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Extracorporeal Membrane Oxygenation as a First-Line Treatment Strategy for ARDS

Is the Evidence Sufficiently Strong?

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THE 2009 INFLUENZA A(H1N1) PANDEMIC WAS ASSOciated with a high attributable mortality among critically ill patients who developed acute respiratory distress syndrome (ARDS) and required mechanical ventilation. In this issue of *JAMA*, Noah and colleagues[1] present evidence in support of extracorporeal membrane oxygenation (ECMO) in combination with lung protective ventilation as a treatment strategy early in the course of ARDS related to H1N1 infection. The authors found that among 80 patients with severe suspected or confirmed H1N1 and ARDS who were transferred to 4 UK specialized centers for treatment with ECMO, 22 died (27.5%) before hospital discharge.[1] This mortality rate was lower than that among matched critically ill patients with equally severe (suspected or confirmed) H1N1 and ARDS who were not transferred for treatment with ECMO. This study adds to a series of recent investigations that favor the use of ECMO for severe respiratory failure in adults.[1-3] In all of these studies, ECMO was initiated in the first 7 days of mechanical ventilation. Average duration of ECMO use was 9 to 10 days, and reported mortalities ranged from 21% to 37%.[1-3]

Use of ECMO in severe respiratory failure, particularly in the treatment of ARDS, is occurring more commonly. Extracorporeal gas exchange may allow the use of low tidal volumes and lower levels of inspired oxygen, and use of higher positive end-expiratory pressure if desired. A treatment strategy that capitalizes on volume and pressure limitation may decrease the risk of regional overdistention of heterogeneously compromised lungs and prevent further injury. The study by Noah et al[1] further suggests that a UK-wide system for referral and use of ECMO can be established quickly and effectively during an influenza epidemic. Furthermore, the Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial reported by Peek et al[2] suggested safety and improved outcomes for patients with severe respiratory failure who were referred to a specialized center for ECMO-based management vs those managed with conventional ventilation.

See related article.

However, some limitations may diminish enthusiasm for wider use of ECMO. First, ECMO can be accomplished effectively only in highly specialized centers; it is invasive, requires anticoagulation for the duration of therapy, and can be associated with serious complications. Second, the design of both the study by Noah et al[1] and the CESAR trial[2] required transfer of patients to highly specialized centers for management of ECMO, making it unclear whether the mortality benefit associated with ECMO was attributable to management of severe respiratory failure in a specialized center or to the use of ECMO. Evidence for the former is that patients who receive mechanical ventilation in tertiary care centers with high case volumes have a lower mortality than patients treated in centers with lower case volumes. In a study by Kahn et al[4] of approximately 20 000 patients who received mechanical ventilation registered in the Acute Physiology and Chronic Health Evaluation clinical information database across 37 centers, hospital mortality was 34% in low-volume sites compared with 26% in the high-volume sites. Nonetheless, a sensitivity analysis conducted by Noah et al[1] revealed that the findings of a survival advantage favoring the group of ECMO-referred patients were unchanged when the group of non–ECMO-referred patients was restricted to the subgroup of patients recruited at high-volume centers.

Other studies highlight how difficult it is to disentangle the effect of treatment with ECMO from the experience and care in a highly specialized center. Hospital mortality for patients with ARDS from all causes enrolled in the US National Institutes of Health's Acute Respiratory Distress Syndrome Network trials and managed with lung protective ventilation between 1996 and 2005[5-7] was similar to that of patients with H1N1-related ARDS managed with ECMO under the treatment strategy presented by Noah et al.[1] Specifically, hospital mortality at 90 days was 29% among 1715 patients with a ratio of Pa_{O_2} to fraction of inspired oxygen of less than 200 mm Hg prior to enrollment in ARDS Network trials. Considering the lower age range (28-46 years) of patients who received ECMO in the study by Noah et al,[1] hospital mortality at 90 days among patients enrolled in ARDS

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Network trials in this age range was 21%. The Canadian Critical Trials Group H1N1 Collaborative reported a 90-day mortality of 21% in 118 adult critically ill patients with confirmed or suspected H1N1 infection, yet less than 5% received treatment with ECMO.[8] The implications of international comparisons, however, are limited because differences in admission criteria and discharge practices may result in different mortality rates.

Therefore, the question remains as to whether there was a true difference in mortality between patients managed at the same highly specialized centers with conventional lung protective ventilation compared with a strategy that incorporates ECMO. In the report by Noah et al,[1] the authors explored whether differences in the quality of care could have influenced their results. While the investigators did not have access to detailed information regarding use of lung protective ventilation strategies, they did restrict the analysis to selection of non–ECMO-referred patients from centers with better than expected severity-adjusted outcomes and found that the results were unchanged.

Third, the study by Noah et al[1] was an observational, prospective study of patients with ARDS from H1N1 infection who received ECMO and lung protective ventilation at 4 referral hospitals (64% of patients were referred to Glenfield Hospital in Leicester, England) compared with patients of similar disease severity who were treated at UK hospitals outside the 4 referral centers. Both ECMO-referred patients and non–ECMO-referred patients were identified from hospitals participating in the Swine Flu Triage study.[9] Even though the study was not randomized, the authors used novel analytic techniques based on propensity score matching to achieve the best possible balance between individual risk factors across the 2 study groups. A critical concept of randomization is that it achieves balance between observed and unobserved factors to prevent systematic differences between treatment groups, therefore allowing for a causal interpretation in findings. While such balance is difficult to achieve in observational studies, propensity score analysis aims to select matched patients from each of the 2 study groups to reduce bias. As such, the authors have provided careful analyses of their data and used several appropriate matching methods. Propensity score matching offers a complementary approach to the analysis of observational studies but does not replace a randomized clinical trial.

