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ORIGINAL ARTICLE

In-Hospital Mortality in Patients With Cardiogenic Shock Requiring Veno-Arterial Extracorporeal Membrane Oxygenation With Concomitant Use of Impella vs. Intra-Aortic Balloon Pump

— A Retrospective Cohort Study Using a Japanese Claims-Based Database —

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Background: Patients with refractory cardiogenic shock (CS) necessitating peripheral veno-arterial extracorporeal membrane oxygenation (VA-ECMO) often require an intra-aortic balloon pump (IABP) or Impella for unloading; however, comparative effectiveness data are currently lacking.

Methods and Results: Using Diagnosis Procedure Combination data from approximately 1,200 Japanese acute care hospitals (April 2018–March 2022), we identified 940 patients aged ≥18 years with CS necessitating peripheral VA-ECMO along with IABP (ECMO-IABP; n=801) or Impella (ECPella; n=139) within 48 h of admission. Propensity score matching (126 pairs) indicated comparable in-hospital mortality between the ECPella and ECMO-IABP groups (50.8% vs. 50.0%, respectively; P=1.000). However, the ECPella cohort was on mechanical ventilator support for longer (median [interquartile range] 11.5 [5.0–20.8] vs. 9.0 [4.0–16.8] days; P=0.008) and had a longer hospital stay (median [interquartile range] 32.5 [12.0–59.0] vs. 23.0 [6.3–43.0] days; P=0.017) than the ECMO-IABP cohort. In addition, medical costs were higher for the ECPella than ECMO-IABP group (median [interquartile range] 9.09 [7.20–12.20] vs. 5.23 [3.41–7.00] million Japanese yen; P<0.001).

Conclusions: Our nationwide study could not demonstrate compelling evidence to support the superior efficacy of Impella over IABP in reducing in-hospital mortality among patients with CS necessitating VA-ECMO. Further investigations are imperative to determine the clinical situations in which the potential effect of Impella can be maximized.

Key Words: Cardiogenic shock; Impella; In-hospital mortality; Intra-aortic balloon pump; Veno-arterial extracorporeal membrane oxygenation

Cardiogenic shock (CS) is a life-threatening condition resulting from cardiac dysfunction.[1] CS decreases cardiac output, causes severe end-organ hypoperfusion, and increases lactate concentrations, and is associated with a reported mortality rate of 30–50%.[2–4] The primary management of CS involves the use of vasopressors and inotropes, which often have limited efficacy.[5] Veno-arterial extracorporeal membrane oxygenation (VA-ECMO), increasingly used worldwide,[6,7] provides essential hemodynamic support.[8,9] However, retrograde aortic perfusion can pose significant left ventricular (LV) afterload challenges, potentially resulting in increased LV end-diastolic pressure, poor LV ejection, aortic and mitral regurgitation, and a decreased coronary artery blood flow, possibly leading to severe pulmonary edema.[6,8]

Studies have suggested that combining unloading devices, such as intra-aortic balloon pumps (IABP) or the newer Impella with VA-ECMO, improves short-term mortality

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in acute refractory CS.[10,11] Impella actively transports blood from the LV to the aorta, thus reducing LV wall stress and oxygen consumption.[12] However, due to limited high-quality evidence, in situations like CS, Impella and IABP are often used interchangeably, based on clinician preferences, despite potential increases in adverse events and costs associated with Impella compared with IABP.[13]

Conducting randomized controlled trials (RCT) in emergency settings for CS is challenging.[14–16] To address this gap, we conducted a retrospective study using a nationwide claims-based database to compare the impact of Impella and IABP on in-hospital mortality in patients with CS requiring VA-ECMO. This real-world data will guide physicians in selecting appropriate concomitant devices for VA-ECMO, providing valuable insights for clinical practice.

Methods

Study Design

This was a retrospective cohort study based on a nationwide claims-based database of inpatients admitted to acute care hospitals in Japan.

Data Source

Data from the Diagnosis Procedure Combination (DPC) database were used. The data were provided by DPC Research Institute.[17] The DPC, which is maintained by the Ministry of Health, Labour and Welfare of Japan, is a classification method for patients admitted to acute care hospitals.[18,19] The DPC database covered 1,757 acute care hospitals in April 2020, accounting for approximately 80% of all acute care hospital beds in Japan.[20] The DPC database has been highly validated, particularly for records of primary diagnoses and procedures.[21] Given that almost all patients with CS requiring VA-ECMO are admitted to acute care hospitals in Japan, using the DPC database to evaluate patients with CS is reasonable.

Study Population

We selected patients aged ≥18 years with CS who were discharged between April 1, 2018 and March 31, 2022. First, we identified patients with CS based on diagnoses coded by the International Classification of Diseases, 10 the revision (ICD-10) using the following codes: I05–I08, I11, I20–I23, I33–I36, I40, I41–42, I46, I47, and I49–I51.[22] Next, to maintain a more uniform population and limit unmeasured confounding factors, we included only patients who underwent peripheral VA-ECMO with concomitant use of Impella (ECPella group) or IABP (ECMO-IABP group) within 48 h of hospital admission. We excluded patients with a diagnosis code of cardiac arrest, those who died within 24 h of admission, and those who were transferred to other hospitals within 5 days of admission. We also excluded patients who received both Impella and IABP during the same hospitalization period because these patients may have required escalation of mechanical circulatory support (MCS). We intended to examine the use of Impella or IABP as a primary strategy.

