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ORIGINAL RESEARCH

Prognosis in Patients With Cardiogenic Shock Who Received Temporary Mechanical Circulatory Support

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ABSTRACT

BACKGROUND Temporary mechanical circulatory support (MCS) is often used in patients with cardiogenic shock (CS), and the type of MCS may vary by cause of CS.

OBJECTIVES This study sought to describe the causes of CS in patients receiving temporary MCS, the types of MCS used, and associated mortality.

METHODS This study used a nationwide Japanese database to identify patients receiving temporary MCS for CS between April 1, 2012, and March 31, 2020.

RESULTS Of 65,837 patients, the cause of CS was acute myocardial infarction (AMI) in 77.4%, heart failure (HF) in 10.9%, valvular disease in 2.7%, fulminant myocarditis (FM) in 2.5%, arrhythmia in 4.5%, and pulmonary embolism (PE) in 2.0% of cases. The most commonly used MCS was an intra-aortic balloon pump alone in AMI (79.2%) and in HF (79.0%) and in valvular disease (66.0%), extracorporeal membrane oxygenation with intra-aortic balloon pump in FM (56.2%) and arrhythmia (43.3%), and extracorporeal membrane oxygenation alone in PE (71.5%). Overall in-hospital mortality was 32.4%; 30.0% in AMI, 32.6% in HF, 33.1% in valvular disease, 34.2% in FM, 60.9% in arrhythmia, and 59.2% in PE. Overall in-hospital mortality increased from 30.4% in 2012 to 34.1% in 2019. After adjustment, valvular disease, FM, and PE had lower in-hospital mortality than AMI: valvular disease, OR: 0.56 (95% CI: 0.50-0.64); FM: OR: 0.58 (95% CI: 0.52-0.66); PE: OR: 0.49 (95% CI: 0.43-0.56); whereas HF had similar in-hospital mortality (OR: 0.99; 95% CI: 0.92-1.05) and arrhythmia had higher in-hospital mortality (OR: 1.14; 95% CI: 1.04-1.26).

CONCLUSIONS In a Japanese national registry of patients with CS, different causes of CS were associated with different types of MCS and differences in survival. (JACC: Asia 2023;3:122–134) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Cardiogenic shock (CS) is a low-cardiac-output state leading to life-threatening end-organ hypoperfusion and hypoxia.[1-3] Acute myocardial infarction (AMI) is the most common cause of CS and accounts for 25%-80% of cases.[4-8] However, CS has other causes, such as decompensation of chronic heart failure (HF) and fulminant myocarditis (FM), and the contribution of these other etiologies to CS has been increasing over time.[5,9] Mechanical circulatory support (MCS) devices can increase cardiac output and maintain organ perfusion without the negative consequences of inotropes.[1-3,10-12] Recent guidelines recommend early consideration of temporary MCS in patients with CS as a bridge to recovery, bridge to decision, and bridge to bridge.[10-12] The intra-aortic balloon pump (IABP) is still the most commonly used MCS device for patients with CS, although the IABP-SHOCK II (Intraaortic Balloon Pump in Cardiogenic Shock II) trial showed no reduction in the primary endpoint of 30-day mortality, or any secondary endpoint, in patients with AMI-associated CS.[13] However, the use of IABP has been declining recently in favor of alternative types of MCS.[5,9,13-15] Extracorporeal membrane oxygenation (ECMO) is recommended in CS when there is poor oxygenation, when an alternative MCS device cannot, or is not expected to, generate adequate circulatory support, or when patients have malignant arrhythmias and cardiopulmonary arrest.[1-3] The Impella device (Abiomed Inc) is a percutaneous ventricular assist device (pVAD) that may provide greater improvement in hemodynamic parameters compared with IABP.[16] It is recommended that a multidisciplinary team with expertise selects the MCS device based on availability and characteristics, patient comorbidities, hemodynamic parameters, the presence of right heart failure, whether there is an indication for heart transplantation or a durable left ventricular assist device, and patient-specific needs.[1,2,17] Based on these considerations, the decision to use MCS and the type of device chosen is likely to influenced by the cause of CS. To date, large epidemiologic reports of the use of temporary MCS in patients with CS have generally focused on AMI or provided little detail about non-AMI cases.[5,9,15] Furthermore, MCS devices are often used in combination, but few reports have described these combinations, the patients in whom they are used, and associated outcomes. Consequently, we have examined the cause of patients with CS receiving MCS, the devices used, and associated mortality in the nationwide registry of JROAD-DPC (Japanese Registry of All Cardiac and Vascular Diseases-Diagnosis Procedure Combination) in Japan, including longitudinal trends.

METHODS

DATA SOURCES. The JROAD-DPC database is a nationwide medical database with information on hospitalization for cardiovascular diseases, created by combining JROAD data and DPC data and managed by the Japanese Society of Cardiology.[18] The JROAD database covers almost all teaching hospitals in Japan with cardiovascular beds. DPC is a mixed patient classification system that is linked to payments at acute-care hospitals in Japan.[19] The DPC database contains data on patient demographics, drugs and devices, therapeutic procedures, discharge status, length of hospital stay, hospitalization costs, and diagnoses based on the International Classification of Diseases-10th Revision (ICD-10) codes. Of the 1,553 facilities that participated in the JROAD survey, 1,243 were JROAD-DPC-eligible facilities that adopted the DPC system. Of the 1,243 facilities, 1,086 provided DPC data to the Japanese Society of Cardiology between April 1, 2012, and March 31, 2020. In compliance with the principles of the Declaration of Helsinki, the study protocol was approved by the local ethics committee (approval number: 2021-0065). The requirement of informed consent was waived by the committee because information specific to individuals was not included.

STUDY POPULATION. We included patients aged 18 years or older who received temporary MCS, including IABP, ECMO, and pVAD, in the setting of emergency hospitalization, based on the procedural codes in the DPC. We excluded patients who did not have disease diagnoses based on the following ICD-10 codes, reflecting the potential cause of CS, in “main diagnosis,” “admission-precipitating diagnosis,” “most resource-consuming diagnosis,” or “second most resource-consuming diagnosis” of DPC disease classification: AMI: I21.x; HF, I50.x; valvular disease: A52.0, I05.x-I08.x, I09.1, I09.8, I34.x-I39.x, Q23.0-Q23.3, Z95.2-Z95.4; FM: I40, I41; ventricular arrhythmia: I470, I472, I490; pulmonary embolism (PE): I26.0, I26.9 (Supplemental Table 1). The accuracy of ICD-10 codes to identify AMI, HF, valvular disease, and PE has been previously validated with high specificity and sensitivity.[20-22] Furthermore, patients who started MCS on or after the day that cardiac surgery was performed were excluded as postcardiotomy.

