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Epidemiology and risk factors of infections among patients with extracorporeal membrane oxygenation in a tertiary heart center

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Abstract. – OBJECTIVE: Extracorporeal membrane oxygenation (ECMO) is an important treatment strategy for severe acute respiratory and/or cardiac failure. Despite advancements in device technology and intensive care, mortality rates, and complications remain high. Patients undergoing ECMO are at an increased risk of infection due to factors such as immunosuppression, the presence of cannulas, and variable antibiotic pharmacokinetics. Unfortunately, an acquired infection in these patients can lead to increased morbidity, longer hospital stays, and even mortality. The purpose of this study was to examine the prevalence, profiles, and sites of ECMO-related infections, as well as underlying risk factors associated with these infections.

PATIENTS AND METHODS: We retrospectively analyzed clinical data from 73 patients who received veno-arterial (VA) and/or venovenous (VV) ECMO support due to severe but potentially reversible cardiac and/or pulmonary failure lasting ≥24 hours. We involved patients with no suspicion of pre-existing infection before ECMO insertion from January 2015 to February 2023, classifying them into either infected or non-infected based on available evidence. The estimated probability for infection according to ECMO-day was established. Significance was set at $p<0.05$. The primary interesting outcome is the infection probability.

RESULTS: Mean age was 52.2±14.8 years in all groups, and 55 (75.3%) were male. Median hospital stay was 6 (2-16) days and duration of ICU was 5 (2-10) days in all groups. The duration of ICU stay was significantly higher in the infected group compared to the non-infected group [10 days (5-15) *vs*. 3 days (2-7)], $p<0.001$, respectively. 66 patients (90.4%) received VA ECMO and 18 of them (94.7%) were infected. In all groups, the ECMO wean ratio was 28.8%. Death before 48 hours occurred in 28 patients (38.4%). 26% of patients under ECMO support consisted of the infected group and had 68 episodes per 1,000 ECMO days. Of these, the most frequent infection site was lower respiratory tract infection (47.3%). The most common pathogen among these was *K. pneumonia*. 39.7% of patients received no antibiotics. The probability of infection was 19% for 1.5 (mean-1SD) ECMO days, approximately 41% for 4 ECMO days, and 52% for (mean+1SD) 6.5 ECMO days.

CONCLUSIONS: Nosocomial infections, which are commonly observed during ECMO procedures, are considered a significant concern. The respiratory system is frequently affected by such infections. Even though the use of antibiotics for prophylaxis remains debatable, it is predicted that there will be an inclination towards the regular application of prophylactic measures and the development of standardized protocols based on solid evidence obtained from prospective research studies in the future.

Key Words:
ECMO-related nosocomial infection, Antibiotic prophylaxis, Klebsiella pneumonia.

Introduction

Extracorporeal membrane oxygenation (ECMO) is an important treatment for severe respiratory and cardiac failure, but it can still lead to complications and a higher risk of infection due to the use of catheters and altered antibiotic effects. This can result in longer hospital stays, increased morbidity, and mortality[1-4].

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While there is not always a clear connection between ECMO-related infections and mortality, it is important to take precautions to minimize the risk of infection in these vulnerable patients[5-7].

According to a 2011 analysis of the Extracorporeal Life Support Organization (ELSO) registry[8], the prevalence of infection among ECMO-supported patients was reported to be 11.7%. However, other studies[9] have reported higher rates of infectious complications, ranging from 9% to 65%, indicating that the actual rate of infections may be much higher than what is included in the ELSO registry. The survival rate for these patients was 56%, but it varied depending on the patient population and healthcare providers. The prevalence, profile, and sites of infections in ECMO patients vary between centers, and each center's approach to preventive measures and institutional acceptance of prophylaxis protocol is different[10]. Our objective is to determine the prevalence, profiles, and sites of infection in patients receiving ECMO support, as well as the underlying risk factors associated with ECMO-related infections.

Patients and Methods

Study Population

Between January 2015 and February 2023, Kosuyolu High Specialization Training and Research Hospital performed ECMO procedures on 1,130 patients. This hospital is a tertiary referral heart center with a capacity of 450 beds, where various cardiac invasive and surgical procedures, such as lung and heart transplantation, are carried out.

