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Original

Medical Resources and Clinical Outcomes for Extracorporeal Membrane Oxygenation Treatment under the Japanese Health Insurance System: A Single-Center Retrospective Observational Study

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Background: Extracorporeal membrane oxygenation (ECMO) is a resource-intensive life support therapy associated with high complication rates. Blood products are a major cost driver, yet their impact on outcomes under the Japanese health insurance system remains unclear. This study investigated the association between transfusion burden and clinical outcomes in ECMO patients.

Methods: We retrospectively analyzed data from 112 adult patients who received ECMO at Nippon Medical School Hospital between 2014 and 2023. Baseline characteristics, laboratory findings, and transfusion volumes of red blood cells (RBCs), fresh frozen plasma (FFP), and platelets were compared in relation to survival and death. Sixty-day mortality was assessed using Kaplan–Meier analysis and Cox proportional hazards models. Predictors of transfusion burden were evaluated with multivariable regression.

Results: Transfusion of FFP (hazard ratio [HR] 2.00, 95% confidence interval [CI] 1.15–3.46) and RBCs (HR 2.37, 95%CI 1.14–4.93) were independently associated with increased 60-day mortality, whereas platelet transfusion was not. Nonsurvivors required significantly larger volumes of all blood products. Transfusion burden was primarily determined by longer ECMO duration and lower fibrinogen levels. Blood products accounted for 56.1% of drug-related expenditures during ECMO.

Conclusions: Transfusion burden was a key determinant of mortality and cost in ECMO patients and was mainly affected by prolonged ECMO duration and low fibrinogen levels. These findings highlight the clinical and economic impact of transfusion practices and underscore the need for prospective multicenter validation to establish evidence-based transfusion strategies in Japan.

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Introduction

Extracorporeal membrane oxygenation (ECMO) is a life support technique used for circulatory failure and respiratory failure that are resistant to conventional treatment methods such as artificial ventilation and circulatory assist devices[1]. ECMO is classified as veno-arterial (VA) and veno-venous (VV). VA ECMO is used for circulatory support, while VV ECMO is used for respiratory support[2]. ECMO has enabled major advances in circuit devices and is used around the world as a treatment for se-

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vere circulatory and respiratory failure[1,3]. In addition, ECMO is an effective therapeutic option for severe pneumonia associated with emerging infectious diseases, including novel influenza viruses and coronaviruses[4,5]. However, the availability of ECMO devices and associated medical resources differs across countries, and patterns of resource utilization and healthcare system structures vary substantially between nations[6–9].

In Japan, ECMO cases are not yet centralized, and treatment strategies, including transfusion thresholds, vary substantially among institutions. Although ECMO therapy is provided under a uniform national health insurance system, with standardized prices for blood products and pharmaceuticals, the associated economic burden sometimes falls on healthcare institutions. While numerous studies have reported that blood products are the costliest medical resource during ECMO[10–12], the relevance of these findings for the Japanese health insurance system is unclear. Therefore, this study evaluated the association of transfusion burden with clinical outcomes in ECMO patients, while also describing the characteristics of resource utilization in a real-world Japanese setting.

Materials and Methods

Study Design and Data Collection

This observational cohort study used data from an administrative claims database linked to the medical records of the Nippon Medical School Hospital. Patient data were collected from the administrative claims database. Clinical data from the medical records, including laboratory data, were electronically added to the database. Data were anonymized and cannot be used to identify specific individuals. This study was approved by the Ethics Committee of Nippon Medical School Hospital (approval no. 2023-1365)[13] and was conducted in accordance with the principles of the Revised Declaration of Helsinki. Consent was obtained using the opt-out method.

Patient Selection and Endpoints

Data on patients who were admitted to the surgical intensive care unit (ICU) of Nippon Medical School Hospital and received ECMO from September 2014 to September 2023 were extracted from the database. Our 20-bed unit provides postoperative management for patients undergoing major invasive procedures, including cardiovascular surgery, as well as non-surgical intensive care for patients with multiple organ dysfunction requiring mechanical support therapies such as renal replacement therapy, extracorporeal membrane oxygenation, and mechanical ventilation for sepsis and severe respiratory failure.