An additional complicating factor in the analysis of an observational study involves having data from multiple centers. Because the main thesis of the current study was that specialized centers that incorporate ECMO make a difference in survival from ARDS related to H1N1 infection, hospitals and not individuals are the unit of analysis. Thus, a better study design and analysis than that conducted by Noah et al[1] may be to compare the averages of hospital mortalities across several centers with or without ECMO-based management. Additional propensity score matching at the hospital level would help reduce bias from differences between centers in case volume, severity of illness, and other important determinants. However, such a design would require many more patients and hospital centers than were available in the current study. It is therefore possible that the current study may have been underpowered to determine if ECMO was associated with a survival advantage when using hospitals as the unit of analysis.

In summary, the study by Noah et al[1] involving critically ill patients with H1N1 joins other recent investigations[2,3] that have revitalized interest in the use of ECMO as a treatment strategy for ARDS. While underlying risk factors may be different, severe respiratory failure from H1N1 infection presents a clinical challenge similar to that involving ARDS from other causes. Despite several decades of investigation into potential treatment strategies, use of low tidal volumes remains the only proven therapy to decrease mortality in ARDS.[5] In light of the large observed differences in mortality with and without ECMO, large consortia of trialists may be enticed to consider ECMO as a potential target for a randomized controlled trial early in the course of severe ARDS from all causes.

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Referral to an Extracorporeal Membrane Oxygenation Center and Mortality Among Patients With Severe 2009 Influenza A(H1N1)

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Context Extracorporeal membrane oxygenation (ECMO) can support gas exchange in patients with severe acute respiratory distress syndrome (ARDS), but its role has remained controversial. ECMO was used to treat patients with ARDS during the 2009 influenza A(H1N1) pandemic.

Objective To compare the hospital mortality of patients with H1N1-related ARDS referred, accepted, and transferred for ECMO with matched patients who were not referred for ECMO.

Design, Setting, and Patients A cohort study in which ECMO-referred patients were defined as all patients with H1N1-related ARDS who were referred, accepted, and transferred to 1 of the 4 adult ECMO centers in the United Kingdom during the H1N1 pandemic in winter 2009-2010. The ECMO-referred patients and the non–ECMO-referred patients were matched using data from a concurrent, longitudinal cohort study (Swine Flu Triage study) of critically ill patients with suspected or confirmed H1N1. Detailed demographic, physiological, and comorbidity data were used in 3 different matching techniques (individual matching, propensity score matching, and GenMatch matching).

Main Outcome Measure Survival to hospital discharge analyzed according to the intention-to-treat principle.

Results Of 80 ECMO-referred patients, 69 received ECMO (86.3%) and 22 died (27.5%) prior to discharge from the hospital. From a pool of 1756 patients, there were 59 matched pairs of ECMO-referred patients and non–ECMO-referred patients identified using individual matching, 75 matched pairs identified using propensity score matching, and 75 matched pairs identified using GenMatch matching. The hospital mortality rate was 23.7% for ECMO-referred patients vs 52.5% for non–ECMO-referred patients (relative risk [RR], 0.45 [95% CI, 0.26-0.79]; $P=.006$) when individual matching was used; 24.0% vs 46.7%, respectively (RR, 0.51 [95% CI, 0.31-0.81]; $P=.008$) when propensity score matching was used; and 24.0% vs 50.7%, respectively (RR, 0.47 [95% CI, 0.31-0.72]; $P=.001$) when GenMatch matching was used. The results were robust to sensitivity analyses, including amending the inclusion criteria and restricting the location where the non–ECMO-referred patients were treated.

Conclusion For patients with H1N1-related ARDS, referral and transfer to an ECMO center was associated with lower hospital mortality compared with matched non–ECMO-referred patients.

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EXTRACORPOREAL MEMBRANE OXYgenation (ECMO) can support gas exchange independently of mechanical ventilation in patients with severe acute respiratory failure. ECMO may be used either as a rescue intervention or to minimize ventilator-associated lung injury[1] and its associated multiple organ dysfunction,[2] both crucial determinants of survival for patients with acute respiratory distress syndrome (ARDS).[3] A recent randomized controlled study indicated that significantly more patients with severe

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ARDS survived without severe disability if they were transferred to a single ECMO center compared with patients who were managed conventionally.[4] However, differences between the centers in mechanical ventilation and other therapies used to manage the conventionally treated patients could have affected outcome independently. Moreover, ECMO doubled hospital costs compared with conventional care.[5] Hence, the role of ECMO in adults with severe ARDS remains controversial.[6-8]

A minority of patients infected during the 2009 influenza A(H1N1) pandemic developed severe, rapidly progressive ARDS, which was often associated with other organ failures.[9-11] The severity of the respiratory failure led to some patients being supported with ECMO. In a case series from Australia and New Zealand, more than 70% of patients with respiratory failure who received ECMO survived.[12] However, the interpretation of this case series is complicated by confounding factors that influence both case selection and patient outcome.

In an attempt to address this limitation, and using an opportunity presented by local variation in referral for ECMO in the United Kingdom during the H1N1 pandemic, we compared the mortality for patients that were referred, accepted, and transferred to UK ECMO centers for H1N1-related ARDS with carefully matched non–ECMO-referred patients. Data were obtained from the Swine Flu Triage study (SwiFT), which was a prospective cohort study of patients with suspected or confirmed H1N1 who were referred and assessed as requiring critical care.[13]

METHODS

Our study used the SwiFT study[13] as the main data source for ECMO-referred patients and non–ECMO-referred patients and supplementary data on ECMO-referred patients from the UK H1N1 ECMO registry. The SwiFT study was a rapid commission from the UK government to monitor the impact of the H1N1 pandemic. A minimal set of clinical data (eMethods and eTable 1 at http://www.jama.com) was prospectively collected from both the point of assessment for critical care and daily while patients were receiving critical care (sufficient for the sequential organ failure assessment[14] and for unit outcome).

The SwiFT data were collected on suspected and confirmed H1N1 cases who were referred and assessed as requiring critical care in 192 participating acute hospitals, and entered into a dedicated, secure Web portal hosted by the Intensive Care National Audit & Research Centre (ICNARC). Data definitions (either as a data collection manual and form, or as help text and answers to frequently asked questions) and error checking were available either for download or built into the design of the Web portal. The SwiFT study was approved by the North West Research Ethics Committee and the National Information Governance Board Ethics and Confidentiality Committee. The SwiFT study data collection began on September 3, 2009, and ended on January 31, 2010.

