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Inter-Facility Transport on Extracorporeal Life Support: Clinical Outcomes and Comparative Analysis with In-house Patients

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Background: Extracorporeal life support (ECLS) is widely used in refractory heart or lung failure, and the demand for inter-facility transportation on ECLS is expanding. However, little is known about post-transportation outcomes, the clinical safety of such transportation, or the characteristics of the transported patients. **Methods:** This was a retrospective review of a 3-year, single-institution experience with inter-facility ECLS transport, as well as a comparative analysis of clinical outcomes with those of in-house patients. We also analyzed the risk factors for hospital mortality in the entire ECLS population using univariate and multivariate analyses to investigate the effects of transport. **Results:** All 44 patients were safely transported without adverse events. The average travel distance was 178.7 km, with an average travel time of 74.0 minutes. Early survival of the transported group seemed to be better than that of the in-house group, but the difference was not statistically significant (70.5% vs. 56.6%, p=0.096). The incidence of complications was similar between the 2 groups, except for critical limb ischemia, which was significantly more common in the transported group than in the in-house group (25.0% vs. 8.1%, p=0.017). After adjusting for confounders, being part of the transported group was not a predictor of early death (adjusted odds ratio, 0.689; p=0.397). **Conclusion:** Transportation of patients on ECLS is relatively safe, and the clinical outcomes of transported patients are comparable to those of in-house ECLS patients. Although matched studies are required, our study demonstrates that transporting patients on ECLS did not increase their risk of hospital mortality after adjustment for other factors.

Key words: 1. Extracorporeal membrane oxygenation
2. Transport

Introduction

Extracorporeal life support (ECLS) has become a popular option for managing severe refractory cardiopulmonary failure. Recently, it has been increasingly commonly applied with broader indications. However, only a small number of medical centers have sophisticated ECLS systems. Thus, transporting patients on ECLS is often unavoidable, and the demand for transportation is expanding because of increased cooperation between medical institutions and specialists, the progressive miniaturization of ECLS

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Table 1. Baseline characteristics of the 44 transported and 173 in-house adult patients undergoing ECLS in the same period

Characteristic	Transported (n=44)	In-house (n=173)	p-value
Age (yr)	47.8±12.3	55.4±15.8	0.003
Gender(male)	28 (64)	110 (64)	0.995
Body mass index (kg/m^2)	25.2±5.4	24.1±4.0	0.147
Underlying diseases			
Hypertension	9 (21)	58 (34)	0.094
Diabetes mellitus	9 (21)	58 (34)	0.094
Coronary artery disease	9 (21)	18 (10)	0.071
Congestive HF	8 (18)	31 (18)	0.968
End-stage renal disease	1 (2)	18 (10)	0.133
Primary diagnoses			
Respiratory failure	20 (45)	43 (25)	
ARDS from pneumonia	13	17	
ARDS from other cause	4	8	
Interstitial lung disease	1	6	
Other	2	12	
Cardiac failure	24 (55)	130 (75)	
Acute coronary syndrome	12	42	
Decompensated HF	6	42	
Other	6	46	
ECLS type			
Veno-venous	16 (36)	37 (21)	
Veno-arterial	28 (64)	136 (79)	
Purpose of ECLS			
Bridge to transplantation	8 (18)	23 (13)	
Bridge to recovery	36 (82)	150 (87)	
Cannulation on CPR (extracorporeal CPR)	12 (27)	68 (39)	0.140

Values are presented as mean±standard deviation or number (%).
ECLS, extracorporeal life support; HF, heart failure; ARDS, acute respiratory distress syndrome; CPR, cardiopulmonary resuscitation.

equipment, and the increasing recognition that high-volume centers achieve better outcomes than smaller hospitals [1,2].

However, inter-facility transportation of critically ill patients on ECLS is a high-risk procedure because of unstable clinical conditions, the lack of diagnostic/therapeutic tools, and the consequences of potential equipment malfunctions [3]. Recently, several groups have reported early results indicating that inter-facility transport on ECLS had acceptable clinical outcomes [4-6]. However, few comparative studies have been done with in-house ECLS patients, which might provide important information about the clinical safety of transportation. Therefore, we reviewed our experience with inter-facility ECLS patient transportation, including a comparative analysis with our hospital's in-house ECLS patients during the same period.

