

# Risk factors and prognosis of nosocomial pneumonia in patients undergoing extracorporeal membrane oxygenation: a retrospective study

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## Abstract

**Objective:** We aimed to examine the risk factors and prognosis of nosocomial pneumonia (NP) during extracorporeal membrane oxygenation (ECMO).

**Methods:** We retrospectively analyzed data of patients who received ECMO at the Affiliated Hangzhou Hospital of Nanjing Medical University between January 2013 and August 2019. The primary outcome was the survival-to-discharge rate.

**Results:** Sixty-nine patients who received ECMO were enrolled, median age 42 years and 26 (37.7%) women; 14 (20.3%) patients developed NP. The NP incidence was 24.7/1000 ECMO days. Patients with NP had a higher proportion receiving veno-venous (VV) ECMO (50% vs. 7.3%); longer ECMO support duration (276 vs. 140 hours), longer ventilator support duration before ECMO weaning (14.5 vs. 6 days), lower ECMO weaning success rate (50.0% vs. 81.8%), and lower survival-to-discharge rate (28.6% vs. 72.7%) than patients without NP. Multivariable analysis showed independent risk factors that predicted NP during ECMO were ventilator support duration before ECMO weaning (odds ratio [OR] = 1.288; 95% confidence interval [CI]: 1.111–1.494) and VV ECMO mode (OR = 10.970; 95% CI: 1.758–68.467).

**Conclusion:** NP during ECMO was associated with ventilator support duration before ECMO weaning and VV ECMO mode. Clinicians should shorten the respiratory support duration for patients undergoing ECMO to prevent NP.

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## Keywords

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## Introduction

Extracorporeal membrane oxygenation (ECMO) is used to support patients with cardiac failure or both cardiac and respiratory failure, despite optimal conventional care, by removing blood from the venous system, oxygenating it, and returning it to either the venous (veno-venous [VV] ECMO) or arterial (veno-arterial [VA] ECMO) system.<sup>1-4</sup> VV ECMO is used to support patients with respiratory failure whereas VA ECMO is used to support patients with cardiac failure or both cardiac and respiratory failure.<sup>1-4</sup> ECMO reduces mortality in adults with severe respiratory distress.<sup>5-9</sup> The use of ECMO in Chinese adult patients has increased rapidly in the past 10 years owing to large-scale multicenter randomized controlled trials (such as the CESAR [conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure] trial) that have been conducted on the treatment of severe respiratory failure.<sup>5,10</sup>

Although ECMO has been used for many decades and the technology is mature, the mortality rate of patients undergoing ECMO is still very high because ECMO is often accompanied by severe complications.<sup>1-4</sup> Among these complications, nosocomial infections result in a high mortality rate.<sup>11,12</sup> Cannulation of the major vessels disrupts the skin barrier protection, and insertion of other invasive devices in addition to ECMO (such as a central venous catheter, endotracheal tube, and urinary catheter) further increases

the risk of nosocomial infection.<sup>12-14</sup> Nosocomial infections in the population of patients undergoing ECMO have been defined as the development of infection either >24 to 48 hours after ECMO cannulation or within 48 to 72 hours of ECMO decannulation.<sup>12,15-17</sup>

Nosocomial infections have been identified as the most prevalent complications among patients undergoing ECMO.<sup>15,18-20</sup> Among those infections, nosocomial pneumonia (NP) represents an important threat to survival in patients undergoing ECMO;<sup>21</sup> however, previous studies examining the specific impact of NP on the prognosis of ECMO have yielded conflicting results. Indeed, NP has been found to be associated with a worse<sup>22,23</sup> as well as a better prognosis.<sup>24</sup>

Differences in ECMO-underlying conditions, comorbidities, and diagnostic methods can lead to large differences in the incidence of NP. Therefore, the aim of this study was to examine the incidence, etiology, risk factors for development, and effects on the prognosis of ECMO-associated NP.

## Methods

### *Study design and patients*

This was a retrospective study of patients who received ECMO at the Department of Critical Care Medicine of the Affiliated Hangzhou Hospital of Nanjing Medical University between January 2013 and

August 2019. This study was approved by the Hangzhou First People's Hospital ethics committee. Because this was a retrospective study, the requirement for informed consent was waived.

