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# Extracorporeal Life Support in Patients with Hematologic Malignancies: A Single Center Experience

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**Background:** Extracorporeal life support (ECLS) in patients with hematologic malignancies is considered to have a poor prognosis. However, to date, there is only one case series reported in the literature. In this study, we compared the in-hospital survival of ECLS in patients with and without hematologic malignancies. **Methods:** We reviewed a total of 66 patients who underwent ECLS for treatment of acute respiratory failure from January 2012 to December 2014. Of these patients, 22 (32%) were diagnosed with hematologic malignancies, and 13 (59%) underwent stem cell transplantation before ECLS. **Results:** The in-hospital survival rate of patients with hematologic malignancies was 5% (1/22), while that of patients without malignancies was 26% (12/46). The number of platelet transfusions was significantly higher in patients with hematologic malignancies (9.69±7.55 vs. 3.12±3.42 units/day). Multivariate analysis showed that the presence of hematologic malignancies was a significant negative predictor of survival to discharge (odds ratio, 0.07; 95% confidence interval, 0.01–0.79); p=0.031). **Conclusion:** ECLS in patients with hematologic malignancies had a lower in-hospital survival rate, compared to patients without hematologic malignancies.

*Key words:* 1. Extracorporeal membrane oxygenation
2. Acute respiratory distress syndrome (ARDS)
3. Hematology

## Introduction

Extracorporeal life support (ECLS) is a modified cardiopulmonary bypass to provide short-term respiratory or circulatory support to critically ill patients. It is frequently performed for treating acute respiratory failure (ARF) when conventional management strategies fail. According to the Extracorporeal Life Support Organization (ELSO) database, the use of ECLS for ARF has been increasing since 2009; this is attributed to the H1N1 influenza pandemic and the publication of the conventional ventilation or extracorporeal membrane oxygenation (ECMO) for severe adult respiratory failure (CESAR) trial [1]. The overall survival to discharge after the ECLS for a respiratory failure was approximately 55%, based on 3,369 adult respiratory failure patients in the ELSO database [1]. The CESAR trial was a prospective randomized study that reported an increased survival rate at 6 months in severe acute respiratory distress syndrome (ARDS) patients who were treated with the ECLS, compared to conventional therapy [2].

ARF is also a major indication for intensive care unit admissions in patients with hematologic malig-

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nancies (HMs) [3-5], and their in-hospital mortality with an invasive ventilator is also high [4-6]. If a patient is refractory to conventional ventilator care, but his or her HM was curable, then ECLS could be considered. However indications and results of ECLS in ARF patients with HMs are not well established. Wohlfarth et al. [7] reported 7 survivals among 14 adult patients with both HM and ARF, who were discharged or transferred to other facilities. This is the only case series published to date for ECLS outcomes in adult ARF patients with HMs, and clarification is much needed for this issue.

The purpose of this study was to determine differences in regard to in-hospital survival between adult patients with and without HMs. We also evaluated factors that may influence survival.

## Methods

Accessing the electronic medical records of our institution, Seoul Saint Mary's Hospital, we identified 68 adult patients with ARF who were treated with ECLS from January 2012 through December 2014. The patients who were treated with ECLS who were transferred to other hospitals during this timeframe were excluded, and patients under 18 years of age were also excluded from this analysis. After reviewing medical records, the patients were categorized into two groups, the HM group and the non-HM group, based on whether or not they had been diagnosed with an HM prior to ECLS therapy. The collection of data was focused on the survival rate, pre-ECLS characteristics including a hematologic profile, the number of transfusions, and the occurrence of major bleeding events. In order to compare pre-ECLS status, the measured physiological variables were used to calculate the Sequential Organ Failure Assessment (SOFA) scores [8], and the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) scores [9].

The HMs are defined as neoplastic diseases of the hematologic and lymphoid tissue, according to the World Health Organization classification [10]. Survival is defined as survival to discharge from the hospital or to transfer to a referring facility. Successful weaning is defined as a weaning from the ECLS followed by survival $>$48 hours. The Berlin Definition of ARDS was used for defining and grading the patients with respiratory failure [11]. The number of daily transfusions was calculated by dividing the total number of transfusions from the first to the last day of the ECLS into the total number of days under the ECLS. Major bleeding was defined as clinically overt bleeding accompanied with a decreased hemoglobin level of at least 2 g/dL, or a transfusion requirement of 1 or more packed red blood cells in a 24-hour period.