The UK H1N1 ECMO registry pooled data on all H1N1 patients referred for ECMO during the pandemic. The data were maintained at the Heartlink ECMO center at Glenfield Hospital in Leicester, England. Detailed demographic and physiological data from the time of referral plus technical ECMO and outcome data were collected. The UK National Research Ethics Service designated the registry as a service evaluation; requiring neither ethics approval nor patient consent.

ECMO-referred patients and non–ECMO-referred patients were initially identified from the SwiFT study. The UK ECMO registry ensured total capture of ECMO-referred patients from the SwiFT study during the H1N1 pandemic and provided more detailed data on ECMO-referred patients. All data for both ECMO-referred patients and non–ECMO-referred patients used in these analyses were collected according to SwiFT study definitions.

ECMO-Referred Patients

ECMO-referred patients were defined as adults with suspected or confirmed H1N1-associated respiratory failure who were referred, accepted, and transferred to 1 of 4 UK ECMO centers between July 14, 2009, and February 19, 2010. Adult ECMO support was provided by the National H1N1 ECMO service and led and coordinated by the Heartlink ECMO center. This center has been providing ECMO support since 1989 and is the only permanently designated respiratory ECMO center for adult patients in the United Kingdom. It cares for approximately 50 patients per year.

Due to the expected, increased demand, 3 other hospitals (Royal Brompton Hospital, Papworth Hospital, and Aberdeen Royal Infirmary) were evaluated, quality assured, and commissioned by the UK government's Department of Health as additional providers of ECMO. Temporary commissioning of the 3 additional centers followed onsite reviews to ensure that they met the national standards of being designated respiratory ECMO centers in relation to equipment, clinical skills, workforce, training, and governance. Prior to the pandemic, all 3 additional centers were using ECMO in various clinical contexts.

In the United Kingdom, suitability of adult patients for ECMO support was defined using the Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial[4] entry criteria (eMethods at http://www.jama.com), and referral was left to local, clinical decision making. Following transfer to the ECMO center, ECMO was instituted if adequate gas exchange could not be achieved with conventional lung-protective ventilation. ECMO aimed to maintain arterial oxygen saturation levels above 85% and arterial carbon dioxide tensions between 30 and 45 mm Hg. Mechanical ventilation during ECMO was reduced to a respiratory rate of 10 breaths per minute, peak inspiratory pressure of less than 30 cm H_2O (ideally 25 cm H_2O), positive end-expiratory pressure of 10 to 15 cm H_2O, and fraction of inspired oxygen (FIO_2) of 0.3. Other

therapeutic strategies considered included neuraminidase inhibitors,[15] conservative use of fluids,[16] and corticosteroids.[17,18]

Non–ECMO-Referred Patients

Non–ECMO-referred patients were defined as adults with suspected or confirmed H1N1-associated respiratory failure who were not referred, accepted, or transferred to 1 of the 4 ECMO centers. Potential non–ECMO-referred patients were excluded if they were (1) not suitable for ECMO (age <16 years or >70 years, not mechanically ventilated, FIO_2 never >0.7 and/or ratio of PaO_2 to FIO_2 never <100 mm Hg, or having chronic respiratory organ dysfunction sufficient to severely impair activities of daily living), (2) treated with ECMO at an undesignated center, (3) referred but not accepted for transfer for ECMO due to a presupposed lack of benefit, (4) missing data either for matching or for the primary outcome. As per usual critical care delivery in the United Kingdom, all non–ECMO-referred patients were treated in intensivist-led, closed critical care units.

The primary outcome was survival to acute hospital discharge determined by linkage to the UK ECMO registry for ECMO-referred patients and to the ICNARC Case Mix Programme (or by telephone follow-up) for non–ECMO-referred patients.

Statistical Analysis

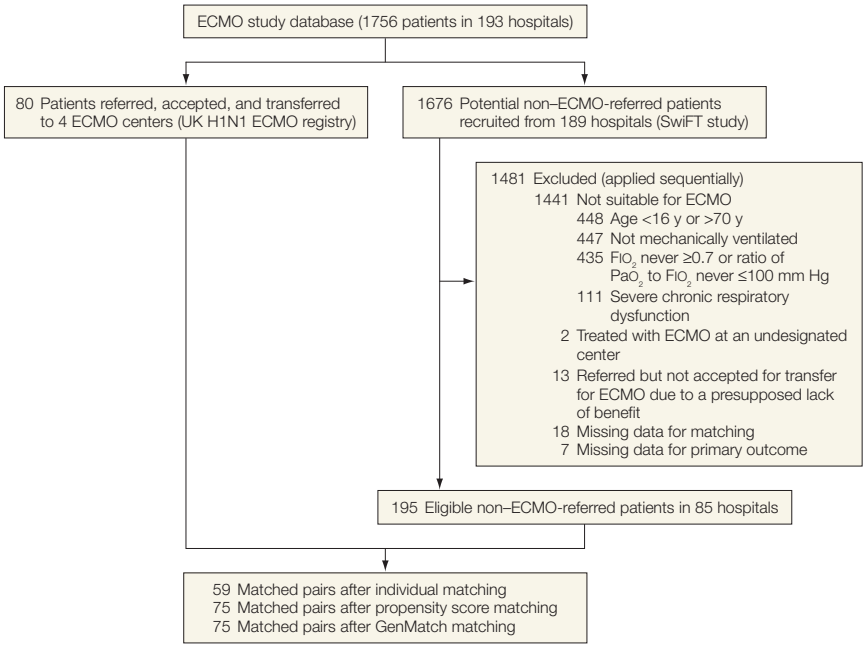
Matched cohort analyses were performed using 3 statistical approaches: individual matching, propensity score matching, and GenMatch matching. The variables selected for matching were those anticipated a priori to be associated with ECMO use and hospital mortality, but only those that were available in the SwiFT study data set were chosen. ECMO-referred patients and non–ECMO-referred patients were matched at a similar time point in the natural history of their illness by matching on the number of days of mechanical ventilation received prior to referral in the ECMO-referred patients with the equivalent number of days of mechanical ventilation in the non–ECMO-referred patients. Non–ECMO-referred patients were not considered for matching on days when the patient was not mechanically ventilated, required an FIO_2 of less than 0.7, had a ratio of PaO_2 to FIO_2 of more than 100 mm Hg, or had been ventilated for more than 20 days; these patients would not be suitable for ECMO (eMethods at http://www.jama.com).