The inclusion criterion was the use of ECMO during the study period. The exclusion criteria were: 1) ECMO support duration of <48 hours (because nosocomial infection could not be determined with a short exposure and treatment duration), or 2) diagnosis of bacterial pneumonia or bloodstream bacterial infections before ECMO.

## ECMO

Tubing was inserted aseptically after disinfection using povidone-iodine solution. The ECMO system used during the study period was the Quadrox PLS life support system (Maquet Getinge Group, Rastatt, Germany), which comprises a polymethylpentene oxygenator. Heparin was used as an anticoagulant in all patients. Tubing size and cannulation site were decided by the surgeon based on the weight of the patient and size of the blood vessels. Selection of the ECMO mode was decided by the ECMO team, according to the patient's condition. In general, the VV mode was chosen for respiratory failure caused by the lungs whereas the VA mode was selected with shock caused by the cardiovascular system or by both the cardiovascular and respiratory systems. Cannulations were routinely conducted via the peripheral femoral artery and vein puncture; a few were conducted via a venous and arterial incision. General anesthesia was induced, and ventilator support was used during cannulation. After cannulation, deep sedation and analgesia were induced, or early endotracheal tube removal was performed based on the patient's condition. The management procedure was conducted based on the Extracorporeal Life Support Organization

(ELSO) guidelines.<sup>25</sup> Patients were cannulated in our critical care unit or in the emergency room by the ECMO team, which included one attending vascular surgeon and two attending intensivists.

## Data collection

We collected the following information from patient medical charts: routine pre-ECMO laboratory tests (within 6 hours prior to starting ECMO), Sequential Organ Failure Assessment (SOFA) score,<sup>26</sup> Glasgow Coma Scale (GCS) score<sup>27</sup> (data within 6 hours before ECMO insertion according to the routine clinical protocol), and data on age, sex, body mass index (BMI), smoking status, underlying disease, length of hospitalization before ECMO, length of stay in the intensive care unit (ICU), deep vein catheter duration, pre-ECMO respiratory treatment duration, ECMO type and mode, ECMO support duration, post-ECMO respiratory treatment duration, intra-aortic balloon pump (IABP) during ECMO, continuous renal replacement therapy (CRRT) during ECMO, corticosteroids (methylprednisolone dose) used before and during ECMO, ventilator time before ECMO weaning, blood and blood product transfusion during ECMO, incidence of NP, bacterial pathogens, total length of hospitalization, weaning success rate, and survival-to-discharge rate. ECMO cardiopulmonary resuscitation (ECPR) was defined as extracorporeal life support (ECLS) used as part of initial resuscitation after cardiac arrest; patients who were hemodynamically unstable and placed on ECLS without cardiac arrest were not considered to have received ECPR.<sup>28</sup>

## Outcomes and definitions

The primary outcome was the survival-to-discharge rate, defined as survival and stable on patient discharge. Successful

weaning was defined as survival for >48 hours after weaning from ECMO and without the need to reinitiate ECMO. Infections were diagnosed retrospectively using definitions of the Centers for Disease Control and Prevention National Nosocomial Infections Surveillance System.<sup>29</sup> Nosocomial infection during ECMO support was defined as a case with confirmed organisms from at least one compartment (blood, respiratory, or urinary cultures) during the period after initiation of ECMO to 48 hours after ECMO weaning.<sup>12,15–17</sup> Microbiological isolations were correlated with the clinical symptoms and typical inflammatory characteristics in blood samples and radiographic findings. ECMO-related NP was defined as pneumonia occurring in patients assisted with ECMO for >48 hours or withdrawn from ECMO for <48 hours;<sup>12,15–17</sup> the diagnosis was confirmed by two independent experts. Reinfection episodes were not included in the incidence rate calculation; only one acquired infection at each site per ECMO course was recorded in the study. Patients with ECMO-related NP were included in the NP group; the remaining patients were included in the non-NP group.

