Supplemental Material

Data S1

Supplemental Methods

Variables

The following variables were extracted from the JROAD-DPC database: age, sex, body mass index, duration of hospital stay, emergency admission, ambulance use, smoking habit (Brinkman index: 0 or >0), Killip classification, activities of daily living (ADL) score (Barthel index: 100 or <100), comorbidities (ischemic heart disease, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, chronic pulmonary disease, peripheral vascular disease, cerebrovascular disease, renal disease, and malignancy), cardiac arrest at admission defined as performing cardio pulmonary resuscitation on admission, cardiac catheterization, revascularization defined as PCI or coronary artery bypass grafting (CABG), mechanical circulatory support (MCS) use (venoarterial extracorporeal membrane oxygenation [VA-ECMO] or/and intraaortic balloon pumping [IABP]), hospital teaching status, the number of hospital beds, the number of board-certified cardiologists per each hospital, coronary care unit, and back up of cardiovascular surgery. Primary PCI was defined as PCI performed on the day of or the next day of admission. The hospital teaching status was classified into three categories, Class A: more than 2 board-certified cardiologists (BCC) and 30 cardiovascular beds, Class B: more than 1 board-certified cardiologists and 15 cardiovascular beds, and Class C: none of the above. As the institutional characteristics, the aging rate and Japanese Circulation Society (JCS)-certified hospital density by the prefecture where the institution was located were used. Data for the aging rate by

prefecture in 2017 were obtained from the Annual Report on the Aging Society :2018.[35] JCS-certified hospital density (hospitals/km2) was calculated by dividing the number of hospitals by inhabitable area where the institution was located. Data for the inhabitable area in 2015 were obtained from the Japanese Government Statistics.[36]

Statistical analysis

Data were presented as the median and interquartile range (IQR) for continuous variables, and number (percentage) for categorical variables. The incidence of each clinical event was described as per 1,000 person days and the risk ratio of the event between the two treatment arms was calculated. To estimate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for associated factors of all-cause mortality, a Cox frailty model was used with random effects to account for institution-related variation.[37] As adjusted factors in multivariate analysis to perform group comparison for VA-ECMO use, the following variables were used: model 1 included age category, sex, full score Barthel index at admission, Killip classification, comorbidities (previous ischemic heart disease, hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, chronic pulmonary disease, peripheral vascular disease, cerebrovascular disease, renal disease, and malignancy), cardiac arrest at admission, and hospital characteristics (hospital with $\geq$500 beds, number of BCC, hospital with coronary care unit (CCU), hospital with cardiac surgery, reginal aging rate, and JCS-certificated hospital density), model 2 included age category, sex, full score Barthel index at admission, Killip classification, cardiac arrest at admission, and the hospital characteristics, and model 3 included age category, sex, full score Barthel index at admission, Killip classification, the comorbidities, and cardiac arrest on admission. To estimate the impact of IABP in conjunction with VA-ECMO on 30-day, 7-day, and in-hospital mortality in AMI-CS

patients, we performed propensity score matching between the VA-ECMO plus IABP group and the VA-ECMO alone group based on the estimated propensity scores to reduce the effect of known possible confounders. The predicted probability of receiving IABP was calculated by applying a logistic regression model, using all clinically relevant variables including age, sex, ADL, Killip classification, the comorbidity, cardiac arrest at admission, MCS use, the institutional characteristics. One participant in the VA-ECMO plus IABP group was matched with 1 patient in the VA-ECMO alone group using nearest-neighbor matching within a caliper width of 0.2 standard deviation without replacement. A comparison of the baseline characteristics between the VA-ECMO plus IABP group and the VA-ECMO alone group in the matched cohort was performed using the absolute standardized mean difference (>0.10 represents meaningful imbalance). In addition, to confirm the robustness of the results, inverse probability of treatment weighting (IPTW) with the same predicted probability used in the propensity score matching was performed as sensitivity analysis for the same outcome. The actuarial survivals of the VA-ECMO plus IABP group and the VA-ECMO alone group were calculated using the Kaplan–Meier method, with the log-rank test used for the comparison between the two groups. A two-sided p value of <0.05 was considered to denote the presence of a statistically significant difference. R programming language
version 3 (R Foundation for Statistical Computing, Vienna, Austria) with a library of epitools was used for calculating rates of per-1000-person-days and risk ratios. The other statistical analyses were conducted using SAS9.4 (SAS Institute, Cary, NC).

