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Original Article

Infection dynamics and management in patients undergoing extracorporeal membrane oxygenation: a retrospective analysis

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Abstract

Introduction: The aim of this study was to summarize the infection situation of patients during extracorporeal membrane oxygenation (ECMO) treatment, and analyze the relevant infectious indexes before and after ECMO treatment; so as to provide clinical evidence for the control of infection after ECMO treatment.

Methodology: A retrospective analysis was conducted from May 2014 to January 2024 on 66 patients treated with ECMO at the Department of Intensive Care Medicine, Daping Hospital, Army Medical University. The patients' general clinical data were collected, focusing on infection types, pathogenic bacteria, anti-infective regimens, infection markers, and coagulation function. Additionally, risk factors for infection in intensive care unit (ICU) patients undergoing ECMO treatment were analyzed.

Results: Pulmonary infections were the most common among the patients in this study, and Gram-negative bacilli were the predominant pathogens. Significant reductions were observed in white blood cell count ($p < 0.05$, n = 57), platelet count ($p < 0.05$, n = 56), and fibrinogen levels ($p < 0.05$, n = 57) 48 hours after ECMO treatment. Of the 66 ECMO patients, 30 survived. The length of stay in the ICU was identified as an independent risk factor for adverse events following ECMO treatment.

Conclusions: Controlling infection during ECMO is the cornerstone of survival and prognosis of patients. Mechanical ventilation time, continuous renal replacement therapy, central venous catheterization time, and antibiotic treatment time may be related to infection after ECMO. Early bacterial culture; and prophylactic, empirical, and targeted antimicrobials contribute to infection control.

Key words: ECMO; infection; ICU; pathogen; management.

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Introduction

Extracorporeal membrane oxygenation (ECMO) is a vital in vitro life support technique that reintroduces oxygenated venous blood into the patient's circulation, providing essential support for those with severe respiratory and circulatory dysfunctions [1]. This technology has become indispensable, particularly in critical care settings. Recent global health crises, including the H1N1 pandemic and the outbreak of the novel coronavirus, have precipitated acute respiratory failures and severe fulminant myocarditis, making ECMO an increasingly crucial therapeutic option [2,3].

Despite high expectations from the medical community, ECMO, as an invasive procedure, is fraught with complications such as heightened infection risks and significant bleeding, which severely challenge patient outcomes [4,5]. A recent systematic review estimated that the incidence of hospital-acquired infections in adults on ECMO is 26% [6]. The infection rates varied across different centers, reflecting variations in treatment strategies [7]. The main types of infection were ventilator-associated pneumonia and bloodstream infections. Pathogen screening results indicated that drug-resistant Gram-negative bacteria were the predominant pathogens [8]. The management of ECMO-associated infections involves basic nosocomial infection prevention and control, targeted antibiotic therapy for the infection site, and the removal or replacement of the central venous catheter, among other measures. However, treatments such as mechanical ventilation and continuous blood purification are often unavoidable, which increases the risk of infection in ECMO patients [9]. However, the survival rate of ECMO patients with infections was significantly lower than that of non-infected patients [6,10,11]. These issues urgently require further research to provide valuable insights.

This study reviewed clinical data from 66 patients who underwent ECMO at the Army Medical Center of the Chinese People's Liberation Army over the past decade, focusing on infection rates during treatment and the evolution of infection-related biomarkers post-

ECMO intervention.

Methodology

Research subjects

This study involved 66 intensive care unit (ICU) patients treated with ECMO at our institution from May 2014 to January 2024. The cohort included 21 males and 45 females with a mean age of 54.56 ± 16.09 years. The diagnoses varied; encompassing 21 cases of severe pneumonia; 15 of cardiogenic shock; 8 of severe myocarditis; 8 of coronary atherosclerotic heart disease; 5 of acute pulmonary embolism; 4 of acute respiratory failure; 2 of severe aortic valve stenosis; and 1 each of aortic dissection, multiple organ failure, and severe asthma (Table 1).

