

Extracorporeal membrane oxygenation improved survival in patients with massive pulmonary embolism

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BACKGROUND: Current guidelines for massive pulmonary embolism (PE) treatment recommend primary reperfusion therapy and the option of extracorporeal membrane oxygenation (ECMO). However, these recommendations might not be optimal for patients with poor prognoses who are in cardiogenic shock (CS) or require cardiopulmonary resuscitation (CPR).

OBJECTIVE: Evaluate the impact of ECMO support on the clinical outcome of patients with massive PE complicated by CPR or CS.

DESIGN: Retrospective review of medical records.

SETTING: A university hospital, South Korea.

PATIENTS AND METHODS: We collected data on patients from 2004 through 2009 (stage 1) and from 2010 through June 2017 (stage 2). Patients with confirmed massive PE received medical therapy (stage 1) or medical therapy that included extracorporeal membrane oxygenation (ECMO) support (stage 2).

MAIN OUTCOME MEASURES: All-cause mortality at 90 days after therapy.

SAMPLE SIZE: 9 patients with confirmed massive PE that received medical therapy (stage 1); 14 patients with confirmed massive PE that received medical therapy with ECMO support (stage 2).

RESULTS: In stage 1, 5 of 9 patients received systemic thrombolysis and 4 patients received anticoagulation. Thirteen of the 14 stage 2 patients received anticoagulation with ECMO support and one patient received systemic thrombolysis with ECMO support. Tricuspid annular plane systolic excursion in stage 1 was lower than in stage 2. Proximal PE in chest CT was more common in stage 2. Survival was significantly improved at 90 days for patients in stage 2 (log-rank, $P=.048$). There were no differences in baseline characteristics, ECMO complications and transfusion between survivors and nonsurvivors in stage 2.

CONCLUSIONS: Anticoagulation with ECMO support is associated with good survival rate outcomes compared with medical therapy alone.

LIMITATIONS: Relatively small number of patients and retrospective design.

CONFLICT OF INTEREST: None.

Pulmonary embolism (PE) is a major cause of morbidity and mortality in the general population. In particular, massive PE is rare and critical. Overall, in-hospital mortality rates for massive PE ranged from 25% for patients with cardiogenic shock (CS), to 65% for those that required cardiopulmonary resuscitation (CPR), while in-hospital mortality rate in stable patients with PE was 8.1%.^{1,2} Primary reperfusion therapy is the treatment of choice for patients with unstable PE with shock or hypotension, based on the European Society of Cardiology (2014) guidelines. Primary reperfusion therapy includes thrombolysis (class IB), surgical pulmonary embolectomy (class IC) and percutaneous catheter-directed embolectomy (class IIaC).³ However, in clinical practice, relatively large numbers of patients cannot receive thrombolysis or embolectomy.² Major contraindications to thrombolytic therapy include recent major surgery or trauma and prolonged CPR. The clinical course of massive PE can rapidly progress before surgical or catheter-directed embolectomy. Based on the International Cooperative Pulmonary Embolism Registry, two-thirds of patients with massive PE did not receive thrombolysis or embolectomy,⁴ and the cases of untreated massive PE remain problematic.

Anticoagulation with peripheral extracorporeal membrane oxygenation (ECMO) support can be a rapid, effective option for patients with massive PE.⁵⁻⁷ Venous-arterial (VA) ECMO is one of the most reliable and quickest ways to decrease right ventricle (RV) overload, improve RV function and hemodynamic status, and restore tissue oxygenation. The impacts of ECMO on survival have not been investigated in massive PE, compared to the medical therapy alone. This study investigated the impact of ECMO on survival in patients with massive PE.

PATIENTS AND METHODS

This was a retrospective study conducted between January 2004 and June 2017. ECMO was introduced into our hospital in May 2009. Prior to 2010, medical therapy including primary reperfusion therapy was the most commonly used therapy in our hospital for massive PE. Patients with confirmed massive PE, complicated by profound CS or that required CPR (n=23), were enrolled in the study to analyze clinical outcomes. PE was diagnosed using the diagnostic strategy tools of the most recent European Society of Cardiology guidelines.³ In the present study, the most useful initial test in suspected PE with CS or requiring CPR is bedside transthoracic echocardiography according to the guidelines. In an unstable patient, echocardiographic evidence of RV dysfunction is sufficient to prompt re-