73 patients who had severe, but reversible cardiac or pulmonary failure received ECMO support and were included in the study. Patients had to be age ≥18 years old and receive veno-arterial (VA) or venovenous (VV) ECMO support for ≥24 hours due to in-hospital cardiac arrest (ECMO-cardiopulmonary resuscitation e-CPR), adult respiratory distress syndrome (ARDS) or cardiogenic shock.

Additionally, they had to have no infections identified by sample culture (blood, sputum, urine, or wound secretions) before ECMO supplementation.

Patients under <18 years of age (n=345), with ECMO duration time less than 24 hours (n=214), received ECMO support in the postcardiotomy period (n=477), and those who received repeated ECMO procedures (n=21) were excluded from the analysis (Figure 1).

The study was conducted at Koşuyolu High Specialization Training and Research Hospital and was approved by the local Institutional Ethical Committee and followed the principles of the Declaration of Helsinki.

Patients' clinical information, demographics, and laboratory findings at the initiation of ECMO were obtained from Patients' demographics, clinical and laboratory findings were obtained from Infection Control Team's surveillance records,

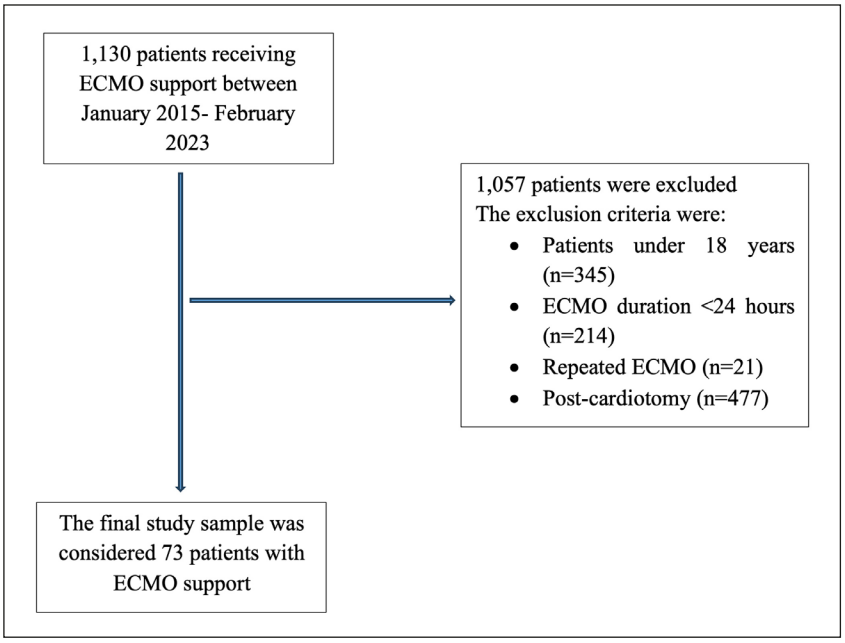

Figure 1. Study flow diagram.

Hospital Information System and National Health Record System. Data included age, sex, body mass index, underlying medical conditions, and medications. In addition, detailed information on ECMO was obtained from a daily ECMO report written by physicians. This information included the reasons for ECMO support (cardiogenic *vs.* respiratory failure), mode of ECMO VA, VV, or veno-arteriovenous (VAV), cannulation site of ECMO catheters, location of catheter cannulation (intensive care unit, emergency room, or operation room). Data on the application of continuous renal replacement therapy (CRRT) were also collected. In addition, data on antibiotic usage, blood culture results during ECMO support, type of organisms isolated, and antibiotic sensitivity test results were collected. Antibiotics administered before or during ECMO cannulation were analyzed in this study.

ECMO Procedure and Weaning

The ECMO team, which includes intensive care specialists, cardiologists, cardiac anesthesiologists, and cardiothoracic surgeons, assessed the patient's medical condition and concluded that ECMO initiation was necessary. They performed cannulation using the Seldinger technique, with preferred sites being the femoral and internal jugular veins for VV ECMO and the femoral vein and artery for VA ECMO. For VA ECMO support, a return cannula was inserted through the left common femoral artery, and a longer, multi-hole drainage cannula was inserted through the right femoral vein after systemic heparinization. A distal perfusion cannula was also placed through the left superficial femoral artery to ensure adequate blood supply and perfusion to the limbs. After stabilizing the patient in the intensive care unit (ICU), diagnostic coronary angiography was performed, followed by percutaneous revascularization for all culprit lesions. If the patient was unstable, pharmacological support was initiated through inotropic and vasopressor therapy. For patients receiving VV ECMO who needed additional cardiogenic support, an arterial catheter was inserted, and the mode was switched to VAV ECMO. Patients were sedated at least 24 hours after VA-ECMO implementation to reduce cardiac metabolism and myocardial oxygen consumption and prevent brain damage. ECMO patients were infused with unfractionated heparin or bivalirudin, with a target-activated coagulation time of 180-200 seconds monitored with the activated coagulation time (ACT). Separate circuits were used for patients requiring the addition of CRRT. ELSO guidelines[11] were followed for ECMO management.

