ORIGINAL ARTICLE

KJIM

Clinical outcomes of extracorporeal membrane oxygenation support in patients with hematologic malignancies

Hye Seon Kang[1],[*], Chin Kook Rhee[1],[*], Hea Yon Lee[1], Young Kyoon Kim[1], Soon Seog Kwon[1], Seok Chan Kim[1], and Jong Wook Lee[2]

Divisions of [1]Pulmonary, Allergy and Critical Care Medicine and [2]Hematology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Correspondence to
Jong Wook Lee, M.D.
Division of Hematology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 137-701, Korea
Tel: +82-2-2258-6050
Fax: +82-2-780-1283
E-mail: jwlee@catholic.ac.kr

*These authors contributed equally to this work.

Background/Aims: The clinical outcomes of patients with hematologic malignancies who were treated with extracorporeal membrane oxygenation (ECMO) after the failu re of optimal conventional therapy were determined.

Methods: The medical records of all patients administered ECMO during their stay in a medical intensive care unit of Seoul St. Mary's Hospital between February 2010 and July 2013 were reviewed retrospectively.

Results: In total, 15 patients with hematologic malignancies were compared to 33 immunocompetent patients with documented cardiorespiratory failure. Underlying hematologic malignancies were significantly associated with lower overall survival (0.0% vs. 24.2%, $p = 0.044$). Mortality was significantly associated with a higher 24 hours ECMO inspired fraction of oxygen (0.71 ± 0.24 vs. 0.47 ± 0.13, $p = 0.015$), the development of infection after ECMO (87.5% vs. 25.0%, $p = 0.001$), and the presence of hyperbilirubinemia (70.0% vs. 0.0%, $p < 0.001$). Matching of the patients based on their Acute Physiology and Chronic Health Evaluation II scores confirmed the greater risk of mortality in patients with hematologic malignancies (survival: 0.0% vs. 40.0%, $p = 0.017$). The mean difference in inotropic-equivalent scores after ECMO was significantly lower in the immunocompetent patients than in those with hematologic malignancies (-59.22 ± 97.83 vs. 53.87 ± 164.46, $p = 0.026$).

Conclusions: Patients with hematologic malignancies who require ECMO for respiratory support have poor outcomes. The incidence of complications in these patients did not significantly differ from that in immunocompetent patients.

Keywords: Extracorporeal membrane oxygenation; Hematologic neoplasms; Adults; Mortality; Complications

INTRODUCTION

Recent advances in chemotherapeutic agents and hematopoietic stem cell transplantation (HSCT) have improved the prognosis of patients with hematologic malignancies [1,2]. Nonetheless, these patients frequently develop life-threatening complications as a result of infection, treatment, and the disease process [3-6]. Complications are particularly likely to develop in the lungs and include pneumonia, pulmonary hemorrhage, bronchiolitis obliterans, and graft-versus-host disease [7,8]. Among the 40% of patients with hematologic malignan-

Kang HS, et al. ECMO for immunocompromised patients

KJIM

cies who are admitted to an intensive care unit (ICU) for respiratory support, half will require mechanical ventilation [9]. However, the need for mechanical ventilation in patients with hematologic malignancies is associated with a poor prognosis [10,11].

Earlier studies evaluated the outcomes of extracorporeal membrane oxygenation (ECMO) in patients with hematologic malignancies. Most of these were clinical studies involving either a mixture of patients with various types of solid tumors or pediatric patients, and the successful use of the technique in both settings was rare [12-14]. The present study provides a systematic assessment of the clinical outcomes of patients with hematologic malignancies who were treated with ECMO after the failure of optimal conventional therapy, based on a retrospective review of the patients' medical records.

METHODS

The present study was based on a retrospective review of the medical records of all adult patients who underwent ECMO for cardiopulmonary support at the medical ICU of Seoul St. Mary's Hospital of The Catholic University of Korea between February 2010 and July 2013. More than 450 HSCT procedures are performed annually at this hospital. The decision to initiate ECMO is made according to the clinical judgment of the intensive care specialist after an assessment of the patient's clinical parameters. During the study period, 76 adult patients underwent ECMO at the medical ICU. From this group, 28 patients with underlying non-hematologic malignancies were excluded from the study. Thus, the baseline demographics and clinical outcomes were compared between patients with hematologic malignancies and immunocompetent controls with acute cardiorespiratory failure, all of whom underwent ECMO.

Patient demographics, disease severity scores as evaluated using the Acute Physiology and Chronic Health Evaluation (APACHE) II, lung injury score, reason for ECMO, type of ECMO, clinical parameters before and during ECMO, complications during ECMO, survival following ECMO decannulation, and the ICU- and hospital-discharge dates were analyzed based on the data available in the patients' medical records. The APACHE II score was recorded for each patient within the first

24 hours after ICU admission. Hyperbilirubinemia was defined as a total bilirubin level > 4 mg/dL, and neutropenia was defined as a neutrophil count < 500 cells/μL.