### Antibiotics strategy

Prophylactic antibiotics were administered routinely at the initial stage of ECMO. If antibiotics were being administered prior to ECMO, they were continued during ECMO. If infection occurred during ECMO, antibiotics were administered or adjusted based on culture results and clinical conditions. Initial prophylactic antimicrobial treatment was determined by the treating intensivist. Prophylactic antibiotic regimens were documented for all patients between 24 hours prior to ECMO catheterization and 48 hours after ECMO catheterization. The dosage was in accordance with the instructions and guidelines.

We classified the antibiotic regimens into three categories: group 1) with anti-*Pseudomonas aeruginosa* activity; group 2) with anti-*P. aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA) activity; and group 3) all other alternatives.

### Statistical analysis

Categorical variables are expressed as frequency and percentage and were analyzed using the Fisher exact test. Continuous variables are expressed as median (range) and were analyzed using the Mann–Whitney U test for nonparametric data. A logistic regression model was used for univariable and multivariable analyses to determine the independent predictive factors of NP. The variables included in the multivariable analysis were selected based on the results of univariable analysis when  $P < 0.20$ , and a backward stepwise logistic regression model for multivariable analysis was used to determine the independent predictive factors of NP. The statistical analyses were performed using IBM SPSS version 21.0 for Windows (IBM Corp., Armonk, NY, USA). All tests were two-tailed, and a value of  $P < 0.05$  was considered statistically significant.

## Results

### Characteristics of patients

We identified 77 adult patients who received ECMO in the department of Critical Care Medicine, Affiliated Hangzhou Hospital of Nanjing Medical University between January 2013 and August 2019. Five patients were excluded because their ECMO support duration was <48 hours. Three patients had acute respiratory distress syndrome comorbid with bacterial pneumonia prior to ECMO treatment. Therefore, 69 patients who received ECMO owing to cardiopulmonary failure were included in the study.

**Table 1.** Characteristics of included patients.

Characteristics	Patients (n = 69)
Demographic features	
Age (years)	42 (18–77)
Female sex	26 (37.7)
Body mass index (kg/m <sup>2</sup> )	22 (16.5–35.2)
Primary disease	
Myocarditis	40 (58.0)
Coronary heart disease	13 (18.8)
Viral pneumonia	6 (8.7)
Pulmonary contusion	3 (4.3)
Pulmonary arterial hypertension	2 (2.9)
Interstitial pneumonia	1 (1.4)
<i>Aspergillus</i> pneumonia	1 (1.4)
Lung cancer with airway obstruction	1 (1.4)
Aortic dissection	1 (1.4)
Allergic shock	1 (1.4)
Laboratory findings (pre-ECMO)	
White blood cells (10 <sup>3</sup> /mm <sup>3</sup> )	11.5 (2.2–37.7)
Hemoglobin (g/dL)	120 (61–176)
Platelets (10 <sup>3</sup> /mm <sup>3</sup> )	174 (11–857)
C-reactive protein (mg/dL)	32 (1–194)
Lactate (mmol/L)	3.8 (1.0–20.0)
Total bilirubin (μmol/L)	14.6 (4.3–131)
Creatinine (μmol/L)	98.5 (44–466)
ECMO-related information	
Pre-ECMO SOFA score	8 (0–22)
VA mode	58 (84.1)
Pre-ECMO ventilator support (days)	0.1 (0.0–9.2)
Pre-ECMO ICU stay (days)	0.2 (0.1–9.2)
Pre-ECMO hospital stay (days)	0.2 (0.1–14.4)
Ventilator time before ECMO weaning (days)	7 (0–32)
ECMO support time (hours)	154 (55–727)

Categorical variables are expressed as frequency and percentage, and continuous variables are expressed as median (range).

ECMO, extracorporeal oxygenation; SOFA, Sequential Organ Failure Assessment; VA, veno-arterial; ICU, intensive care unit.

Characteristics of the included patients are shown in Table 1. Among the 69 patients, the median age was 42 (18–77) years and 26 (37.7%) patients were women. The length of pre-ECMO hospitalization, length of pre-ECMO stay in the ICU, and duration of pre-ICU respiratory support were 0.2 (0.1–14.4), 0.2 (0.1–9.2), and 0.1 (0.0–9.2) days, respectively. The VA mode was mainly used in 58 (84.1%)

patients, and the VV mode was used in 11 patients (15.9%). The median ECMO support duration was 154 (55–727) hours.

