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Original Research

Incidence, outcomes and risk factors of barotrauma in veno-venous extracorporeal membrane oxygenation for acute respiratory distress syndrome

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ABSTRACT

Background: Although acute respiratory distress syndrome (ARDS) patients are provided a lung rest strategy during extracorporeal membrane oxygenation (ECMO) treatment, the exact conditions of barotrauma is unclear. Therefore, we analyzed the epidemiology and risk factors for barotrauma in ARDS patients using ECMO in a single, large ECMO center in China.

Methods: A retrospective analysis was performed on 127 patients with ARDS received veno-venous (VV) ECMO who met the Berlin definition. The epidemiology and risk factors for barotrauma during ECMO were analyzed.

Results: Among 127 patients with ARDS treated with ECMO, barotrauma occurred in 24 (18.9%) during ECMO and 9 (7.1%) after ECMO decannulation, mainly in the late stage of ARDS (75%) and ≥8 days during ECMO (54.2%). Univariate and multivariate analyses showed that younger ARDS patients (OR = 0.953, 95%CI 0.923–0.983, p = 0.003) and those with pneumocystis jirovecii pneumonia (PJP) (OR = 3.15, 95%CI 1.070–9.271, p = 0.037), elevated body temperature after establishing ECMO (OR = 2.997, 95%CI 1.325–6.779, p = 0.008) and low platelet count after establishing ECMO (OR = 0.985, 95%CI 0.972–0.998, p = 0.02) had an increased risk of barotrauma during ECMO. There was no difference in ventilator parameters between patients with and without barotrauma. Barotrauma during ECMO was mainly related to the etiology of the disease and disease state.

Conclusion: There is a high incidence of barotrauma in ARDS patients during ECMO, even after ECMO decannulation. Young age, PJP, elevated body temperature and low platelet count after establishing ECMO are risk factors of barotrauma, and those patients should be closely monitored by imaging, especially in the late stage of ARDS.

1. Introduction

Acute respiratory distress syndrome (ARDS) is a relatively common fatal or crippling syndrome in critically ill patients [1]. Due to the heterogeneity of ARDS patients, the development of treatments and strategies has become very complex. One challenging therapeutic aspect is that mechanical ventilation may perpetuate lung injury because of overdistention of ventilated lung units and repetitive opening and

Abbreviations: ARDS, Acute respiratory distress syndrome; ECMO, Extracorporeal membrane oxygenation; PJP, Pneumocystis jirovecii pneumonia; BMI, Body mass index; VT, Tidal volume; MV, Minute ventilation; PIP, Peak inspiratory pressure; FIO_2, Fraction of inspired oxygen; RR, Respiratory rate; Pplat, Plateau pressure; OI, Oxygenation index; WBC, White blood cell; Neu, Neutrophile granulocyte; Lym, Lymphocyte; CRP, C-reactive protein; PCT, Procalcitonin; BNP, Brain natriuretic peptide; PT, Prothrombin time; NPPV, Noninvasive positive pressure ventilation; IPPV, Invasive positive pressure ventilation; COPD, Chronic Obstructive Pulmonary Disease; PP, Prone position; PEEP, Positive end expiratory pressure; VILI, Ventilator-induced lung injury; SARS, Severe acute respiratory syndrome.

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closing of other lung units [2]. Studies have found that ARDS patients are at high risk of barotrauma [3]; an early study showed that the overall incidence of barotrauma in patients with mechanical ventilation was 24.5%, especially in patients with ARDS (66%), with high mortality and poor prognosis after the development of mediastinal emphysema and pneumothorax [4]. Later, after lung protective ventilation was proposed, compared with traditional ventilation strategies, the incidence of barotrauma was significantly reduced. Boussarsar's study analyzed a series of ARDS-related studies and found that between 1994 and 2000, the incidence of ARDS barotrauma was approximately 0%–49% [5]. One approach to avoiding the potentially injurious aspects of mechanical ventilation is extracorporeal membrane oxygenation (ECMO) [6]. Some evidence supports the increasing efficacy and safety of ECMO in ARDS patients [7]. The EOLIA randomized controlled trial published in 2018 did not show a significant difference in its prespecified primary endpoint of 60-day mortality between the ECMO group and the control group receiving conventional mechanical ventilation [6]. However, a post hoc Bayesian analysis of EOLIA data showed a high probability of a survival benefit from ECMO [8]. A meta-analysis also showed that ECMO is effective in some adult patients with severe ARDS [9].

Major advances have been made in the past few years regarding the technology of ECMO circuits [10]. ECMO is thought to reduce lung injury even further by facilitating the application of very low tidal volumes and airway pressures and reducing the respiratory rate, an approach sometimes referred to as "lung rest" [11–14], and may be of particular benefit to severe ARDS patients. However, a number of problems following from ECMO cannot be ignored; specifically, the matter of barotrauma during ECMO has received little attention and been the subject of few studies. In an international clinical trial in 2018, the incidence was shown to be approximately 14% [6]. We found in recent years, barotrauma during ECMO use in ARDS patients has remained common in clinical practice, and some patients still suffer from barotrauma after ECMO decannulation. At present, most studies have mainly focused on barotrauma in ARDS patients during mechanical ventilation alone, without considering the incidence during ECMO treatment. Therefore, the purpose of this study was to report the epidemiology and associated high-risk factors for barotrauma during ECMO in ARDS patients in a large ECMO center in China.

