

# Outcomes of Extracorporeal Membrane Oxygenation in Blood Culture Positive Septic Patients

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## Abstract

**INTRODUCTION:** Extracorporeal membrane oxygenation (ECMO) is commonly used for refractory cardiac or respiratory failure. There are reported cases of successful use of ECMO in patients with septic shock; however, there is a lack of evidence to prove its overall efficacy. Thus, we conducted this study to analyze the relationship between sepsis and ECMO in our own patients. **METHODS:** 305 patients who were placed on ECMO between 2010 and 2020 were identified within an IRB-approved database. Their clinical outcomes were analyzed with a specific focus on patients who were septic before or during ECMO, defined as a positive blood culture. Group S was composed of patients with a positive blood culture before or during ECMO, while Group N was composed of all patients without a positive blood culture before or during ECMO. The primary outcome compared between groups was ECMO survival rate. **RESULTS:** Among the 305 patients on ECMO, 58 (19%) were in Group S and 247 (81%) were in Group N. ECMO survival rates were 45% in Group S and 62% in Group N ( $p = 0.017$ ). **CONCLUSION:** Of our 305 patients, patients who were septic upon ECMO placement or those who developed sepsis during ECMO had worse ECMO survival rates than non-septic patients. Ultimately, patients who are septic or have a high probability of becoming septic may not be indicated for ECMO placement, and cautious administration of ECMO to these patients may be necessary.

## Keywords

Extracorporeal Membrane Oxygenation, Shock, Sepsis

## 1. Introduction

Extracorporeal Membrane Oxygenation (ECMO) is a temporary form of me-

chanical cardiopulmonary support for patients with severe cardiac and/or respiratory shock. Since its first clinical use in 1972, the utilization of ECMO has progressively increased and by the 2000s was an established form of treatment for pediatric patients [1]. In the last decade, ECMO use in both pediatric and adult populations has exponentially increased, partially due to expanded indication criteria in adult patients [2].

Due to the poor outcomes of septic shock, septic patients were traditionally contraindicated from ECMO placement. However, some studies in the 1990s argued that sepsis may no longer be a contraindication for ECMO, with one study finding that neither sepsis nor blood culture could predict a patient's mortality [3] [4]. As a result, the indication criteria for ECMO has been broadened to include select septic patients with severe cardiopulmonary failure, and ECMO has recently been researched as a rescue therapy for septic shock itself [2] [5]

Despite this expanded indication criteria, there remains a lack of research on survival outcomes and the overall efficacy of ECMO in septic patients defined as positive blood culture. The purpose of this paper is to better understand the outcomes of septic patients who are placed on ECMO.

## 2. Methods

Consecutive adult patients who underwent ECMO at the Thomas Jefferson University Hospital from 2010 to 2020 were included in this study. Patients were identified by an IRB-approved, prospectively maintained ECMO database (IRB approval # 11D.185). The data from these patients was retrospectively extracted and details were further studied by reviewing medical records. Those who had missing pre-ECMO data were excluded from this study. Both VA-ECMO and VV-ECMO were included in this study. All ECMO patients were treated by a single group of cardiovascular intensivists.

Sepsis was defined as a positive blood culture prior to or during ECMO treatment. Routine blood culture was performed on ECMO day #1 and whenever a patient demonstrated increased white blood cell count and/or fever (101.5°F or higher). All eligible patients were distributed into 2 groups based on their status of sepsis. Group S was composed of all patients positive for sepsis, while Group N was composed of all patients negative for sepsis. The primary endpoint of this study was ECMO survival, which was defined by withdrawal of care or death within 24 hours of decannulation. Group S and Group N were further divided by primary indication for ECMO, and the ECMO survival rates of the sub-groups were examined.

Data was expressed as the number with percentage, mean  $\pm$  standard deviation, or median (quantile) as appropriate. Two groups were compared using chi-squared tests for categorical variables and standard t-tests for continuous variables as appropriate.

