

Extracorporeal Life Support in Adult Patients with Hematologic Malignancies and Acute Circulatory and/or Respiratory Failure

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Background: The primary goal of this study was to characterize the clinical outcomes of adult patients with hematologic malignancies (HM) who were treated with extracorporeal membrane oxygenation (ECMO) support when conventional treatments failed. **Methods:** In this retrospective, observational study at a tertiary medical center, we reviewed the clinical course of 23 consecutive patients with HM requiring ECMO who were admitted to the intensive care unit at Asan Medical Center from March 2010 to April 2015. **Results:** A total of 23 patients (8 female; median age, 44 years; range, 29–51 years) with HM and severe acute circulatory and/or respiratory failure received ECMO therapy during the study period. Fourteen patients received veno-arterial ECMO, while 9 patients received veno-venous ECMO. The median ECMO duration was 104.7 hours (range, 37.1–221 hours). Nine patients were successfully weaned from ECMO. The in-hospital mortality rate was 91.1% (21 of 23). There were complications in 3 patients (cannulation site bleeding, limb ischemia, and gastrointestinal bleeding). **Conclusion:** ECMO is a useful treatment for patients with circulatory and/or pulmonary failure. However, in patients with HM, the outcomes of ECMO treatment results were very poor, so it is advisable to carefully decide whether to apply ECMO to these patients.

Key words: 1. Extracorporeal membrane oxygenation
2. Hematologic neoplasms
3. Adult
4. Mortality

Introduction

Extracorporeal life support (ECLS), or extracorporeal membrane oxygenation (ECMO), is used to support critically ill patients with acute circulatory and/or respiratory failure when conventional treatments have failed. ECMO is indicated in various circumstances. Veno-arterial (VA) ECMO is indicated

for conditions involving cardiogenic shock, such as acute coronary syndrome, myocarditis, post-cardiotomy syndrome, primary graft dysfunction, and the bridge period to destination therapy [1]. Veno-venous (VV) ECMO is indicated for severe hypoxemia under mechanical ventilation (MV) due to various diseases [2]. The outcomes of ECMO vary depending on the underlying disease [3].

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It is increasingly common for patients with hematologic malignancies (HM) to require hospitalization in the intensive care unit (ICU) for life-threatening events due to immunosuppression and/or the malignancy itself [4]. Some studies have reported recent advances in chemotherapy and conditioning regimes; in particular, hematopoietic stem cell transplantation (HSCT) and general ICU care have led to better outcomes for these patients [5]. Patients with HM who need ICU treatment are often considered to have an improved, but not good, long-term prognosis [6-8]. In patients receiving MV, mortality ranges from 35% to 70% depending on the associated organ dysfunction and the presence of graft versus host disease [4].

ECMO treatment can even be considered in HM patients with severe circulatory and/or pulmonary dysfunction. Several studies have reported outcomes of ECMO in patients with HM [9-12]. Although ECMO in HM patients is still considered to have an unsatisfactory prognosis [9,11], its use has not been reported. The primary goal of this study was to characterize the clinical outcomes of adult patients with HM who were treated with ECMO when conventional treatments failed, based on a retrospective review of the patients' medical records.

Methods

We retrospectively studied the clinical outcomes of all adult patients (18 years or older) with HM and circulatory and/or respiratory failure treated with ECMO between March 2010 and April 2015 at a tertiary center in Korea. The study protocol was approved by the institutional review board of Asan Medical Center (IRB approval no., 2016-0665). The requirement for informed consent from individual patients was waived due to the retrospective nature of the study.

The baseline characteristics of patients were evaluated. Additionally, disease severity scores were calculated using the Acute Physiology and Chronic Health Evaluation (APACHE) II, Murray Lung Injury Score, the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction Score, and the Simplified Acute Physiology Score (SAPS) II. The type of HM, the reason for ECMO, the type of ECMO, clinical considerations before and during ECMO, complications during ECMO, and the success or failure of ECMO weaning were analyzed based on the data

available in the patients' medical records. Laboratory data, including hemoglobin, white blood cell count, platelet count, C-reactive protein, blood urea nitrogen (BUN), creatinine, albumin, and liver function tests were collected during the ICU stay. The period of ICU admission, length of hospital stay, and time in hospital before ICU admission were noted.