perfusion without further testing. When the patient was stabilized, CT angiography was performed. CS was defined as follows: Chest radiograph that showed pulmonary edema or end-organ failure with systolic blood pressure less than 90 mm Hg that did not respond to fluid supply and required a vasopressor agent. Of the predisposing factors, orthopedic surgery includes total knee replacement arthroplasty, total hip replacement arthroplasty, carpal tunnel release, and surgical treatment of wrist fracture. Bleeding complications were reported using the Global Utilization of Streptokinase and TPA for Occluded arteries (GUSTO) classification.^{8,9} Briefly, severe life-threatening bleeding was defined as intracerebral bleeding or bleeding that caused substantial hemodynamic compromise and required treatment (GUSTO 1). GUSTO 2 defined moderate bleeding that required blood transfusion, whereas GUSTO 3 referred to other bleeding that did not require transfusion or cause hemodynamic compromise. Data obtained from medical records, clinical case histories, and laboratory investigations were retrospectively reviewed. Follow-up data were collected from outpatient clinic records or via telephone. The composite outcome was all-cause mortality at 90 days. This study was approved by the Institutional Review Board of the Catholic University of Korea, St. Vincent's Hospital (IRB approval number: VC17RESI0146). The study was exempted from requirements for written informed consent because the medical records were retrospectively reviewed. All data records were de-identified and analyzed anonymously.

ECMO and management

The ECMO team consisted of interventional cardiologists, cardiovascular surgeons, and perfusionists. A Capiiox emergency bypass system (Terumo, Tokyo, Japan) was used in all cases. VA-ECMO indications included acute refractory cardiac failure, defined as evidence of tissue hypoxia concomitant with adequate intravascular volume status, severely diminished right ventricular or left ventricular ejection fraction (RV/LVEF), low cardiac index (cardiac output from left ventricle in one minute to body surface area, <2.2 L/min/m²), and sustained hypotension despite high-dose catecholamine infusion. ECMO exclusion criteria were as follows: Malignancies with fatal prognosis within 5 years or irreversible neurological pathologies and decisions to limit therapeutic interventions. VA-ECMO cannulas were inserted by trained cardiovascular surgeons with a femoral-femoral approach. The tip of the arterial sheath (15-16F catheter) was placed in the common iliac artery, and the tip of the venous sheath (22-23F catheter)

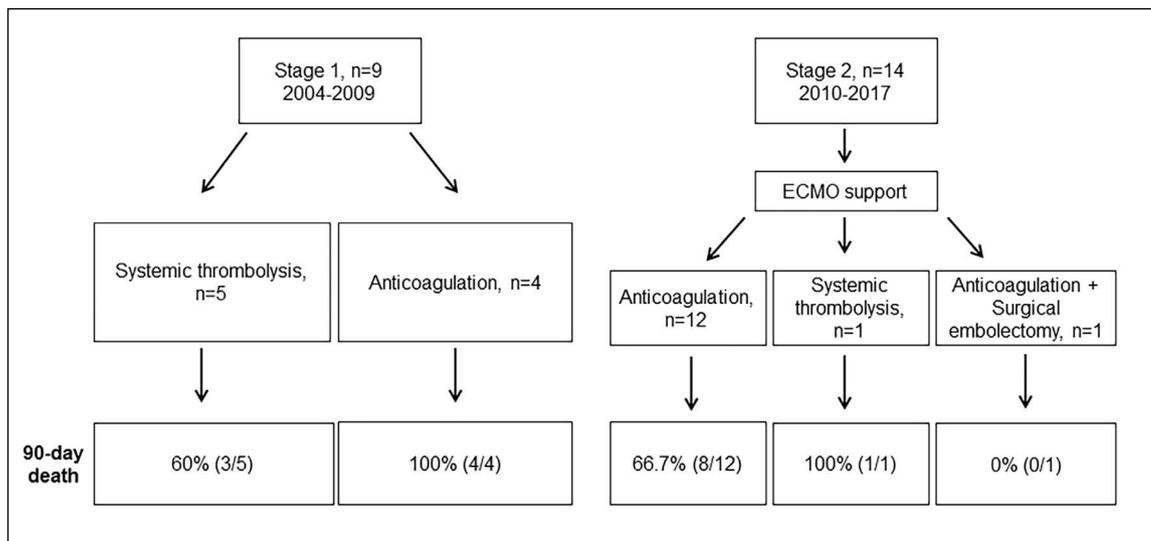


Figure 1. Study flow chart.

reached the junction between the right atrium and inferior vena cava. The remaining test method was described in detail in a previous paper.¹⁰

Statistical analysis

Continuous variables are presented as the median and interquartile ranges or the means and standard deviation (SD), and compared using the Mann-Whitney U test or t test. Categorical variables are presented as numbers and percentages, and compared using the chi-squared or Fisher's exact tests. The survival of stage 1 and stage 2 was determined using the Kaplan-Meier method and compared using a log rank test. A *P* value <.05 was considered statistically significant. Analyses were performed using Statistical Analysis Software (SAS, version 9.2, SAS Institute, Cary, NC, USA).

