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Outcomes of the NHS England National Extracorporeal Membrane Oxygenation Service for adults with respiratory failure: a multicentre observational cohort study

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Abstract

Background: Extracorporeal membrane oxygenation (ECMO) is increasingly used to support adults with severe respiratory failure refractory to conventional measures. In 2011, NHS England commissioned a national service to provide ECMO to adults with refractory acute respiratory failure. Our aims were to characterise the patients admitted to the service, report their outcomes, and highlight characteristics potentially associated with survival.

Methods: An observational cohort study was conducted of all patients treated by the NHS England commissioned ECMO service between December 1, 2011 and December 31, 2017. Analysis was conducted according to a prespecified protocol (NCT: 03979222). Data are presented as median [inter-quartile range, IQR].

Results: A total of 1205 patients were supported with ECMO during the study period; the majority (n=1150; 95%) had veno-venous ECMO alone. The survival rate at ECMO ICU discharge was 74% (n=887). Survivors had a lower median age (43 yr [32–52]), compared with non-survivors (49 y [39–60]). Increased severity of hypoxaemia at time of decision-to-cannulate was associated with a lower probability of survival: survivors had a median Sa_{O_2} of 90% (84–93%; median Pa_{O_2}/Fi_{O_2}, 9.4 kPa [7.7–12.6]), compared with non-survivors (Sa_{O_2} 88% [80–92%]; Pa_{O_2}/Fi_{O_2} ratio: 8.5 kPa [7.1–11.5]). Patients requiring ECMO because of asthma were more likely to survive (95% survival rate (95% CI, 91–99%), compared with a survival of 71% (95% CI, 69–74%) in patients with respiratory failure attributable to other diagnoses.

Conclusion: A national ECMO service can achieve good short-term outcomes for patients with undifferentiated respiratory failure refractory to conventional management.

Clinical trial registration: NCT 03979222.

Keywords: ARDS; ECMO; extracorporeal membrane oxygenation; mechanical ventilation; National Health Service; respiratory failure

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Editor's key points

- Extracorporeal membrane oxygenation (ECMO) is increasingly used to support adults with severe respiratory failure refractory to conventional therapy.
- NHS England commissioned a national service to provide ECMO to adults with refractory acute respiratory failure in 2011.
- This prospective observational study characterised reasons for admission, complications, and mortality after ECMO.
- Overall, 887/1205 (74%) patients survived to at least discharge from ECMO ICU, which is the highest reported in contemporary adult respiratory ECMO cohorts.

In 2009, the Conventional Ventilatory Support *vs* Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Failure trial (CESAR) found that adults with refractory respiratory failure had increased survival if treated in a specialist centre with extracorporeal membrane oxygenation (ECMO) capability.[1] A subsequent Health Technology Assessment economic evaluation by the National Institute for Health Research predicted a cost per quality-adjusted life year of £19 252 for this therapy.[2] These findings, in addition to high survival rates observed in patients treated with ECMO during the 2009 H1N1 influenza pandemic,[3–5] led NHS England to commission a national ECMO service for adult patients with refractory respiratory failure.[6]

The appropriate use of ECMO in this context remains debated. The 2018 ECMO for Severe Acute Respiratory Distress Syndrome trial (EOLIA) showed a non-significant (11%) absolute mortality reduction in patients who received ECMO, but was stopped early on the grounds of statistical futility to detect the trial's predefined absolute mortality reduction of 20%.[7] A subsequent Bayesian analysis indicated a high posterior probability of survival benefit with ECMO even with sceptical priors.[8] Although the evidence base remains incomplete, many consensus groups and leading experts recommend the use of ECMO in selected patients with severe respiratory failure refractory to conventional measures.[9–11]

