Prone Position Ventilation for Pediatric Acute Respiratory Distress Syndrome with Extracorporeal Membrane Oxygenation: A Propensity Score-Matched Retrospective Multicenter Cohort Study

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Research

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Abstract

Background: Extracorporeal membrane oxygen (ECMO) has used for rescuing severe pediatric acute respiratory distress syndrome (PARDS) for half a century. Prone position ventilation (PPV) has been suggested according to the surviving sepsis campaign (SSC) guideline in children in 2020. We aimed to compare the outcomes and effect of PARDS patients with ECMO+PPV and ECMO only.

Design: Retrospective Multicenter pair-matched Study

Setting: In the present study, propensity score matching was conducted and the outcomes of severe PARDS patients were analyzed. The effect of PPV was compared as well. The efficiency of PPV included PaO_2 , Oxygen Index (OI), $\text{PaO}_2/\text{FiO}_2$, compliance of respiratory system and resistance of airway. The primary outcome was hospital mortality. Secondary outcomes included ECMO running time, PICU time, hospital days and mechanical ventilation time of survivors.

Patients: 137 PARDS patients with criteria of ECMO from 11 hospitals in 5 years.

Interventions: No interventions.

Measurements and Main Results: Among 137 patients, 93 patients received ECMO+PPV at the same time and 44 patients didn't. After matching, we got 34 pairs. For the survivors receiving ECMO+PPV, the PaO_2 , OI and $\text{PaO}_2/\text{FiO}_2$ increased significantly during the PPV period ($P<0.01$) and sustained for 4 hours at least. However, the hospital mortality of both groups showed no significant difference (50.0 vs. 55.9%, $P=0.808$).

Conclusions: By far, there has been no ECMO+PPV efficiency study in PARDS patients. This study found that PPV was associated with improved oxygen state during ECMO. However, PPV was not associated with survival rate with PARDS patients on ECMO.

Clinical Trial Registration: This study was registered at <http://www.chictr.org.cn/index.aspx> (chiCTR.gov; Identifier: ChiCTR1800019555). Registered 18 November 2018. Name of the registry: Extracorporeal membrane oxygenation in critical ill children with severe acute respiratory distress syndrome - A multicenter study.

Take Home Message:

1. Our study investigated prone position ventilation (PPV) could improve the oxygen state during ECMO for patients with severe PARDS.
2. The results indicated PPV had no influence on the mortality of PARDS with ECMO.

Background

In 2015 the Pediatric Acute Lung Injury Consensus Conference (PALICC) produced a consensus definition for pediatric acute respiratory distress syndrome (PARDS)[1], according to a meta-analysis, the mortality of severe PARDS still remains 34% per year[2]. Extracorporeal membrane oxygen (ECMO), an artificial means for supporting patients with respiratory and (or) cardiac failure, has been applied worldwide since 1970s[3]. The latest report from extracorporeal life support organization (ELSO) showed that in 2019, 680 pediatric patients received ECMO for respiratory support and 500 survived, with a survival rate of 73%[4]. To rescue severe ARDS prone position ventilation (PPV) was applied since 1976. The ARDS Prone Position Network (APRONET) study showed the PPV was safe and efficient in improving the oxygenation and decreasing the driving pressure in 2018[5]. Although the combination uses of ECMO and PPV in adults ARDS have been proved to be safe in some experienced centers[6], the efficiency of PPV during ECMO in support for severe ARDS still remains unclear[7]. By far, there has been no ECMO + PPV efficiency study in PARDS patients. We wondered whether PPV could be associated with improving survival rate during severe PARDS patients on ECMO. We performed a retrospective study of severe PARDS patients supported with ECMO combined with PPV. The primary outcome was the hospital mortality and the secondary outcomes in survivors included ECMO running time, PICU time, hospital time and mechanical ventilation time. The other objective was the alteration of oxygen index (OI) before, during and after PPV under ECMO, as well as the compliance of respiratory system and the safety of the process.

Materials And Methods

This is a retrospective multi-center study from May 2015 to December 2019 in eleven hospitals. Among the 11 hospitals, each patient in 4 hospitals received PPV during ECMO and those in another 5 hospitals not. Meanwhile, physicians in 2 of the 11 hospitals both used PPV and supine position during ECMO. The protocol was approved by the Ethics Committee of the seventh medical center of PLA general hospital (previously known as PLA Army general hospital, No.2018-14). This study was registered at <http://www.chictr.org.cn/index.aspx> (ChiCTR.gov; Identifier: ChiCTR1800019555).

