Efficacy of extracorporeal membrane oxygenation for acute respiratory failure with interstitial lung disease; a case control nationwide dataset study in Japan

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Research

Keywords: extracorporeal membrane oxygenation, interstitial lung disease, macrolides, mortality, respiratory failure

Posted Date: April 6th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-152666/v2

Version of Record: A version of this preprint was published at Respiratory Research on July 24th, 2021.
See the published version at https://doi.org/10.1186/s12931-021-01805-w.

Abstract

Background: Since it is uncertain whether acute respiratory failure in patients with interstitial lung disease is reversible, indications for extracorporeal membrane oxygenation in these patients remain controversial, except for bridging to lung transplantation. The objective of this study was to clarify in-hospital mortality and prognostic factors in interstitial lung disease patients undergoing extracorporeal membrane oxygenation.

Methods: Case-control study. Using the Japanese Diagnosis Procedure Combination database from 2010 to 2017, we reviewed hospitalized interstitial lung disease patients receiving invasive mechanical ventilation and extracorporeal membrane oxygenation. As we focused on the efficacy of extracorporeal membrane oxygenation as an intervention for managing merely acute respiratory failure, patients treated with extracorporeal membrane oxygenation as a bridge to lung transplantation were excluded.

Results: A total of 164 interstitial lung disease patients receiving extracorporeal membrane oxygenation were included. In-hospital mortality of them was 74.4% (122/164). Compared with survivors, non-survivors were older and received high-dose cyclophosphamide, protease inhibitors, and antifungal drugs more frequently but macrolides and anti-influenza drugs less frequently. Multivariate analysis revealed the following factors were associated with in-hospital mortality: advanced age with an odds ratio (OR) of 1.048 and a 95% confidence interval (CI) of 1.015–1.082, non-use of macrolides (OR, 0.264; 95% CI, 0.118–0.589), and use of antifungal drugs (OR, 3.158; 95% CI, 1.377–7.242).

Conclusions: Approximately three quarters of interstitial lung disease patients undergoing extracorporeal membrane oxygenation died in hospital. Moreover, advanced age, non-use of macrolides, and use of antifungal drugs were found to correlate with a poor prognosis.

Background

Regardless of the type of interstitial lung disease (ILD), its associated acute respiratory failure (ARF) leads to a poor prognosis, especially in patients requiring invasive mechanical ventilation (IMV) [1–3]. Extracorporeal membrane oxygenation (ECMO), also known as extracorporeal life support, is a life-saving procedure established for severe respiratory failure, cardiac shock, and cardiac arrest. Veno-venous ECMO serves as an artificial lung that provides oxygenation and carbon dioxide removal by draining and reinfusing the blood through cannulas located in central veins. ECMO enables lung-protective ventilation and reduces complications such as ventilator-induced lung injury and oxygen toxicity [4]. Ever since ECMO therapy proved successful in influenza A (H1N1)-induced severe acute respiratory distress syndrome (ARDS) [5] as well as severe adult respiratory failure (CESAR trial) [6] in 2009, the use of ECMO for respiratory failure in adults has grown rapidly.

ECMO therapy is indicated in patients with potentially reversible causes of respiratory failure or those awaiting lung transplantation [7, 8]. Due to difficulties in predicting the reversibility of respiratory failure, which arise from its heterogeneous causes, the indications for ECMO in ILD patients with ARF are a

matter that should be discussed. Meanwhile, even in-hospital mortality and prognostic factors in ILD patients receiving ECMO have not been clarified. The aim of this study was to elucidate the mortality rate and prognostic factors in these patients by using nationwide data from the Japanese Diagnosis Procedure Combination (DPC) database.