Collection of Data on Baseline Characteristics and Management During Hospitalization

Information on the following patient background characteristics and management during hospitalization was obtained: age, sex, height, weight, body mass index (BMI), type of hospital (university hospital or not), number of beds in the hospital (bed capacity), number of peripheral VA-ECMO per year per hospital, emergency hospitalization, consciousness on admission as defined by the Japan Coma Scale (JCS), underlying cardiac disease (arrhythmia, cardiomyopathy, heart failure, infectious endocarditis, ischemic heart disease, myocarditis, takotsubo syndrome, or valvular heart disease), pre-ECMO chronic kidney disease (ICD-10 code: N18), and pre-ECMO chronic liver disease (ICD-10 code: K70–77). Data on management during hospitalization included the use of MCS devices (peripheral VA-ECMO, Impella, and IABP), mechanical ventilator use, continuous renal replacement therapy (CRRT), invasive treatments (percutaneous coronary intervention [PCI] and cardiac surgery [coronary artery bypass grafting, valve surgery, and repair surgery for mechanical complications of acute myocardial infarction]), blood transfusion (red blood cell [RBC], platelet, and fresh frozen plasma [FFP]), drug prescriptions (dopamine, dobutamine, epinephrine, norepinephrine, phosphodiesterase 3 inhibitor [PDE3i], vasopressin, amiodarone, nifekalant, lidocaine, and sodium bicarbonate) and the number of computed tomography (CT) scans taken during hospitalization.

Outcome Measures

The primary outcome was in-hospital mortality. Secondary outcomes were 60-day mortality, the duration of mechanical ventilator support, the length of hospital stay (LOS), and medical costs.

Statistical Analyses

Nominal data are expressed as percentages, whereas continuous variables are expressed as the median with interquartile range (IQR). Nominal-level data were compared using the χ^2 test. Continuous variables were compared using Wilcoxon rank-sum tests. The percentage of missing values across the variables was as follows: BMI, 86 (9.1%); duration of mechanical ventilator use, 72 (7.7%). These missing values were imputed using a multiple imputation model employing bootstrapping and predictive mean matching.[23]

To account for differences in baseline characteristics between the 2 groups, we conducted propensity score (PS) analyses.[24] A PS for predicting the concomitant use of Impella or IABP was established using a logistic regression model, incorporating 32 clinically plausible confounding variables available in the DPC database: age, sex, height, weight, BMI, type of hospital (university hospital or not), bed capacity, number of peripheral VA-ECMO per year per hospital, emergency hospitalization, JCS consciousness on admission, underlying cardiac disease, chronic kidney disease, chronic liver disease, mechanical ventilator use, CRRT, PCI, cardiac surgery (coronary artery bypass grafting, valve surgery, and repair surgery for mechanical complications of acute myocardial infarction), blood transfusion (RBC, platelets, and FFP), use of cardiovascular agents (dopamine, dobutamine, epinephrine, norepinephrine, PDE3i, and vasopressin), use of antiarrhythmic agents (amiodarone, nifekalant, and lidocaine), and use of sodium bicarbonate.[22] Since the abovementioned treatments had to precede the use of Impella or IABP when calculating PS, those performed within 48 h of admission were identified. The concordance (C)-statistic was used to evaluate the goodness of fit. A 1 : 1 PS matching was then performed using the nearest neighbor matching method without replacement, with caliper widths set at 20% of the

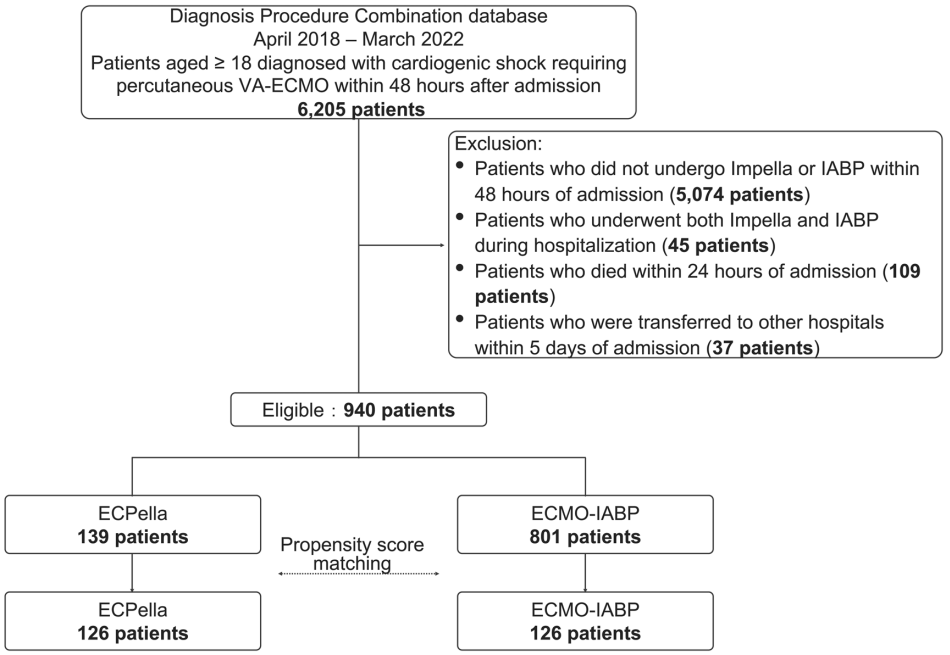

Figure 1. Flow diagram of the study population. ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump.

standard deviation of the PS. Differences between the 2 groups after PS matching were assessed using standardized mean differences (SMD).[25]

The primary outcome was compared using χ^2 tests. Sixty-day mortality, one of the secondary outcomes, was evaluated using the χ^2 test and Kaplan-Meier method with a log-rank test between the 2 groups before and after PS matching. We performed subgroup analysis comparing the primary and secondary outcomes in patients diagnosed with ischemic heart disease, non-ischemic heart disease, myocarditis, those aged <70 years, and those aged ≥70 years after PS matching.

To assess the potential effect of unmeasured or uncontrolled confounding factors on the observed treatment effects, we conducted a sensitivity analysis using the E-value.[26] All statistical tests were 2-sided, with a significance level of 5%. Statistical analyses were performed using RStudio version 4.0.0 (R Core Team, Vienna, Austria).

Ethical Considerations

This study was approved by the Ethics Committee of Yokohama City University (Approval no. F221200005) and conducted in accordance with the ethical standards described in the 2002 Declaration of Helsinki. The requirement for informed consent was waived due to the anonymous nature of the data.