Patients selection

All of the patients were between 28 days to 14 years old and diagnosed with severe PARDS following the PALICC criteria[1]. The patients were divided into two groups: the ECMO group and the ECMO + PPV group. The patients in ECMO group didn't receive PPV during the support of ECMO while the patients in ECMO + PPV group received. For patients in the ECMO + PPV group, 64 patients were finally excluded as the clinical data were not integrated. The remaining 28 patients were divided into two subgroups according to whether they survived to discharge from the hospital.

ECMO management

The patients were supported for VA-ECMO or VV-ECMO according to the following criteria: $\bar{O}_2$ oxygen index of over 40 for at least 4 hours under a FiO_2 at 100%, $\bar{P}aO_2$ to FiO_2 ration of less than 80 for at least 2

hours under a FiO_2 at 100% with a PEEP level over 14 cmH_2O , severe respiratory acidosis with $\text{pH} \leq 7.10$ despite respiratory rate $\geq 35/\text{min}$ ^[8, 9]. The mode of ECMO was selected based on the weight of the patient: VA-ECMO through right jugular vein (RJV) and right common carotid artery (RCCA) for patients less than 15 kg and VV mode through right femoral vein (RFV) and RJV for those over 15 kg. The staffs in the eleven hospitals followed the same ECMO inclusion criteria and instructions for running published on ELSO. All the eleven centers used centrifugal pumps (Bio-Console 560, Medtronic, USA; DataStream DP3, Medos, Germany; SCPC, Sorin, Italy; ROTAFLOW, MAQUET, USA) with the flow differs from 111.11 mL/kg/min to 168.89 mL/kg/min in all the patients. During the process, the gas flow of the oxygenator was modulated according to the analysis of blood gas (ABG) and the gas to blood ratio was from 0.5:1 to 10:1. The oxygenators (Hilite 2800/7000, Medos; Lilliput, Sorin) were selected according to the body weight of the patient to get blood flow of 150 mL/kg. The catheters (Medtronic) used for each patient were inserted by a surgeon. Once the ECMO initiating, ABG and activated clotting time (ACT) were measured every four to six hours. Complete blood count (CBC) and anticoagulation test were analyzed every 12 hours. The heparin was continuously administrated to maintain the activated partial thromboplastin time (APTT) between 55 to 80 sec.

Ventilation management

All the patients on ECMO were ventilated in pressure control mode. The ventilator was set as follows: Positive End-Expiratory Pressure (PEEP) of 10–15 cmH_2O , Peak Inspiratory Pressure (PIP) of 26–30 cmH_2O , respiratory rate of 12–20/min, the Inspiratory Time (Ti) of 0.60-1.00 sec. The fraction of oxygen delivered (FDO_2) to the oxygenator was modulated to maintain the transcutaneous oxygen saturation (SpO_2) of 90 ~ 95%, and the FiO_2 of the ventilator was adjusted to obtain the SpO_2 above 85% while the FDO_2 set at 100%. The SpO_2 was always measured distal to the return cannula, such the lower limb for the jugular cannulation and right arm for the femoral cannulation.

Prone position ventilation

All the patients in the ECMO + PPV group were set on PPV after the hemodynamic state stable except any contraindications. The PPV was used as a routine treatment for severe PARDS patients in ECMO + PPV group and each patient received PPV for at least 14 hours per day. During the PPV period, all the patients were deeply sedated with midazolam and paralyzed with rocuronium bromide. The FDO_2 was set at 100% for patients who need PPV. Six staffs were involved in turning over one patient a time. The ECMO perfusionist was the leader of the process and responsible for the monitoring of the whole system. A PICU doctor and four nurses carried out the whole operation. The last one doctor was specially in charge of the whole circuit and monitoring the position of catheters. The detailed process was followed the study of Guervilly et al[10].

Efficiency of PPV + ECMO

For 28 patients with complete data in ECMO + PPV group, the alteration of PaO_2 , $\text{PaO}_2/\text{FiO}_2$ and OI before, during and after PPV was measured to evaluate the efficiency of PPV. We also recorded the dynamic compliance of respiratory system (Crs) and resistance of airway (Raw) before and after PPV.