2. Methods

2.1. Patients

This retrospective single-center study enrolled patients older than 14 years who met the Berlin definition of ARDS and required veno-venous (VV) ECMO treatment in China-Japan Friendship Hospital from December 2013 to December 2021. We excluded patients with COVID-19.

The study was conducted in accordance with the amended Declaration of Helsinki of 2013. Given the retrospective nature and the non-interventional design of the study, informed consent was waived.

2.2. Data

Age, sex, body mass index (BMI), previous history, infection type, ventilator parameters, ventilation mode, status before ECMO, status during ECMO, laboratory examination results, organ failure, complications and prognosis were recorded. The included patients were specifically evaluated for the occurrence of barotrauma, barotrauma type, barotrauma occurrence period, pathogen infection type, prone position, tidal volume (VT), peak inspiratory pressure (PIP), fraction of inspired oxygen (FIO_2), minute ventilation (MV), respiratory rate (RR), plateau pressure (Pplat), vital signs, pH, partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2), bicarbonate (HCO_3), lactate (LAC), oxygenation index (OI), white blood cells (WBC), hemoglobin (HB), neutrophile granulocytes (Neu), lymphocytes (Lym), platelets (PLT), procalcitonin (PCT), C-reactive protein (CRP), brain natriuretic peptide (BNP), D-Dimer, prothrombin time (PT), noninvasive positive pressure ventilation (NPPV) and invasive positive pressure ventilation (IPPV) time before ECMO, length of stay at other hospitals, onset time before ECMO, RESP score, PRESERVE score, APACHE II score, SOFA score, Murray score, lung compliance, tracheostomy, days of awake ECMO, use of vasoactive drugs, invasive ventilation mode, noninvasive ventilation mode, high-flow nasal cannula oxygen, ECMO weaning adverse events, hospital-acquired infection, kidney failure, circulatory failure, hepatic failure, hematologic failure, central nervous system failure, mechanical complications, bleeding complications, neurological complications, metabolic block, renal complications, total ECMO run time, invasive ventilation time, length of ICU stay, length of hospital stay, total ICU costs, total hospital costs, in-hospital mortality, and six-month follow-up mortality.

2.3. Statistical analysis

The SPSS 23.0 and R 4.1.0 statistical software packages were used for data analysis. If the measurement data had a normal distribution and homogeneity of variance, they were expressed as the mean and standard deviation (SD). Two-independent samples T tests were used for comparisons between two groups. If continuous data did not demonstrate a normal distribution or variance, they are expressed as the median and interquartile range, and the nonparametric Mann–Whitney *U* test was used for comparisons between two groups. Categorical data are expressed as numbers and percentages, and the chi-square test was used to compare ratios in each group. Univariate and multivariate logistic regression analyses were used to investigate the risk factors for barotrauma during ECMO, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of included patients

A total of 127 ECMO patients with ARDS were included in the study. Twenty-one patients (16.5%) had barotrauma before ECMO. Barotrauma occurred in 33 patients (26.0%) after establishing ECMO, including 24 (18.9%) during ECMO and 9 (7.1%) after ECMO decannulation. There was no barotrauma in 73 patients (57.5%).

Among the 24 patients with barotrauma during ECMO, pneumothorax occurred in 18 (75%), including 7 with bilateral pneumothorax, 2 with left pneumothorax, and 9 with right pneumothorax. Subcutaneous emphysema was observed in 16 patients (66.67%). Thirteen (54.17%) had mediastinal emphysema. Three patients (12.5%) had interstitial emphysema, 2 bilateral and 1 right. Six patients (25%) had barotrauma within 7 days after ARDS onset, 5 patients (20.8%) had barotrauma within 8–14 days after ARDS onset, and 13 patients (54.2%) had barotrauma more than 14 days after ARDS onset. Barotrauma occurred 8 days or more after the onset of ARDS in 75.0% of patients, with an average of 18.7 days (fibrosis stage) and a median of 13.5 days. In patients with barotrauma during ECMO, 11 (45.8%) experienced barotrauma within 7 days after establishing ECMO, 7 (29.2%) 8–14 days after establishing ECMO, and 6 (25.0%) more than 14 days after establishing ECMO. Barotrauma occurred at or more than 8 days after establishing ECMO, accounting for 54.2% of patients. The average time after establishing ECMO for the development of barotrauma was 11.4 days, and the median was 8.5 days.