Methods

1) Study design and population

This study was approved by the Sungkyunkwan University Institutional Review Board and patient consent was waived based on the retrospective nature of this study (SMC 2017-04-065-001). From May 2013 to May 2016, 251 adult patients underwent ECLS support. We excluded 34 failed extracorporeal cardiopulmonary resuscitation (ECPR) cases in patients who experienced in-hospital cardiac arrest. The remaining 217 adult patients in whom ECLS support was successfully initiated were included and reviewed in this study. We divided the study population into 2 groups: 44 patients who were transported to our center from other institutions by our mobile ECLS team (transported group) and 173 patients who were not transported (in-house group).

The transported group did not include patients who were transported by physicians from other hospitals.

The mean ages of the transported and in-house groups were 47.8±12.3 years and 55.4±15.8 years, respectively. Primary cardiac failure, rather than respiratory failure, was the main indication for ECLS support, accounting for 55% (n=24) and 75% (n=130) of the groups, respectively. Venoarterial (VA) ECLS was more frequently initiated than venovenous (VV) ECLS in both groups, accounting for 64% (n=28) of the transported group and 79% (n=136) of the in-house group. Twelve patients (27%) from the transported group and 68 patients (39%) from the in-house group were cannulated during cardiopulmonary resuscitation (successful ECPR). Detailed baseline characteristics of the 2 groups are presented in Table 1.

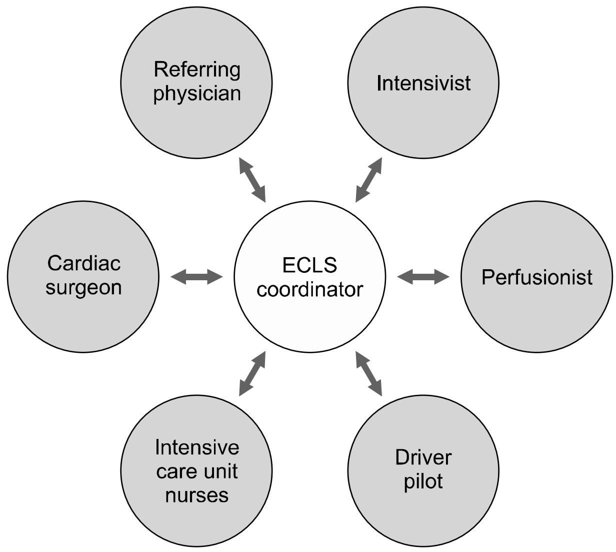

Fig. 1. Interactions between personnel members involved in the transportation process. ECLS, extracorporeal life support.

2) Program development and initiation of the transportation process

As a tertiary hospital, we previously accept patients on ECLS from other hospitals transported by their own staff. After seeing serious mistakes made by inexperienced transport personnel, such as running out of battery power or oxygen, we decided to build an ECLS transport service for referring hospitals. We published our initial experience in 2014, and we have extended our capability over time and become more inclusive in terms of patient selection. As a result, our yearly volume of transportation cases has steadily increased.

In our system, an initial transportation request is made through the Samsung Medical Center referral system or directly to an ECLS team. After receiving a request, physicians on the ECLS team assess the patient's condition in the referring hospital. Criteria for rejecting referral are obvious and severe brain injury, hemodynamic instability under optimal ECLS management, no expected favorable benefit from inter-facility transport, no available intensive care unit bed, and inability to arrange a safe mode of transport. Final decisions are made by the leader of the ECLS transport team (Y.H.C).

3) Transportation protocol

Our protocol for transport on ECLS was described previously [7]. After deciding the optimal method and time for transportation, the ECLS coordinator arranges for a perfusionist and a nurse or emergency medical technician to participate in the transportation process (Fig. 1). The cardiac surgeon of the ECLS team performs cannulation in the referring hospital if required, and is also responsible for identifying the development of ECLS-related complications. The intensivist takes responsibility for the overall medical management of the patient, including the use of a volume expander, inotropics, and/or vasoactive drugs.

We prefer to use the prolonged life support (PLS) system (Prolonged Life Support System; Maquet Inc., Rastatt, Germany) because it is furnished with a manual crank for use when the battery is not charged. We also prepare a primed circuit for system exchange if the patient is on a different system prior to transport. We usually ask the sending hospital to minimize the number of continuous intravenous medicines because we have to prepare the same number of infusion pumps. In cases involving helicopter transport, we ask that medicines be prepared in a 50-mL syringe to fit the built-in syringe pumps in our helicopter [7].