Outcomes of PPV and ECMO

The primary outcome of our study was the hospital mortality for patients receiving ECMO with or without PPV from initiation of ECMO. The secondary outcomes included the running time of ECMO, the mechanical ventilation time, PICU time and time in hospital of survivors.

Complications associated with PPV

The primary and most life-threatening complications associated with PPV was displacement of catheters and any other problems of the circuit. These life-threatening problems contains: significant hemorrhage requiring red blood cells transfusion, tubing rupture, thrombosis in the circuit causing a drop-down of ECMO flow etc. The second complications associated with PPV is the displacement of tube linked to the patients (such as endotracheal tube, central venous line or chest tube). Another life-threatening complication during the PPV was hemodynamically unstable, especially drop of the arterial blood pressure. The other complications during the process of PPV were mainly the pressure ulcer of skin and edema of dependent region.

Statistical analysis

Clinical characteristics of all the patients with severe PARDS were analyzed and compared with generalized estimating equations as a cluster variable for matching. Pair-matched cohort analysis were performed after propensity score matching on the basis of variable associated with the severity of the disease and the use of ECMO. As a result, a 1:1 matching pair was made without replacement on the basis of observation before ECMO. The OI value before ECMO and the causes of severe PARDS were recorded as the covariates for the multivariable logistic regression. The regression was used for estimation of the probability of PPV combining with ECMO treatment to get a propensity score matching. After that, the smallest difference in the propensity scores was the standard for each ECMO + PPV and ECMO supported paired observation.

The statistical analysis was performed with SPSS 24.0 (SPSS Inc., Chicago, USA). The continuous variables are shown as median and interquartile range. The Wilcoxon signed-rank test were used to compare the ABG, $\text{PaO}_2/\text{FiO}_2$, OI and hemodynamic index during and after PPV. We defined the P value < 0.05 as significant difference.

Results

During the five years, 137 children were involved in the study with 86 males and 51 females (Figure.1). The basic characteristics of the patients before propensity score matching is shown in Table 1.

Considering the causes of ARDS, 45 patients were diagnosed with viral pneumonia, 27 patients with bacterial pneumonia, 8 with mycoplasma pneumoniae (MP), 2 with ARDS post-surgery, one patient with pneumocystis pneumonia and one patient got ARDS with aspiration, while 53 patients showed no positive pathogens when supported on ECMO. Among all the patients, one child was tested positive both of H1N1 influenza a virus and MP (Table 1 & 2).

Before matching, the patients in ECMO group had higher Pediatric Pulmonary Rescue with Extracorporeal Membrane Oxygenation Prediction Score (P-RESP) suggesting those had a higher risk of mortality before ECMO running. The causes of PARDS showed no obvious differences in all the 137 children, as well as the demographic characters, the Sepsis Organ Failure Assessment (SOFA) score and the results of ABG. We got 34 pairs of patients after propensity matching, covariates reached a good balance for all matched variables and the results were shown in Table 2.

The efficiency of PPV

For 28 patients with complete data analyzed in ECMO + PPV group, all received PPV more than one time. Most of the children in our study received 3 times of PPV and 5 children received more than 6 times of PPV with 3 succeed to discharge from hospital. The average time of total PPV period for the survivors is 80.37 hours vs. 127.00 hours in the non-survivors ($P = 0.020 < 0.05$). The PPV duration for each patient each time was between 9 hours and 38 hours in both groups with the median duration of hours of PPV of 16 hours. However, considering the times of PPV, the mean period of each PPV showed no significance between the two groups (23.24 hours vs. 27.34 hours, $P = 0.342 > 0.05$).

The PaO_2 , $\text{PaO}_2/\text{FiO}_2$ and OI increased significantly after 6 hours from PPV ($P < 0.05$) and still persisted for nearly 4 hours after returning the patients to the supine position ($P < 0.05$) (Fig. 2). Especially in the last 3 times of PPV, for the survivors, the magnitude of improvement of PaO_2 was exactly higher than the non-survivors. We also tested the dynamic compliance and resistance of respiratory system during the whole period. No differences were shown in all the patients received PPV with severe PARDS during the support of ECMO.