After ECMO decannulation, 9 ARDS patients developed barotrauma, including 5 pneumothorax (55.6%), 0 bilateral pneumothorax, 2 left pneumothorax, and 3 right pneumothorax. Subcutaneous emphysema was observed in 4 patients (44.4%). Mediastinal emphysema was present in 4 patients (44.4%). Two patients (22.2%) had interstitial emphysema, 1 bilateral and 1 right lung. The mean duration of ECMO use in patients with barotrauma after ECMO was 13.4 days, and the

median was 10 days. The average time of occurrence of barotrauma after ECMO decannulation was 8.3 days, with a median of 7 days. The mean age of patients with barotrauma after ECMO decannulation was 56 years, and the median age was 60 years. Seven (77.8%) were male, and two (22.2%) were female. Barotrauma occurred on average 26.2 days after the onset of ARDS, with a median of 23 days. Among these patients, 0% had barotrauma within 7 days after the onset of ARDS, 1 (11.1%) had barotrauma within 8–14 days, and 8 (88.9%) had barotrauma over 14 days. The mean time of total invasive ventilation was 36.8 days, and the median time was 21 days. The mean and median length of ICU stay were 30 days and 30 days, respectively. The mean length of hospitalization was 43.6 days, and the median length was 32.5 days. The average hospitalization cost was 628212.3 Chinese yuan, and the median cost was 562369.0 Chinese yuan. There were 6 (66.7%) deaths and 3 (33.3%) survivors in the hospital.

There were 97 patients with or without barotrauma during ECMO. Details of the patient characteristics are provided in Table 1. Of note, the median age of patients with barotrauma was 38 years old, and that of patients without barotrauma was 54 years old; the difference was statistically significant ($P < 0.05$). There were more male patients than female patients in both groups, but there was no sex difference between the two groups ($P > 0.05$). In the barotrauma group, the proportion with PJP was significantly higher than that in the no barotrauma group ($P < 0.05$). The total duration of ECMO, total invasive ventilation time, length of ICU stay, length of hospital stay, ICU cost and hospitalization cost were significantly higher in the barotrauma group than in the no barotrauma group ($P < 0.05$). There was no significant difference between the two groups in in-hospital mortality or six-month follow-up mortality ($P > 0.05$).

BMI: Body mass index; PJP: Pneumocystis jirovecii pneumonia; PP: Prone position; COPD: Chronic Obstructive Pulmonary Disease; PEEP: Positive end expiratory pressure; VT: Tidal volume; MV: Minute ventilation; FIO_2: Fraction of inspired oxygen; PIP: Peak inspiratory pressure; RR: Respiratory rate; NPPV: Noninvasive positive pressure ventilation; T: Temperature; Pplat: Plateau Pressure; IPPV: Invasive positive pressure ventilation;

Some variables have missing values, and the superscript letters represent the actual analysis sample size for the variable. a: n = 96; b: n = 84; c: n = 60; d: n = 55; e: n = 65; f: n = 89; g: n = 88; h: n = 87; i: n = 54; j: n = 91; k: n = 90; l: n = 75; m: n = 48; n: n = 93; o: n = 85; p: n = 54; q: n = 94; r: n = 36; s: n = 28; t: n = 81; u: n = 95; v: n = 77; w: n = 59.

3.2. Vital signs and respiratory and hemodynamic variables

Temperature, RR, heart rate (HR), mean arterial pressure (MAP), VT, PEEP, MV, PIP, FIO_2, Pplat, driving pressure, ventilation mode; pH, PCO_2, PO_2, HCO_3, LAC, OI, WBC, Neu, Lym, HB, PLT, CRP, PCT, BNP, D-Dimer, and PT were collected 6 h before ECMO and 1–7 days during ECMO **(supplementary materials Tables S1–S28).** After the establish of ECMO, the median body temperature of ARDS patients decreased from 37.9 °C to 36.8 °C. The MAP increased from 77 mmH_2O to 83 mmH_2O. On the 4th and 6th days during ECMO, the body temperature of patients with barotrauma was higher than that of those without barotrauma ($P < 0.05$). The RR of patients with barotrauma during ECMO was higher than that of patients without barotrauma on day 1 during ECMO ($P < 0.05$). There was no difference in the MAP between the two groups ($P > 0.05$). After the initiation of ECMO, the median VT decreased from 6.2 ml/kg to 4.1 ml/kg. The median MV decreased from 10.5 L/min to 3.8 L/min. The median PEEP decreased from 12 cmH_2O to 10 cmH_2O. The median PIP decreased from 26.0 cmH_2O to 22.0 cmH_2O. The median FIO_2 decreased from 100% to 50%. There were no differences in VT, MV, PEEP, PIP, FIO_2, Pplat and driving pressure between patients with and without barotrauma during ECMO ($P > 0.05$). On the third day during ECMO, PCO_2 in the barotrauma group was higher than that in the no barotrauma group ($P < 0.05$). On day 4 during ECMO, PO_2 in the barotrauma group was lower than that in the no barotrauma group ($P < 0.05$). On days 4 and 7 during ECMO, HCO_3 in the barotrauma group was significantly higher than that in the no barotrauma group ($P < 0.05$). The PLT count of the group with barotrauma during ECMO was significantly lower than that of the group without barotrauma at days 3, 4 and 5 during ECMO ($P < 0.05$). No significant difference was found in other parameters between the two groups ($P > 0.05$) (Fig. 1A–I).

