ACUTE MEDICINE & SURGERY
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The epidemiology and volume-outcome relationship of extracorporeal membrane oxygenation for respiratory failure in Japan: A retrospective observational study using a national administrative database

Journal:	*Acute Medicine & Surgery*
Manuscript ID	AMS-2019-0137.R1
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	n/a
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Keywords:	Respiration
Optional Keywords:	Extracorporeal membrane oxygenation
Abstract:	Aim: To describe the epidemiology of patients on extracorporeal membrane oxygenation (ECMO) and investigate the possible association between outcomes for respiratory ECMO patients and hospital volume of ECMO treatment for any indications. Methods: Using data from the Diagnosis Procedure Combination database, a nationwide Japanese inpatient database, between July 1, 2010, and March 31, 2018, we identified inpatients aged ≥ 18 years who underwent ECMO. Institutional case volume was defined as the mean annual number of ECMO cases; eligible patients were categorized into institutional case volume tertile groups. The primary outcome was in-hospital mortality. For ECMO patients with respiratory failure, the association between institutional case volume group and in-hospital mortality rate was analyzed using a multilevel logistic regression model including multiple imputation. Results: ECMO was performed on 25,384 patients during the study period; of those, 1,227 cases were for respiratory failure. Respiratory cases were categorized into low- (<8 cases/year), medium- (8–16 cases/year), and high-volume groups (≥17 cases/year). The overall in-hospital mortality rate for respiratory ECMO was 62.5% in low-, 54.7% in medium-, and 50.4% in high-volume institutions. With reference to low-volume institutions, the adjusted odds ratios (95% confidence interval) of the medium- and high-volume institutions for in-hospital mortality were 0.72 (0.50–1.04; P = 0.082) and 0.65 (0.45–0.95; P = 0.024), respectively.

	Conclusions: The present study showed that accumulating the experience of using ECMO for any indications may positively affect the outcome of ECMO treatment for respiratory failure, which suggests the effectiveness of consolidating ECMO cases in high-volume centers in Japan.

Title

The epidemiology and volume-outcome relationship of extracorporeal membrane oxygenation for respiratory failure in Japan: A retrospective observational study using a national administrative database

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Abstract

Aim: To describe the epidemiology of patients on extracorporeal membrane oxygenation (ECMO) and investigate the possible association between outcomes for respiratory ECMO patients and hospital volume of ECMO treatment for any indications.

Methods: Using data from the Diagnosis Procedure Combination database, a nationwide Japanese inpatient database, between July 1, 2010, and March 31, 2018, we identified inpatients aged ≥ 18 years who underwent ECMO. Institutional case volume was defined as the mean annual number of ECMO cases; eligible patients were categorized into institutional case volume tertile groups. The primary outcome was in-hospital mortality. For ECMO patients with respiratory failure, the association between institutional case volume group and in-hospital mortality rate was analyzed using a multilevel logistic regression model including multiple imputation.

Results: ECMO was performed on 25,384 patients during the study period; of those, 1,227 cases were for respiratory failure. Respiratory cases were categorized into low- (<8 cases/year), medium- (8–16 cases/year), and high-volume groups (≥17 cases/year). The overall in-hospital mortality rate for respiratory ECMO was 62.5% in low-, 54.7% in medium-, and 50.4% in high-volume institutions. With reference to low-volume institutions, the adjusted odds ratios (95% confidence interval) of the medium- and high-volume institutions for in-hospital mortality were 0.72 (0.50–1.04; *P* = 0.082) and 0.65 (0.45–0.95; *P* = 0.024), respectively.

Conclusions: The present study showed that accumulating the experience of using ECMO for any indications

may positively affect the outcome of ECMO treatment for respiratory failure, which suggests the effectiveness of consolidating ECMO cases in high-volume centers in Japan.