The outcome of PARDS patients

In propensity score-matched PARDS patients, the hospital mortality was 50.0% for ECMO + PPV group vs. 55.9% for ECMO group ($P = 0.808$, Table 4). The ECMO running time was 144.48 hours (interquartile range [IQR], 111.66-259.14 h) for the ECMO + PPV group vs. 187.20 h (150.78-337.44 h) for ECMO group ($P = 0.542$). The PICU time was 18.0 days (9.50-36.25 days) for the ECMO + PPV group vs. 26.0 days (13.50–37.50 days) for ECMO group ($P = 0.516$) and hospital time was 34.0 days (11.92-61.00 days) for the ECMO + PPV group vs. 30.00 days (22.50-51.00days) for ECMO group ($P = 0.718$). The mechanical ventilation time was 284.28 h (189.90–708.00 h) for the ECMO + PPV group vs. 456.72 h (216.00–714.96 h) for the ECMO group ($P = 0.820$, Table 5).

The safety of PPV during ECMO for PARDS patients

No lethal complications were observed during the total 100 PPV procedures both in the survivor group and non-survivor group. The major complications included accidental extubation and pressure sores. During our observation, one patient has got pressure score which need a surgery after she survived to wean from ECMO. Two accidental extubations were observed when the patients on the prone position while they were intubated again as soon as the extubations were observed. The minor complications mainly indicated facial edema and bleeding. Fifteen patients (53.57%) got facial edema when their PPV time beyond 15 hours during our observation. According to the definition of major bleeding event[11], no major bleeding event were observed during the whole PPV procedures. However, minor bleeding events were still recorded by our team especially in the site of Invasive arterial blood lines.

Discussion

Extracorporeal membrane oxygen (ECMO) is a kind artificial means to acquire gas exchange for children with ARDS who fail mechanical ventilation since 1970s[3]. Since the negative results from the RESTORE[8] and EOLIA[12] study published, the number of cases on ECMO dropped slightly globally according to the registry data from ELSO. However, the bayesian analysis of data from EOLIA study showed its benefits of ECMO in saving patients with ARDS[13] and ECMO is still a rescuing method for those patients with severe ARDS. According to data from ELSO, over 500 children received ECMO for respiratory support in 2019. It is still a retrospective means for rescuing severe ARDS who failure with all the other treatment.

Till today, although series of trials has been developed, truly useful methods for rescuing PARDS especially severe PARDS remains limited. For severe PARDS, prone position ventilation has been suggested according to the surviving sepsis campaign (SSC) guideline in children[14]. Prone positioning has been used for many years to improve oxygenation in patients who require mechanical ventilatory support for management of ARDS[15]. Randomized, controlled trials have confirmed that oxygenation is significantly better when patients are in the prone position than when they are in the supine position[16–18]. However, till nowadays, there still no absolute evidence to support that the prone position ventilation used in the severe pediatric acute respiratory distress syndrome (PARDS) to be treated with ECMO. To test its effectiveness, we designed the propensity score matching multi-center cohort study to collect the data from 2015 to 2019 in eleven ECMO centers in China for patients diagnosed with severe PARDS.

To our knowledge, this is the first multi-center cohort study about efficiency and safety of combining use of PPV and ECMO in the treatment of severe PARDS patients. Although bias could be eliminated partially by the propensity score matching method, no obvious changes in the survival rate, hospital days and PICU days have been observed between the ECMO + PPV group and ECMO group. Considering the limitation of the sample size of our study, it may be difficult to detect the differences. As recommendation for adult patients for PPV is $\text{PaO}_2/\text{FiO}_2$ lower than 100, all the patients in our study diagnosed with severe PARDS with $\text{PaO}_2/\text{FiO}_2$ lower than 100, it may be another reason for the failure of ECMO + PPV.

