Original Article

Respiratory extracorporeal membrane oxygenation for severe sepsis and septic shock in adults: a propensity score analysis in a multicenter retrospective observational study

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Aim: This multicenter retrospective observational study aimed to evaluate the efficacy of extracorporeal membrane oxygenation (ECMO) support for septic patients with severe respiratory failure using propensity score analyses.

Methods: The data of severe sepsis patients from 42 intensive care units between January 2011 and December 2013 were retrospectively collected. Propensity score matching analyses were undertaken for severe respiratory failure patients with/without veno-venous ECMO support. The main outcome was in-hospital all-cause mortality.

Results: Of 3195 patients with severe sepsis, 570 had severe respiratory failure. Forty patients in the ECMO group were matched with 150 patients in the control group. A survival time analysis revealed no difference in the in-hospital survival (hazard ratio, 0.854; 95% confidence interval, 0.531–1.373; $P = 0.515$). Two-hundred and eighty-five patients had severe respiratory failure induced by lung infection. Twenty-five ECMO group patients were matched with 89 patients in the control group. In the ECMO group, the survival time was longer than in the control group (hazard ratio, 0.498; 95% confidence interval, 0.279–0.889; $P = 0.018$). The number of renal replacement therapy- and vasopressor-free days improved. The ECMO group received more red blood cells transfused than the control group, but there was no significant difference in the rate of severe bleeding complications between the groups.

Conclusions: There was no difference in the in-hospital survival between the ECMO group and control group among overall septic patients with severe respiratory failure. However, in sepsis patients with severe respiratory failure induced by lung infection, ECMO support may improve their survival time.

Key words: extracorporeal membrane oxygenation, infection, mortality, respiratory failure, sepsis

INTRODUCTION

AMONG PATIENTS WITH sepsis, the lung is the most common infection site[1–3] and the presence of respiratory failure in these patients was found to be an independent risk factor for hospital mortality.[1,2] Therefore, the treatment of severe respiratory failure constitutes a significant portion of the sepsis treatment regimen. However, the mortality rate in such patients with respiratory failure remains relatively high (40%).[3]

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Recently, extracorporeal membrane oxygenation (ECMO) support has been used as a rescue therapy for patients with severe respiratory failure.[4] The conventional ventilation versus ECMO for severe adult respiratory failure (CESAR) trial first reported a significant improvement in 6 months disability-free survival in the ECMO group, when compared to conventional ventilation patients.[5] Since then, several studies have shown the effectiveness of ECMO for influenza A (H1N1)-related severe acute respiratory failure in 2009–2010.[6,7] Following the pandemic of influenza A (H1N1), however, few reports have explored the benefits of ECMO.[8] Furthermore, in patients with severe sepsis, ECMO support has been historically regarded as a contraindication because of the high complication rate.[9] Therefore, whether or not ECMO support is effective in patients with severe sepsis except for influenza A (H1N1) remains unclear.

The aim of this study was to analyze the efficacy of ECMO support in patients with severe sepsis using a propensity score analysis.

METHODS

Study design and setting

THIS RETROSPECTIVE OBSERVATIONAL study (Japan Septic Disseminated Intravascular Coagulation [JSEPTIC DIC] study) reviewed information obtained from patients who were admitted to 42 intensive care units (ICUs) at 40 institutions throughout Japan to undergo treatment of severe sepsis or septic shock between January 2011 and December 2013.[10] The JSEPTIC DIC study was approved by the institutional review board at each hospital, and the requirement for informed consent was waived because of the retrospective design. The present study analyzed the unlinkable anonymized database of the JSEPTIC DIC study, which was registered in the University Hospital Medical Information Network Individual Case Data Repository (UM IN000012543, http://www.umin.ac.jp/icdr/index-j.html).

Patient selection and data collection

The JSEPTIC DIC study included cases of severe sepsis and septic shock,[10,11] as defined at the International Sepsis Definitions Conference.[12] Patients younger than 16 years or who had developed severe sepsis or septic shock after ICU admission were excluded. The following data were collected: age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score,[13] Sequential Organ Failure Assessment (SOFA) score[14] (days 1, 3, and 7), systemic inflammatory response syndrome score[15] (days 1, 3, and 7), primary infection site, blood culture results, microorganisms responsible for the sepsis, daily results of laboratory tests during the first week after ICU admission, lactate levels (days 1, 3, and 7), transfusion amounts, bleeding complications during the first week after ICU admission, and in-hospital all-cause mortality.

