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ABSTRACT

***Background*:** Immunocompromised children are likely to develop a refractory acute respiratory distress syndrome (ARDS). The usefulness of providing extracorporeal life support (ECLS) to these patients is a subject of debate. The aim of our study was to report the outcomes and to compare factors associated with mortality between immunocompromised and non-immunocompromised children supported with veno-venous ECMO.

Methods: We performed a retrospective monocentric study in the French pediatric ECMO center of Armand Trousseau Hospital, including all pediatric patients aged from 1 month to 18 years requiring ECLS for ARDS.

Results: Between 2007 and 2018, one hundred and eleven (111) patients underwent ECMO for respiratory failure; among them twenty-five (25) were immunocompromised. Survival rate at 6 months after intensive care discharge was significantly lower for immunocompromised patients compared to non-immunocompromised ones (41.7% vs. 62.8%; p = 0.04). ARDS severity was similar between the 2 groups. Fungal pneumonias were reported only in immunocompromised patients (12.5% versus 0% in the control group; p = 0.001). Bleeding complications were significantly more frequent in the immunocompromised group and blood product transfusions were also more frequently required in this group.

Conclusion: Six months after intensive care discharge, survival rate of immunocompromised children supported with ECMO for pediatric ARDS is lower than for non-immunocompromised patients. But, the expectation for a favorable outcome is real and it is worth it if their condition is likely to be compatible with a good long-term quality of life.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a life-threatening condition associated with significant morbidity and mortality in children [1,2]. In 2015, the Pediatric Acute Lung Injury Consensus Conference (PALICC) expert group has specifically defined pediatric ARDS (P-ARDS) so as to offer recommendations regarding therapeutic support, including consideration of Extracorporeal Life Support (ECLS) [3]. Overall survival has been stable around 60% of the time over the last 25 years in pediatric patients supported with respiratory ECLS. However, there is a sharp increase of associated comorbidities, including immune compromise conditions [4,5]. Immunocompromised children are likely to develop infections and pulmonary complications due to their underlying condition or secondary to the immunosuppressive treatments [6,7]. Thus, they can suffer from acute hypoxemic respiratory failure. It has been previously reported that clinically significant immunodeficiency is associated with an increased risk of death in patients with ARDS [2,8–11]. Before 2000, immunodeficiency was considered as a potential contraindication for ECMO. However, in the last decade, more and more patients benefited from ECMO with controversial results. A recent study of 203 immunocompromised adults with ARDS and undergoing ECMO reported a survival rate of 30% [12] re-opening the debate concerning the usefulness of this treatment in this specific population [13].

Although the negative effect of preexisting immunodeficiency on the survival of P-ARDS patients has been already established, factors associated with mortality, including ECMO-related complications, have not been properly investigated so far.

Our study hypothesis is that survival rate of immunocompromised patient undergoing ECMO for ARDS is increasing. Our aims were first, to report outcomes of immunocompromised children supported with ECMO for P-ARDS and second, to identify

risk factors associated with mortality, before and during ECMO runs, including ECMO-related complications; compared with non-immunocompromised children.

METHODS

We performed a retrospective monocentric study from January 2007 to December 2018 in the ECMO reference center of Armand-Trousseau Hospital, Paris, France.

All pediatric patients aged from 1 month to 18 years old and requiring extracorporeal membrane oxygenation for refractory acute respiratory distress syndrome were included. Immunocompromised children were defined as having solid tumor under chemotherapy, solid-organ transplantation, bone marrow transplantation, hematological malignancy or congenital immunodeficiency syndrome.

Exclusion criteria were missing data or parental opposition.