### *ECMO-associated nosocomial pneumonia (NP)*

The prophylactic antibiotic regimens are shown in Table 2. Empiric piperacillin/tazobactam was started in 56 (81.2%) patients,

**Table 2.** Prophylactic antibiotics classification and use.

Regimens	Prophylactic antibiotics	N=69
Anti- <i>Pseudomonas</i> regimen	Piperacillin/tazobactam	32
	Cefoperazone/sulbactam	2
	Meropenem	2
	Imipenem/cilastatin	2
	Piperacillin/tazobactam+moxifloxacin	2
	Moxifloxacin	1
Anti- <i>Pseudomonas</i> and MRSA regimen	Cefoperazone/sulbactam+moxifloxacin	1
	Piperacillin/tazobactam+teicoplanin	6
	Piperacillin/tazobactam+linezolid	6
	Piperacillin/tazobactam+daptomycin	6
	Piperacillin/tazobactam+vancomycin	4
	Imipenem/cilastatin+teicoplanin	1
Other regimens	Cefmetazole	1
	Cefuroxime	1
	Amoxicillin/clavulanic acid	1
	Ceftriaxone	1

Variables are expressed as frequency.

MRSA, methicillin-resistant *Staphylococcus aureus*.

teicoplanin in seven (10.1%), daptomycin in six (8.7%), linezolid in six (8.7%), and vancomycin in four (5.8%) patients. Twenty-six (37.7%) patients received different combinations of antibiotics.

The ECMO weaning success rate and discharge rate of patients who underwent ECMO was 75.4% (n = 52) and 63.8% (n = 44), respectively. Thirty (43.5%) patients developed 43 nosocomial infections. Fourteen (20.3%) patients developed NP. The incidence of NP was 24.7/1000 ECMO days.

Table 3 lists the pathogens involved in NP, all identified from lower respiratory tract sputum culture specimens. The main cause of respiratory tract infection was gram-negative bacteria. The top four causes of NP in descending order were *Klebsiella pneumoniae* (5/14, 35.7%), *Acinetobacter baumannii* (3/14, 21.4%), *Burkholderia cepacia*, and *P. aeruginosa* (2/14, 14.3%).

**Table 3.** Microorganisms causing nosocomial pneumonia during ECMO support (lower respiratory tract sputum culture specimens).

Microorganism species	NP (N=14)
<i>Klebsiella pneumoniae</i>	5 (35.7)
<i>Acinetobacter baumannii</i>	3 (21.4)
<i>Burkholderia cepacia</i>	2 (14.3)
<i>Pseudomonas aeruginosa</i>	2 (14.3)
<i>Escherichia coli</i>	1 (7.1)
<i>Enterobacter aerogenes</i>	1 (7.1)

Categorical variables are expressed as frequency and percentage.

ECMO, extracorporeal membrane oxygenation; NP, nosocomial pneumonia.

### Risk factors and prognosis of patients with and without ECMO-associated NP

Table 4 lists the baseline data of 55 non-NP patients and 14 patients with NP. There were no significant differences between the