Statistical analysis

Statistical analysis was performed using Fisher exact test for discrete variables and the Mann-Whitney U test for continuous variables. A two-sided $p < 0.05$ indicated statistical significance. In view of the differences in disease severity between the two groups, an individualized APACHE II score-matched analysis was used to adjust for the effects of the underlying risk factors on the clinical outcomes. Each patient in the hematologic disease group was matched to a patient in the immunocompetent general disease group (1:1 match) who had the closest APACHE II score. A maximal difference of 5% in the APACHE II score was allowed in the matching process. If there was more than one possible match based on an identical APACHE II score, the patients were matched for age (first secondary-matching variable) and Glasgow coma score (backup secondary-matching variable). Matched patients were reanalyzed as described above. Survival was analyzed using the Kaplan-Meier method. All of the statistical analyses were performed using the SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Ethics statement

The study protocol was approved by the Institutional Review Board (IRB) of Seoul St. Mary's Hospital (IRB no. KC13RISI0589). In view of the retrospective nature of the study, the need for informed consent from the patients was waived.

RESULTS

Demographic characteristics

The study population consisted of 15 immunocompromised patients with hematologic malignancies, and 33 immunocompetent patients with other general diseases. All of the 48 patients had received ECMO.

Hematologic malignancies

Among the patients with hematologic malignancies, 10 had leukemia, including eight with acute myelogenous leukemia and two with acute lymphoblastic leukemia.

One patient each had Hodgkin lymphoma, multiple myeloma, myelodysplastic syndrome, hematophagocytic lymphohistiocytosis, and primary myelofibrosis. Five of the patients with acute myelogenous leukemia, one with primary myelofibrosis, and one with acute lymphoblastic leukemia underwent HSCT. Six of the HSCT procedures were allogeneic and one was autologous. In these patients, ECMO was indicated for pulmonary support (Table 1).

Hematologic and general disease

The demographics and ECMO variables of the patients with hematologic malignancies and the immunocompetent patients are compared in Table 2. The survival rate was lower in patients with hematologic malignancies (24.2% vs. 0.0%, p = 0.044). Immunocompetent patients were significantly older than patients with hema-

tologic malignancies (58.45 ± 18.60 years vs. 46.60 ± 13.62 years, p = 0.014). The latter group had a lower mean pH after 24 hours of ECMO (7.36 ± 0.11 vs. 7.43 ± 0.11, p = 0.023). The mean duration of ECMO and the type of cannulation did not differ between the two groups.

Survivors and non-survivors

The demographics and ECMO variables of the survivors and non-survivors are compared in Table 3. Fig. 1 shows the Kaplan-Meier survival curves for the two groups. Mortality was significantly associated with underlying hematologic malignancies (0.0% vs. 37.5%, p = 0.044), the development of infection after ECMO (87.5% vs. 25.0%, p = 0.001), hyperbilirubinemia (0.0% vs. 70.0%, p < 0.001), and worse ventilation parameters after 24 hours of ECMO, especially with a higher inspired fraction of oxygen (0.71 ± 0.24 vs. 0.47 ± 0.13, p = 0.015). Inotropic-equiv-

Table 1. Individual characteristics and outcomes of patients with hematologic malignancies

Patient no.	Disease	Therapy status (days posttherapy)	Etiology of ARF	APACHE II score	LIS	ECMO days	Bleeding	Outcome	Cause of death
1	PHG	-	Pneumonia	8	2.5	22	Minor	Died	Sepsis
2	MDS	Danazol	PAP	11	2.75	41	Major	Died	Pneumonia
3	HLH	Induction on ECMO	Pneumonia	14	2.5	13	-	Died	Pneumonia
4	AML	Allo SCT (30)	Pneumonia	31	1.75	5	Major	Died	Pulmonary hemorrhage
5	AML	Allo SCT (420)	Pneumonia	23	2.25	28	-	Died	Pneumonia
6	PMF	Allo SCT (84)	Pneumonia	12	2	13	-	Died	RV failure
7	MM	Chemotherapy (55)	Pneumonia	25	3	27	-	Died	Sepsis
8	HD	Chemotherapy (22)	Pneumonia	16	2.5	8	-	Died	Sepsis
9	AML	Induction (10)	RAS syndrome	13	2	2	Major	Died	Pulmonary hemorrhage
10	AML	Allo SCT (2,190)	cGVHD	17	2.5	3	-	Died	Pneumonia
11	AML	Allo SCT (1,735)	Pneumonia	22	3	9	-	Died	Sepsis
12	AML	Allo SCT (417)	Pneumonia	13	2	1		Died	MOF
13	AML	Induction (22)	Pneumonia	16	2.25	8	Major	Died	Pulmonary hemorrhage
14	AML	Allo SCT (73)	Pneumonia	13	2.5	5	-	Died	MOF
15	ALL	Induction (27)	Pneumonia	32	2.25	7	-	Died	Sepsis