Individual case matching compared individual factors in the following order: (1) the number of days of continuous mechanical ventilation (nearest in absolute value to a maximum difference of 2 days); (2) FIO_2 (1.0 or 0.70-0.99) associated with the arterial blood gas with the lowest PaO_2; (3) ratio of PaO_2 to FIO_2 from the arterial blood gas with the lowest PaO_2; (4) Sequential Organ Failure Assessment Score (nearest in absolute value to a maximum difference of 3 points); (5) age (nearest in absolute value to a maximum difference of 10 years); (6) pregnancy status (defined as currently pregnant, pregnant within the previous 42 days, or not pregnant); and (7) body mass index (BMI) category (calculated either from recorded weight in kilograms divided by height in meters squared or assessed subjectively; very thin or thin: BMI <18.6; average weight, overweight, or obese: BMI, 18.6-39.9; or morbidly obese: BMI ≥40).

Propensity score matching was undertaken by estimating the likelihood of referral, acceptance, and transfer for ECMO using a logistic regression model including the following variables: number of days of continuous mechanical ventilation; FIO_2; ratio of PaO_2 to FIO_2; Sequential Organ Failure Assessment Score; pregnancy; BMI category; H1N1 status (suspected or confirmed); prior use of inhaled nitric oxide, high-frequency oscillation, or prone positioning; advanced cardiovascular support; renal support; antiviral therapy; and age. Each ECMO-referred patient was matched with a non–ECMO-referred patient with the closest absolute propensity score (predicted log odds of referral, acceptance, and transfer for ECMO).

GenMatch is a matching technique that combines propensity score matching with multivariate matching.[19-21] Un-

Figure 1. Enrollment and Matching of Patients



ECMO indicates extracorporeal membrane oxygenation; FIO_2 fraction of inspired oxygen; SwiFT, Swine Flu Triage.

Table 1. Characteristics of ECMO-Referred and Non–ECMO-Referred Patients Before and After Matching

	Mean (SD)			
	ECMO-Referred Patients	Non–ECMO-Referred Patients	*D* Statistic	*P* Value
Prior duration of mechanical ventilation, d				
Before matching[a]	4.4 (3.7)	3.2 (4.1)	0.3	<.001
After propensity score matching[b]	4.4 (3.7)	4.3 (3.9)	0.1	.97
After GenMatch matching[b]	4.4 (3.7)	4.2 (4.2)	0.1	.79
After individual matching[c]	3.2 (2.7)	3.1 (2.9)	0.1	.47
Ratio of Pa_{O_2} to F_{IO_2}, mm Hg				
Before matching[a]	54.9 (14.3)	68.4 (16.9)	0.4	<.001
After propensity score matching[b]	54.9 (14.3)	54.9 (13.9)	0.1	.44
After GenMatch matching[b]	54.9 (14.3)	55.2 (11.5)	0.1	.42
After individual matching[c]	53.2 (13.5)	53.0 (11.6)	0.1	.57
Age, y				
Before matching[a]	36.5 (11.4)	42.8 (13.4)	0.2	<.001
After propensity score matching[b]	36.5 (11.4)	38.5 (13.0)	0.1	.40
After GenMatch matching[b]	36.5 (11.4)	37.1 (12.5)	0.1	.64
After individual matching[c]	38.6 (11.1)	37.6 (11.2)	0.1	.84
SOFA score				
Before matching[a]	9.1 (2.9)	9.8 (3.7)	0.1	.06
After propensity score matching[b]	9.1 (2.9)	9.7 (3.3)	0.1	.22
After GenMatch matching[b]	9.1 (2.9)	8.9 (3.1)	0.1	.67
After individual matching[c]	9.2 (2.8)	8.8 (2.9)	0.1	.71
	No. (%)		*t* Statistic	
F_{IO_2} = 1.0				
Before matching[a]	60 (80.0)	168 (34.6)	0.5	<.001
After propensity score matching[b]	60 (80.0)	63 (84.0)	0	.41
After GenMatch matching[b]	60 (80.0)	60 (80.0)	0	>.99
After individual matching[c]	48 (81.4)	48 (81.4)	NA	NA
Currently or recently pregnant[d]				
Before matching[a]	20 (26.7)	24 (4.9)	–0.4	<.001
After propensity score matching[b]	20 (26.7)	9 (12.0)	–0.3	.03
After GenMatch matching[b]	20 (26.7)	20 (26.7)	0	>.99
After individual matching[c]	10 (16.9)	10 (16.9)	NA	NA
BMI <18.6[e]				
Before matching[a]	4 (5.3)	33 (6.8)	0	.61
After propensity score matching[b]	4 (5.3)	5 (6.7)	0	.74
After GenMatch matching[b]	4 (5.3)	1 (1.3)	0	.18
After individual matching[c]	0	0	NA	NA
BMI between 18.6 and 39.9[e]				
Before matching[a]	63 (84.0)	412 (84.9)	0	.84
After propensity score matching[b]	63 (84.0)	62 (82.7)	0	.84
After GenMatch matching[b]	63 (84.0)	66 (88.0)	0	.49
After individual matching[c]	54 (91.5)	54 (91.5)	NA	NA
BMI ≥40[e]				
Before matching[a]	8 (10.7)	40 (8.2)	0	.53
After propensity score matching[b]	8 (10.7)	8 (10.7)	0	>.99
After GenMatch matching[b]	8 (10.7)	8 (10.7)	0	>.99
After individual matching[c]	5 (8.5)	5 (8.5)	NA	NA
Use of alternative ventilation strategies[f]				
Before matching[a]	38 (50.7)	164 (33.8)	0.2	.01
After propensity score matching[b]	38 (50.7)	31 (41.3)	0.1	.27
After GenMatch matching[b]	38 (50.7)	36 (48.0)	0	.53
After individual matching[c]	29 (49.2)	33 (55.9)	–0.1	.43

Abbreviations; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; F_{IO_2}, fraction of inspired oxygen; NA, data not applicable due to perfect match; SOFA, Sequential Organ Failure Assessment.