For patients on a PLS system, we simply change the device to our PLS system. For patients on an emergency bypass system (EBS), we attempt to change the system to our PLS system before transport. If our PLS system is unavailable, we use an EBS with a Quadrox-D oxygenator (Maquet Inc.), which is more

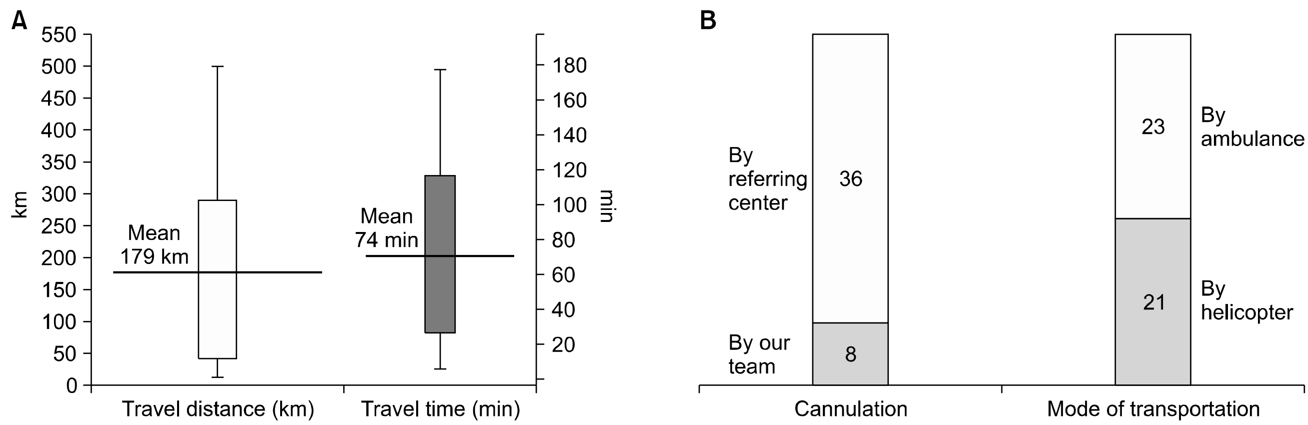

Fig. 2. Transportation data. (A) Box-plot showing mean travel distance and travel time. (B) Bar chart showing the proportion of cannulation by our team and the mode of transportation.

durable than the original EBS oxygenator. The circuit change is performed by our transport team in coordination with the referring physicians [7]. Before departure, we routinely obtain informed consent about the possibility of a traffic accident from caregivers. Because the Korean National Insurance System does not cover the cost of inter-facility transport, patients are responsible for the transportation fee. Because the cost for helicopter transportation is too high for most patients, Samsung Medical Center generally pays the full cost for helicopter transport as a form of charitable activity.

4) Statistical analysis

All data were extracted from the Samsung Medical Center ECLS Registry or the electronic medical record system of our hospital. Patient outcomes are reported through July 2016. We present categorical variables as number and percent and continuous variables, which we compared using the Student t-test, as mean±standard deviation. We performed a univariate analysis to identify the predictors of hospital mortality using the chi-square test and the following variables: transport status, age, sex, body mass index (BMI), hypertension, diabetes, coronary artery disease, congestive heart failure, end-stage renal disease (ESRD), ECPR, and ECLS data. Variables with p-values <0.2 in the univariate analysis, along with variables considered clinically relevant, were entered into the multiple logistic regression model. We used multivariate logistic regression to identify independent predictors of hospital mortality. All p-values <0.05 were considered to indicate statistical significance. All statistical analyses were carried out using IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA).

Results

1) Transportation results

All 44 patients were transported safely to our center. No adverse events occurred during transportation, such as mechanical failure requiring hand-cranking of the pump, circuit problems, hemodynamic compromise including inadequate flow, or death during transportation. The average travel distance was 178.7±152.5 km with a range of 13 to 500 km. The average travel time was 74.0±52.5 minutes with a range of 15 to 180 minutes. Twenty-three patients (52%) were transported by ambulance, with the remainder traveling by helicopter (Fig. 2).