Table S1. Patient and institutional characteristics after propensity matching cohorts.

	VA-ECMO plus IABP (n=846)	VA-ECMO alone (n=846)	Absolute standardized mean difference
Age, years	69 (61, 77)	69 (60, 78)	0.01
Age categories			
≥20 to <50 years	74 (8.7)	71 (8.4)	
≥50 to <60 years	99 (11.7)	126 (14.9)	
≥60 to <70 years	258 (30.5)	228 (27.0)	
≥70 to <80 years	263 (31.1)	254 (30.0)	
≥80 to <90 years	145 (17.3)	154 (18.2)	
≥90	5 (0.7)	13 (1.5)	
Males	652 (77.1)	664 (78.5)	0.04
Full score Barthel Index as admission	87 (10.3)	75(8.9)	0.05
Killip classification			0.02
Killip 3	44 (5.2)	47 (5.6)	
Killip 4	802 (94.8)	799 (94.4)	
Prior ischemic heart disease	11 (1.3)	8 (1.0)	0.03
Hypertension	166 (19.6)	154 (18.2)	0.04
Dyslipidemia	99 (11.7)	92 (10.9)	0.02
Diabetes mellitus	145 (17.1)	134 (15.8)	0.03
Atrial fibrillation	18 (2.1)	12 (1.4)	0.05
Chronic pulmonary disease	5 (0.6)	6 (0.7)	0.01
Peripheral vascular disease	41 (4.9)	42 (5.0)	0.01
Cerebrovascular disease	25 (3.0)	26 (3.1)	0.01
Renal disease	198 (6.7)	57 (6.7)	0.03
Malignancy	13 (1.5)	9 (1.1)	0.04
Cardiac arrest at admission	140 (16.6)	140 (16.6)	<0.01
Hospital teaching status: class A	796 (94.1)	803 (94.9)	0.04
Hospital with the number of hospital beds ≥500	412 (48.7)	422 (49.9)	0.02
Number of board-certified cardiologists per hospital ≥6	412 (48.6)	422 (48.7)	<0.01
Hospital with CCU	810 (95.7)	814 (96.2)	0.03
Hospital with cardiac surgery	715 (84.5)	720 (85.1)	0.02

Values are median (interquartile range) or n (%). CCU indicates coronary care unit; IABP, intraaortic balloon pumping; VA-ECMO, venoarterial extracorporeal membrane oxygenation. The hospital teaching status of class A indicates more than 2 board-certified cardiologists and 30 cardiovascular beds.

Table S2. Cox proportional hazard ratios of 30-day, 7-day and in-hospital mortality in AMI-CS patients managed with VA-ECMO plus IABP compared with VA-ECMO alone.

	30-day mortality	7-day mortality	In-hospital mortality
Univariable	0.43 (0.39, 0.47)	0.36 (0.33, 0.40)	0.44 (0.40, 0.48)
Multivariable			
Model 1	0.44 (0.40, 0.43)	0.38 (0.34, 0.42)	0.45 (0.41, 0.49)
Model 2	0.43 (0.39, 0.47)	0.37 (0.33, 0.41)	0.44 (0.40, 0.48)
Model 3	0.44 (0.40, 0.48)	0.37 (0.34, 0.41)	0.45 (0.41, 0.49)
PSM	0.50 (0.45, 0.56)	0.42 (0.37, 0.47)	0.51 (0.46, 0.57)
IPTW	0.41 (0.38, 0.44)	0.35 (0.33, 0.38)	0.42 (0.39, 0.45)

Values are Cox proportional hazard ratio and 95% confidence intervals (lower, and upper). The following variables were used for the multivariable adjustment: Model 1 included age category, sex, full score Barthel index at admission, Killip classification, comorbidities, cardiac arrest at admission, and hospital characteristics, model 2 included age category, sex, full score Barthel index at admission, Killip classification, cardiac arrest at admission, and the hospital characteristics, and model 3 included age category, sex, full score Barthel index at admission, Killip classification, the comorbidities, and cardiac arrest on admission. AMI-CS indicates acute myocardial infarction complicated by cardiogenic shock; IABP, intraaortic balloon pumping; IPTW, inverse probability of treatment weighting; PSM, propensity score matching; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

Table S3. Subgroup analysis stratified by cardiac arrest, sex and age: odds ratios of 7-day, 30-day and in-hospital mortality in AMI-CS patients managed with VA-ECMO plus IABP compared with VA-ECMO alone.