RESULTS

From 2004 through 2009, 9 patients presented at our medical center with confirmed massive PE and these patients received medical therapy alone without ECMO; this was defined as stage 1. However, only five of these patients received systemic thrombolysis and four patients received anticoagulation due to recent major surgery and prolonged CPR. From 2010 through June 2017, 14 patients presented at our medical center with confirmed massive PE, this was defined as stage 2. All patients received ECMO support. Thirteen of the 14 stage 2 patients received anticoagulation due to recent major surgery and prolonged CPR and one of these patients received the additional surgical embolectomy due to unresolved thrombus burden. One patient received systemic thrombolysis (**Figure 1**). Tricuspid an-

nular plane systolic excursion (TAPSE) in stage 1 was lower than in stage 2. Proximal PE in chest CT was also diagnosed more frequently in stage 2 (**Table 1**). There was no difference in predisposing factors and laboratory findings for cardiogenic shock between those two groups. The stage 2 group had a higher survival rate at 90 days after therapy (**Figure 2**) (log-rank, *P*=.048). There were no differences in baseline characteristics between survivors and non-survivors in the stage 2 group (**Table 2**). Moreover, there was no differences in ECMO complications between those two groups (**Table 3**). Seven (50%) patients had a moderate to severe hemorrhage classified as GUSTO ≤ 2 , such as cannula site bleeding (n=4), pulmonary hemorrhage (n=2) and ulcer bleeding (n=1). Compartment syndrome, pseudoaneurysm, and cannula site infection occurred in one patient, respectively. In addition, there were three patients with pneumonia, seven patients with acute kidney injury, four patients with multiple organ failure, two patients with leg ischemia, five patients with hypoxic brain injury, and two patients with neuropathy. There were no differences in transfusion, mechanical ventilation duration, and ECMO duration. However, hospital duration was longer in survivors than in non-survivors.

DISCUSSION

We investigated the impact of ECMO on survival in patients with massive PE. Medical therapy was the primary treatment approach in stage 1, while anticoagulation with ECMO support was the primary treatment in stage 2. ECMO support was used as a bridge therapy. ECMO helps to decrease right ventricle overload and stabilize the hemodynamic status. Anticoagulation therapy was

Table 1. Baseline characteristics.

	Stage 1 Without ECMO (n=9)	Stage 2 With ECMO (n=14)	P
Male	0 (0.0)	4 (28.6)	.127
Mean age (years)	65.4 (14.8)	53.6 (17.7)	.110
BMI	25.1 (3.1)	26.0 (4.4)	.577
Smoking	0 (0.0)	4 (28.6)	.127
DM	2 (22.2)	2 (14.3)	>.999
Hypertension	4 (44.4)	3 (21.4)	.363
Cancer	2 (22.2)	0 (0.0)	.142
Predisposing factor			
Post orthopedic surgery	6 (66.7)	3 (21.4)	.077
Immobility	3 (33.3)	5 (35.7)	>.999
Previous DVT	1 (11.1)	0 (0.0)	.391
Trauma	0 (0.0)	2 (14.3)	.502
Cancer	2 (22.2)	0 (0.0)	.142
Unknown	0 (0.0)	3(21.4)	.253
TTE parameter			
RVSP	35.1 (28.4)	42.9 (13.3)	.455
TAPSE	6.3 (6.2)	11.9 (4.3)	.027
RV dilation	7 (77.8)	13 (92.9)	.538
Chest CT finding			
Proximal PE	3 (33.3)	12 (85.7)	.023
Cardiac arrest			
IHCA	7 (77.8)	7 (50.0)	.228
OHCA	1 (11.1)	4 (28.6)	.611
Cardiogenic shock	1 (11.1)	3 (21.4)	>.999
Treatment			
Heparin	2 (22.2)	13 (92.9)	.001
LMWH	2 (22.2)	0 (0.0)	.142
Urokinase	4 (44.4)	1 (7.1)	.056
tPA	1 (11.1)	0 (0.0)	.391
Surgical embolectomy	0 (0.0)	1 (7.1)	>.999

Table 1 (cont). Baseline characteristics.