Results

Patient Selection and Baseline Characteristics

Between April 1, 2018 and March 31, 2022, 6,205 patients aged ≥18 years who were diagnosed with CS requiring percutaneous VA-ECMO within 48 h of admission were identified. Of these patients, 5,265 were excluded. Ultimately, a total of 940 patients with CS (median age 69 years, 76.9% male) who required peripheral VA-ECMO with concomitant use of Impella or IABP within 48 h of hospital admission were included in the study. Of these patients, 139 required ECPella and 801 received ECMO-IABP. A flow diagram of the study population is shown in **Figure 1**. The number of patients with CS who underwent ECPella increased annually, whereas the number of patients with CS who received ECMO-IABP decreased from 2018 to 2021 (**Figure 2**, **Supplementary Figure**).

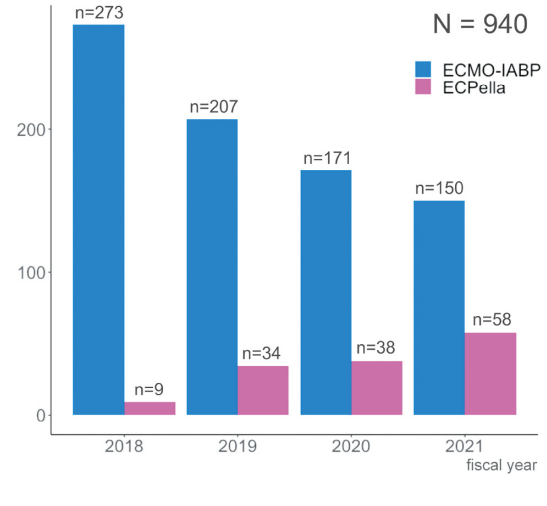

Figure 2. Frequency distribution of the incidence of patients with cardiogenic shock requiring early mechanical circulatory support within 48 h of hospital admission in the full cohort (n=940) between 2018 and 2021 fiscal year. ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump.

Table 1. Patient Characteristics and Initial Treatments Within 48 h of Hospital Admission: Analysis of the Cohort Before and After Propensity Score Matching

	Before matching				After matching			
	ECMO-IABP (n=801)	ECPella (n=139)	SMD	P value	ECMO-IABP (n=126)	ECPella (n=126)	SMD	P value
Age (range), years	69.0 (59.0–77.0)	68.0 (55.5–74.5)	0.168	0.090	68.0 (58.3–77.0)	69.0 (56.3–76.0)	0.008	0.740
Female sex	191 (23.8)	26 (18.7)	0.126	0.223	26 (20.6)	24 (19.0)	0.040	0.874
BMI (range), kg/m^2	24.0 (21.5–27.3)	23.3 (21.2–25.8)	0.167	0.117	23.4 (20.8–26.2)	23.6 (21.3–26.1)	0.023	0.756
University hospital	130 (16.2)	66 (47.5)	0.712	<0.001*	55 (43.7)	54 (42.9)	0.016	1.000
Bed capacity (range)	432.0 (314.0–535.0)	530.0 (428.5–646.0)	0.600	<0.001*	539.0 (454.0–631.8)	518.0 (409.0–641.5)	0.012	0.371
No. VA-ECMO per year (range)	13.8 (8.5–22.2)	18.0 (12.5–27.2)	0.421	<0.001*	18.8 (11.0–30.2)	17.5 (12.6–26.2)	0.038	0.536
Emergency hospitalization	745 (93.0)	134 (96.4)	0.152	0.189	121 (96.0)	121 (96.0)	<0.001	1.000
JCS on admission			0.139	0.510			0.049	0.985
0	377 (47.1)	68 (48.9)			59 (46.8)	62 (49.2)		
1–3	98 (12.2)	22 (15.8)			21 (16.7)	20 (15.9)		
10–30	54 (6.7)	7 (5.0)			6 (4.8)	6 (4.8)		
100–300	272 (34.0)	42 (30.2)			40 (31.7)	38 (30.2)		
Underlying cardiac disease			0.315	0.100			0.073	0.997
Ischemic heart disease	602 (75.2)	97 (69.8)			90 (71.4)	89 (70.6)		
Arrhythmia	69 (8.6)	7 (5.0)			7 (5.6)	7 (5.6)		
Myocarditis	56 (7.0)	18 (12.9)			16 (12.7)	16 (12.7)		
Heart failure	36 (4.5)	10 (7.2)			8 (6.3)	8 (6.3)		
Valvular disease	23 (2.9)	4 (2.9)			4 (3.2)	4 (3.2)		
Cardiomyopathy	8 (1.0)	3 (2.2)			1 (0.8)	2 (1.6)		
Infectious endocarditis	5 (0.6)	0 (0.0)			0 (0.0)	0 (0.0)		
Takotsubo syndrome	2 (0.2)	0 (0.0)			0 (0.0)	0 (0.0)		
Renal disease	64 (8.0)	6 (4.3)	0.153	0.178	5 (4.0)	6 (4.8)	0.039	1.000
Liver disease	3 (0.4)	5 (3.6)	0.233	0.001*	3 (2.4)	4 (3.2)	0.048	1.000
Ventilator	696 (86.9)	112 (80.6)	0.172	0.065	100 (79.4)	104 (82.5)	0.081	0.630
CRRT	187 (23.3)	32 (23.0)	0.008	1.000	28 (22.2)	30 (23.8)	0.038	0.881
PCI	576 (71.9)	95 (68.3)	0.078	0.449	88 (69.8)	88 (69.8)	<0.001	1.000
Bypass	58 (7.2)	1 (0.7)	0.338	0.006	1 (0.8)	1 (0.8)	<0.001	1.000
Mechanical complication surgery	27 (3.4)	1 (0.7)	0.188	0.154	2 (1.6)	1 (0.8)	0.073	1.000
Valve surgery	22 (2.7)	1 (0.7)	0.156	0.258	1 (0.8)	1 (0.8)	<0.001	1.000
RBC	615 (76.8)	117 (84.2)	0.187	0.068	107 (84.9)	105 (83.3)	0.043	0.863
Platelet	204 (25.5)	36 (25.9)	0.010	0.998	30 (23.8)	34 (27.0)	0.073	0.664
FFP	490 (61.2)	88 (63.3)	0.044	0.702	91 (72.2)	80 (63.5)	0.188	0.177
Dopamine	306 (38.2)	27 (19.4)	0.424	<0.001	23 (18.3)	27 (21.4)	0.080	0.636
Dobutamine	487 (60.8)	80 (57.6)	0.066	0.530	72 (57.1)	72 (57.1)	<0.001	1.000
Epinephrine	507 (63.3)	74 (53.2)	0.205	0.031	71 (56.3)	66 (52.4)	0.080	0.613
Norepinephrine	690 (86.1)	112 (80.6)	0.150	0.114	101 (80.2)	103 (81.7)	0.040	0.873
PDE3i	81 (10.1)	9 (6.5)	0.132	0.234	8 (6.3)	8 (6.3)	<0.001	1.000
Vasopressin	60 (7.5)	9 (6.5)	0.040	0.804	9 (7.1)	9 (7.1)	<0.001	1.000
Amiodarone	423 (52.8)	76 (54.7)	0.037	0.753	70 (55.6)	67 (53.2)	0.048	0.800
Nifekalant	31 (3.9)	2 (1.4)	0.152	0.235	2 (1.6)	2 (1.6)	<0.001	1.000
Lidocaine	182 (22.7)	27 (19.4)	0.081	0.452	30 (23.8)	24 (19.0)	0.116	0.443
Sodium bicarbonate	456 (56.9)	66 (47.5)	0.190	0.048	62 (49.2)	59 (46.8)	0.048	0.801