Keywords

Acute respiratory failure, Extracorporeal membrane oxygenation, In-hospital mortality, Volume-outcome relationship

Manuscript

Introduction

Extracorporeal membrane oxygenation (ECMO) is used for patients with acute severe cardiac or respiratory failure who are refractory to optimal conventional therapy.[1] Recent studies reported on the increasing number and improving outcomes of ECMO cases, especially for patients on ECMO for respiratory support.[2,3] Significantly, most of the favorable outcomes of adult respiratory ECMO were reported by high-volume ECMO centers.[4-7]

Because ECMO is a complex and high resource-using procedure, consolidating ECMO treatment in high-volume, dedicated centers has been proposed to improve outcomes and optimize health-care resources.[8] It has been also suggested that any ECMO indications would contribute to the accumulation of experience in respiratory ECMO, as ECMO for respiratory failure may be one component of the full spectrum of extracorporeal support.[8]

By contrast, in Japan, insufficient centralization of respiratory ECMO treatment is clinically often said to adversely affect mortality and pursuing the centralization of respiratory ECMO cases remains an issue.[9] However, few studies other than some involving small- sized questionnaire surveys or registry data have attempted to describe institutional ECMO volume in Japan,[10,11] which implies that the efficacy of centralizing ECMO cases remains unclear.

Thus, the aim of this study was two-fold: to investigate the epidemiology of ECMO in Japan by using a national-level inpatient database and to examine the possible association between mortality in respiratory ECMO cases and the institutional case volume of ECMO for any indications.

Methods

<Data source>

For our analysis, we used the national level Diagnosis Procedure Combination (DPC) administrative claims database. The DPC system involves a case-mix classification for insurance reimbursements and is used in more than 1,700 acute-care hospitals with approximately 490,000 beds. In 2018, DPC hospitals accounted for 83% of all acute-care beds in Japan.[12] The data were collected by the DPC Study Group, funded by the Japanese Ministry of Health, Labour and Welfare, and were obtained from approximately 80% of all DPC hospitals, with approximately 8 million inpatient episodes per year. The DPC data contain not only claims data for all clinical procedures and prescribed drugs during hospitalization, but also clinical summaries of the hospitalizations, such as patient demographics, diagnoses, comorbidities, and outcomes at discharge. Diseases are classified on the basis of the *International Classification of Diseases, 10th Revision* (*ICD-10*), codes.

<Patient selection>

We identified patients aged ≥ 18 years who underwent ECMO between July 1, 2010, and March 31, 2018. ECMO procedure codes in DPC contain codes for cardiopulmonary bypass used in the operating room for cardiac surgery, so we excluded patients who underwent ECMO only on the operation day. Based on previous studies using an administrative database, ECMO indications for ECMO-treated patients were classified by the operation codes or highest resource-use diagnoses as follows: post-cardiotomy, cardiogenic shock (ICD-10 codes, I05–08, I20–28, I33–35, I40–42, I46, and I49–51), cardiopulmonary failure (I26–28), respiratory failure (J09–18 and J40–99), trauma/hypothermia/drowning (S%, T0%, T68, T751, and W65–74), sepsis (A40–41), pre- and post-heart transplant status, and pre- and post-lung transplant status.[3,13,14] The classification process was performed by using a hierarchical system of diagnostic or procedure code criteria to create mutually exclusive groups.

<Variables and outcomes>

Institutional case volume, the main independent variable of interest, was defined as the mean annual number of patients receiving any ECMO at each institution during the study period. We calculated this mean annual number of cases considering the data available periods of each of the institutions. The institutions were categorized into tertiles based on the institutional case volume, with approximately equal numbers of patients in each group. We included patient age, sex, and the institutional case volume group as baseline characteristics of the ECMO cases classified by ECMO indication. The primary outcome was all-cause in-hospital mortality. The secondary outcome was the fraction of patients who were transferred to other institutions while on ECMO.

For the patients with ECMO indications for respiratory failure, the following patient characteristics, stratified by institutional volume, were also evaluated based on several variables included in the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) Score,[15] the model for predicting survival for patients receiving ECMO for respiratory failure. These variables were age (18–49, 50–59, and ≥ 60 years), immunocompromised status, central nervous system dysfunction, acute associated nonpulmonary infection, cardiac arrest, the etiologies of acute respiratory failure, and procedures performed before ECMO including bicarbonate infusion, neuromuscular blockade agents, and the duration of mechanical ventilation use prior to initiation of ECMO (0–2, 3–6, and ≥ 7 days). The etiologies of acute respiratory failure were extracted based on the RESP score as well, such as viral pneumonia (ICD- 10 codes, J13–18), bacterial pneumonia (J09–12 and A%), asthma (J45–46), trauma and burn (S60–70 and T60–70), aspiration pneumonia (J69), other acute respiratory diagnoses (J90–94), or nonrespiratory and chronic respiratory diagnoses.[15]