Research methods

The inclusion criteria for this study were patients with cardiogenic shock resulting from various causes, including acute myocardial infarction and fulminant myocarditis; and pulmonary dysfunction due to multiple factors, such as moderate to severe acute respiratory distress syndrome (ARDS) and acute massive pulmonary embolism.

The exclusion criteria were cardiopulmonary resuscitation lasting more than 30 minutes, severe multiple organ dysfunction, uncontrolled active bleeding, irreversible severe brain injury, left ventricular thrombosis, severe aortic insufficiency, and other similar conditions.

The dataset included general information such as age, gender, medical history, and diagnosis. The clinical indicators included length of ICU stay, ECMO running time, successful ECMO weaning, infections during ECMO, duration of continuous renal replacement therapy (CRRT), mode and duration of mechanical ventilation, and duration of central venous catheterization. Additionally, venous whole blood anticoagulated with EDTA was collected both before and after ECMO treatment to measure parameters such as white blood cell count, procalcitonin (PCT) levels, lymphocytes, neutrophils, and platelets. Venous plasma anticoagulated with citrate was collected to assess coagulation parameters, including fibrinogen, prothrombin time, thrombin time, international normalized ratio, activated partial thromboplastin time, and D-dimer. Importantly, the use of antibiotics in ECMO patients was reviewed (Table 2).

Statistical analysis

Infection sites, pathogen distributions, and class of antibiotics among the ECMO patients were evaluated using descriptive statistics. Data analyses were performed using SPSS 25 (IBM Corp., Armonk, NY, USA) and count data were presented as numbers (n) and

Table 1. Demographic and clinical characteristics of 66 patients with ECMO.

Project	value
Age (years)	54.56 ± 16.09
Male/female (n)	21/45
Primary disease (%)	
Severe pneumonia	31.8
Cardiogenic shock	22.7
Severe myocarditis	12.1
Coronary atherosclerotic heart disease	12.1
Acute pulmonary embolism	7.6
Acute respiratory failure	6.1
Severe aortic stenosis	3.0
Aortic dissection	1.5
Multiple organ failure	1.5
Severe asthma	1.5
ICU length of stay (days)	10.00（5.0–20.25）
ECMO treatment time (days)	5.00（2.10–8.00）
Successfully divorced from ECMO (cases)	33
VA-ECMO (cases)	44
VV-ECMO（cases）	22
Noninvasive ventilation(cases)	2
Tracheal intubation(cases)	19
Tracheostomy ventilation(cases)	44
Cure (cases)	30
Death (cases)	36

ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; VA-ECMO: venoarterial extracorporeal membrane oxygenation; VV-ECMO: venovenous extracorporeal membrane oxygenation.

Table 2. Types and proportion of antibiotic use in ECMO patients.

Category	n	(%）
b-lactam antibiotics		
Carbapenems		
Imipenem cilastatin sodium	36	54.55
Meropenem	19	28.79
Ertapenem	2	3.03
Cephalosporins		
Cefothialil	2	3.03
Cefoperazone	6	9.10
Cefuroxime	3	4.55
Ceftriaxone	1	1.51
Cefmetazole	1	1.51
B-amidase inhibitor compound preparation		
Piperacillin/Tazobactam	20	30.3
Ceftazidime/Avibactam	2	3.03
Cefoperazone/Sulbactam	2	3.03
Quinolone antibiotics		
Levofloxacin	2	3.03
Moxifloxacin	6	9.10
Tetracycline		
Tigacycline	17	25.76
Glycopeptides		
Vancomycin	12	18.18
Teicalnine	28	42.42
Oxazolidinones		
Linezolid	5	7.56
Polypeptide		
Colistin sulfate	3	4.55
Macrolides		
Azithromycin	3	4.55
Sulfonamides		
Compound sulfamethoxazole	5	7.56

ECMO: extracorporeal membrane oxygenation.