The present study selected patients with a SOFA score for the respiratory system of 4 points, which indicates a ratio of arterial partial pressure of oxygen to the fraction of inspired oxygen less than 100 mmHg, during the first week after ICU admission from the dataset of the JSEPTIC DIC study, who were defined as patients with severe respiratory failure. The timing of ECMO initiation was within 7 days from the ICU admission. In addition, in this study, patients who received veno-arterial (V-A) ECMO were excluded, because V-A ECMO was mainly used for cardiovascular failure rather than respiratory failure. Patients with severe respiratory failure were divided into the following two groups: the ECMO group (received veno-venous [V-V] ECMO support) and the control group (did not receive V-V ECMO support). Next, we undertook a subgroup analysis for patients with severe respiratory failure induced by lung infection. Similarly, patients with severe respiratory failure induced by lung infection were also divided into an ECMO group and control group.

Outcome measure

The primary outcome of this study was in-hospital all-cause mortality. The secondary outcomes were event-free days (ICU-, ventilator-, renal replacement therapy (RRT)-, and vasopressor-free days) and the frequency of bleeding complications. The number of event-free days within a 28-day period was calculated by subtracting the duration from 28 days. If a patient was discharged before 28 days after ICU admission, then the number of event-free days was calculated by subtracting the duration from 28 days. Patients who died were assigned the worst possible outcome of zero event-free days.

Statistical analysis

The data are expressed as the number (%), or median (interquartile range), as appropriate. A propensity analysis was carried out to adjust for potential confounders. We undertook one-to-four nearest neighbor matching between the ECMO group and control group based on the estimated propensity scores for each patient. To estimate the propensity score, we used a logistic regression model including the following variables: age, APACHE II score, SOFA score (on day 1), and lung infection (primary infection site). A caliper width of 0.15 of the standard deviation of the logit of the propensity score was used. The standardized difference was used to evaluate the covariate balance, and an absolute standardized difference of >10% represents a meaningful imbalance.[16] For propensity score-matched patients, we carried out a logistic regression analysis fitted with generalized estimating equations to examine the association between ECMO support and in-hospital all-cause mortality, accounting for the matched nature of the matched pairs.[17] A Cox regression analysis was undertaken to assess the differences in the in-hospital survival rates between the propensity score-matched ECMO and control groups. Intergroup comparisons were made using the Wilcoxon signed-rank test or McNemar's test in the propensity score-matched groups.

The R version 3.1.3 software program with the MatchIt package (R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical

Computing, Vienna, Austria, http://www.R-project.org/) was used for the propensity score estimation and matching, and the SAS(R) version 9.4 software program (SAS Institute, Cary, NC, USA) was used for other analyses. The reported *P*-values are two-sided, and significance was set at $P < 0.05$.

RESULTS

THE JSEPTIC DIC study included 3195 patients with severe sepsis or septic shock. In the present study, 2600 patients without severe respiratory failure and 25 patients who received V-A ECMO were excluded. In addition, there were no patients in whom treatment was converted from V-A ECMO into V-V ECMO in this study. The 570 patients (202 with severe sepsis and 368 with septic shock) diagnosed with severe respiratory failure were enrolled in this study (Fig. 1). Of these patients with severe respiratory failure, 40 received ECMO support. Of the 285 patients diagnosed with severe respiratory failure induced by lung infection, 25 received ECMO support.

Among the total patients with severe respiratory failure, 150 in the control group were matched with 40 in the ECMO group by propensity score matching (Fig. 1). Table 1 shows the characteristics of the patients with severe respiratory failure in the unmatched and propensity score-matched groups. After the propensity score matching, the total SOFA score on day 1 in the ECMO group was higher than that in the control group. Table 2 shows the mortality rate in the propensity score-matched group. No significant differences were noted in the 28-day and in-hospital mortality rates. A survival time analysis revealed no marked difference in the in-hospital survival between the propensity score-matched groups (hazard ratio, 0.854; 95% confidence interval, 0.531–1.373; $P = 0.515$).