Data collection:

Data collected were age, gender, weight, ARDS etiology and severity score (PIM II [14] and PELOD score [15], vasoactive-inotropic score [16]), oxygenation features (PaO$_2$/FiO$_2$ ratio, oxygenation index and the oxygenation saturation index) lab characteristics (PaCO$_2$, pH, lactate, white blood cells, neutrophils, lymphocytes and platelets count). We looked for pre-ECMO previous treatment such as mechanical ventilation settings (plateau pressure, positive end expiratory pressure, driving pressure, mean pressure, inspiratory pressure), the use of prone positioning, nitric oxide, exogenous surfactant, neuromuscular blockers and high frequency oscillation. We also gathered ECMO-related complications (massive hemorrhage, brain death or stroke, ventilator acquired pneumonia and central line associated bloodstream infection, fluid overload and need for renal replacement therapy), the need for blood and

blood product transfusions. We collected outcome criteria as the median duration of ECMO, the length of invasive mechanical ventilation, the length of intensive care stay and the survival rate following intensive care (ICU) discharge and 6 months after ICU discharge.

Statistics:

Data analyses were performed using Stata version 13.0 (Stata Corp, College Station, TX). Categorical variables were expressed in percentage and compared using Fischer exact-test. Kolgomorov analysis was performed to test the normal distribution of our continuous variables. Continuous variables were normally expressed as median and range and compared with Mann-Whitney test. For non-normally distribute variables, Kruskall Wallis for non-parametric datas was used. $P < 0.05$ was considered significant. Chi square test was used to assess the significance of the difference between percent rates.

The study was approved by the Ethic Committee of our institution as an observational study and the computerized data collection was approved by the French Data Protection Authority (n°2121127V0).

RESULTS

Patients' characteristics

One-hundred and eleven pediatric patients (1 month-18 years) with refractory ARDS were supported by ECMO over the 11-year study period. Among them, 25 (22%) were immunocompromised. Four patients suffered from having a solid tumor, one patient had a bone marrow transplant for sickle cell disease, one patient had a congenital immunodeficiency syndrome, two patients had solid organ transplantation, and seventeen patients suffered from acute lymphoblastic leukemia (Figure I). There was no statistical difference regarding demographic characteristics between the two groups of patients (Table I). PIM II score was

significantly higher in immunocompromised patients compared to immunocompetent ones (23 ± 22 versus 13.5 ± 18.7; p=0.02). Oxygenation features (PaO_2/FiO_2 ratio, Oxygenation Saturation Index (OSI) and Oxygenation Index (OI)) were not significantly different between the two groups. ARDS main etiology was pneumonia in both groups. Fungal infection frequency was significantly higher in the immunocompromised patients (12.5 % versus 0% in the control group; p = 0.001).

Pre-ECMO clinical and lab characteristics

There was no significant difference, either in blood gas values, or in ventilator settings, including tidal volume and positive end expiratory pressure (Table II). Significantly higher fluid resuscitation volumes were used non-immunocompromised patients compared to the immunocompromised group, respectively 65 ± 46 ml/kg versus 25 ± 19 ml/kg (p = 0.05). No significant difference was found in the blood cells count of immunocompromised patients compared to the non-immunocompromised group.

Patient outcomes

ECMO weaning rate was significantly higher in the non-immunocompromised group compared to immunocompromised patients (73% versus 52%; p : 0.0005). Survival rate 6 months after ICU discharge was significantly lower in immunocompromised patients than in the control group (41.7% versus 62.8%; p = 0.04). The decision to withdraw life-sustaining measures was significantly more frequent for immunocompromised patients (33.3% versus 8.4% ; p = 0.001). There was no significant difference in length of hospitalization, length of ECMO or mechanical ventilation settings between immunocompromised children and the non-immunocompromised group. We observed that immunocompromised children experienced more frequently multi-organ failure than non-immunocompromised ones (Table III).

Intensive Care and ECMO-related complications

Nasopharyngeal, gastro-intestinal and urogenital hemorrhage occurred significantly more often in immunocompromised group, respectively 50% vs 13,5% (p = 0.001), 37.5% vs 9.6% (p = 0.003) and 16.7% vs 3.6% (p = 0.004). No significant difference between the groups was found for ventilator-acquired pneumonia or central line associated bloodstream infection (Table IV).