ARF, acute respiratory failure; APACHE, Acute Physiology and Chronic Health Evaluation; LIS, lung injury score, Murray score; ECMO, extracorporeal membrane oxygenation; PHG, panhypogammaglobulinemia; MDS, myelodysplastic syndrome; PAP, pulmonary alveolar proteinosis; HLH, hematophagocytic lymphohistiocytosis; AML, acute myelogenous leukemia; SCT, stem cell transplantation; PMF, primary myelofibrosis; MM, multiple myeloma; HD, Hodgkin's disease; RAS, retinoic acid syndrome; cGVHD, chronic lung graft versus host disease; MOF, multisystem organ failure; ALL, acute lymphoblastic leukemia.

Kang HS, et al. ECMO for immunocompromised patients

KJIM

Table 2. Clinical characteristics of patients with hematologic malignancies and immunocompetent controls who underwent ECMO

Characteristic	Hematologic malignancies (n = 15)	Immunocompetent controls (n = 33)	p value
Demographics			
Age, yr	46.60 ± 13.62	58.45 ± 18.60	0.014[a]
Male sex	12/15 (80.0)	26/33 (78.8)	1.000
Arrest before ECMO	0/15 (0)	5/33 (15.2)	0.167
APACHE II score	17.13 ± 7.27	14.97 ± 8.49	0.090
Blood gas analysis			
Pre-ECMO pH	7.30 ± 0.17	7.30 ± 0.14	0.842
Pre-ECMO pO_2	73.11 ± 28.01	66.85 ± 23.82	0.475
Pre-ECMO pCO_2	51.16 ± 23.55	53.45 ± 31.03	0.842
Pre-ECMO A-a differences	12.93 ± 51.21	24.44 ± 58.24	0.632
Pre-ECMO P/F ratio	98.45 ± 81.01	86.29 ± 66.92	0.556
Pre-ECMO FiO_2	0.87 ± 0.20	0.83 ± 0.22	0.487
24-ECMO pH	7.36 ± 0.11	7.43 ± 0.11	0.023[a]
24-ECMO pO_2	115.10 ± 116.29	94.85 ± 81.22	0.761
24-ECMO pCO_2	38.29 ± 7.69	35.88 ± 7.68	0.598
24-ECMO A-a differences	−12.96 ± 111.92	18.77 ± 84.67	0.322
24-ECMO P/F ratio	159.65 ± 112.39	163.95 ± 209.98	0.697
24-ECMO FiO_2	0.71 ± 0.25	0.65 ± 0.23	0.437
Inotropic equivalent score[b]			
Pre-ECMO	36.62 ± 91.07	77.30 ± 172.35	0.461
24-hour ECMO	90.50 ± 243.36	75.57 ± 188.20	0.912
Inotropic difference	53.87 ± 164.46	−1.63 ± 191.96	0.183
MV to ECMO time, hr	109.47 ± 97.49	120.33 ± 155.25	0.805
Lag from cardiopulmonary event to ECMO, day	12.40 ± 9.48	8.00 ± 8.04	0.103
ECMO			
Duration of ECMO, hr	304.13 ± 273.379	281.24 ± 253.39	0.778
Type of support			0.294
Pulmonary	15/15 (100)	29/33 (65.9)	
Cardiac	0/15 (0)	4/33 (12.1)	
ECPR	0/15 (0)	0/33 (0)	
Type of cannulation			0.189
Venoarterial	0/15 (0)	3/33 (9.1)	
Venovenous	14/15 (93.3)	30/33 (90.9)	
Venovenous and venoarterial	1/15 (6.7)	0/33 (0)	

Values are presented as mean ± SD or number (%).

ECMO, extracorporeal membrane oxygenation; APACHE, Acute Physiology and Chronic Health Evaluation; pO_2, oxygen partial pressure; pCO_2, carbon dioxide partial pressure; A-a difference, alveolar-arterial Gradient; P/F ratio, the ratio of arterial oxygen concentration to the fraction of inspired oxygen; FiO_2, the fraction of inspired oxygen; MV, mechanical ventilation; ECPR, extracorporeal life support for cardiopulmonary resuscitation.

[a]Mann-Whitney U test.

[b]Calculated from the doses of dopamine + dobutamine (in µg/kg/min) + [doses of epinephrine + norepinephrine + isoproterenol (in µg/kg/min)] × 100 + dose of milrinone (in µg/kg/min) × 15 [26].