3.3. Analysis of risk factors for barotrauma during ECMO

We further explored the risk factors for barotrauma during ECMO. The results of univariate analysis of factors associated with the risk of barotrauma during ECMO are shown in Table 2 (body temperature, RR, PCO_2, PO_2, HCO_3, and PLT were selected the first day during ECMO with a significant difference between the two groups). In short, for ARDS patients with young age, PJP, elevated body temperature and low platelets during ECMO, the risk of barotrauma was increased during ECMO treatment. After the four factors were included in the multivariate analysis **(Table 3)**, the P values were all <0.05. When we conducted age adjustment to account for the potential impact of age differences on the study outcome, these characteristics were still present **(Table 4).**

4. Discussion

ECMO uses an ultraprotective ventilation strategy involving low-volume, low-pressure ventilation designed to reduce ventilator-induced lung injury (VILI). For patients with severe ARDS, VV-ECMO can not only replace lung function to improve gas exchange but also allow the lungs to rest and reduce lung damage. In theory, the incidence of barotrauma should be low, but our study found a relatively high incidence in ARDS patients, 18.9% during ECMO and 7.1% after ECMO decannulation. Terzi et al. also noted that although in severe ARDS patients, the application of ECMO allows a reduction in peak and mean airway pressures, tidal volumes, ventilator rate, minute volume and inspiratory oxygen concentration, pneumothorax remains one of the most frequent complications [15]. In our study, although there was no statistically significant difference in mortality between the barotrauma group and the no barotrauma group ($P > 0.05$), barotrauma was not found to be a poor prognostic marker. Patients with barotrauma were more likely to have bleeding complications during ECMO than patients without barotrauma, and the total running time of ECMO, total invasive ventilation time, ICU stay time, hospital stay time, ICU stay cost, and hospital stay cost were higher ($P < 0.05$). This demonstrates the urgent need to focus on the possibility of barotrauma during ECMO. The occurrence of barotrauma after ECMO decannulation also suggests that the timing of weaning should be reconsidered and delayed if necessary.

In an earlier study by Gattinoni et al., the incidence of pneumothorax in 84 ARDS patients was 48.8%, and the incidence of pneumothorax in the early, middle and late stages was 30%, 46%, and 87%, respectively [16]. In our study, we found that within 7 days after the onset of ARDS, barotrauma occurred during ECMO in 25% of patients, 8–14 days after the onset of ARDS in 20.8%, and more than 14 days after the onset of ARDS in 54.2%. In general, barotrauma occurring 8 or more days after the onset of ARDS accounted for 75.0% of all patients with barotrauma, with an average of 18.7 days and a median of 13.5 days. Thus, barotrauma often occurs at a later stage of ARDS. One study found that 64% of ARDS patients developed histopathological changes characterized by fibrosis within 12 days of onset [17]. We also found that barotrauma was more likely to occur during the fibrotic phase of ARDS. ARDS develops into pulmonary fibrosis at a later stage, with reduced lung compliance. In addition, ECMO can control the respiratory drive for chronic respiratory diseases such as COPD or for patients waiting for lung transplantation, but for ARDS patients, the respiratory drive is still strong during ECMO, and the greater the transpulmonary pressure is, the higher the risk of lung injury [18]. The lungs of ARDS patients have a

Table 1
Baseline characteristics and comparison between patients with and without barotrauma during ECMO.