Methods

Study design and data source

This was a retrospective case-control study using a nationwide inpatient database of acute care hospitals in Japan (i.e., the DPC database) to assess the efficacy of ECMO therapy for ARF in ILD patients treated between 2010 and 2017. The DPC is a case-mix classification system that is linked with a lump-sum payment system for inpatient care reimbursement. The Japanese DPC database includes data on the following characteristics: age, sex, body weight, admission and discharge status, main diagnosis, admission-precipitating diagnosis, resource-consuming diagnosis, comorbidities, complications, surgery, and procedures and medications administered during hospitalization. Diagnoses are recorded using International Classification of Diseases, 10th revision, codes by attending physicians. Surgery and procedures performed during hospitalization are recorded according to the Japanese fee schedule for reimbursement.

In April 2020, this system included 1,757 hospitals with a total of 483,180 beds, which is thought to be enough to cover almost all acute inpatients in Japan [9]. The specificity and sensitivity of diagnoses and procedures recorded in the DPC database had already been validated by Yamana et al. [10]. Since all patient data were obtained in an anonymous manner, the requirement for individual informed consent was waived. This study was approved by the institutional review board of General Clinical Research Center, Oita University Hospital, on May 20, 2019 (approval no. 1613).

Patient selection and data extraction

Adult patients with both ILD codes (ICD-10: J670, J671, J672, J673, J674, J675, J676, J677, J678, J679, J700, J701, J702, J703, J704, J708, J82, J840, J841, J849, M0510, M313, M321, M330, M331, M332, M348, M351) and IMV codes were drawn from the 2010–2017 DPC database. After 388 cases with an ECMO code were found, ILD patients on ECMO for cardiac and temporary perioperative reasons were excluded so as to confine the study to those receiving ECMO for ARF. That is, patients with diagnostic or surgical codes pertaining to cardiovascular diseases such as coronary artery bypass grafting, intra-aortic balloon pumping, aortic dissection, cardiac arrest, and cardiogenic shock as well as those with codes related to lung cancer surgery, lung transplantation, and pulmonary alveolar proteinosis were excluded from this analysis (Fig. 1).

Statistical analysis

Statistical analyses were performed using IBM SPSS statistics software (version 22; IBM SPSS, Tokyo, Japan). Continuous variables were described as median ± interquartile range (IQR), and categorical variables as frequency and percentage. The confidence interval in two-sided analyses was set at 95%.

The odds ratio of in-hospital mortality for each variable was estimated using a logistic regression model. Variables that were found to be significantly different ($p < 0.05$) between survivors and non-survivors on univariate analysis were entered into multivariate analysis in a stepwise manner. Statistical significance was defined as a p-value < 0.05 for all analyses.

Results

This study enrolled 164 ILD patients undergoing ECMO for ARF in 88 hospitals, of whom 122 (74.4%) died during hospitalization. The median age was 65 years (IQR, 57–71), with patients over 70 years old constituting 31% of the study population. Survivors were found to be significantly younger than non-survivors; however, no significant differences were observed in gender and body mass index (BMI) between the 2 groups (Table 1).

Table 1
Comparison of clinical characteristics between non-survivors group and survivors group.

	Non-survivors (n = 122)	**Survivors (n = 42)**	**Crude odds ratio**	**p value**
Female	39 (32.0)	12 (28.6)	1.175 (0.544–2.537)	0.682
Age, year	67 (58–73)	61 (53–68)	1.037 (1.008–1.067)	0.013
20–29	1 (0.8)	1 (2.4)	n/a	n/a
30–39	2 (1.6)	3 (7.1)		
40–49	10 (8.2)	6 (14.3)		
50–59	22 (18.0)	5 (11.9)		
60–69	43 (35.2)	20 (47.6)		
70–79	39 (32.0)	6 (14.3)		
80≤	5 (4.1)	1 (2.4)		
Age ≥ 65	71 (58.2)	14 (33.3)	2.784 (1.334–5.810)	0.006
BMI, kg/m^2	23.4 (21.1–26.5)	22.1 (20.1–24.6)	1.045 (0.956–1.141)	0.331
Ambulance transportation	75 (61.5)	26 (61.9)	0.982 (0.477–2.021)	0.961
Hospital stay, day	30 (18–48)	48 (31–89)	0.990 (0.982–0.998)	0.017
Diabetes	29 (23.7)	9 (21.4)	1.143 (0.490–2.666)	0.756
Connective tissue disease	32 (26.2)	7 (16.7)	1.778 (0.718-4.400)	0.213

Data are expressed as number of patients (%) and median (IQR). BMI: body mass index; IQR: interquartile range; n/a: not assessed.

