Extracorporeal life support for adults with refractory septic shock

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ABSTRACT

Objective: Although the use of extracorporeal membrane oxygenation (ECMO) in shock patients is increasing worldwide, studies concerning this treatment for adult septic shock are limited. This study aimed to analyze the outcome of venoarterial ECMO in adult patients with septic shock refractory to conventional treatment.

Methods: A total of 71 consecutive patients who presented with septic shock and underwent venoarterial ECMO were reviewed. Clinical parameters were compared between survivors and nonsurvivors. Weaning and survival outcomes of these patients were compared with the control group of 253 patients who received venoarterial ECMO for cardiogenic shock.

Results: The mean age was 56.0 ± 12.3 years. Of the 71 septic shock patients, 11 (15.5%) were successfully weaned from ECMO after a median of 7.9 [interquartile range (IQR), 6.3-10.2] days, 5 of whom (7.0%) survived to discharge. Pre- and 6 hours post-procedural lactate levels were significantly higher in the nonsurvivors (11.6 [IQR, 7.5-15.0] vs 5.8 [IQR, 4.3-5.9], $P = .036$; 15.0 [IQR, 11.1-15.0] vs 5.2 [IQR, 4.7-5.4], $P = .002$). Rates of successful weaning from venoarterial ECMO (15.5% vs 45.5%), and of survival up to hospital discharge (7.0% vs 28.9%) were significantly lower in septic shock than in cardiogenic shock patients ($n = 253$; $P < .001$).

Conclusions: Outcomes of ECMO in refractory septic shock patients were poor with a very low probability of survival. This finding raises questions concerning the utility of applying ECMO for medically refractory septic shock. Elevated arterial lactate levels pre- and post-ECMO were associated with risk of in-hospital death. Further large-scale studies are needed to validate the results of this study. (J Thorac Cardiovasc Surg 2018;156:1104-9)

Overall survival of the septic shock and the cardiogenic shock groups.

Central Message

The outcomes of ECMO in refractory septic shock were poor with very low survival probabilities. This finding raises a futility issue of applying ECMO for medically refractory septic shock.

Perspective

Despite the increasing use of extracorporeal life support, studies of venoarterial ECMO for adult septic shock are limited. Because of the poor survival outcomes for venoarterial ECMO in septic shock patients compared with non-septic shock patients in this study, the benefit of venoarterial ECMO in adult septic shock patients remains uncertain.

See Editorial Commentaries pages 1110 and 1112.

Since extracorporeal life support (ECLS) was first introduced as a salvage treatment for cardiac arrest unresponsive

to conventional treatment in the 1960s,¹ miniaturization of membrane oxygenators and the centrifugal pumps has made the heart-lung machine compact and portable, and thin-walled cannulae have enabled rapid implantation of the device via peripheral routes.² These technical developments have led to widespread use of ECLS. The application of venoarterial extracorporeal membrane oxygenation (ECMO) has also been expanded to a variety of conditions such as

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Abbreviations and Acronyms

ECLS	= extracorporeal life support
ECMO	= extracorporeal membrane oxygenation
IQR	= interquartile range
SOFA	= sepsis-related organ failure assessment

septic shock unresponsive to conventional treatment, rather than being confined to cardiogenic shock, the traditional indication for venoarterial ECMO. However, the role of venoarterial ECMO in septic shock remains controversial and the clinical outcomes were inconsistent. Whereas some authors reported in-hospital mortalities of 85% (44 of 52) and 78% (25 of 32), others reported a satisfactory in-hospital mortality of 29% (4 of 14).³⁻⁵ Moreover, publications concerning the clinical outcomes of venoarterial ECMO in adult patients with refractory septic shock are limited. We aimed to analyze the early outcomes of venoarterial ECMO performed in patients presenting with refractory septic shock and to identify risk factors for post-ECMO mortality.

METHODS

Study Populations

All patients who underwent ECMO at our institution were prospectively registered in the ECMO database, which consists of baseline patient characteristics, detailed information on the ECMO setup, periprocedural complications, and in-hospital outcomes. We reviewed this registry to identify adult patients (age 20 years or older) who underwent venoarterial ECMO support to manage refractory shocks of various origins from January 2005 through August 2012. Patients who initially received venovenous ECMO were not included in the study cohort. Of 339 patients identified who met inclusion criteria, 71 patients (20.9%) received ECMO for septic shock and they were selected for the main study cohort. Of the remaining 268 patients (79.1%), 253 patients who received ECMO for cardiogenic shock (74.6%) served as the comparator group, with the exclusion of 15 patients (4.4%), who received ECMO for hypovolemic shock or other causes to maintain the homogeneity of the group.