In this study, the indications for ECMO were defined by using the Extracorporeal Life Support Organization (ELSO) Guidelines for Adult Respiratory and Cardiac Failure[14]. For hypoxemic respiratory failure of any cause, ECMO was considered when the predicted mortality rate exceeded 50% and recommended when it exceeded 80%. These thresholds corresponded to an FIO_2 >90% with a PaO_2/FIO_2 ratio <150 and <80, respectively. ECMO was also considered appropriate in cases of hypercapnic respiratory failure due to status asthmaticus or refractory hypercapnia ($PaCO_2$ >80 mm Hg) in which safe ventilatory pressures for lung protection (plateau pressure ≤30 cm H_2O) could not be maintained, and in cases of severe air leak syndrome and worsening respiratory failure in registered lung transplant candidates requiring endotracheal intubation. In addition, ECMO was indicated for conditions unresponsive to conventional therapy that could rapidly progress to circulatory or respiratory collapse, such as massive pulmonary embolism or upper airway obstruction.

For respiratory indications, VV ECMO was primarily used for patients with severe respiratory failure refractory to optimal conventional management. For cardiac indications, VA ECMO was initiated in patients with refractory cardiogenic shock or low-output syndrome after cardiac surgery when adequate perfusion could not be maintained despite administration of vasoactive drugs or intra-aortic balloon pump support. In all cases, ECMO was started only when the underlying condition was potentially reversible and there were no absolute contraindications, such as irreversible multi-organ failure or uncontrollable bleeding. Patients younger than 18 years were excluded. Participants were classified as survivors and nonsurvivors by survival status at 60 days after ECMO initiation. In our ICU, transfusion management during ECMO was supervised by a specialized team, in accordance with ELSO guidelines in effect at the time. Before 2021, institutional transfusion criteria for platelets and fresh frozen plasma (FFP) were also defined in accordance with contemporaneous ELSO recommendations and local practice. Platelet transfusion was generally considered in order to maintain a platelet count of ≥ 50,000/μL, and FFP was administered to support fibrinogen levels in patients with clinical bleeding or coagulation abnormalities, typically targeting a level of ≥200 mg/dL. Importantly, these criteria were used as reference

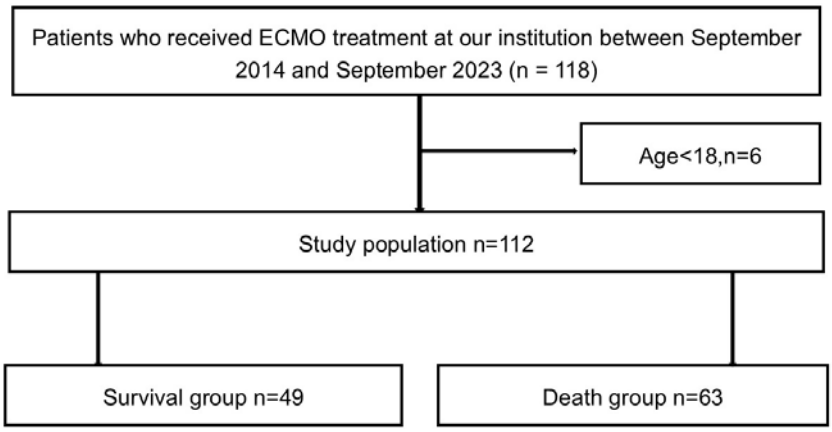

Figure 1 Flowchart of total study population, n = 118
Patients younger than 18 years (n = 6) were excluded from the study population.

guidelines rather than strict thresholds, and final transfusion decisions were made by the ECMO care team after consideration of the individual patient's clinical condition.

Variables

Patient information obtained from the administrative claims database included age, sex, ECMO implementation, administered medications, length of stay in the surgical ICU, total hospitalization period, medical resources used, discharge status, and post-discharge outcomes. In addition, laboratory data on the day of ECMO initiation were retrieved from the electronic medical records.

