



Year: 2015

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Abstract: **BACKGROUND:** Extracorporeal life support (ECLS) as a bridge to lung transplantation (LuTx) is a promising option for patients with end-stage lung disease on the transplant waiting list. We investigated the outcome of patients bridged to lung transplantation on ECLS technologies, mainly extracorporeal membrane oxygenation (ECMO). **METHODS:** Between January 2007 and October 2013, ECLS was implanted in 30 patients with intention to bridge to LuTx. Twenty-six patients (26/30) were successfully bridged to LuTx on ECLS. The most common diagnosis was cystic fibrosis (N = 12). Venovenous ECMO was used in 10, venoarterial in 4, interventional lung assist in 5, and stepwise combination of them in 7 recipients. **RESULTS:** Two patients weaned from ECMO, and 2 patients died on ECMO on the waiting list. Median duration of ECLS was 21 days (1-81 years). Six patients were awake and spontaneously breathing during ECLS support. Thirty-day, 1-year, and 2-year survivals were 89%, 68%, and 53%, respectively, for bridged patients and 96%, 85%, and 79%, respectively, for control group (P = 0.001). Three months conditional survivals were 89% and 69% at 1 and 2 years for ECLS group, compared to 92% and 86% for control group (P = 0.03). Cystic fibrosis recipients had 82% survival rate at 1 and 2 years. All recipients bridged to LuTx on awake ECLS (N = 6) are alive with a median follow-up of 10.8 months (range, 6-21 months). **CONCLUSIONS:** Our data show significantly lower survival in this high-risk group compared to patients transplanted without preoperative ECLS. Awake and ambulatory ECLS provides the best prognosis for these high-risk patients.

DOI: <https://doi.org/10.1097/TP.0000000000000653>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-117881>

Journal Article

Published Version

Originally published at:

Inci, Ilhan; Klinzing, Stephanie; Schneiter, Didier; Schuepbach, Reto A; Kestenholz, Peter; Hillinger, Sven; Benden, Christian; Maggiorini, Marco; Weder, Walter (2015). Outcome of extracorporeal membrane oxygenation as a bridge to lung transplantation: an institutional experience and literature review. *Transplantation*, 99(8):1667-1671.

DOI: <https://doi.org/10.1097/TP.0000000000000653>

Outcome of Extracorporeal Membrane Oxygenation as a Bridge To Lung Transplantation: An Institutional Experience and Literature Review

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Background. Extracorporeal life support (ECLS) as a bridge to lung transplantation (LuTx) is a promising option for patients with end-stage lung disease on the transplant waiting list. We investigated the outcome of patients bridged to lung transplantation on ECLS technologies, mainly extracorporeal membrane oxygenation (ECMO). **Methods.** Between January 2007 and October 2013, ECLS was implanted in 30 patients with intention to bridge to LuTx. Twenty-six patients (26/30) were successfully bridged to LuTx on ECLS. The most common diagnosis was cystic fibrosis (N = 12). Venovenous ECMO was used in 10, venoarterial in 4, interventional lung assist in 5, and stepwise combination of them in 7 recipients. **Results.** Two patients weaned from ECMO, and 2 patients died on ECMO on the waiting list. Median duration of ECLS was 21 days (1-81 years). Six patients were awake and spontaneously breathing during ECLS support. Thirty-day, 1-year, and 2-year survivals were 89%, 68%, and 53%, respectively, for bridged patients and 96%, 85%, and 79%, respectively, for control group ($P = 0.001$). Three months conditional survivals were 89% and 69% at 1 and 2 years for ECLS group, compared to 92% and 86% for control group ($P = 0.03$). Cystic fibrosis recipients had 82% survival rate at 1 and 2 years. All recipients bridged to LuTx on awake ECLS (N = 6) are alive with a median follow-up of 10.8 months (range, 6-21 months). **Conclusions.** Our data show significantly lower survival in this high-risk group compared to patients transplanted without preoperative ECLS. Awake and ambulatory ECLS provides the best prognosis for these high-risk patients.

(*Transplantation* 2015;99: 1667–1671)

Lung transplantation (LuTx) is an established therapeutic option for patients with end-stage lung disease.¹ Although the number of lung transplantations has been increased, the number of available donor lung grafts is still a main limitation factor in this treatment option resulting in waiting list mortality.