DISCUSSION

Our report is the first French study, and one of the largest studies regarding ECMO, studying pediatric ARDS (P-ARDS) in immunocompromised patients. As expected, children with immunodeficiency had a lower survival rate than immunocompetent patients (41,7% versus 62.8%). We found a survival rate six month after PICU discharge of 41% in the immunocompromised population, which is higher than previously reported by Zabrocki *et al.* (30-34%) [4], Gupta *et al.* (31%) [17] and *Gow et al.* (35%) in pediatric population [18] and 32% in adult patients [19]. This gap can be explained by the continuous improvement of materials used for ECMO. Moreover, we use in our unit a lung protocol aiming at tidily control ventilatory pressure during ECMO. Moreover, a multidisciplinary evaluation is made before every ECMO implantation in an immunocompromised patient. Finally, due to the low reported survival rate [11], we actually do not use ECMO for refractory ARDS in a patient after a bone marrow transplantation. Gow *et al.* reported 42% who survived to ECLS runs in children immunocompromised population [18] and 39% in adult immunocompromised population [19], which is consistent with our findings. These results corroborate that survival is lower for immunocompromised children respiratory supported by ECMO compared to overall survival in extracorporeal life supported pediatric patients across all categories. The latter is

being reported around 60% this past 25 years according to the Extracorporeal Life Support Organization (ELSO) registry report [5]. However, this survival rate appears reasonable relative to pediatric Extracorporeal Cardiopulmonary Resuscitation (ECPR) survival rate of 42% reported by ELSO [5] or lower reported by Wolf et al. [20], or in cases of pediatric ECLS provided for respiratory failure due to pertussis (32%) [5,21,22].

Another major result of our study is the etiology of the P-ARDS; all fungal pneumonia occurred in an already known immunodeficiency or revealed this severe pathology. It seems to us that all P-ARDS in a supposed immunocompetent child should lead to specific immunodeficiency research. Furthermore, all P-ARDS in immunocompromised patients might benefit from probabilistic anti-fungal therapy.

P-ARDS severity did not seem to explain the higher mortality rate in immunocompromised group. Indeed, there was no difference between the two groups, either in PaO_2/FiO_2 ratio, or in OI or OSI (according to PALICC severity stratification). In a secondary analysis of the Large observational study to Understand the Global Impact of Severe Acute respiratory Failure (LUNG SAFE) study [23] database, Cortegiani et al. [6] found similar ARDS severity, according to the Berlin definition criteria, between immunocompromised and non-immunocompromised adult patients treated with conventional management for ARDS. It should be noted that PIM II score [14] was significantly higher in the immunocompromised population.

Contrary to Bailly et al. [24] and Zabrocki et al. [4], there was no significant difference among the clinical or biological data gathered prior to ECMO between the two groups. As a consequence of this findings associated with the expected survival rate, it seems to us that it could be useful to consider ECMO for P-ARDS in all immunocompromised children even if

severe congenital immune deficiency and bone marrow transplantation remain challenging pathologies to implant [11,25].

However, ECMO use in immunocompromised children is associated with more ECMO-related complications. We reported in our study a higher rate of bleeding complications, especially for nasopharyngeal, gastrointestinal and urogenital hemorrhage, in the immunocompromised group compared to the control group. Moreover, bleeding complications are already known to be associated with a higher mortality rate. Dalton *et al.* reported that bleeding events occurring in neonatal and pediatric patients during ECMO runs were independently associated with a higher risk of death [26,27]. Besides, Schmidt *et al.*[12] showed that major bleeding related to ECMO was associated with higher mortality in adult immunocompromised patients supported with ECMO for severe ARDS. Due to this higher risk of hemorrhage, in addition to the potential risk of anemia and/or thrombocytopenia secondary to their underlying disease or treatments, immunocompromised children supported with ECMO significantly needed more blood products transfusions. Smith *et al.* reported red cell transfusion as an independent predictor of mortality among patients undergoing ECMO for respiratory failure. Also, platelets consumption was significantly higher among non-survivors compared to survivors [28]. Red bloods cells and platelets consumption is strongly linked to a higher cost of care.