Unless indicated otherwise, data are given as n (%). Nominal-level data were compared using the χ^2 test. Continuous variables were compared using Wilcoxon rank-sum tests. BMI, body mass index; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; IABP, intra-aortic balloon pump; JCS, Japan Coma Scale; PCI, percutaneous coronary intervention; PDE3i, phosphodiesterase 3 inhibitor; RBC, red blood cells; SMD, standardized mean differences; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

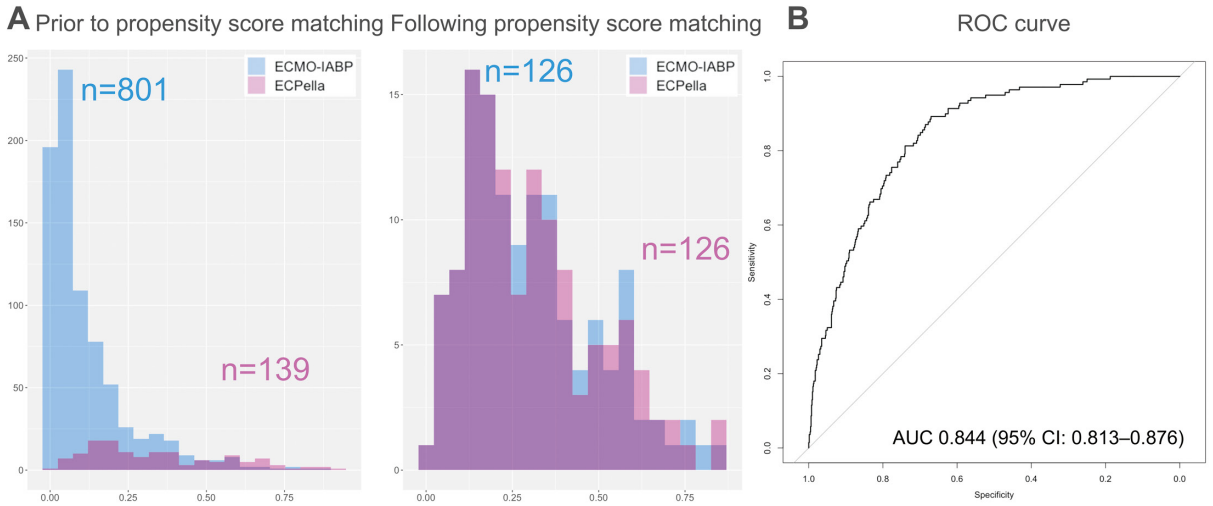

Figure 3. (**A**) Distribution of propensity scores prior to and following matching and (**B**) the receiver operating characteristic (ROC) curve for the concomitant use of Impella or intra-aortic balloon pump (IABP) with extracorporeal membrane oxygenation (ECMO). AUC, area under the curve; CI, confidence interval.

Before PS matching, the 2 groups (i.e., ECPella [n=139] and ECMO-IABP [n=801]) exhibited similarities in age, sex, BMI, consciousness on admission as indicated by the JCS, and underlying cardiac disease (**Table 1**). Approximately three-quarters (699/940; 74.4%) of the study population consisted of individuals with ischemic heart disease. Patients who underwent ECPella were more frequently admitted to university hospitals (47.5% vs. 16.2%; P<0.001) and were admitted to hospitals with higher bed capacities (530.0 [IQR 428.5–646.0] vs. 432.0 [IQR 314.0–535.0]; P<0.001) and higher VA-ECMO volumes (18.0 [IQR 12.5–27.2] vs. 13.8 [IQR 8.5–22.2]; P<0.001) than those who received ECMO-IABP.

After 1:1 PS matching, 126 patients who underwent ECPella were matched with 126 patients who underwent ECMO-IABP. As shown in **Figure 3A**, a well-balanced PS distribution was observed after matching. The model established for estimating PSs had a C-statistic of 0.844 (95% confidence interval [CI] 0.813–0.876; **Figure 3B**).