PATIENT CLASSIFICATION. Patients were categorized in 6 groups according to the cause of CS described herein. If a patient had ICD-10 codes for

ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

CS = cardiogenic shock

ECMO = extracorporeal membrane oxygenation

FM = fulminant myocarditis

HF = heart failure

IABP = intra-aortic balloon pump

ICD-10 = International Classification of Diseases-10th Revision

MCS = mechanical circulatory support

OR = odds ratio

PE = pulmonary embolism

pVAD = percutaneous ventricular assist device

TABLE 1 Patient Characteristics According to Causes of CS

	All (N = 65,837)	AMI (n = 50,948)	HF (n = 7,185)	Valvular Disease (n = 1,763)	FM (n = 1,677)	Arrhythmia (n = 2,946)	PE (n = 1,318)
Age, y[a]	69.0 ± 13.2	69.8 ± 12.3	70.4 ± 13.2	75.8 ± 11.6	54.6 ± 17.3	60.4 ± 14.9	61.1 ± 15.4
Age groups							
18-49	5,998 (9.1)	3,669 (7.2)	583 (8.1)	51 (2.9)	663 (39.5)	690 (23.4)	342 (25.9)
50-59	8,388 (12.7)	6,478 (12.7)	708 (9.9)	109 (6.2)	272 (16.2)	579 (19.7)	242 (18.4)
60-69	16,462 (25.0)	13,173 (25.9)	1,622 (22.6)	296 (16.8)	351 (20.9)	752 (25.5)	268 (20.3)
70-79	19,683 (29.9)	15,433 (30.3)	2,384 (33.2)	547 (31.0)	286 (17.1)	712 (24.2)	321 (24.4)
≥80	15,305 (23.2)	12,194 (23.9)	1,888 (26.3)	760 (43.1)	105 (6.3)	213 (7.2)	145 (11.0)
Male	48,823 (74.2)	38,973 (76.5)	5,011 (69.7)	886 (50.3)	994 (59.3)	2,400 (81.5)	559 (42.4)
Body mass index, kg/m^2[b]	23.6 ± 4.7	23.8 ± 4.8	23.1 ± 4.6	22.1 ± 4.0	22.7 ± 3.8	23.6 ± 4.4	25.4 ± 5.5
Body mass index categories, kg/m^2							
≤18.4	4,544 (7.9)	3,043 (6.9)	796 (12.1)	269 (16.6)	180 (12.0)	205 (9.1)	51 (4.7)
18.5-24.9	34,720 (60.5)	26,820 (60.4)	4,013 (61.0)	1,044 (64.3)	953 (63.8)	1,348 (59.7)	542 (49.7)
25.0-29.9	14,560 (25.4)	11,765 (26.5)	1,381 (21.0)	253 (15.6)	299 (20.0)	530 (23.5)	332 (30.4)
≥30.0	3,608 (6.3)	2,755 (6.2)	392 (6.0)	57 (3.5)	62 (4.1)	176 (7.8)	166 (15.2)
Chronic kidney disease	5,843 (8.9)	3,975 (7.8)	1,189 (16.5)	341 (19.3)	46 (2.7)	250 (8.5)	42 (3.2)
Diabetes mellitus	19,241 (29.2)	15,540 (30.5)	2,633 (36.6)	378 (21.4)	149 (8.9)	394 (13.4)	147 (11.2)
Annual number of MCS use at each facility							
1-10	16,151 (24.5)	13,217 (25.9)	1,593 (22.2)	251 (14.2)	384 (22.9)	423 (14.4)	283 (21.5)
11-20	19,288 (29.3)	14,703 (28.9)	2,181 (30.4)	537 (30.5)	532 (31.7)	907 (30.8)	428 (32.5)
21-30	13,250 (20.1)	10,145 (19.9)	1,418 (19.7)	346 (19.6)	319 (19.0)	749 (25.4)	273 (20.7)
≥31	17,148 (26.0)	12,883 (25.3)	1,993 (27.7)	629 (35.7)	442 (26.4)	867 (29.4)	334 (25.3)
Hospital, bed size[c]							
0-349	14,172 (21.5)	11,491 (22.6)	1,558 (21.7)	287 (16.3)	244 (14.5)	392 (13.3)	200 (15.2)
350-499	15,758 (23.9)	12,499 (24.5)	1,641 (22.8)	378 (21.4)	363 (21.6)	570 (19.3)	307 (23.3)
500-649	17,000 (25.8)	13,180 (25.9)	1,810 (25.2)	439 (24.9)	455 (27.1)	738 (25.1)	378 (28.7)
≥650	18,902 (28.7)	13,773 (27.0)	2,176 (30.3)	659 (37.4)	615 (36.7)	1,246 (42.3)	433 (32.9)
Procedure							
Cardiopulmonary resuscitation[d]	13,122 (19.9)	9,072 (17.8)	1,178 (16.4)	207 (11.7)	288 (17.2)	1,676 (56.9)	701 (53.2)
Intubation	38,563 (58.6)	26,937 (52.9)	5,282 (73.5)	1,454 (82.5)	1,257 (75.0)	2,453 (83.3)	1,180 (89.5)
Right heart catheterization	29,353 (44.6)	20,971 (41.2)	4,065 (56.6)	1,330 (75.4)	1,252 (74.7)	1,182 (40.1)	553 (42.0)
Renal replacement therapy	4,318 (6.6)	2,901 (5.7)	826 (11.5)	254 (14.4)	118 (7.0)	176 (6.0)	43 (3.3)
Cardiac surgery	4,882 (7.4)	3,273 (6.4)	614 (8.5)	753 (42.7)	35 (2.1)	56 (1.9)	151 (11.5)
Combination patterns of MCS							
IABP alone	48,643 (73.9)	40,340 (79.2)	5,679 (79.0)	1,164 (66.0)	576 (34.3)	836 (28.4)	48 (3.6)
ECMO+IABP	12,625 (19.2)	8,748 (17.2)	994 (13.8)	337 (19.1)	943 (56.2)	1,276 (43.3)	327 (24.8)
ECMO alone	3,873 (5.9)	1,388 (2.7)	420 (5.8)	243 (13.8)	71 (4.2)	809 (27.5)	942 (71.5)
ECMO+pVAD[e]	373 (0.6)	240 (0.5)	43 (0.6)	12 (0.7)	61 (3.6)	16 (0.5)	1 (0.1)
pVAD alone[f]	323 (0.5)	232 (0.5)	49 (0.7)	7 (0.4)	26 (1.6)	9 (0.3)	0 (0.0)

Values are mean ± SD or n (%). [a]1 patient was described as being aged 121 years and was regarded as missing data. [b]Height recorded as <50 cm and weight recorded as <20 kg or 600 kg were regarded as missing data. There were 8,405 missing data. [c]There were 5 missing data. [d]On or before the date when MCS was introduced. [e]IABP was used in 123 patients (33.0%). [f]IABP was used in 79 patients (24.5%).

