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ORIGINAL RESEARCH

Effectiveness of an Impella Versus Intra-Aortic Balloon Pump in Patients Who Received Extracorporeal Membrane Oxygenation

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BACKGROUND: It is unclear whether an intra-aortic balloon pump (IABP) or percutaneous ventricular assist device (Impella) in combination with extracorporeal membrane oxygenation (ECMO) is better.

METHODS: Using the Japanese Diagnosis Procedure Combination database from September 2016 to March 2022, we identified inpatients who received an Impella or IABP in combination with ECMO (ECPella or ECMO+IABP group, respectively). The primary outcome was in-hospital mortality, and the secondary outcomes included the length of hospital stay, length of ECMO, total hospitalization cost, complications, and durable mechanical circulatory support implantations. Propensity score matching was performed to compare the outcomes between the groups.

RESULTS: Of 14 319 eligible patients, 590 (4.1%) received ECPella and 13 729 (96%) received ECMO+IABP. The mean age of patients was 65 years, 77% were men, and 57% had acute coronary syndrome. After propensity score matching, the patient characteristics were well balanced between the groups. The 14-day mortality rate was lower in the ECPella group than in the ECMO+IABP group (28.0% versus 36.8%; risk difference, −8.2% [95% CI, −13.8 to −2.7]), whereas there was no significant difference in in-hospital mortality between the groups (58.3% versus 56.6%; risk difference, 2.4% [95% CI, −3.5 to 8.2]). The ECPella group had a higher total hospitalization cost, increased renal replacement therapy during hospitalization, and more durable mechanical circulatory support implantations than the ECMO+IABP group.

CONCLUSIONS: This nationwide inpatient database study showed no significant difference in in-hospital mortality between the groups, but ECPella was associated with a higher total hospitalization cost, increased renal replacement therapy during hospitalization, and more durable mechanical circulatory support implantations than ECMO+IABP.

Key Words: cardiogenic shock ■ extracorporeal membrane oxygenation ■ heart assist device ■ intra-aortic balloon pump ■ mechanical circulatory support

Venoarterial extracorporeal membrane oxygenation (ECMO) provides strong hemodynamic support to patients with cardiogenic shock through retrograde aortic blood flow in addition to oxygenation[1]; however, even the latest evidence does not support a survival benefit with the routine use of ECMO in patients

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CLINICAL PERSPECTIVE

What Is New?

- To the best of our knowledge, this nationwide cohort study had the largest number of patients among the studies comparing a percutaneous ventricular assist device (Impella) versus intra-aortic balloon pump (IABP) in combination with venoarterial extracorporeal membrane oxygenation (ECMO) (ECPella versus ECMO+IABP).
- The 14-day mortality was lower in the ECPella group than in the ECMO+IABP group, whereas there was no significant difference in in-hospital mortality between the groups.
- ECPella was significantly associated with a higher total hospitalization cost, increased renal replacement therapy during hospitalization, and more durable mechanical circulatory support implantations than ECMO+IABP.

What Are the Clinical Implications?

- The present study provided no evidence of whether the use of IABP or Impella was better for in-hospital mortality after 14 days in combination with ECMO; however, it did indicate a higher total hospitalization cost, increased renal replacement therapy, and more durable mechanical circulatory support implantations for ECPella, suggesting that ECPella should be implemented in carefully selected patients.
- Further studies are warranted to investigate the outcomes according to the cause of the cardiogenic shock, learning curves for Impella use, and readmissions in patients who received the Impella.

Nonstandard Abbreviations and Acronyms

ECPella	combination of venoarterial extracorporeal membrane oxygenation and Impella
ECPR	extracorporeal cardiopulmonary resuscitation
IABP	intra-aortic balloon pump
RECORD	Reporting of Studies Conducted Using Observational Routinely Collected Health Data

with cardiogenic shock.[2,3] Potential reasons may include bleeding complications, peripheral vascular ischemia, pulmonary edema, and myocardial ischemia induced by an increased left ventricular (LV) afterload due to a strong retrograde aortic blood flow.[1]

Previous studies have suggested that LV unloading with an intra-aortic balloon pump (IABP) or percutaneous ventricular assist device (Impella, Abiomed) in combination with ECMO (ECMO+IABP or ECPella) is associated with a lower mortality.[4–8] Those studies primarily focused on the effectiveness of LV unloading with an IABP or Impella, using patients who received ECMO alone as controls. The IABP reduces the LV afterload and provides indirect LV unloading through a negative systolic pressure in the descending aorta,[9] whereas the Impella can directly decrease the LV overload and restore the pulmonary flow in patients with ECMO who present with severe LV dysfunction.[10] No randomized controlled trial has compared the outcomes of using the Impella versus IABP in combination with ECMO. A recent meta-analysis of 7 small-scale observational studies showed no survival benefit of ECPella compared with ECMO+IABP; however, those studies had a high heterogeneity, and the results of the meta-analysis were underpowered to assess the comparative effectiveness.[11] It remains unclear whether differences in the device characteristics between the IABP and Impella affect the clinical outcomes in patients with ECMO who require LV unloading. Therefore, the present study aimed to evaluate the effectiveness of an Impella versus IABP on in-hospital mortality and other clinical outcomes, using a nationwide inpatient database in Japan.