The study was approved by the institutional ethics committee/review board of the Asan Medical Center, Seoul, Korea, and the requirement for informed patient consent was waived in view of the retrospective nature of the study.

Indication for ECMO and Management

Severe sepsis was defined as acute organ dysfunction secondary to infection and septic shock was defined as severe sepsis with hypotension not reversed by fluid resuscitation. When the patients were diagnosed as septic shock, they were primarily treated with aggressive fluid challenge, adequate antibiotics, and vasoactive agents.⁶ Venoarterial ECMO was indicated only for patients with persistent circulatory collapse despite these aggressive medical treatments. When the attending physician called the ECMO team, the on-call cardiovascular surgeon of the ECMO team decided whether to deploy ECMO and, if so, the cardiovascular surgeon in charge managed the patient thereafter.

Peripheral cannulation was performed in all patients; the common femoral artery was used as an arterial cannulation route in all patients and the common femoral vein, internal jugular vein, and both were used as the venous cannulation route in 65 (91.7%), 2 (2.8%), and 4 patients

(5.6%), respectively. In most cases arterial and venous cannulae could be implanted percutaneously using the Seldinger technique, but cutdown procedures were unavoidable in a few cases. Either 14- to 21-French arterial cannulae or 17- to 28-French venous drainage cannulae were used depending on the individual patient's body surface area. The ECMO system consisted of a centrifugal pump, a hollow-fiber membrane oxygenator with an integral heat exchanger, and a heparin-coated circuit. Three types of ECMO system were used; the Capiiox Emergency Bypass System (Terumo, Tokyo, Japan), the Permanent Life Support system (MAQUET, Hirrlingen, Germany), and the Bio-Consol 560 system (Medtronic, Minneapolis, Minn).

Administration of an intravenous heparin bolus of 50 to 100 U/kg before cannulation was followed by continuous intravenous heparin infusion to maintain the activated clotting time within 180 to 200 seconds. In patients with a bleeding tendency, nafamostat mesilate (Futhan; Torii Pharmaceutical, Tokyo, Japan) was used as an anticoagulant alternative to heparin depending on the physician's judgement.^{7,8} An antegrade perfusion catheter for distal limb perfusion was routinely inserted distal to the arterial cannulation site, and the flow through the dorsalis pedis and posterior tibial arteries of the affected limb was assessed using a portable Doppler device. The arterial cannula was repositioned to the opposite side of the femoral artery if the affected limb showed signs of ischemic injury. ECMO blood flow was aimed at a cardiac index of 2.4 L/min/m² or more. Vasoconstrictors such as vasopressin were preferred over inotropic agents for maintaining mean arterial pressure at 60 to 70 mm Hg, and blood products were transfused appropriately to maintain hematocrit at 30% to 35% and platelet count $\geq 100,000/\text{mm}^3$.

Several parameters were used to determine the timing of weaning from ECMO, including increased mean arterial pressure, increased pulse pressure, and decreased central venous and/or pulmonary artery pressures. Weaning was initiated when echocardiographic findings showed adequate ventricular filling and an ejection fraction $\geq 30\%$ to 35% at ECMO flow with a cardiac index of 1.0 L/min/m². Several hemodynamic parameters were assessed while ECMO flow was gradually reduced. If the patient remained stable at an ECMO flow of 0.5 per minute over 30 minutes, ECMO was removed at the bedside. Successful weaning was defined as weaning from ECMO followed by survival for at least 48 hours.⁹

Data Collection and Statistical Analysis

In addition to the data available from the ECMO database, the following information was retrieved using a retrospective medical chart review; sepsis-related organ failure assessment (SOFA) score at the start of ECMO implantation, and data regarding pathogenic microorganisms and antibiotic use. Blood laboratory findings (complete blood cell count, blood chemistry, arterial blood gas analysis, blood lactate, etc) just before the initiation of ECLS were also obtained.