Initial Management

Regarding the initial treatments implemented within 48 h of admission, coronary artery bypass grafting (7.2% vs. 0.7%; P=0.006) was more frequently performed, and dopamine (38.2% vs. 19.4%; P<0.001), epinephrine (63.3% vs. 53.2%; P=0.031), and sodium bicarbonate (56.9% vs. 47.5%; P=0.048) were more frequently administered to the ECMO-IABP than ECPella group.

After PS matching, the patient characteristics and initial treatments within 48 h of admission were almost well-balanced between the ECMO-IABP and ECPella groups, except for differences in FFP (72.2% vs. 63.5%, respectively; SMD=0.188) and lidocaine administration (23.8% vs. 19.0%, respectively; SMD=0.116).

Management During Hospitalization

A comprehensive list of treatments implemented during hospitalization is presented in **Table 2**. Before PS matching, RBC (99.3% vs. 94.1%; P=0.019), platelets (75.5% vs. 59.3%; P<0.001), and FFP (83.5% vs. 73.9%; P=0.021) were more frequently transfused, and CT scans were more frequently performed (2.0 [IQR 1.0–4.0] vs. 2.0 [IQR 1.0–3.0]; P=0.008) in the ECPella than ECMO-IABP group. In contrast, the use of dopamine (46.8% vs. 31.7%; P=0.001) and epinephrine (69.3% vs. 59.7%; P=0.033) was more frequent in the ECMO-IABP than ECPella group. After PS matching, platelet transfusion (77.0% vs. 59.5%; P=0.004) and PDE3i administration (23.8% vs. 12.7%; P=0.034) were more frequent in the ECPella than ECMO-IABP group.

In-Hospital Outcomes

In-hospital mortality did not differ between the 2 groups before and after PS matching (**Table 3**). Approximately 50% of patients experienced in-hospital mortality in both groups. The risk ratio (RR) for in-hospital mortality in the post-matched cohort was 1.016 (95% CI 0.795–1.298). Similarly, no significant differences in 60-day mortality rates were observed between the 2 groups before or after PS matching. **Figure 4** shows the Kaplan-Meier curves of 60-day mortality before and after PS matching. The survival probability did not differ between the 2 groups after PS matching.

The duration of mechanical ventilator support was longer in the ECPella than ECMO-IABP group before and after PS matching (**Table 3**). LOS was significantly longer in the ECPella than ECMO-IABP group both before and after PS matching. Medical costs were significantly higher in the ECPella than ECMO-IABP group both before and after PS matching.

The subgroup analysis revealed no significant differences in in-hospital mortality between the 2 groups in patients with ischemic heart disease, non-ischemic heart disease, myocarditis, and those aged <70 or ≥70 years (**Table 4**). In-hospital mortality was lower for those with non-ischemic heart disease (27.8% vs. 37.8% for the ECMO-IABP

Table 2. Analyses of Management During Hospitalization Before and After Propensity Score Matching of Cohorts

	Before matching			After matching		
	ECMO-IABP (n=801)	ECPella (n=139)	P value	ECMO-IABP (n=126)	ECPella (n=126)	P value
Ventilator	770 (96.1)	131 (94.2)	0.425	118 (93.7)	120 (95.2)	0.783
CRRT	329 (41.1)	64 (46.0)	0.316	48 (38.1)	58 (46.0)	0.251
PCI	581 (72.5)	95 (68.3)	0.362	88 (69.8)	88 (69.8)	1.000
Bypass	61 (7.6)	4 (2.9)	0.064	1 (0.8)	4 (3.2)	0.366
Mechanical complication surgery	36 (4.5)	4 (2.9)	0.520	3 (2.4)	4 (3.2)	1.000
Valve surgery	29 (3.6)	7 (5.0)	0.573	3 (2.4)	7 (5.6)	0.333
RBC	754 (94.1)	138 (99.3)	0.019	123 (97.6)	125 (99.2)	0.614
Platelet	475 (59.3)	105 (75.5)	<0.001	75 (59.5)	97 (77.0)	0.004
FFP	592 (73.9)	116 (83.5)	0.021	105 (83.3)	107 (84.9)	0.863
Dopamine	375 (46.8)	44 (31.7)	0.001	36 (28.6)	43 (34.1)	0.415
Dobutamine	611 (76.3)	111 (79.9)	0.416	97 (77.0)	102 (81.0)	0.536
Epinephrine	555 (69.3)	83 (59.7)	0.033	80 (63.5)	75 (59.5)	0.605
Norepinephrine	745 (93.0)	130 (93.5)	0.968	114 (90.5)	117 (92.9)	0.649
PDE3i	139 (17.4)	32 (23.0)	0.139	16 (12.7)	30 (23.8)	0.034
Vasopressin	127 (15.9)	28 (20.1)	0.257	21 (16.7)	27 (21.4)	0.422
Amiodarone	517 (64.5)	93 (66.9)	0.658	82 (65.1)	83 (65.9)	1.000
Nifekalant	48 (6.0)	4 (2.9)	0.200	5 (4.0)	4 (3.2)	1.000
Lidocaine	244 (30.5)	39 (28.1)	0.638	37 (29.4)	36 (28.6)	1.000
Sodium bicarbonate	497 (62.0)	76 (54.7)	0.121	69 (54.8)	68 (54.0)	1.000
No. CT scans (range)	2.0 (1.0–3.0)	2.0 (1.0–4.0)	0.008	2.0 (1.0–3.0)	2.0 (1.0–4.0)	0.269

Unless indicated otherwise, data are given as n (%). Nominal-level data were compared using the X^2 test. Continuous variables were compared using Wilcoxon rank-sum tests. CT, computed tomography. Other abbreviations as in Table 1.