Subgroup classification in this study was defined strictly according to the ECMO mode at the time of initiation. Patients who received VA-ECMO for circulatory failure were assigned to the VA-ECMO group, whereas those who received VV-ECMO for refractory respiratory failure were assigned to the VV-ECMO group. Patients supported with VA−V configurations or those who underwent subsequent mode conversions were also categorized based on initial ECMO mode. Primary diagnosis categories (circulatory failure, respiratory failure, postoperative status, septic shock, and cardiac arrest) were determined through detailed chart review by board-certified ECMO specialists. These diagnoses represent the underlying condition leading to ECMO initiation and were used to describe the clinical context at baseline.

Statistical Analysis

Categorical variables are expressed as counts and percentages and were compared with the χ^2 test or Fisher's exact test, as appropriate. Continuous variables are reported as medians with interquartile ranges and were compared using the Mann−Whitney U test because normality was not assumed. Because bleeding is a major complication of ECMO and may necessitate hemostatic procedures such as interventional radiology (IVR) and endoscopic gastrointestinal hemostasis, all cases were identified, and both the timing of the procedure and subsequent transfusion volumes were recorded.

Sixty-day all-cause mortality was analyzed with the Kaplan−Meier method, and group differences were assessed with the log-rank test. Independent prognostic factors were evaluated with multivariable Cox proportional hazards models including age, sex, continuous renal replacement therapy (CRRT) use, and presence of transfusions of FFP, red blood cells (RBCs), and platelets. Effect modification by ECMO indication (respiratory vs. circulatory failure) was explored by adding multiplicative interaction terms. For transfusion-volume analysis, cumulative units of FFP, RBC, and platelets were log-transformed using log1p; log-transformed ECMO duration was entered as an offset term. Multivariable linear regression models were fitted with age, sex, fibrinogen concentration, and hemoglobin level as predictors.

A two-sided p-value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using R software version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Cohort and Baseline Characteristics

Among 118 patients who underwent ECMO between September 2014 and September 2023, 6 patients younger than 18 years were excluded, leaving 112 for analysis (**Figure 1**). No significant differences between the 2 groups were identified in age, sex, body mass index, un-

derlying diagnosis, ECMO duration, CRRT use, or baseline laboratory values, including white blood cell count, C-reactive protein, electrolytes, albumin, bilirubin, creatinine, prothrombin time/international normalized ratio, activated partial thromboplastin time, D-dimer, and fibrinogen. However, nonsurvivors had significantly lower hemoglobin and fibrinogen levels at ECMO initiation (both $p < 0.01$), longer prothrombin time ($p < 0.05$), and more frequent initial transfusions of RBCs and FFP (**Table 1**).

In addition, baseline characteristics were compared between patients who received VA ECMO (n = 56) and those who received VV ECMO (n = 56) (**Supplementary Tables 1** and **2**). Patients in the VA ECMO group were significantly older and had a shorter ECMO duration. They more frequently received catecholamines, RBCs, FFP, and platelet transfusions. Laboratory findings showed higher chloride, calcium, and prothrombin time-international normalized ratio (PT-INR) values and lower C-reactive protein (CRP) and fibrinogen levels in the VA ECMO group than in the VV ECMO group.

Transfusion Burden and Medication Costs during ECMO

Table 2 summarizes the 15 medications with the highest total expenditures among the 112 patients who underwent ECMO therapy. The total hospitalization cost was ￥938,983,121, comprising ￥250,767,411 for pharmaceuticals and ￥139,258,904 for reimbursable materials. The most expensive items were blood products, including platelet concentrates (￥78.8 million), red blood cell products (￥33.7 million), and FFP (￥28.2 million), which together accounted for ￥140.7 million—representing 15.0% of the total hospitalization cost and 56.1% of the total drug cost. These findings underscore the considerable economic burden associated with transfusion therapy during ECMO, which tends to increase with prolonged ECMO duration, owing to the high unit cost of blood products. Other major contributors to total drug expenditure included sedatives, anticoagulants, antimicrobials, and inotropic agents, reflecting the intensive pharmacologic support required during ECMO management.