After stabilizing the patient's hemodynamics with or without percutaneous revascularization, they are monitored for at least three to five days before deciding whether to discontinue VA-ECMO support. This is done to prevent any potential complications related to ECMO. The patient's arterial blood gas levels are closely monitored to determine whether artificial gas exchange support is still necessary. If the patient's circulatory functions are monitored echocardiographically and their mean arterial pressure (MAP) hemodynamically remains above 65 mmHg, the ECMO flow rate may be temporarily decreased. If the patient's cardiac functions are deemed sufficient, ECMO support is stopped, their cannulas are removed, and they are observed closely for at least 12 hours for any possible complications. The patient is kept stable with mechanical ventilation, an intraaortic balloon pump (IABP), and inotropic support, while daily echocardiographic control of their cardiac functions is maintained. The patient is weaned from all supportive treatments step by step, including decreasing inotropic support, extubation, and removal of counter-pulsation, based on their stable condition.

Respiratory Management During ECMO

The lung protective ventilation strategy was applied to all patients under ECMO support. For this purpose, mechanical ventilator settings were adjusted to provide tidal volume 3 mL/kg, positive end-expiratory pressure (PEEP) 5-8 cm H_2O, positive airway pressure 15-20 mmHg, PO_2>80 mmHg, and PCO_2 35-45 mmHg.

Definition of ECMO-Related NI

Nosocomial infection (NI) occurring 24 h after initiation and 48 h after discontinuation of ECMO was defined as ECMO-related NI[12]. The type of ECMO-related NI included bloodstream infection (BSI), respiratory tract infection (RTI), urinary tract infection (UTI), and cannula insertion site infections (CISI). The diagnosis and definition of ECMO-related NI were based on the Centers for Disease Control and Prevention definitions for NI[13] or based on the patient's clinical status. Isolation of pathogenic microorganisms was related to clinical symptoms, typical inflammation characteristics in blood samples, and radiographic findings.

Anti-Infective Therapy

At the beginning of ECMO support, patients were administered antibiotic prophylaxis using

first-generation cephalosporins or glycopeptide. In case of any ECMO-related nosocomial infections, antibiotics were adjusted based on culture results and comprised antipseudomonal beta-lactam/beta-lactamase inhibitors or carbapenems. The dose was then initiated at a conventional level and monitored according to renal function. Although our center has only recently adopted the ECMO procedure, standardization in antibiotic prophylaxis measures has needed to be improved in prior times due to various factors, including emergency/elective conditions for insertion, extended patient hospitalizations, and local resistance patterns within the facility. Despite these challenges faced by many institutions alike, there remains variability among centers when administering standardized approaches towards antibiotic prophylaxis during ECMO procedures.

Statistical Analysis

We used R studio 4.22 software (Vienna, Austria) to perform statistical analysis. Continuous variables were expressed as a median and interquartile range [IQR] [quartile 1-quarter 3] or mean standard deviation. To compare the two groups, we used either Mann-Whitney U or a *t*-test. The Fisher's exact test was used to compare categorical variables, which were presented as numbers and percentages. We established the estimated probability for infection based on the ECMO day. Our primary interested outcome was infection probability with significance set at $p<0.05$.

Results

Between 2015 and 2023, our institution implanted 1,130 ECMO devices. However, only 73 patients met the inclusion criteria. Most patients were males (75.3%) with a mean age of 52.2 years. The median hospital stay for all patients was 6 (2-16) days, and the ICU stay was 5 (2-10) days. The infected group had a significantly longer ICU stay than the non-infected group (10 days *vs*. 3 days, $p<0.001$). 90.4% of patients received VA ECMO, and of those, 94.7% were infected. The ECMO wean ratio for all groups was 28.8%. 38.4% of patients died within 48 hours of admission. The most common underlying disease was coronary artery disease, and patients were frequently admitted to the hospital with acute coronary syndrome. The demographic and clinical characteristics of the patients are shown in Table I.