Table 3. Comparison of survivors and non-survivors following ECMO

Characteristic	Survivor (n = 8)	Nonsurvivors (n = 40)	p value
Demographics			
Age, yr	54.88 ± 21.55	54.73 ± 17.44	0.945
Male sex	6/8 (75.0)	32/40 (80.0)	0.666
Hematologic malignancies	0/8 (0)	15/40 (37.5)	0.044[a]
APACHE II score	15.13 ± 7.66	16.00 ± 8.33	0.818
Blood gas analysis			
Pre-ECMO pH	7.37 ± 0.139	7.29 ± 0.149	0.141
Pre-ECMO pO_2	70.48 ± 25.93	68.65 ± 25.33	0.763
Pre-ECMO P/F ratio	88.58 ± 89.38	90.39 ± 68.29	0.924
24-ECMO pH	7.48 ± 0.07	7.39 ± 0.11	0.025[b]
24-ECMO pO_2	150.71 ± 158.93	92.61 ± 76.05	0.367
24-ECMO P/F ratio	312.26 ± 399.05	132.68 ± 81.37	0.149
Inotropic equivalent score[c]			
Pre-ECMO	207.03 ± 345.87	42.59 ± 85.44	0.010[b]
24-hour ECMO	89.39 ± 205.82	78.83 ± 207.69	0.834
Inotropic difference	−77.05 ± 127.25	34.27 ± 189.03	0.183
Ventilation			
Pre-ECMO SBP	115.57 ± 27.20	119.03 ± 28.83	0.826
Pre-ECMO DBP	56.43 ± 8.62	68.20 ± 15.78	0.026[b]
Complications			
Infection before ECMO	1/8 (12.5)	17/40 (42.5)	0.229
Infection after ECMO	2/8 (25.0)	35/40 (87.5)	0.001[a]
Hyperbilirubinemia	0/8 (0)	28/40 (70.0)	< 0.001[a]

Values are presented as mean ± SD or number (%).

ECMO, extracorporeal membrane oxygenation; APACHE, Acute Physiology and Chronic Health Evaluation; pO_2, oxygen partial pressure; P/F ratio, the ratio of arterial oxygen concentration to the fraction of inspired oxygen; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a]Fisher exact test.

[b]Mann-Whitney U test.

[c]Inotropic equivalent score was calculated from the doses of dopamine + dobutamine (in μg/kg/min) + [doses of epinephrine + norepinephrine + isoproterenol (in μg/kg/min)] × 100 + dose of milrinone (in μg/kg/min) × 15 [26].

alent scores before ECMO were significantly higher in survivors, but after 24 hours of ECMO, they were similar because of the resulting blood pressure stabilization in those patients. The APACHE II score, pre-ECMO ventilator parameters, time between mechanical ventilation and ECMO, running time of ECMO, and types of support and cannulation were not different between the two groups.

Individualized APACHE-II-score-matched analysis

Patients in the two groups were matched based on their APACHE II scores to adjust for the effect of disease severity upon ICU admission (Table 4). After matching, mortality was higher in patients with hematologic malignancies (100.0% vs. 60.0%, $p = 0.017$). Inotropic-equivalent scores 24 hours after ECMO treatment were significantly lower in the immunocompetent controls (53.87 ± 164.46 vs. −59.22 ± 97.83, $p = 0.026$). There was no association of mortality with sex, blood gas parameters before and 24 hours after ECMO, time from mechanical ventilation to ECMO initiation, running time of ECMO, or types of support and cannulation. The causes of
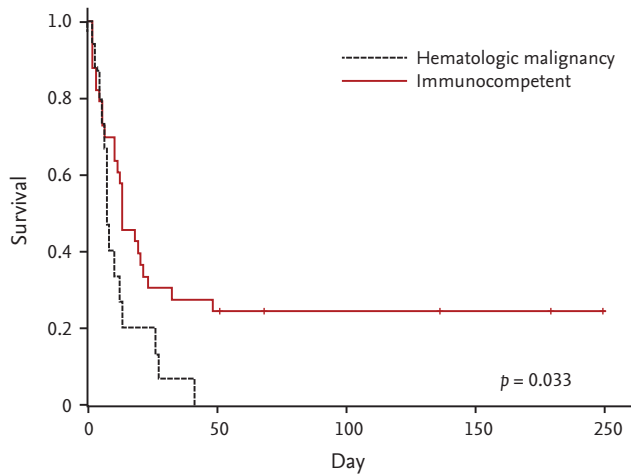
Kang HS, et al. ECMO for immunocompromised patients

KJIM

Figure 1. Kaplan-Meier survival analysis of patients with hematologic malignancies and immunocompetent controls matched for their Acute Physiology and Chronic Health Evaluation II scores. The survival distribution of the two groups was compared using a log-rank test. Median survival was 8.00 days versus 13.00 days, respectively.

death (in order of occurrence) in patients with hematologic malignancies were sepsis, pneumonia, pulmonary hemorrhage, multisystem organ failure, and right heart failure; in the immunocompetent controls, they were sepsis, pneumonia, and pulmonary hemorrhage.