As shown in Table 2, most of the patients received broad-spectrum antibiotics, high-dose systemic steroids defined as the equivalent of methylprednisolone ≥ 500 mg/day, and low-dose systemic steroids defined as the equivalent of methylprednisolone < 500 mg/day. Survivors were treated more frequently with macrolides and anti-influenza drugs and less frequently with high-dose cyclophosphamide and protease inhibitors. ECMO duration was significantly longer in non-survivors than in survivors. Kaplan-Meier cumulative survival curve showed that successful weaning from ECMO occurred mostly during the early days after its initiation (Fig. 2).

Table 2
Comparison of drugs and procedures between non-survivors and survivors.

	Non-survivors (n = 122)	Survivors (n = 42)	Crude odds ratio	p value
Beta-lactam antibiotics	65 (53.3)	21 (50.0)	1.140 (0.565-2.300)	0.714
Penicillin	60 (49.2)	21 (50.0)	0.968 (0.480–1.951)	0.927
Cephem	99 (81.1)	30 (71.4)	1.722 (0.767–3.865)	0.188
Carbapenem				
Macrolide	41 (33.6)	25 (59.5)	0.344 (0.167–0.708)	0.004
Fluoroquinolone	68 (55.7)	21 (50.0)	1.259 (0.624–2.542)	0.520
Tetracycline	18 (14.8)	5 (11.9)	1.281 (0.444–3.695)	0.647
Trimethoprim-sulfamethoxazole	78 (63.9)	31 (73.8)	0.629 (0.288–1.373)	0.245
Anti-MRSA drugs	83 (68.0)	24 (57.1)	1.596 (0.777–3.279)	0.203
Anti- influenza drugs	10 (8.2)	9 (21.4)	0.327 (0.123–0.873)	0.026
Anti-cytomegalovirus drugs	29 (23.8)	8 (19.0)	1.325 (0.552–3.182)	0.529
Anti-fungal drugs	64 (52.5)	13 (31.0)	2.462 (1.169–5.182)	0.018
Low-dose Steroid	116 (95.1)	41 (97.6)	0.472 (0.055–4.035)	0.493
High-dose Steroid	105 (86.1)	33 (78.6)	1.684 (0.686–4.133)	0.255
High-dose cyclophosphamide	38 (31.1)	6 (14.3)	2.714 (1.055–6.986)	0.038
Other immunosuppressant	42 (34.4)	8 (19.0)	2.231 (0.948–5.251)	0.066
Protease inhibitor	66 (54.1)	14 (33.3)	2.357 (1.132–4.910)	0.022

Data are expressed as number of patients (%).CHDF: Continuous hemodialysis filtration; ECMO: extracorporeal membrane oxygenation; MRSA: methicillin-resistant *Staphylococcus aureus*.

	Non-survivors (n = 122)	Survivors (n = 42)	Crude odds ratio	p value
Recombinant human soluble thrombomodulin	43 (35.2)	12 (28.6)	1.361 (0.633–2.926)	0.430
Sivelestat sodium	64 (52.5)	18 (42.9)	1.471 (0.726–2.983)	0.284
Duration of ECMO, day	14 (7.75–27.25)	7.5 (4-14.25)	1.043 (1.010–1.077)	0.010
CHDF	79 (64.8)	16 (38.1)	2.985 (1.446–6.165)	0.003

Data are expressed as number of patients (%).CHDF: Continuous hemodialysis filtration; ECMO: extracorporeal membrane oxygenation; MRSA: methicillin-resistant *Staphylococcus aureus*.