Categorical variables are presented as numbers and percentages and were compared using the χ^2 and Fisher exact tests. Continuous variables are expressed as mean $\pm$ SD or median value with interquartile range (IQR) on the basis of the results of the Shapiro-Wilk normality test and were compared using the *t* test or the Mann-Whitney *U* test, as appropriate. Survival curves were plotted using the Kaplan-Meier method and survival rates were compared using the log-rank test. *P* values $< .05$ were considered statistically significant. SPSS version 18.0 (SPSS, Inc, Chicago, Ill) and R statistics, version 3.3.3 (<http://www.r-project.org>) were used for all statistical analyses.

RESULTS

Baseline Characteristics

Mean age was 56.0 ± 12.3 years. Table 1 shows a summary of the baseline characteristics, including SOFA scores and circulatory and laboratory parameters of the survivors and non-survivors. The mean SOFA score was slightly lower in the survivor group than in the nonsurvivor group, but the

TABLE 1. Baseline characteristics between survivors and nonsurvivors for patients receiving ECLS for septic shock

Variable	Survivors (n = 5)	Nonsurvivors (n = 66)	P value
Age, y	58.0 (58.0-63.0)	57.5 (48.0-65.0)	.37
Male sex, n (%)	3 (60.0)	37 (56.1)	>.99
Body mass index, kg/m ²	21.4 (19.8-24.7)	22.4 (19.5-26.0)	.75
Body surface area, m ²	1.54 (1.53-1.64)	1.62 (1.51-1.73)	.75
Diabetes mellitus, n (%)	3 (60.0)	16 (24.2)	.22
Hypertension, n (%)	3 (60.0)	17 (25.8)	.26
Chronic renal failure, n (%)	0 (0)	6 (9.1)	>.99
Liver cirrhosis, n (%)	3 (60.0)	34 (51.5)	>.99
ARDS, n (%)	3 (60.0)	31 (47.0)	.92
Immunosuppressed, n (%)	2 (40.0)	34 (51.5)	.67
SOFA score	18.0 (13.0-20.0)	19.0 (15.0-22.0)	.39
Shock to ECMO time, hours	4.0 (3.7-4.2)	18.0 (6.7-53.7)	.052
Circulatory			
MAP, mm Hg	64.3 ± 10.3	58.3 ± 11.6	.27
Urine output, mL/d	125.0 (120.0-875.0)	124.5 (25.0-727.0)	.61
Use of vasopressin, n (%)	1 (20.0)	39 (59.1)	.22
CPR before ECLS, n (%)	0	9 (13.6)	.85
Laboratory*			
pH	7.26 (7.25-7.37)	7.23 (7.13-7.30)	.19
PaO ₂ /FiO ₂	73.0 (70.0-86.3)	63.5 (46.0-84.0)	.32
Arterial lactate, mmol/L	5.8 (4.3-5.9)	11.6 (7.5-15.0)	.036
Platelet count, ×10 ³	59.0 (38.0-90.0)	37.0 (22.0-88.0)	.16
Creatinine, mg/dL	1.7 (1.5-1.9)	1.4 (0.9-2.0)	.35
Total bilirubin, mg/dL	2.6 (1.7-3.3)	5.4 (1.6-13.0)	.35

ARDS, Acute respiratory distress syndrome; SOFA, sequential organ failure assessment score; ECMO, extracorporeal membrane oxygenation; MAP, mean arterial pressure; CPR, cardiopulmonary resuscitation; ECLS, extracorporeal life support. *Blood was sampled before starting ECLS.

difference was not statistically significant (18.0 [IQR, 13.0-20.0] vs 19.0 [IQR, 15.0-22.0], $P = .42$). Among the pre-procedure laboratory parameters, arterial lactate was significantly higher in the nonsurvivor group (11.6 [IQR, 7.5-15.0] mmol/L vs 5.8 [IQR, 4.3-5.9] mmol/L, $P = .036$), whereas platelet count was lower (37.0 [IQR, 22.0-88.0] vs 59.0 [IQR, 38.0-90.0], $P = .16$), and total bilirubin level was higher (5.4 [IQR, 1.6-13.0] vs 2.6 [IQR, 1.7-3.3] mg/dL, $P = .35$), both without statistical significance.