The primary outcome was in-hospital mortality, defined as the number of patients with HM and ECLS support who died in-hospital during the study period. The secondary outcomes were the ECMO weaning rate and complication rate. ECMO support was applied using the Capiiox Emergency Bypass System (Terumo, Tokyo, Japan) and/or Permanent Life Support (Maquet Cardiopulmonary AG, Hirrlingen, Germany). Vascular access was established peripherally (femoral artery, femoral vein, and/or internal jugular vein).

Data were presented as medians and interquartile ranges (25th and 75th percentiles) for continuous variables and as numbers (percentages) for categorical variables. Data were compared using the Mann-Whitney U-test for continuous variables and the chi-square or Fisher exact test for categorical variables. All tests were 2-sided, and a p-value of <0.05 was considered to indicate statistical significance. Data were analyzed using PASW SPSS Statistics ver. 17.0 (SPSS Inc., Chicago, IL, USA) and R Statistical Software ver. 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, a total of 23 patients with HM received ECMO treatment. Fifteen of the patients were men, and the median age was 44 years (range, 29-51 years). There were several types of blood cancer diagnoses among the patients. Nine patients had leukemia (acute myeloid leukemia [n=6], chronic myeloid leukemia [n=2], and both [n=1]). Four patients had multiple myeloma (n=1), and 1 patient had anaplastic anemia (n=1). Three patients had myelodysplastic syndrome (n=3). One patient had hemophagocytic lymphohistiocytosis (n=1). Five patients had lymphoma (n=5). Ten patients underwent HSCT and 9 patients received chemotherapy. Before ECMO was initiated, the median SAPS II score was 58.0 (range, 51.0-68.5) and the median APACHE II score

Table 1. Comparison of pre-ECMO characteristics between patients who were and were not weaned from ECMO

| Characteristic | Total (N=23) | Weaned from ECMO (N=9) | Not weaned from ECMO (N=14) | p-value |
|---|-----------------------|------------------------|-----------------------------|---------|
| Age (yr) | 44.0 (29.0 to 51.0) | 30.0 (23.0 to 44.0) | 49.0 (41.0 to 56.0) | 0.021 |
| Male | 15 (65.2) | 6 (66.7) | 9 (64.3) | >0.999 |
| APACHE II | 29.0 (24.0 to 32.0) | 24.0 (24.0 to 29.0) | 31.0 (26.0 to 36.0) | 0.076 |
| SAPS II | 58.0 (51.0 to 68.5) | 54.0 (47.0 to 58.0) | 67.0 (58.0 to 73.0) | 0.043 |
| SOFA | 14.0 (13.0 to 17.0) | 14.0 (13.0 to 16.0) | 15.0 (14.0 to 18.0) | 0.278 |
| RESP | 1.0 (-1.0 to 3.0) | 2.0 (-3.0 to 2.0) | 1.0 (0.0 to 3.0) | 0.703 |
| Murray lung injury score | 2.3 (2 to 2.5) | 2.3 (2 to 2.5) | 2.4 (2 to 2.7) | 0.307 |
| Diagnosis to ECMO (day) | 159.0 (89.0 to 718.5) | 140.0 (114.0 to 342.0) | 318.5 (79.0 to 783.0) | 0.688 |
| ICU admission to ECMO initiation (day) | 1.0 (0.0 to 2.0) | 0.0 (0.0 to 1.0) | 1.5 (0.0 to 4.0) | 0.044 |
| Pre-treatment | | | | |
| Chemotherapy | 19 (82.6) | 8 (88.9) | 11 (78.6) | 0.941 |
| HSCT | 10 (43.5) | 3 (33.3) | 7 (50.0) | 0.722 |
| Pre-ECMO laboratory tests | | | | |
| Hemoglobin (g/dL) | 9.1 (7.6 to 11.4) | 11.3 (9.1 to 12.2) | 8.6 (7.0 to 11.2) | 0.078 |
| Leukocyte ($\times 10^3/\mu\text{L}$) | 1.9 (0.2 to 13.2) | 2.4 (1.9 to 13.9) | 0.9 (0.1 to 5.3) | 0.242 |
| Platelet ($\times 10^3/\mu\text{L}$) | 64.0 (47.0 to 86.0) | 85.0 (62.0 to 94.0) | 56.5 (25.0 to 74.0) | 0.027 |
| Creatinine (mg/dL) | 1.4 (0.7 to 1.8) | 0.9 (0.7 to 1.7) | 1.6 (0.9 to 1.9) | 0.469 |
| Blood urea nitrogen (mg/dL) | 24.0 (17.5 to 31.5) | 18.0 (17.0 to 21.0) | 30.0 (23.0 to 37.0) | 0.017 |
| Bilirubin (mg/dL) | 1.2 (0.9 to 3.1) | 1.2 (1.0 to 2.9) | 1.3 (0.5 to 3.4) | 0.729 |
| Prothrombin time (INR) | 1.5 (1.1 to 1.7) | 1.2 (1.1 to 1.6) | 1.6 (1.1 to 1.8) | 0.614 |
| Lactate (mmol/L) | 4.5 (2.0 to 11.4) | 2.8 (1.9 to 14.6) | 4.8 (2.2 to 7.9) | 0.900 |
| Precondition | | | | |
| Immuno-compromised state ^{a)} | 15 (65.2) | 5 (55.6) | 10 (71.4) | 0.740 |
| Cardiopulmonary resuscitation | 6 (26.1) | 4 (44.4) | 2 (14.3) | 0.262 |
| LVEF (%) | 34.0 (27.0 to 55.0) | 33.0 (30.0 to 54.0) | 35.0 (27.0 to 55.0) | 0.939 |
| PaO ₂ /FiO ₂ | 63.0 (49.5 to 107.5) | 63.0 (50.0 to 94.0) | 62.5 (49.0 to 108.0) | >0.99 |