Despite sophisticated mechanical ventilator techniques on the intensive care unit (ICU) for patients awaiting a suitable lung graft, refractory hypercapnia, or hypoxemia might develop.² For these patients, extracorporeal life support (ECLS) is the only chance to survive until a lung graft becomes available.²

Although the early experience with extracorporeal membrane oxygenation (ECMO) as a bridge to lung transplantation was discouraging, improvements in artificial lung device technologies have made it possible to bridge these patients successfully to lung transplantation.^{2,3} Recent studies using ECLS as a bridge to LuTx have reported comparable short- and mid-term results to recipients undergoing LuTx without preoperative ECLS.⁴⁻²³

We describe our experience with ECLS technologies mainly ECMO as a bridge to lung transplantation in patients with refractory respiratory failure.

METHODS

We performed a retrospective review of prospectively collected data of all recipients undergoing ECLS with either ECMO or interventional lung assist (iLA) as a bridge to lung transplantation from January 2007 to October 2013 at Zurich University Hospital. Bridged recipients (ECLS group, N = 26) were compared with recipients that underwent LuTx without preoperative ECLS (control group, N = 160). Censor date for survival analysis was April 22, 2014.

Data Analysis

Statistical analysis was performed using the Statistical Package for the Social Science version 21.0 (SPSS IBM, New York, NY). Continuous variables are shown as mean \pm standard deviation or median (range or interquartile ranges). The non-parametric Mann-Whitney test was used to compare independent continuous variables between the 2 groups. The Fischer exact test was used to determine the association

Received 4 July 2014. Revision requested 3 November 2014.

Accepted 11 December 2014.

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The authors declare no funding or conflicts of interest.

I.I. participated in research design, in the writing of the paper, and in data analysis. S.K. participated in data analysis. D.S. participated in data analysis. R.A.S. participated in the writing of the paper and data analysis. P.K. participated in data analysis. S.H. participated in data analysis. C.B. participated in the writing of the paper and in data analysis. M.M. participated in data analysis. W.W. participated in research design, in the writing of the paper, and in data analysis.

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ISSN: 0041-1337/15/9908-1667

DOI: 10.1097/TP.0000000000000653

TABLE 1.
Patient characteristics

	ECLS group	Control group	P
N	26	160	
Recipient age, y	44.5 (14-65)	56 (10-70)	0.6
Recipient sex (m/f)	12/14	85/75	0.5
Waiting list time, d	31 (5-1965)	196 (1-914)	0.4
Donor age, y	43 (13-74)	50 (11-81)	0.4
Donor sex (m/f)	17/9	98/62	0.4
Transplant type			0.1
Unilateral	3	7	
Bilateral	23	153	
Retransplantation	4	6	0.2
Size reduction	16	76	0.8
Lobar transplant	13	54	
ECMO/CPB use	26	76	0.001
Cold ischemic time			
Right lung, min	278 ± 104	250 ± 97	0.2
Left lung, min	359 ± 80	334 ± 100	0.2
Intubation time, d	6 (IQR, 1-23)	1 (IQR, 1-2)	0.001
ICU stay, d	18 (IQR, 3-38)	3 (IQR, 2-10)	0.001

Data presented as median (range or IQR) or mean ± standard deviation.
CPB, cardiopulmonary bypass; IQR, interquartile ranges.

between 2 categorical variables. Kaplan-Meier analysis was used to calculate actuarial survival. The log-rank test was used to test the difference in Kaplan-Meier survival curve between the groups. A *P* value of 0.05 or less was considered as statistical significance.

RESULTS

During the study period, 186 lung transplantations were performed, 26 (13.9%) received ECLS (ECMO or iLA) before transplantation (ECLS group), and 160 had no support before transplantation (control group). An additional 4 patients were placed on ECMO with the intention to transplant, but 2 died and 2 weaned from ECMO and successfully transplanted.