Among the patients with severe respiratory failure induced by lung infection, 89 in the control group were matched with 25 in the ECMO group (Fig. 1). Table 3

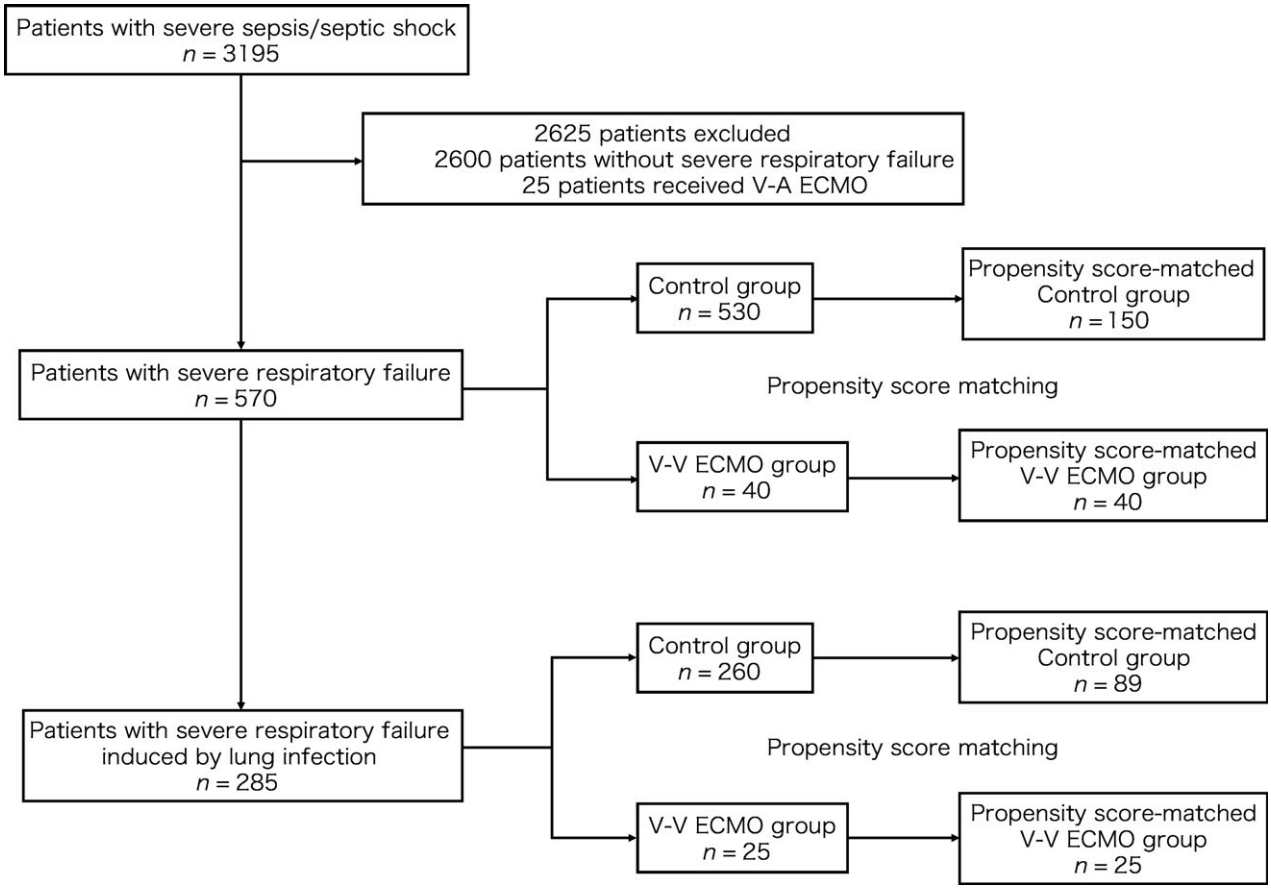

Fig. 1. Patient selection process for inclusion in this study of respiratory extracorporeal membrane oxygenation (ECMO) for severe sepsis and septic shock in adults. V-A, veno-arterial; V-V, veno-venous.