The initiation of the ECLS was decided either by the discretion of the cardiac surgeon, thoracic surgeon, or pulmonologist. Thus, there were no absolute criteria for initiating ECLS. All ECLSs were performed via peripheral cannulation. Veno-arterial ECMO was used in 8 patients (12%) and the pumpless extracorporeal lung assist was used in 7 patients (10%). During ECLS, protective lung ventilation was performed. Continuous intravenous heparin was administered and titrated to achieve an activated clotting time of 180s. No specific anticoagulation protocol for patients with HMs was followed. Packed red blood cells and platelets were administered to maintain a hematocrit $>$35% and a platelet count $>$100,000/$\mu$L. Weaning from the ECLS was attempted according to the ELSO guidelines [12].

Data were described as mean±standard deviation or median and interquartile ranges (25%–75%), unless otherwise indicated. Dichotomous data were presented as a number and percentage. The comparison between groups was made with the Student t-test for normally distributed variables and the Mann-Whitney rank sum test for those with non-normal distribution. The $\chi^2$ and Fisher exact tests were used for categorical variables. Multivariate logistic regression analysis was performed to identify significant risk factors associated with survival. The differences were considered to be statistically significant with $p<0.05$.

## Results

During the study period, 105 patients underwent ECLS, and 71 suffered from ARF. Of those 71 patients, 66 who underwent ECLS for ARF met the study criteria and 5 were excluded according to the exclusion criteria. Two patients without HMs underwent 2 episodes of ECLS during different hospital admissions. The mean age of all patients was 55.1±18.3 and 47 were male (69%). Prior to ECLS, the partial pressure of arterial oxygen ($P_aO_2$)/fractional inspired

**Table 1.** Characteristics and outcomes between patients with HMs and patients without HMs

| Characteristic | HM (n=22) | Non-HM (n=44) | p-value |
|---|---|---|---|
| Age (yr) | 47.4±11.8 | 58.7±19.8 | <0.01 |
| Male sex | 16 (72.7) | 31 (67.4) | 0.78 |
| Hours from ventilator to ECLS (hr) | 76 (14–159) | 56 (11.25–142.5) | 0.04 |
| Duration of ECLS (hr) | 162 (60.25–251.25) | 217.5 (112.75–322) | 0.13 |
| Acute respiratory failure diagnosis groups | | | 0.02 |
| Bacterial pneumonia | 7 (31.8) | 16 (34.8) | |
| Fungal pneumonia | 8 (36.4) | 5 (10.9) | |
| Viral pneumonia | 4 (18.2) | 4 (8.7) | |
| Other acute respiration failure | 3 (13.6) | 19 (41.3) | |
| Unknown | 0 | 2 (4.3) | |
| $PaO_2/FiO_2$ ratio | 62 (50.9–76.1) | 64.5 (49.6–73.6) | 0.33 |
| SOFA score[a)] | 12.7±3.5 | 10.9±3.6 | 0.06 |
| RESP score[b)] | −1.59±3.26 | −0.15±3.11 | 0.08 |
| Cardiac arrest | 2 (9.1) | 5 (10.9) | 0.59 |
| Veno-arterial type | 3 (13.6) | 5 (10.9) | 0.74 |
| Pre-ECLS blood test | | | |
| pH | 7.25±0.13 | 7.30±0.13 | 0.17 |
| $PaCO_2$ (mmHg) | 63.08±21.18 | 50.11±25.35 | 0.04 |
| Hemoglobin (g/dL) | 9.41±1.84 | 10.61±2.25 | 0.01 |
| Leukocyte (G/L) | 11.2±10.6 | 14.2±8.2 | 0.2 |
| Platelets (G/L) | 78.6±80.8 | 154.4±89.0 | <0.01 |
| Prothrombin time (%) | 1.3 (1.2–1.42) | 1.29 (1.22–1.42) | 0.30 |
| Major bleeding events | 4 (18.2) | 5 (10.9) | 0.32 |
| Use of continuous venovenous hemodialysis | 9 (40.9) | 27 (58.7) | 0.13 |
| Transfusion | | | |
| Red blood cells (unit/day) | 1.75±1.63 | 1.17±0.73 | 0.07 |
| Fresh frozen plasma (unit/day) | 1.17±1.69 | 0.60±0.98 | 0.37 |
| Platelet (unit/day) | 9.69±7.55 | 3.12±3.42 | <0.01 |
| Weaning success | 2 (9.1) | 14 (30.4) | 0.046 |
| Survival to discharge | 1 (4.5) | 12 (26.1) | 0.03 |