2) Clinical outcomes of the transported group compared with the in-house group

The mean ECLS support durations in the 2 groups were 17.1±15.4 days and 8.6±15.3 days, respectively (p=0.002). There was a significant difference in the initial ECLS flow rate between the transported and in-house groups (4.28±1.24 L/min versus 3.40±0.83 L/min, p=0.001). In the transported group, 33 patients (75.0%) had overall weaning success and 31 (70.5%) survived to discharge. In the in-house group, 125 patients (72.3%) had overall weaning success and 98 (56.6%) survived to discharge. The weaning success and survival to discharge rates did not differ sig-

Table 2. Clinical outcomes

Variable	Transported (n=44)	In-house (n=173)	p-value
Hospital stay (day)	47.5±52.0 (2–232)	30.0±28.5 (2–138)	0.035
ECLS results			
Duration of ECLS (day)	17.1±15.4 (2–68)	8.6±15.3 (1–80)	0.002
Initial blood flow (L/min)	4.28±1.24	3.40±0.83	0.001
Outcomes for all patients			
Overall ECLS weaning success	33 (75.0)	125 (72.3)	0.715
Overall survival to discharge	31 (70.5)	98 (56.6)	0.096
Outcomes for venovenous ECLS	16	37	
ECLS weaning success	13 (81.3)	21 (56.8)	0.088
Survival to discharge	13 (81.3)	15 (40.5)	0.006
Outcomes for VA ECLS	28	136	
ECLS weaning success	20 (71.4)	104 (76.5)	0.572
Survival to discharge	18 (64.3)	83 (61.0)	0.747
ECLS-related complications			
Critical limb ischemia (requiring fasciotomy or amputation)	7 (25.0)[a)]	11 (8.1)[a)]	0.017
Bleeding (requiring surgical exploration)	3 (6.8)	16 (9.2)	0.771
Major thromboembolism	1 (2.3)	4 (2.3)	1.000
Infection (cannulation site, mediastinitis)	3 (6.8)	20 (11.6)	0.583
Acute kidney injury (requiring continuous renal replacement therapy)	20 (45.5)	58 (33.5)	0.141

Values are presented as mean±standard deviation (range) or number (%).
ECLS, extracorporeal life support; VA, venoarterial.
[a)]Calculated in VA subgroup.

nificantly between the 2 groups (p=0.715 and p=0.096, respectively).

We performed a subgroup analysis for VA ECLS and VV ECLS. In the VA subgroup, the weaning success rate did not differ significantly between the transported and in-house groups (71.4% versus 76.5%, p=0.572), nor did the survival to discharge rate differ significantly (64.3% versus 61.0%, p=0.747). However, in the VV subgroup, we did find a significant difference in the survival to discharge rate between the transported and in-house groups (81.3% versus 40.5%, p=0.006), but the difference in the weaning success rate did not reach statistical significance (81.3% versus 56.8%, p=0.088). The incidence of most complications did not differ significantly between the 2 groups, including bleeding, major thromboembolism such as ischemic stroke or myocardial infarction, surgical site infection, and acute kidney injury (AKI). However, the incidence of critical limb ischemia in VA ECLS was significantly higher in the transported group than in the in-house group (25.0% versus 8.1%, p=0.017). A detailed comparison of the 2 groups is shown in Table 2.

3) Risk factor analysis for hospital mortality

To investigate the effect of transportation while adjusting for the effects of other variables, we performed a risk factor analysis for the whole study population. Our univariate analysis found that the variables yielding p-values <0.2 were age, BMI, transport status, ECPR, presence of underlying conditions (hypertension, diabetes, ESRD), the primary diagnosis for ECLS initiation (acute respiratory distress syndrome [ARDS] from conditions other than pneumonia or acute coronary syndrome), and AKI requiring continuous renal replacement therapy (CRRT).

Our multivariate analysis revealed that age (adjusted odds ratio [OR], 1.029; p=0.025), ECPR (adjusted OR, 2.996; p=0.004), ESRD as an underlying condition (adjusted OR, 3.900; p=0.017), and AKI requiring CRRT (adjusted OR, 5.872; $p<0.001$) were independent risk factors for hospital mortality. Interestingly, being in the transported group was not a predictor of early death (adjusted OR, 0.689; p=0.397). In addition, acute coronary syndrome as a primary diagnosis for ECLS initiation was a significant protective factor against hospital mortality (adjusted OR, 0.231; p=0.002) (Table 3).