METHODS

Data Availability

The data sets analyzed during the current study are not publicly available owing to contracts with the hospitals providing the data to the database.

Design and Ethical Statement

This was a retrospective cohort study using an inpatient administrative database, and the study conformed to RECORD (Reporting of Studies Conducted Using Observational Routinely Collected Health Data) guidelines.[12] This study was conducted in accordance with the amended Declaration of Helsinki and was approved by the institutional review board of The University of Tokyo (approval number, 3501-(5); May 19, 2021). Because the data were anonymous, the institutional review board waived the requirement for informed consent.

Data Source

We used the Japanese Diagnosis Procedure Combination inpatient database, which contained administrative claims data and discharge abstracts from >1500 acute care hospitals and covers ≈90%

of all tertiary emergency hospitals in Japan.[13] The database includes the following patient-level data for all hospitalizations: age, sex, diagnoses (main diagnosis, admission-precipitating diagnosis, most resource-consuming diagnosis, second-most resource-consuming diagnosis, comorbidities present at admission, and complications arising after admission) recorded with the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes, daily procedures recorded using Japanese medical procedure codes, daily drug administration, and discharge status.[13] A previous validation study showed that the specificity of the recorded diagnoses in the database exceeded 96%, the sensitivity of the diagnoses ranged from 50% to 80%, and the specificity and sensitivity of the procedures both exceeded 90%.[14]

Study Population

We identified all patients who received ECMO during hospitalization from September 28, 2016, to March 31, 2022. September 28, 2016, was the date when the Impella was approved for reimbursement under the national health insurance in Japan. We excluded patients younger than 18 years, those who had received neither an Impella nor an IABP within 2 days before or after the ECMO initiation, and those with aortic disease as a primary diagnosis on admission. All patients were followed up until they died or were discharged from the hospital.

Treatment Groups

Patients who received an Impella within 2 days before or after the ECMO initiation were defined as the ECMO+Impella (ECPella) group. Patients who received IABP within 2 days before or after the ECMO initiation were defined as the ECMO+IABP group. Patients who received both an Impella and an IABP within 2 days before or after the ECMO initiation were assigned to the group with the later initiation date of the Impella or IABP or were defined as the ECPella group if the Impella or IABP was initiated on the same day. The present study was unable to identify whether the patients received an Impella 2.5, Impella CP, or Impella 5.0 in the ECPella group due to the nature of the administrative claims data.

Outcomes

Outcome data were collected only during hospitalization. The primary outcome was in-hospital mortality. The secondary outcomes were the 14-day mortality, 30-day mortality, length of hospital stay, length of ECMO, total hospitalization cost (including the detailed hospitalization costs), complications including major bleeding, an ischemic stroke, vascular complications, renal replacement therapy during hospitalization, durable mechanical circulatory support (MCS) implantations, and replacement of MCS devices during hospitalization. Durable MCS devices were defined as an extracorporeal ventricular assist device or implantable LV assist device (LVAD). Major bleeding was defined as the presence of either intracranial bleeding, intraspinal bleeding, pericardial hematomas, intra-abdominal or retroperitoneal hematomas, intra-articular bleeding, intraocular bleeding, or compartment syndrome, which was in accordance with the International Society of Thrombosis and Hemostasis definition.[15] An ischemic stroke was defined as the presence of a cerebral infarction or transient ischemic attack. Vascular complications were defined as an injury to a blood vessel, noncoronary artery dissection, acquired arteriovenous fistula, acute limb thrombosis, and hemorrhage or hematoma following a circulatory system procedure.[16] Those outcomes are defined by the *ICD-10* codes listed in Table S1.

Covariates

The covariates were the fiscal year on admission, age, sex, body mass index on admission, Japan Coma Scale on admission,[17] Charlson comorbidity index score, comorbidity of peripheral vascular diseases, physical function measured by the Barthel index score on admission,[18] cognitive function before admission, home medical care before admission, place before admission, ambulance use, primary diagnoses on admission (acute coronary syndrome [ACS], cardiac arrest, ventricular tachycardia or fibrillation, heart failure, valve disease, myocarditis, and cardiomyopathy), extracorporeal cardiopulmonary resuscitation (ECPR), interventions (percutaneous coronary intervention, coronary artery bypass grafting, surgical valve procedures, or percutaneous valve procedures) before ECMO initiation, organ failure support on the day of the ECMO initiation other than ECMO and mechanical ventilation,[19] and hospital characteristics (teaching hospital, tertiary emergency hospital, and annual hospital volume of ECMO). The primary diagnosis on admission was defined when it appeared as a main diagnosis, admission-precipitating diagnosis, most resource-consuming diagnosis, or second most resource-consuming diagnosis,[13] and was defined by the *ICD-10* codes listed in Table S1. ECPR was defined as receiving chest compressions on the same day of the ECMO initiation.