Among patients receiving ECMO support, 26% were infected, resulting in 68 episodes per 1,000 ECMO days. The infections were primarily located in the lower respiratory tract, bloodstream, and cannula insertion site, accounting for 47.3%, 26.3%, and 15.7% of cases, respectively. The most prevalent pathogen responsible for these infections was *Klebsiella pneumonia* (*K. pneumonia*). Infection sites and causative agents are shown in Table II.

Out of all the patients, 39.7% did not receive antibiotics for their treatment. Out of those who did receive them, 28.7% received a single antibiotic as prophylaxis, while 19.1% received two or more antibiotics as empirical treatment during the ECMO implantation (Table III).

The probability of infection increased with the number of ECMO days, with a 19% probability for 1.5 days (mean-1SD), approximately 41% for four days, and 52% for 6.5 days (mean+1SD) (Table IV and Figure 2).

The best ECMO days' cut-off value for the development of infection was three days, with a sensitivity of 83% and specificity of 38%, as indicated in Figure 2, with a receiver operating characteristic (ROC) area under curve (AUC) of 0.603 (Figure 3).

Discussion

Our study revealed that 26% of patients on ECMO had NI, which is higher than what was reported in the 2011 ELSO registry. Although different studies[14] have reported varying infection rates, it is consistent that NI is a severe complication of ECMO that increases morbidity and mortality, despite the advances in ECMO management. The rates of ECMO-related NI vary between case series and registries due to differences in definitions, reporting methods, and surveillance practices. For instance, Selçuk et al[15] found a 36.5% rate of NI among pediatric and adult patients, while Wang et al[16] similarly found this rate to be 40%.

The importance of advanced cardiac care and ECMO is increasing worldwide. Infection is still one of the most important causes of mortality among ECMO patients. Our study emphasized the importance of infection in ECMO patients and in the light of larger studies, may generate attention for routine antibiotic prophylaxis in ECMO.

Our study focused on adult patients who received ECMO support for cardiogenic shock, car-

Table I. Demographic and clinical characteristics of ECMO patients.

	All groups	Non infection	Infection	*p*-value
Age	52.2±14.8	53.5±15.1	48.2±13.2	0.18
Gender (male), n (%)	55 (75.3)	40 (74.1)	15 (78.9)	0.67
BMI (kg/m^2)	26.1±4.1	25.7±4.0	27.3±4.2	0.16
Length of hospital stay (days)	6 (2-16)	4 (2-15)	12 (5-17)	**0.04**
Duration of ICU (days)	5 (2-10)	3 (2-7)	10 (5-15)	**<0.001**
Duration of ECMO (days)	2 (1-5)	2 (1-3)	3 (3-7)	**0.002**
ECMO type				
VA	66 (90.4)	48 (88.9)	18 (94.7)	0.46
VV	7 (9.6)	6 (11.1)	1 (5.3)	
ECMO wean (all group)	21 (28.8)	12 (22.2)	9 (47.4)	
Death <48 h	28 (38.4)	28 (51.9)	–	
Underlying diseases				
CAD	36 (49.3)	26 (48.1)	10 (52.6)	0.74
HT	34 (46.6)	24 (4.4)	10 (52.6)	0.54
DM	22 (30.1)	15 (27.8)	7 (36.8)	0.46
COPD	8 (11)	5 (9.3)	3 (15.8)	0.42
HF	12 (16.9)	9 (17.3)	3 (15.8)	0.99
CVA	6 (8.2)	4 (7.4)	2 (10.5)	0.65
Admission diagnosis				
PT	9 (12.3)	8 (14.8)	1 (5.3)	0.49
CHF	11 (15.1)	9 (16.7)	2 (10.5)	
ACS	40 (54.8)	26 (48.1)	14 (73.7)	
Cardiac arrest	5 (6.8)	4 (7.4)	1 (5.3)	
Cardiogenic shock	3 (4.1)	2 (3.7)	1 (5.3)	
Arrhythmia	5 (6.8)	5 (9.3)	–	
ECMO Indication				
Cardiac arrest	43 (58.9)	28 (51.9)	15 (78.9)	0.10
Cardiogenic shock	24 (32.9)	20 (37)	4 (21.1)	
ARDS	6 (8.2)	6 (11.1)	–	
CRRT	26 (35.6)	19 (35.2)	7 (36.8)	0.99
IABP	45 (61.6)	31 (57.4)	14 (73.7)	0.28