Two patients failed bridge to transplant on ECMO while waiting an available lung graft. One patient with idiopathic pulmonary fibrosis (IPF) diagnosis died due to heart failure, and the other cystic fibrosis (CF) patient died due to sepsis and multiorgan failure. Therefore, our bridge to transplant success rate was 86.6% (26/30). The indications for ECLS were respiratory insufficiency due to chronic lung allograft dysfunction (*N* = 1), primary graft dysfunction (*N* = 2), hypercapnia and right heart failure (*N* = 4), hypercapnia (*N* = 9), and hypercapnia and hypoxemia (*N* = 10). The type of ECLS was venovenous ECMO (VV ECMO) (*n* = 10), venoarterial ECMO (*n* = 4), iLA (*n* = 5), and stepwise combination of them (*n* = 7). In VV ECMO, the femoral vein and internal jugular vein were the most common cannulation sites. In 12 cases, we used dual lumen catheter (Avalon; MAQUET Cardiopulmonary AG, Rastatt, Germany) for VV ECMO. In VA ECMO, femoral vein-femoral artery, internal jugular vein-femoral arteries, axillary artery-femoral vein were the most common cannulation sites. In 2 patients with iLA, one was on Novalung (Novalung GmbH, Heilbronn, Germany) femoral artery-femoral vein, the other was on ProLung (Estor S.P.A, Milano, Italy) cannulated via the internal jugular vein (Sheldon Catheter).

To prevent limb ischemia and local complications with peripheral cannulation, we use a synthetic vascular graft (8 mm) in end-to-side anastomosis fashion to the femoral or axillary artery, which is passed through a separate skin incision. The arterial cannula is passed through the vascular graft until the tip of the cannula reached the anastomosis and pointed to the proximal site of the artery.

The median duration of pretransplant ECLS support was 21 days (range, 1-81). In our series, 20 patients were sedated and mechanically ventilated while they were at the same time on ECLS. The median duration of mechanical ventilation before ECLS was 2.5 days (range, 1-35). Recipient age, recipient sex, donor age, and donor sex were comparable between pretransplant ECLS group and control group (Table 1). One patient developed heparin-induced thrombocytopenia during bridging. This patient successfully underwent unilateral lung transplantation. Cystic fibrosis (46.1%) was the most common diagnosis in the pretransplant ECLS group followed by idiopathic pulmonary fibrosis (38.4%) (Table 2). One patient received lung from donation after cardiac death donor, and 1 patient received unilateral lobar lung retransplantation after ex vivo lung evaluation.

In the pretransplant ECLS group, 88.4% (23/26) of the recipients underwent bilateral lung transplantation, whereas 95.6% (153/160) of the patients in the control group underwent bilateral lung transplants (*P* = 0.14). The rate of retransplantations was comparable between the groups (*P* = 0.16) (Table 1). Sixty-one percent of the recipients in the pretransplant ECLS group and 47.5% in the control group underwent size reduction during the transplantation (*P* = 0.14). Cadaveric lobar lung transplantation was performed in 13 recipients in the pretransplant ECLS group and in 54 recipients in the control group. During the transplant procedure, ECMO was used in ECLS group, whereas only 47.5% (76/160) of the patients required ECMO or cardiopulmonary bypass in the control group. The cold ischemic times were comparable between the 2 groups (Table 1).

Posttransplant ECMO support was necessary in 14 of 26 patients in the pretransplant ECLS group with a median of 2 days (range, 1-9). The intubation time and ICU stay were significantly longer in the pretransplant ECLS group compared with the control group (*P* = 0.001) (Table 1).

The complications related to ECMO for ECLS group are shown in Table 3. Tracheostomy was required in 19 (11 have already had tracheostomy on the ICU) of 26 patients (73%), whereas 27.5% (44/160) required tracheostomy in the control group (*P* = 0.001) (Table 4). The rate of primary graft dysfunction grade 2 or 3 at 72 hours as defined by the International Society for Heart and Lung Transplantation²⁴ was 23% (6/26) in the pretransplant ECLS group compared

TABLE 2.
Diagnosis

	ECLS group (N = 26)	Control group (N = 160)
Cystic fibrosis	12	39
COPD	3	51
IPF	10	44
PPH	1	6
Other	—	20

COPD, chronic obstructive pulmonary disease; PPH, primary pulmonary hypertension.