<Statistical analyses>

Continuous variables were calculated as means and standard errors; categorical variables were calculated as percentages (proportions). The Kruskal-Wallis test and the Pearson χ^2 test were performed as appropriate to assess differences between groups. For the respiratory failure group, a multivariable logistic regression analysis was performed to investigate the association of in-hospital mortality with various factors, including institutional case volume and several components of the RESP score,[15] while also accounting for the correlation among the patients treated at the same institution using random effects models. As some values for the duration of mechanical ventilation use prior to initiation of ECMO were missing, we performed multiple imputation to replace these missing values with a set of substituted plausible values by creating 20 filled-in complete datasets using the chained equations technique that modifies the predictive mean matching method to impute missing data.[16] We regarded the missing pattern as missing completely at random or missing at random, and assumed that any systematic differences between the missing and observed values could be explained by differences in the observed data.[17] We performed complete case analysis as well. As a sensitivity analysis, we examined the volume-outcome relationship by redefining the institutional case volume groups as the cutoff points 6 <, 6–14, 15–30, and > 30 based on previous studies on institutional volume of ECMO.[7] All hypotheses were tested using a two-sided test with a significance level of 0.05, and all statistical analyses were performed using the R statistical version 3.5.0 software.

<Ethical considerations>

This study was approved by the ethics committee of the Kyoto University Graduate School of Medicine (approval No. R0135). In accordance with the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects as stipulated by the Japanese national government, the requirement for informed consent was waived in the present study because of the patients' anonymity.

Results

<Epidemiology of ECMO in Japan>

We identified 25,384 patients from 725 hospitals who received ECMO during the study period. Table 1 presents the size, baseline characteristics, and outcome variables of each indication group. 1277 cases of respiratory ECMO were performed at 347 hospitals during the study period. Of all the ECMO indications, the fraction of respiratory failure was 5.0%, while that of cardiogenic shock was 70.5%. With regard to institutional case volume, ECMO for respiratory failure, trauma, sepsis, and heart or lung transplant tended to be performed in high-volume institutions. The in-hospital mortality rate was lowest in the respiratory failure group other than the transplant groups. In the respiratory failure group, the fraction of patients who were transferred to other institutions after initiating ECMO was not as high as in the other groups.

<Baseline variables of ECMO for respiratory failure>

Table 2 shows the backgrounds and outcomes of the respiratory ECMO cases stratified by the institutional case volume groups. These respiratory cases were categorized into 400 low- (<8 cases/year, n = 200 institutions), 419 medium- (8–16 cases/year, n = 96 institutions), and 498 high-volume groups (≥17 cases/year, n = 51 institutions). No significant differences were found in the distribution of patient age, sex, respiratory ECMO indications, central nervous system dysfunction, acute associated nonpulmonary infection, or use neuromuscular blockade agents before ECMO among the three institutional-volume groups. The most common cause of respiratory ECMO was bacterial infection. The high-volume group tended to initiate

ECMO soon after starting mechanical ventilation. While the number of patients with cardiac arrest before ECMO was significantly high in the high-volume group, the number of those with immunocompromised status and those with bicarbonate infusion before ECMO was significantly low in the high-volume group. The low-, medium-, and high-volume groups showed mortality rates of 62.5%, 54.7%, and 50.4%, respectively. The number of patients referred to other institutions while on ECMO was quite small and nearly equal among the three groups.

<Predictors of respiratory ECMO>

Table 3 shows the results of a multivariable logistic regression model clustered by institutions with multiple imputation. After adjusting for the institutional case volume, baseline patient characteristics, respiratory ECMO etiologies, and medical procedures before ECMO, the high-volume group showed a significantly lower mortality rate than the low-volume group (odds ratio [OR], 0.65; 95% confidence interval [CI], 0.45–0.95; *P* = 0.024), whereas the mortality rate in the medium-volume group tended to be lower, but not significantly so, than that in low-volume group (OR, 0.72; 95% CI, 0.50–1.04; *P* = 0.082). The same tendency was observed in the complete case analysis and the sensitivity analysis involving redefining the cutoff points of annual institutional case volume (Table 4, 5).