Data regarding infection sites and types of pathogen are presented in Table 2. The most common infection site was lung, accounting for 70% of cases. Thirty patients (42.9%) gave positive blood cultures and they were all nonsurvivors. The most common pathogen was *Acinetobacter baumannii*, followed by *Staphylococcus* species and *Pseudomonas aeruginosa*. The distribution of pathogenic microorganisms tended to differ in the 2 groups, but the difference was not statistically significant probably because of the small number of survivors.

Table 3 shows the variables related to ECMO management. Intravenous corticosteroid was used in 18 patients (25.4%). Lactate level 6 hours after the initiation of ECLS was significantly higher in the nonsurvivor group

(15.0 [IQR, 11.1-15.0] vs 5.2 [IQR, 4.7-5.4], $P = .002$). Survivors received ECLS for longer than nonsurvivors (179.3 [IQR, 122.3-190.2] hours vs 26.4 [IQR, 12.7-56.9] hours, $P = .006$).

Clinical Outcomes of Venoarterial ECMO in Patients With Septic Shock and Comparison With Venoarterial ECMO in Patients With Cardiogenic Shock

Of the total of 71 patients who underwent venoarterial ECMO for refractory septic shock, 11 (15.5%) were successfully weaned off the ECMO after a median of 7.9 (IQR, 6.3-10.2) days (Figure 1). Of these patients, only 5 (7.0%) survived to discharge (Figure 1). Finally, in-hospital mortality was 93.0% (66 of 71) and 30-, 60-, and 90-day mortality rates were 87.3%, 91.5%, and 93.0%, respectively. A color change was noted in the affected limb of 1 patient whose distal limb had not been perfused via an antegrade perfusion catheter before the start of ECMO and the distal limb was perfused thereafter. No long-term disability was reported in the 5 hospital survivors.

For comparison, 253 patients who received venoarterial ECMO for cardiogenic shock during the same study period

TABLE 2. Infection sites and types of pathogenic microorganisms

Variable	Survivors (n = 5)	Nonsurvivors (n = 66)	P value
Infection site, n (%)			.35
Lung	3 (60.0)	46 (69.7)	
Blood	0 (0)	10 (15.2)	
Abdomen	1 (20.0)	7 (10.6)	
Urinary tract	1 (20.0)	2 (3.0)	
Other*	0 (0)	1 (1.5)	
Positive blood culture, n (%)	0 (0)	30 (45.5)	.069
Microorganism types, n (%)			.055
Gram-positive			
<i>Staphylococcus</i> species	1 (20.0)	11 (16.7)	
<i>Enterococcus</i> species	0 (0)	2 (3.0)	
Other gram-positive bacteria†	0 (0)	1 (1.5)	
Gram-negative			
<i>Acinetobacter baumannii</i>	0 (0)	15 (22.7)	
<i>Pseudomonas aeruginosa</i>	0 (0)	9 (13.6)	
<i>Klebsiella pneumonia</i>	0 (0)	6 (9.1)	
<i>Escherichia coli</i>	0 (0)	6 (9.1)	
<i>Enterobacter</i> species	1 (20.0)	1 (1.5)	
Other gram-negative bacteria‡	0 (0)	4 (6.1)	
Fungal			
<i>Candida</i> species	1 (20.0)	7 (10.6)	
<i>Cryptococcus</i>	0 (0)	1 (1.5)	
<i>Aspergillus</i>	0 (0)	1 (1.5)	
Other			
<i>Mycobacterium</i>	2 (40.0)	2 (3.0)	

*A patient with skin infection. †Other gram-positive bacteria included *Corynebacterium*. ‡Other gram-negative bacteria included *Achromobacter xylosoxidans*, *Rickettsia tsutsugamushi*, and *Stenotrophomonas maltophilia*.

served as controls (Table E1). Of these, 115 (45.5%) were successfully weaned from the ECMO, a significantly higher proportion than in the patients with septic shock (Table E2). Survival to hospital discharge in the non-septic shock patients was 28.9%, which was also significantly higher than in those with septic shock (Table E2). As shown in Figure 2, the overall survival of the septic shock patients who received venoarterial ECMO was lower than that of the patients with cardiogenic shock who received ECMO ($P < .001$).