Statistical Analysis

We performed a propensity score–matching analysis to compare the outcomes between the ECPella and ECMO+IABP groups.[20] A multivariable logistic regression model using all of the covariates listed in Table 1

Table 1. Patient Characteristics

	Before matching			After matching		
	ECPella (*n* = 590)	ECMO+IABP (*n* = 13729)	SMD	ECPella (*n* = 590)	ECMO+IABP (*n* = 590)	SMD
Fiscal year on admission, *n* (%)						
2016	0 (0.0)	1272 (9.3)	−0.452	0 (0.0)	0 (0.0)	0
2017	14 (2.4)	2813 (20.5)	−0.594	14 (2.4)	10 (1.7)	0.048
2018	46 (7.8)	2781 (20.3)	−0.365	46 (7.8)	46 (7.8)	0
2019	128 (21.7)	2477 (18.0)	0.092	128 (21.7)	127 (21.5)	0.004
2020	164 (27.8)	2337 (17.0)	0.260	164 (27.8)	165 (28.0)	−0.004
2021	238 (40.3)	2049 (14.9)	0.592	238 (40.3)	242 (41.0)	−0.014
Age, mean (SD), y	63.1 (14.5)	65.1 (14.1)	−0.142	63.1 (14.5)	63.1 (15.1)	−0.005
Men, *n* (%)	454 (76.9)	10502 (76.5)	0.011	454 (76.9)	451 (76.4)	0.012
Body mass index on admission, kg/m^2, *n* (%)						
<18.5	41 (6.9)	840 (6.1)	0.034	41 (6.9)	36 (6.1)	0.034
18.5–24.9	309 (52.4)	6515 (47.5)	0.098	309 (52.4)	324 (54.9)	−0.051
25.0–29.9	137 (22.4)	3291 (24.0)	−0.038	132 (22.4)	133 (22.5)	−0.004
≥30.0	45 (7.6)	1050 (7.6)	−0.001	45 (7.6)	34 (5.8)	0.075
Missing data	63 (10.7)	2033 (14.8)	−0.124	63 (10.7)	63 (10.7)	0
Japan Coma Scale on admission, *n* (%)						
0 (alert)	302 (51.2)	6019 (43.8)	0.147	302 (51.2)	299 (50.7)	0.010
1–3 (dizzy)	82 (13.9)	1148 (8.4)	0.177	82 (13.9)	67 (11.4)	0.077
10–30 (somnolent)	25 (4.2)	555 (4.0)	0.010	25 (4.2)	27 (4.6)	−0.017
100–300 (coma)	181 (30.7)	6007 (43.8)	−0.273	181 (30.7)	197 (33.4)	−0.058
Charlson comorbidity index score, mean (SD)	1.1 (1.2)	1.2 (1.3)	−0.023	1.1 (1.2)	1.1 (1.2)	0.008
Comorbidity of peripheral vascular diseases, *n* (%)	16 (2.7)	408 (3.0)	−0.016	16 (2.7)	14 (2.4)	0.022
Physical function on admission, *n* (%)						
Total/severe dependence (BI 0–60)	402 (68.1)	8539 (62.2)	0.125	402 (68.1)	394 (66.8)	0.029
Slight/moderate dependence (BI 61–99)	13 (2.2)	380 (2.8)	−0.036	13 (2.2)	19 (3.2)	−0.063
Independent (BI = 100)	83 (14.1)	2548 (18.6)	−0.122	83 (14.1)	78 (13.2)	0.025
Missing	92 (15.6)	2262 (16.5)	−0.024	92 (15.6)	99 (16.8)	−0.032
Cognitive function before admission, *n* (%)						
No dementia	394 (66.8)	10296 (75.0)	−0.181	394 (66.8)	400 (67.8)	−0.022
Mild dementia	30 (5.1)	754 (5.5)	−0.018	30 (5.1)	33 (5.6)	−0.023
Moderate/severe dementia	20 (3.4)	465 (3.4)	0.000	20 (3.4)	17 (2.9)	0.029
Missing	146 (24.7)	2214 (16.1)	0.215	146 (24.7)	140 (23.7)	0.024
Home medical care before admission, *n* (%)	5 (0.8)	170 (1.2)	−0.038	5 (0.8)	3 (0.5)	0.041
Place before admission, *n* (%)						
Home	461 (78.1)	12557 (91.5)	−0.378	461 (78.1)	491 (83.2)	−0.129
Other hospitals	123 (20.8)	1067 (7.8)	0.380	123 (20.8)	93 (15.8)	0.132
Nursing home	6 (1.0)	105 (0.8)	0.027	6 (1.0)	6 (1.0)	0
Ambulance use, *n* (%)	463 (78.5)	10405 (75.8)	0.064	463 (78.5)	459 (77.8)	0.016
Primary diagnosis, *n* (%)						
Acute coronary syndrome	334 (56.6)	7818 (56.9)	−0.007	334 (56.6)	345 (58.5)	−0.038
Cardiac arrest	94 (15.9)	3556 (25.9)	−0.247	94 (15.9)	95 (16.1)	−0.005
Ventricular tachycardia or fibrillation	50 (8.5)	1586 (11.6)	−0.103	50 (8.5)	49 (8.3)	0.006
Heart failure	85 (14.4)	1537 (11.2)	0.096	85 (14.4)	88 (14.9)	−0.014
Valve disease	27 (4.6)	749 (5.5)	−0.040	27 (4.6)	27 (4.6)	0

(*Continued*)