The practical guidelines for adult ARDS from American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine[17] suggested patients with moderate to severe ARDS received PPV for over 12hr/d. In our observation of patients received PPV, each patient received more than 1 period of PPV during the support of ECMO with the shortest time of PPV over 12 hours. Our data also showed the patients could receive benefits of PaO_2 from PPV for over 12 hours per day without increasing the complications of the whole respiratory system. Since Guttinoni et al. firstly showed the dependent pathological changes of lungs in the patients with ARDS, discussion about mechanisms of PPV has puzzled the physicians all around the world for half a century. Although evidences of the changes of compliance of respiratory system in patients with severe ARDS is still controversial[6, 19], our data showed no significant alteration no matter the patients were put on the prone position or the supine position. The same phenomenon was also observed in the record of resistance of respiratory system. For the patients who finally failed to survive from the disease, the PaO_2 , $\text{PaO}_2/\text{FiO}_2$ and OI also showed a significant increase during the period of PPV. Our results suggested that the improvement of PaO_2 lasted for at least 4 hours after the patients were turned back to the supine position, especially for those patients who received PPV for over 16 hours per day. Similar to the results from Guerin et al.[16] and Rilinger et al. [20], PPV still showed its efficiency on the improvement of the pathophysiological changes of the respiratory system. Both these two studies suggested that the patients should receive PPV for over 16 hours per day and the latest study form Rilinger et al. showed that patients would benefit from early PPV when ECMO initiating.

Although the guidelines suggested that the period of PPV should be over 12 hours per day[17], however, no absolute suggestions for exact duration of PPV for severe PARDS patients on ECMO were given out. The duration of PPV in our observation were between 9 hours and 38 hours in both groups and most of the patients received over PPV for over 12 hours. However, the effect and safe duration of PPV on ECMO still need to be tested by the other clinical studies.

As a retrospective cohort study, there are still some limitations in our study. Firstly, although this is a multi-center cohort study, the sample size is relatively small. As the development of pediatric ECMO support in China is still very slow, only a few patients could receive ECMO all around the country. It may be that our study was underpowered to detect a difference. Secondly, limited by the retrospective method, the control of the bias during the PPV, such as the duration of PPV, could not been avoided. Thirdly, most of patients in our study received VA ECMO, however, VV ECMO has shown its impact in surviving severe PARDS patients. Due to a lack of double lumen catheter, Chinese physicians could only use VA ECMO for patients under 20 kg. The preponderance of VA ECMO on supporting both pulmonary and cardiovascular function. The more details of PPV for severe PARDS patients on ECMO are still needed perspective random trials.

Conclusion

By far, there has been no ECMO + PPV efficiency study in PARDS patients. This study found that PPV could improve the oxygen state during ECMO. However, PPV had no influence on the mortality of PARDS

patients with ECMO. A rigorous multi-center randomized controlled clinical trial should be performed for the efficiency of PPV with ECMO in severe PARDS patients to provide solid conclusions.

Declarations

Conflicts of Interest

The authors declare no conflicts of interest.

Funding

This present study was supported by Capital's Funds for Health Improvement and Research (2020-2-5093).

Ethics declarations

Ethical Approval and Consent to participate

This is a retrospective multi-center study from May 2015 to December 2019 in eleven hospitals. The protocol was approved by the Ethics Committee of the seventh medical center of PLA general hospital (previously known as PLA Army general hospital, No.2018-14). This study was registered at <http://www.chictr.org.cn/index.aspx> (chiCTR.gov; Identifier: ChiCTR1800019555).

Consent for publication

Not Applicable.

Availability of supporting data

Not Applicable.

Competing interests

The authors have no conflict of interest.

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Authors' contributions

Xiaoyang Hong, Yucai Zhang, Zhichun Feng were responsible for the concept, design.

Zhe Zhao, Guoping Lu, Shuanglei Li were responsible for the data analysis, interpretation.

Zhe Zhao, Xiaoyang Hong were responsible for preparation and manuscript review.

Zhe zhao, Baowang Yang, Huiling Zhang, Ye Cheng, Yiping Zhou, Yun Cui, Wenzhe Cheng, Jie Wang, Yibing Cheng, Yingfu Chen, Chengjun Liu, Dongliang Cheng, Changsong Shi, Yuxiong Guo, Yan Hu, Yi Hui, Dong Qu, Chengxiang Kong, Ping Jin, Bin Yu, Xiulan Lu, Youpeng Jin, Huiying Yan contributed importantly to data acquisition, manuscript preparation and final approval.