## 3. Results

During this study period, 318 patients underwent ECMO placement. 13 patients

were excluded from this study due to incomplete data, giving a total of 305 eligible patients. Based on the presence of sepsis, 58 patients (19%) were placed in Group S and 247 patients (81%) were placed in Group N. The demographics of the groups are displayed in **Table 1**. Group S was significantly lower in age ( $p = 0.02$ ), lower in rates of pre-ECMO cardiogenic shock ( $p = 0.037$ ), and higher in rates of liver failure ( $p = 0.003$ ). Group S also had lower use of VA-ECMO and higher use of VV-ECMO ( $p = 0.005$ ). There was no significant difference between the two groups among other characteristics. The majority of sepsis was due to gram-positive cocci (47%) or gram-negative rods (47%) (**Table 2**). Most of the patients grew a single organism on blood culture; however, one patient cultured positive for both *Klebsiella* and *Pseudomonas*, one patient cultured positive for both *Citrobacter* and *MSSA*, one patient cultured positive for *Enterococcus* and *MSSA*, and one patient cultured positive for both *Serratia* and *Klebsiella*.

Of the 58 septic patients, 30 (52%) were found to be septic before ECMO. There were 19 cases of gram-positive cocci (61%), 10 cases of gram-negative rods (32%), and 2 cases of fungi (7%) that resulted in sepsis in these patients (**Table 2**). Among the 30 patients who had positive blood culture before ECMO, 19 (63%) were placed on ECMO within our institution and 11 patients (37%) were placed on ECMO outside of our institution.

**Table 1.** Demographics of studied patients. Data is expressed with number (percentage) or mean  $\pm$  standard deviation.

	All patients n = 305	Group S n = 58	Group N n = 247	P-value
<b>Characteristics</b>				
Age (years)	49.4 $\pm$ 14.7	45.28 $\pm$ 15.35	50.3 $\pm$ 14.5	0.020
Male	210 (68.9%)	36 (62.1%)	174 (70.5%)	0.215
Body surface area (cm <sup>2</sup> )	2.03 $\pm$ 0.3	2.01 $\pm$ 0.32	2.03 $\pm$ 0.30	0.652
Body mass index	31.35 $\pm$ 9.95	31.93 $\pm$ 10.20	31.21 $\pm$ 9.87	0.62
<b>Underlying Conditions</b>				
Smoking	103 (34%)	16 (28%)	87 (35%)	0.268
Coronary artery disease	106 (35%)	15 (26%)	91 (37%)	0.214
Chronic lung disease	55 (18%)	13 (22%)	42 (17%)	0.335
Diabetes	74 (24%)	10 (17%)	64 (26%)	0.166
Liver failure	24 (8%)	10 (17%)	42 (6%)	0.003
Chronic immunosuppression	35 (11%)	7 (12%)	64 (11%)	0.875
Cardiogenic shock	194 (64%)	30 (52%)	164 (66%)	0.037
<b>Mode of ECMO</b>				
Veno-arterial ECMO	211 (69%)	33 (57%)	186 (75%)	0.005
Veno-veno ECMO	94 (30%)	25 (43%)	61 (25%)	0.005

**Table 2.** Bacteriology of positive blood cultures in Group S. Patients may have multiple positive blood cultures.

	Group S	Positive Culture pre-ECMO	Positive Culture on-ECMO
	n = 58	n = 30	n = 28
<b>Gram-positive cocci</b>	29 (47%)	19 (61%)	10 (32%)
Methicillin-resistant <i>Staphylococcus aureus</i>	4 (6.5%)	3 (9.7%)	1 (3.2%)
Methicillin-sensitive <i>Staphylococcus aureus</i>	4 (6.5%)	3 (9.7%)	1 (3.2%)
<i>Staphylococcus epidermidis</i>	5 (8.1%)	2 (6.5%)	3 (9.7%)
<i>Streptococcus</i>	8 (13%)	7 (23%)	1 (3.2%)
<i>Enterococcus</i>	5 (8.1%)	1 (3.2%)	4 (13%)
<b>Gram-negative rods</b>	29 (47%)	10 (32%)	19 (61%)
<i>Pseudomonas</i>	8 (13%)	1 (3.2%)	7 (23%)
<i>Klebsiella</i>	7 (11%)	2 (6.5%)	5 (16%)
<i>Citrobacter</i>	3 (4.8%)	3 (9.7%)	0 (0%)
<i>Enterobacter</i>	2 (3.2%)	0 (0%)	2 (6.5%)
<i>E. coli</i>	3 (4.8%)	2 (6.5%)	1 (3.2%)
<i>Serratia</i>	3 (4.8%)	0 (0%)	3 (9.7%)
<i>Bacteroides</i>	1 (1.6%)	1 (3.2%)	0 (0%)
Other gram-negative	2 (3.2%)	1 (3.2%)	1 (3.2%)
<b>Fungus</b>	4 (6.5%)	2 (6.5%)	2 (6.5%)