Characteristics	No Barotrauma (n = 73)	Barotrauma (n = 24)	P value
Age (years), median [IQR]	54.0 [40.0,64.0]	38.0 [30.0,52.0]	**0.003**
Sex, n (%)			0.772
Men	48 (65.8%)	15 (62.5%)	
Women	25 (34.2%)	9 (37.5%)	
BMI, median [IQR][a]	24.8 [21.6,27.8]	23.9 [21.6,26.7]	0.542
Hypertension, n (%)	26 (35.6%)	3 (12.5%)	0.320
Diabetes, n (%)	17 (23.3%)	7 (29.2%)	0.563
Heart failure, n (%)	3 (4.1%)	0 (0.0%)	0.313
Chronic kidney disease, n (%)	2 (2.7%)	3 (12.5%)	0.061
COPD, n (%)	1 (1.4%)	0 (0.0%)	0.564
Asthma, n (%)	2 (2.7%)	1 (4.2%)	0.726
Tuberculosis, n (%)	2 (2.7%)	1 (4.2%)	0.726
Cancer, n (%)	4 (5.5%)	0 (0.0%)	0.242
Cerebrovascular disease, n (%)	3 (4.1%)	0 (0.0%)	0.313
Surgery, n (%)	19 (26.0%)	8 (33.3%)	0.488
Using hormones and/or immunosuppressants, n (%)	28 (38.4%)	9 (37.5%)	0.940
Smoking, n (%)	28 (38.4%)	7 (29.2%)	0.416
Drinking, n (%)	15 (20.5%)	2 (8.3%)	0.321
Viral infection, n (%)	46 (63.0%)	17 (70.8%)	0.563
Bacterial infection, n (%)	7 (9.6%)	3 (12.5%)	0.684
PJP, n (%)	10 (13.7%)	8 (33.3%)	**0.032**
Fungal non-PJP infection, n (%)	15 (20.5%)	9 (37.5%)	0.986
Atypical pathogens infection, n (%)	8 (11.0%)	0 (0.0%)	0.090
PP was not implemented before ECMO, n (%)	46 (63.0%)	11 (45.8%)	0.138
PEEP before ECMO (cmH_2O), median [IQR][b]	12.000 [8.000,14.000]	10.000 [6.000,12.000]	0.150
VT before ECMO (ml/kg), median [IQR][c]	5.935 [4.748,7.678]	6.640 [5.295,8.720]	0.359
MV before ECMO (L/min), median [IQR][d]	10.500 [8.700,14.200]	8.600 [7.000,13.200]	0.395
PIP before ECMO (cmH_2O), median [IQR][e]	26.000 [22.000,30.000]	26.000 [22.000,29.000]	0.897
FIO_2 before ECMO (%), median [IQR][f]	100.000 [100.000,100.000]	100.000 [95.000,100.000]	0.450
RR before ECMO (bpm), median [IQR][g]	28.000 [22.000,33.000]	30.000 [25.000,36.000]	0.186
Pplat before ECMO (cmH_2O), median [IQR][e]	24.000[22.000,28.000]	25.000[20.000,27.000]	0.844
Driving pressure before ECMO (cmH_2O), median [IQR][e]	14.000[10.464,18.972]	15.000[12.530,22.000]	0.266
T before ECMO (°C), median [IQR][h]	37.800 [36.800,38.500]	38.000 [37.100,39.000]	0.379
NPPV before ECMO (days), median [IQR][i]	2.0 [1.0,5.0]	1.0 [1.0,4.0]	0.229
IPPV before ECMO (hours), median [IQR][h]	40.0 [16.0,94.0]	72.0 [10.0,96.0]	0.450
Ventilation time before ECMO (hours), median [IQR]	63.0 [38.0,144.0]	96.0 [33.0,144.0]	0.558
Length of stay at other hospitals (days), median [IQR]	3.0 [1.0,7.0]	6.0 [1.0,8.0]	0.226
Onset time before ECMO (days), median [IQR]	11.0 [7.0,17.0]	12.0 [10.0,19.0]	0.503
Oxygenation index 6 h before ECMO, median [IQR][l]	68.8 [59.1,84.2]	64.0 [50.7,93.8]	0.554
RESP score, median [IQR]	1.0 [-1.0,4.0]	2.0 [0.0,4.0]	0.375
PRESERVE score, median [IQR]	5.0 [3.0,6.0]	4.000 [3.0,5.0]	0.371
APACHE II score 6 h before ECMO, median [IQR][j]	18.0 [12.0,22.0]	17.0 [12.0,22.0]	0.985
APACHE II score 24–48 h during ECMO, median [IQR][k]	13.0 [8.0,17.0]	14.0 [10.0,18.0]	0.624
SOFA score 6 h before ECMO, median [IQR][n]	9.0 [6.0,12.0]	9.0 [7.0,10.0]	0.623
SOFA score 24–48 h during ECMO, median [IQR][k]	9.0 [6.0,13.0]	10.0 [7.0,12.0]	0.825
RASS score, median [IQR][o]	−1.000[-1.000,0.000]	−1.000[-1.000,0.000]	0.923
Compliance, n (%)[p]			0.848
20–39 ml/cmH_2O	18 (24.7%)	6 (25.0%)	
<19 ml/cmH_2O	14 (19.2%)	4 (16.7%)	
Tracheostomy, n (%)[q]	11 (15.1%)	6 (25.0%)	0.857
Time to start ECMO treatment after admission to ICU (days), median [IQR]	2.0 [1.0,4.0]	1.0 [0.0,5.0]	0.450
Awake ECMO, n (%)[r]	24 (32.9%)	8 (33.3%)	0.478
Days of awake ECMO, median [IQR][s]	6.0 [2.0,10.0]	10.0 [5.0,20.0]	0.136
Vasoactive drugs, n (%)	62 (84.9%)	19 (79.2%)	0.509
NPPV use during ECMO, n (%)	18 (24.7%)	3 (12.5%)	0.210
PP during ECMO, n (%)	21 (28.8%)	11 (45.8%)	0.123
ECMO weaning adverse events, n (%)	13 (17.8%)	4 (16.7%)	0.898
Hospital-acquired infection, n (%)	33 (45.2%)	15 (62.5%)	0.142
Kidney failure, n (%)	34 (46.6%)	12 (50.0%)	0.771
Circulatory failure, n (%)	44 (60.3%)	14 (58.3%)	0.866
Hepatic failure, n (%)	19 (26.0%)	7 (29.2%)	0.763
Hematologic failure, n (%)	21 (28.8%)	7 (29.2%)	0.970
Central nervous system failure, n (%)	22 (30.1%)	5 (20.8%)	0.378
Mechanical complications, n (%)	29 (39.7%)	11 (45.8%)	0.598
Bleeding complications, n (%)	34 (46.6%)	17 (70.8%)	**0.039**
Neurological complication, n (%)	14 (19.2%)	5 (20.8%)	0.859
Metabolic block, n (%)	32 (43.8%)	12 (50.0%)	0.599
Renal complications, n (%)	41 (56.2%)	14 (58.3%)	0.852
Total ECMO run time (days), median [IQR][a]	9.0 [4.0,13.0]	29.0 [14.0,44.0]	**<0.001**
Invasive ventilation time (days), median [IQR][t]	12.0 [7.0,18.0]	39.0 [17.0,57.0]	**<0.001**
Length of ICU stay (days), median [IQR][u]	16.0 [9.0,24.7]	35.4 [20.0,54.0]	**0.001**
Length of hospital stay (days), median [IQR][a]	16.0 [10.0,29.0]	43.0 [29.0,83.0]	**<0.001**
Total ICU costs (Chinese yuan), median [IQR][v]	299992.0 [202937.0,431513.0]	685641.0 [311980.0,885937.9]	**0.009**
Total hospital costs (Chinese yuan), median [IQR][w]	291306.6 [179436.0,431513.0]	743450.0 [311980.0,893348.8]	**0.003**
In-hospital mortality, n (%)	43 (58.9%)	15 (62.5%)	0.755
Six-month follow-up mortality, n (%)[j]	48 (68.6%)	16 (76.2%)	0.503