Complications

The reported complications were divided into hemorrhagic, neurologic, renal, cardiovascular, pulmonary, infectious, and hepatic complications, and are summarized in Table 5. Common complications were low blood pressure requiring inotropics, culture-positive infection, renal failure requiring continuous renal replacement therapy, acute renal failure (creatinine level of 1.5 to 3.0 mg/dL), and gastrointestinal hemorrhage. There were no significant differences in the incidence of complications between patients with underlying hematologic malignancies and the immunocompetent controls. A comparison of the complications in ECMO survivors and non-survivors showed a significantly higher incidence of hyperbilirubinemia and the development of infection after ECMO in the latter.

Infection

Infections before ECMO initiation were documented in 18 of the 48 patients (37.5%). The infectious agents were *Acinetobacter baumannii* (n = 6), *Candida* spp. (n = 3), *Steno-*

trophomonas maltophilia (n = 2), *Pseudomonas aeruginosa* (n = 1), coagulase-negative *Staphylococcus* (n = 1), methicillin-sensitive *Staphylococcus aureus* (n = 1), methicillin-resistant *S. aureus* (n = 1), and *Enterobacter* spp. (n = 1).

Infection after the initiation of ECMO was one of the factors influencing mortality. After ECMO initiation, 37 of the 48 patients (77.0%) had documented infections; 87.5% were non-survivors and 25.0% were survivors. In total, two or more species of bacteria were isolated from 14 of these 37 patients (37.8%). The identified microorganisms were *A. baumannii* (n = 26), *P. aeruginosa* (n = 4), methicillin-resistant coagulase-negative *Staphylococcus* (n = 4), *Candida* spp. (n = 5), *S. maltophilia* (n = 3), *Enterobacter* spp. (n = 3), methicillin-resistant *S. aureus* (n = 1), extended-spectrum β-lactamase-producing *Klebsiella pneumonia* (n = 1), *Serratia marcescens* (n = 1), and *Clostridium difficile* (n = 1). The same organisms were isolated in nine of 37 patients before and after ECMO initiation; whether these were new or previous infections that were not completely treated is unknown.

DISCUSSION

Patients with hematologic malignancies frequently develop life-threatening complications as a result of infection, treatment, and the disease process [3-6]. These complications often involve the lungs [7]. Chemotherapy-related pulmonary complications in patients with hematologic malignancies include pneumonia, pulmonary hemorrhage, and neoplastic infiltration, and account for the poor outcomes [15]. Early-phase complications in patients undergoing HSCT include viral, fungal, and bacterial infections and pulmonary hemorrhage, whereas common late-phase complications are bronchiolitis obliterans, bronchiolitis obliterans with organizing pneumonia, and graft-versus-host disease [8,16]. Acute respiratory failure is the leading cause of ICU admission in patients with hematologic malignancies, and 50% to 70% of these patients will require mechanical ventilation [9,17]. However, the need for mechanical ventilation is a prognostic for a poor clinical outcome [9-11,18-20].

Most clinical studies of ECMO have either been based on mixed groups of patients with various types of solid tumors or on pediatric patients [12-14]. Earlier studies

Table 4. Clinical characteristics and outcomes ECMO in patients with hematologic malignancies and immunocompetent controls when matched for their APACHE II scores

Characteristic	Hematologic malignancies (n = 15)	Immunocompetent controls (n = 15)	p value
Demographics			
Age, yr	48.60 ± 13.62	59.20 ± 19.21	0.021[a]
Male sex	12/15 (80.0)	11/15 (73.3)	1.000
Arrest before ECMO	0/15 (0)	3/15 (20.0)	0.224
Survival	0/15 (0)	6/15 (40.0)	0.017[a]
APACHE II score	17.73 ± 7.27	17.67 ± 7.68	0.902
Blood gas analysis			
Pre-ECMO pH	7.30 ± 0.17	7.33 ± 0.13	0.775
Pre-ECMO pO_2	73.11 ± 28.01	67.95 ± 22.96	0.595
Pre-ECMO pCO_2	51.16 ± 23.55	45.07 ± 20.21	0.412
Pre-ECMO A-a differences	12.93 ± 51.21	25.70 ± 29.28	0.713
Pre-ECMO P/F ratio	98.45 ± 81.01	90.27 ± 66.79	0.967
Pre-ECMO FiO_2	0.87 ± 0.20	0.83 ± 0.21	0.519
24-ECMO pH	7.36 ± 0.11	7.43 ± 0.57	0.056
24-ECMO pO_2	115.10 ± 116.29	113.14 ± 113.29	0.967
24-ECMO pCO_2	38.29 ± 7.69	35.39 ± 6.59	0.461
24-ECMO A-a differences	−12.96 ± 111.92	−7.37 ± 111.71	0.744
24-ECMO P/F ratio	159.65 ± 112.39	215.86 ± 300.46	0.713
24-ECMO FiO_2	0.71 ± 0.25	0.66 ± 0.23	0.567
Inotropic equivalent score[b]			
Before ECMO	36.62 ± 91.07	111.46 ± 229.76	0.162
24-hour ECMO	90.50 ± 243.36	52.23 ± 142.68	0.595
Inotropic difference	53.87 ± 164.46	−59.22 ± 97.83	0.026[a]
MV to ECMO time, hr	109.47 ± 97.49	106.53 ± 107.97	0.806
ECMO			
Duration of ECMO, hr	304.13 ± 273.38	251.93 ± 166.23	0.935
Type of support			1.000
Pulmonary	15/15 (100)	14/15 (93.3)	
Cardiac	0/15 (0)	1/15 (66.7)	
ECPR	0/15 (0)	0/15 (0)	
Type of cannulation			0.483
Venoarterial	0/15 (0)	1/15 (66.7)	
Venovenous	13/15 (86.75)	14/15 (93.3)	
Venovenous and venoarterial	2/15 (13.3)	0/15 (0)	
Complications			
Infection before ECMO	6/15 (40.0)	5/15 (33.3)	1.000
Infection after ECMO	13/15 (86.7)	11/15 (73.3)	0.651
Hyperbilirubinemia	9/15 (60.0)	8/15 (53.3)	1.000
Causes of death			
Sepsis	5/15	5/9	
Pneumonia	4/15	3/9	
Pulmonary hemorrhage	3/15	1/9	
Multisystem organ failure	2/15	0/9	
Right heart failure	1/15	0/9	