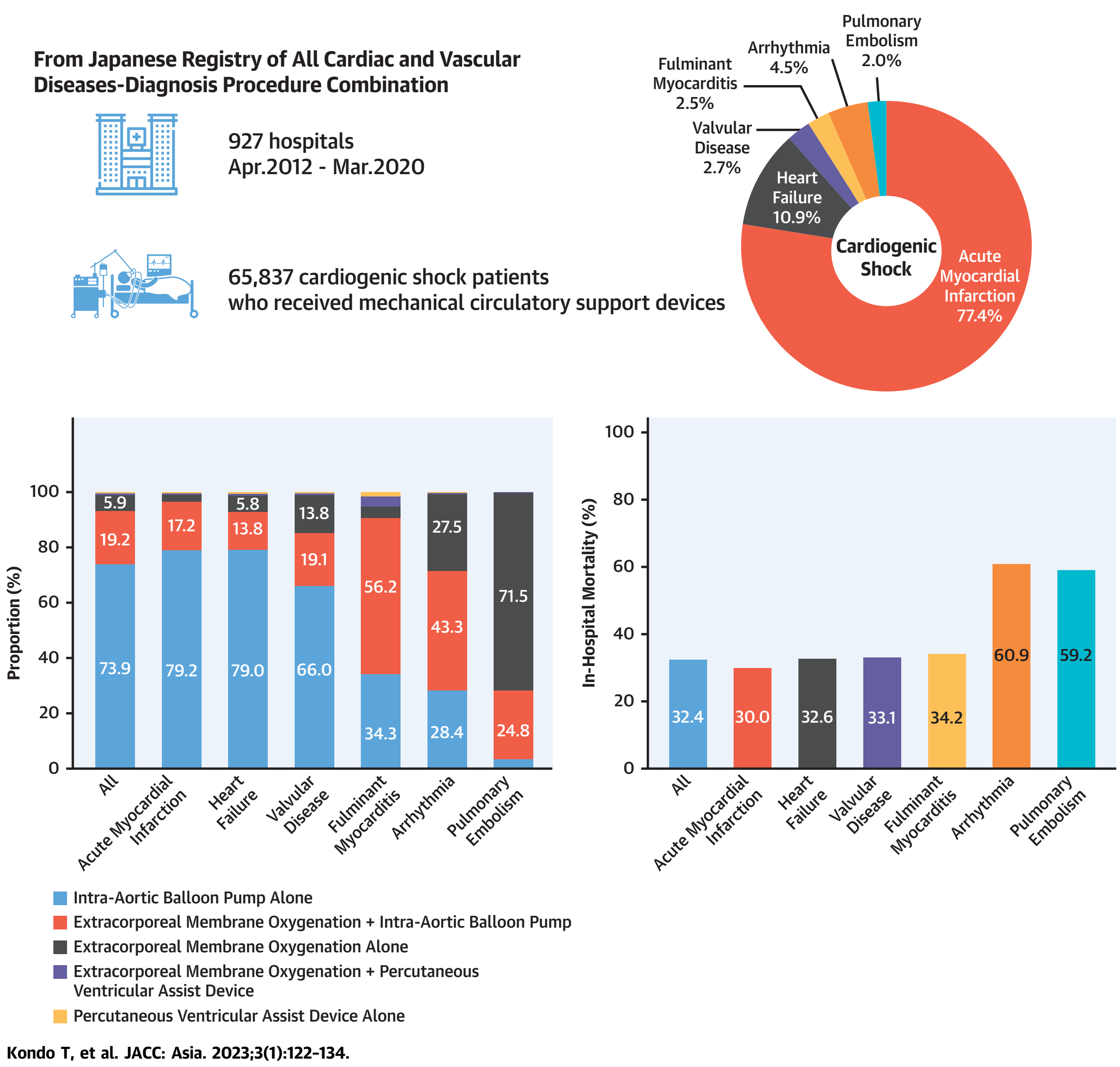
AMI = acute myocardial infarction; CS = cardiogenic shock; ECMO = extracorporeal membrane oxygenation; FM = fulminant myocarditis; HF = heart failure; IABP = intra-aortic balloon pump; MCS = mechanical circulatory support; PE = pulmonary embolism; pVAD = percutaneous ventricular assist device.

multiple causes, the diagnosis priority order was defined as FM, PE, AMI, valvular disease, HF, and then arrhythmia. The MCS device used was identified from the device supplies recorded and procedural codes. Regarding the combination patterns of MCS, patients who used both IABP and pVAD were classified into the group using pVAD, and then classified into the following 5 groups: IABP alone; ECMO+IABP; ECMO alone; ECMO+pVAD; and pVAD alone.

OUTCOME. The outcome measures in this study were in-hospital mortality, length of hospital stay, duration of MCS support, and hospitalization costs. The subgroup with fewer than 20 cases was omitted from the assessment of mortality. Hospitalization costs were converted to US dollars at the current exchange rate ($1 USD = 110.0 Japanese yen).

STATISTICAL ANALYSIS. Continuous variables were expressed as mean ± SD or median (IQR), and categorical variables were expressed as frequencies with percentages. The Cochran-Armitage trend test was used to evaluate the trend of in-hospital mortality according to year or age category. Multivariable logistic

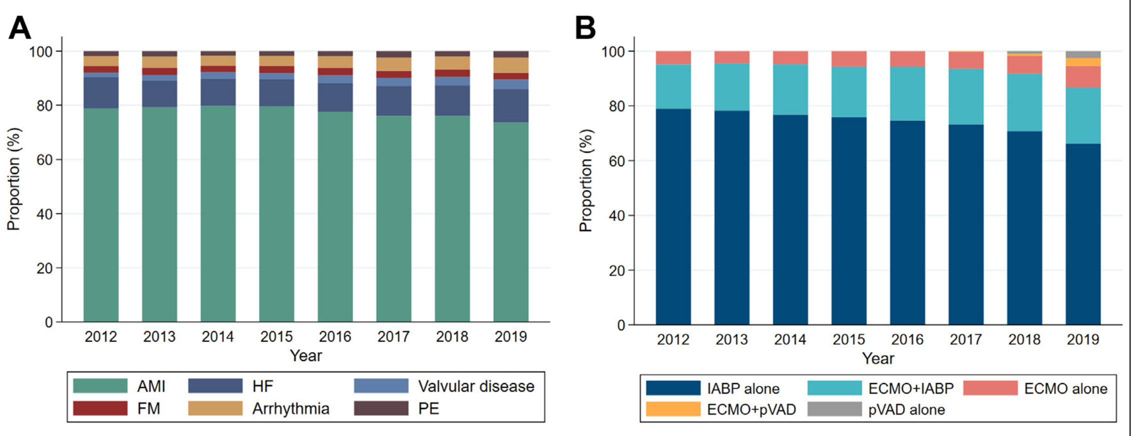
CENTRAL ILLUSTRATION Cause of Cardiogenic Shock, Mechanical Circulatory Support Patterns, and In-Hospital Mortality in Cardiogenic Shock



Three-quarters of cases of cardiogenic shock (CS) in patients who received mechanical circulatory support (MCS) were caused by acute myocardial infarction (AMI), but other causes account for about one-quarter of the cases. The combinations of MCS used for each cause of CS vary widely. Large variations in in-hospital mortality rates were observed. ECMO = extracorporeal membrane oxygenation; FM = fulminant myocarditis; HF = heart failure; IABP = intra-aortic balloon pump; JROAD-DPC = Japanese Registry of All Cardiac and Vascular Diseases—Diagnosis Procedure Combination; PE = pulmonary embolism; pVAD = percutaneous ventricular assist device.