Table 1. Continued

	Before matching			After matching		
	ECPella	ECMO+IABP		ECPella	ECMO+IABP	
	(*n*=590)	(*n*=13729)	SMD	(*n*=590)	(*n*=590)	SMD
Myocarditis	74 (12.5)	629 (4.6)	0.287	74 (12.5)	79 (13.4)	−0.025
Cardiomyopathy	46 (7.8)	494 (3.6)	0.182	46 (7.8)	43 (7.3)	0.019
ECPR, *n* (%)	137 (23.2)	6163 (44.9)	−0.469	137 (23.2)	146 (24.7)	−0.036
Interventions before ECMO, *n* (%)						
Percutaneous coronary intervention	302 (51.2)	7566 (55.1)	−0.079	302 (51.2)	317 (53.7)	−0.051
Coronary artery bypass grafting	32 (5.4)	763 (5.6)	−0.006	32 (5.4)	29 (4.9)	0.023
Surgical valve procedures	22 (3.7)	438 (3.2)	0.029	22 (3.7)	21 (3.6)	0.009
Percutaneous valve procedures	4 (0.7)	219 (1.6)	−0.087	4 (0.7)	3 (0.5)	0.022
Organ failure supports on ECMO initiation, *n* (%)						
Red blood cell transfusion	437 (74.1)	8503 (61.9)	0.262	437 (74.1)	439 (74.4)	−0.008
Fresh frozen plasma transfusion	339 (57.5)	6514 (47.4)	0.201	339 (57.5)	342 (58.0)	−0.010
Platelet transfusion	139 (23.6)	2076 (15.1)	0.215	139 (23.6)	127 (21.5)	0.049
Dopamine	117 (19.8)	4608 (33.6)	−0.314	117 (19.8)	120 (20.3)	−0.013
Dobutamine	304 (51.5)	6072 (44.2)	0.146	304 (51.5)	308 (52.2)	−0.014
Noradrenaline	456 (77.3)	10493 (76.4)	0.020	456 (77.3)	470 (79.7)	−0.058
Adrenaline	305 (51.7)	9646 (70.3)	−0.387	305 (51.7)	307 (52.0)	−0.007
Vasopressin	39 (6.6)	959 (7.0)	−0.015	39 (6.6)	49 (8.3)	−0.064
Renal replacement therapy	123 (20.8)	2549 (18.6)	0.057	123 (20.8)	110 (18.6)	0.055
Hospital characteristics						
Teaching hospital, *n* (%)	583 (98.8)	13489 (98.3)	0.047	583 (98.8)	583 (98.8)	0
Tertiary emergency hospital, *n* (%)	435 (73.7)	8697 (63.3)	0.225	435 (73.7)	427 (72.4)	0.031
Annual hospital volume of ECMO, mean (SD)	69.1 (28.1)	52.4 (30.9)	0.564	69.1 (28.1)	68.9 (32.6)	0.008

BI indicates Barthel Index; ECMO, extracorporeal membrane oxygenation; ECPella, combination of extracorporeal membrane oxygenation and Impella; ECPR, extracorporeal cardiopulmonary resuscitation; IABP, intra-aortic balloon pump; and SMD, standardized mean difference.

was employed to compute the propensity scores for the patients in the ECPella group. Then, we performed one-to-one nearest-neighbor matching that randomly selected a patient from the treatment group and subsequently paired that patient with the patient in the control group with the closest propensity score.[21] In the present study, each time a patient in the ECPella group was identified, the one-to-one nearest-neighbor matching without replacement was performed for the estimated propensity scores using a caliper width set at 20% of the SD of the propensity scores in the patients in the ECMO+IABP group for the exact same calendar year and month.[20] To assess the performance of the matching, the covariates were compared using standardized differences, with absolute standardized differences of ≤10% considered to denote negligible imbalances between the 2 groups.[22] After propensity score matching, the primary and secondary outcomes for the 2 groups were assessed through a multilevel generalized linear model accompanied by the hospital variables as random effects, using the meglm command in STATA (StataCorp LLC).[23,24] Risk differences and their 95% CIs were calculated with multilevel generalized linear models using the identity link function irrespective of the outcome types. To provide a clear visual indication of the change in in-hospital mortality over time, at 14 and 30 days, we generated Kaplan–Meier curves and performed log-rank tests in the matched cohort. In those survival analyses, patients who were discharged alive within 14 and 30 days were analyzed as censored, respectively.

All analyses were performed using STATA/SE 17.0 software. Continuous variables are presented as the mean and SD, and categorical variables are presented as the number and percentage. We considered all reported *P* values as 2-sided and $P<0.05$ as statistically significant.

Subgroup Analysis

We performed subgroup analyses, depending on the presence or absence of ACS, which accounted for more than half of the primary diagnoses. We performed those subgroup analyses among the matched cohort created and analyzed in the same manner as the main analysis.

Sensitivity Analysis

We performed 4 sensitivity analyses. First, we performed an overlap weighting analysis.[25] The overlap weighting analysis emphasized the target population with the most overlap in the observed characteristics between the 2 groups. The differences and their 95% CIs were calculated with weighted multilevel generalized linear models to compare the outcomes. Second, patients who received ECPR may have had a substantially different clinical course in terms of postcardiac arrest syndrome and the prognosis as compared with those with cardiogenic shock who did not receive ECPR. Therefore, we performed sensitivity analyses excluding the patients who received ECPR. Third, to assess the robustness of the identity link function, we performed multilevel generalized linear models using the logit link function for binary outcomes and negative binominal and Poisson distributional assumptions for count outcomes. Fourth, we performed analyses dealing with the matched pair as random effects instead of hospitals in the multilevel generalized linear models.