Values are presented as mean ± SD or number (%).

ECMO, extracorporeal membrane oxygenation; APACHE, Acute Physiology and Chronic Health Evaluation; pO_2, oxygen partial pressure; pCO_2, carbon dioxide partial pressure; A-a difference, alveolar-arterial gradient; P/F ratio, the ratio of arterial oxygen concentration to the fraction of inspired oxygen; FiO_2, the fraction of inspired oxygen; ECPR, extracorporeal life support for cardiopulmonary resuscitation.

[a]Mann-Whitney U test.

[b]Inotropic equivalent score was calculated from the doses of dopamine + dobutamine (in µg/kg/min) + [doses of epinephrine + norepinephrine + isoproterenol (in µg/kg/min)] × 100 + dose of milrinone (in µg/kg/min) × 15 [26].

Table 5. Comparison of complications in patients with hematologic malilgnancies and immunocompetent controls who underwent ECMO

Variable	Hematologic malignancies (n = 15)	Immunocompetent controls (n = 33)	p value
Hemorrhagic complications			
GI hemorrhage	5 (33.3)	4 (12.1)	0.115
Cannula site hemorrhage	1 (6.7)	8 (24.2)	0.239
Hemolysis	1 (6.7)	1 (3.0)	0.532
Pulmonary hemorrhage	5 (33.3)	6 (18.2)	0.283
Neurological complications			
Brain death	0	0	1.000
CNS infarction	0	0	1.000
CNS hemorrhage	1 (6.7)	2 (6.1)	1.000
Renal complications			
Creatinine 1.5–3.0 mg/dL	4 (26.7)	5 (15.2)	0.432
Creatinine > 3.0 mg/dL	1 (6.7)	3 (9.1)	1.000
Dialysis required	10 (66.7)	18 (54.5)	0.535
Cardiovascular complications			
Inotropics on ECMO	11 (73.3)	18 (54.5)	0.341
CPR required	1 (6.7)	4 (12.1)	1.000
Cardiac arrhythmia	2 (13.3)	4 (12.1)	1.000
Pneumothorax	3 (20.0)	6 (18.2)	1.000
Infectious complications			
Culture positive infection	10 (66.7)	20 (60.6)	0.757
Hyperbilirubinemia	10 (66.7)	18 (54.5)	0.535

Values are presented as number (%).

ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; CNS, central nervous system; CPR, cardiopulmonary resuscitation.

evaluated the outcomes of patients with hematologic malignancies who received ECMO after the failure of conventional mechanical ventilation [21-23]. However, the successful treatment of these patients was rare, which has raised ethical concerns regarding the use of ECMO in this setting. Thus, in the present study we analyzed the medical records of patients with hematologic malignancies who were treated with ECMO to determine the clinical outcomes. Our results provide relevant data for clinicians considering ECMO in patients in whom optimal conventional therapy has failed. Specifically, the outcome of ECMO was compared in patients with hematologic disease and immunocompetent patients with acute cardiorespiratory failure. Survival was higher among the immunocompetent patients than among

those with hematologic malignancies. An analysis of the factors predictive of a favorable outcome after ECMO identified a reduced oxygen requirement and a reduced inotropic-equivalent score 24 hours after ECMO. Factors associated with a poor prognosis were culture-proven infection and hyperbilirubinemia during ECMO. Pre-ECMO ventilator parameters and APACHE II scores were not significantly different between survivors and non-survivors. These results suggest that the high mortality rate of patients with hematologic disease was related to the progression of organ dysfunction and infections induced by underlying conditions, such as the immunocompromised state and the disease process. Our results are consistent with previous report of the poor prognosis of pediatric patients requiring ECMO

for cardiopulmonary disease after HSCT. In these patients, the development of organ failure is a predictor of mortality [12].