[a] There were 75 ECMO-referred patients (successfully matched by propensity score and GenMatch matching) and 485 observations from 195 non–ECMO-referred patients.

[b] There were 75 ECMO-referred patients and 75 matched non–ECMO-referred patients.

[c] There were 59 ECMO-referred patients and 59 matched non–ECMO-referred patients.

[d] Recently pregnant defined as within 42 days prior to referral and assessment for critical care.

[e] Calculated either from recorded weight in kilograms divided by height in meters squared or assessed subjectively.

[f] Prone positioning, inhaled nitric oxide, and/or high-frequency oscillation received at any time up to and including the day of referral for ECMO.

like individual matching, the multivariate matching used by GenMatch does not drop observations that cannot be exactly matched but seeks to make the multivariate distribution of covariates in the matched groups as similar as possible (ie, maximizing the balance of the observed covariates). GenMatch weights the propensity score and the observed individual variables based on an automated search algorithm. The GenMatch algorithm iteratively checks the balance and directs the search toward the best matches (those that optimize balance).[22,23]

GenMatch selects matched pairs using a generalized Mahalanobis distance metric,[24] which weights each baseline covariate included in the matching. The weights define alternative distance metrics that differ in the relative importance given to matching each covariate. The automated search algorithm selects those weights, and hence the corresponding distance metric, that gives the best covariate balance in the matched samples. The balance statistics are chosen a priori from recommended measures such as *t* statistics from paired *t* tests, *D* statistics from Kolmogorov-Smirnov tests, and weighted standardized differences.[25]

The search algorithm improves covariate balance to the extent possible given the data.[19,21] Compared with matching on propensity score alone, GenMatch matching has been shown to reduce covariate imbalance and bias from confounding.[19,20] Previous cohort studies have assessed the relative effectiveness of other clinical interventions using GenMatch matching to balance baseline covariates.[20,26,27] In this study, GenMatch matching was based on the propensity score and the same individual covariates included in the propensity score model but aimed to improve covariate balance by comparing the distribution of each covariate across the groups using paired *t* tests and Kolmogorov-Smirnov tests.

All matching was performed on a 1-to-1 basis with replacement. Nearest neighbor matching was applied

within a caliper of 1 standard deviation on the propensity score and for the number of days of mechanical ventilation. The balance between ECMO-referred patients and matched non–ECMO-referred patients was assessed using *t* statistics from paired *t* tests and *D* statistics from Kolmogorov-Smirnov tests and was reported for the same number of ECMO-referred patients and non–ECMO-referred patients before and after matching with the propensity score and GenMatch.

The relative risks (RRs) of death prior to hospital discharge for ECMO-referred patients compared with matched non–ECMO-referred patients were estimated by Poisson regression and were conditional on the matched data. Standard errors were estimated using the nonparametric bootstrapping method. The analysis was performed according to the intention-to-treat principle for ECMO.

A priori–agreed sensitivity analyses were conducted to ascertain whether inclusion criteria and restricting the location where the non–ECMO-referred patients were treated influenced the base-case findings. For the former, analyses were repeated excluding ECMO-referred patients and non–ECMO-referred patients that met the following criteria: (1) FIO_2 of less than 1.0 for the arterial blood gas with lowest PaO_2 on the calendar day of referral; (2) ECMO-referred patients transferred for ECMO who did not subsequently receive ECMO; (3) ECMO-referred patients in whom H1N1 infection was suspected but not confirmed; and (4) all of these criteria combined.

For the latter, the analyses were repeated to limit comparisons of ECMO-referred patients with non–ECMO-referred patients who had been treated in critical care units with characteristics generally associated with good outcomes; data from before the pandemic (January to December 2008) were used from the ICNARC Case Mix Programme. The non–ECMO-referred patient pool was therefore limited to critical care units with relatively low mortality rates (standardized hospital mortality ratio of <1.0 estimated using the ICNARC model) and to those with a higher volume of patients receiving ventilation (above the median).

Additional sensitivity analyses were undertaken that excluded those patients who were admitted during the first influenza wave prior to October 15, 2009. Multilevel models were applied post-matching to allow for the hierarchical nature of the data (ie, that outcomes may be more similar within than across critical care units) and to adjust for any residual differences in patient factors between the groups. Finally, the sensitivity of the results to unmeasured confounding was assessed.[28]

Statistical analyses were conducted using Stata software version 11 (StataCorp, College Station, Texas) and R software version 2.10.1 (R Foundation for Statistical Computing, http://www.r-project.org/). Two-sided testing was used with a *P* value significance level of less than .05.

Table 2. Deaths Analyzed by Matching Methods

	No. of Deaths/ Total No. of Patients (%)			
	ECMO-Referred	Non–ECMO-Referred	RR (95% CI)	*P* Value
Matching method				
Propensity score	18/75 (24.0)	35/75 (46.7)	0.51 (0.31-0.84)	.008
GenMatch	18/75 (24.0)	38/75 (50.7)	0.47 (0.31-0.72)	.001
Individual	14/59 (23.7)	31/59 (52.5)	0.45 (0.26-0.79)	.006

Abbreviations: ECMO, extracorporeal membrane oxygenation; RR, relative risk.