**Table 4.** Characteristics of patients with and without nosocomial pneumonia during ECMO.

Risk factors	Non-NP group (N = 55)	NP group (N = 14)	P value
Age (years)	40 (18–77)	45.5 (18–67)	0.403
Female sex	23 (41.8)	3 (21.4)	0.222
BMI (kg/m <sup>2</sup> )	22.0 (16.6–35.2)	22.5 (18.0–32.1)	0.675
Smoking	14 (25.5)	4 (28.6)	>0.999
Primary disease			
Myocarditis	28 (50.9)	4 (28.6)	0.229
Respiratory failure	6 (10.9)	6 (42.9)	0.005
Coronary artery disease	18 (32.7)	2 (14.3)	0.322
Laboratory findings (pre-ECMO)			
White blood cells (10 <sup>3</sup> /mm <sup>3</sup> )	11.5 (2.20–36.7)	10.8 (2.8–37.7)	0.230
Hemoglobin (g/L)	120 (61–176)	119 (70–174)	0.189
Platelets (10 <sup>3</sup> /mm <sup>3</sup> )	180 (76–396)	113.5 (11–857)	0.018
Lactate (mmol/L)	3.8 (1.0–20.0)	3.0 (1.0–19)	0.821
Total bilirubin (μmol/L)	14.6 (4.3–131.0)	14.4 (9.7–63.9)	0.731
Creatinine (μmol/L)	104 (44–466)	92 (55–293)	0.629
CRP (mg/dL)	32 (1–194)	27 (1–176)	0.243
Pre-ECMO data			
ECMO CPR	21 (38.2)	4 (28.6)	0.756
VV ECMO mode	4 (7.3)	7 (50)	0.001
Pre-ECMO SOFA score	8 (0–21)	9 (4–22)	0.182
Length of ICU stay >1 day	11 (20)	7 (50)	0.022
Ventilator duration >1 day	12 (21.8)	8 (57.1)	0.009
Length of hospital stay >1 day	20 (36.4)	10 (71.4)	0.032
Pre-ECMO GCS	15 (3–15)	12.5 (3–15)	0.515
During-ECMO data			
IABP	17 (30.9)	4 (28.6)	>0.999
CRRT	22 (40)	8 (57.1)	0.248
Corticosteroids (mg)	520 (0–2860)	680 (0–3100)	0.342
ECMO support duration (hours)	140 (55–727)	276 (152–624)	<0.001
Before ECMO weaning data			
Ventilator duration (days)	6 (0–21)	14.5 (7–32)	<0.001
Plasma infusion (mL)	800 (0–5890)	1065 (0–3836.3)	0.524
RBC infusion (units)	6 (0–37.5)	13.25 (0–32.5)	0.181
PLT infusion (units)	0 (0–51)	0 (0–65)	0.057
Prognosis data			
ECMO weaning success	45 (81.8)	7 (50.0)	0.014
Length of hospital stay (days)	19 (2–42)	27.5 (15–40)	0.025
Survival-to-discharge rate	40 (72.7)	4 (28.6)	0.004

Corticosteroid was the methylprednisolone dose. If other hormones were used, they were converted to methylprednisolone dose.

Categorical variables are expressed as frequency and percentage, and continuous variables are expressed as median (range).

NP, nosocomial pneumonia; ECMO, extracorporeal membrane oxygenation; BMI, body mass index; COPD, chronic obstructive lung disease; CRP, C-reactive protein; ICU, intensive care unit; CPR, cardiopulmonary resuscitation; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; CRRT, continuous renal replacement therapy; IABP, intra-aortic balloon pump; RBC, red blood cell; PLT, platelets; VV, veno-venous.

two groups in terms of age, sex, BMI, smoking status, primary disease, white blood cells, hemoglobin, lactate, total bilirubin, creatinine, C-reactive protein, ECPR, SOFA scores, GCS scores, IABP, CRRT, corticosteroids, plasma infusion, red blood cell infusion, and platelet infusion. Platelets in the NP group were lower than platelets in the non-NP group (113.5 [11–857] vs. 180 [76–396]  $10^3/\text{mm}^3$ ;  $P=0.018$ ). The proportion of patients in the NP group who received VV ECMO was significantly higher than the proportion in the non-NP group (7 [50%] vs. 4 [7.3%];  $P=0.001$ ). The proportions of patients with ICU stay more than 1 day, ventilator use more than 1 day, and hospitalization longer than 1 day before ECMO initiation were higher in the NP group than these proportions in the non-NP group (7 [50%] vs. 11 [20%];  $P=0.022$ ), (8 [57.1%] vs. 12 [22.8%];  $P=0.009$ ), and (10 [71.4%] vs. 20 [36.4%];  $P=0.032$ ), respectively. ECMO support duration in the NP group was longer than that in the non-NP group (276 [152–624] vs. 140 [55–727] hours;  $P<0.001$ ). The total ventilator support duration (before ECMO weaning) was longer in the NP group than that in the non-NP group (14.5 [7–32] vs. 6 [0–21] days;  $P<0.001$ ). The ECMO weaning success rate was higher in the non-NP group than that in the NP group (45 [81.8%] vs. 7 [50.0%];  $P=0.014$ ). Longer hospitalization was observed in the NP group than in the non-NP group (27.5 [15–40] vs. 19 [2–42] days;  $P=0.025$ ). The survival-to-discharge

rate in the NP group was lower than that in the non-NP group (4 [28.6%] vs. 40 [72.7%],  $P=0.004$ ).