DISCUSSION

The efficacy of venoarterial ECMO for refractory septic shock in neonates and children has been established by several studies.¹⁰⁻¹⁴ It was reported that 87% of neonates and 74% of children who underwent venoarterial ECMO for septic shock survived to discharge.^{11,14} Reflecting these high survival rates, the guidelines of the American College of Critical Care Medicine and the Extracorporeal Life Support Organization currently recommend venoarterial ECMO for pediatric septic shock refractory to conventional treatment.^{5,15} In contrast, the mortality rates of adult patients who underwent venoarterial ECMO

TABLE 3. Extracorporeal life support data

Variable	Survivors (n = 5)	Nonsurvivors (n = 66)	P value
Use of nafamostat mesylate, n (%)	0 (0)	7 (10.6)	>.99
Use of corticosteroid, n (%)	1 (20.0)	17 (25.8)	>.99
Hemofiltration, n (%)	1 (20.0)	6 (9.1)	.99
Duration of ECLS, hours	179.3 (122.3-190.2)	26.4 (12.7-56.9)	.006
Lactate, 6 h, mmol/L	5.2 (4.7-5.4)	15.0 (11.1-15.0)	.002

ECLS, Extracorporeal life support.

for refractory septic shock have been relatively high, and the reported outcomes have been inconsistent. Brechot et al analyzed 14 adult patients who underwent venoarterial ECMO for cardiovascular dysfunction during septic shock and reported a satisfactory in-hospital mortality of 29%.¹⁶ However, they excluded patients with conserved cardiac function from their study and this favorable outcome might not accurately represent the real-world situation because the hemodynamic presentations of septic shock vary. Older children and adults are usually in a hyperdynamic state with high cardiac output,¹⁷ whereas infants and younger children commonly have cardiovascular dysfunction.¹⁰⁻¹² Moreover, it is not realistic to use venoarterial ECMO only in patients manifesting refractory septic shock combined with cardiovascular dysfunction because venoarterial ECMO is seen as a treatment of last resort. Indeed, Huang et al and Park et al reported high in-hospital mortalities in their studies concerning venoarterial ECMO for adult refractory septic shock.^{3,4} In the current study, the in-hospital mortality rate of the 71 septic shock patients who received venoarterial ECMO was 93%, which is higher than in other studies. These poor results might be explained by the following factors. First, we did not exclude hyperdynamic septic shock patients, whose prognosis is expected to be much worse. Second, more than half of the patients (37 of 71; 52.1%) had liver cirrhosis, including post-liver transplantation patients. Although liver cirrhosis could not be statistically confirmed as a risk factor for mortality because of the lack of parameters representing its severity, such a high proportion of comorbid liver cirrhosis would undoubtedly be associated with high mortality. The relatively high SOFA scores (mean $\pm$ SD, 18.2 ± 4.0) might also be related to the poor outcomes of the current study.

Some authors have reported poorer outcomes of venoarterial ECMO for septic shock in patients 60 years or older and have suggested the use of central ECMO on the basis of pediatric experience.³ Theoretically, central ECMO would appear to be superior to peripheral ECMO; however, many physicians and surgeons hesitate to use it because of

FIGURE 1. Flow chart of the outcomes of VA ECMO in septic shock patients. VA, Venoarterial; ECMO, extracorporeal membrane oxygenation.

its invasiveness and patients' comorbidities. In the real world, it is certainly challenging to switch cannulation routes from peripheral to central vessels via additional sternotomy or thoracotomy incisions especially in unstable patients. In the current study, peripheral cannulation was performed in all patients, as in the other studies.^{3,4,16}

In this study, the arterial lactate level 6 hours after initiation of ECMO was the only significant factor associated with in-hospital mortality. A correlation between improved outcomes and early lactate clearance in severe sepsis and septic shock has been noted in other studies.¹⁸ In this context, early lactate clearance might also be an appropriate indicator of outcomes, or of the adequacy of the treatment, in patients who undergo venoarterial ECMO for septic shock. When the spectrum of patients' disease in our ECMO database was extended from septic shock to many other kinds of shock, the preprocedural arterial lactate level was found to be an independent predictor of the outcomes of

venoarterial ECMO. This suggests that the arterial lactate level could be helpful in deciding when to start ECLS.