BMI: Body mass index, CAD: Coronary artery disease, HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, HF: Heart failure, CVA: Cerebrovascular accident, PT: Pulmonary thromboembolism, CHF: Congestive heart failure. ACS: Acute coronary syndrome, CRRT: Continuous renal replacement therapy, IABP: Intraaortic ballon pump.

diac arrest (e-CPR), and ARDS. We discovered that the rate of nosocomial infections (NIs) in these patient groups was 26%, with 68 episodes per 1,000 ECMO days. This is a higher rate than the 21% reported in the ELSO registry[8] for the adult ECMO population. Previous case series[7] estimated NI rates for ECMO patients between 8-45.1%. Our findings suggest that the higher NI rate may be due to the complexity of patients evaluated in different centers and referred to us for further examination or ECMO support in emergency situations.

The types of pathogens that can cause infections associated with ECMO are changing with the advancements in antibiotics and new treatments. According to the ELSO registry[17], the most frequent causative agents during ECMO treatment for respiratory and cardiac failure were yeast, *S. aureus*, and *Pseudomonas* sp in the respiratory tract, and Coagulase negative *Staphylococcus* (CoNs), yeast and *Enterococcus* sp. in bloodstream In our study, we found that the most common pathogens isolated in the lower respiratory tract were *K. pneumoniae*, *B. cepacia*, *P. aeruginosa* and in the bloodstream were *K. pneumoniae, E. faecalis, S. maltophilia,* respectively.

The respiratory tract is the most common site of acquired infections in pediatric and adult ECMO patients[7,9,18], followed by the bloodstream and cannula insertion sites our findings are simi-

Table II. Distribution of infection by sites and microorganisms.

	All patients (n=73) n	%	Episodes per 1,000 ECMO days
All infections	19	26	68
LRTIs	9	47.3	32
K. pneumoniae	3	33.3	
B. cepacia	2	22.2	
P. auroginosa	1	11.1	
E. cloaca	1	11.1	
P. mirabilis	1	11.1	
Causative agent unknown	1	11.1	
BSIs	5	26.3	18
K. pneumoniae	2	40	
E. faecalis	2	40	
S. maltophilia	1	20	
CISIs	3	15.7	11
Causative agent unknown	2	66.6	
E. coli	1	33.3	
MSIs BSI+ LRTI	2	5.2	7
S. maltophilia + K. pneumoniae	1	50	
R. picketti + A. baumanii	1	50	

LRTIs: Lower respiratory tract infections, *K. pneumoniae: Klebsiella pneumoniae, B.cepacia: Burkholderia cepacia, P.aeruginosa: Pseudomonas aeruginosa E. cloaca: Enterobacter cloaca, P. mirabilis: Proteus mirabilis,* BSIs: Bloodstream infections *S. maltophilia: Stenotrophomonas maltophilia,* CISIs: Cannula insertion site infections, *E.coli: Escherichia coli,* MSIs: Multiple site infections, *A. baumanii: Acinetobacter baumanii.*

Table III. Regimens of antibiotics treatment.

Reason for initiating antibiotics	Antibiotics name	No. of patients (n: 73)
No antibiotics group, n (%)	–	29 (39.7)
Prophylaxis group, n (%)		21 (28.7)
	Cefazolin	12 (57.1)
	Vancomycin	7 (33.3)
	TZP	2 (9.5)
Empirical treatment group, n (%)		14 (19.1)
	TZP+ vancomycin	7 (50)
	Vancomycin	2 (14.2)
	MRP	1 (7.1)
	MRP+ vancomycin	1 (7.1)
	CRO+clarithromycin	1 (7.1)
	FEP	1 (7.1)
	TZP+levofloxacin	1 (7.1)
Targeted treatment, n (%)		9 (12.3)
	TMP/SMX	2 (22.2)
	ETP	2 (22.2)
	Vancomycin	2 (22.2)
	MRP+colistin	1 (11.1)
	MRP	1 (11.1)
	Levofloxacin	1 (11.1)

TZP: Piperacillin/tazobactam, MRP: Meropenem, CRO: Ceftriaxon, FEP: Cefepime, TMP/SMX: Trimethoprim-sulfamethoxazole, ETP: Ertapenem.