The APACHE II score is used to predict mortality in critically ill patients with hematologic malignancies [9]. Therefore, in the present study, it was used to match patients in the two groups and thereby reduce the selection bias caused by differences in the baseline risks for poor outcomes. After matching, the significance of hematologic malignancy as a predictor of high mortality was even greater. The inotropic-equivalent score after ECMO was significantly lower in patients with hematologic disease than in immunocompetent patients, suggesting an association between hemodynamic instability during ECMO and poor outcome. Previous study of critically ill patients with hematologic malignances, regardless of ECMO treatment, supports our results [18].

The development of complications in our patients was associated with a poor prognosis. Patients with cardiorespiratory failure had a large number of complications during ECMO treatment. In addition, hyperbilirubinemia and the development of infection after ECMO were significantly more common in non-survivors. However, the overall incidence of complications was not significantly different between patients with hematologic malignancies and the immunocompent controls.

In critically ill patients with hematologic malignancies, the development of multiorgan dysfunction is associated with a worse prognosis [9,24]. Bleeding and infection, as the main complications related to ECMO, have a significant impact on mortality [25,26]. Thus, underlying hematologic disease has been a relative contraindication for ECMO because of the risk of bleeding. However, our study suggests that ECMO can be performed safely even in patients with hematologic malignancies, as bleeding events were not significantly more frequent in those patients than in the controls. This finding is strongly supported by a recent study in which the incidence of bleeding complications was not higher in patients with hematologic malignancies than in control patients [27].

The present study had several limitations. First, it was a retrospective observational study. However, because there are ethical concerns about conducting clinical trials of ECMO in patients with hematologic malignancies, a prospective randomized clinical trial of the efficacy of ECMO in patients with hematologic malignancies is currently not possible. Second, this was a single-center study. Nonetheless, our institution is one of the largest centers in Asia that deals with hematologic malignancies; thus, we were able to include a relatively large number of patients who received ECMO. A further advantage was that a single protocol was followed in the treatment and management of the patients. Clinical decisions were made by a multidisciplinary team that included critical care specialists. Therefore, there was little variation in patient management and ECMO treatment strategies. Third, all of the patients with hematologic malignancies who underwent ECMO died, probably because these critically ill patients are known to have a poor prognosis [9,20]. However, a recent study showed a relatively good clinical outcome of patients with hematologic malignancies who were treated with ECMO [27]. A simple comparison of the outcomes in that study with those in our study is difficult because of differences in the treatment and the subsets of hematologic disease between the two study populations. For example, the majority of our patients with hematologic disease had acute leukemia, whereas in the study by Wohlfarth et al. [27], most patients had lymphoma. It is well known that patients with acute leukemia have a poorer prognosis than those with other hematologic malignancies. Further investigations of the safety of ECMO according to the subset of hematologic malignancy are needed.

In conclusion, our study showed that patients with hematologic disease who require ECMO for cardiopulmonary support have poor outcomes. Increased mortality was associated with the development of infection and hyperbilirubinemia during ECMO. However, the incidence of complications in patients with hematologic malignancy did not significantly differ from that in immunocompetent patients. Therefore, the use of ECMO in patients with hematologic disease deserves further consideration. Evidence to support ECMO as therapy in these high-risk patients must come from a well-designed randomized controlled study.

KEY MESSAGE

1. Patients with hematologic disease who require extracorporeal membrane oxygenation (ECMO) for cardiopulmonary support have poor outcomes.

Kang HS, et al. ECMO for immunocompromised patients

KJIM

2. The incidence of complications in patients with hematologic malignancy did not significantly differ from that in immunocompetent patients.

3. The use of ECMO in patients with hematologic disease in whom optimal conventional therapy failed merits further consideration.

Conflict of interest

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

REFERENCES

1. Bay JO, Guieze R, Ravinet A, et al. Major therapeutic advances and new perspectives in onco-hematology. Bull Cancer 2013;100:587-599.

2. William BM, de Lima M. Advances in conditioning regimens for older adults undergoing allogeneic stem cell transplantation to treat hematologic malignancies. Drugs Aging 2013;30:373-381.

3. Mulabecirovic A, Gaulhofer P, Auner HW, et al. Pulmonary infiltrates in patients with haematologic malignancies: transbronchial lung biopsy increases the diagnostic yield with respect to neoplastic infiltrates and toxic pneumonitis. Ann Hematol 2004;83:420-422.

4. Vento S, Cainelli F, Temesgen Z. Lung infections after cancer chemotherapy. Lancet Oncol 2008;9:982-992.

5. Altena R, Perik PJ, van Veldhuisen DJ, de Vries EG, Gietema JA. Cardiovascular toxicity caused by cancer treatment: strategies for early detection. Lancet Oncol 2009;10:391-399.