As shown in **Table 3**, nonsurvivors received significantly larger volumes of all blood products than did the survivor group: FFP (median 22 vs. 6 units, $p < 0.001$), RBCs (28 vs. 10 units, $p < 0.001$), and platelet concentrate (70 vs. 20 units, $p < 0.001$). The proportion of patients undergoing IVR did not differ significantly between groups. No patients required hemostatic procedures other than IVR, such as endoscopic gastrointestinal hemostasis. To further clarify the clinical context of IVR use, the characteristics and outcomes of these 13 cases are summarized below. IVR was performed for hemorrhagic events in 13 patients, including 1 case of cannulation-site bleeding and 12 cases of bleeding from other organs. In all cases, arterial embolization of the culprit vessel was performed, resulting in hemostasis in 12 of 13 patients; 1 patient with hemothorax required surgical hemostasis after unsuccessful intercostal artery embolization. **Figure 2** shows the distribution of transfusion volumes. Most patients received 1–10 units of RBCs and FFP, whereas platelet transfusions were more widely distributed, with a notable subgroup receiving more than 120 units.

Survival and the Impact of Transfusion on Mortality

Supplementary Figure 1 shows the Kaplan–Meier curve for overall 60-day survival in the entire ECMO cohort. **Table 4** presents the results of multivariable Cox proportional hazards models adjusted for age, sex, and disease severity at ECMO initiation, as assessed by SOFA score. After this additional adjustment, transfusion of FFP (hazard ratio [HR] 1.85, 95% confidence interval [CI] 1.06–3.25, $p = 0.031$) and RBCs (HR 2.14, 95% CI 1.01–4.55, $p = 0.047$) remained independently associated with increased 60-day mortality, whereas platelet transfusion did not (HR 1.26, 95% CI 0.72–2.23, $p = 0.415$). Age, sex, and SOFA score at ECMO initiation were not independently associated with mortality in these models. **Supplementary Figure 2** shows stratified HR for transfusions by ECMO mode. Although FFP, RBC, and platelet transfusions were associated with higher mortality in both the VA and VV ECMO groups, the interaction p values were not significant (FFP: $p = 0.078$; RBC: $p = 0.557$; platelets: $p = 0.197$), indicating no significant effect modification by ECMO mode.

Table 5 shows the results of linear regression analyses for log-transformed transfusion volumes. Longer ECMO duration was consistently associated with greater transfusion volume for all blood products. Lower fibrinogen levels were significantly associated with increased use of FFP, RBCs, and platelets. In addition, male sex was independently associated with lower platelet transfusion volume ($\beta = -0.721$, $p = 0.044$).

Discussion

This analysis of a single-center cohort spanning a decade demonstrated that ECMO imposes substantial demands on healthcare resources, including dedicated equipment,

Table 1 Characteristics of patients, by survival outcome at 60 days after start of ECMO treatment