Values are presented as median (interquartile range) for continuous variables or as number (%) for non-continuous variables.

ECMO, extracorporeal membrane oxygenation; APACHE II, Acute Physiology and Chronic Health Evaluation II; SAPS II, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; RESP, Respiratory Extracorporeal Membrane Oxygenation Survival Prediction Score; ICU, intensive care unit; HSCT, hematopoietic stem cell transplantation; INR, international normalized ratio; LVEF (%), left ventricular ejection fraction on echocardiography before ECMO application.

^{a)}The criteria for an immune-compromised state were as follows: human immunodeficiency virus, a primary immune deficiency, hematologic malignancy such as lymphoma, post-chemotherapy status, an absolute neutrophil count <1,000, steroid medication (>0.5 mg/kg) for more than 3 weeks, or post-transplantation status.

was 29 (range, 24–32).

The numbers of patients for each indication of ECMO treatment were as follows: septic shock (n=5), acute respiratory distress syndrome (ARDS, n=8), ARDS and septic shock (n=2), cardiogenic shock (n=6), pulmonary hemorrhage (n=1), and stress-induced cardiomyopathy (n=1). Leukopenia ($<4\times 10^3/\mu\text{L}$) was present in 15 patients. All study participants had thrombocytopenia ($<100\times 10^3/\mu\text{L}$), except for 3 individuals. The basic characteristics and baseline conditions of the patients before ECMO initiation are presented in Table 1 according to ECMO weaning status. The mean age was older, BUN levels at ECMO ini-

tiation were higher, and the time until ECMO application after ICU admission was longer in patients who were not weaned from ECMO than in those who were.

Of the 23 patients who received ECMO treatment, 14 received VA ECMO. Six of the 14 patients who had received VA ECMO were weaned successfully, but the remaining 8 patients failed to be weaned. Among the 6 successfully weaned patients, 2 died in the ICU, 3 died in the hospital, and only 1 survived. Three of the 9 patients who received VV ECMO were weaned successfully, but the remaining 6 patients failed to be weaned. Among the 3 successfully weaned patients, 2 died in the hospital, and only 1