regression models were constructed to identify independent variables associated with in-hospital mortality for the overall CS population and patients within each cause of CS. The model included age category, sex, body mass index, comorbidities, annual number of MCS devices used, therapeutic procedure, combination patterns of MCS, cause of CS, and era. In the temporal trends analyses, a year was defined as the period from April in that particular year to March of the following year (eg, year 2015 covered the period

FIGURE 1 Trends in Causes of CS and Combination Patterns of MCS



Temporal trends in cause of cardiogenic shock (CS), 2012-2019 **(A)** and combination patterns of mechanical circulatory support (MCS), 2012-2019 **(B)**. The proportion of patients with acute myocardial infarction (AMI) decreased over time (*P* for trend < 0.001). The proportion of use of intra-aortic balloon pump (IABP) alone decreased over time (*P* for trend < 0.001). Percutaneous ventricular assist device (pVAD) was introduced clinically in 2017. All *P* values for trend were statistically significant (ie, <0.05) except for the heart failure (HF) and fulminant myocarditis (FM) groups. ECMO = extracorporeal membrane oxygenation; PE = pulmonary embolism.

from April 1, 2015, to March 31, 2016). Renal replacement therapy and cardiac surgery were excluded from variables for multivariable analysis because these procedures were performed a median of 2 and 3 days later than the start of MCS, respectively. As some covariables were missing (age missing in <0.1%, body mass index in 12.8%, and hospital bed size in <0.1%), multivariable analyses were conducted with multiple imputation by chained equations; 20 imputed data sets were created and the estimates of analysis per data set were integrated using Rubin's rule. As sensitivity analyses, multivariable models, adjusted only for cause of CS and combination patterns of MCS, were conducted. All statistical analyses were performed using Stata/MP (version 16.1, Stata Corp). Values of $P < 0.05$ were considered statistically significant.

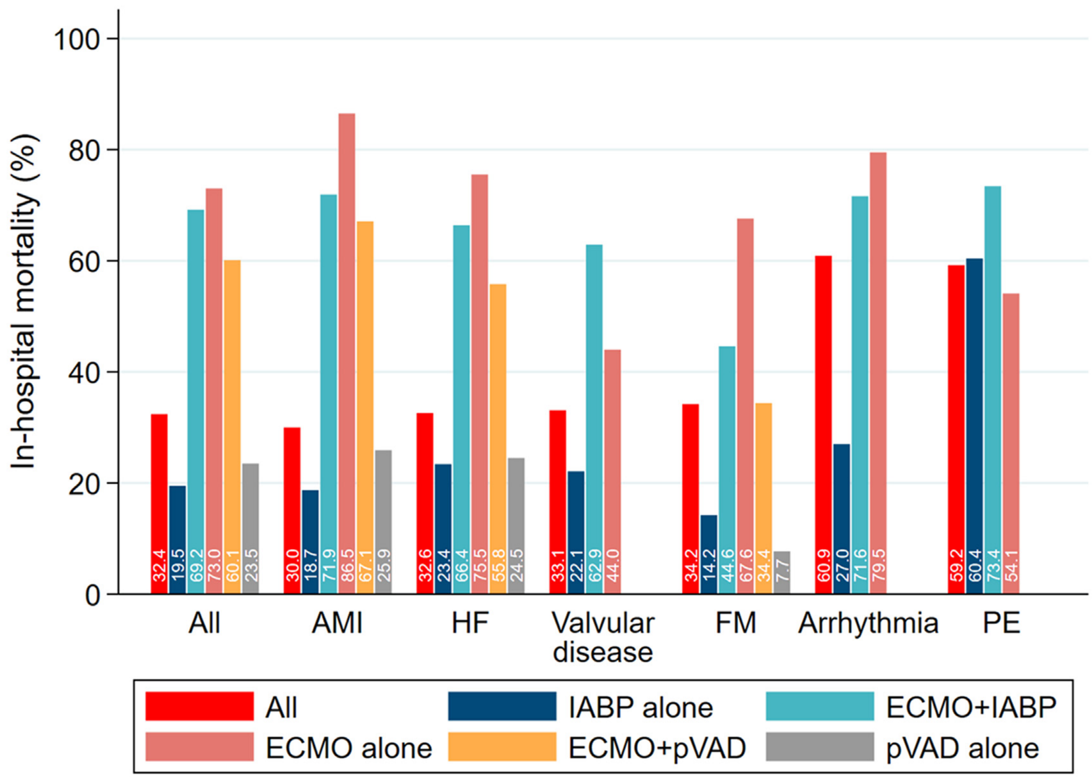
RESULTS

The JROAD-DPC database included 9,825,635 health records from 1,086 hospitals between April 1, 2012, and March 31, 2020. Overall, 114,874 patients aged 18 years or older received temporary MCS during hospitalization. We excluded 18,282 patients with nonemergent admissions, 24,402 patients without the disease diagnoses prespecified as a potential cause of CS, and 6,353 patients of postcardiotomy (Supplemental Figure 1). The remaining 65,837 patients from 927 hospitals (mean age: 69.0 years) were analyzed in this study.

PATIENT CHARACTERISTICS. Of the 65,837 qualifying patients receiving temporary MCS for CS, 50,948 (77.4%) had an AMI, 7,185 (10.9%) HF, 1,763 (2.7%) valvular disease, 1,677 (2.5%) FM, 2,946 (4.5%) an arrhythmia, and 1,318 (2.0%) a PE. Patient characteristics according to causes of CS are shown in **Table 1**. Patients in the AMI, HF, and valvular disease groups were older and those in the FM, arrhythmia, and PE groups were younger. There were more men than women overall, although there were more women in the valvular disease and PE groups. Patients in the arrhythmia and PE groups received cardiopulmonary resuscitation more frequently on or before the date MCS was started. Patients in the valvular disease group received right heart catheterization and underwent cardiac surgery more frequently. Percutaneous coronary intervention or coronary artery bypass graft during hospitalization was performed in 89.9% and 5.4% of patients, respectively, in the AMI group; 39.5% and 6.9%, respectively, in the HF group; 11.5% and 15.4%, respectively, in the valvular disease group; and 18.1% and 1.6%, respectively in the arrhythmia group. The breakdown of the type of valvular disease is shown in Supplemental Table 2. The median duration from hospital arrival to initiation of MCS was 0 days except for patients in the HF and valvular disease groups, where the median time was 1 day.