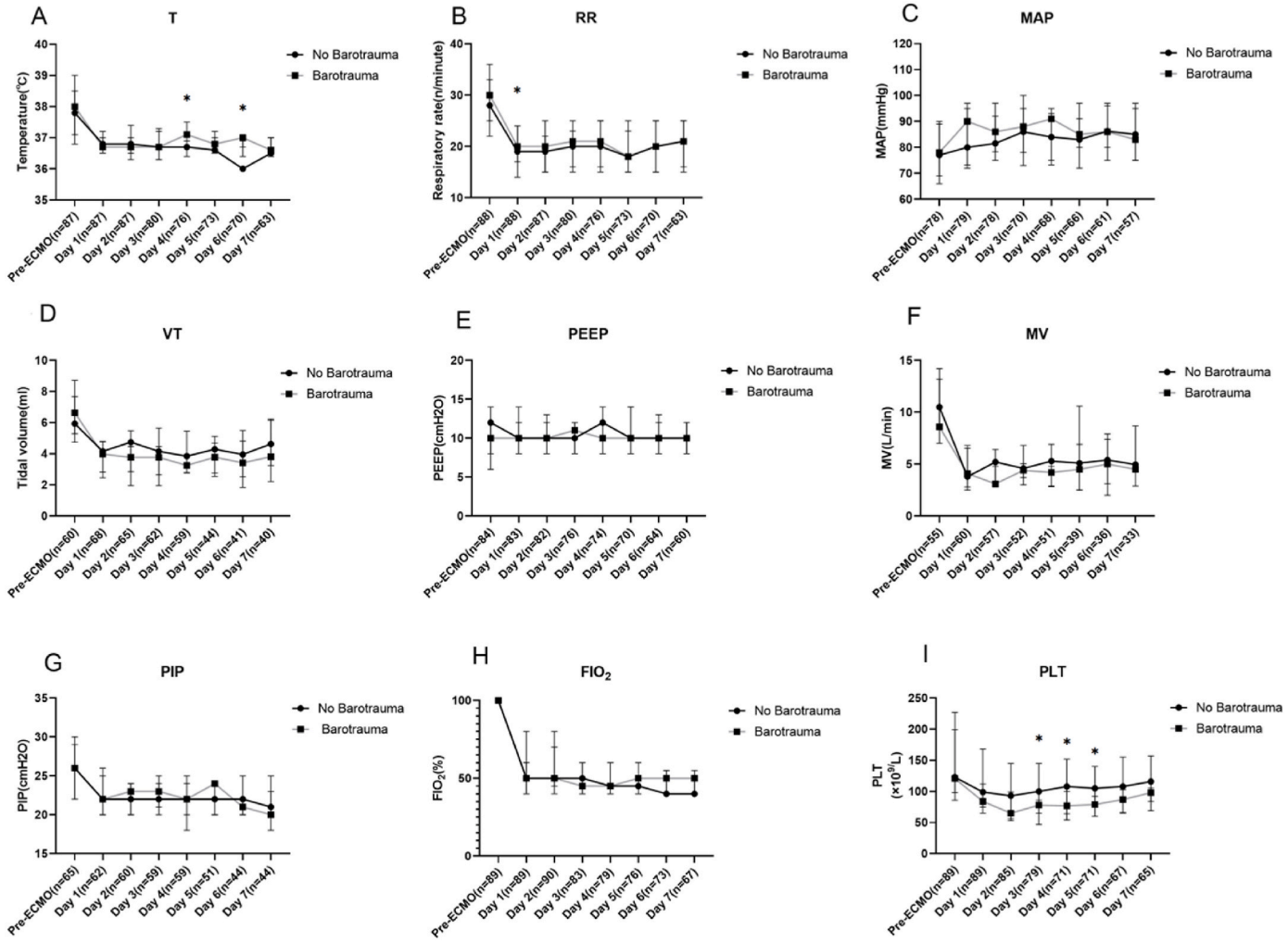

Fig. 1. Some continuous dynamic variables were compared between the barotrauma group and the no barotrauma group. A: Body temperature before and during ECMO. B: RR before and during ECMO. **C**: MAP before and during ECMO. D: VT before and during ECMO. E: PEEP before and during ECMO. F: MV before and during ECMO. G: PIP before and during ECMO. H: FIO_2 before and during ECMO. I: PLT before and during ECMO.
*: The difference between the two groups was statistically significant ($P < 0.05$)
T: Temperature; RR: Respiratory rate; MAP: Mean arterial pressure; VT: Tidal volume; PEEP: Positive end expiratory pressure; MV: Minute ventilation; PIP: Peak inspiratory pressure; FIO_2: Fraction of inspired oxygen; PLT: Platelet.

