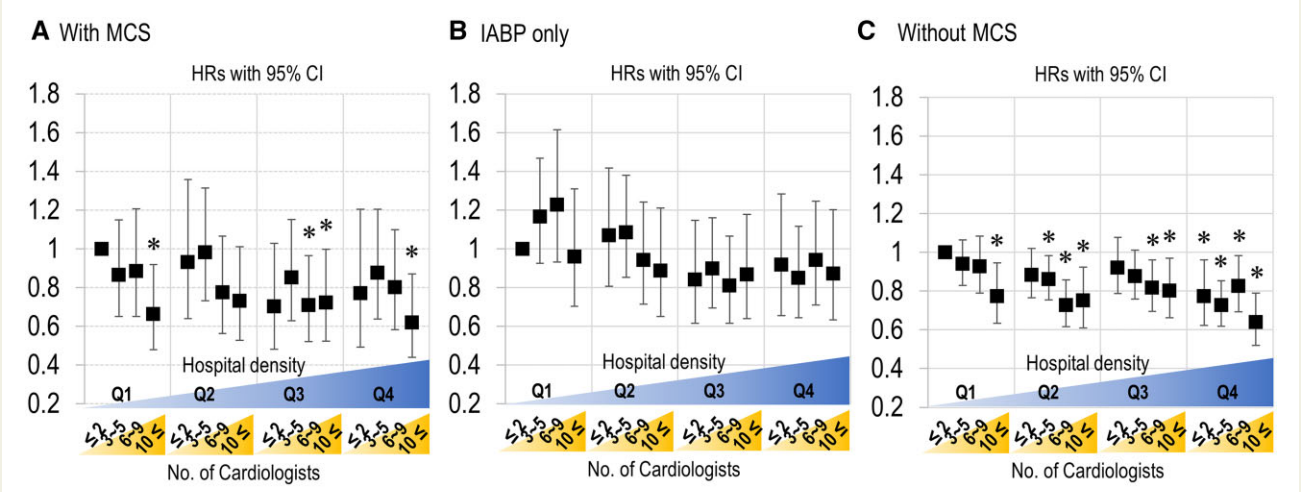


Figure 5 Thirty-day mortality risk of patients with acute myocardial infarction complicated by cardiogenic shock stratified by hospital density and number of cardiologists. Hazard ratios and 95% confidence intervals were adjusted for age category, sex, activities daily of living at admission, Killip classification, comorbidities (ischaemic heart disease, hypertension, dyslipidaemia, diabetes, atrial fibrillation, chronic pulmonary disease, peripheral artery disease, cerebrovascular disease, renal disease, or malignancy), cardiac arrest at admission, hospital with >500 beds, hospital with coronary care unit, hospital with cardiac surgery, regional ageing rate, and mechanical circulatory support (extracorporeal membrane oxygenation, intra-aortic balloon pumping). *P < 0.05. CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; IABP, intra-aortic balloon pumping; MCS, mechanical circulatory support.

in Killip class III. Therefore, a higher number of AMI patients might have been diagnosed with CS by using the SCAI classification including Killip class III as one of the findings of stage C, rather than the traditional definition that used Killip IV alone as CS.

To improve reduced cardiac output after AMI and maintain end-organ perfusion, MCS devices, which are considered a promising therapeutic option for CS, have been widely used. Although IABP is most contemporarily used in patients undergoing PCI with

hemodynamic instability, the use of IABP has decreased over time after the publication of neutral results of the IABP-SHOCK II trial.[6,23,24] Using the National Cardiovascular Data Registry CathPCI registry database from 2009 to 2013, Sandhu *et al.*[23] showed that 45% of patients undergoing PCI with CS received an IABP in 2009 and the use of IABP decreased at an average rate of 0.3% per quarter. Conversely, the proportion of patients receiving other MCS, such as ECMO, has remained unchanged or slightly increased,[6,23] and the proportion of patients receiving Impella has significantly increased in recent years.[25] In the present study, the following proportions of patients receiving MCS: 9.7% with MCS (ECMO with/without IABP), 35.2% with IABP alone, and 55.2% without MCS; these results are almost consistent with previous reports regarding the proportion of MCS use. In the present study, few patients received an Impella because Impella was launched in Japan during September 2017. The increased common use of Impella in the future would reduce the use of IABP in Japan.