Most patients (79.2%) with AMI received an IABP alone, with the combination of ECMO and IABP used

FIGURE 2 **In-Hospital Mortality According to CS Cause and MCS Patterns**



Large variations in in-hospital mortality rates were observed according to combination patterns of MCS in each cause of CS. pVAD alone and ECMO+pVAD groups in patients with valvular disease, arrhythmia, and PE were excluded from the analysis because these group contained fewer than 20 cases. Abbreviations as in **Figure 1**.

in 17.2% (**Table 1, Central Illustration**). The pattern was similar in patients with HF and valvular disease. In patients with FM, the most commonly used MCS was the combination of ECMO and IABP (56.2%) with 34.3% receiving IABP alone. In patients with an arrhythmia, 43.3% received the combination of ECMO and IABP, 28.4% IABP alone, and 27.5% ECMO alone. In patients with PE, the most common MCS used was ECMO alone (71.5%) followed by the combination of ECMO and IABP (24.8%). Patient characteristics categorized by combination patterns of MCS and by age groups are shown in Supplemental Tables 3 and 4. FM, arrhythmia, and PE accounted for a higher proportion of causes of CS in younger patients. The older the patient, the less frequently ECMO was used and the more frequently IABP was used.

TEMPORAL TREND OF PATIENTS CHARACTERISTICS. Temporal trends in patient characteristics are shown in Supplemental Table 5. Over time, patients became older, with a substantial increase in the proportion aged >80 years; 20.8% in 2012-2013 and 24.9% in 2018-2019. The proportion of patients with AMI decreased over time, whereas the proportion with HF increased (**Figure 1A**). pVADs were introduced clinically in 2017, and the number of cases receiving a pVAD gradually increased, whereas the proportion of patients treated with IABP alone fell by about 10% during the period of observation (**Figure 1B**). Temporal trends in combination patterns of MCS according to causes of CS are shown in detail in Supplemental Table 6 and Supplemental Figure 2. The use of pVADs increased markedly in the FM group.

PATIENT OUTCOMES. The in-hospital mortality for each combination pattern of MCS according to causes of CS is shown in **Figure 2**. The in-hospital mortality for patients with CS, overall, was 32.4%. The in-hospital mortality was similar in patients with AMI (30.0%), HF (32.6%), valvular disease (33.1%), and FM (34.2%), but it was significantly higher in patients with arrhythmia (60.9%) or PE (59.2%). For patients with

TABLE 2 Length of Hospital Stay, Duration of MCS, and Costs by Causes of CS

	All	AMI	HF	Valvular Disease	FM	Arrythmia	PE
Length of hospital stay, days	19 (10-32)	18 (10-29)	28 (16-47)	31 (16-52)	21 (8-39)	9 (2-31)	13 (3-35)
Patients discharged alive	23 (16-37)	21 (15-33)	32 (21-53)	38 (24-58)	27 (16-45)	35 (23-53)	40 (25-62)
Patients discharged dead	5 (2-17)	5 (2-16)	17 (6-35)	16 (6-35)	9 (4-21)	2 (1-7)	4 (2-10.5)
Duration of MCS, days	3 (2-5)	3 (2-4)	4 (2-6)	3 (2-6)	6 (3-9)	3 (2-5)	3 (2-5)
Patients discharged alive	3 (2-4)	3 (2-4)	3 (2-6)	3 (2-5)	6 (4-8)	4 (2-5)	3 (2-5)
Patients discharged dead	3 (2-6)	3 (1-6)	4 (2-8)	4 (2-8)	6 (3-12)	2 (1-4)	3 (1-5)
Hospitalization costs, thousand USD	30.1 (21.5, 44.8)	29.4 (21.7-42.2)	34.4 (22.1-53.5)	63.4 (35.2-83.7)	33.8 (21.4-52.7)	24.1 (11.4-47.6)	28.8 (15.4-46.4)
Patients discharged alive	31.9 (23.7-45.9)	30.6 (23.4-42.4)	36.1 (24.3-55.0)	67.6 (49.7-84.0)	34.6 (24.2-52.1)	51.8 (33.9-74.9)	44.7 (32.2-59.0)
Patients discharged dead	24.9 (16.0-41.9)	25.4 (17.1-41.6)	30.1 (16.6-50.4)	45.0 (21.3-82.6)	31.2 (16.4-54.6)	13.9 (8.7-24.7)	18.7 (11.8-31.2)

Values are median (IQR).
Abbreviations as in Table 1.

CS, overall, the in-hospital mortality was 19.5%, 69.2%, 73.0%, 60.1%, and 23.5% for patients who were treated with IABP alone, ECMO with IABP, ECMO alone, ECMO with pVAD, and pVAD alone, respectively. In-hospital mortality with IABP alone or ECMO with IABP was lowest in the FM group, and in-hospital mortality with ECMO alone was lowest in the valvular disease group. The median length of hospital stay for patients with CS who were discharged alive was 23 days, with the shortest stay in the AMI group (21 days) and the longest in the PE group (40 days) (Table 2). MCS was used for 3 (IQR: 2-4) days for patients with CS who were discharged alive, and patients in the FM group received MCS for about twice as long (6 days) as the other groups. The median cost of hospitalization for management of CS was $30.1 (IQR: $21.5-$44.8) thousand USD and was highest in the valvular disease group. Length of hospital stay, duration of MCS use, and hospitalization cost by combination patterns of MCS used are described in Table 3. Length of hospital stay tended to be longer in patients discharged alive who received ECMO alone, ECMO with IABP, and ECMO with pVAD, and hospitalization costs tended to be higher in patients who received pVAD alone and ECMO with pVAD. The in-hospital mortality according to age subgroups is shown in Figure 3. In-hospital mortality tended to increase with age in the AMI and FM groups; 21.7% in patients aged 18-40 years and 40.2% in patients aged ≥80 years in the AMI group, and 22.9% and 60.0% in the FM group, respectively. But this trend was less pronounced in the HF, valvular disease, arrhythmia, and PE groups. In-hospital mortality tended to increase with age for all combination patterns of MCS. The in-hospital mortality by sex and procedures is presented in Supplemental Table 7.

TEMPORAL TRENDS IN PATIENT OUTCOMES. The in-hospital mortality for patients with CS, overall, increased slightly from 30.4% in 2012 to 34.1% in 2019 ($P < 0.001$) (Figure 4A). By cause of CS, in-hospital mortality increased over time in the AMI group from 27.7% in 2012 to 32.1% in 2019, but decreased in the FM group from 44.2% in 2012 to 30.5% in 2019. However, length of hospital stay, duration of MCS support, and hospitalization costs did not show large differences over time (Supplemental Table 8). Examination of combinations of MCS, showed that in-hospital mortality for patients receiving ECMO or ECMO with an IABP improved over time, but this trend was not observed in patients with an IABP alone (Figure 4B). Temporal trends in the in-hospital mortality for each combination pattern of MCS according to causes of CS are shown in detail in Supplemental Table 8 and Supplemental Figure 3.