TABLE 3.
Complications of related to ECMO cannulation

	N	%
Infection	1	6.3
Bleeding + infection	3	18.8
Thrombosis	3	18.8
Lymphocele	4	6.3
Brachial plexus injury	1	6.3

to 15.6% (25/160) in the control group ($P = 0.36$). In the pretransplant ECLS group, 34.6% of the patients underwent early rethoracotomy (<10 days) for hemothorax (Table 4). In the ECLS group, 11 of 26 patients (42.3%) required renal replacement therapy, and 53.8% developed critical illness myopathy, compared to 15.6% and 2.5%, respectively, in the control group. There were no bronchial anastomotic complications in the pretransplant ECLS group, whereas only 2 patients in the control group underwent surgery for bronchial anastomotic complication at days 5 and 12.

The 30-day mortality in the pretransplant ECLS group was 11.5% (3/26) and 3.7% (6/160) in the control group ($P = 0.1$). The causes of early mortality in control group were hemorrhagic shock in 1, sepsis/MOF in 1, intracranial bleeding in 2, and severe graft dysfunction in 2 patients. For ECLS group, the causes were refractory cardiogenic shock with intra-abdominal and intrathoracic bleeding in 2 and sepsis and multiorgan failure in 1. The median age for 30-day mortality was 58 years (range, 29-60) for the ECLS group and 65 years (range, 57-70) for the control group.

The rate of late mortality (>3 months) in the control group was 22% (35/160) and 23% (6/26) in the ECLS group. The causes of late mortality are shown in Table 5.

Unadjusted 30-day, 1-year, and 2-year survivals were 89%, 68%, and 53%, respectively, for bridged patients and 96%, 85%, and 79%, respectively, in the control group ($P = 0.001$, log rank) (Figure 1). Ninety-day conditional survivals were 89% and 69% at 1 and 2 years for ECLS group, compared to 92% and 86% for control group ($P = 0.03$). In CF patients ($N = 12$), 1-year and 2-year survival rates were 82%, whereas it was 50% and 25%, respectively, for IPF recipients.

TABLE 4.
Postoperative complications

	ECLS group	Control group	P
No	26	160	
Tracheostomy	19	44	0.001
Thoracic hernia	0	6	0.3
Lymphocele	4	10	0.2
PGD 2/3 at T72	6	25	0.4
Hemothorax	12	30	0.03
Early (<10 d)	9	16	
Late (>10 d)	3	14	
Abdominal complication	0	15	0.8
Phrenic nerve injury	1	1	0.1
Dialysis	11	25	0.001
Technical complication	1	4	0.6
Critical illness myopathy	14	4	0.001

PGD, Primary graft dysfunction grade 2 or 3 at time 72 hours.

TABLE 5.
Causes of late (>3 months) mortality

	Control group (N)	ECLS group (N)
Sepsis/multiorgan failure	14	4
Intracranial bleeding	2	—
Heart failure	1	—
Malignancy	4	—
BOS	11	—
Renal failure	—	1
Unknown	3	1

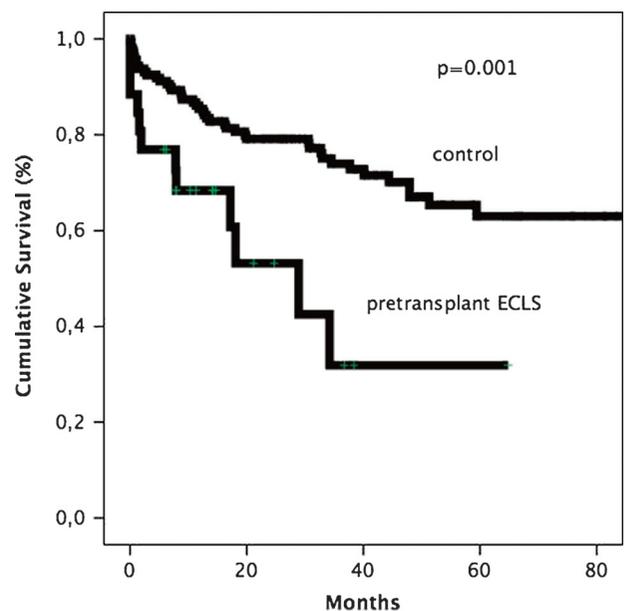
BOS, bronchiolitis obliterans syndrome.

All of the 6 patients that were bridged to lung transplantation on awake ECMO are still alive with a median follow-up of 10.8 months (range, 6-21 months).