Variables	Survival (n = 49)	Death (n = 63)	*p* value
Age, years	63.0 [44–76]	66.0 [55–74]	0.460
Male, n (%)	37 (75.5%)	44 (69.8%)	0.651
BMI, kg/m^2	21.3 [19.9–25.4]	22.0 [19.4–24.3]	0.699
VA/VV ECMO	22 (44.9)/27 (55.1)	34 (54.0)/29 (46.0)	0.446
Primary diagnosis (%)			0.109
CPA	6 (12.2)	18 (28.6)	
Respiratory failure, n (%)	26 (53.1)	32 (50.8)	
Postoperative LOS, n (%)	9 (18.4)	4 (6.3)	
Circulatory failure, n (%)	5 (10.2)	7 (11.1)	
Septic shock, n (%)	3 (6.1)	2 (3.2)	
ICU stay, days	22.0 [16.0–43.0]	22.0 [6.0–39.0]	0.044
ECMO duration, days	6.0 [3.0–11.0]	7.0 [2.0–21.0]	0.476
CRRT, n (%)	13 (26.5%)	18 (28.6%)	0.979
FFP transfusion, n (%)	21 (42.9%)	41 (65.1%)	0.031
RBC transfusion, n (%)	32 (65.3%)	54 (85.7%)	0.021
Platelet transfusion, n (%)	22 (44.9%)	35 (55.6%)	0.353
Catecholamines, n (%)			
Norepinephrine	37 (75.5%)	53 (84.1%)	0.369
Dopamine	2 (4.1%)	3 (4.8%)	1.000
Dobutamine	19 (38.8%)	16 (25.4%)	0.190
Epinephrine	25 (51.0%)	35 (55.6%)	0.775
SOFA score	12 [10–14]	13 [10–15]	0.297
WBC, $\times 10^3/\mu L$	120 [57–174]	103 [26–172]	0.347
Hemoglobin, g/dL	10.7 [9.4–12.2]	9.5 [8.5–10.5]	0.004
Albumin, g/dL	2.3 [2.0–2.7]	2.2 [1.6–2.7]	0.238
Creatinine, mg/dL	1.06 [0.74–1.89]	1.13 [0.70–2.05]	0.988
Sodium, mEq/L	140 [136–142]	142 [138–147]	0.093
Chloride, mEq/L	104 [103–107]	105 [102–108]	0.766
Potassium, mEq/L	4.4 [4.0–4.7]	4.3 [4.0–4.8]	0.758
Calcium, mg/dL	7.9 [7.7–8.7]	8.0 [7.3–8.5]	0.534
Total bilirubin, mg/dL	1.2 [0.6–1.8]	1.0 [0.6–2.4]	0.812
CRP, mg/dL	8.7 [2.7–15.7]	6.2 [1.7–11.2]	0.111
Platelet count, $\times 10^4/\mu L$	9.4 [6.8–13.7]	8.5 [5.8–14.5]	0.382
D-dimer, μg/mL	8.3 [3.7–19.5]	10.6 [4.9–22.7]	0.244
PT–INR	1.36 [1.19–1.57]	1.52 [1.30–2.49]	0.012
APTT, sec	46.4 [33.5–58.9]	50.7 [37.0–109.2]	0.167
Fibrinogen, mg/dL	349 [248–490]	242 [136–478]	0.026

BMI, body mass index; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; CPA, cardiopulmonary arrest; LOS, low output syndrome; CRRT, continuous renal replacement therapy; FFP, fresh frozen plasma; RBC, red blood cell; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell; CRP, C-reactive protein; PT–INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time.

circuit-related consumables, pharmaceuticals, laboratory testing, blood products, and considerable personnel time. ECMO is also associated with a high incidence of serious complications. This reimbursement structure may place a considerable economic burden on healthcare institutions responsible for ECMO management.

Within this broad spectrum of resource utilization, blood products were the predominant driver of clinical outcomes and economic burden, accounting for 56.1% of total drug expenditures. RBC/FFP transfusion was associated with higher 60-day mortality, cumulative transfusion exposure accounted for the largest proportion of total costs, and FFP quantity provided meaningful risk discrimination. These patterns were further supported by

Table 2 The 15 most frequently used drugs during ECMO treatment and their cost

Rank	Generic name	Total cost (JPY)
1	Platelet concentrate, human	¥78,834,654
2	Red blood cell product, human	¥33,694,170
3	Fresh frozen plasma, human	¥28,179,174
4	Dexmedetomidine hydrochloride	¥11,856,996
5	Concentrated antithrombin III, dried	¥8,164,640
6	Lidocaine hydrochloride	¥7,592,432
7	Dialysis solution	¥6,907,795
8	Landiolol hydrochloride	¥6,095,707
9	Micafungin sodium	¥4,679,575
10	Morphine hydrochloride hydrate	¥4,645,102
11	Amphotericin B	¥3,952,676
12	PEG-treated immunoglobulin, dried	¥3,274,387
13	Fibrinogen formulation	¥2,937,221
14	Nafamostat mesylate	¥2,350,223
15	Human serum albumin	¥2,231,110