Surprisingly, we did not observe any significant difference between groups regarding nosocomial infections. These results are consistent with previous adults' studies [12,29] which have reported that the occurrence of any ECMO-related infections was not associated with increased mortality.

Our study has several limitations that need to be considered. For a start, the data are limited because of retrospective collection. Also, ECMO techniques and general management

of PARDS have gradually evolved over the past ten years. Because it is a single experienced ECMO center observational study, the limited number of patients and their heterogeneity may have weakened the statistical power of the study and the generalizability of our results may be limited. Despite the wild range of age and the small number of patients, our data are supported by recent publications [30].

CONCLUSION

Survival rate of immunocompromised children supported with ECMO for P-ARDS is lower than non-immunocompromised children, but the expectation for a great outcome is real and it is worth it if their condition is likely to be compatible with a good long-term quality of life. ECMO support will remain one of the most challenging decisions for the clinician and each case should be evaluated in a multidisciplinary meeting before implementation.

AUTHORS SECTION AREA

All authors read and approved the final version of the manuscript

BR collected the data, wrote the manuscript

IG performed the statistical analysis

JJ, SJ, YS, JEP and PLL reviewed the manuscript

JS reviewed and proofread the manuscript to assure an English translation

JR proposed the concept, wrote, reviewed, and performed some analysis of the manuscript.

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Figure caption

Figure I : Flow chart

Demographic datas	Non- Immunocompromised (N : 86)	Immunocompromised (N : 25)	p value
Demographic characteristics			
Age (days)	872 ± 1286	1366 ± 1492	NS
Weight (kg), mean ± SD	11.6 ± 12.7	15.9 ± 17.7	NS
Gender, male, n (%)	54.6	60.0	NS
Pre-ECMO severity scores			
AaDO2 Score	565 ± 49	555 ± 46	NS
Oxygenation index	40 ± 18	35 ± 12	NS
Oxygenation saturation index	24 ± 10	25 ± 8	NS
PELOD score (%)	17 ± 23	15 ± 25	NS
PaO_2/FiO_2 ratio	63 ± 31	71 ± 35	NS
PIM II score (%)	13.5 ± 18.7	23 ± 22	0.02
SpO_2/FiO_2 ratio	86 ± 22	92 ± 25	NS
ARDS etiology			
Status asthmaticus (%)	3.6	0	NS
Pneumonia (%)	80.1	64.2	NS
Bacterial infection (%)	51.8	25.1	0.02
Fungal infection (%)	0	12.5	0.001
Viral infection (%)	54.9	33.3	NS

Table I : Patients characteristics

Findings prior to ECMO	Non-Immunocompromised (N : 86)	Immunocompromised (N : 25)	p value
Hemodynamic data's			
Cardiac output (l/m$_2$/min)	3.3 ± 1.9	3.4 ± 1.5	NS
Fluid resuscitation (ml/kg)	65 ± 46	25 ± 19	0.05
Vasoactive score (µg/kg/min)	49 ± 60	50 ± 101	NS
LVEF (%)	66 ± 9	52 ± 20	NS
Lactate (mmol/l)	2.5 ± 2.8	3.6 ± 4.7	NS
Respiratory data's			
Pre ECMO length of invasive ventilation (days)	4.6 ± 3.9	3.7 ± 3.2	NS
Inspiratory pressure (cmH$_2$0)	46 ± 13	42 ± 8	NS
Tidal volume (ml/kg)	6.8 ± 1.7	6.2 ± 1.3	NS
Plateau pressure (cmH$_2$0)	37.1 ± 8.3	35.7 ± 5.7	NS
Driving pressure (cmH$_2$0)	27 ± 9	24 ± 6	NS
Positive end expiratory pressure (cmH$_2$O)	10.1 ± 4.1	10.8 ± 3.1	NS
Mean airway pressure (cmH$_2$O)	20.4 ± 6.3	21 ± 3.3	NS
Inspired fraction of oxygen (%)	98 ± 7	98 ± 7	NS
PaO$_2$ (mmHg)	58 ± 23	62 ± 18	NS
PaCO$_2$ (mmHg)	66 ± 25	71 ± 27	NS
pH	7.2 ± 0.2	7.2 ± 0.2	NS
Neuromuscular blockers (%)	98.8	96.1	NS
Prone positioning (%)	42.8	44.1	NS
Metabolic data's			
CRP (mg/l)	120 ± 108	113 ± 101	NS
Serum creatinine (µmol/l)	36 ± 35	44 ± 42	NS