Table 3. In-Hospital Outcomes: Cohort Analyses Before and After Propensity Score Matching

	Before matching			After matching		
	ECMO-IABP (n=801)	ECPella (n=139)	P value	ECMO-IABP (n=126)	ECPella (n=126)	P value
In-hospital mortality	445 (55.6)	70 (50.4)	0.297	63 (50.0)	64 (50.8)	1.000
60-day mortality	428 (53.4)	62 (44.6)	0.067	62 (49.2)	56 (44.4)	0.528
VA-ECMO duration (days) (range)	1.0 (1.0–3.0)	1.0 (1.0–2.0)	0.023	1.0 (1.0–3.0)	1.0 (1.0–2.0)	0.060
Impella duration (days) (range)	–	7.0 (4.0–10.5)		–	7.0 (4.0–10.0)	
IABP duration (days) (range)	5.0 (3.0–8.0)	–		5.0 (3.0–8.0)	–	
Ventilator duration (days) (range)	8.0 (4.0–15.0)	11.0 (5.0–19.0)	0.001	9.0 (4.0–16.8)	11.5 (5.0–20.8)	0.008
Length of stay (days) (range)	20.0 (6.0–43.0)	32.0 (12.0–57.5)	0.001	23.0 (6.3–43.0)	32.5 (12.0–59.0)	0.017
Discharge location			0.611			0.958
Home	192 (24.0)	36 (25.9)		33 (26.2)	31 (24.6)	
Nursing home	2 (0.2)	0 (0.0)		0 (0.0)	0 (0.0)	
Transfer	162 (20.2)	33 (23.7)		30 (23.8)	31 (24.6)	
Medical cost (million Japanese yen) (range)	4.99 (3.35–7.19)	8.80 (7.16–11.73)	<0.001	5.23 (3.41–7.00)	9.09 (7.20–12.20)	<0.001

Unless indicated otherwise, data are given as the median (interquartile range) or n (%). Nominal-level data were compared using the X^2 test. Continuous variables were compared using Wilcoxon rank-sum tests. In Japan, medical costs for inpatients admitted to acute care hospitals are calculated according to the Diagnosis Procedure Combination per-diem payment system. Medical costs are expressed as fee-for-service costs. As of March 2022, 1 US dollar was equal to 115 Japanese yen. Abbreviations as in Table 1.

and ECPella groups, respectively) than for those with ischemic heart disease (58.9% vs. 56.2% for the ECMO-IABP and ECPella groups, respectively). Moreover, LOS was longer among patients who underwent ECPella in the subgroup with ischemic heart disease. Medical costs were higher in the ECPella than ECMO-IABP group for all subgroups.

By incorporating E-values as a sensitivity analysis to assess the impact of unmeasured confounding factors, we found that a shift in the observed estimate of the RR from 1.016 to 0.900 required an E-value of 1.51. Moreover, to alter the upper limit of the 95% CI from 1.298 to 0.990, an E-value of 1.95 was necessary. In contrast, the E-values required to shift the observed estimate of RR from 1.016

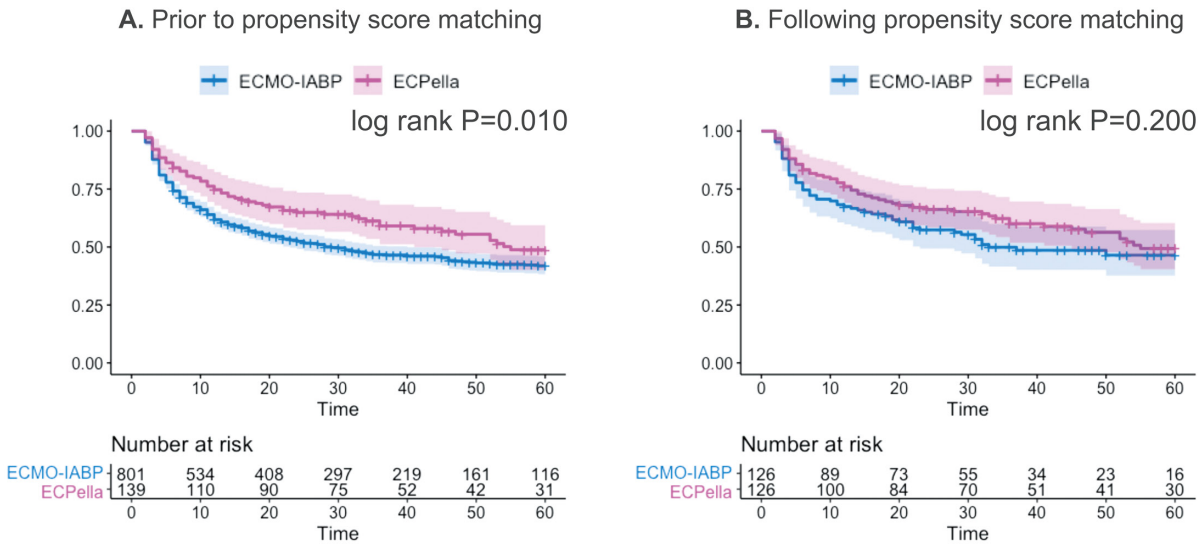

Figure 4. Kaplan-Meier curves of 60-day mortality for patients with cardiogenic shock who underwent veno-arterial extracorporeal membrane oxygenation (ECMO) with Impella or an intra-aortic balloon pump (IABP) before (**A**) and after (**B**) propensity score matching.