markedly heterogeneous distribution on chest CT, with patchy infiltrates interspersed with normal lung tissue, resulting in multicompartmental lungs. This variable lung structure and function over time may be described as restrictive lung disease with superimposed emphysema-like lesions in the late stage of ARDS. The structure and function of the lung are more complicated in the late stage, and the incidence of barotrauma is increased [16].

Ventilator-induced lung injury (VILI) is the result of the interaction between mechanical ventilation and the lung parenchyma and is caused by excessive mechanical stress or strain in the lung parenchyma. The etiology of VILI should consider both mechanical ventilation and lung pathophysiology/mechanics [19]. With the deepening of mechanical ventilation research, both clinicians and respiratory therapists are very cautious about the setting of ventilator parameters and perform strict ultraprotective ventilation during ECMO. In our study, no correlation was found between barotrauma and ventilator parameters during ECMO, and we found that the occurrence of barotrauma was mainly related to disease etiology and disease severity. In risk factor analysis, we found that younger age, PJP, hyperthermia and low platelets during ECMO were high-risk factors for barotrauma during ECMO in ARDS patients. In our clinical experience, young ARDS patients are more prone to agitation during ECMO treatment. Compared with elderly patients, they have an advantage in strength and often need greater sedation, which results in more difficult restraint management, thus placing these patients at increased risk of barotrauma compared with older patients. Choi et al. found that PJP patients with acute respiratory failure were prone to developing pneumothorax during treatment [20]. The pathogenesis of pneumothorax in PJP is unclear but was suggested to involve tissue destruction from direct tissue toxicity by the pathogen, overdistention of bronchioles, and prolonged presence of macrophages with increased elastase and other enzymes [21]. As a result, cysts and bullae form, and lung parenchyma tissue is vulnerable to the development of barotrauma [22]. The increase in body temperature during ECMO treatment may indicate poor control of the primary disease and the possibility of secondary infection, and the risk of barotrauma in these patients is increased. In our multivariate analysis, we found that a low platelet count was also a risk factor for barotrauma, and we also found that bleeding complications in patients with barotrauma were much higher than those in patients without barotrauma ($P < 0.05$). Platelets have been increasingly recognized for their roles in ARDS outcomes, which are likely mediated by their involvement in inflammatory responses and disseminated intravascular coagulation. Other studies have suggested that thrombocytopenia and a decline in platelet count may reflect the same pathophysiologic disturbances, including vitamin

Table 2
Univariate analysis of factors associated with barotrauma during ECMO.

Characteristics	OR	95% CI	*P* value
Age	0.953	0.923,0.983	**0.003**
Prone position before ECMO	0.497	0.195,1.263	0.142
Prone position during ECMO	2.095	0.811,5.415	0.127
Awake ECMO	0.333	0.040,2.769	0.309
Days of awake ECMO	1.096	0.991,1.213	0.074
Length of stay at other hospitals	1.026	0.984,1.069	0.23
Ventilation time before ECMO	1.001	0.998,1.004	0.649
Onset time before ECMO	0.991	0.969,1.013	0.415
Temperature before ECMO	1.186	0.772,1.820	0.436
Temperature during ECMO	2.997	1.325 , 6.779	**0.008**
Respiration rate before ECMO	1.039	0.980,1.102	0.196
Respiration rate during ECMO	1.058	0.989,1.132	0.099
PCO_2 before ECMO	0.966	0.916,1.020	0.213
PCO_2 during ECMO	1.039	0.975,1.108	0.239
PO_2 before ECMO	0.993	0.977,1.009	0.387
PO_2 during ECMO	0.98	0.955,1.007	0.142
HCO_3 before ECMO	1.027	0.952,1.109	0.489
HCO_3 during ECMO	1.094	0.979,1.222	0.113
PJP	3.15	1.070,9.271	**0.037**
PLT during ECMO	0.985	0.972,0.998	**0.02**

PCO_2: partial pressure of carbon dioxide; HCO_3: Bicarbonate; PJP: Pneumocystis jirovecii pneumonia; PLT: Platelets; PO_2: partial pressure of oxygen.

Table 3
Multivariate analysis of factors associated with barotrauma during ECMO.

Characteristics	OR	95% CI	*P* value
Age	0.953	[0.923,0.983]	0.003
Temperature during ECMO	2.997	[1.325,6.779]	0.008
PJP	3.15	[1.070,9.271]	0.037
PLT during ECMO	0.985	[0.972,0.998]	0.02

PJP: Pneumocystis jirovecii pneumonia; PLT: Platelets.