6. Gonzalez-Rodriguez AP, Payer AR, Acebes-Huerta A, et al. Lenalidomide and chronic lymphocytic leukemia. Biomed Res Int 2013;2013:932010.

7. Poletti V, Salvucci M, Zanchini R, et al. The lung as a target organ in patients with hematologic disorders. Haematologica 2000;85:855-864.

8. Haddad IY. Stem cell transplantation and lung dysfunction. Curr Opin Pediatr 2013;25:350-356.

9. Yeo CD, Kim JW, Kim SC, et al. Prognostic factors in critically ill patients with hematologic malignances admitted to the intensive care unit. J Crit Care 2012;27:739.e1-739.e6.

10. Epner DE, White P, Krasnoff M, Khanduja S, Kimball KT, Knaus WA. Outcome of mechanical ventilation for adults with hematologic malignancy. J Investig Med 1996;44:254-260.

11. Gristina GR, Antonelli M, Conti G, et al. Noninvasive versus invasive ventilation for acute respiratory failure in patients with hematologic malignancies: a 5-year multicenter observational survey. Crit Care Med 2011;39:2232-2239.

12. Gow KW, Wulkan ML, Heiss KF, et al. Extracorporeal membrane oxygenation for support of children after hematopoietic stem cell transplantation: the Extracorporeal Life Support Organization experience. J Pediatr Surg 2006;41:662-667.

13. Gupta M, Shanley TP, Moler FW. Extracorporeal life support for severe respiratory failure in children with immune compromised conditions. Pediatr Crit Care Med 2008;9:380-385.

14. Gow KW, Lao OB, Leong T, Fortenberry JD. Extracorporeal life support for adults with malignancy and respiratory or cardiac failure: the Extracorporeal Life Support experience. Am J Surg 2010;199:669-675.

15. Ewig S, Glasmacher A, Ulrich B, Wilhelm K, Schafer H, Nachtsheim KH. Pulmonary infiltrates in neutropenic patients with acute leukemia during chemotherapy: outcome and prognostic factors. Chest 1998;114:444-451.

16. Feuillet S, Meignin V, Briere J, et al. Endobronchial Epstein-Barr virus associated post-transplant lymphoproliferative disorder in hematopoietic stem cell transplantation. Clin Med Case Rep 2009;2:11-15.

17. Azoulay E, Mokart D, Pene F, et al. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium: a groupe de recherche respiratoire en reanimation onco-hematologique study. J Clin Oncol 2013;31:2810-2818.

18. Ferra C, Marcos P, Misis M, et al. Outcome and prognostic factors in patients with hematologic malignancies admitted to the intensive care unit: a single-center experience. Int J Hematol 2007;85:195-202.

19. Benoit DD, Vandewoude KH, Decruyenaere JM, Hoste EA, Colardyn FA. Outcome and early prognostic indicators in patients with a hematologic malignancy admitted to the intensive care unit for a life-threatening complication. Crit Care Med 2003;31:104-112.

20. Rhee CK, Kang JY, Kim YH, et al. Risk factors for acute respiratory distress syndrome during neutropenia recovery in patients with hematologic malignancies. Crit Care 2009;13:R173.

21. Aboud A, Marx G, Sayer H, Gummert JF. Successful

treatment of an aggressive non-Hodgkin's lymphoma associated with acute respiratory insufficiency using extracorporeal membrane oxygenation. Interact Cardiovasc Thorac Surg 2008;7:173-174.

22. Gorjup V, Fister M, Noc M, Rajic V, Ribaric SF. Treatment of sepsis and ARDS with extracorporeal membrane oxygenation and interventional lung assist membrane ventilator in a patient with acute lymphoblastic leukemia. Respir Care 2012;57:1178-1181.

23. Liao WI, Tsai SH, Chiu SK. Successful use of extracorporeal membrane oxygenation in a hematopoietic stem cell transplant patient with idiopathic pneumonia syndrome. Respir Care 2013;58:e6-e10.

24. Soubani AO, Kseibi E, Bander JJ, et al. Outcome and prognostic factors of hematopoietic stem cell transplantation recipients admitted to a medical ICU. Chest 2004;126:1604-1611.

25. Aubron C, Cheng AC, Pilcher D, et al. Factors associated with outcomes of patients on extracorporeal membrane oxygenation support: a 5-year cohort study. Crit Care 2013;17:R73.

26. Wu MY, Lin PJ, Tsai FC, et al. Postcardiotomy extracorporeal life support in adults: the optimal duration of bridging to recovery. ASAIO J 2009;55:608-613.

27. Wohlfarth P, Ullrich R, Staudinger T, et al. Extracorporeal membrane oxygenation in adult patients with hematologic malignancies and severe acute respiratory failure. Crit Care 2014;18:R20.