Table 3 Characteristics of patients, by survival outcome during ECMO treatment

Variables	Survival (n = 49)	Death (n = 63)	*p* value
Hemostatic procedures: Interventional radiotherapy, n (%)	4 (8.2%)	9 (14.3%)	0.383
Fresh frozen plasma transfusion, units	6 (0–18)	22 (10–59)	<0.001
Red blood cell transfusion, units	10 (4–30)	28 (18–58)	<0.001
Platelet concentrate transfusion, units	20 (0–60)	70 (20–170)	<0.001

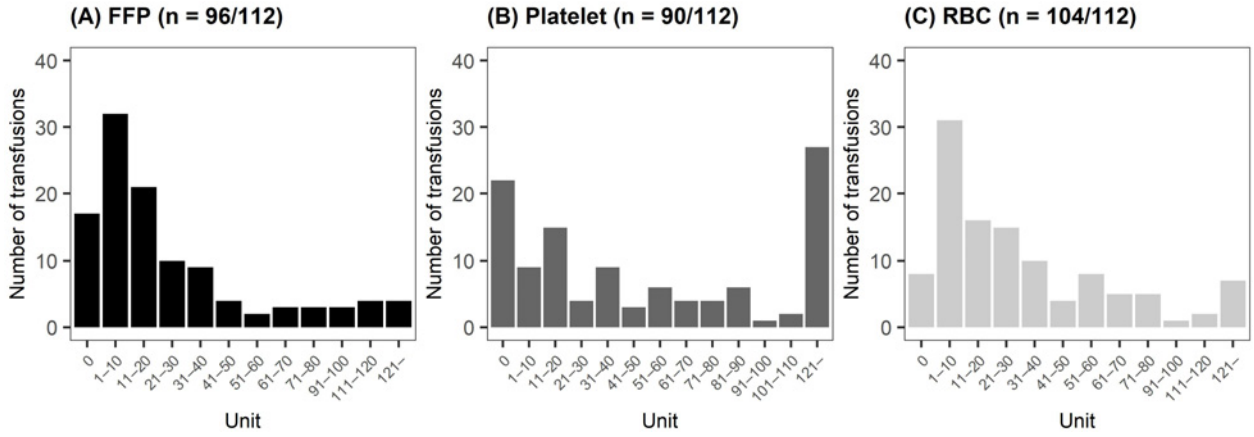

Figure 2 Distribution of transfusion volume (units) among patients who received extracorporeal membrane oxygenation (ECMO) support

Panels show the distribution of administered units for (A) fresh frozen plasma (FFP), (B) platelet concentrates, and (C) red blood cells (RBCs). The x-axis represents transfusion volume categorized by unit ranges, and the y-axis indicates the number of transfusion episodes. Numbers in parentheses indicate the number of patients who received each blood product among the total ECMO cohort (n = 112).

procedural and transfusion-related data observed during the ICU course, which showed that nonsurvivors required markedly greater volumes of RBCs, FFP, and platelets, despite similar rates of hemostatic interventions between survivors and nonsurvivors. Importantly, the higher transfusion burden for nonsurvivors cannot be fully explained by procedural bleeding alone. This finding suggests that non-procedural mechanisms—such as

Table 4 Hazard ratios for 60-day all-cause mortality associated with transfusion of fresh frozen plasma, red blood cell transfusion, and platelet concentrate transfusion (Cox proportional hazards models adjusted for age and sex)

Factor	FFP transfusion model HR (95% CI)	*p* value	RBC transfusion model HR (95% CI)	*p* value	Platelet transfusion model HR (95% CI)	*p* value
Age	1.00 (0.99–1.02)	0.882	1.00 (0.99–1.02)	0.809	1.00 (0.99–1.02)	0.689
Male	1.01 (0.57–1.78)	0.982	0.98 (0.56–1.72)	0.952	0.90 (0.51–1.60)	0.728
SOFA score	1.05 (0.98–1.12)	0.199	1.04 (0.97–1.12)	0.252	1.06 (0.98–1.13)	0.142
FFP transfusion	1.85 (1.06–3.25)	0.031	–	–	–	–
RBC transfusion	–	–	2.14 (1.01–4.55)	0.047	–	–
Platelet transfusion	–	–	–	–	1.26 (0.72–2.23)	0.415

FFP, fresh frozen plasma; RBC, red blood cell.