Schwartz clearance (μmol/ml/min)	124 ± 79	136 ± 69	NS
Urine output (ml/kg/h)	3.3 ± 2.5	3.1 ± 2.5	NS
Hematologic data's			
Hemoglobin (g/dl)	10.5 ± 1.9	10.4 ± 1.9	NS
White blood cells (/mm$_3$)	16153 ± 9615	12879 ± 10648	NS
Lymphocytes (/mm$_3$)	2565 ± 3325	1030 ± 1120	NS
Neutrophils count (/mm$_3$)	7805 ± 6370	8045 ± 8633	NS
Platelets (/mm$_3$)	232083 ± 152782	160120 ± 132534	NS

Table II : Clinical and Biological findings prior to ECMO

LVEF: Left Ventricular Ejection Fraction; PaO$_2$: Partial pressure of arterial Oxygen; PaCO$_2$: Carbon dioxide partial pressure; CRP : C-Reactive Protein

Outcomes	Non-Immunocompromised (N : 86)	Immunocompromised (N : 25)	p value
Fibrinogen concentrate (unit)	0.4 ± 1.2	0.1 ± 0.3	NS
Platelet consumption (unit)	4.8 ± 7.8	12.1 ± 15.1	0.002
Red blood cell consumption (unit)	2.9 ± 3.5	4.8 ± 4.5	0.04
AT III consumption (unit)	0.9 ± 1 .6	0.9 ± 1.9	NS
Fresh frozen plasma concentrate (unit)	0.8 ± 1.9	0.6 ± 1.1	NS
Length of ECMO (days)	11.2 ± 10.8	13.3 ± 10.1	NS
Length of invasive mechanical ventilation (days)	24.7 ± 21.3	17.9 ± 13.2	NS
Length of vasoactive support (days)	5.9 ± 5.5	6.8 ± 8.3	NS
ECMO weaning rate (%)	73	52	0.0005
Intensive care discharge rate (%)	64	44	NS
Survival rate at 6 months (%)	62.8	41.7	0.004
Palliative care (%)	8.4	33.3	0.001
Multi-organ failure (%)	12.1	29.2	0.05

Table III: Clinical and biological endpoints
AT III = Antithrombin III

Complications	Non- Immunocompromised (N : 86)	Immunocompromised (N : 25)	p value
Fluid overload at weaning (%)	8.2 ± 6.1	8.9 ± 6.1	NS
Renal replacement therapy (%)	4.3	6.5	NS
Ischemic Stroke (%)	4.8	0	NS
Cerebral hemorrhage (%)	6.1	8.3	NS
Cannula hemorrhage (%)	24.4	45.8	NS
Gastro-intestinal hemorrhage (%)	9.6	37.5	0.003
Nasopharyngeal hemorrhage (%)	13.3	50.1	0.001
Pulmonary hemorrhage (%)	8.5	20.8	NS
Urogenital hemorrhage (%)	3.6	16.7	0.04
Central line associated bloodstream infection (%)	10.8	12.5	NS
Ventilator associated pneumonia (%)	21.7	25.1	NS

Table IV : Intensive Care and ECMO-related complications