MULTIVARIABLE ANALYSIS FOR IN-HOSPITAL MORTALITY. After adjustment for background variables and choice of MCS, including combinations, patients in the valvular disease, FM, and PE groups had better survival (valvular disease: OR: 0.56, 95% CI: 0.50-0.64; FM: OR: 0.58, 95% CI: 0.52-0.66; PE: OR: 0.49, 95% CI: 0.43-0.56) than those in the AMI group did, whereas patients in the HF group had similar survival (OR: 0.99; 95% CI: 0.92-1.05) and those in the arrhythmia group had worse survival (OR: 1.14, 95% CI: 1.04-1.26) (Table 4). Patients with any combination of MCS had a worse prognosis than those managed with an IABP alone. In-hospital mortality varied significantly according to the cause of CS and the combination of MCS used (*P* interaction < 0.001). In-hospital mortality tended to improve over time (OR: 0.81; 95% CI: 0.76-0.86 in 2018-2019, with 2012-2013 as reference). In addition, older age, low or high body mass index, annual number of MCS devices used, need for cardiopulmonary resuscitation, intubation, and nonuse of right heart catheterization were also associated with poor survival. Stratified by the cause of CS, patients treated with

TABLE 3 Length of Hospital Stay, Duration of MCS Support, and Costs by Combination Patterns of MCS

	IABP Alone	ECMO+IABP	ECMO Alone	ECMO+pVAD	pVAD Alone
Length of hospital stay, days	20 (13-32)	11 (3-32)	4 (1-22)	23 (8-49)	27 (17-45)
Patients discharged alive	22 (15-34)	39 (24-61)	36 (22-56)	49 (28-78)	30 (19-49)
Patients discharged dead	8 (2-24)	5 (2-15)	2 (1-6)	13 (5-24)	13 (3-32)
Duration of MCS support, days	3 (2-4)	4 (2-8)	2 (1-3)	8 (4-14)	4 (2-8)
Patients discharged alive	3 (2-4)	5 (3-, 8)	2 (1-4)	7 (4-10)	4 (2-7)
Patients discharged dead	3 (2-6)	4 (2-8)	1 (1-2)	9 (4-16.5)	6 (2-9.5)
Hospitalization costs, thousand USD	29.5 (21.9-41.7)	36.5 (22.7-57.1)	18.2 (9.0-37.1)	79.1 (56.9-108.5)	60.6 (48.9-79.9)
Patients discharged alive	30.3 (23.1-42.0)	53.3 (39.6-74.2)	45.5 (31.5-67.0)	81.5 (65.4-112.6)	60.6 (49.7-79.1)
Patients discharged dead	24.1 (15.6-40.5)	28.9 (20.1-46.4)	13.1 (7.8-21.6)	77.1 (52.9-105.3)	62.7 (44.9-90.0)

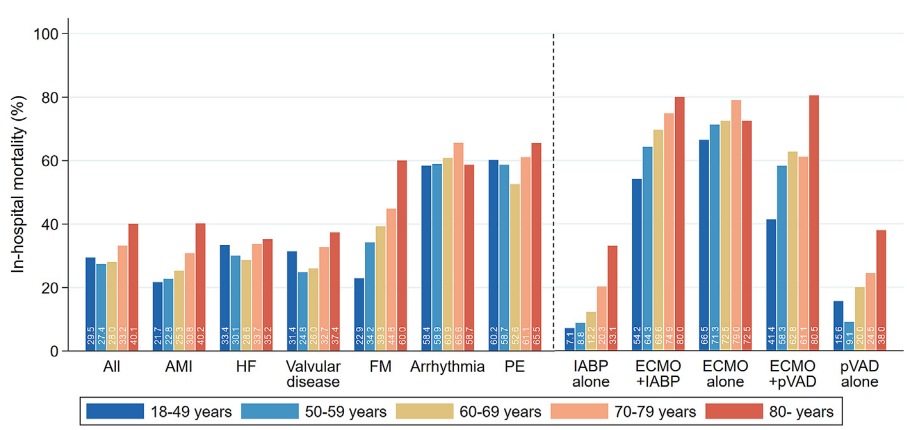
Values are median (IQR).
Abbreviations as in Table 1.

ECMO alone or the combination of ECMO and IABP had a worse prognosis compared to IABP alone, and the OR was higher in the AMI group when compared to the HF and PE groups. The relationship between older age and worse prognosis was more pronounced in the AMI and FM groups. The need for cardiopulmonary resuscitation was associated with 2-3 times higher risk of in-hospital mortality for all causes of CS. Over time, in-hospital adjusted mortality tended to improve for all causes of CS. As sensitivity analyses, multivariable models including only either cause of CS or combination patterns of MCS are shown in Supplemental Table 9.

DISCUSSION

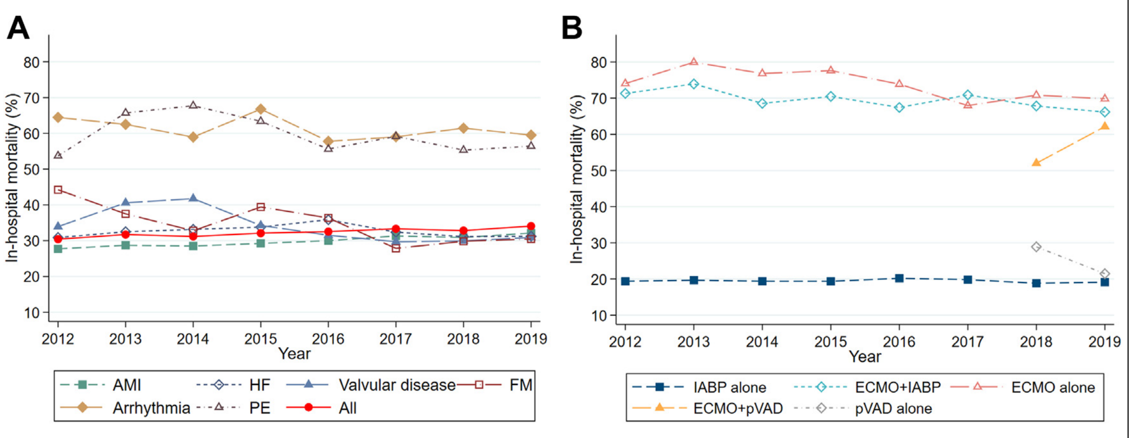
Our nationwide data set of more than 65,000 patients with CS who received temporary MCS described contemporary causes of CS in Japan and the types of MCS used for each cause of CS, including combinations of devices. In addition, we have described the changing trends in causes of CS, patient characteristics, MCS used, and survival. There were clear differences in mortality depending on the cause of CS and in the types of MCS used to treat different causes of CS. In-hospital mortality was about twice as high as in patients with arrhythmia or PE as the cause of CS compared to AMI, HF, or FM. There were also substantial differences in duration of MCS support, overall length of hospital stay, and hospitalization costs between causes of CS and between the type of MCS used, alone or in combination. Over time, the frequency of AMI decreased, the frequency of HF increased, the use of IABP decreased, the use of ECMO increased, and adjusted in-hospital mortality improved over time.

FIGURE 3 In-Hospital Mortality According to CS Cause, MCS Patterns, and Age



In-hospital mortality tended to increase with age in the AMI and FM groups, but this was less pronounced in the HF, arrhythmia, and PE groups. In-hospital mortality tended to increase with age for all combination patterns of MCS. *P* values for trend were statistically significant (ie, <0.05) for all groups except the PE group. Abbreviations as in Figure 1.