RESULTS

Patient Characteristics and Outcomes

During the study period, we identified 14 319 eligible patients from 661 hospitals (Figure 1). Of those, 590 (4.1%) were identified as the ECPella group and 13 729 (96%) as the ECMO+IABP group. Of the overall 661 hospitals, Impella was used in 155 (23%).

Table 1 shows the patient characteristics before and after propensity score matching. In the overall cohort, the mean age of patients was 65 years, 77% were men, and 57% had ACS. Before propensity score matching, the patients in the ECPella group tended to be younger, had poor physical and cognitive function on admission, were transferred from another hospital, had myocarditis and cardiomyopathy, received blood transfusions and dobutamine, and were admitted to a tertiary emergency hospital with a high annual hospital volume of ECMO. In contrast, the patients in the ECMO+IABP group tended to have poor consciousness, were admitted from home, had a cardiac arrest and ventricular tachycardia or fibrillation, and required ECPR, dopamine, and adrenaline. One-to-one propensity score matching created 590 matched pairs. The distributions of the propensity scores before and after the matching are shown in Figures S1 and S2. After propensity score matching, the patient characteristics were well-balanced between the 2 groups (Table 1).

Table 2 shows the outcomes before and after propensity score matching. The crude in-hospital mortality was 58.3% in the ECPella group and 65.3% in the ECMO+IABP group. After propensity score matching, there was no significant difference in in-hospital mortality between the ECPella and ECMO+IABP groups (58.3% versus 56.6%; risk difference, 2.4% [95% CI, −3.5 to 8.2]). There was also no significant difference in the 30-day mortality between the ECPella and ECMO+IABP groups (41.7% versus 46.8%; risk difference, −4.7% [95% CI, −10.6 to 1.2]), whereas the 14-day mortality was lower in the ECPella group than in the ECMO+IABP group (28.0% versus 36.8%; risk difference, −8.2% [95% CI, −13.8 to −2.7]). Kaplan–Meier analysis with the log-rank test showed that the 14-day and 30-day mortality was lower in the ECPella group than in the ECMO+IABP group (*P* value for both <0.001) (Figure 2). There was no significant difference in the length of hospital stay (mean, 43.4 days versus 36.7 days; risk difference, 4.9 days [95%

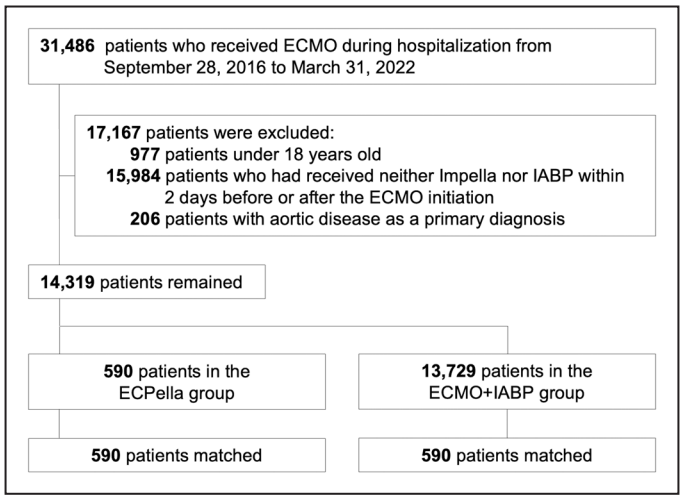

Figure 1. Patient flowchart.
ECMO indicates extracorporeal membrane oxygenation; ECPella, combination of extracorporeal membrane oxygenation and Impella; and IABP, intra-aortic balloon pump.

Table 2. Outcomes Before and After Propensity Score Matching

	Before matching		After matching			
	ECPella	ECMO+IABP	ECPella	ECMO+IABP	Risk difference	
	(*n* = 590)	(*n* = 13729)	(*n* = 590)	(*n* = 590)	(95% CI)	*P* value
In-hospital mortality, *n* (%)	344 (58.3)	8962 (65.3)	344 (58.3)	334 (56.6)	2.4 (–3.5 to 8.2)	0.429
14-day mortality, *n* (%)	165 (28.0)	6303 (45.9)	165 (28.0)	217 (36.8)	–8.2 (–13.8 to –2.7)	0.004
30-day mortality, *n* (%)	246 (41.7)	7779 (56.7)	246 (41.7)	276 (46.8)	–4.7 (–10.6 to 1.2)	0.122
Length of hospital stay, mean (SD), d	43.4 (60.5)	28.7 (42.7)	43.4 (60.5)	36.7 (63.2)	4.9 (–2.6 to 12.4)	0.197
Length of ECMO, mean (SD), d	3.9 (7.5)	2.3 (8.1)	3.9 (7.5)	3.2 (16.6)	0.7 (–0.8 to 2.2)	0.373
Total hospitalization cost, mean (SD), $\times 10^3$ yen	12567 (10379)	5633 (5256)	12567 (10379)	7050 (9034)	5094 (3937–6251)	<0.001
Complications, *n* (%)						
Major bleeding	22 (3.7)	277 (2.0)	22 (3.7)	19 (3.2)	0.5 (–1.6 to 2.6)	0.624
Ischemic stroke	22 (3.7)	442 (3.2)	22 (3.7)	26 (4.4)	–0.6 (–2.9 to 1.7)	0.612
Vascular complications	24 (4.1)	262 (1.9)	24 (4.1)	14 (2.4)	2.0 (–0.1 to 4.1)	0.065
Renal replacement therapy during hospitalization	299 (50.7)	5339 (38.9)	299 (50.7)	220 (37.3)	14.2 (8.3–20.1)	<0.001
Durable MCS implantations, *n* (%)	24 (4.1)	72 (0.5)	24 (4.1)	8 (1.4)	2.3 (0.4–4.2)	0.019

ECMO indicates extracorporeal membrane oxygenation; ECPella, combination of extracorporeal membrane oxygenation and Impella; IABP, intra-aortic balloon pump; and MCS, mechanical circulatory support.