Of the 58 septic patients, 28 (48%) developed sepsis during ECMO. There were 10 cases of gram-positive cocci (32%), 19 cases of gram-negative rods (61%), and 2 cases of fungi (7%) that resulted in sepsis in these patients (**Table 2**). Among these cultures, 8 patients (28%) were associated with ongoing pneumonia, 3 patients (11%) were associated with ischemic bowel or *C. difficile* colitis, and 17 patients (61%) had an unknown infection source, as the infections were discovered in blood cultures. No patients developed infection at the site of ECMO placement. Among the 28 patients who developed positive blood culture during ECMO, 23 patients (82%) were placed on ECMO within our institution and 5 patients (18%) were placed on ECMO outside of our institution.

Group S and Group N were divided into 6 sub-groups based on primary indication for ECMO. The groupings and outcomes are displayed in **Table 3**. Within Group S, the most common indication was pneumonia (22 patients), with 2 patients suffering from viral pneumonia, 15 patients from non-viral pneumonia (14 bacterial and 1 fungal), and 5 patients from viral pneumonia with overlapping bacterial or fungal pneumonia (3 viral and bacterial, 1 viral and fungal, and 1 viral, bacterial, and fungal). The other indications, in order of decreasing prevalence, were cardiogenic shock, post-cardiotomy failure, septic shock, non-infectious pulmonary disease, and ARDS due to sepsis. Among the

**Table 3.** ECMO survival rate stratified by primary indication for ECMO.

Indication	Group S		Group N	
	Patients	ECMO survival rate	Patients	ECMO survival rate
Septic shock	4 (6.9%)	0 (0%)	0 (0%)	N/A
Post-cardiotomy failure	13 (22.4%)	5 (38.5%)	35 (14.2%)	18 (51.4%)
Pneumonia	22 (37.9%)	10 (45.5%)	58 (23.5%)	47 (81%)
Cardiac	13 (22.4%)	6 (46.2%)	125 (50.6%)	66 (52.8%)
Non-infectious pulmonary disease	4 (6.9%)	3 (75%)	29 (11.7%)	22 (75.9%)
ARDS due to sepsis	2 (3.5%)	2 (100%)	0 (0%)	N/A

indications, the lowest ECMO survival rate was observed in patients whose primary indication was septic shock, followed by post-cardiotomy failure and pneumonia.

Within Group N, the most common indication was cardiac (125 patients), followed by pneumonia (58 patients), post-cardiotomy failure (35 patients), and non-infectious pulmonary disease (29 patients). The lowest ECMO survival rate was observed in patients whose primary indication was post-cardiotomy failure.

Overall ECMO survival rate was 45% (26/58 patients) in Group S and 62% (153/247 patients) in Group N ( $p = 0.017$ ). Of the 32 patients in Group S who did not survive, 30 (94%) died of progressive septic shock.

#### 4. Discussion

The primary finding of this study was that septic patients have significantly worse ECMO survival rates than non-septic patients. In our sample, Group S had an ECMO survival rate of 45%, which was significantly lower than the Group N rate of 62%. Also, it appears that primary indication for ECMO is correlated with ECMO survival rate. No patient whose primary indication was septic shock survived ECMO, while every other indication had at least 39% survive.

It is possible there was selection bias in this study, as ECMO placement was determined by individual physicians' judgement. In our practice sepsis is typically viewed as a poor prognosis for ECMO survival and often is a contraindication for ECMO placement. Thus, our center does not typically place individuals with septic shock on ECMO, unless there is proper source control. Most of the positive blood culture patients had an unknown blood culture when placed on ECMO, and the positive blood culture was typically discovered after cannulation.

Our study demonstrates that once a patient becomes septic either pre-ECMO or during ECMO, sepsis needs to be controlled to increase the chance of patient survival. Uncontrolled sepsis can lead to multiorgan failure and patient death. No patients in our center developed ECMO site infection, which may be due to

careful cannulation, sterile dressing, local bleeding control, and other proactive measures. However, 17 patients (5.6% of entire ECMO cohort) who developed sepsis after placement of ECMO had an infection from an unknown origin.