percentages (%). Normally distributed data were shown as mean ± standard deviation, and non-normally distributed data as medians with interquartile ranges (P25~P75). Comparisons of leukocyte, procalcitonin, lymphocyte, neutrophil, platelet counts, and clotting term before and after ECMO treatment were conducted using paired sample t tests, with a p value of < 0.05 indicating statistical significance. Regression analysis was conducted by incorporating relevant influencing factors and the occurrence of endpoint events following ECMO treatment, with a significance level set at $p < 0.05$. In the multivariate logistic regression analysis, factors with $p < 0.05$ were considered independent risk factors for post-ECMO endpoint events.

Results

Infection sites and pathogen distribution among ECMO inpatients

In this cohort of 66 ECMO inpatients, 51 suffered from infections: pulmonary infections were most prevalent, affecting 47 (71.2%) patients, followed by bloodstream infections in 12 (18.2%), and urinary tract infections in 6 (9.1%). In terms of infection sites, 37 (56.1%) patients had a single-site infection, 13 (20%) had infections at 2 sites, and 1 (1.5%) at 3 sites. Fifteen (22.7%) patients exhibited no infections (Table 3). It is important to note that not all of the 55 infections observed during ECMO treatment in this study were a result of ECMO-related complications. Rather, the majority of these patients required ECMO due to the worsening of underlying lung diseases.

Pathogen analysis among the 51 infected patients revealed that 42 (82.35%) strains were Gram-negative bacteria, including 15 (29.41%) cases of *Acinetobacter baumannii*, 10 (19.61%) cases of *Klebsiella pneumoniae*, and 5 (9.80%) cases involved *Pseudomonas aeruginosa* and *Escherichia coli*. There were 6 (11.76%) instances of Gram-positive bacteria, predominantly *Staphylococcus aureus* (3 cases, 5.88%). Fungal infections were identified in 3 (5.88%) patients, with 2 (3.92%) cases of *Candida albicans*, and 1 (1.96%) of yeast-like fungal spores (Table 4).

Table 3. Infection sites in ECMO patients.

Position	n	(%)
Lung infection	47	71.2
Blood flow infection	12	18.2
Urinary tract infection	6	9.1
Single site infection	37	56.1
Infection in two sites	13	20
Three-site infection	1	1.5
No infection	15	22.7

ECMO: extracorporeal membrane oxygenation.

Table 4. Distribution and constituent ratio of pathogens in ECMO patients.

Pathogenic bacteria composition	cases (n)	(%)
Gram-negative bacteria	**42**	**82.35**
Acinetobacter baumannii	15	29.41
Klebsiella pneumoniae	10	19.61
Pseudomonas aeruginosa	5	9.80
Escherichia coli	5	9.80
Haemophilus influenzae	3	5.88
Stenotrophomonas maltophilia	2	3.92
Burkholderia onion	1	1.96
Mannitol-decomposing rolston bacteria	1	1.96
Gram-positive bacteria	**6**	**11.76**
Staphylococcus aureus	3	5.88
Staphylococcus hominis	1	1.96
Enterococcus faecium	1	1.96
Streptococcus pneumoniae	1	1.96
Fungus	3	5.88
Candida albicans	2	3.92
Yeast-like fungal spores	1	1.96

ECMO: extracorporeal membrane oxygenation.

Clinical treatment timelines for ECMO patients

Among the patients, 47 tested positive for sputum culture infections, with an average detection time of 2.66 (range 2.00–3.50) days; 12 for bloodstream infections at an average of 0.54 (range 0.41–0.88) days; and 6 for urinary tract infections, averaging 2.00 (range 1.00–3.25) days. The average duration of antibiotic therapy for ECMO patients (n = 62) was 8.00 (range 4.75–14.25) days. The average times for central venous catheter use, continuous renal replacement therapy, and mechanical ventilation were 8.00 (range 5.00–15.00) days, 5.00 (range 3.00–10.00) days, and 9.00 (range 5.00–15.00) days, respectively (Table 5).