Table 4
Multivariate analysis of factors associated with barotrauma during ECMO after age correction.

Characteristics	OR adjusted	95% CI adjusted	*P* value adjusted
Temperature during ECMO	2.735	[1.170,6.395]	0.02
PJP	4.409	[1.331,14.612]	0.015
PLT during ECMO	0.985	[0.971,0.999]	0.033

PJP: Pneumocystis jirovecii pneumonia; PLT: Platelets.

deficiencies, macrophage activation, drug-induced toxicity, severe infection or sepsis, and severity of illness in many nonmalignant medical conditions [23]. Wei et al. showed that a lower baseline platelet count or a larger decrease in platelet count after admission to the ICU was associated with poor prognosis in patients with ARDS in the ICU [24]. The occurrence of barotrauma is related to the disease state to a certain extent. ARDS patients with low platelet counts tend to have more serious diseases and a high incidence of barotrauma.

Kao et al. found that severe acute respiratory syndrome (SARS) patients with barotrauma showed a higher RR after admission and more obvious hypoxemia and hypercapnia during hospitalization and that there was no significant difference in ventilator parameters between patients with and without pneumothorax [25]. In our study, we also found that the RR of barotrauma patients during ECMO was higher, and hypoxemia and hypercapnia were more obvious ($P < 0.05$). However, in the subsequent univariate and multivariate analyses, these indicators were not statistically significant. Other studies also support our findings. Anzueto et al. conducted a prospective cohort study of 5183 patients with mechanical ventilation for more than 12 h in 361 intensive care units from 20 countries. They found that 154 patients (2.9%) had barotrauma, and there was no difference in any ventilator parameters between patients with and without barotrauma. Logistic regression analysis confirmed that the independent factors associated with barotrauma included ARDS [RR 4.23 (95% CI 1.78–10.03)]; indeed, ARDS was the main cause of barotrauma. Furthermore, case-control analysis showed that ICU hospitalization was prolonged in patients with barotrauma [26]. Boussarsar et al. retrospectively analyzed the prospective trial data of 116 patients with ARDS and found that 15 (12.3%) developed pneumothorax. Similar to the study by Anzueto et al., ARDS patients demonstrated a higher incidence of barotrauma than all mechanically ventilated patients, indicating that ARDS patients are more prone to barotrauma. Boussarsar et al. also found that there was no significant relationship between ventilation parameters and pneumothorax, and the duration of mechanical ventilation in pneumothorax was longer [5]. In some recent COVID-19 studies, barotrauma was not an independent indicator of poor prognosis, but it was associated with a longer median hospital stay in the ICU (17 days vs. 7 days, $P = 0.03$) and a longer median hospital stay (26 days vs. 14 days, $P < 0.001$). There was no difference in VT or PIP between the barotrauma group and the no barotrauma group, which was mainly related to the pathophysiology of the disease state and the products of increased inflammatory reactions leading to rampant acute lung injury [27,28].

Future studies should investigate whether ultra-protective mechanical ventilation also could be feasible and effective in preventing barotrauma in high-risk patients. And investigate whether different management strategies could actually prevent barotrauma development. Finally, randomized controlled trials will be needed to confirm that prevention of barotrauma translates into improved outcomes.

4.1. Limitations

Our study has several limitations, including its retrospective design. We cannot rule out biasing in our results due to residual confounding not accounted for in this study. In addition, the collected data span a period of 10 years. Over the last decade, the management of patients with ARDS, including those undergoing VV-ECMO, has improved considerably. Therefore, we cannot rule out time-dependent effects that may have affected our analysis. Some of the parameters in the study, including ventilator parameters, are dynamic and may be adjusted multiple times throughout the day depending on the patient's condition. We focused on the period spanning 6 h before ECMO and days 1–7 during ECMO. However, to determine whether the data obtained 7 days after ECMO have an impact on the analysis, larger prospective studies are needed.

5. Conclusion

Although the lung rest strategy is adopted for ARDS patients during ECMO treatment, the incidence of barotrauma is very high in practice. For ARDS patients with young age, PJP, elevated body temperature and low platelets during ECMO, the risk of barotrauma is increased, the hospitalization time is prolonged, and the hospitalization cost and the burden on the family is increased. These patients should undergo close imaging monitoring, especially in the late stage of ARDS and for ECMO treatments lasting longer than 8 days.

Ethics approval and consent to participate

The ethics committee of China-Japan Friendship Hospital approved this study (2015-ST-4). Written informed consent was not required due to our retrospective study design, which was in accordance with the institutional requirements.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used or analyzed in the study are available from the corresponding author on reasonable request.

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CRediT authorship contribution statement

Yu Bai: Data curation, Software, Writing – original draft, Writing – review & editing, Writing – review & editing. **Shengsong Chen:** Data curation, Software, Writing – original draft. **Zeyu Zhang:** Visualization, Investigation, Validation. **Xu Huang:** Visualization, Investigation, Validation. **Jingen Xia:** Supervision, Conceptualization, Methodology. **Min Li:** Conceptualization, Methodology, Supervision. **Qingyuan Zhan:** Supervision, Conceptualization, Methodology.

Declaration of competing interest

All the authors have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2023.107248.

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