Discussion

The present study characterized the current practices of ECMO cases in Japan and revealed a volume-outcome relationship for adult respiratory ECMO by using nationwide administrative data. Contrary to previous studies using Extracorporeal Life Support (ELSO) registry data or an administrative database in the US, the present study showed that the majority of the ECMO indications were for cardiac support; the proportion of ECMO indications for respiratory failure was relatively small. Thus, the selection of pumps, oxygenators, or cannulae might not be especially well-suited for respiratory support in some institutions, a fact that may affect the prognosis of respiratory ECMO.

The present study showed a mortality rate for respiratory ECMO of 55.6%, which was less than the rate from the ELSO registry data but comparable to the rate shown in the US administrative data.[2,13] During the H1N1 pandemic, the survival rate of patients on respiratory ECMO in Japan was markedly low compared to that in other countries.[9] Therefore, the Japanese Society of Respiratory Care Medicine started a training course for organized ECMO-based respiratory programs in 2012 to introduce the routine practice of respiratory ECMO and to build a functional ECMO network system in Japan.[18] Recent studies demonstrated that outcomes for ECMO use in cases involving influenza-associated acute respiratory failure in Japan markedly improved between 2009 and 2016.[19] One of the contributing factors may be an improvement of the ECMO management skills for adult respiratory failure due to such ECMO training courses.

To the best of our knowledge, this is the first study based on administrative data to suggest that accumulating experience in the use of ECMO for any indications may positively affect the outcome of ECMO for respiratory failure. Generally, a volume-outcome relationship has been found in some medical or surgical cases.[20,21] Previous studies using registry data between 1989 and 2013 showed a traditional volume-outcome relationship in ECMO for respiratory failure; however, a study using US administrative data between 2002 and 2011 did not.[7,13] Of course, ECMO is merely a procedure for supportive care, so volume alone does not guarantee best practices or good outcomes; still, high-volume centers may maintain robust expertise in the care and ventilatory management of patients with severe respiratory failure. Moreover, the criteria for determining ECMO implementation may differ depending on ECMO experience. Thus, consolidating ECMO cases by assigning them to expert referral centers may contribute to the improvement of outcomes.

Despite evidence suggesting the efficacy of consolidation, this study found that only a few patients under ECMO were transferred to higher-volume facilities, which may indicate that consolidating ECMO cases has been promoted only on a very limited basis in Japan. Of course, transferring patients under severe conditions always involves risks. However, several studies have indicated that the transfer of patients on ECMO may not significantly increase mortality beyond the already-high risk of ECMO itself when accompanied by high-level technical expertise or equipment.[22,23] Recently, the establishment of a mobile ECMO system has been underway in Japan, a development that can be expected to advance the centralization of ECMO cases.[24]

This study has several limitations. First, the DPC database does not include complete data on physiology, illness severity, or the details of medical procedures, such as ventilator settings or cannulation strategies. This lack of clinical information is a fundamental limitation of administrative data. Therefore, the severity adjustment in this study may be insufficient. However, we employed the high impact factors included in the RESP score—the prognostic factors of hospital discharge for respiratory ECMO—as independent variables.[15] Moreover, we determined the robustness of our model by imputing variables with missing values using the multiple imputation method or through sensitivity analysis. Second, our study samples were restricted to hospitals in the DPC Study Group, which may lead to a certain degree of selection bias. Nonetheless, this database included approximately 8 million inpatient records from > 80% of all acute-care beds in Japan.[12] Thus, the large sample size and diverse characteristics of the hospitals may reduce the potential selection bias. Given these factors, our sample may be reasonably considered representative of ECMO cases in Japan. Finally, the present study sampled only ECMO cases, which means that the results do not represent all patients with severe respiratory failure. Since there may be no explicit standard for the introduction of ECMO, the criteria for determining ECMO implementation may differ between institutions. Further studies investigating severe respiratory failure both with and without ECMO are desirable for supporting our results.

Conclusions

The present study showed that many of the institutions in Japan performed ECMO mainly for cardiac support. For cases involving ECMO for respiratory failure, a higher institutional case volume of ECMO treatment for any indications was significantly associated with lower in-hospital mortality. Centralizing ECMO cases may improve the outcomes of patients needing respiratory ECMO.

Acknowledgement

This study was supported by Health Sciences Research Grants (H30-seisaku-shitei-004; http://www.mhlw.go.jp) from the Ministry of Health, Labour and Welfare of Japan, and Grant-in-Aid for Scientific Research (Grant No. [A] 16H02634 and [A] 19H01075; https://www.jsps.go.jp/j-grantsinaid/) from Japan Society for the Promotion of Science. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure

Approval of the research protocol: This study was approved by the ethics committee of the Kyoto University Graduate School of Medicine (approval No. R0135).