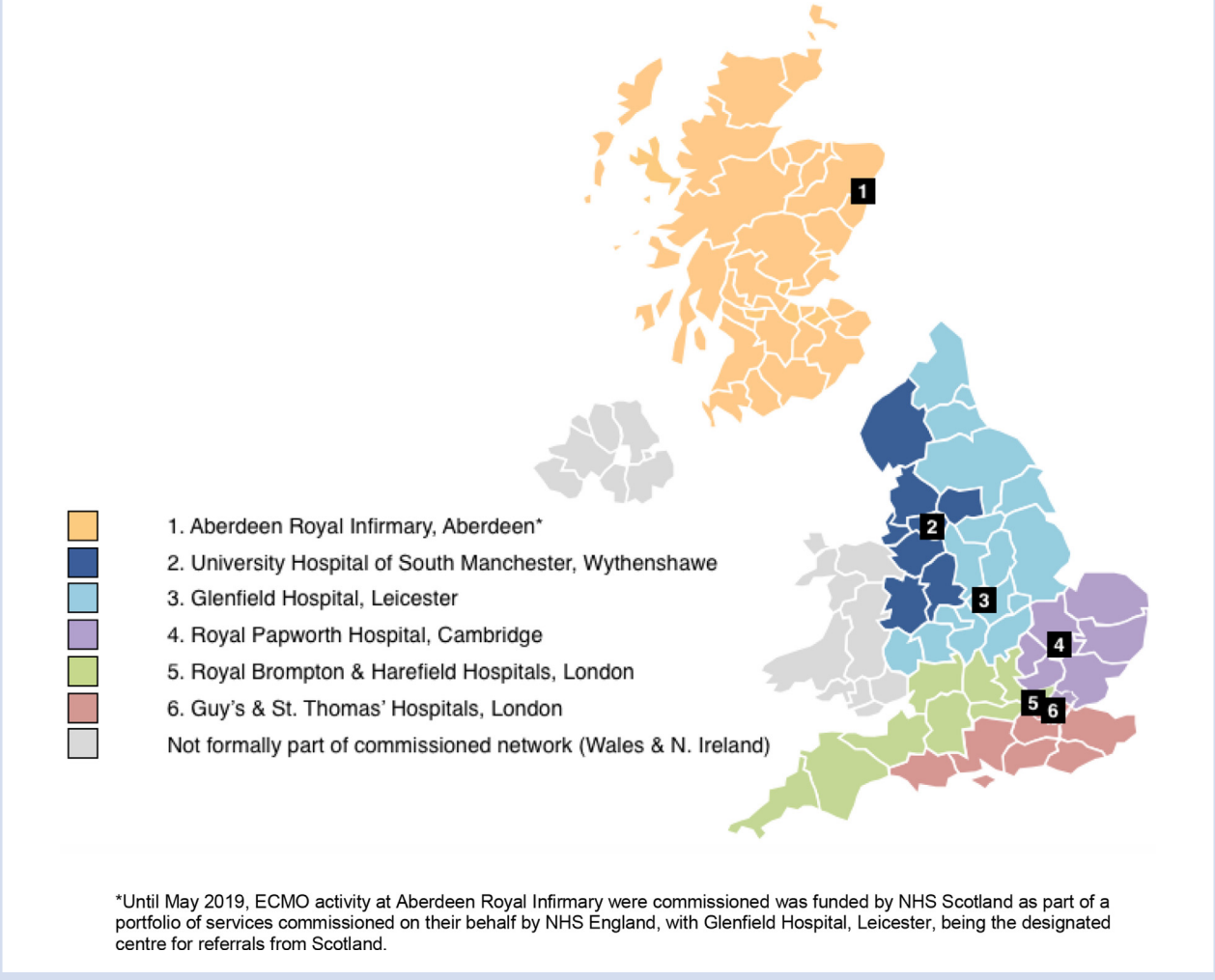

Fig 1. Geographic distribution of the NHS ECMO network across England and Scotland. ECMO, extracorporeal membrane oxygenation.

The aim of this prospective observational cohort study was to characterise the patients treated in the first 6 yr of the NHS England-commissioned national ECMO service, report their outcomes, and identify any factors potentially associated with survival.

Methods

Study design

The study involved the retrospective use of anonymised data routinely collected as part of the NHS England-commissioned service, without breach of confidentiality or privacy. Under the definitions of the NHS Health Research Authority, this study qualified as a service evaluation, and therefore formal research ethics committee approval was advised not to be necessary. A version-tracked statistical analysis protocol (National Clinical Trials registered trial: NCT 03979222) was drafted before analysis by the study committee and approved by all participating centres before data extraction. All statistical analyses and methodology are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[12] Full details on UK commissioning, patient selection, and routine clinical care for ECMO patients are provided in the Supplementary data.