Changes in infection and coagulation parameters before and after ECMO treatment

Data on white blood cells, procalcitonin, neutrophils, lymphocytes, platelets, and blood coagulation test were collected and analyzed before and after ECMO treatment. Notable findings included significant reductions in leukocyte ($p < 0.05$, n = 57), platelet counts ($p < 0.05$, n = 56), and fibrinogen ($p <$

Table 5. ECMO clinical treatment time window.

Project	n	value
Time to report positive sputum culture (days)	47	2.66 (2.00–3.50)
Time to report positive blood flow infection (days)	12	0.54 (0.41–0.88)
Time to report positive urinary tract infection (days)	6	2.00 (1.00–3.25)
Average treatment time of antibiotics (days)	62	8.00 (4.75–14.25)
Average indwelling time of central venous catheter (days)	65	8.00 (5.00–15.00)
Average time of continuous renal replacement therapy (days)	47	5.00 (3.00–10.00)
Average time of mechanical ventilation treatment (days)	65	9.00 (5.00 ± 15.00)

ECMO: extracorporeal membrane oxygenation.

Table 6. Changes in infection and coagulation parameters before and after ECMO treatment.

Project	WBC 10^9/L (n：57)	PCT ng/mL (n: 52)	Lymphocyte 10^9/L (n: 56)	Neutrophil 10^9/L (n: 57)	PLT 10^9/L (n: 56)	TT seconds (n = 53)	FIB g/L (n = 57)
Before ECMO treatment	14.50 ± 9.86	14.70 ± 27.20	1.10 ± 1.67	86.26 ± 13.06	160.16 ± 83.17	22.26 ± 21.61	3.99 ± 2.14
48 hours after ECMO treatment	11.29 ± 5.32	15.49 ± 27.81	0.73 ± 0.52	83.75 ± 14.84	69.68 ± 44.17	34.41 ± 6.27	3.30 ± 1.47
t value	2.72	-0.228	1.72	1.06	9.72	-1.69	2.32
p value	0.009	0.82	0.091	0.30	0.000	0.09	0.02

ECMO: extracorporeal membrane oxygenation; WBC: white blood cell; PCT: procalcitonin; TT: thrombin time; FIB: fibrinogen.

0.05, n = 57) within 48 hours post-ECMO. Lymphocyte counts also decreased, though not significantly (p = 0.09, n = 56). Neutrophil and PCT levels showed no significant changes (Table 6). In contrast, thrombin time (TT), prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), and D-dimer levels tended to be prolonged or elevated; however, these differences were not statistically significant.

Logistic regression analysis of relevant factors and endpoint events after ECMO treatment

Of the 66 patients in this study, 33 were successfully weaned from the ventilator, of whom 30 survived and 3 died after weaning. Ultimately, 36 patients passed away (Table 1). Univariate regression analysis identified central venous catheterization time, ICU stay duration, and mechanical ventilation time as independent risk factors for mortality following ECMO treatment ($p < 0.05$). Factors such as ECMO mode; age; gender; type and duration of antibiotics; duration of continuous renal replacement therapy; and changes in white blood cells, platelets, and fibrinogen after ECMO treatment; did not show statistical significance regarding endpoint events. Among these, only ICU stay duration remained statistically significant in the multivariate analysis, as an independent risk factor for survival after ECMO treatment (Table 7).

Discussion

ECMO is a critical treatment modality for severe respiratory and circulatory failures in the ICU. However, susceptibility to co-infections during ECMO presents significant patient prognosis and survival challenges. Effective management of co-infections is essential for improving outcomes [12]. Studies have consistently demonstrated that ECMO is associated with a high risk of nosocomial infections, and prolonged use is a recognized independent risk factor for such infections [4,13,14]. Furthermore, the duration of mechanical ventilation and the retention of central venous catheters are strongly correlated with increased risks of nosocomial infection and mortality in ECMO patients [15,16].