Table 1. Characteristics of patients with severe respiratory failure in the unmatched and propensity-matched groups

	Unmatched group		Unmatched standardized difference (%)	Matched group		Matched standardized difference (%)
	Control n = 530	ECMO n = 40		Control n = 150	ECMO n = 40	
Age, years	70 ± 14	66 ± 12	−31.53	66 ± 15	66 ± 12	−3.76
Men	356 (67.2)	31 (77.5)	−23.25	101 (67.3)	31 (77.5)	−22.90
Severity						
APACHE II score	27 (21–33)	28 (21–33)	−8.20	25 (20–31)	28 (21–33)	7.53
SOFA score total	12 (9–15)	13 (10–15)	21.21	12 (9–15)	13 (10–15)	14.53
SIRS score	3 (3–4)	3 (3–4)	12.09	3 (3–4)	3 (2–4)	23.00
Severe sepsis	194 (36.6)	8 (20.0)	37.50	49 (32.7)	8 (20.0)	29.06
Septic shock	336 (63.4)	32 (80.0)		101 (67.3)	32 (80.0)	
Mechanical ventilation used on day 1	478 (90.2)	39 (97.5)	30.78	134 (89.3)	39 (97.5)	33.39
Lactate, mmol/L	3.8 (2.0–7.0)	3.4 (1.9–9.0)	5.28	3.8 (2.0–6.8)	3.4 (1.9–9.0)	7.43
Primary infection site						
Lung	260 (49.1)	25 (62.5)	27.32	94 (62.7)	25 (62.5)	−0.34
Non-lung	270 (50.9)	15 (37.5)		56 (37.3)	15 (37.5)	
Abdomen	124 (23.4)	8 (20.0)		26 (17.3)	8 (20.0)	
Urinary tract	44 (8.3)	0 (0.0)		8 (5.3)	0 (0.0)	
Bone or soft tissue	38 (7.2)	3 (7.5)		7 (4.7)	3 (7.5)	
Cardiovascular	9 (1.7)	0 (0.0)		1 (0.7)	0 (0.0)	
Central nervous system	6 (1.1)	0 (0.0)		2 (1.3)	0 (0.0)	
Catheter-related	9 (1.7)	0 (0.0)		2 (1.3)	0 (0.0)	
Other	6 (1.1)	1 (2.5)		1 (0.7)	1 (2.5)	
Focus unknown	34 (6.4)	3 (7.5)		9 (6.0)	3 (7.5)	
Blood culture						
Positive	219 (41.3)	19 (47.5)	12.46	69 (46.0)	19 (47.5)	3.01
Negative	280 (52.8)	20 (50.0)	−5.66	73 (48.7)	20 (50.0)	2.67
Not taken	31 (5.8)	1 (2.5)	−16.80	8 (5.3)	1 (2.5)	−14.64
Microorganisms causing sepsis						
Gram-negative rod	187 (35.3)	8 (20.0)	−34.68	50 (33.3)	8 (20.0)	−30.50
Gram-positive coccus	125 (23.6)	9 (22.5)	−2.58	40 (26.7)	9 (22.5)	−9.69
Fungus	12 (2.3)	2 (5.0)	14.66	3 (2.0)	2 (5.0)	16.38
Virus	4 (0.8)	1 (2.5)	13.83	1 (0.7)	1 (2.5)	14.73
Mixed infection	79 (14.9)	9 (22.5)	19.57	26 (17.3)	9 (22.5)	12.96
Other	9 (1.7)	4 (10.0)	35.94	2 (1.3)	4 (10.0)	38.16
Unknown	114 (21.5)	7 (17.5)	−10.13	28 (18.7)	7 (17.5)	−3.03

Data are expressed as a number (%), mean ± standard deviation, or median (interquartile range).
APACHE, Acute Physiology and Chronic Health Evaluation; ECMO, extracorporeal membrane oxygenation; SIRS, Systemic Inflammatory Response Syndrome; SOFA, Sequential Organ Failure Assessment.

Table 2. Event-free days and mortality in propensity score-matched groups of patients with severe respiratory failure

	Control	ECMO	*P*-value
Patients with severe respiratory failure	*n* = 150	*n* = 40	
Event-free days (out of 28 days)			
ICU-free days	0 (0–16)	0 (0–11)	0.042
Ventilator-free days	4 (0–19)	0 (0–13)	0.010
RRT-free days	16 (2–28)	20 (0–23)	0.234
Vasopressor-free days	16 (0–25)	13 (0–22)	0.417
Mortality			
28-day mortality	66 (44%)	17 (42.5%)	0.739
In-hospital mortality	82 (54.7%)	21 (52.5%)	0.807
Patients with severe respiratory failure induced by lung infection	*n* = 89	*n* = 25	
Event-free days (out of 28 days)			
ICU-free days	0 (0–11)	0 (0–11)	0.504
Ventilator-free days	0 (0–14)	0 (0–14)	0.496
RRT-free days	9 (1–28)	22 (1–23)	0.012
Vasopressor-free days	11 (0–24)	19 (11–22)	0.002
Mortality			
28-day mortality	42 (47.2%)	8 (32%)	0.168
In-hospital mortality	54 (60.7%)	10 (40%)	0.070