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Tables

Table 1 the characteristics of patients with severe PARDS between the PPV+ECMO and ECMO Group before ECMO support, median (IQR)

Characteristics	PPV+ECMO group (N=93)	ECMO group (N=44)	P value
Basic Information			
Age (Years)	2 (0.78~4.92)	3.56(0.82~5.49)	0.778
Body weight (kg)	12(9.00~19.00)	14.5(9.62~21.00)	0.028*
ECMOmode			0.159
VA-mode, N (%)	79(84.9%)	33(75.0%)	
VV-mode, N (%)	14(15.1%)	11(25.0%)	
Sex, N (%)			0.097
Male	54(58.1%)	32(72.7%)	
Female	39(41.9%)	12(27.3%)	
P-PREP	7.50(6.25~8.00)	8.00(7.00~11.00)	0.006*
SOFA	9.50(8.00~11.00)	9.00(8.00~10.00)	0.067
Lac	5.40(0.53~11.00)	3.75(1.12~7.00)	0.103
OI	39.25(20.50~41.58)	40.00(28.00~49.75)	0.082
PaO₂/FiO₂	58.26(42.00~72.50)	55.75(46.50~60.75)	0.792
Causes/Pathogens			0.485
Virus			
ADV	14(15.1%)	15(34.1%)	
RSV	3(3.2%)	1(2.3%)	
H1N1	7(6.5%)	1(2.3%)	
Flu B	1(1.1%)	1(2.3%)	
CMV	0(0.0%)	1(2.3%)	
HRV	0(0.0%)	1(2.3%)	
HPIV	1(1.1%)	0(0.0%)	
Bacteria			
ABA	9(9.7%)	2(4.5%)	
S.aureus	2(2.2%)	0(0.0%)	
SPn	1(1.1%)	0(0.0%)	

KPn	2(2.2%)	1(2.3%)
PAe	3(3.2%)	0(0.0%)
BPe	2(2.2%)	0(0.0%)
CMe	1(1.1%)	1(2.3%)
ALow	1(1.1%)	0(0.0%)
EFa	1(1.1%)	1(2.3%)
Mycoplasma		
MP	5(5.4%)	3(6.8%)
PCP	0(0.0%)	1(2.3%)
Post-surgery	2(2.2%)	0(0.0%)
Inhalation	1(1.1%)	0(0.0%)
Unknown	38(40.9%)	15(34.1%)

*, P<0.05.

#, One patient was converted from VV-mode to VA-mode as he got severe heart failure during the support.

VA, Veno-Arterial; VV, Veno-Venous; MV, Mechanical Ventilation; ECMO, Extracorporeal Membrane Oxygenation; P-PREP, Pediatric Pulmonary Rescue with Extracorporeal Membrane Oxygenation Prediction Score; SOFA, Sepsis Organ Failure Assessment Score; Lac, Lactate; OI, Oxygen Index. ADV, Adenovirus; RSV, Respiratory Syncytial Virus; H1N1, H1N1 Influenza A Virus; Flu B, Influenza B Virus; CMV, Cytomegalovirus; HRV, Human rhinovirus; HPIV, Human Parainfluenza Virus; ABA, Acinetobacter Baumannii; S. aureus, Staphylococcus aureus; SPn, Streptococcus pneumoniae; KPn, Klebsiella Pneumoniae; PAe, Pseudomonas aeruginosa; BPe, Bordetella pertussis; CMe, Chryseobacterium meningosepticum; ALow, Acinetobacter lwoffii; EFa, Enterococcus Faecium; MP, Mycoplasma Pneumoniae; PCP, pneumocystis pneumonia

Table 2 numbers of patients on PPV in each ECMO center

Center	Patients on PPV	Patients without PPV	Sum
No. 01	23	5	28
No. 02	31	17	48
No. 03	0	9	9
No. 04	6	0	6
No. 05	18	0	18
No. 06	13	0	13
No. 07	0	7	7
No. 08	0	3	3
No. 09	4	0	4
No. 10	0	2	2
No. 11	0	1	1
Sum	95	44	139

Table 3 the characteristics of patients with severe PARDS between the PPV+ECMO and ECMO Group before ECMO support after propensity score matching, median (IQR)