### Multivariable analysis of risk factors for ECMO-associated NP

Pre-selected independent variables were included in the logistic regression analysis. The candidate variables included respiratory failure, hemoglobin, platelets, VV ECMO mode, pre-ECMO SOFA score, pre-ECMO ICU stay, pre-ECMO ventilator duration, pre-ECMO length of hospitalization, ECMO support duration, and ventilator duration before ECMO weaning. Results showed that ventilator duration before ECMO weaning (odds ratio [OR] per day: 1.288; 95% confidence interval [CI]: 1.111–1.494;  $P=0.001$ ) and VV ECMO mode (OR: 10.970; 95% CI: 1.758–68.467;  $P=0.010$ ) were independent risk factors for NP (Table 5).

### Discussion

In the present study, the incidence of ECMO-associated NP was 20.3% ( $n=14$ ). The top four causes of NP were *K. pneumonia*, *A. baumannii*, *B. cepacia*, and *P. aeruginosa*. The proportion of patients who used VV ECMO was higher and ECMO support duration was longer in the NP group than in the non-NP group. Ventilator support duration before ECMO weaning was longer and the ECMO weaning success rate was higher in the non-NP

**Table 5.** Multivariable analysis of risk factors for nosocomial pneumonia.

Variables	Adjusted OR (95% CI)	P value
Ventilator time before ECMO weaning (days)	1.288 (1.111–1.494)	0.001
VV ECMO mode	10.970 (1.758–68.467)	0.010

OR, odds ratio; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; VV, veno-venous.

Variables with  $P<0.20$  in univariable analyses were candidates for multivariable analysis. The candidate variables were respiratory failure, hemoglobin, platelets, VV ECMO mode, pre-ECMO SOFA score, pre-ECMO ICU stay, pre-ECMO ventilator time, pre-ECMO hospital stay, ECMO support duration, and ventilator time before ECMO weaning.



group than in the NP group. The survival-to-discharge rate was lower in the NP group than in the non-NP group. Multivariable analysis showed that ventilator duration before ECMO weaning and VV ECMO mode were the primary independent risk factors for NP. These results suggest that NP during ECMO is associated with ventilator support duration before ECMO weaning and the VV ECMO mode.

Patients who undergo ECMO have multiple factors that increase the risk of nosocomial infection. Mechanical ventilation, central venous access, urinary catheterization, ECMO insertion via surgical routes, use of sedative and analgesic drugs, and decreased immunity are all factors that increase the risk of infection.<sup>12–14</sup> Therefore, the incidence of nosocomial infection is higher in these patients than in patients in the ICU who are not receiving ECMO. The reported incidence of NP during ECMO is 8.7% to 64%.<sup>17,30–32</sup> Schmidt et al.<sup>30</sup> analyzed 220 patients with cardiogenic shock in France to determine the incidence and pathogens involved; they found that the incidence of ventilator-associated pneumonia (VAP) was 55.4 infections/1000 ECMO days. The pathogens and incidence of nosocomial infections in that study were similar to those in the present study, but the ventilator duration was longer in the previous report. Thus, NP incidence was higher in that study than in the present one. We found that the main pathogen causing ECMO-associated NP was Gram-negative bacteria, which is similar to previous studies.<sup>17,30,31,33</sup> Infectious complications of ECMO are associated with increased mortality and morbidity. Among patients undergoing ECMO, nosocomial infections increase the risk of death by 38% to 63%.<sup>34,35</sup> We also observed a higher mortality rate in our study; at the same time, the ECMO weaning success rate was decreased.