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
HM, hematologic malignancies; ECLS, extracorporeal life support; $PaO_2$, partial pressure of arterial oxygen; $FiO_2$, fractional inspired oxygen concentration; $PaCO_2$, partial pressure of arterial carbon dioxide.
[a)]Sequential Organ Failure Assessment Score at ECLS baseline [8]. [b)]Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score at ECLS baseline [9].

oxygen concentration ($FiO_2$) ratios of 66 patients (97%) were <100. Two patients (2.9%) underwent ECLS because of an uncontrolled hypercapnia, despite the fact that their $P_aO_2/FiO_2$ ratios were >100. The median duration of the ECLS was 203 hours (range, 82.5–305.5 hours) and the mean ventilator to ECLS time was 74 hours (range, 13.75–162.5 hours). The weaning success rate was 23.5% (16/68) and the in-hospital survival rate was 19.1% (13/68).

Twenty-two patients (32%) were diagnosed with an HM, and 13 (59%) underwent stem cell transplantation (SCT) before the ECLS. Acute myeloid leukemia was the most common type of underlying HM (14 patients, 64%). Moreover, there were 4 cases of acute lymphoblastic leukemia, 2 cases of Hodgkin's lymphoma, 1 case of multiple myeloma, and 1 case of myelodysplastic syndrome. In the patients who underwent a SCT, a complete remission was achieved prior to ECLS in 9 patients and transplantation within 1 year was performed in 6 patients. Six patients with HMs, but who had not undergone a SCT, had recently received chemotherapy.

Baseline demographics and characteristics of the HM and the non-HM groups, including SOFA and

**Table 2.** Characteristics and outcomes between in-hospital survivors and non-survivors

| Characteristic | Survivors | Non-survivors | p-value |
|---|---|---|---|
| Age (yr) | 53.23±21.06 | 55.49±17.83 | 0.69 |
| Male sex | 6 (46.2) | 41 (74.5) | 0.09 |
| Hours from ventilator to ECLS (hr) | 107.5±170.5 | 114.4±125.9 | 0.11 |
| Duration of extracorporeal membrane oxygenation (hr) | 230.7±156.2 | 240.2±220.3 | 0.88 |
| Acute respiratory failure diagnosis groups | | | 0.19 |
| Bacterial pneumonia | 4 (30.8) | 19 (34.5) | |
| Fungal pneumonia | 0 | 13 (23.6) | |
| Viral pneumonia | 2 (15.4) | 6 (10.9) | |
| Other acute respiration failure | 7 (53.9) | 17 (30.9) | |
| Unknown | 2 (3.6) | 0 | |
| $PaO_2/FiO_2$ ratio | 71.8±37.6 | 66.5±24.5 | 0.53 |
| SOFA score[a)] | 9.7±2.8 | 11.9±3.7 | 0.049 |
| RESP score[b)] | 1.31±2.53 | −1.07±3.20 | 0.02 |
| Cardiac arrest | 1 (14.3) | 6 (10.9) | 0.73 |
| Pre-ECLS pH | 7.33±0.11 | 7.27±0.13 | 0.17 |
| Pre-ECLS $PaCO_2$ (mmHg) | 44.8±20.5 | 56.5±25.2 | 0.13 |
| Veno-arterial type | 2 (15.4) | 6 (10.9) | 0.64 |
| Major bleeding events | 0 | 9 (16.4) | 0.19 |
| Use of continuous venovenous hemodialysis | 5 (38.5) | 31 (56.4) | 0.36 |
| Transfusion | | | |
| Red blood cells (unit/day) | 1.14±0.96 | 1.40±1.16 | 0.07 |
| Fresh frozen plasma (unit/day) | 0.30±0.56 | 0.90±1.36 | 0.07 |
| Platelet (unit/day) | 1.73±2.20 | 6.08±6.25 | 0.006 |

Values are presented as mean±standard deviation or number (%).
ECLS, extracorporeal life support; $PaO_2$, partial pressure of arterial oxygen; $FiO_2$, fractional inspired oxygen concentration; $PaCO_2$, partial pressure of arterial carbon dioxide.
a)Sequential Organ Failure Assessment Score at ECLS baseline [8].
b)Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score at ECLS baseline [9].