Table 3. Factors associated with hospital mortality (univariate & multivariate analyses)

Variable	Univariate analysis		Multivariate analysis	
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age	1.029 (1.010–1.048)	0.003	1.029 (1.004–1.055)	0.025
Gender (female vs. male)	0.918 (0.522–1.614)	0.766		
Body mass index (≥25 kg/m^2 vs. <25 kg/m^2)	1.468 (0.841–2.563)	0.176	1.214 (0.616–2.393)	0.574
Transported	0.548 (0.268–1.119)	0.096	0.689 (0.291–1.631)	0.397
Extracorporeal cardiopulmonary resuscitation	1.708 (0.975–2.992)	0.061	2.996 (1.421–6.315)	0.004
Underlying conditions				
Hypertension	2.189 (1.218–3.933)	0.008	1.860 (0.857–4.040)	0.117
Diabetes mellitus	1.676 (0.936–3.003)	0.081	1.562 (0.741–3.293)	0.241
Coronary artery disease	1.688 (0.752–3.792)	0.201		
Congestive HF	0.787 (0.383–1.615)	0.513		
End-stage renal disease	2.752 (1.038–7.297)	0.036	3.900 (1.277–11.916)	0.017
Primary diagnoses				
ARDS from pneumonia	1.142 (0.524–2.489)	0.738		
ARDS from other cause	3.125 (0.911–10.719)	0.072	4.226 (0.946–18.873)	0.059
Acute coronary syndrome	0.474 (0.242–0.927)	0.027	0.203 (0.082–0.503)	0.001
Decompensated HF	1.321 (0.692–2.520)	0.399		
ECLS mode (venovenous vs. venoarterial)	1.431 (0.767–2.673)	0.259		
Acute kidney injury requiring continuous renal replacement therapy	3.624 (2.025–6.484)	<0.001	5.872 (2.840–12.143)	<0.001
ECLS-related complications	1.203 (0.652–2.218)	0.554	0.791 (0.381–1.644)	0.530

OR, odds ratio; CI, confidence interval; HF, heart failure; ARDS, acute respiratory distress syndrome; ECLS, extracorporeal life support.

Discussion

ECLS use is rapidly expanding, particularly in the adult population [8]. According to the Extracorporeal Life Support Organization (ELSO) registry, more than 78,000 patients have received ECLS [9]. Regarding the clinical outcomes of ECLS support, recent studies have securely established that ECLS centers with more than 30 annual adult ECLS cases have significantly lower ECMO mortality than units with fewer than 6 cases per year [10]. However, patients in need of ECLS support are frequently seen first in peripheral centers with a low volume. Therefore, it is unsurprising that many worldwide ECLS centers have developed and now manage their own ECLS transport programs. Accordingly, ELSO published guidelines for ECLS transport in 2015 [11].

It is well known that inter-facility transport of critically ill patients receiving conventional therapy is a high-risk procedure [3]. Therefore, many clinical issues regarding the safe transportation of ECLS patients have been suggested and studied. To date, more than 1,400 ECLS patient transports have been described in papers by Western groups, mostly as small series and case reports [12]. Among them, only 8 publications included more than 50 cases. Most studies presented their clinical outcomes descriptively, and only a few studies have compared their outcomes with the ELSO registry or in-house ECLS patients [5,6,13]. Therefore, up-to-date data comparing transported and in-house ECLS patients will be helpful for understanding the clinical characteristics of transported patients and might help improve clinical safety.

In Korea, our mobile ECLS team first described our initial experience with 4 inter-facility transports of patients on ECLS [7]. Since then, such transports have become more common at our institution. To date, we have participated in more than 50 transports (including 8 pediatric patients). Herein, we report our single-center experience and compare outcomes between transported and in-house adult ECLS patients.

According to the ELSO guidelines, an ECLS transport system should include the following components: (1) an experienced team composed of a cannulating physician, an ECLS physician, an ECLS specialist, and a transport nurse/respiratory therapist; (2) mobile ECLS components (pumps, oxygenator, gas tanks, etc.); (3) transport equipment (patient monitor, portable ventilator, point-of-care device, infusion pumps with medications and fluids); and (4) appropriate vehicles (ambulance, helicopter, or fixed-wing aircraft) [11]. Our mobile ECMO team meets all of these recommended requirements, especially in terms of personnel. Our mobile ECLS team consists of a referral center, an ECLS coordinator, critical care physicians, and cardiac surgeons who are involved in the entire transportation process.