Characteristics	PPV+ECMO group (N=34)	ECMO group (N=34)	P value
Basic Information			
Age (Years)	2.54(0.72~5.67)	3.11(0.67~4.34)	0.651
Body weight (kg)	12.00(8.37~20.25)	14.25(7.50~18.5)	0.721
ECMOmode			0.549
VA-mode, N (%)	26(76.5%)	28(82.4%)	
VV-mode, N (%)	8(23.5%)	6(17.6%)	
Sex, N (%)			0.798
Male	22(64.7%)	23(67.6%)	
Female	12(35.3%)	11(32.4%)	
P-PREP	8.00(8.00~10.00)	8.00(7.00~11.00)	0.472
SOFA	9.00(8.75~10.25)	9.00(8.00~10.00)	1.000
Lac	3.35(1.35~8.45)	4.45(1.42~8.97)	0.575
OI	50.00(40.00~50.00)	40.00(33.50~50.00)	0.634
PaO₂/FiO₂	58.00(46.10~62.40)	55.10(45.75~59.25)	0.834
Causes/Pathogens			
Virus			0.972
ADV	6(17.6%)	8(23.5%)	
RSV	1(2.9%)	1(2.9%)	
H1N1	2(5.9%)	1(2.9%)	
Flu B	0(0.0%)	0(0.0%)	
CMV	0(0.0%)	1(2.9%)	
HRV	0(0.0%)	1(2.9%)	
HPIV	0(0.0%)		
Bacteria			
ABA	3(8.8%)	2(5.9%)	
S.aureus	0(0.0%)	0(0.0%)	
SPn	0(0.0%)	0(0.0%)	

KPn	1(2.9%)	1(2.9%)
PAe	1(2.9%)	0(0.0%)
BPe	2(5.9%)	0(0.0%)
CMe	0(0.0%)	1(2.9%)
ALow	1(2.9%)	0(0.0%)
EFa	0(0.0%)	1(2.9%)
Mycoplasma		
MP	2(5.9%)	3(8.8%)
PCP	1(2.9%)	1(2.9%)
Post-surgery	0(0.0%)	0(0.0%)
Inhalation	0(0.0%)	0(0.0%)
Unknown	14(41.2%)	13(38.2)

*, P<0.05.

#, One patient was converted from VV-mode to VA-mode as he got severe heart failure during the support.

VA, Veno-Arterial; VV, Veno-Venous; MV, Mechanical Ventilation; ECMO, Extracorporeal Membrane Oxygenation; P-PREP, Pediatric Pulmonary Rescue with Extracorporeal Membrane Oxygenation Prediction Score; SOFA, Sepsis Organ Failure Assessment Score; Lac, Lactate; OI, Oxygen Index. ADV, Adenovirus; RSV, Respiratory Syncytial Virus; H1N1, H1N1 Influenza A Virus; Flu B, Influenza B Virus; CMV, Cytomegalovirus; HRV, Human rhinovirus; HPIV, Human Parainfluenza Virus; ABA, Acinetobacter Baumannii; S. aureus, Staphylococcus aureus; SPn, Streptococcus pneumoniae; KPn, Klebsiella Pneumoniae; PAe, Pseudomonas aeruginosa; BPe, Bordetella pertussis; CMe, Chryseobacterium meningosepticum; ALow, Acinetobacter lwoffii; EFa, Enterococcus Faecium; MP, Mycoplasma Pneumoniae; PCP, pneumocystispneumonia

Table 4 The Primary Outcomes of patients between the PPV+ECMO and ECMO group after propensity score matching, median (IQR)

outcomes	PPV+ECMO group	ECMO group	P value
hospital Mortality, N (%)	17(50.0%)	19(55.9%)	0.808
Survived ECMO, N (%)	17(50.0%)	15(44.1%)	

Table 5 The Secondary Outcomes of patients between the PPV+ECMO and ECMO group in survivors after propensity score matching, median (IQR)

outcomes	PPV+ECMO group (N=34)	ECMO group (N=34)	P value
Running time (hours)	144.48(111.66~259.14)	187.20(150.78~337.44)	0.542
PICU time (days)	18.00(9.50~36.25)	26.00(13.50~37.50)	0.516
Hospital days (days)	34.00(11.92~61.00)	30.00(22.50~51.00)	0.718
MV time (hours)	284.28(189.90~708.00)	456.72(216.00~714.96)	0.820

Figures

Figure 1

Flow chart for the exclusion and matching of subjects in the study in the study for ECMO and PPV in saving severe PARDS patients

Figure 2

The alteration of PaO₂, PaO₂/FiO₂ and OI before, during and after PPV