RESP scores, are presented in Table 1. The mean age was significantly younger ($p<0.01$) and the pre-ECLS ventilator time was longer (p=0.04) in the HM group than in the non-HM group. In regard to hematologic findings just before the ECLS, the serum hemoglobin and the platelet counts were significantly lower (p=0.04) in the HM group. There was also a significant difference (p=0.02) in the etiology of the ARF between the two groups. The proportion of fungal pneumonia was 25% higher in the HM group compared to the non-HM group. There were no statistically significant differences in the other pre-ECLS variables: SOFA and RESP scores, cardiac arrest, and $P_aO_2/FiO_2$ ratio. Successful weaning was achieved in only 2 patients with an HM (9%) and discharge alive from the hospital occurred in only 1 patient (5%), compared to 12 cases (26%) in the non-HM group. No patient who received a SCT survived to discharge with ECLS. The only survival in the HM group was a 58-year-old woman who had been undergoing a course of induction chemotherapy for acute myeloid leukemia. The patient suffered from intractable bacterial pneumonia, but was discharged from the hospital after 300 hours of ECLS therapy. No complications such as hemorrhage or renal failure occurred during ECLS sessions.

In regard to transfusions per day, the number of platelet transfusions was significantly higher in patients with HMs than those without HMs (9.69±7.55 vs. 3.12±3.42 units/day, $p<0.001$). In regard to red blood cell transfusions, the rate was higher in the HM group, but the difference was not statistically significant (p=0.071). Major bleeding events were documented in 9 cases (13%). Episodes of major bleeding were higher in the HM group (n=4, 18.2%) than in the non-HM group (n=5, 10.9%); however, the difference was not statistically significant (p=0.32). Specifically, bleeding events in the HM group occurred as 2 cases of massive pulmonary hemorrhage, 1 case of gastrointestinal bleeding, and 1 case of hematuria. Three cases were treated conservatively with transfusions and discontinuation of anticoagulation; however, the patient with pulmonary hemorrhage expired from uncontrolled hemorrhage accompanied by progressive respiratory failure. The patient with gastrointestinal bleeding was successfully weaned from the ECLS, but he expired from recurrent pneumonia following chemotherapy.

No difference was found in risk factors between survivors and non-survivors, including age, duration of mechanical ventilation before ECLS, and bleeding events during ECLS (Table 2). The SOFA score and the RESP score revealed that more risk factors were present in non-survivors than in survivors before ECLS. The number of platelet transfusions was significantly higher ($p<0.01$) in the non-survivors. The number of red blood cell transfusions was also higher in non-survivors, but the difference was not statistically significant (p=0.07). Multivariate analysis performed

**Table 3.** Multivariate logistic regression analysis for mortality

| Variable | Odds ratio (95% confidence interval) | p-value |
|---|---|---|
| Age (yr) | 0.99 (0.95–1.02) | 0.42 |
| Male sex | 4.02 (0.93–17.40) | 0.06 |
| Acute respiratory failure diagnosis groups | 1.04 (0.62–1.75) | 0.88 |
| Pre-ECLS cardiac arrest | 0.58 (0.05–6.83) | 0.66 |
| Use of continuous venovenous hemodialysis | 0.24 (0.05–1.08) | 0.06 |
| Hours from ventilator to ECLS | 1.00 (0.99–1.01) | 0.92 |
| Hematologic malignancies | 0.07 (0.01–0.79) | 0.03 |

ECLS, extracorporeal life support.

on all ARF patients with ECLS comprised common risk factors: age, male sex, etiology of ARF, cardiac arrest before ECLS, renal replacement therapy, mechanical ventilation duration before initiation of ECLS, and diagnosis of an HM [9]. Only the presence of an HM was significantly associated with in-hospital survival (p=0.03) (Table 3).

## Discussion

This study was the largest and the first to compare the outcomes of ECLS therapy in adult ARF patients with HMs to non-HMs. The in-hospital survival rate of ECLS in adult patients with HMs was significantly lower (p=0.03) than that of adult patients without HMs. Similar to several other studies, there were no differences between the two groups in regard to other risk factors: age, gender, renal replacement therapy, pre-ECLS $P_aO_2/FiO_2$ ratio, arterial pH, or diagnostic classification of ARF [9,13,14]. The presence of an HM was a significant risk factor for in-hospital survival, as shown in multivariate logistic regression analysis.