Table 4. Subgroup Analysis After Propensity Score Matching

	ECMO-IABP	ECPella	P value
Ischemic heart disease			
No. patients	90	89	
In-hospital mortality	53 (58.9)	50 (56.2)	0.829
Length of stay (days)	20.0 (5.3–37.0)	32.0 (8.00–60.5)	0.036
Medical cost (million Japanese yen) (range)	5.36 (3.47–7.29)	9.08 (7.15–11.80)	<0.001
Non-ischemic heart disease			
No. patients	36	37	
In-hospital mortality	10 (27.8)	14 (37.8)	0.506
Length of stay (days)	31.0 (20.0–46.3)	34.0 (23.0–53.0)	0.371
Medical cost (million Japanese yen) (range)	4.32 (3.18–6.64)	9.11 (7.28–13.17)	<0.001
Myocarditis			
No. patients	16	16	
In-hospital mortality	5 (31.2)	6 (37.5)	1.000
Length of stay (days)	23.5 (20.0–38.5)	32.0 (26.3–41.0)	0.152
Medical cost (million Japanese yen) (range)	3.85 (2.53–5.53)	8.86 (7.75–11.20)	<0.001
Age <70 years			
No. patients	65	66	
In-hospital mortality	27 (41.5)	25 (37.9)	0.803
Length of stay (days)	23.0 (7.0–38.0)	34.5 (14.8–60.8)	0.005
Medical cost (million Japanese yen) (range)	3.93 (3.22–6.81)	9.20 (7.19–11.72)	<0.001
Age ≥70 years			
No. patients	61	60	
In-hospital mortality	34 (55.7)	39 (65.0)	0.392
Length of stay (days)	20.0 (5.0–43.0)	24.0 (8.8–53.0)	0.265
Medical cost (million Japanese yen) (range)	5.17 (3.26–7.17)	8.76 (7.22–12.51)	<0.001

Unless indicated otherwise, data are given as the median (interquartile range) or n (%). In Japan, medical costs for inpatients admitted to acute care hospitals are calculated according to the Diagnosis Procedure Combination per-diem payment system. Medical costs are expressed as fee-for-service costs. As of March 2022, 1 US dollar was equal to 115 Japanese yen. Abbreviations as in Table 1.

to 1.110 and to shift the observed lower limit of 95% CI from 0.795 to 1.010 were 1.38 and 1.86, respectively.

Discussion

Clinical data regarding the comparative effectiveness of Impella and IABP combined with VA-ECMO in patients with CS are limited. To the best of our knowledge, this is the first nationwide study comparing the effects of Impella and IABP on in-hospital mortality in patients with CS requiring peripheral VA-ECMO. Impella 2.5 and 5.0, Impella CP, and Impella 5.5 have been commercially available in Japan since September 2017, May 2019, and February 2022, respectively. Therefore, in our study, we compared the initial outcomes of Impella 2.5, Impella 5.0, and Impella CP with those of IABP in Japan. The novel and important findings of our study are as follows. First, the concomitant use of Impella and peripheral VA-ECMO did not lead to a significant improvement in short-term prognosis compared with the concomitant use of IABP and peripheral VA-ECMO in patients with acute refractory CS. Second, our study revealed noteworthy differences in the demand for medical care between patients who underwent VA-ECMO with Impella and those who underwent VA-ECMO with IABP. Specifically, the former group required more frequent platelet transfusions, a longer duration of mechanical ventilator support, and had a longer LOS, resulting in higher medical costs even after PS matching. Further research is necessary to determine the clinical situations in which the potential effect of Impella can be maximized.

Impact of the Concomitant Use of Impella With VA-ECMO on In-Hospital Mortality

Our findings align with those of previous RCTs, namely the ISAR-SHOCK trial,[14] the IMPRESS in Severe Shock trial,[16] and the ECLS-SHOCK trial, [27] in which Impella failed to demonstrate improvement in 30-day mortality compared with IABP or control in patients with CS induced by acute myocardial infarction. Notably, the earlier RCTs were confined to patients with acute myocardial infarction, whereas our study involved a cohort of patients experiencing CS caused by various cardiac diseases. In addition, the earlier RCTs assessed the effects of Impella alone vs. IABP alone[14,16] or Impella alone vs. control,[27] whereas our investigation focused on assessing the impact of the concurrent use of Impella or IABP with VA-ECMO.

A previous Japanese observational study reported a beneficial effect of ECPella on mid-term mortality compared with ECMO-IABP in patients with CS induced by acute coronary syndrome.[28] Although the 365-day mortality was significantly lower in the ECPella than ECMO-IABP group (43.5% vs. 75.6%, respectively; P=0.010), 30-day mortality was similar between the 2 groups (39.1% vs. 56.1%, respectively; P=0.193),[28] which concurs with the findings of our study. In contrast, a recent study reported that the rate of in-hospital death was higher in the ECPella than ECMO-IABP group (70.8% vs. 42.6%).[29] In that study, the severity of CS was greater in the ECPella group, as evidenced by higher average age, higher mean baseline creatinine concentration, and more frequent cardiopulmonary resuscitation.[29] Furthermore, the study included patients with pulmonary embolism, which is a right-sided heart disease; therefore, the included patients were highly heterogeneous.[29] In our study, which included a larger population, the in-hospital mortality was similar in both groups before and after PS matching. To decrease the heterogeneity within the study population, we exclusively enrolled patients with CS primarily induced by left-sided heart disease who underwent peripheral VA-ECMO with Impella or IABP within 48 h of hospital admission.

Our study has several strengths. First, the use of an exhaustive administrative database allowed for a nationwide evaluation encompassing the largest possible population. Second, PS matching was used to adjust for confounding variables, thereby enhancing the validity of the findings. Calculated E-values of 1.38–1.95 suggest that the observed RR of 1.016 could potentially be explained by an unmeasured confounder. If the unmeasured confounding factors exhibit a greater than 1.38- to 1.95-fold association with both treatment (selection of Impella or IABP) and outcome (in-hospital mortality) after accounting for the measured confounders, the current observed outcomes, wherein the similarity of effects between the concurrent use of Impella or IABP with VA-ECMO was apparent, may be overturned.

In real-world clinical practice, the decision to use Impella may be influenced by a high volume of cases in facilities, such as university hospitals. Before PS matching, Impella was more commonly initiated along with VA-ECMO in relatively younger patients who had a lower incidence of mechanical ventilator use, coronary artery bypass grafting surgery, inotropic support (dopamine and epinephrine), and sodium bicarbonate administration. This trend could be associated with the observed tendency towards improved 60-day mortality in these patients prior to PS matching. However, despite this trend, there was no subsequent improvement in 60-day mortality after PS matching. Moreover, no overall improvement in in-hospital mortality was observed.