CI, –2.6 to 12.4]) and length of ECMO (mean, 3.9 days versus 3.2 days; risk difference, 0.7 days [95% CI, –0.8 to 2.2]). The total hospitalization cost was significantly higher in the ECPella group than in the ECMO+IABP group (12567000 yen versus 7050000 yen; risk differences, 5094000 yen [95% CI, 3937000 to 6251000]). The detailed hospitalization costs are shown in Table S2. Renal replacement therapy during hospitalization more frequently occurred in the ECPella group than in the ECMO+IABP group (50.7% versus 37.3%; risk difference, 14.2% [95% CI, 8.3–20.1]). There were no significant differences in the other complications, including major bleeding (3.7% versus 3.2%; risk difference, 0.5% [95% CI, –1.6 to 2.6]), ischemic strokes (3.7% versus 4.4%; risk difference, –0.6% [95% CI, –2.9 to 1.7]), and vascular complications (4.1% versus 2.4%; risk difference, 2.0% [95% CI, –0.1 to 4.1]). The ECPella group more frequently received durable MCS implantations than the ECMO+IABP group (4.1% versus 1.4%; risk difference, 2.3% [95% CI, 0.4–4.2]). No patients in either group received a heart transplant. In the ECPella group, 13.7% of the patients in the ECPella group required a replacement

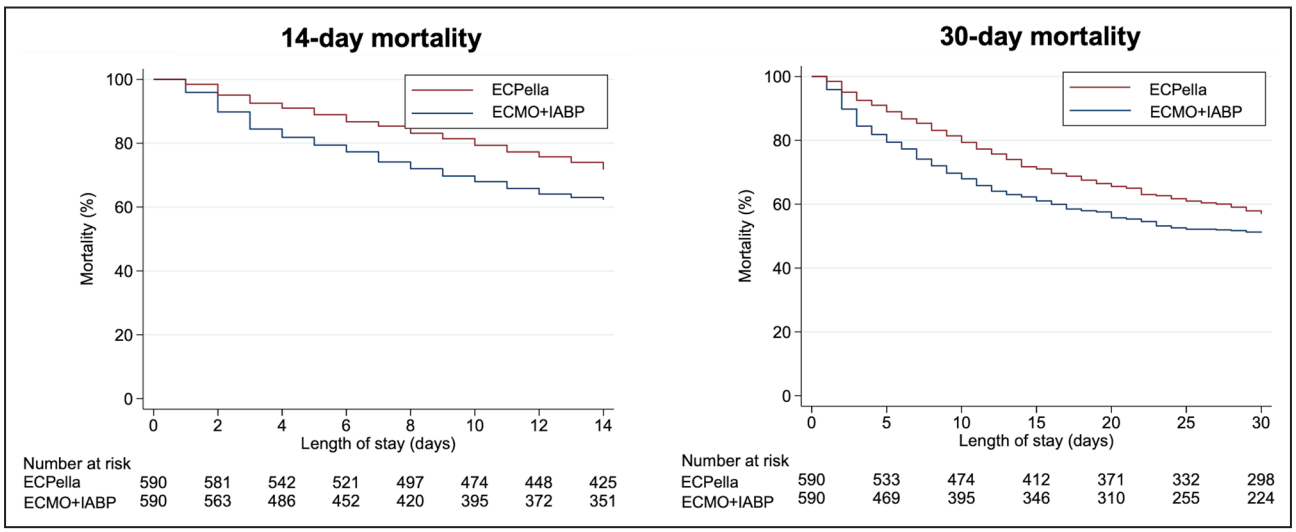

Figure 2. Kaplan–Meier curves for the 14-day and 30-day mortality.
ECMO indicates extracorporeal membrane oxygenation; ECPella, combination of extracorporeal membrane oxygenation and Impella; and IABP, intra-aortic balloon pump.