The patients admitted to the intensive care unit with hematologic malignancies were at high risk of death. In recent studies that reported employment of an invasive mechanical ventilator, the mortality rate ranged from 60.5%–72.2% [4-6]. In patients with severe ARF, significant survival improvement with ECLS is well-known. The CESAR trial randomly assigned 180 patients with severe ARF to either undergo ECMO or conventional management. The ECMO group had a significant increase in survival rate compared to the conventional management group [2]. However, ECLS was only used in a small number of patients with HMs. The RESP score is an ECMO outcome prediction score that was developed by ELSO; an HM was included in the score as an immunocompromised status, and regarded to be one of the risk factors for in-hospital mortality [9]. However, other diseases, including solid tumors, human immunodeficiency virus, and cirrhosis were also included in the same category; thus, the actual risk of an HM was unknown. To date, the literature contains only one report of ECLS outcomes in adult patients with HMs and another of ECLS outcomes in pediatric patients [7,15]. Wohlfarth et al. [7] reported the outcomes of 14 adult patients with HMs and ARF who underwent ECLS. Seven patients were successfully discharged even after 6 major bleeding events. However, none of the patients who had SCT prior to ECLS survived and most of survivals were patients with lymphoma. A study using ELSO data in 19 pediatric patients who required ECLS for cardiopulmonary support after SCT was reported by Gow et al. [15]. Fifteen (79%) died during ECLS, and only 1 patient survived to discharge from the hospital. In our study, only 1 patient survived to discharge and no patient who received SCT was discharged home. It is worth noting that we experienced a case of a 44-year-old female who underwent SCT 460 days previously and was successfully discharged after 6 days of V-A type ECLS for pericarditis. However, that patient was not included in this study.

The reason for the lower survival rate of ECLS in patients with ARDS and HMs has not been elucidated; however, the primary disease process underlying ARF in patients with HMs may influence the survival difference. Diagnostic groups of ARF differ, and treating patients with HMs is much more difficult than it is in those without malignancies. In our series, diagnoses of the cause of respiratory failure in 8 of 22 patients with HMs were fungal pneumonia, and of these most were *Pneumocystis* pneumonia. A study reported a mortality of *Pneumocystis* pneumonia ranging from 90%–100% without appropriate antibiotic therapy [16]; moreover, a mortality rate of 59% was reported for intubated patients with appropriate antibiotic administration [17]. Hemorrhage is another issue confronted when treating patients with HMs. In our study, there were no specific strategies regarding how to manage anticoagulation in patients with HMs; however, all anticoagulants were suspended when bleeding was suspected. Four major bleeding episodes occurred in our study, and most of them (3/4, 75%) were eventually controlled with conservative management, which included transfusions and discontinuation of anticoagulants. However, optimal transfusion and anticoagulation strategies for ECLS in patients with HMs were not established.

Aided by the advancement of stem cell transplantation therapy and chemotherapy, there has been a great increase in the survival of patients with HMs within the last several decades. According to the recent report of 48,380 patients with acute myeloid leukemia in England, the 5-year survival rate of patients under the age of 60 was only 10.8% in the 1980s; while it became much higher after 2001 (8.4%) [18]. Thus, in the case where the patient's HM is curable, ECLS can be considered when the patient has no possibility of surviving intractable respiratory failure. However, survival of these patients was rare in our study, which raises ethical concerns regarding the use of ECLS in these patients. Therefore, before initiation of ECLS in patients with HMs, the status of the hematologic disease and the possibility of survival should be taken into consideration.

This study has several significant limitations. First, while this is, to the best of our knowledge, the largest reported outcome study of ECLS in adult patients with HMs, the sample was small. Second, undocumented information could not be used. Third, no unified protocol for initiating and maintaining ECLS was used. Finally, we were inexperienced regarding ECLS in patients with HMs during the study period.

Despite the poor outcomes of our patients with HMs in this study, more research is needed to determine the true risks of patients with HMs undergoing ECLS. To attain more reliable results, well-designed prospective studies under a unified protocol are needed; however, this is difficult with critically ill patients. Until the establishment of its efficacy and associated risks is understood and documented, the application of ECLS to patients with HMs should be cautiously performed, particularly in regard to anticoagulation and transfusions when they are refractory to conventional treatment.

In conclusion, in our experience, the in-hospital survival rate of adult patients with HMs was lower than that of adult patients without HMs. The presence of an HM was a negative prognostic factor for survival to discharge after ECLS. Well-designed prospective studies are necessary to validate the effect of HMs with ECLS for ARF patients.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

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