RESULTS

Eighty patients were referred, accepted, and transferred to 1 of the 4 UK ECMO centers (eTable 2 at http://www.jama.com), of whom 69 received ECMO (86.3%; eTable 3). No patients were refused transfer for ECMO based on lack of bed availability. Of the 80 patients referred, accepted, and transferred to 1 of the 4 UK ECMO centers, 10 were prior to and 3 were after the SwiFT study. The lead center at Glenfield Hospital (Heartlink ECMO center) received 51 ECMO-referred patients. The Royal Brompton Hospital received 18 ECMO-referred patients, the Papworth Hospital received 7 ECMO-referred patients, and the Aberdeen Royal Infirmary received 4 ECMO-referred patients. Of 1676 potential non–ECMO-referred patients, 195 were eligible for matching after exclusion criteria had been applied (FIGURE 1). The majority (n=1441; 86.0%) of exclusions were for patients who were not suitable for ECMO.

Prior to matching, there were differences between the ECMO-referred patients and non–ECMO-referred patients for all patient characteristics apart from BMI (TABLE 1). ECMO-referred patients were younger, more likely to be currently or recently pregnant, had received longer duration of mechanical ventilation including use of alternative ventilation strategies, and had worse respiratory physiological characteristics.

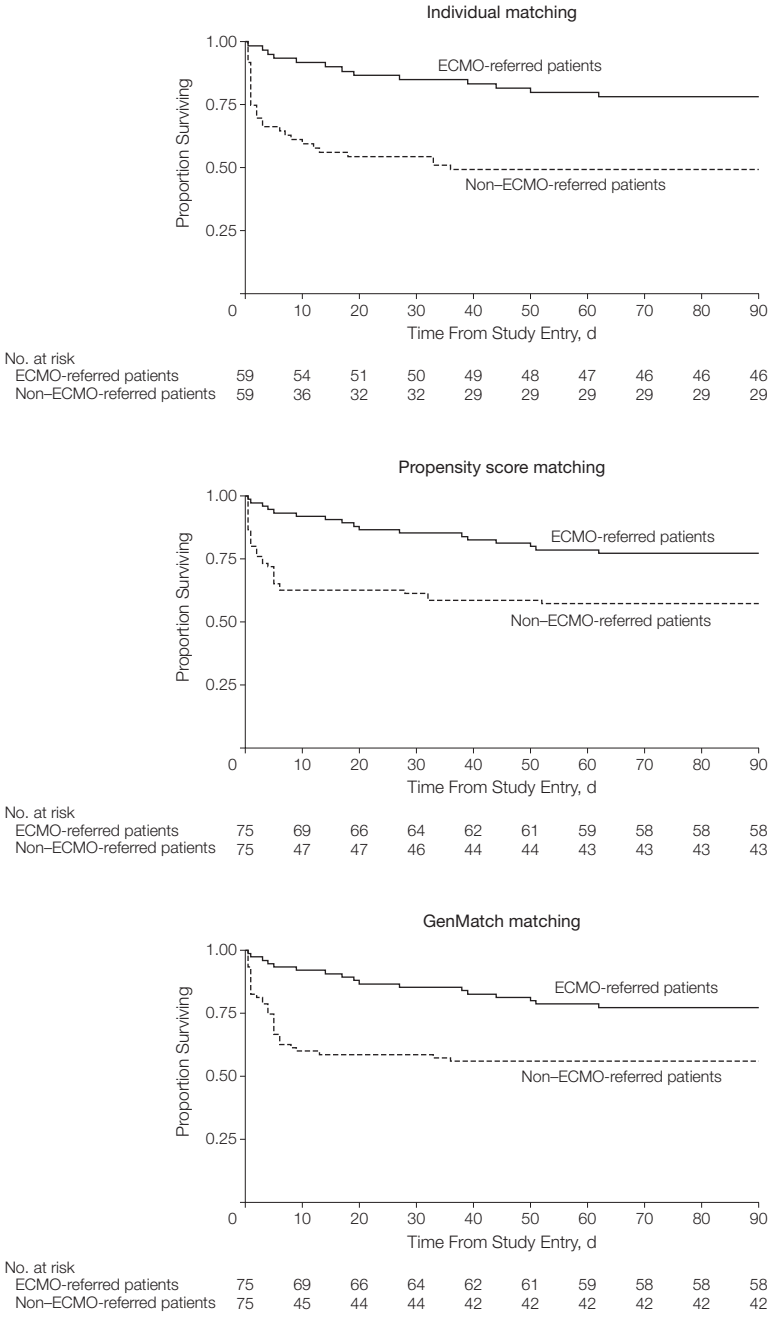
The individual matching technique identified 59 non–ECMO-referred patients for 59 ECMO-referred patients, but excluded many pregnant or postpartum women. Propensity score and GenMatch matching identified 75 non–ECMO-referred patients for 75 ECMO-referred patients. All of the matching methods improved covariate balance (Table 1). Following propensity score matching, there were proportionally more ECMO-referred patients currently or recently pregnant compared with non–ECMO-referred patients. Following GenMatch and individual matching, this potential confounder was well-balanced.

Outcome

Twenty-two patients (27.5%) who had been transferred to 1 of the 4 UK ECMO centers died. The hospital mortality rate was 23.7% for ECMO-referred patients vs 52.5% for non–ECMO-referred patients (RR, 0.45 [95% CI, 0.26-0.79]; *P*=.006) when individual matching was

used; 24.0% vs 46.7%, respectively (RR, 0.51 [95% CI, 0.31-0.84]; *P* = .008) when propensity score matching was used; and 24.0% vs 50.7%, respectively (RR, 0.47 [95% CI, 0.31-0.72]; *P* = .001) when GenMatch matching was used (TABLE 2). The survival curves indicate a considerable number of early deaths among the non–ECMO-referred patients (FIGURE 2). The benefit of ECMO persisted after repeating the survival analysis and excluding the matched pairs in which either the ECMO-referred patient or the non–ECMO-referred patient died during the first 48 hours (eFigure at http://www.jama.com).

Figure 2. Survival Curves for ECMO-Referred Patients vs Matched Non–ECMO-Referred Patients



Study entry was defined as the day of transfer to an extracorporeal membrane oxygenation (ECMO) center for ECMO-referred patients and the equivalent day of mechanical ventilation for matched non–ECMO-referred patients.