	Stage 1 Without ECMO (n=9)	Stage 2 With ECMO (n=14)	P
ECG finding			
Asystole	2 (22.2)	4 (28.6)	>.999
PEA	5 (55.6)	5 (35.7)	.417
VT/V.fib	1 (11.1)	2 (14.3)	>.999
Sinus tachycardia	1 (11.1)	3 (21.4)	>.999
GCS	11.1 (5.6)	6.3 (4.1)	.056
APACHE II score	22.1 (10.8)	22.4 (6.9)	.932
Laboratory finding at cardiogenic shock			
pH	7.2 (0.3)	7.2 (0.2)	.972
HCO ₃ (mmol/L)	14.7 (5.7)	12.6 (3.1)	.281
Potassium (mEq/L)	4.3 (0.9)	4.0 (0.9)	.466
Creatinine (mg/dL)	1.6 (1.3)	1.3 (0.7)	.526
Platelet (×10 ⁹ /L)	183.0 (86.9)	175.4 (83.7)	.841
D-dimer	3.4 (1.7)	11.6 (12.9)	.148
CK-MB (ng/mL)	13.1 (14.8)	6.5 (5.9)	.125
Death in hospital	7 (77.8)	8 (57.1)	.400

Data are expressed as mean(standard deviation) or N (%); ECMO, extracorporeal membrane oxygenation; BMI, body mass index; DM, diabetes mellitus; DVT, deep vein thrombosis; TTE, trans-thoracic echocardiography; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; CT, computed tomography; PE, pulmonary embolism; IHCA, in-hospital cardiac arrest; OHCA, out of hospital cardiac arrest; LMWH, low molecular weight heparin; tPA, tissue plasminogen activator; ECG, electrocardiography; PEA, pulseless electrical activity; VT, ventricular tachycardia; V.fib, ventricular fibrillation; GCS, Glasgow Coma Scale; APACHE II, Acute Physiology and Chronic Health Evaluation II; CK-MB, creatine kinase MB.

used as a definite therapy in stage 2 after stabilizing the status with ECMO support. The stage 2 group showed a higher survival rate at 90 days. There were no differences in baseline characteristics, ECMO complications, and transfusion between survivors and non-survivors in the stage 2 group.

Based on current guidelines, primary reperfusion therapy with systemic thrombolytic agents or surgical pulmonary embolectomy is the treatment of choice for

Table 2. Survivors versus non-survivors in ECMO-treated massive PE patients.

	Survivor (n=6)	Non-survivor (n=8)	P
Male	2 (33.3)	2 (25.0)	>.999
Mean age (years)	49.8 (8.9)	56.4 (22.5)	.516
BMI	24.2 (0.9)	27.4 (5.5)	.152
Smoking	2 (33.3)	2 (25.0)	>.999
DM	1 (16.7)	1 (12.5)	>.999
Hypertension	0 (0.0)	3 (37.5)	.209
Cancer	0 (0.0)	0 (0.0)	-
Predisposing factor			
Post orthopedic surgery	1 (16.7)	2 (25.0)	>.999
Immobility	1 (16.7)	4 (50.0)	.301
Trauma	2 (33.3)	0 (0.0)	.165
Unknown	1 (16.7)	2 (25.0)	>.999
TTE parameter			
RVSP	45.4 (6.4)	41.1 (17.0)	.524
TAPSE	12.1 (3.8)	11.7 (4.8)	.877
RV dilation	6(100.0)	7 (87.5)	>.999
Chest CT finding			
Proximal PE	6 (100.0)	6 (75.0)	.473
Cardiac arrest			
IHCA	3 (50.0)	4 (50.0)	>.999
OHCA	2 (33.3)	2 (25.0)	>.999
Cardiogenic shock	1 (16.7)	2 (25.0)	>.999
Treatment			
Heparin	6 (100.0)	7 (87.5)	>.999
Urokinase	0 (0.0)	1 (12.5)	>.999
Surgical embolectomy	1 (16.7)	0 (0.0)	.429
ECG finding			
Asystole	2 (33.3)	2 (25.0)	>.999
PEA	3 (50.0)	2 (25.0)	.580

Table 2 (cont). Survivors versus and non-survivors in ECMO-treated massive PE patients.