Table 5 Linear regression analysis of log-transformed transfusion units during ECMO

Model	Predictor	Estimate (95% CI)	*p* value
FFP	Age (per year)	0.022 (0.007 – 0.037)	0.006
	Male (vs. Female)	–0.160 (–0.711 – 0.391)	0.565
	Fibrinogen (mg/dL)	–0.003 (–0.004 – –0.002)	<0.001
	Hemoglobin (g/dL)	0.025 (–0.007 – 0.057)	0.129
	log(ECMO days)	0.390 (0.185 – 0.595)	<0.001
RBC	Age (per year)	0.013 (–0.001 – 0.027)	0.059
	Male (vs. Female)	–0.255 (–0.718 – 0.208)	0.283
	Fibrinogen (mg/dL)	–0.002 (–0.003 – –0.001)	0.001
	Hemoglobin (g/dL)	0.003 (–0.025 – 0.031)	0.808
	log(ECMO days)	0.585 (0.412 – 0.758)	<0.001
Plt	Age (per year)	0.014 (–0.006 – 0.034)	0.156
	Male (vs. Female)	–0.721 (–1.414 – –0.028)	0.044
	Fibrinogen (mg/dL)	–0.002 (–0.003 – –0.001)	0.001
	Hemoglobin (g/dL)	–0.010 (–0.050 – 0.030)	0.644
	log(ECMO days)	0.758 (0.499 – 1.017)	<0.001

Outcome = log(units + 1); offset = log(ECMO days).

diffuse coagulopathy, ECMO-related hemolysis, systemic inflammatory activation, and impaired hemostatic inefficiency—contributed to sustained transfusion requirements. Transfusion burden was primarily determined by longer ECMO duration and low fibrinogen levels. Although overall survival did not differ by indication, adverse outcomes were more likely in cases of bleeding or IVR. These findings indicate that decisions regarding ECMO initiation and continuation should be made with great care and should explicitly account for considerations of resource stewardship. Furthermore, they underscore the need to minimize potentially harmful and costly transfusion exposures through proactive hemostatic management and implementation of strategies to reduce the duration of support whenever clinically feasible.

In this retrospective analysis of patients who underwent ECMO, transfusion of RBCs and FFP was significantly associated with increased 60-day mortality. Furthermore, our regression analysis identified lower fibrinogen levels and longer ECMO duration as key predictors of transfusion burden. During ECMO support, multiple blood products are often required[10]. This demand arises from bleeding related to cannulation and circuit manipulation, hypercoagulability driven by the inflammatory response to the underlying disease, bleeding tendencies associated with anticoagulation for supportive management, concomitant blood-purification therapies, and hemolysis within the ECMO circuit[11]. Prolonged ECMO duration is associated with increased transfusion requirements[15]. One study reported that when hemoglobin levels fell below 7 g/dL during ECMO, the risk of mortality increased, whereas RBC transfusion was associated with improved survival[16]. Consequently, a restrictive transfusion strategy targeting a hemoglobin threshold of 7–8 g/dL has been increasingly endorsed in recent

years[17,18]. These findings underscore the prognostic relevance of transfusion practices and highlight the need for more refined strategies to optimize blood product utilization during ECMO support.

Before 2020, specific recommendations and randomized controlled trial (RCT) data regarding transfusion strategies in ECMO patients were limited, as most earlier RCTs primarily targeted general ICU or cardiac surgery populations rather than ECMO-specific cohorts. RCTs focusing on transfusion requirements in the ICU or after cardiac surgery typically did not include ECMO patients[19,20]. As a result, blood product management practices varied widely across centers.