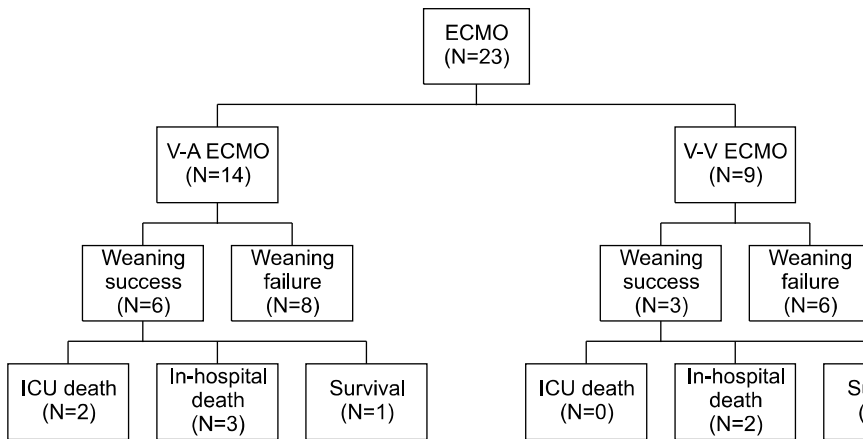


Fig. 1. Treatment algorithm and outcomes. ECMO, extracorporeal membrane oxygenation; V-A, veno-arterial; V-V, veno-venous; ICU, intensive care unit.

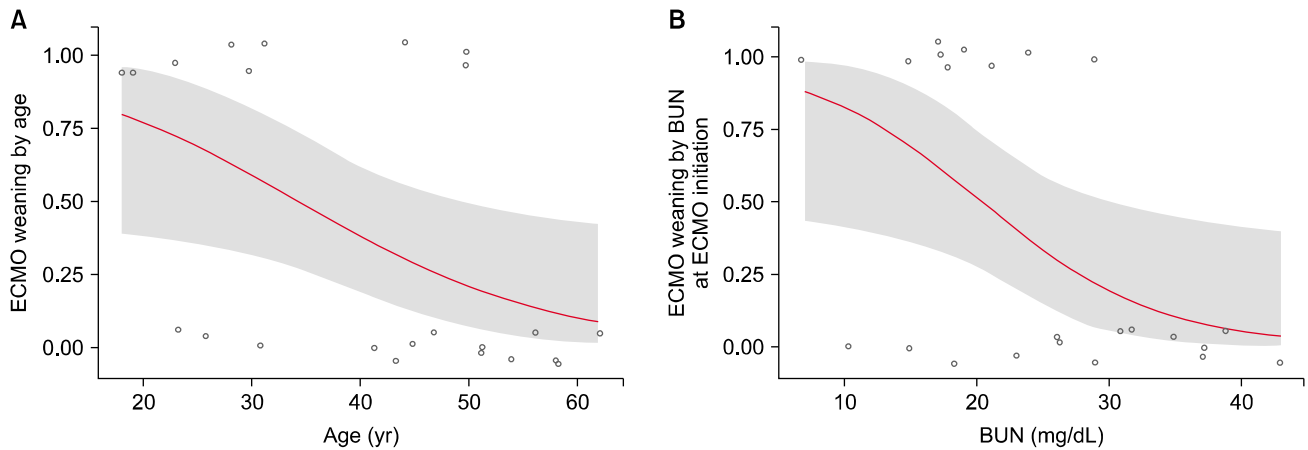


Fig. 2. Age (A) and BUN levels at ECMO initiation (B) in patients weaned from ECMO were significantly lower than in those who were not weaned from ECMO in the univariate analysis (age: $p=0.03$; BUN: $p=0.03$) in a logistic regression model. ECMO, extracorporeal membrane oxygenation.

patient survived (Fig. 1). ICU mortality was 70% (16 of 23), and the in-hospital mortality rate was 91% (21 of 23). Multivariate analysis was performed of HM patients with the following risk factors for unsuccessful weaning from ECMO: age, APACHE II score, SAPS II score, BUN level, hemoglobin level, platelet level at ECMO initiation, lactate level on the first day of ECMO, and the time from ICU admission to ECMO initiation. In the univariate analysis, the age and BUN level at ECMO initiation in the patients who were weaned from ECMO were significantly lower than in the patients who were not ($p<0.05$) (Fig. 2, Table 2). The median survival period was 80 days (range, 39–168 days) in the ECMO weaning group. There was no significant difference in survival between the VV and VA ECMO groups. The ECMO-related outcomes are presented in Table 3 according to

whether ECMO weaning was successful.

Fifteen patients (65.2%) did not receive anti-coagulants because of bleeding tendency or platelet reduction. In 2 patients, the ECMO oxygenator had to be changed within a week. There were complications in 3 patients: cannulation site bleeding ($n=1$), gastrointestinal bleeding ($n=1$), and limb ischemia ($n=1$). These patients did not need surgical treatment.