Table 3. Overlap Weighting

	After overlap weighting			
	ECPella	ECMO+IABP	Risk difference (95% CI)	*P* value
In-hospital mortality, %	59.6	57.3	2.3 (–3.8 to 8.5)	0.454
14-day mortality, %	29.0	36.8	–7.8 (–13.6 to –2.0)	0.009
30-day mortality, %	42.9	47.7	–4.8 (–11.0 to 1.4)	0.132
Length of hospital stay, mean (SD), d	41.7 (57.2)	33.9 (48.8)	7.7 (1.0–14.4)	0.025
Length of ECMO, mean (SD), d	3.8 (7.3)	2.8 (12.1)	1.0 (–0.3 to 2.2)	0.123
Total hospitalization cost, mean (SD), $\times 10^3$ yen	12 116 (9529)	6644 (6932)	5336 (4268–6405)	<0.001
Complications, %				
Major bleeding	3.7	2.5	1.1 (–1.0 to 3.3)	0.306
Ischemic stroke	3.8	3.8	–0.03 (–2.4 to 2.4)	0.983
Vascular complications	4.0	2.4	1.6 (–0.6 to 3.8)	0.152
Renal replacement therapy during hospitalization	49.8	40.4	9.4 (3.2–15.6)	0.003
Durable MCS implantations, %	3.4	1.2	2.0 (0.1–3.9)	0.037

ECMO indicates extracorporeal membrane oxygenation; ECPella, combination of extracorporeal membrane oxygenation and Impella; IABP, intra-aortic balloon pump; and MCS, mechanical circulatory support.

of the Impella, and more patients in the ECPella group underwent replacements of the ECMO pump than in the ECMO+IABP group (26.3% versus 11.1%; risk difference, 13.6% [95% CI, 8.9–18.2]) (Table S2). The sensitivity analyses, using an overlap weighting analysis, showed similar results to those for the main analyses (Table 3 and Table S3).

Table S4 shows the results of the subgroup analyses according to the presence of ACS in the matched cohort. There were no significant differences in in-hospital mortality regardless of whether the patients had ACS or not. Among the patients without ACS, the 14-day mortality was lower in the ECPella group than in the ECMO+IABP group (18.4% versus 32.2%; risk difference, –12.9% [95% CI, –20.6 to –5.2]), and vascular complications more frequently occurred in the ECPella group than in the ECMO+IABP group (5.9% versus 1.6%; risk difference, 4.5% [95% CI, 1.1–7.8]). The results of the other secondary outcomes were consistent with the main analyses.

Table S5 shows the results of the sensitivity analyses excluding patients who received ECPR. After excluding 6360 patients (44%) who received ECPR, there was no significant difference in in-hospital mortality between the ECPella and ECMO+IABP groups (57.3% versus 50.9%; risk difference, 6.5% [95% CI, –0.2 to 13.2]). The results of the secondary outcomes were also consistent with the main analyses.

Table S6 shows the results of the sensitivity analyses using the logit link function for binary outcomes and the negative binominal and Poisson distributional assumptions for the count outcomes. The results of the primary and secondary outcomes were consistent with the main analyses except for the length of hospital stay and ECMO.

Table S7 shows the results of the sensitivity analyses dealing with the matched pair as random effects instead of hospitals in the multilevel generalized linear models. The results of the primary and secondary outcomes were consistent with the main analyses.

DISCUSSION

To the best of our knowledge, this nationwide cohort study had the largest number of patients among the studies comparing ECPella versus ECMO+IABP. The 14-day mortality was lower in the ECPella group than in the ECMO+IABP group, whereas there was no significant difference in in-hospital mortality between the ECPella and ECMO+IABP groups. Furthermore, ECPella was significantly associated with a higher total hospitalization cost, increased renal replacement therapy during hospitalization, and more durable MCS implantations than ECMO+IABP.

The present study found that very early mortality within 14 days was lower for ECPella as compared with ECMO+IABP, but there was no significant difference in in-hospital mortality after 14 days. This was consistent with the results of previous studies.[8,11] One of those studies, from the Extracorporeal Life Support Organization registry, showed a considerably higher proportion of Impella use in combination with ECMO (33% versus 4.1%).[8] This study performed a propensity score–matching analysis and concluded that ECPella as compared with ECMO+IABP was associated with similar survival in the 560 matched pairs.[8] Randomized controlled trials comparing the LV unloading strategies are needed to reach any conclusions. To investigate the comparative effectiveness of Impella or IABP use

in combination with ECMO, future studies may need to consider the following. First, the cause of cardiogenic shock may be a key issue. Underlying diseases with severe impairment of LV contractility, such as fulminant myocarditis, could receive a pathophysiological benefit from ECPella as a bridge to recovery[26,27]; however, the current number of cases could not substantiate this subgroup analysis. Indeed, the present study included only 153 of 1180 (13.0%) patients with myocarditis. Second, the relationship between the procedural volume (ie, learning curves) and outcomes should also be considered. Data are scarce for Impella, but the association between the procedural volume and outcomes has been shown for ECMO.[28] Hence, when involving data early after the approval of the Impella, as in the present study, the survival benefit of ECPella may be underestimated. Finally, early recognition of cardiogenic shock and its stabilization by appropriate timing of MCS device use may be more critical than that in which an MCS device is used.[29,30]