Multivariate analysis, which involved constructing multiple models adjusted for statistically significant variables on univariate analysis in a stepwise manner, revealed that advanced age, non-use of macrolides, and use of antifungal drugs were significantly associated with in-hospital mortality (Table 3). Patients who were treated with macrolides were administered concurrently with other antibiotics in all except 1 case. To be more precise, azithromycin was prescribed to 57/66 patients (86.4%); erythromycin, 7/66 (10.6%); and clarithromycin, 6/66 (9.1%), overlap permitted.

Table 3
Multivariate logistic regression analysis used to identify variables associated with in-hospital death.

	Adjusted odds ratio	p value
Age, years	1.048 (1.015–1.082)	0.004
Macrolides	0.264 (0.118–0.589)	0.001
High-dose cyclophosphamide	2.392 (0.881–6.493)	0.087
Antifungal drugs	3.158 (1.377–7.242)	0.007

Discussion

This study illustrated that in-hospital mortality of ILD patients receiving ECMO for ARF was approximately 75%. It also demonstrated that advanced age, non-use of macrolides, and use of antifungal drugs were significantly associated with in-hospital mortality among these patients.

A systematic review of ILD patients treated in intensive care units without ECMO showed that mortality was 65% in patients with idiopathic pulmonary fibrosis during the period 2005–2017 and 48% in mixed ILD patients between 2010 and 2017 [2]. In our study, the rate of in-hospital mortality (74.4%) in mixed ILD patients treated with ECMO turned out to be higher than previously reported mortality rates among patients receiving conventional treatments without ECMO. Possible reasons for the higher mortality in ECMO cases are that more severe patients who were refractory to conventional IMV were included, and that they might also have had complications associated with ECMO.

The decision regarding the time of ECMO weaning in successful cases or ECMO withdrawal in refractory cases needs to be discussed carefully. In this study, survivors were successfully weaned from ECMO after a median period of 8 days (IQR, 4–14) whereas ECMO was withdrawn in non-survivors at a median of 14 days (IQR, 8–27). Indeed, Kaplan-Meier survival curve indicated that successful weaning from ECMO was more frequent in the early days after its initiation. On the other hand, 67.2% of non-survivors died on the day of withdrawal, which implies that they relied entirely on ECMO as a life-sustaining procedure at the end of their lives. Our results suggest that continuation of ECMO over 14 days is less likely to produce any favorable outcome.

Here, we found that advanced age was significantly associated with high in-hospital mortality. The Respiratory EMO Survival Prediction score [11] and Predicting Death for Severe ARDS on Veno-venous ECMO (PRESERVE) score [12] have described young age as one of the favorable factors for receiving ECMO, regardless of the type of respiratory failure. Besides, the Extracorporeal Life Support Organization Guidelines for Adult Respiratory Failure published in 2017 have suggested considering a higher risk of a poor prognosis with increasing age [13]. Furthermore, the Extracorporeal Life Support Organization Coronavirus Disease 2019 Interim Guidelines have referred to age $\geq$ 65 years as a relative contraindication for ECMO [14]. Our results in ILD patients are consistent with these guidelines. ECMO therapy consumes considerable medical resources, so the cost-benefit balance needs to be considered on a case-by-case basis, especially in elderly patients.

There was no significant difference in BMI between survivors and non-survivors, which is not in agreement with the PRESERVE scoring system stating that a BMI value > 30 kg/m^2 is related to a favorable prognosis [12]. This disparity in results could be attributed to the number of obese patients in our study (n = 9), which might have been too small to be meaningful for statistical analyses. Further research is needed to determine how obesity affects the prognosis of ILD patients undergoing ECMO.

In the present study, use of macrolides was found to significantly correlate with a favorable prognosis. It is known that macrolides have immunomodulatory effects [15–17] and their combinational administration is capable of diminishing mortality in critically ill patients with community-acquired pneumonia [18]. In fact, an official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America has recommended macrolide-containing regimens for the treatment of hospitalized patients with severe pneumonia [19]. Besides, the effectiveness of azithromycin for treatment of acute exacerbation of idiopathic pulmonary fibrosis has been reported that mortality in

patients treated with azithromycin was significantly lower than in those treated with fluoroquinolones [20]. Therefore, antibiotic therapy with macrolide-containing regimens might prove effective not only in patients with severe community-acquired pneumonia but also in ILD patients receiving ECMO.