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None declared.

References

1. Extracorporeal Life Support Organization. General Guidelines for all ECLS cases. [cited 2 Octover 2019.] https://www.elso.org/Portals/0/ELSO%20Guidelines%20General%20All%20ECLS%20Version%201_4.pdf

248 2. Thiagarajan RR, Barbaro RP, Rycus PT et al. Extracorporeal Life Support Organization Registry
249 International Report 2016. ASAIO J. 2017;63:60–7.
250 3. Sanaiha Y, Bailey K, Downey P et al. Trends in mortality and resource utilization for extracorporeal
251 membrane oxygenation in the United States: 2008–2014. Surgery. 2019;165:381–388.
252 4. The Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza
253 Investigators, Davies A, Jones D et al. Extracorporeal Membrane Oxygenation for 2009 Influenza
254 A(H1N1) Acute Respiratory Distress Syndrome. JAMA. 2009;302(17):1888–95.
255 5. Noah MA, Peek GJ, Finney SJ et al. Referral to an extracorporeal membrane oxygenation center and
256 mortality among patients with severe 2009 influenza A(H1N1). JAMA. 2011;306(15):1659–68.
257 6. Roch A, Lepaul-Ercole R, Grisoli D et al. Extracorporeal membrane oxygenation for severe influenza
258 A (H1N1) acute respiratory distress syndrome: A prospective observational comparative study.
259 Intensive Care Med. 2010;36(11):1899–905.
260 7. Barbaro RP, Odetola FO, Kidwell KM et al. Association of hospital-level volume of extracorporeal
261 membrane oxygenation cases and mortality: Analysis of the extracorporeal life support organization
262 registry. Am J Respir Crit Care Med. 2015;191(8):894–901.
263 8. Combes A, Brodie D, Bartlett R et al. International ECMO Network (ECMONet). Position paper for
264 the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in
265 adult patients. Am J Respir Crit Care Med. 2014;190(5):488–96.
266 9. Takeda S, Kotani T, Nakagawa S et al. Extracorporeal membrane oxygenation for 2009 influenza

A(H1N1) severe respiratory failure in Japan. Journal of Anesthesia. 2012;26(5):650–7.

10. Japanese society of Percutaneous Cardio-Pulmonary Support/Extracorporeal Membrane Oxygenation. Questionnaire result. (in Japanese.) [cited 2 Octover 2019.] http://www2.convention.co.jp/pcps/dl/enquete.pdf

11. Nonprofit Organization Japanese Society of Education for Physicians and Trainees in Intensive Care. Questionnaire result. (in Japanese.) [cited 2 Octover 2019.] http://www.jseptic.com/rinsho/questionnaire.html

12. Ministry of Health, Labour and Welfare. Overviews of revised medical fee in 2018. (in Japanese.) [cited 2 Octover 2019.] https://www.mhlw.go.jp/file/06-Seisakujouhou-12400000-Hokenkyoku/0000197983.pdf

13. McCarthy FH, McDermott KM, Spragan D et al. Unconventional Volume-Outcome Associations in Adult Extracorporeal Membrane Oxygenation in the United States. Ann Thorac Surg. 2016;102(2):489–95.

14. Bailey KL, Downey P, Sanaiha Y et al. National trends in volume-outcome relationships for extracorporeal membrane oxygenation. J of surg res. 2018;231:421–7.

15. Schmidt M, Bailey M, Sheldrake J et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure: The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. Am J Respir Crit Care Med. 2014;189(11):1374–82.

16. Rubin DB, Schenker N. Multiple Imputation in Health-Care Databases : an Overview and Some

Applications. Stat Med. 1991;10(4):585–98.

17. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.

18. Japanese Society of Respiratory Care Medicine. Overviews of simulation-based training of ECMO. (in Japanese.) [cited 2 Octover 2019.] http://square.umin.ac.jp/jrcm/contents/ecmo/index.html

19. Ohshimo S, Shime N, Nakagawa S, Nishida O, Takeda S. Committee of the Japan ECMO project. Comparison of extracorporeal membrane oxygenation outcome for influenza-associated acute respiratory failure in Japan between 2009 and 2016. J Intensive Care. 2018;11(6):38.

20. Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, Rubenfeld GD. Hospital volume and the outcomes of mechanical ventilation. N Engl J Med. 2006;355(1):41–50.

21. Nallamothu BK, Gurm HS, Ting HH et al. Operator Experience and Carotid Stenting outcomes in Medicare beneficiaries. JAMA. 2011;306(12):1338–43.

22. Bryner B, Cooley E, Copenhaver W et al. Two decades' experience with interfacility transport on extracorporeal membrane oxygenation. Ann Thorac Surg. 2014;98:1363–70.

23. Biscotti M, Agerstrand C, Abrams D et al. One hundred transports on extracorporeal support to an extracorporeal membrane oxygenation center. Ann Thorac Surg. 2015;100:34–9.

24. Hagiwara Y, Shimizu K, Suzuki M et al. Simulation training aimed at the establishment of a mobile ECMO system. (in Japanese.) Journal of Japanese Association for Acute Medicine. 2017;28:314–20.

Table 1. Patient demographics and outcomes of ECMO cases in Japan classified by ECMO indications

	Respiratory failure	Cardiogenic shock	Post-cardiotomy	Sepsis	Cardiopulmonary failure	Trauma/hypothermia /drowning	Lung transplant	Heart transplant	P value
Number of patients	1277	17887	3184	1330	1167	478	49	12	
Number of institutions	347	709	448	350	427	208	9	4	
Male (%)	938 (73.5)	13680 (76.5)	1971 (61.9)	984 (74.0)	448 (38.4)	303 (63.4)	25 (51.0)	9 (75.0)	<0.001
Age (mean (SD))	61.35 (15.2)	63.2 (14.8)	66.77 (13.9)	62.37 (14.8)	59.85 (16.1)	64.11 (20.4)	42.76 (12.0)	39.42 (8.1)	<0.001
Institutional case volume (cases/year) (%)									<0.001
Low (8<)	400 (31.3)	6550 (36.6)	1242 (39.0)	427 (32.1)	521 (44.6)	140 (29.3)	15 (30.6)	0 0.0	
Medium (8-16)	419 (32.8)	5711 (31.9)	1021 (32.1)	418 (31.4)	365 (31.3)	147 (30.8)	3 (6.1)	0 0.0	
High (≥17)	458 (35.9)	5626 (31.5)	921 (28.9)	485 (36.5)	281 (24.1)	191 (40.0)	31 (63.3)	12 (100.0)	
Transfer while on ECMO (%)	7 (0.5)	180 (1.0)	2 (0.1)	2 (0.2)	18 (1.5)	4 (0.8)	0 0.0	0 0.0	<0.001
Death (%)	710 (55.6)	12558 (70.2)	2065 (64.9)	1035 (77.8)	721 (61.8)	294 (61.5)	15 (30.6)	3 (25.0)	<0.001

Comparison between the groups was evaluated with the Kruskal-Wallis test for numeric variables and Pearson χ^2 test for categorical variables.

ECMO, extracorporeal membrane oxygenation.

Table 2. Baseline characteristics and outcomes of ECMO for respiratory failure categorized by annual institutional volume