Data are presented as the median (interquartile range).
ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; RRT, renal replacement therapy.

shows the characteristics of patients with severe respiratory failure induced by lung infection in the unmatched and propensity score-matched groups. A survival time analysis revealed a statistically significant difference in the in-hospital survival between the propensity score-matched groups (hazard ratio, 0.498; 95% confidence interval, 0.279–0.889; $P = 0.018$) (Fig. 2). The number of event-free days in the matched groups is presented in Table 2. No significant differences were noted in the number of ICU- and ventilator-free days between the groups among patients with severe respiratory failure induced by lung infection. However, the numbers of RRT- and vasopressor-free days were significantly higher in the ECMO group than in the control group.

The frequency of bleeding complications is shown in Table 4. Although the rates of bleeding requiring transfusion in the ECMO group were non-significantly higher than in the control group, there was no marked difference in the rate of severe bleeding complications between the two groups. The amounts of red cells transfused in the ECMO group were significantly higher than in the control group (Table 5).

DISCUSSION

THE PRESENT MULTICENTER retrospective study using propensity score matching showed that there was no marked difference in the in-hospital all-cause mortality between the ECMO group and control group among overall septic patients with severe respiratory failure. However, among the septic patients with severe respiratory failure induced by lung infection, the survival time in the ECMO group was significantly longer than in the control group.

Previous studies have shown that the mortality rate among patients with non-pulmonary sepsis-induced acute respiratory distress syndrome (ARDS) was higher than in patients with pulmonary sepsis-induced ARDS.[18,19] Nesseler *et al.*[19] questioned the efficacy of ECMO support in patients with intra-abdominal sepsis-induced ARDS, because of its high mortality rate. In the present study, we observed obvious survival benefits of ECMO support in patients with respiratory failure induced by lung infection. However, the benefits of ECMO support were obscure in patients with respiratory failure induced by non-pulmonary sepsis. These results are similar to the report of Nesseler *et al.*

In the present study, the numbers of RRT- and vasopressor-free days were significantly higher in the ECMO group than in the control group. Skinner *et al.*[20] speculated that V-V ECMO for pediatric septic patients provided better coronary oxygenation than V-A ECMO, thus leading to an improved cardiac function and better renal and tissue perfusion. The study of Skinner *et al.* is in agreement with the

results of our study. However, in adult septic patients, our search of published works revealed no studies in which V-V ECMO improved the cardiac function.

Recently, several predictive mortality risk scores to help clinicians target the patients most likely to benefit from ECMO have been proposed.[18,21,22] Among these, age[9,18,21–24] and SOFA score[21–24] were found to be particularly closely associated with hospital mortality and were independent prognostic factors in ARDS patients receiving ECMO support. Roch *et al.*[22] suggested a predictive mortality score using age, SOFA score, and the cause of ARDS. In the present study, a majority of patients who received ECMO (85%, 34/40 patients) were predicted to have a very low 28-day survival rate (under 20%) using Roch's score.[22] However, we observed a high 28-day survival rate (more than 60%) in the severe patients who received ECMO in the present study. We cannot explain these results, but a recent study reported that the survival of patients ≥65 years of age was good at the ECMO Center Karolinska.[25] These findings suggest that the survival rate of ECMO may be associated with not only these prognosis factors but also with management skill by an ECMO specialist.

The present study showed that there was no significant difference in the number of severe bleeding complications between the ECMO group and the control group; the rate of minor bleeding complications tended to be higher in the ECMO group than in the control group. However, the patients in the ECMO group received significantly more transfused red blood cells than the patients in the control group. During sepsis, the oxygen consumption increases, and cytopathic hypoxia induces multiple organ failure.[26] Veno-venous ECMO support increases oxygen delivery and meets the oxygen requirements to hypoxic tissue. The hemoglobin level is an important factor of oxygen delivery together with the arterial oxygen saturation and cardiac output during V-V ECMO. Generally, during ECMO support, maintaining an adequate hemoglobin level (12–14 g/dL) with red blood cell transfusion is recommended.[27] As a result, the patients in the ECMO group may require more transfused blood than those in the control group.