Table IV. Probability of infection according to ECMO days.

	ECMO day	Probability	Standard error
Mean - SD	1.5	19%	0.10
Mean	4	41%	0.07
Mean + SD	6.5	52%	0.11

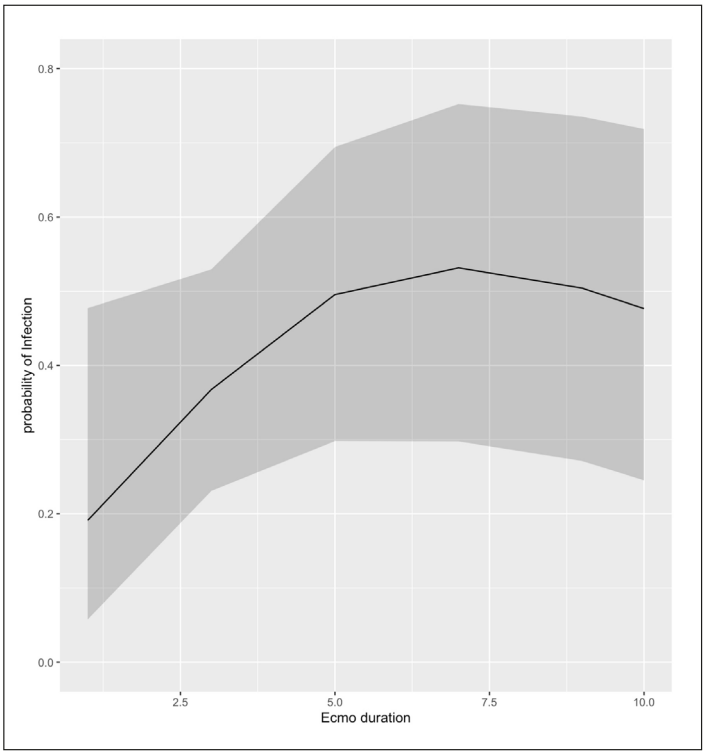

Figure 2. ECMO duration and infection probability.

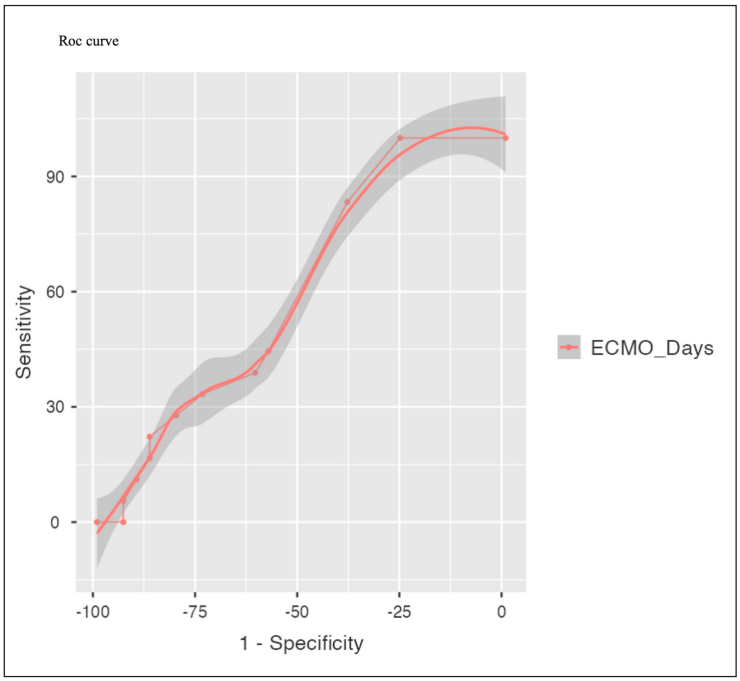

Figure 3. ECMO days best cut-off value for the development of infection.

lar to this. Urinary tract infections, however, were not detected in our patients.