For ECMO-referred patients transferred to an ECMO center (from the UK ECMO registry), 10 died while receiving ECMO therapy (7 had cerebral hemorrhage, 1 had precannulation cardiac arrest, 1 had multiorgan failure, and 1 had massive pulmonary hemorrhage), 6 died after receiving ECMO therapy and prior to discharge from the center (1 had neutropenic sepsis, 2 had irrecoverable lung damage, 1 had rhabdomyolysis, and 2 had multiorgan failure), 4 died after being transferred back to the referring hospital (1 had pulmonary embolism, 1 had cerebrovascular accident, and 2 had multiorgan failure), and 2 died after being managed without ECMO (1 intracranial and 1 pulmonary hemorrhage).

Sensitivity Analyses

The sensitivity analyses indicated that the results were robust to alternative exclusion criteria (FIGURE 3A). The mean RRs of death for ECMO-referred patients vs non–ECMO-referred patients remained between 0.4 and 0.6 when the analyses were restricted to patients with confirmed H1N1 infection; ECMO-referred patients receiving ECMO; and patients with an FIO_2 of 1.0. When all restrictions were applied, the mean risk of death for ECMO-referred patients vs non–ECMO-referred patients was between 0.5 and 0.9. In some of these analyses, the sample size was much reduced and the 95% CIs for the RRs of death spanned unity, but these findings were still consistent with the base-case result.

The results also were robust to the location where non–ECMO-referred patients were treated (Figure 3B). The mean RRs of death for ECMO-referred patients vs non–ECMO-referred patients remained between 0.4 and 0.7 when the non–ECMO-referred patient pool was limited to critical care units with a standardized hospital mortality ratio of less than 1.0 and a volume

of patients receiving ventilation above the median of 233 per year. Similarly, limiting analyses to patients admitted during the second pandemic wave (after October 15, 2009) yielded mean RRs between 0.4 and 0.7.

The overall results were robust to postmatching regression (eg, the postmatching multilevel models before and after adjusting for differences in patient factors reported RRs of death of 0.39 [P=.04] and 0.48 [P=.01]). Finally, the sensitivity analysis assessing the potential impact of an unmeasured confounder showed that to change the finding that transfer for ECMO was associated with lower hospital mortality, the odds ratio for this confounder would have to exceed 1.8.

ECMO-Related Adverse Events

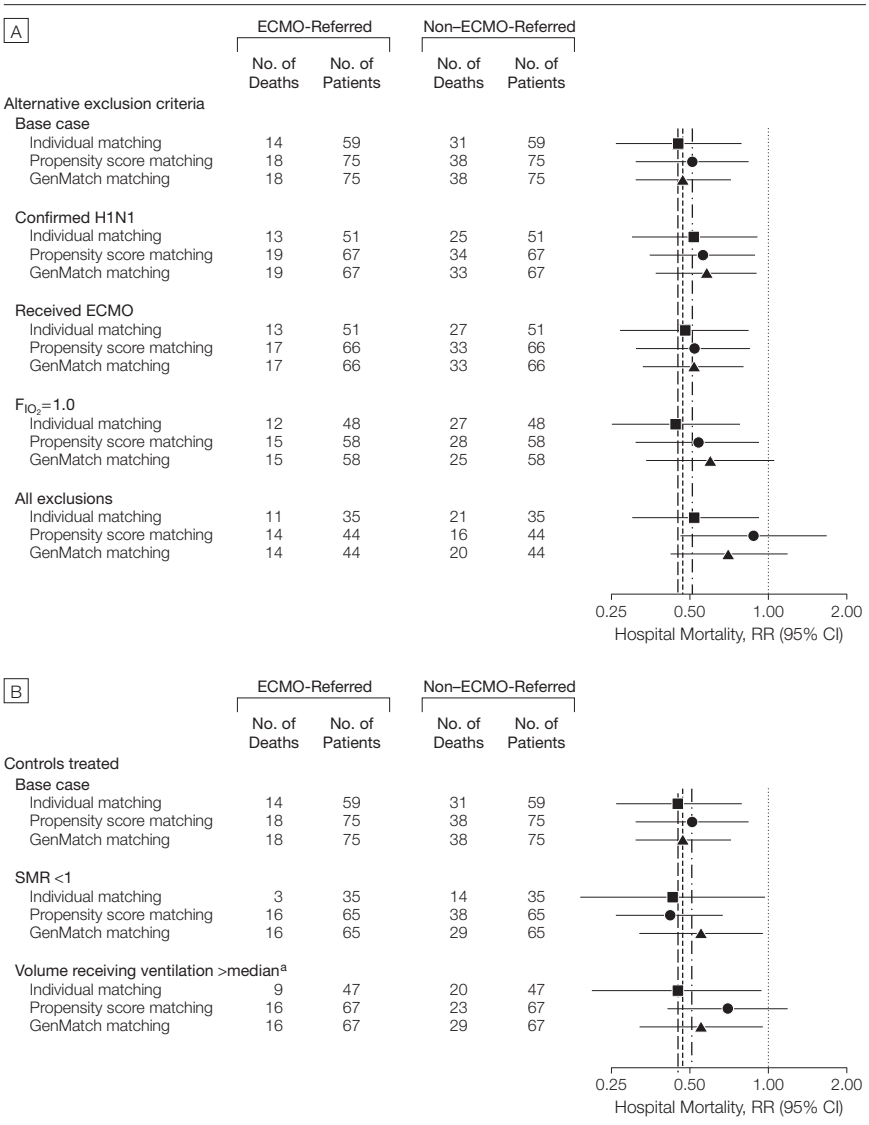
All patients survived transfer to the ECMO center. One patient had cardiac perforation and tamponade during cannulation; this was successfully repaired surgically. Hemorrhagic complications associated with ECMO included intracranial hemorrhage (n=8), cesarean delivery wound hematoma (n=5), laparotomy wound hematoma (n=1), fatal pulmonary hemorrhage (n=1), cannula site hematoma (n=3), spontaneous intraperitoneal hemorrhage (n=1), hemothorax (n=4), retroperitoneal hemorrhage (n=2), minor upper airway bleeding (n=9), and gastrointestinal tract bleeding (n=2). One patient developed heparin-induced thrombocytopenia.