Despite limited evidence, ELSO has issued guidance. The 2017 ELSO guidelines recommended daily monitoring of fibrinogen and targeting of levels between 250 and 300 mg/dL, with FFP or fibrinogen administered as indicated[21]. Subsequent studies have underscored the prognostic significance of FFP transfusion in ECMO. A nationwide cohort study of more than 11,000 patients in Korea reported that FFP transfusion, when adjusted for length of hospital stay, was strongly associated with increased 90-day mortality, and machine learning models consistently ranked this among the most influential predictors of outcome[22]. Similarly, a large population-based study in Taiwan reported that adults undergoing ECMO who required massive transfusions received substantially greater volumes of FFP[23]. Importantly, a higher FFP-to-RBC ratio (≥1.0) showed a dose-dependent association with increased in-hospital mortality. Complementary evidence from a multicenter prospective cohort indicated that inappropriate or large-volume FFP administration (≥7 units) was independently associated with increased 28-day mortality[24], and Luo et al.[25] further confirmed that greater FFP volumes (in milliliters per kilogram bodyweight per day) correlated with excess in-hospital mortality in ECMO-supported patients. Collectively, these findings indicate that greater FFP exposure not only reflects severe coagulopathy and refractory bleeding but also functions as a prognostic marker of poor outcome. While higher transfusion requirements generally mirror greater disease severity and complex hemostatic derangements, the independent association observed in multivariable analyses suggests that FFP administration itself may directly contribute to adverse outcomes, potentially through mechanisms such as immune modulation or volume overload. Nevertheless, definitive causality can only be established in prospective RCTs directly comparing transfusion strategies. Although RBC and FFP transfusions showed a clear association with increased mortality, platelet transfusion was not associated with increased mortality in our cohort.

This finding is consistent with prior studies, which reported no independent association between platelet transfusion volume and mortality in ECMO populations[26]. Several explanations are possible. First, platelet transfusion primarily corrects thrombocytopenia and improves hemostatic competence, whereas RBC and FFP transfusions are more often markers of ongoing bleeding or severe coagulopathy. Platelet administration may therefore be less reflective of underlying disease severity than large-volume FFP and RBC exposure. Second, unlike FFP—which carries risks of volume overload and immune-mediated complications—platelet transfusion may have fewer direct adverse physiological effects. Notably, recent multicenter analyses have shown that while platelet transfusion is frequently required during VA-ECMO, its association with mortality is attenuated after adjustment for bleeding severity and ECMO indications[27]. Taken together, these findings suggest that although platelet transfusion constitutes a substantial proportion of transfusion-related costs, it may be a necessary and clinically justified expense rather than a prognostic driver of adverse outcomes. Overall, the present neutral association observed for platelet transfusion likely reflects the complex interplay among bleeding phenotype, transfusion triggers, and the distinct physiological roles of each blood product.

This study has several limitations. First, it was a single-center retrospective study of data solely from an administrative claims database linked to medical records. Second, no control group (i.e., a patient group that did not receive ECMO) was included. Third, the ELSO guidelines that inform transfusion thresholds were revised during the study period. However, because most ECMO cases occurred before 2021 and followed the 2013 guidelines, the dataset does not permit a comparison of transfusion volumes or clinical outcomes before and after the guideline revision. Finally, the medical resources available for ECMO treatment vary depending on the medical insurance policies and supply of medical resources in each country. Therefore, this study cannot be directly compared with reports on usage from other countries.

Conclusion

This single-center retrospective study highlighted the substantial clinical and economic burdens imposed by ECMO, with transfusion practices emerging as a key de-

terminant of prognosis and resource utilization. RBC and FFP transfusions were independently associated with higher 60-day mortality, underscoring their prognostic significance beyond disease severity alone. Transfusion burden was primarily driven by prolonged ECMO duration and low fibrinogen levels, reflecting the complex interplay of bleeding, anticoagulation, and circuit-related hemolysis inherent to ECMO management. Importantly, blood products were the predominant cost driver in the Japanese health insurance system, further reinforcing the necessity of careful stewardship. Although causality cannot be proven by a retrospective study, the present significant association between higher transfusion exposure and poor survival is consistent with previous findings in other countries. Future prospective multicenter studies should attempt to clarify optimal transfusion thresholds, evaluate causal effects of individual blood products, and harmonize ECMO-related hemostatic management in Japan.

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