The clinical outcomes in this study show that the survival to discharge rate did not differ significantly between the transported and in-house groups (70.5% versus 56.6%, p=0.096). Our survival to discharge rate in the transported group (70.5%) is comparable to those reported in prior studies: 62% (by Bryner et al. [5]) and 63% (by Biscotti et al. [4]). Our results are also consistent with prior reports in that no significant difference was found between the 2 groups. However, our clinical outcomes should be interpreted with caution. In particular, the mean age of our in-house group was significantly higher than that of our transported group. Thus, it is possible that transported patients, who had survived several crises before being referred for transport, might have been selected for their younger age and the reversibility of their condition. However, our multivariate analysis revealed that transport status did not affect the survival outcome, even after we adjusted for age. We surmise that event-free transportation might contribute to an acceptable clinical outcome. Another important factor affecting the outcomes of transported patients is qualified, intensive aftercare. At our hospital, patients receive a thorough systematic evaluation by a multidisciplinary team immediately upon arrival, including identification of ECLS-related complications and decision-making about further treatment.

Interestingly, in the VV subgroup analysis, the transported group showed significantly higher rates of survival to discharge than the in-house group (81.3% versus 40.5%, p=0.006). The favorable outcome of transport on VV ECLS can be explained by the fact that our study enrolled only the patients who had conditions making transportation possible. Thus, selection bias was likely present in our subgroup analysis.

Our study also found that critical limb ischemia in VA ECLS patients developed more frequently in the transported group. Its relatively high incidence (25%) could be explained by the time-limited nature of the transport procedure. Detection and decision-making in limb ischemia sometimes delays the whole transport procedure because our strategy is focused on minimizing the time spent at the referring center after cannulation, if the patient's condition is not immediately life-threatening. If limb ischemia is suspected before or during transportation, we communicate with our colleagues in our center to prepare for the proper intervention, including distal perfusion catheter insertion or fasciotomy. Because it can rapidly lead to sepsis and hemodynamic instability, prompt management of this problematic complication is critical.

Although this may be beyond the primary scope of our study, in our multivariate analysis we found that age, ECPR, the presence of underlying ESRD, and the development of AKI requiring CRRT were independent risk factors for hospital mortality. These findings are quite plausible and relevant to prior studies. Thus, as in general ECLS management, the early detection and management of AKI in transported patients are of paramount importance. Moreover, the decision to transport patients on ECLS with advanced age, a history of ECPR, or underlying ESRD requires extra attention and a careful approach.

Patients who had acute coronary syndrome as a primary diagnosis had a significantly lower risk of hospital mortality than those with other diagnoses (adjusted OR, 0.203; p=0.001). Characteristically, this group of patients mostly underwent successful revascularization before or after ECLS initiation, which might have had reversible and quite protective effects. We also found that ARDS from other causes, which might have more irreversible effects on the respiratory system than pneumonia, tended to increase hospital mortality, although that trend did not reach statistical significance (adjusted OR, 4.226; p=0.059).

Our study has several limitations. It was a retrospective, non-randomized study at a single institution. We included a small number of patients, so our statistical power may have been limited. Moreover, the 2 groups showed heterogeneity in their baseline characteristics, which makes direct comparisons difficult and inconclusive. In particular, the mean age of the in-house group was significantly higher than that of the transported group. However, we found that transportation was performed safely by our experienced multidisciplinary ECLS team without any adverse events, and that the survival of transported patients was acceptable in comparison to the in-house group.

In conclusion, transporting patients on ECLS is relatively safe, and the clinical outcomes of patients transported while on ECLS are acceptable and comparable to those of in-house ECLS patients. In addition to previous studies, our study provides supplemental evidence for the safety and feasibility of inter-facility transport on ECLS. When transporting VA ECLS patients, physicians should recognize that limb ischemia might be more frequent than usual in ECLS cases. However, a larger, prospective multicenter study would be necessary to confirm our findings.

Conflict of interest

No potential conflicts of interest relevant to this article are reported.

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