In the present study, the total hospitalization cost was ≈5.5 million yen higher in the ECPella group than in the ECMO+IABP group. Of that difference, ≈4.3 million (77%) was mainly due to the subcategory of surgery and anesthesia, which included the surgical and anesthesia fees, blood transfusion fees, and the cost of the specific medical materials such as MCS devices, cardiac catheters, disposable medical materials, and hygienic materials. While the direct causes of a higher hospitalization cost were not examined, this was partly because the cost of the Impella itself was considerably higher than that of an IABP or ECMO; it was ≈2.4 million yen higher than an IABP and 2.1 million yen higher than ECMO, according to the national health reimbursement data in Japan.[31] Moreover, more replacements of MCS devices including the Impella and ECMO, increased renal replacement therapy during hospitalization, and more durable MCS implantations may have contributed to the higher total hospitalization cost. A recent study using the nationwide inpatient database in Japan, which included patients who required MCS early after admission, also showed higher medical costs for ECPella than ECMO+IABP, potentially attributable to more frequent blood transfusions, a longer duration of ventilator support, and increased length of hospital stay.[32] It should also be noted that Japan has adopted a universal health care system, ensuring all citizens have access to high-quality medical care at a low out-of-pocket cost.[33] In previous studies focusing on the temporal trends before and after the approval of the Impella, the hospitalization cost in the Impella era was higher than that in the pre-Impella era in Japan as well as in the United States, especially in hospitals where the Impella was more frequently used.[34,35] Unplanned readmissions may be an important quality indicator in patients who received an Impella, with limited previous studies showing a high incidence of 30-day readmission of >10%.[36] Unless the survival benefit and reduction in readmissions for ECPella as compared with ECMO+IABP is confirmed, clinicians should be cautious about the patient selection for Impella use in combination with ECMO for LV unloading. On the other hand, from a cost-effectiveness perspective, expensive devices may be economically favorable in certain circumstances because cardiogenic shock is a highly morbid disease with a high mortality and expense.[37] Given the lack of data on the cost-effectiveness of the use of MCS devices for cardiogenic shock in the acute setting, any discussion of cost-sharing or reimbursement for MCS devices would be premature.

Another aspect was that ECPella may have been more frequently used as a bridge-to-durable MCS or destination therapy than ECMO+IABP. In Japan, the waiting time for a bridge-to-transplant has increased over the years to >5 years because of a severe shortage of donors.[38] In recent years, the annual number of heart transplants has ranged from only 80 to 120.[37] Indeed, this study did not include any patients who received heart transplants. Patients on the waiting list for heart transplants often receive long-term LVAD support as a bridge-to-transplant. Implantable LVADs have been increasingly used in Japan since 2011 when they were reimbursed as a bridge-to-transplant. A nationwide registry database from 2011 to 2018 showed that Japanese patients with a bridge-to-transplant had a good prognosis with a 720-day survival rate of ≈90%.[39] After a 10-year delay from the reimbursement for implantable LVADs, a destination therapy, which is the indication to implant an LVAD in patients with stage D heart failure who are not candidates for heart transplants, was finally approved and reimbursed in 2021. All of those reimbursed treatments, including a bridge-to-transplant, bridge-to-durable MCS, destination therapy, and even a replacement of the MCS, are covered by the universal health care system. Hence, medical costs are not a barrier to those additional interventions in Japan.

Our results include some important clinical implications. First, the present study provided no evidence of whether the use of IABP or Impella was better for in-hospital mortality after 14 days in combination with ECMO; however, it did indicate a higher total hospitalization cost, increased renal replacement therapy during hospitalization, and more durable MCS implantations for ECPella. This suggests that ECPella should be implemented in carefully selected patients. Second, further studies are warranted to investigate the outcomes according to the cause of the cardiogenic shock, learning curves for Impella use, and readmissions in patients who received the Impella.

The present study also has several limitations. First, the decision whether to use an IABP or Impella was at

the individual clinician's discretion because of the nature of the present study using the observational database, which led to confounding by indication. We attempted to control for the measured confounding factors using the propensity score analyses; however, we were unable to control for any possible unmeasured variables, such as vital signs, laboratory data, or LV function. Second, the present study was unable to identify whether patients initially received IABP or Impella and then ECMO or whether they initially received ECMO and then IABP or Impella for LV unloading. In addition, we defined 152 patients (40%) who received Impella and IABP in combination with ECMO on the same day as the ECPella group; however, some patients might have been downgraded from the Impella to IABP because of Impella-related complications. Therefore, misclassifications may have led to a bias in our study. The order and combination of the MCS devices depended on the changing severity of the cardiogenic shock, suggesting that it would be difficult to accurately categorize those complex processes even if additional information was available during hospitalization. Third, the present study was also unable to identify whether the patients received an Impella 2.5, Impella CP, or Impella 5.0 in the ECPella group. Fourth, the incidence of complications in the present study was considerably lower than in previous studies.[8,11] Given that the sensitivity of the diagnosis might have been low in our database, there was a possibility of underreporting complications. Fifth, many patients in the present study received vasoactive drugs, including dopamine and adrenaline. That might have delayed the MCS initiation, and caution should be taken in interpreting our results. Sixth, given that the present database contained information collected only during hospitalization, we were unable to analyze the short-term as well as long-term outcomes after discharge, such as the social reintegration and readmission rates. Future studies should include longitudinal data beyond the in-hospital outcomes to better understand the implications of the use of MCS devices on longer-term outcomes, such as readmissions and social reintegration. Furthermore, the Kaplan–Meier curves that focused only on in-hospital mortality may have been misleading in assessing the true difference in the effectiveness between the groups. Finally, caution should be taken when applying the present results on medical coststo those in other countries because each country has a different health care system.

CONCLUSIONS

The present study using a nationwide inpatient administrative database showed no significant difference in in-hospital mortality between the groups, but ECPella was associated with a higher total hospitalization cost, increased renal replacement therapy during hospitalization, and more durable MCS implantations as compared with ECMO+IABP.

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Supplemental Material

Tables S1–S7
Figures S1–S2

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