Annual institutional case volume groups (cases/year)		Low-Volume (<8)		Medium-Volume (8–16)		High-Volume (≥17)		P value
Number of patients		400		419		458		
Number of institutions		200		96		51		
Age group, years (%)								0.877
	18–49	86	(21.5)	96	(22.9)	97	(21.2)	
	50–59	63	(15.8)	67	(16.0)	82	(17.9)	
	≥60	251	(62.7)	256	(61.1)	279	(60.9)	
Male (%)		285	(71.3)	320	(76.4)	333	(72.7)	0.228
Immunocompromised status (%)		75	(18.8)	66	(15.8)	55	(12.0)	0.023
Duration of mechanical ventilation use before ECMO, days (%)								0.004
	≤2	213	(53.2)	268	(64.0)	308	(67.2)	
	3–6	46	(11.5)	39	(9.3)	41	(9.0)	
	≥7	65	(16.2)	51	(12.2)	52	(11.4)	
	Null	76	(19.0)	61	(14.6)	57	(12.4)	
Acute respiratory diagnosis group (%)								0.58
	Viral pneumonia	24	(6.0)	40	(9.5)	44	(9.6)	
	Bacterial pneumonia	170	(42.5)	181	(43.2)	200	(43.7)	
	Asthma	19	(4.8)	14	(3.3)	15	(3.3)	
	Trauma and burn	5	(1.2)	4	(1.0)	5	(1.1)	
	Aspiration pneumonia	21	(5.2)	17	(4.1)	27	(5.9)	
	Other acute respiratory diagnoses	69	(17.2)	57	(13.6)	65	(14.2)	
	Nonrespiratory and chronic respiratory diagnoses	92	(23.0)	106	(25.3)	102	(22.3)	
Central nervous system dysfunction before ECMO (%)		20	(5.0)	26	(6.2)	21	(4.6)	0.542
Acute associated nonpulmonary infection (%)		113	(28.2)	130	(31.0)	153	(33.4)	0.265
Neuromuscular blockade agents before ECMO (%)		229	(57.2)	259	(61.8)	279	(60.9)	0.369
Bicarbonate infusion before ECMO (%)		125	(31.2)	146	(34.8)	123	(26.9)	0.037
Cardiac arrest before ECMO (%)		11	(2.8)	11	(2.6)	29	(6.3)	0.006
Transferred to other institutions while on ECMO (%)		2	(0.5)	3	(0.7)	2	(0.4)	0.845
Death (%)		250	(62.5)	229	(54.7)	231	(50.4)	0.002

Comparison between the three groups was evaluated with the Pearson χ^2 test for categorical variables.

ECMO, extracorporeal membrane oxygenation.

Table 3. Multivariable logistic regression with multiple imputation for analysis of annual institutional volume and other variables clustered within institutions

		OR	(95% CI)	P value
Institutional case volume groups (cases/year)				
	Low (<8)		Reference	
	Medium (8–16)	0.72	(0.50–1.04)	0.082
	High (≥17)	0.65	(0.45–0.95)	0.024
Age group, years				
	18–49		Reference	
	50–59	1.59	(1.06–2.41)	0.027
	≥60	2.85	(2.05–3.96)	<0.001
Immunocompromised status		1.30	(0.91–1.88)	0.151
Duration of mechanical ventilation use before ECMO, days				
	≤2		Reference	
	3–6	1.75	(1.12–2.75)	0.016
	≥7	1.50	(0.97–2.31)	0.077
Acute respiratory diagnosis group				
	Viral pneumonia		Reference	
	Bacterial pneumonia	1.10	(0.68–1.77)	0.694
	Asthma	0.91	(0.41–2.01)	0.817
	Trauma and burn	0.93	(0.25–3.42)	0.910
	Aspiration pneumonitis	1.23	(0.60–2.54)	0.570
	Other acute respiratory diagnosis	1.16	(0.66–2.03)	0.607
	Nonrespiratory and chronic respiratory diagnosis	0.76	(0.44–1.29)	0.308
Central nervous system dysfunction before ECMO		1.90	(1.06–3.42)	0.032
Acute associated nonpulmonary infection		1.16	(0.84–1.60)	0.377
Neuromuscular blockade agents before ECMO		0.53	(0.41–0.70)	<0.001
Bicarbonate infusion before ECMO		2.70	(2.01–3.62)	<0.001
Cardiac arrest before ECMO		0.94	(0.49–1.80)	0.846

OR, odds ratio; CI, confidence interval; ECMO, extracorporeal membrane oxygenation.

Table 4. Adjusted odds ratios of annual institutional volume and other variables clustered within institutions in complete case analysis

	OR	(95% CI)	P value
Institutional case volume groups (cases/year)			
Low (<8)		Reference	
Medium (8–16)	0.77	(0.52–1.15)	0.201
High (≥17)	0.58	(0.39–0.87)	0.008

OR, odds ratio; CI, confidence interval.

Results of multivariable logistic regression analysis with adjustment for the same factors as those listed in Table 3.

Table 5. Adjusted odds ratios of annual institutional volume (cutoff points: 6 <, 6–14, 15–30, and > 30) and other variables clustered within institutions with multiple imputation

	OR	(95% CI)	P value
Annual institutional case volume, cases/year			
<6		Reference	
6–14	0.87	(0.59–1.28)	0.478
15–30	0.6	(0.40–0.91)	0.016
>30	0.78	(0.41–1.46)	0.436

OR, odds ratio; CI, confidence interval.

Results of multivariable logistic regression analysis including multiple imputation with adjustment for the same factors as those listed in Table 3.