	In-hospital mortality		**7-day mortality**		**30-day mortality**	
	OR (95% CI)	P for interaction	OR (95% CI)	P for interaction	OR (95% CI)	P for interaction
With cardiac arrest	0.47 (0.25, 0.89)	0.87	0.31 (0.18, 0.51)	0.85	0.43 (0.24, 0.78)	0.87
Without cardiac arrest	0.48 (0.37, 0.61)		0.31 (0.25, 0.38)		0.41 (0.32, 0.51)	
Male	0.48 (0.38, 0.62)	0.45	0.31 (0.25, 0.38)	0.59	0.41 (0.32, 0.52)	0.83
Female	0.35 (0.18, 0.67)		0.26 (0.15, 0.43)		0.34 (0.19, 0.60)	
Age ≥75	0.27 (0.16, 0.45)	0.025	0.25 (0.17, 0.37)	0.36	0.28 (0.18, 0.45)	0.11
Age <75	0.53 (0.41, 0.69)		0.32 (0.26, 0.40)		0.44 (0.35, 0.57)	

Values are odds ratio and 95% confidence intervals (lower, and upper). AMI-CS indicates acute myocardial infarction complicated by cardiogenic shock; IABP, intraaortic balloon pumping; and VA-ECMO, venoarterial extracorporeal membrane oxygenation.

Table S4. Clinical outcomes of AMI-CS patients treated with VA-ECMO plus IABP versus VA-ECMO alone before and after propensity score matching.

	VA-ECMO plus IABP	VA-ECMO alone	Risk ratio (95%CI)	*P* value
Before PSM	**n = 2,964**	**n = 851**		
In-hospital death	35.1	93.7	0.37 (0.34, 0.41)	<0.001
Stroke	0.6	0.5	1.15 (0.41, 3.23)	0.79
Major bleeding	9.5	11.7	0.81 (0.65, 1.01)	0.064
Intracranial bleeding	0.6	0.5	1.12 (0.40, 3.15)	0.832
Gastrointestinal bleeding	1.8	2.6	0.70 (0.43, 1.12)	0.14
After PSM	**n = 846**	**n = 846**		
In-hospital death	37.9	93.1	0.41 (0.37, 0.45)	<0.001
Stroke	0.7	0.5	1.28 (0.41, 4.02)	0.67
Major bleeding	10.9	11.8	0.92 (0.72, 1.19)	0.54
Intracranial bleeding	0.7	0.5	1.28 (0.41, 4.02)	0.67
Gastrointestinal bleeding	1.9	2.6	0.74 (0.43, 1.30)	0.30

The incidence rate was described as per 1000 person days. Risk ratios and 95% confidence intervals (lower, upper) of each adverse event of the VA-ECMO plus IABP versus VA-ECMO alone groups were calculated. AMI-CS indicates acute myocardial infarction complicated by cardiogenic shock; IABP, intraaortic balloon pumping; PSM, propensity score matching; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

Table S5. Additional mechanical support for AMI-CS patients treated with VA-ECMO plus IABP versus VA-ECMO alone

	VA-ECMO plus IABP (n=2964)	VA-ECMO alone (n=851)	Risk ratio (95%CI)	*P* value
Hemodialysis	3.4	3.8	0.88 (0.60, 1.29)	0.50
Mechanical ventilator	47.1	97.2	0.49 (0.45, 0.53)	<0.001
Ventricular assist device	0.1	0.1	1.15 (0.41, 3.23)	0.79

The incidence rate was described as per 1000 person days. Risk ratios and 95% confidence intervals (lower, upper) of each event of the VA-ECMO plus IABP versus VA-ECMO alone groups were calculated. AMI-CS indicates acute myocardial infarction complicated by cardiogenic shock; IABP, intraaortic balloon pumping; VA-ECMO, venoarterial extracorporeal membrane oxygenation.