In our study, severe pneumonia, respiratory failure, and heart failure were prevalent among ECMO patients, with the average duration of ECMO use being 5.00 (range 2.1–8.0) days. The rate of successful weaning was 50%, and the overall recovery rate was 45.45%. Infections were reported in 56 patients, including pulmonary infections (71.2%), bloodstream infections (18.2%), and urinary infections (9.1%). Gram-negative

Table 7. Logistic regression analysis of surviving-related factors after ECMO treatment.

Variable	Single factor analysis		Multifactor analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	0.997 (0.967–1.028)	0.855		
Gender	0.857 (0.302–2.435)	0.772		
ECMO type	0.758 (0.269–2.136)	0.6		
Central venous catheter insertion time	1.271 (1.006–1.141)	0.033	0.977 (0.860–1.110)	0.721
Length of ICU stay	1.284 (1.027–1.143)	0.003	1.173 (1.029–1.336)	0.17
ECMO treatment time	1.211 (0.925–1.105)	0.803		
Duration of antibiotic treatment	1.056 (0.992–1.125)	0.087		
Mechanical ventilation time	1.069 (1.003–1.141)	0.041	0.919 (0.792–1.067)	0.267
Time of CRRT therapy	1.028 (0.944–1.12)	0.527		
WBC value of difference	1.015 (0.955–1.079)	0.63		
PLT value of difference	1.001 (0.994–1.009)	0.725		
FIB value of difference	1.09 (0.859–1.382)	0.48		
G- bacterial infection	0.976 (0.357–2.672)	0.963		
G+ bacterial infection	0.571 (0.097–3.36)	0.536		
β-lactam antibiotics alone	0.7 （0.202–2.421）	0.573		
β-lactam in combination with other antibiotics	1.001 (0.413–3.549)	1.21		

HR: hazard ratio; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; CRRT: continuous renal replacement therapy; WBC: white blood cell; PCT: procalcitonin; FIB: fibrinogen.

bacteria emerged as the predominant pathogens.

A review involving 196 ECMO patients in China found that 110 experienced nosocomial infections, including 59 pulmonary, 36 bloodstream, and 10 urinary infections; further confirming the prevalence of Gram-negative bacteria [17]. Another study examined 363 post-cardiac surgery ECMO patients and identified advanced age (≥ 65 years), abnormal white blood cell counts (< 4 or > 12 × 10^9/L), and prolonged mechanical ventilation as key predictors of nosocomial infections [18]. Our ECMO patients had an average mechanical ventilation duration of 9.00 (5.00–15.00) days, correlating with a 71.2% infection rate. This evidence underscores that the duration of ECMO treatment, mechanical ventilation, and central venous catheter use are significant factors contributing to the risk of nosocomial infections. The results of the univariate analysis in this study suggest that the duration of mechanical ventilation and central venous catheter placement are significant factors influencing the endpoint events of ECMO.

Notably, a significant reduction in white blood cell counts was observed within 48 hours following ECMO, potentially due to the broad-spectrum antibiotics administered. Historically, leukopenia has been a common complication during ECMO treatment. The drop in platelet counts also warrants attention, as it suggests a profound interaction within the ECMO in vitro environment between leukocytes and platelets that may drive pro-inflammatory, pro-coagulant, and immunosuppressive responses [19]. This interaction, possibly exacerbated by factors such as heparin usage, heightened inflammatory responses, and platelet activation, appears to frequently result in thrombocytopenia, with a noted prevalence of 23% [20]. The observed phenotypic and functional changes in leukocytes and platelets shortly after ECMO are significant and likely to influence patient outcomes, meriting further investigation [21,22]. This comprehensive understanding of cellular behavior post-ECMO could elucidate potential therapeutic targets to mitigate such complications.