While our results indicate that septic patients have worse outcomes on ECMO, there has historically been conflicting research regarding the use of ECMO in septic patients. Sepsis was traditionally viewed as a contraindication for ECMO placement, as ECMO has consistently been associated with the adverse outcome of bacterial colonization and infection [6]. It is understood that both the time of ECMO duration and the presence of ECMO cannulas put patients at risk of infection, and as the average duration of ECMO procedures has increased, today's patients are at particular risk [7] [8] [9] [10]. These infections related to ECMO cannulation can progress to septic shock, which would increase a patient's rate of mortality.

In the 1990s, the opinions regarding the use of ECMO in septic patients changed when two studies concluded that sepsis was not a contraindication for ECMO [3] [4]. In 1997, Stewart *et al.* discovered that 74% of their septic patients survived ECMO, which was similar to the 1996 ECMO survival rate of 77%. [3] However, this study focused solely on neonatal and pediatric patients, which have significantly different outcomes than the adults in our patient population. Also, this study defined sepsis as a positive blood, urine, or nasopharyngeal culture or a positive urine latex agglutination, which may include patients without true sepsis. In 1998, Rich *et al.* found that among 100 patients placed on ECMO, the 14 septic patients actually had a slightly higher ECMO survival rate compared to the overall group (64% and 54%, respectively) [4]. In this study, sepsis was determined by clinical manifestations such as hemodynamic instability, fluid responsiveness, coagulopathy, and thrombocytopenia, rather than positive blood culture, as there were 36 cases of positive blood culture included in their study. Since these studies were published, ECMO technology has advanced tremendously and is used more commonly in adult patients.

Two more recent studies focused on the mortality rate for ECMO placement in patients with ARDS due to sepsis [5] [11]. Hemmila *et al.* investigated 280 adult ECMO patients with respiratory failure. The study found 22 cases of septic lung injury with a hospital survival rate of 50%, although their definition of septic shock was not clear. Interestingly, sepsis was not listed as these patients' cause of death [11]. A 2005 study by Dalton *et al.* found similar results. In a review of the Extracorporeal Life Support (ELSO) Registry, the study found that 51% of adult patients with "ARDS not due to surgery or trauma" survived ECMO, which was similar to the overall ECMO survival rate of 53% [12]. Patients with "ARDS not due to surgery or trauma" are thought to be due to sepsis despite unknown culture status. These studies both concluded that septic patients with ARDS can be treated effectively with ECMO, although their definitions of sepsis were more likely based on clinical manifestation of sepsis rather than positive blood culture, which was the definition used in our study.

Despite these optimistic reports, other research supports our finding that patients with positive blood cultures have significantly worse outcomes on ECMO [7] [10]. In 2013, Aubron *et al.* reported that 17% of their ECMO patients had a bloodstream infection, with 25% of these positive blood cultures secondary to pneumonia [10]. They found a higher mortality rate in infected patients (42%) than non-infected patients (32%), which is comparable to our results. Kim *et al.* reported similar findings in a 2016 study in which 28% of their ECMO patients had a bloodstream infection [7]. Infected patients were found to have a significantly lower hospital survival rate (8%) than non-infected patients (82%), and the duration of ECMO was longer in the infected group. Furthermore, the study found that 6 of the 13 patients with positive blood culture (46%) had ECMO cannula colonization at the time of ECMO removal. While our study did not address cannula colonization, it is possible that some of our patients with an unknown infection source may have had colonization in ECMO cannula, oxygenator, or pump. These two studies demonstrate that the use of ECMO in septic patients is an ongoing discussion, as their results contradict past research that found no difference in ECMO outcomes between septic and non-septic patients. Thus, we conducted our study to better understand the risk of ECMO placement in patients with positive blood culture.

Our study is limited by being based in a single center with a relatively small sample size. There is also a lack of data on septic patients who were not placed on ECMO or those who were consulted for ECMO but declined due to other reasons, typically multiorgan failure.

It should be noted that our paper defines sepsis as positive blood culture. There is a lack of uniformity between past research studies in the definition of sepsis, so further studies should be cognizant when comparing our results to those of similar papers. Our study specifically focuses on the population of ECMO patients with positive blood culture.

Despite its limitations, this study offers a novel understanding of how septic patients perform on ECMO compared to non-septic patients and should provide a good reference for future research on the use of ECMO in septic patients.

## 5. Conclusion

Based on our results, we conclude that ECMO placement in patients with positive blood culture should be carefully considered, especially in patients with septic shock or those who are at high risk of developing septic shock.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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