COMMENT

In a cohort of 80 patients with severe H1N1-related ARDS who were referred, accepted, and transferred to UK ECMO centers, 27.5% died before hospital discharge. Hospital mortality for matched non–ECMO-referred patients was approximately twice that of the ECMO-referred patients. This result was consistent across 3 alternative matching methods and robust to a priori–determined sensitivity analyses, including restriction to non–ECMO-referred patients treated in critical care units with characteristics generally associated with good outcomes.

Survival in UK ECMO centers was similar to other patients with H1N1-related ARDS who had been treated with ECMO, both from the Extracorporeal Life Support Organization registry (of 167 patients, 102 survivors [61%] aged ≥15 years [Peter Rycus, MPH, written communication, October 2, 2010]) and from Australia and New Zealand (of 68 patients, 54 survivors [79%] at the time of reporting; however, 22 patients [32%] remained in the hospital and 2 patients [3%] remained on ECMO).[12] However, the UK ECMO-referred patients may have had more organ dysfunction compared with the case series from Australia and New Zealand because they were receiving more vasopressors and renal support at referral (eTable 2 at http://www.jama.com).

Figure 3. Sensitivity Analyses for ECMO-Referred Patients vs Matched Non–ECMO-Referred Patients



Vertical dashed lines indicate the relative risks (RRs) in the base-case analyses. ECMO indicates extracorporeal membrane oxygenation; F_{IO_2} fraction of inspired oxygen; H1N1, 2009 influenza A(H1N1); SMR, standardized hospital mortality ratio.
[a]The median volume of patients receiving ventilation was 233.

The unique value of this study lies in the homogeneity of the patients with H1N1-related ARDS and the matching methods used. The patient characteristics included in the matching were defined a priori and included those that have an effect on outcome (age,[29] degree of hypoxemia,[30,31] organ dysfunction,[3,32] pregnancy,[33,34] obesity,[35] and the use of alternative ventilatory strategies). Individual matching ensured perfect balance on some variables, but resulted in nearly one-quarter of the sample, including almost half of the currently or recently pregnant ECMO-referred patients, remaining unmatched. Propensity score and GenMatch matching matched most of the ECMO-referred patients, with GenMatch matching achieving the best balance on all observed covariates.

This study has several limitations. First, despite attempting to minimize confounding at both the design and analysis stages, the role of unobserved confounders in explaining the differences in outcome cannot be discounted. It is possible that the non–ECMO-referred patient group included patients judged to be "too sick for ECMO," and while the matching attempted to compensate for this, matching was limited to those variables available from the SwiFT study. These included few data characterizing respiratory function (lowest Pa_{O_2} and associated F_{IO_2}); for example, a single worst ratio of Pa_{O_2} to F_{IO_2} may have been affected by fluid overload or suboptimal mechanical ventilation. However, a sensitivity analysis reported that an unmeasured confounder, with a perfect association with hospital mortality, would have to be relatively prevalent in ECMO-referred patients rather than in non–ECMO-referred patients (with an odds ratio >1.8) before a conclusion of no difference in hospital mortality was inferred. An analogous odds ratio for pretreatment high-frequency oscillation is 1.3. Hence, any unmeasured confounder would have to be much more imbalanced at baseline to overturn the study's results.

Second, management of non–ECMO-referred patients was not part of the study's protocol. It is not possible to ascertain whether lung protective ventilation was used. One indication for using ECMO is that it enables lung protective ventilation despite life-threatening hypoxemia or hypercarbia. Further reductions in tidal volume and plateau pressure may confer additional advantage.[36-38]

Caution must be exercised in generalizing these results. First, the patients with H1N1 who became ECMO-referred patients were not representative of all patients with H1N1. ECMO-referred patients were younger, more likely to be currently or recently pregnant, had received longer durations of mechanical ventilation including use of alternative ventilation strategies, and had worse respiratory physiological characteristics compared with eligible non–ECMO-referred patients.

Second, the survival benefit associated with transfer for ECMO could be attributed to other factors associated with 4 specialized, highly resourced centers. Such factors may be related, for example, to available facilities, the number, availability, and skill of the clinical staff, differences in ventilatory and other care processes, and volume of ECMO-referred patients.[39] However, when the analyses were restricted to comparison with non–ECMO-referred patients treated in critical care units with characteristics generally associated with good outcomes following standard care, the association with survival remained.

Furthermore, patients with H1N1 infection may have been particularly likely to benefit from transfer for ECMO because the infection was likely to resolve with appropriate antiviral therapy[15,34] and the patients were relatively young. Indeed, while the survival in the non–ECMO-referred patients in this and in the CESAR study were almost identical, the survival rates in the ECMO-referred patients were 73% and 63%, respectively.[4] Whether advances in ECMO technology in the intervening period between these studies account for some of this improvement is not known.

The role of ECMO in ARDS is debated.[6-8] Several reports[5,12,40-42] and our study demonstrate that ECMO can be undertaken without the prohibitive morbidity and adverse events seen in the 1970s.[43] The data from our study are complementary to those of the CESAR randomized trial,[4] which demonstrated a reduction in the composite outcome of death and severe disability at 6 months in patients with severe ARDS who were transferred for consideration for ECMO, of whom 76% were supported with ECMO.

During the influenza pandemic of 2009-2010 and despite global concern, no randomized clinical trial for patients with H1N1 was funded, established, and completed. Instead, our study uses 3 different forms of case-matching to minimize confounding when estimating effectiveness from observational data. Our study found that transfer to an ECMO center for patients with H1N1-related ARDS was associated with lower hospital mortality compared with matched non–ECMO-referred patients. This finding was consistent across all 3 matching methods used.

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Online-Only Material: The eMethods, eTables 1-3, and the eFigure are available at http://www.jama.com.

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