	Survivor (n=6)	Non-survivor (n=8)	P
VT/V.fib	0 (0.0)	2 (25.0)	.473
Sinus tachycardia	1 (16.7)	2 (25.0)	>.999
GCS	5.8 (3.1)	6.6 (4.9)	.737
APACHE II score	19.0 (4.5)	25.0 (7.6)	.111
Pre-ECMO laboratory findings			
pH	7.3 (0.1)	7.2 (0.2)	.133
HCO ₃ (mmol/L)	14.4 (2.6)	11.3(2.9)	.056
Potassium (mEq/L)	3.8 (0.4)	4.1 (1.2)	.534
Creatinine (mg/dL)	1.0 (0.1)	1.6 (0.8)	.080
Platelet (×10 ⁹ /L)	197.3 (81.3)	158.9 (86.9)	.417
D-dimer	21.3 (16.8)	5.6 (4.0)	.106
CK-MB (ng/mL)	4.0 (2.9)	8.4 (7.1)	.178
CA-ECMO time	22.5 (15.5)	53.6 (68.0)	.246

Data are expressed as mean(standard deviation) or N (%); ECMO, extracorporeal membrane oxygenation; BMI, body mass index; DM, diabetes mellitus; DVT, deep vein thrombosis; TTE, trans-thoracic echocardiography; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; CT, computed tomography; PE, pulmonary embolism; IHCA, in-hospital cardiac arrest; OHCA, out of hospital cardiac arrest; LMWH, low molecular weight heparin; tPA, tissue plasminogen activator; ECG, electrocardiography; PEA, pulseless electrical activity; VT, ventricular tachycardia; V.fib, ventricular fibrillation; GCS, Glasgow Coma Scale; APACHE II, Acute Physiology and Chronic Health Evaluation II; CK-MB, creatine kinase MB.

patients with unstable PE with shock or hypotension.³ However, those recommendations may not be optimal for patients with poor prognoses in CS or CPR. In real clinical practice, a relatively large number of patients do not receive thrombolysis or embolectomy because thrombolysis takes time to be effective and surgery is not immediately available. In addition, the clinical course of massive PE can rapidly advance before surgical or catheter-directed embolectomy can be achieved.

Anticoagulation with ECMO support can be a rapid, effective option for patients with massive PE to stabilize hemodynamic instability. Many studies have reported that ECMO support is also effective for patients with life-threatening massive PE.^{6,11-16} However, these re-

ports were only based on ECMO applied for managing massive PE. The reports did not investigate the impact of ECMO on survival in patients with massive PE, compared to the medical therapy alone. Hashiba et al have reported that the ECMO survival rate at discharge was 83.3%. The outcome could be attributable to lower proportions of patients with cardiac arrest, compared with our study population.¹¹ Maggio et al have found that the survival rate of ECMO for massive PE was 13 of 21 or 62%. However, only 8 of 21 patients experienced cardiac arrest, which was a smaller percentage than in our study. Surprisingly, Maggio et al reported cases of emboli resolved with anticoagulation in 10 of 13 survivors and required no additional therapy.¹² Those results are similar to the results of our study. Munakata et al reported that the 30-day mortality of ECMO for massive PE was 30%. All patients had a diagnosis of PE, which was confirmed by pulmonary angiography. Systemic or catheter-based thrombolysis was administered to all of the patients in that study.¹³ A French study group recently reported that VA-ECMO could be applied as a lifesaving rescue therapy for patients with high risk and massive PE. The 90-day survival was 47%, although 15 of 17 patients suffered cardiac arrest.⁶

Cho et al reported that surgical embolectomy is also associated with lower cardiac mortality risk than thrombolysis and is a viable option after cardiac arrest.^{15,17} Compared to other studies, the number of patients in our study that received surgical or catheter-directed embolectomy was small. This could have impacted the low survival rate observed in the present study. Surgical or catheter directed embolectomy should be actively considered if RV failure does not improve.

Moreover, 7 (50%) of 14 patients had a moderate to severe hemorrhage. Four of these patients had cannula site bleeding. In our study, ECMO cannulation was performed without imaging modalities because all cases were urgent. In addition, development of vascular complications is associated with worse survival outcome.^{18,19} That is one of the reasons for the low survival rate in our study, compared to other studies. Imaging modalities, including ultrasound and fluoroscopy can reduce vascular complications.²⁰ Therefore, we should actively utilize imaging modalities to reduce bleeding events for ECMO cannulation. In our study, there were no differences in baseline characteristics, ECMO complications, and transfusion between survivors and non-survivors in the stage 2 group. These results are likely attributable to the small sample size.