DISCUSSION

This is a large single-center experience of the use of pretransplant ECLS, mostly ECMO, as a bridge to lung transplantation over a 7-year period (2007-2013). At our center, pretransplant ECLS constituted approximately 14% (26/186) of our transplant experience in that period of time, which is the largest percentage among reported series from large transplant centers.^{10,13,20} In 2013, this rate was 35.7% of our overall lung transplant activity, which reflects the high number of urgent recipients undergoing lung transplantation.

Because of improved technologies, the transplant candidates can tolerate ECMO for longer periods of time; however, because of several reasons, such as muscular deconditioning of the patients, hemolysis, bleeding, infection, and stroke, systemic or pulmonary thromboembolism shorter bridging time brings

**FIGURE 1.** Cumulative survival curve that compares control group versus pretransplantation ECLS group. Number at risk:

Months	0	12	24	36	48	60
Control	180	130	97	65	43	25
Pre-Tx ECLS	26	12	7	2	1	1

better outcomes.^{8,10} Median support time reported in the literature varies from 3 to 17 days (range, 1-229).^{4,6,8-14,16,17,21-23} Our median support time was 21 days (range, 1-81) which is longer than in all reported series. To demonstrate the possible effect of ECLS time on outcomes, Crotti et al⁸ analyzed survival dividing patients according to their waiting time on ECMO as early (14 days) and late (>14 days). This group demonstrated significantly better 1-year survival (82%) in the early study group compared to late study group (29%).⁸ Our results (not shown in *Results* section) are in contrast to the data reported by Crotti et al. Our “late” patients' survival was superior compared to the “early” patients, although the difference was not statistically significant. In our series, 1-year and 2-year survival was 67% and 50% in the early group (N = 9), respectively, compared to 74% and 59% in the late group (N = 17) (*P* = 0.29). Although the numbers are small to draw any final conclusions, the reasons for that might be the higher percentage of CF recipients (9 vs 3) and patients on awake ECMO (4 vs 2) in the “late” ECMO group compared to the “early” ECMO group.

In patients requiring pretransplant ECLS, high rates of primary graft dysfunction have been reported.¹⁰⁻²⁰ The reasons, although not clear, for higher rates of primary graft dysfunction include the systemic inflammatory status and coagulopathy, requiring more blood transfusions.^{10,14} We transferred 14 patients to the ICU with ECMO. The reason for that is not only primary graft dysfunction. In our center, patients who were on ECMO for a long time with secondary pulmonary arterial hypertension, or right heart failure, were not removed from ECMO at the operating room after the transplantation. We give them time to recover, especially, the cardiac function. On the other hand, in a patient who is on VV ECMO only for hypercapnia, we remove the ECMO in the operating room if the graft function is good.

An important development in the field of bridging patients on ECLS is the concept of awake and ambulatory ECMO. The Hannover Group based on their clinical success in patients with pulmonary hypertension and end-stage right ventricular failure adopted this strategy for other forms of

end-stage lung diseases.^{14,25} The main advantage of the awake ECMO concept is the avoidance of complications and drawbacks associated with sedation, intubation, and long-term ventilation.^{14,25} Prolonged mechanical ventilation results in nasocomial infection rate, critical illness myopathy, leading to difficult and prolonged weaning after transplantation, resulting in longer ventilation and ICU stay after transplantation than those in the awake ECMO group.^{4,14,25} The Gothenburg Group reported 40% critical illness myopathy in their cohort which resulted in longer ICU and hospital stay.⁴ In our series, critical illness myopathy occurred in 54% (14 of 26) of patients resulting in significantly longer ICU stay and intubation time compared to control group. The 6-month survival rate reported by Hannover Group in patients on awake ECMO who reached transplantation was 80%.¹⁴ We successfully bridged 6 patients to transplantation on awake ECMO, and all of them are alive with a median follow-up of 10.8 months (range, 6-21). Awake ECMO should be aimed for in any case possible to obtain better posttransplant outcomes. Our number is very low to draw a strong conclusion, and our observation in these groups of patients corresponds to other publications that favor this mode of bridging.¹⁴