Limitations

Several limitations associated with the present study warrant mention. First, this retrospective multicenter study was not specially designed to evaluate the effects of ECMO. The collected data could not include important information about the induction of V-V ECMO, the mechanical

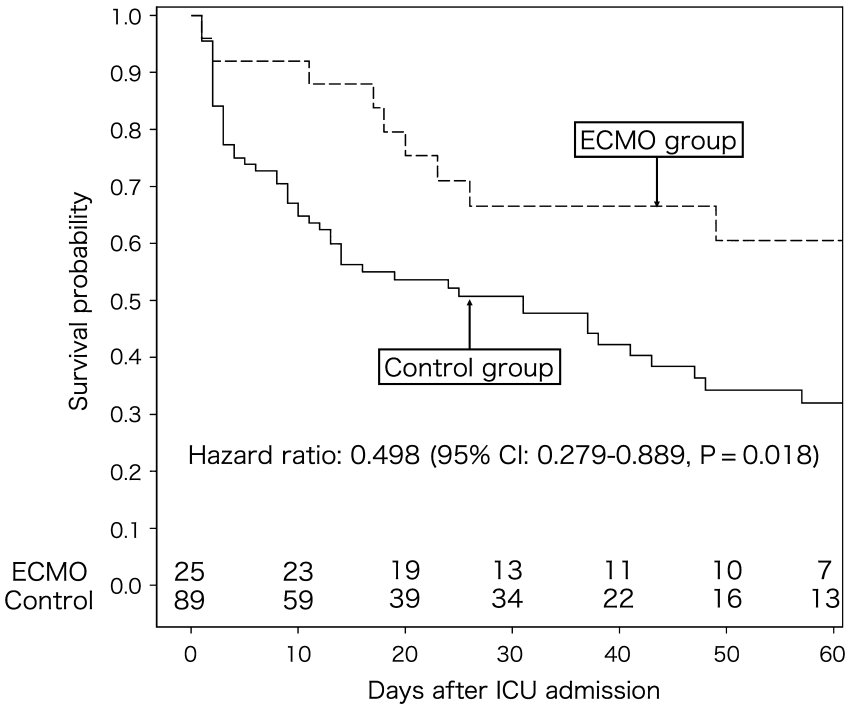

Fig. 2. Survival plots for patients with severe respiratory failure induced by lung infection in propensity score-matched control and extracorporeal membrane oxygenation (ECMO) groups. The survival rate in the ECMO group was significantly higher than in the control group. CI, confidence interval; ICU, intensive care unit.

Table 3. Characteristics of patients with severe respiratory failure induced by lung infection in the unmatched and propensity-matched groups

	Unmatched group		Unmatched standardized difference (%)	Matched group		Matched standardized difference (%)
	Control *n* = 260	ECMO *n* = 25		Control *n* = 89	ECMO *n* = 25	
Age, years	70 ± 14	64 ± 10	−41.88	65 ± 14	64 ± 10	−7.94
Men	200 (76.9)	21 (84.0)	−17.92	69 (77.5)	21 (84.0)	−16.48
Severity						
APACHE II score	26 (20–31)	26 (20–32)	−13.74	27 (20–30)	26 (20–32)	−11.35
SOFA score total	11 (8–13)	12 (9–14)	35.33	12 (10–14)	12 (9–14)	1.75
SIRS score	3 (3–4)	3 (3–4)	2.24	3 (3–4)	3 (3–4)	−2.06
Severe sepsis	123 (47.3)	6 (24.0)	50.17	31 (34.8)	6 (24.0)	23.94
Septic shock	137 (52.7)	19 (76.0)		58 (65.2)	19 (76.0)	
Mechanical ventilation used on day 1	245 (94.2)	25 (100.0)	34.99	83 (93.3)	25 (100.0)	38.02
Lactate, mmol/L	3.1 (1.7–6.1)	3.2 (1.9–6.1)	4.06	3.2 (1.9–6.1)	2.3 (1.9–4.5)	−2.46
Blood culture						
Positive	83 (31.9)	9 (36.0)	8.62	37 (41.6)	9 (36.0)	−11.46
Negative	165 (63.5)	15 (60.0)	−7.13	50 (56.2)	15 (60.0)	7.75
Not taken	12 (4.6)	1 (4.0)	−3.03	2 (2.2)	1 (4.0)	10.09
Microorganisms causing sepsis						
Gram-negative rod	81 (31.2)	4 (16.0)	−36.28	36 (40.4)	4 (16.0)	−56.44
Gram-positive coccus	71 (27.3)	6 (24.0)	−7.58	21 (23.6)	6 (24.0)	0.95
Fungus	8 (3.1)	1 (4.0)	5.00	5 (5.6)	1 (4.0)	−7.57
Virus	2 (0.8)	1 (4.0)	21.30	1 (1.1)	1 (4.0)	18.28
Mixed infection	40 (15.4)	5 (20.0)	12.12	11 (12.4)	5 (20.0)	20.86
Other	5 (1.9)	4 (16.0)	50.85	4 (4.5)	4 (16.0)	38.64
Unknown	53 (20.4)	4 (16.0)	−11.38	11 (12.4)	4 (16.0)	10.45