Discussion

In most industrialized countries, the number of HM patients has increased over the last 2 decades [13]. This is due to more effective diagnoses and treatments, which have improved the prognosis of patients with blood cancers [14]. However, mortality among patients with HM admitted to the ICU still

Table 2. Univariate and multivariate analysis of risk factors

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---------------------|---------|-----------------------|---------|
| | OR (95% CI) | p-value | OR (95% CI) | p-value |
| Age | 0.92 | 0.03 | 0.06 | >0.99 |
| SAPS II | 0.93 | 0.08 | 0.78 | >0.99 |
| ICU admission to ECMO application (day) | 0.38 | 0.1 | | >0.99 |
| Pre-ECMO laboratory tests | | | | |
| Blood urea nitrogen (mg/dL) | 0.86 | 0.03 | | >0.99 |
| Platelets ($\times 10^3 / \mu\text{L}$) | 1.01 | 0.13 | 3.32 | >0.99 |

OR, odds ratio; CI, confidence interval; SAPS II, Simplified Acute Physiology Score; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation.

Table 3. Comparison of ECMO-related outcomes between patients who were and were not weaned from ECMO

| Variable | Total (N=23) | Weaned from ECMO (N=9) | Not weaned from ECMO (N=14) | p-value |
|---|-----------------------|------------------------|-----------------------------|---------|
| ECMO mode | | | | |
| Veno-arterial | 14 (60.9) | 6 (66.7) | 8 (57.1) | 0.985 |
| Veno-venous | 9 (39.1) | 3 (33.3) | 6 (42.9) | |
| Post-ECMO laboratory tests | | | | |
| Leukocyte ($\times 10^3 / \mu\text{L}$) | 1.8 (0.2 to 4.8) | 2.6 (0.6 to 4.3) | 1.1 (0.1 to 7.8) | 0.449 |
| Lactate (mmol/L) | 3.6 (2.2 to 10.2) | 2.7 (2.2 to 3.2) | 6.2 (3.5 to 14.6) | 0.03 |
| Positive culture study (blood and sputum) during ECMO application | 13 (56.5) | 6 (66.7) | 7 (50.0) | 0.722 |
| ECMO anticoagulation | | | | |
| None | 15 (65.2) | 6 (66.7) | 9 (64.3) | 0.910 |
| Heparin | 6 (26.1) | 2 (22.2) | 4 (28.6) | |
| Nafamostat (Futhan) | 2 (8.7) | 1 (11.1) | 1 (7.1) | |
| ECMO transfusion | | | | |
| Red blood cells | 22 (95.7) | 9 (100.0) | 13 (92.9) | 1.000 |
| Platelets | 22 (95.7) | 9 (100.0) | 13 (92.9) | 1.000 |
| Platelets (pints) | 48.0 (16.0 to 104.0) | 48.0 (16.0 to 88.0) | 44.0 (10.0 to 160.0) | 0.850 |
| CRRT application | 15 (65.2) | 6 (66.7) | 9 (64.3) | 1.000 |
| ECMO duration (hr) | 104.7 (37.1 to 221.2) | 92.0 (75.2 to 130.1) | 111.9 (18.4 to 290.3) | 0.975 |
| Intensive care unit stay (day) | 10.0 (6.0 to 15.5) | 15.0 (12.0 to 24.0) | 6.5 (2.0 to 13.0) | 0.014 |

Values are presented as number (%) for non-continuous variables or median (interquartile range) for continuous variables. ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy.

ranges from 35% to 70% [4,8,15]. Patients with HM commonly develop life-threatening complications as a result of the treatment process [10], and those who require MV are known to have a poor prognosis [6-8,12]. Seong et al. [8] noted that among patients with blood cancer who entered the ICU, the mortality rate was 80% for patients receiving renal replacement therapy. Rhee et al. [16] reported that intensive chemotherapy and subsequent HSCT commonly caused neutropenia, and that recovery in patients with HM might be prolonged compared to those with

solid tumors due to malignant infiltration of the bone marrow. Several studies on heterogeneous allogeneic HSCT recipients undergoing MV due to acute respiratory failure have recently reported survival rates of approximately 30% [12].