Our study also demonstrated an association between using antifungal drugs and increased in-hospital mortality. Since observational studies are unable to determine causal relationships, it remains unclear whether antifungal drug use or fungal infections could have impacted the results. Antifungal drugs are generally administered when patients are thought to develop fungal infections during immunosuppressive therapy. Thus, a diagnosis of fungal infections, rather than antifungal drug use per se, might influence patients' prognosis.

In the current study, use of anti-influenza virus drugs was significantly associated with survival to discharge in the univariate analysis but lost its statistical significance in the multivariate analysis. The efficacy of ECMO in H1N1-related ARDS has been reported [5]. In this regard, while ECMO might be beneficial for influenza-related respiratory disorder itself, its efficacy could be limited when this disease is accompanied by ILD.

The strength of this study is that a large number of patients from a nationwide database were included to be analyzed. However, some limitations derived from the retrospective nature of the study. First, the subtype of ILD was uncertain because input of them was not required in DPC database. However, antifibrotic agents which were covered by Japanese health insurance only for patients with idiopathic pulmonary fibrosis in the study period were used in only 12 cases. Presumably, the number of idiopathic pulmonary fibrosis cases would be limited. Second, no standardized ECMO initiation and management protocol exists among hospitals, giving rise to selection and intervention bias. Finally, long-term outcomes could not be clarified owing to the lack of post-discharge information.

Conclusions

In conclusion, in-hospital mortality of ILD patients receiving ECMO for ARF would be nearly 75%. The indications for ECMO in ILD patients who are not lung transplantation candidates should be carefully considered. Advanced age, non-use of macrolides, and use of anti-fungal drugs may be associated with a poor prognosis in ILD patients undergoing ECMO therapy.

Abbreviations

ARF: acute respiratory failure

BMI: body mass index

DPC: The Japanese Diagnosis Procedure Combination

ECMO: extracorporeal membrane oxygenation

ILD: interstitial lung disease

IMV: invasive mechanical ventilation

IQR: interquartile range

Declarations

Ethical approval

The study protocol was approved by the institutional ethics committee of Oita University (approval no. 1613; approval date: May 20, 2019).

Consent for participation and publication

Since all patient data were obtained in an anonymous manner, the requirement for individual informed consent was waived.

Availability of data and materials statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors have stated that there are no competing interests in connection with this article.

Funding information

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authorship statement

YU, KK, KF, KH, and JK designed this study and drafted the manuscript. YU, KK MY, and KF contributed to data collection, data analysis, and manuscript preparation.

Acknowledgement

Not applicable.

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Tables

Table 1 Comparison of clinical characteristics between non-survivors group and survivors group.

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Table 2 Comparison of drugs and procedures between non-survivors and survivors.

	Non-survivors (n=122)	Survivors (n=42)	Crude odds ratio	p value
Beta-lactam antibiotics				
Penicillin	65 (53.3)	21 (50.0)	1.140 (0.565-2.300)	0.714
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Sivelestat sodium	64 (52.5)	18 (42.9)	1.471 (0.726-2.983)	0.284
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Data are expressed as number of patients (%).CHDF: Continuous hemodialysis filtration; ECMO: extracorporeal membrane oxygenation; MRSA: methicillin-resistant *Staphylococcus aureus*.

Table 3 Multivariate logistic regression analysis used to identify variables associated with in-hospital death.