FIGURE 4 Temporal Trends in In-Hospital Mortality



Temporal trends in in-hospital mortality according to causes of CS, 2012-2019 **(A)**, and in-hospital mortality according to combination patterns of MCS, 2012-2019 **(B)**. The in-hospital mortality, overall, increased from 30.4% in 2012 to 34.1% in 2019 ($P < 0.001$). In-hospital mortality for patients receiving ECMO or ECMO with an IABP improved over time, but not in patients with an IABP alone. *P* values for trend were statistically significant (ie, <0.05) in all, AMI, valvular disease, FM, ECMO+IABP, and ECMO alone groups. *The mortality in patients with pVAD alone in 2017 were excluded from the analysis in **B** because this group contained fewer than 20 cases. Abbreviations as in Figure 1.

CAUSES OF CS AND TYPES OF MCS USED FOR DIFFERENT CAUSES OF CS. In addition to documenting the changing trends in causes of CS over time, we have also described the types of MCS used according to cause of CS and the fact that MCS devices are often used in combination. These combinations differ markedly by cause of CS, which we believe have not been well reported before. The combinations of MCS devices used seemed to reflect the cause-specific pathophysiological characteristics of the patients with CS; for example, IABP may have been used in AMI to enhance coronary blood flow and ECMO may have been used in CS caused by an arrhythmia to provide extracorporeal cardiopulmonary resuscitation. ECMO was probably chosen more often in FM because of biventricular failure and in PE because of right-ventricular failure.

MORTALITY RELATED TO CAUSE OF CS AND MCS USED. In previous studies of this type, a binary classification of causes of CS has usually been reported, with patients categorized as having an AMI or a non-AMI cause, with a more detailed classification of non-AMI causes of CS rarely described.[5,9] We have provided a more granular breakdown of non-AMI causes of CS and shown clear evidence of clearly different cause-specific mortality rates among patients with CS who received temporary MCS. Survival was associated not only with the cause of CS, but also the type of MCS used and differences in patient characteristics. It was evident that patients receiving ECMO had higher in-hospital mortality than those managed with an IABP alone, which is in line with some other reports.[5,6,14] Interestingly, whereas the crude in-hospital mortality in patients with valvular disease and FM was higher than in those with AMI, the ORs were lower after adjustment for the type of MCS used and other variables. Furthermore, the relationship between the type of MCS used and in-hospital mortality differed significantly by cause of CS. For example, there was a 53% difference in mortality between CS caused by AMI treated with IABP only, compared with the combination of IABP and ECMO; however, this difference was only 30% for CS caused by FM. This might reflect the fact that the severity of CS varies according to the cause of CS, even when the same MCS device is used.

Recently, a comprehensive approach to management of CS, including diagnostic and therapeutic algorithms, use of shock teams, and specialized patient transport systems, has been advocated to improve outcomes from CS.[7,8,23-25] Our results suggest that a more detailed approach, taking account of different causes of CS, may also be needed to further optimize the treatment and prognosis of CS. However, because the relationship between age and mortality in the present study was different for certain causes of CS, the criteria for age in determining the indication for MCS may need to vary for each cause of CS.

TABLE 4 Multivariable Analysis for In-Hospital Mortality by Causes of CS

	All	AMI	HF	Valvular Disease	FM	Arrhythmia	PE
Age groups, y							
18-49	Reference	Reference	Reference	Reference	Reference	Reference	Reference
50-59	1.35 (1.23-1.49)	1.44 (1.27-1.65)	1.15 (0.87-1.53)	0.58 (0.25-1.35)	2.13 (1.50-3.02)	1.37 (1.06-1.78)	1.01 (0.70-1.44)
60-69	1.76 (1.62-1.92)	2.02 (1.79-2.28)	1.24 (0.97-1.60)	0.60 (0.29-1.26)	2.66 (1.92-3.67)	1.73 (1.35-2.23)	0.76 (0.54-1.07)
70-79	2.88 (2.64-3.13)	3.40 (3.01-3.82)	1.82 (1.43-2.32)	1.11 (0.55-2.24)	3.58 (2.52-5.07)	2.57 (1.97-3.36)	1.10 (0.78-1.54)
≥80	5.34 (4.88-5.85)	6.94 (6.14-7.85)	2.30 (1.79-2.95)	1.52 (0.75-3.05)	12.61 (7.43-21.39)	2.63 (1.78-3.89)	1.39 (0.89-2.16)
Male	0.87 (0.83-0.92)	0.83 (0.78-0.87)	0.92 (0.81-1.04)	1.12 (0.88-1.42)	0.97 (0.76-1.23)	1.03 (0.82-1.29)	1.24 (0.97-1.57)
Body mass index categories, kg/m^2							
≤18.4	1.16 (1.07-1.26)	1.21 (1.09-1.34)	1.10 (0.92-1.33)	1.11 (0.81-1.52)	0.72 (0.48-1.09)	0.87 (0.62-1.22)	1.58 (0.84-2.95)
18.5-24.9	Reference	Reference	Reference	Reference	Reference	Reference	
25.0-29.9	1.08 (1.03-1.14)	1.08 (1.02-1.15)	0.95 (0.81-1.11)	1.10 (0.79-1.54)	1.06 (0.78-1.44)	1.56 (1.24-1.97)	1.07 (0.80-1.43)
≥30.0	1.56 (1.42-1.71)	1.58 (1.41-1.78)	1.14 (0.87-1.48)	2.75 (1.49-5.09)	1.29 (0.67-2.51)	1.81 (1.23-2.65)	1.64 (1.11-2.45)
Chronic kidney disease	1.69 (1.58-1.81)	1.62 (1.49-1.76)	1.87 (1.62-2.17)	2.01 (1.52-2.66)	2.39 (1.23-4.67)	1.43 (1.04-1.97)	0.68 (0.35-1.31)
Diabetes mellitus	0.66 (0.63-0.69)	0.65 (0.61-0.68)	0.75 (0.66-0.85)	0.67 (0.50-0.90)	1.23 (0.82-1.86)	0.59 (0.46-0.76)	0.69 (0.48-1.01)
Annual number of MCS used at each facility							
1-10	Reference	Reference	Reference	Reference	Reference	Reference	Reference
11-20	0.85 (0.81-0.90)	0.84 (0.79-0.90)	0.92 (0.78-1.07)	0.87 (0.60-1.24)	1.07 (0.77-1.48)	0.80 (0.60-1.05)	0.85 (0.61-1.18)
21-30	0.71 (0.67-0.75)	0.65 (0.60-0.70)	0.78 (0.66-0.93)	1.26 (0.86-1.86)	1.18 (0.82-1.69)	0.95 (0.71-1.27)	0.80 (0.55-1.15)
≥31	0.74 (0.70-0.79)	0.70 (0.65-0.75)	0.84 (0.72-0.99)	0.95 (0.66-1.35)	0.99 (0.71-1.39)	0.94 (0.70-1.24)	0.86 (0.61-1.22)
Procedure							
Cardiopulmonary resuscitation[a]	2.93 (2.78-3.08)	3.02 (2.84-3.21)	3.06 (2.63-3.56)	3.31 (2.31-4.74)	2.48 (1.84-3.34)	2.13 (1.78-2.56)	2.28 (1.80-2.88)
Intubation	3.00 (2.86-3.15)	3.54 (3.35-3.73)	2.11 (1.83-2.44)	1.63 (1.18-2.24)	1.77 (1.26-2.49)	0.63 (0.49-0.81)	0.57 (0.38-0.86)
Right heart catheterization	0.75 (0.72-0.79)	0.75 (0.72-0.79)	0.86 (0.76-0.97)	0.63 (0.49-0.83)	0.53 (0.40-0.70)	0.59 (0.49-0.72)	0.63 (0.50-0.81)
Combination patterns of MCS[b]							
IABP alone	Reference	Reference	Reference	Reference	Reference	Reference	Reference
ECMO+IABP	7.94 (7.52-8.38)	8.62 (8.08-9.19)	5.35 (4.55-6.30)	5.12 (3.84-6.83)	5.75 (4.11-8.06)	7.28 (5.84-9.08)	2.07 (1.06-4.03)
ECMO alone	9.08 (8.24-10.00)	18.76 (15.82-22.25)	7.14 (5.55-9.19)	2.29 (1.64-3.19)	11.2 (5.97-21.04)	8.74 (6.72-11.36)	0.81 (0.43-1.51)
ECMO+pVAD	8.36 (6.65-10.51)	10.00 (7.45-13.42)	5.75 (3.04-10.89)		4.75 (2.40-9.39)		
pVAD alone	1.52 (1.15-2.00)	1.70 (1.23-2.34)	1.33 (0.67-2.65)		0.79 (0.17-3.62)		
Cause of CS							
AMI	Reference						
HF	0.99 (0.92-1.05)						
Valvular disease	0.56 (0.50-0.64)						
FM	0.58 (0.52-0.66)						
Arrhythmia	1.14 (1.04-1.26)						
PE	0.49 (0.43-0.56)						
Era							
2012-2013	Reference	Reference	Reference	Reference	Reference	Reference	Reference
2014-2015	0.91 (0.86-0.97)	0.88 (0.82-0.95)	1.08 (0.91-1.29)	0.90 (0.62-1.31)	0.85 (0.60-1.21)	0.80 (0.60-1.06)	1.34 (0.92-1.94)
2016-2017	0.90 (0.85-0.96)	0.93 (0.87-1.00)	1.05 (0.89-1.24)	0.57 (0.40-0.82)	0.66 (0.47-0.93)	0.65 (0.50-0.85)	0.90 (0.64-1.26)
2018-2019	0.81 (0.76-0.86)	0.82 (0.76-0.88)	0.85 (0.72-1.01)	0.55 (0.39-0.79)	0.66 (0.46-0.94)	0.73 (0.56-0.95)	0.87 (0.62-1.22)