HSCT is one of the major treatments for HM patients. Patients receiving HSCT often have a fatal prognosis if they experience side effects of treatment. The most frequent complications of HSCT are lung-related. After HSCT, initiation of MV is associated with low survival rates [17]. Corcia et al. [18]

reported that among patients who received HSCT treatment, 11% needed ICU treatment, with 83.3% of those patients dying in the ICU and 91.7% dying in the hospital. All patients who required invasive MV died in the ICU [18]. In our study, 10 patients received HSCT before ECMO, and the ECMO weaning rate of those patients was 30%. However, among those not successfully weaned, 80% died in the ICU, and all patients died in the hospital. ECMO treatment is not effective in patients receiving HSCT treatment when cardiac or respiratory shock occurs.

ECLS technology has been used for decades and was stimulated by the development of membrane oxygenators. Although ECLS was initially used primarily to provide respiratory support, it quickly became obvious that ECLS was a suitable method for providing circulatory and/or respiratory support to patients with life-threatening conditions. More recently, advances in oxygenator, pump, and cannula technology have rapidly expanded the use of ECLS [3]. According to the Extracorporeal Life Support Organization registry [3], the ECMO weaning rate of adult respiratory dysfunction patients was 66% and the discharge rate was 58%. The ECMO weaning rate for adult heart failure patients was 56% and the discharge rate was 41%.

In general, ECMO is considered to be ineffective in patients with HM [9,10], and it is contraindicated in post-HSCT patients with respiratory complications [12,19]. Poor prognoses have been reported in patients receiving ECMO therapy with intractable ARDS after Autologous stem cell transplantation (ASCT). Choi et al. [9] reported that successful weaning was accomplished in only 2 patients with HM (9%) and only 1 patient was discharged from the hospital (5%). Kang et al. [10] showed that patients with hematologic diseases who required ECMO for cardiopulmonary support had poor outcomes, and increased mortality was associated with infection and hyperbilirubinemia development during ECMO due to immunosuppression, as well as bleeding from thrombocytopenia [12].

ECMO treatment in patients with HM can cause bleeding or thrombosis. These patients may have platelet reduction due both to their original disease and ECMO. Three cases of complications were observed in our study. In 2 cases where the number of platelets was less than 50,000/ μ L and an anticoagulant

could not be used, the ECMO oxygenator had to be exchanged several times. In the other case, gastrointestinal bleeding occurred. Choi et al. [9] reported that major bleeding events occurred in 18.2% of patients in their study. Likewise, Park et al. [20] described bleeding events in 4 patients (27%) in their study. In our study, there was a statistically significant difference in the ECMO weaning rate depending on platelet count, so it is important to keep the platelet count at or greater than a certain set level.

One group reported results of ECMO patients with HM that were similar to those in general patients [11]. Wohlfarth et al. [11] reported 14 cases of ECMO application in HM, with a survival rate of 50% (10 of 17), and proposed cooperation among medical personnel—intensivists, hematologists, and cardiovascular surgeons—as a way to improve outcomes. Continuous progress is being made, which warrants hope that targeted and personalized treatments will soon be widely available to prevent life-threatening disease- and treatment-related complications [4]. As research and treatment develop for HM, it is possible that the outcomes of ECMO in patients with HM may improve [4,21,22].

This study has several limitations. First, this was a retrospective study. Second, the number of patients in this study was small. Third, the ECMO application criteria were not clearly defined in objective terms, and showed significant variation according to various factors, including the preference of the doctor in charge.

In conclusion, patients with HM who require ECMO for acute circulatory and/or respiratory support have poor outcomes. When ECMO was applied to patients with HM, the ECMO weaning rate was 39% (9 of 23) and the in-hospital mortality rate during the same hospitalization period was 91% (21 of 23). In the ECMO weaning group, the age was slightly younger and the BUN level before the procedure tended to be lower, but not enough to consider these factors to be decisive. Before ECMO treatment in patients with HM, medical staff should comprehensively consider relevant medical, ethical, and economic aspects. It is also important to inform and explain these issues to both patients and caregivers if possible. In reality, there will be a demand for ECMO application in patients with HM who do not respond to conventional therapy. More research is needed to improve ECMO results in these patients.

Conflict of interest

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

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