Recently, gram-negative pathogens in intensive care unit patients have been causing alarm because of the increase in resistance to 3 or more classes of antibiotics.¹⁹ Gram-negative infections are often associated with inappropriate initial antibiotic therapy, which might eventually lead to multidrug resistance and increased hospital mortality.^{20,21} There was also a tendency in the present study for gram-negative pathogens to be more frequently detected in non-survivors than survivors (20.0% vs 62.1%; $P = .055$), although the statistical power was limited because of the small cohort size.

From the viewpoint of cost, \$6168 USD (\$4791 USD for ECMO setup, \$496 USD per day of ECMO maintenance) on average was charged only for the ECMO in this study cohort. Because approximately 80% of the cost can be covered by the national medical insurance system in this country, individual out-of-pocket payments might not be so high, but the social costs might be substantial. This might further raise the futility issue given such grave outcomes of ECMO in the setting of septic shock.

This study has some limitations. First, it was difficult to obtain high statistical power when comparing survivors and nonsurvivors because of the numerical imbalance between the 2 groups, although the study cohort was not small compared with other recent studies. Second, the absence of protocols or established guidelines for calling the ECMO team might have made it difficult to correctly time the onset of ECMO support. The clinical outcomes of venoarterial ECMO for septic shock in this study might have been poorer than in those performed in other clinical settings because of the generous policy of performing ECMO in many patients with advanced end-organ failure, such as liver transplant recipients.

CONCLUSIONS

The outcomes of venoarterial ECMO in refractory septic shock were poor in terms of weaning success and survival up to hospital discharge. Higher arterial lactate level pre- and post-ECMO might be associated with higher mortality risk. Further large-scale studies are needed to establish whether venoarterial ECMO has a role in the treatment of adult septic shock patients.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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FIGURE 2. Overall survival of the septic shock patients receiving venoarterial extracorporeal membrane oxygenation (ECMO) versus that of the cardiogenic shock patients receiving venoarterial ECMO.

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Key Words: extracorporeal membrane oxygenation, septic shock, survival

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TABLE E1. Baseline characteristics of cardiogenic shock and septic shock groups

Variable	Cardiogenic shock (n = 253)	Septic shock (n = 71)	P value
Age, y	61.0 (51.0-71.0)	58.0 (49.0-65.0)	.044
Male sex, n (%)	154 (60.9)	40 (56.3)	.58
Body mass index, kg/m ²	23.4 (21.2-25.8)	22.1 (19.6-25.7)	.063
Body surface area, m ²	1.68 (1.55-1.80)	1.62 (1.52-1.73)	.010
Diabetes mellitus, n (%)	58 (22.9)	19 (26.8)	.61
Hypertension, n (%)	99 (39.1)	20 (28.2)	.12
Chronic renal failure, n (%)	16 (6.3)	6 (8.5)	.72
Liver cirrhosis, n (%)	19 (7.5)	37 (52.1)	<.001
CPR before ECLS, n (%)	80 (31.6)	9 (12.7)	.003
Laboratory*			
pH	7.29 (7.18-7.37)	7.24 (7.15-7.30)	.013
Arterial lactate, mmol/L	9.2 (4.8-13.7)	11.1 (6.3-15.0)	.041
Platelet count, ×10 ³	128.0 (78.0-197.0)	38.0 (22.5-89.0)	<.001
Creatinine, mg/dL	1.4 (1.0-2.0)	1.5 (0.9-2.0)	.65
Total bilirubin, mg/dL	1.4 (0.9-2.9)	4.5 (1.7-12.2)	<.001
Hemofiltration, n (%)	26 (10.3)	7 (9.9)	>.99
Duration of ECLS, hours	71.0 (27.6-132.9)	27.5 (13.4-68.2)	.001

CPR, Cardiopulmonary resuscitation; ECLS, extracorporeal life support. *Blood was sampled before starting ECLS.

TABLE E2. Clinical outcomes of cardiogenic shock and septic shock groups

Outcomes	Cardiogenic shock (n = 253)	Septic shock (n = 71)	P value
Successful weaning, n (%)	115 (45.5)	11 (15.5)	<.001
Survival to discharge, n (%)	73 (28.9)	5 (7.0)	<.001
30-d mortality, n (%)	167 (66.0)	62 (87.3)	.001
60-d mortality, n (%)	176 (69.6)	65 (91.5)	<.001
90-d mortality, n (%)	177 (70.0)	66 (93.0)	<.001