	Adjusted odds ratio	p value
Age, years	1.048 (1.015-1.082)	0.004
Macrolides	0.264 (0.118-0.589)	0.001
High-dose cyclophosphamide	2.392 (0.881-6.493)	0.087
Antifungal drugs	3.158 (1.377-7.242)	0.007

Figures

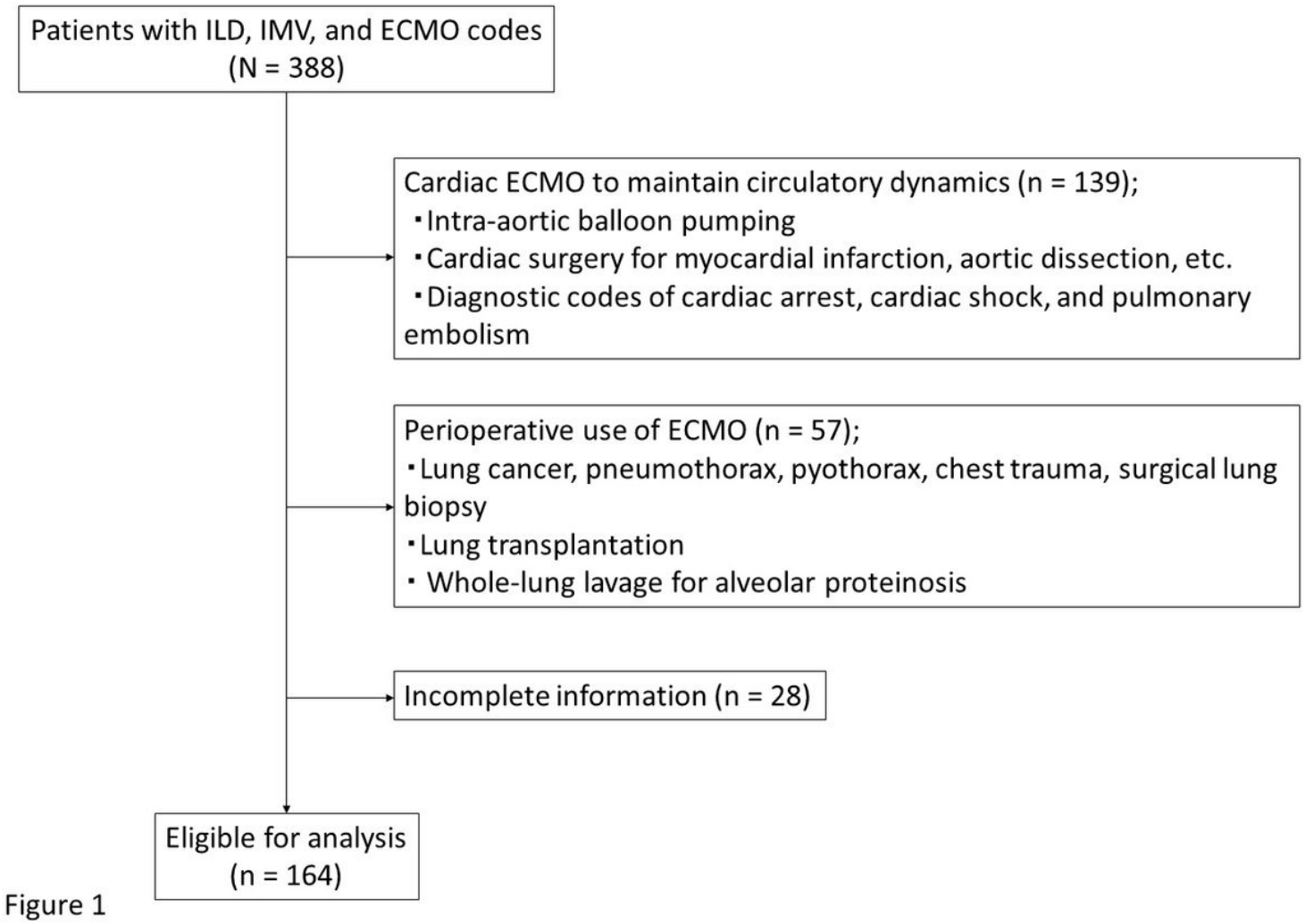

Figure 1

Figure 1

Patient selection diagram.