The IABP and Impella functionally unload the LV in different ways.[30] The Impella, as a microaxial pump positioned across the aortic valve, directly alleviates the cardiac workload by drawing blood from the LV and propelling it forward into the aorta, ensuring a continuous flow.[12] In contrast, IABP achieves LV unloading indirectly and non-continuously because it reduces afterload during systole through deflation.[31] Therefore, Impella is anticipated to unload the LV more effectively than IABP, potentially resulting in superior outcomes. The National Cardiogenic Shock Initiative, a single-arm prospective multicenter study, indicated the advantage of early (i.e., within 90 min from shock onset) delivery of MCS using Impella, prior to PCI or escalating inotropes.[32]

Impella has demonstrated its capability to reduce pulmonary capillary wedge pressure and improve pulmonary flow by reducing the right ventricular afterload in patients requiring VA-ECMO.[33,34] However, a recent observational study demonstrated no difference in the 24-h hemodynamic changes, including systolic, diastolic, and mean pulmonary arterial pressure, and central venous pressure, induced by ECMO with Impella vs. ECMO with IABP.[29]

Notably, we excluded patients who experienced out-of-hospital cardiac arrest (OHCA); therefore, our finding cannot be extrapolated to this population. The IABP-SHOCK II trial, a randomized prospective open-label multicenter trial comparing the effect of IABP with conventional therapy on CS complicating acute myocardial infarction, revealed that 45.0% of 600 patients experienced resuscitation before randomization.[35] The Japanese Circulation Society Cardiovascular Shock registry showed

that 28.1% of 979 patients with cardiovascular shock and 28.7% of 495 patients with CS induced by acute coronary syndrome experienced OHCA.[36,37] OHCA was identified as an independent risk factor for 30-day mortality in patients with cardiovascular shock (odds ratio 1.62).[36] Further studies are warranted to examine the effect of the concomitant use of Impella or IABP with VA-ECMO in patients who experience OHCA.

Increased Healthcare Demand and Medical Costs for Impella vs. IABP

The insurance reimbursement price for IABP ranges from 154,000 to 177,000 Japanese yen, whereas Impella, at 2,570,000 Japanese yen, is approximately 14- to 17-fold more expensive. Furthermore, transfusions, including RBC, platelets, and FFP, as well as CT scans and longer mechanical ventilator support, were required more frequently in the ECPella than ECMO-IABP group in the entire cohort. Consequently, the ECPella group had longer LOS and higher medical costs. After PS matching, the pattern of more frequent platelet transfusions and PDE3i administration, along with longer mechanical ventilator support, persisted in the ECPella group. Notably, our assessment of blood component transfusions was based on the percentage of patients requiring them and did not account for the total amount of blood transfused. Thus, the total transfusion volume may have been higher in the ECPella than ECMO-IABP group. Previous studies have consistently reported that Impella use is associated with higher rates of adverse events, including bleeding, access site-related ischemia, abdominal compartment syndrome, and kidney injury requiring renal replacement therapy, which contributes to higher medical costs.[13,29,38] Our results align with these findings.

The causal relationship between Impella use and higher healthcare demand and medical costs could not be determined. A potential selection bias may have favored the use of Impella in patients with reduced lung oxygenation attributed to pulmonary congestion, atelectasis, or pneumonia. Future research should incorporate detailed information on lung condition and gas exchange capability at the initiation of VA-ECMO.

Study Limitations

Our study had several limitations. First, despite the adjustment for PS, this was an observational study and cannot prove causation, and the comparative effectiveness results cannot rule out unmeasured confounding factors or selection bias. One of the unmeasured confounding factors was the severity of CS as indicated by the serum lactate concentration, degree of cardiac dysfunction, severity of coronary artery lesions, and hemodynamic parameters. We also could not determine the presence of LV thrombus, aortic valve prosthesis, and peripheral arterial disease, which would all dictate the decision of IABP or Impella as an unloading strategy. E-values were calculated as a sensitivity analysis to assess the minimum strength of association with both the treatment and outcome required for unmeasured confounders to shift point estimates or one limit of the CI away from the null hypothesis. Second, not all variables were equivalent between the 2 groups after PS matching. However, most of the variables highly relevant to the primary outcome were comparable. Third, our analyses did not consider the specific type of Impella device used, such as Impella 2.5, Impella CP, or Impella 5.0. Moreover, our analyses did not consider the approach site, whether femoral or axial. These factors may influence the degree of hemodynamic flow support provided, emergency availability, and may be associated with different types of adverse events. Furthermore, as the sequence of MCS delivery could not be ascertained, our study may encompass cases where VA-ECMO was introduced following either Impella or IABP.

To overcome the aforementioned limitations, a prospective study, ideally a controlled trial, which would include comprehensive and detailed information, should be conducted in the future. However, conducting randomized controlled trials in the emergency setting of CS is difficult due to its relatively low incidence, difficulties in obtaining informed consent from patients and their families, and time constraints, making it challenging to achieve an adequate sample size. [15] Thus, our claims database-based study has a certain value.

Perspectives

Given the presence of unmeasured confounding factors and the heterogeneity of our study population, interpreting our study results requires caution. Future studies should aim to clarify the specific subgroups and clinical contexts in which Impella is effective. Moreover, these studies should include comprehensive information regarding the severity of CS, comorbidities, lung conditions, and gas exchange capabilities at the initiation of VA-ECMO. Furthermore, the outcomes based on the type of Impella device also need clarification through these studies.

Conclusions

Our nationwide study could not demonstrate compelling evidence to support the superior efficacy of Impella over IABP in reducing in-hospital mortality among patients with CS necessitating VA-ECMO. Furthermore, the concomitant use of Impella with VA-ECMO was associated with more frequent transfusion, a longer duration of mechanical ventilator support, longer LOS, and higher medical costs than the concomitant use of IABP with VA-ECMO. Further investigations are imperative to determine the clinical situations in which the potential effect of Impella can be maximized.

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Disclosures

The authors declare that there are no conflicts of interest.

IRB Information

This study was approved by the Ethics Committee of Yokohama City University (Approval no. F221200005).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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