Moreover, the implications of PCT levels, a critical inflammatory marker, are thought-provoking. PCT is highly sensitive to bloodstream infections and plays a crucial role in pathogen identification, clinical diagnosis, and the management of antibiotics in sepsis patients [23,24]. Our study assessed PCT levels before and after ECMO treatment and observed no significant changes. Given that the kidneys primarily metabolize PCT, the absence of significant fluctuation in its levels may be explained by the fact that many critically ill patients either maintain stable circulation or suffer acute renal failure, with CRRT frequently employed before ECMO initiation. Previous research has demonstrated that CRRT significantly lowers inflammatory markers, including PCT, in critically ill patients [25]. In our cohort, CRRT was administered to 48 patients during ECMO, which likely influenced the observed PCT outcomes.

Previous studies on coagulation parameters of ECMO therapy, particularly fibrinogen, have focused on its association with ECMO-related bleeding complications. These studies consistently found that fibrinogen levels were significantly lower after ECMO than before treatment, ultimately leading to bleeding related adverse events [26,27]. In contrast, there are few studies examining the relationship between fibrinogen (FIB) and ECMO-related infections. Interestingly, an early preliminary study on ECMO for treating sepsis patients at risk of circulating infections suggested that a decrease in fibrinogen may be linked to an increased risk of infection [28]. The findings regarding fibrinogen changes after ECMO treatment are inconsistent. For example, a single-center study on thrombotic complications following ECMO treatment for coronavirus disease 2019 (COVID-19) found that fibrinogen levels were significantly elevated when thrombotic events occurred [29]. In contrast, studies involving pigs with sepsis undergoing ECMO treatment also reported elevated levels of coagulation-related indicators, including fibrinogen [30]. These findings highlight the need for further investigation into the differences and variations in fibrinogen levels during ECMO treatment.

Both empirical and targeted antimicrobial strategies are crucial in ECMO treatment and infection control, with beta-lactam antibiotics such as imipenem, meropenem, and piperacillin being particularly important. The efficacy of prophylactic antibiotic use during ECMO treatment, however, is not uniform. Nonetheless, several studies have indicated that prophylactic antibiotics can reduce the risk of nosocomial mortality and pneumonia in patients undergoing ECMO [31,32]. More prospective studies are needed to confirm this conclusion. In our ECMO cohort, 51 patients had positive bacteriological cultures, and antibiotics were ultimately administered to 62 patients. Of these, 9 received prophylactic antibiotics, while the majority were treated with empirical and targeted antimicrobial strategies based on drug susceptibility results. The primary antibiotics used were β-lactams, followed by glycopeptides and tetracyclines. However, we did not find a statistically significant association between the classified use of antibiotics and changes in outcomes after ECMO treatment. Adverse events post-ECMO may be more influenced by overall ICU management, complication control, and the patient's underlying condition. Nevertheless, it is clear that appropriate antibiotic use enhances infection control during ECMO, and further research on the long-term outcomes after ECMO treatment is warranted.

Conclusions

A high incidence of nosocomial infections was observed among the 66 ECMO patients studied. The infections were predominantly pulmonary infections, followed by bloodstream infections. These infections were not only linked to the patients' underlying conditions but were also heavily influenced by clinical interventions such as central venous catheterization and mechanical ventilation. Gram-negative bacteria remained the predominant pathogens. It is recommended to use a combination of preventive, empirical, and targeted antibiotics; with β-lactam antibiotics as the cornerstone. When necessary, based on drug sensitivity results, other options such as tetracyclines, glycopeptides, and polypeptides should be considered, especially for multi-drug-resistant bacteria. Significant decreases in leukocyte, platelet and fibrinogen counts post-ECMO highlight the need for vigilant anticoagulation, infection, and inflammation management. Additionally, a reduced length of ICU stay serves as a predictive criterion for effectively evaluating ECMO endpoint events. While ECMO is a critical treatment for cardiopulmonary failure, effective infection control remains crucial for enhancing patient survival rates.

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Conflict of interests

No conflict of interests is declared.

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