Fungal infections are also frequently seen in the respiratory tract of ECMO patients. In addition, Aspergillus or Candida sp. in the bloodstream have been shown[19] to increase mortality. In our study, fungal infection was not detected in ECMO patients.

Antibiotic prophylaxis is widely used in ECMO centers, despite the lack of conclusive evidence of the benefit of antibiotic use in ECMO and the ELSO Infectious Disease Task Force recommendations[20-22] against this practice. Given that most patients are already taking antimicrobial agents at the start of ECMO, it is debatable whether antibiotics or antifungal prophylaxis are definitively recommended or affect the incidence of nosocomial infections. Although there was no standardization in antibiotic prophylaxis approach in our center formerly, 60.2% of patients had been receiving antibiotics for other purposes at the time of ECMO initiation. This approach may not be applied in the same way in all centers due to the different patient profiles, and the patient's condition at the time of ECMO implantation may predispose to various infections. Therefore, prevention or empirical treatment of patients under ECMO support should be decided by considering the epidemiological characteristics of the center or according to the patient's condition.

Compared to cardiovascular systems, the coexistence of acute or chronic kidney injury, respiratory failure, and sepsis increases the number of procedures, such as mechanical ventilation and CRRT. As a result, critically ill patients are intrinsically susceptible to many complications related to the underlying disease's severity and the need for intensive care treatments. Many of these complications are associated with increased morbidity and mortality and often result in greater resource use, healthcare expenses, and longer ICU lengths of stay[23,24]. However, some of these are potentially preventable, and their incidence rates are used as quality metrics within state-of-the-art ICU settings[25].

Additionally, ECMO patients followed in the ICU are long hospitalized; foreign surfaces are prone to infections. Together with significant bleeding and renal failure, conditions are among the most frequent complications observed in ECMO patients[26,27].

As mentioned above, 26% of ECMO patients had NI in our study, which is higher than reported in the 2011 ELSO registry. An essential difference between our study and those in the ELSO registry is that it comprised a predominantly pediatric population. As a result, the prevalence of infection was higher, with 21% of the adult patients in the ELSO registry, with other institutions reporting a range between 8-45.1% for acquired infections in ECMO patients[7].

Patients who require ECMO support often have multiple health issues and may have undergone invasive procedures, increasing their risk of ECMO-related infections.

In addition to the need for prolonged mechanical ventilation, patients may also require central venous and urinary catheters, contributing to disease risk. The use of IABP during VA ECMO support or CRRT due to hemodynamic conditions further increases the likelihood of ECMO-related infections. Our result was in line with previous studies[28], and we found that prolonged duration of ECMO support, ICU, and length of hospital stay were independent risk factors for ECMO-related NI.

Limitations

It is important to note that our study has some limitations. Firstly, it was designed retrospectively and only included adult patients under ECMO support for respiratory or cardiac failure, cardiogenic shock, or arrest. Therefore, our findings may differ from those of other groups, such as post-cardiotomy or pediatric patients. Additionally, the length of stay in the cardiac ICU and ECMO duration were shorter than in other groups. Furthermore, we only analyzed a relatively small number of patients as we excluded pediatric, bridge-to-transplant, and postcardiotomy patients. However, we aim to address these limitations in future studies by including multicenter, prospective, and similar patient groups.

Conclusions

Nosocomial infections are frequently identified as an essential entity during the ECMO process. The respiratory tract is the most common site of infection. However, bloodstream, urinary tract, and cannula insertion site infections should also be considered. Although antibiotic prophylaxis is still a controversial issue, it is expected that there is a tendency towards routine prophylaxis, and standardized protocols will be established in the future as a result of high-level evidence from prospective studies.

Informed Consent
Consent form was obtained from the patient or relatives before invasive procedures by ECMO team.

Ethics Approval
The study was approved by the Ethical Committee "Istanbul Kosuyolu Yuksek Ihtisas Egitim ve Arastirma Hastanesi Bilimsel Arastirmalar Etik Kurulu" and followed the principles of the Declaration of Helsinki (approval number: 2020/13/391).

Availability of Data and Materials
None.

Conflict of Interest
The authors declare that they have no competing interests.

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Authors' Contributions
ŞK, YUK, and MKK were responsible for drafting, editing, and supervising the manuscript. AK, ŞK, and MEG were responsible for the literature review. AK and SDK were responsible for editing. All authors have read and approved the final manuscript.

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