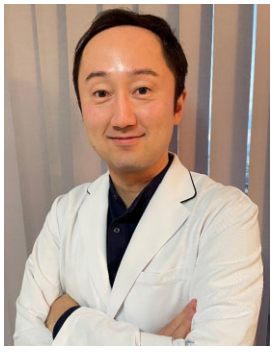
In the present study, the 30-day mortality rate of AMI patients with CS was 36.1%, which was consistent with those in previous studies.[3–5] In addition, multivariable analysis revealed that patients with MCS were significantly associated with a high risk of 30-day mortality compared with those with IABP only. However, this result does not mean that the use of MCS deteriorates the prognosis for AMI with CS compared with IABP. Although many available variables were adjusted because of the observational nature of the study, residual confounders, whereby patients receiving MCS showed greater severity of illness than those receiving IABP, might have affected the results. Previous retrospective, observational studies have also showed that the use of MCS (mainly, Impella) compared with IABP was associated with a higher risk of in-hospital adverse outcomes.[5,25] Based on the results of these studies, a higher incidence of bleeding-related complication was observed during the use of MCS than that of IABP, which may be one of the leading causes of in-hospital death in patients receiving MCS.[2] Although randomized controlled trials or meta-analysis could not reveal the benefits of MCS on in-hospital survival of AMI patients complicated by CS,[26–29] previous large-cohort, prospective studies have reported the benefits of primary PCI on in-hospital survival of those patients,[1] which was re-confirmed by the present study using propensity score analyses. Moreover, even for patients aged >80 years, the association of primary PCI with a low risk of 30-day mortality was observed.

Based on the above factors, the routine use of MCS for AMI patients with CS is better avoided, and the appropriate use of MCS should be considered in individual cases prior to introduction. Furthermore, proactive indication of primary PCI could be recommended after fully considering factors such as patient background and reperfusion time, even for older AMI patients. For further improvement in the short-term prognosis of CS patients, coronary intervention at early onset and/or constant hemodynamic/pathological monitoring and timely intensive therapeutic interventions are crucially needed. Increasing the number of cardiologists per hospital may improve the prognosis, as previously described[11,12]; however, given the limited resources, plans for staffing at each hospital need to be considered. The present study showed that a lower number of BCCs, even in higher density hospitals, was not associated with a low risk of 30-day mortality, than those in the lowest density hospitals, whereas a large number of BCCs, even in the lowest density hospitals, was significantly associated with a low risk of 30-day mortality, especially in patients with CS and MCS, suggesting that consolidating cardiologists into one hospital in the area rather than distributing cardiologists across multiple hospitals could further improve the prognosis of AMI patients complicated by CS.

This study has several limitations. First, unmeasured confounding, severity parameters, and clinical prognostic factors such as cardiac biomarkers or left ventricular function after AMI might have biased the results, as this was a retrospective, observational study using an administrative claims database. Second, while comparing the mortality between patients with and without MCS use or primary PCI, confounding by indication might have an effect. We therefore performed propensity score matching and IPTW to reduce the effect of treatment-selection bias and possible confounders, stating that primary PCI was significantly associated with a low risk of 30-day mortality in AMI patients complicated by CS. Third, we could not assess a cause-specific death because no information was available on the cause of death in the administrative claims database. Like the J-PCI registry,[30] a system that even the administrative claims database can collect information on predefined cause-specific death should be built in the future. Fourth, we could not investigate the prognostic effect of Impella on AMI patients with CS, because Impella was launched in Japan in September 2017, and a few patients were treated with Impella during this study period.

In conclusion, this study showed the clinical characteristics and 30-day mortality in AMI patients complicated with CS in a real-world setting. The results indicated a prognostic effect of primary PCI and the association of cardiovascular healthcare resources with 30-day mortality, suggesting the need to establish a medical system that can appropriately allocate and supply cardiovascular workforce to improve the prognosis of AMI patients complicated by CS.

Lead author biography



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Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Data Availability statement

The data underlying this article were provided by Japanese Circulation Society under licence / by permission. Data will be shared on request to the corresponding author with permission of Japanese Circulation Society.

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