Data are expressed as a number (%), mean ± standard deviation, or median (interquartile range).
APACHE, Acute Physiology and Chronic Health Evaluation; ECMO, extracorporeal membrane oxygenation; SIRS, Systemic Inflammatory Response Syndrome; SOFA, Sequential Organ Failure Assessment.

Table 4. Bleeding complications in propensity score-matched groups of patients with severe respiratory failure

	Control	ECMO	*P*-value
Patients with severe respiratory failure	*n* = 150	*n* = 40	
Bleeding requiring transfusion	18 (12.0%)	13 (32.5%)	0.077
Bleeding requiring therapeutic intervention	3 (2.0%)	2 (5.0%)	1.000
Intracranial hemorrhage	1 (0.7%)	0 (0.0%)	NA
Bleeding to death	1 (0.7%)	0 (0.0%)	NA
Patients with severe respiratory failure induced by lung infection	*n* = 89	*n* = 25	
Bleeding requiring transfusion	9 (10.1%)	7 (28.0%)	0.070
Bleeding requiring therapeutic intervention	2 (2.2%)	2 (8.0%)	NA
Intracranial hemorrhage	0 (0.0%)	0 (0.0%)	NA
Bleeding to death	1 (1.1%)	0 (0.0%)	NA

Data are presented as number (percentage).
ECMO, extracorporeal membrane oxygenation; NA, not applicable.

Table 5. Transfusion amounts in propensity score-matched groups of patients with severe respiratory failure

	Control	ECMO	*P*-value
Patients with severe respiratory failure	*n* = 150	*n* = 40	
Red blood cell concentration, units	0 (0–4)	6 (0–14)	0.000
Fresh frozen plasma, units	0 (0–4)	0 (0–10)	0.019
Platelet concentration, units	0 (0–15)	10 (0–30)	0.001
Patients with severe respiratory failure induced by lung infection	*n* = 89	*n* = 25	
Red blood cell concentration, units	0 (0–4)	4 (0–10)	0.000
Fresh frozen plasma, units	0 (0–2)	0 (0–2)	0.365
Platelet concentration, units	0 (0–10)	0 (0–25)	0.915

Data are presented as the median (interquartile range).
ECMO, extracorporeal membrane oxygenation.

ventilator settings, the duration from intubation to ECMO initiation, the duration of ECMO, the use of prone positioning, and inhaled nitric oxide. Second, the number of patients with ECMO was relatively low in the present study. Given these limitations, it was difficult to perform a propensity adjustment using more variables. The findings from study may not, therefore, be statistically robust. However, few clinical studies have reported on the use of ECMO for sepsis. Further studies in a larger number of patients are needed to determine whether or not the results of this study are appropriate.

CONCLUSIONS

THIS STUDY USING propensity score analyses found that the survival time of the ECMO group was significantly longer than that of the control group among patients with severe respiratory failure induced by lung infection. However, there was no difference among overall septic patients with severe respiratory failure. Furthermore, the numbers of RRT- and vasopressor-free days in the ECMO group were higher than in the control group. The ECMO group received more red blood cells transfused than the control group, but there was no significant difference in the rate of severe bleeding complications between the groups.

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DISCLOSURE

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