One- and 2-year survival rates for bridged patients vary between 33% to 100% and 60% to 100% in published series (Table 6).^{4,6,8-14,16,17,21-23} Our 2-year survival is somehow lower than the reported series but we think that these high-risk patients would have 100% mortality rate without transplant. Our 3-month conditional survivals were 89% and 69% at 1 and 2 years for ECLS group, which seems acceptable in this high-risk group. In addition, the type of pretransplant diagnosis is very important. In our series, CF recipients had 82% 1- and 2-year survival rates compared to 50% and 25% for IPF recipients, respectively. Most of the reported series have unfortunately not reported in detail survival rates related to diagnosis. The French Group reported 2-year survival rate of 71% in CF and 42.9% in IPF recipients, showing a survival advantage for CF recipients.⁶ Although the experience is limited, the underlying diagnosis for bridging

TABLE 6.**Experience with ECLS as a bridge to lung transplant (series with more than 7 cases)**

Author Year Reference	N	% Tx Activity With ECLS	ECLS Duration	Mode of ECLS	Bridge %	30 d surv	1-y surv	2-y surv	CF, %	IPF, %
Toyoda et al ¹⁰	24	3,4	91 h (171-242)	VV VA	77,4	88	74	74	21	33
Fuehner et al ¹⁴	16	NA	9 d (1-45)	VV VA	61,5	NA	80*	NA	19	35
Bermudez et al ¹⁶	17	1,3	3,3 d (1-49)	VV VA	NA	81	74	NA	23	35
Lafarge et al ⁶	30 (9 centers)	NA	3,5 d (0-11)	VV VA	83	80	66,5	60,5	56	30
Dellgren et al ⁴	16	NA	9 d (1-229)	VV VA	80	81	75	70	15	60
Hoopes et al ⁹	31 (2 centers)	NA	13,7 d (2-53)	VV VA	NA	NA	93	80	20	42
Hämmäinen et al ¹⁷	13 (2 centers)	NA	17 d (1-59)	VV VA	81	NA	92	NA	8	37
Lang et al ¹³	34	NA	4,5 d (1-63)	VV VA, iLA	89	NA	60	NA	44	23
Bittner et al ¹²	9	NA	6 h to 15 d	iLA VV VA	NA	63	33	NA	33	22
Anile et al ⁵	7	3,5	Mean d 6 ± 2,1	VV VA	58,3	100	87,5	NA	85	—
Javidfar et al ¹¹	10	4	6 d (3,5-18)	VV VA	56	100	100	100	NA	NA
Puri et al ²³	10	2,9	32 h (0-1048)	VV VA	62,5	NA	33	NA	7	—
Cypel et al ²¹	12	NA	Mean 7 d	VV VA, iLA	100	100	83			
Crotti S et al ⁸	17 (2 centers)	NA	1-51 d	VV VA	68	NA	76		24	35
Fischer et al ²²	12	6,8	Mean 15 d (4-32)	iLA	83	80	80	NA	16	33
Zurich, present series 2014	26	14	21 d (1-81)	VV VA, iLA	86	89	68	53	46	38

Tx, transplantation; VA, venoarterial; NA, not available; surv, survival.

such patients should be taken into consideration, and potential candidates for bridging to transplantation are selected very carefully. The expectation after bridge to transplantation should be, of course, an outcome comparable to those who did not need ECLS before transplantation. When we refer to the literature, we can see that 1-year and 2-year survival rates range between 33% to 100% and 60% to 100%, respectively (Table 6). The centers with low 1-year survival rates, however, did not publish their 2-year survival rates which makes comparison difficult for us. Underlying disease is an important factor affecting the outcome. We know that CF patients do better than other diagnosis, especially better than IPF patients who usually have secondary pulmonary hypertension.

In our series, 20 patients were sedated and mechanically ventilated while they were at the same time on ECLS. The outcomes are poor if these patients are paralyzed and mechanically supported. This might be one of the explanations of our poor outcomes. Of 12 CF patients, 2 were awake while on ECLS. This might be a reason of poor outcome even for CF cases.

Our study has several limitations. This is a single-center retrospective study using a historical control group. Although we included 26 patients, the number of study patients is still low.

In conclusion, the present data add to the available data and highlight the risks that we suspected based on clinical intuition. Our data show significantly lower survival in this high-risk group compared to those transplanted without preoperative ECLS. The underlying diagnosis should be taken into consideration when selecting candidates. Awake and ambulatory ECMO provides a superior prognosis for these patients and should be aimed for whenever possible. The literature will grow in this field by continually tracking case series like this in a registry. Continuing to revisit data in a registry format will help guide patient selection and management.

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