Values are odds ratio (95% CI). [a]On or before the date when MCS was introduced. [b]pVAD alone or ECMO+pVAD were excluded from the models in the valvular disease, arrhythmia, and PE groups because these group contained fewer than 20 cases.

Abbreviations as in Table 1.

TEMPORAL TRENDS OF CAUSE OF CS, MCS USED, AND MORTALITY. By salvaging jeopardized myocardium, early coronary reperfusion has reduced the extent of myocardial necrosis in patients with AMI.[26] Consistent with this, we found the incidence of CS attributed to AMI had declined over time, as was described by other investigators.[5,9]

Regarding choice of MCS device, the pVAD was introduced in Japan in 2017, and its use has been increasing gradually since then. The use of ECMO has also increased and, as a result, the relative use of IABP has decreased over time, in line with reports from other countries, although the IABP is still the most frequently used MCS device overall. Following the IABP-SHOCK II trial, the use of IABP for AMI has decreased worldwide, although this trend varies widely by region and may reflect regional differences in guideline recommendations and health systems.[5,13,15,26-29]

Although there have been a number of reports on mortality trends in CS over time, these analyses have rarely adjusted for changes in patient characteristics and changes in the severity of CS.[6] When these factors were adjusted for in our population, the risk of death decreased over time, although crude mortality increased slightly. The improvement in adjusted survival may be related to better prognosis among severely ill patients requiring ECMO. However, to date, there are no randomized controlled trials proving any specific MCS device improves the outcome of CS, and randomized controlled trials evaluating pVAD or ECMO are now underway.[30]

DIFFERENCES IN MORTALITY AND STRATEGIES WITH OTHER STUDIES. The mortality rate for CS in other studies has been reported to be around 40%-50%,[1-3,5,6,9,13,14] which is somewhat higher than our mortality rate of 32.4%. This discrepancy may be explained by several factors. First is difference in revascularization rate. Early revascularization has been proven to improve the prognosis of AMI, and the rate of percutaneous coronary intervention was only 40%-60% in prior reports,[5,9,31] compared with almost 90% in our study. The use of right heart catheterization has been reported to be associated with better prognosis[32] and was shown to be an independent prognostic factor in our study. Right heart catheterization was performed in 44.6% in our patients, compared with a much lower rate of around 15% in previous studies.[5,9] The high rates of percutaneous coronary intervention and right heart catheterization may also reflect a better overall system of care than in prior studies, including early triage and transport systems, and so on. Conversely, differences in indications and thresholds between countries for use of MCS may explain the differences observed in in-hospital mortality.

STUDY LIMITATIONS. Although we used a large nationwide database, our study has several limitations. Laboratory data, data on physiological tests, and hemodynamic data were not available, and we did not have information on the Society for Cardiovascular Angiography and Interventions shock stage classification.[33] Consequently, our multivariable analysis may not have fully adjusted for all potential prognostic variables, including information on sufficiency of circulatory support and adequacy of end-organ perfusion. The differences in mortality related to use of specific types of MCS reflect associations and not cause and effect. We may not have adjusted for all the selection biases influencing choice of MCS device. Although the classification of cause of CS is based on both a well-validated code and clinical usefulness, there is still the possibility of misclassification bias caused by recorded codes. We excluded patients who received MCS because of postcardiotomy and who were admitted in the setting of planned hospitalization. Whereas we were able to identify use of more than 1 type of MCS, we did not always know whether these were used simultaneously or sequentially. Consequently, we were unable to analyze whether the prognosis differed according to the sequence of use of MCS in patients receiving more than 1 device. Finally, our analysis was limited to data for Japan; therefore, our findings may not be generalizable to other countries or health care systems.

CONCLUSIONS

From a large nationwide medical database, we identified the causes of CS and the type of MCS used, and how choice of device varied by cause of CS with annual trends. We showed that prognosis was different according to the cause of CS, as was the choice of MCS used for each cause of CS. Crude mortality related to CS increased over time, but this reflected changes in patient characteristics, cause of CS, and choice of MCS devices used over time.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: There were clear differences in mortality depending on the cause of CS and in the types of MCS used to treat different causes of CS.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine the most appropriate combination patterns of MCS according to the cause and severity of CS.

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APPENDIX For supplemental figures and tables, please see the online version of this paper.