The VV ECMO modality is associated with an increased risk of infectious complications, in comparison with VA ECMO.<sup>16</sup> We reached a similar conclusion in the present study. The likelihood of infection with the VV modality was higher, which may be owing to longer ECMO treatment and ventilator support duration in patients receiving VV ECMO.

Similarly, the present study showed that ECMO support duration is a risk factor for infection, which has been reported in previous studies to be the most important risk factor for infection during ECMO.<sup>17,30,32–35</sup> We also observed that the ECMO support duration was associated with NP. As our sample size was small, we were unable to show that the ECMO support duration was an independent risk factor for NP.

Notably, the occurrence of infection may delay weaning from ECMO, and longer ECMO courses are likely to increase the risk of infection. Ventilator support is both the cause and result of NP. Bataillard et al.<sup>36</sup> studied 178 patients who received ECMO, among which 41 patients underwent early extubation; the incidence of VAP in these 41 patients was 5% vs. 15% ( $P=0.11$ ), in comparison with non-extubated patients; the incidence of VAP in these 41 patients was 5% vs. 28% ( $P=0.001$ ), in comparison with patients who were not extubated without a determined cause. This suggests that the incidence of VAP is lower in patients who receive early extubation. Similar findings have been obtained in other studies.<sup>37–39</sup> The reason for ventilator support duration affecting the occurrence of VAP may be owing to deep sedation and analgesia and the use of invasive procedures.

The primary aim of using a ventilator in patients receiving VA ECMO is to prevent pulmonary edema caused by circulatory failure, to strengthen sedation, and to reduce risk of the ECMO tube pulling out or twisting, leading to bleeding or

obstruction.<sup>1-4</sup> To achieve these goals, as few extubations as possible are conducted before ECMO weaning. Therefore, NP during ECMO generally does not affect the duration of ventilator use. The present study confirmed that the duration of mechanical ventilation before ECMO weaning was an independent risk factor for NP. These results suggest that we should evaluate the role of mechanical ventilation in patients receiving ECMO support. Ventilator weaning during ECMO may be one method to reduce ECMO-associated NP and mortality;<sup>37,40,41</sup> however, under permissible situations, ECMO support should be used alone.

In this study, six patients had viral pneumonia, and one had *Aspergillus* pneumonia. It is important to distinguish these entities from ECMO-associated NP so as to provide adequate treatment. The patients with viral pneumonia were diagnosed using PCR and antigen detection when they were admitted to the hospital, together with their medical history, clinical manifestations, laboratory tests, and imaging tests. Aspergillosis was detected by sputum smear, culture, and alveolar lavage galactomannan antigen assay during hospitalization, and the diagnosis was confirmed using the combination of medical history, clinical manifestations, laboratory tests, and imaging examinations.

The present study has several limitations. First, this was a single-center retrospective study, and more meaningful conclusions could be obtained owing to the small sample size. ECMO support duration was significantly associated with NP, but regression analysis showed that ECMO support duration was not an independent factor; this may be owing to the small sample size. Second, some patients received VV ECMO. Although this allowed us to compare the differences between VV ECMO and VA ECMO, this introduced some heterogeneity in disease etiology, and

interventions may increase the confounding factors. Third, although the ELSO does not recommend the use of antibiotics during ECMO,<sup>25,42</sup> the inadequate isolation conditions in our ICUs and relatively high nosocomial infections led to our decision to provide antibiotic prophylaxis. Fourth, underlying lung disease was also likely to be a factor involved in NP; however, confirmation of this was impossible because of the small sample size.

In this study, the main cause of the high occurrence of NP during ECMO was gram-negative bacteria. The occurrence of NP during ECMO was associated with ventilator support duration before ECMO weaning and VV ECMO mode. NP during ECMO is associated with poor outcomes; therefore, clinicians should assess the possibilities of ventilator weaning during VA ECMO support and of shortening the ventilator duration in patients receiving ECMO.

### Authors' contributions

WJR conceived and supervised the study; HW designed investigation; CXY collected the data; HWH and ZY analyzed the data; WJR wrote the manuscript; HJY made manuscript revisions. All authors reviewed the results and approved the final version of the manuscript.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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