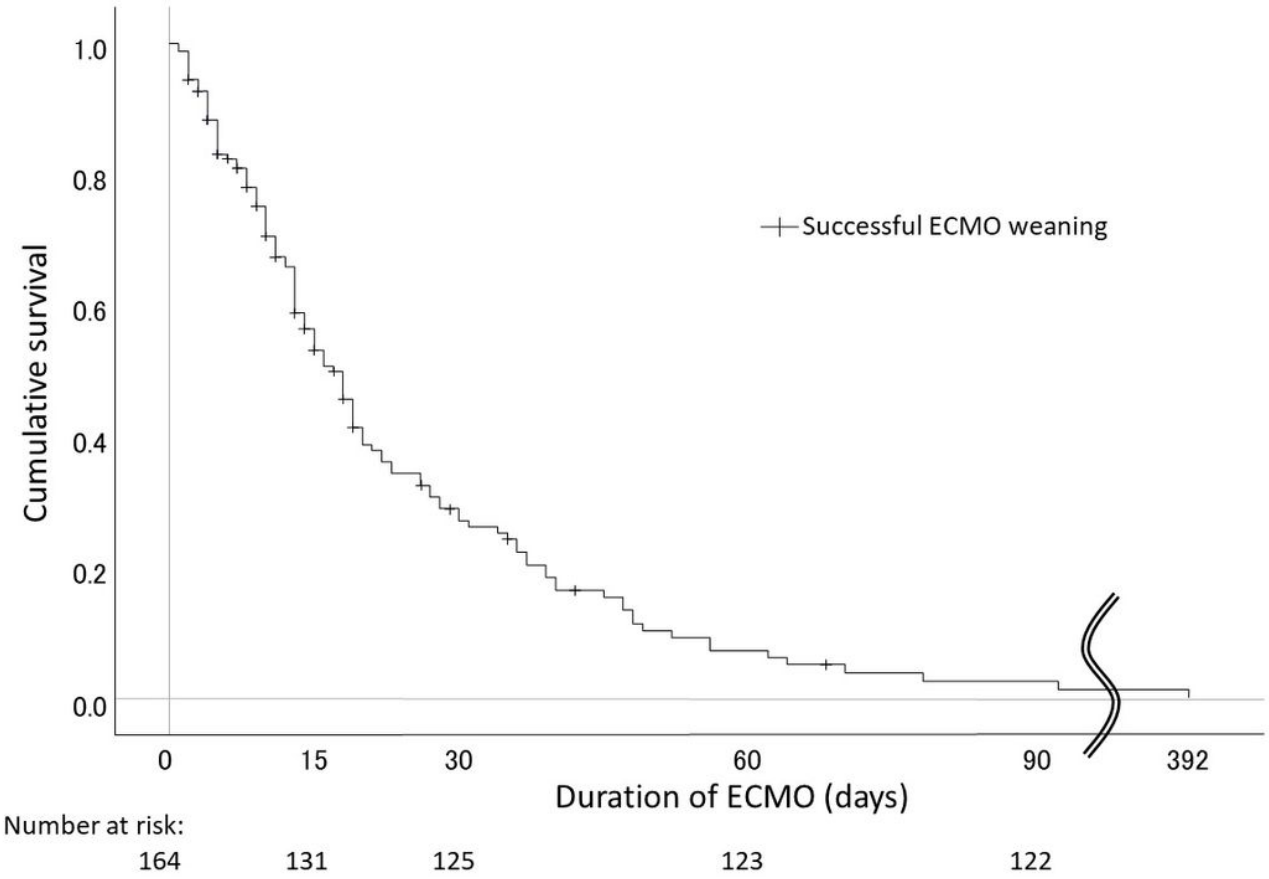

Figure 2

Figure 2

Kaplan-Meier curve plotted for cumulative survival in relation to the duration of extracorporeal membrane oxygenation for acute respiratory failure among interstitial lung disease patients.