In our study, the survival rates in patients with massive PE that were treated with anticoagulation with ECMO, compared to the medical therapy alone, were a notable

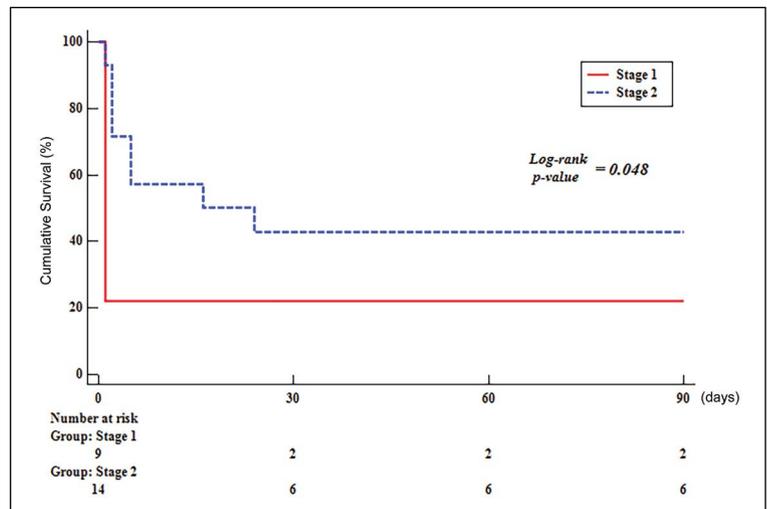


Figure 2. 90 day Kaplan-Meier survival curves by treatment. Kaplan-Meier analysis showing the survival rate of stage 2 (n=14) compared with stage 1 (n=9). (Stage 1, medical therapy alone; stage 2, medical therapy with ECMO support).

Table 3. Complications and outcomes of ECMO-treated massive PE patients.

	Survivor (n=6)	Non-survivor (n=8)	P
Complications			
Cannula site bleeding	3 (50.0)	1 (12.5)	.245
Pulmonary hemorrhage	0 (0.0)	2 (25.0)	.473
Ulcer bleeding	0 (0.0)	1 (12.5)	>.999
Compartment syn.	1 (16.7)	0 (0.0)	.429
Pseudoaneurysm	1 (16.7)	0 (0.0)	.429
Cannula site infection	1 (16.7)	0 (0.0)	.429
Pneumonia	2 (33.3)	1 (12.5)	.539
AKI	3 (50.0)	4 (50.0)	>.999
MOF	0 (0.0)	4 (50.0)	.085
Leg ischemia	1 (16.7)	1 (12.5)	>.999
Hypoxic brain injury	2 (33.3)	3 (37.5)	>.999
Neuropathy	2 (33.3)	0 (0.0)	.165
Transfusion			
PRC (mL/kg)	138.4 (121.1)	81.0 (81.1)	.308
FFP (mL/kg)	32.2 (57.7)	48.2 (63.0)	.635
PC (mL/kg)	143.4 (147.1)	345.0 (451.6)	.268
Ventilator duration, days	11.5 (5.5)	7.1 (7.8)	.267
Hospital duration, days	41.5 (15.1)	13.9 (15.0)	.005
ECMO duration, days	7.8 (3.3)	8.0 (8.1)	.963

Data are expressed as mean(standard deviation) or N (%); ECMO, extracorporeal membrane oxygenation; PE, pulmonary embolism; Syn, syndrome; AKI, acute kidney injury; MOF, multiple organ failure; PRC, packed red blood cell; FFP, fresh frozen plasma; PC, platelet concentrate.

outcome. However, the present study has several limitations. First, the present study was the retrospective observational study and a small sample size. Second, the period was different in stage 1 and 2. Therefore it might be possible that the improved outcome in stage 2 is associated with improved management for massive PE. Third, TAPSE scores were higher in stage 2. This situation might have affected the improved outcomes in stage 2. Finally, the differences in medical therapy between stage 1 and 2 might be a confounding factor. Because of these limitations, bias and confounding pa-

rameters could not be eliminated. Moreover, it would be difficult to perform a randomized study because the condition of patients with massive PE is often critical.

In conclusion, ECMO can provide lifesaving hemodynamic support in patients with massive PE who are too unstable to tolerate primary reperfusion therapy. Anticoagulation with ECMO support is associated with good survival rate outcomes, compared with medical therapy alone. However, further randomized, multicenter, controlled, and larger studies are needed to identify the role of ECMO in massive PE.

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