Patient care and commissioning

The NHS England service was commissioned in 2011 and consists of five centres in England, with an additional 'satellite centre' for patients in Scotland in conjunction with one of the English centres (Fig. 1).[6] Full details on commissioning of ECMO services and patient care are provided in the Supplementary data. As of 2020, NHS Scotland has now commissioned a centre directly. Patients in Wales and Northern Ireland are treated on an *ad hoc* basis without formalised referral pathways.

Inclusion criteria for ECMO

Although the inclusion and exclusion criteria listed below are specified in the commissioning document, acceptance is ultimately at the discretion of the clinical team at the accepting centre.[6] Inclusion criteria require demonstrable severe respiratory failure from a noncardiac cause, or contraindication to positive pressure ventilation. Severe respiratory failure may be defined as a Murray Lung Injury score[13] of 3.0 or higher, or uncompensated hypercapnia with a pH <7.20, but these are not essential criteria for either referral or acceptance. Patients must have failed optimal conventional management, including trials of prone positioning where advised by the accepting centre.

Exclusion criteria for ECMO

Exclusion criteria include any patient with contraindication to continuation of active treatment (e.g. unsurvivable extrapulmonary disease), severe life-limiting comorbidity such that ECMO support is unlikely to result in survival with quality of life (e.g. advanced malignancy, severe immunocompromise), and any clinical feature likely to lead to dependency on ECMO and inability to wean (e.g. profound muscle weakness, significant irreversible pulmonary fibrosis caused by either underlying disease or duration of mechanical ventilation).

Data collection

A registry was created of all adult patients (age ≥16 yr) treated by the national service between December 1, 2011 and December 31, 2017. Each participating centre submitted a data record to a tracker administered by NHS England for each patient treated under the national respiratory ECMO service. Staff at each participating centre entered contemporaneous data to the international Extracorporeal Life Support Organization (ELSO) registry. These data were extracted for the period of the national service and cross-referenced with the NHS England tracker to form the NHS ECMO registry. Demographic data collected included age, sex, weight, admission time, time of intubation, ECMO start time, ECMO discontinuation time, and primary diagnosis. Biochemical data were taken from the arterial blood gas and Fio_2 closest to the decision-to-cannulate for ECMO. Mode of ECMO was classified as veno-venous (vv-ECMO), veno-arterial (va-ECMO), veno-veno-arterial (vva-ECMO), or veno-venous extracorporeal carbon dioxide removal (vv-ECCO$_2$R). Where patients had multiple ECMO runs within the same admission, data from the initial presentation were used, except for total ECMO time and ECMO ICU length of stay, which were combined from both runs.

Diagnostic classification

Diagnosis data were recorded in the form of International Classification of Diseases codes (ICD), either the 9th or 10th edition, as available. Where multiple ICD codes were listed, one was identified as the primary diagnosis. These were classified into one of the following nine categories: asthma, aspiration pneumonitis, bacterial pneumonia, burns, postoperative, trauma, viral pneumonia, other respiratory diagnosis, other non-respiratory diagnosis, and unspecified. Patients with concomitant viral and bacterial pneumonia were classified as viral pneumonia, as were those with viral pneumonia and asthma, unless status asthmaticus was present. Patients with postoperative respiratory failure coded as a primary diagnosis were presumed to have non-traumatic aetiology unless traumatic injuries or mechanisms were coded as secondary diagnoses. In other cases, where multiple diagnoses occurred concurrently, the diagnosis identified by the reporting clinician as the 'primary diagnosis' was used for classification. The full list of the ICD codes included in each category is provided in Supplementary Table S1.

Primary outcome

The primary outcome was survival to ECMO ICU discharge.

Secondary outcomes

We assessed the following secondary outcomes:

1. Duration of ECMO
2. ECMO ICU length of stay
3. Complications, which are listed according to the definitions in the ELSO data entry form (Supplementary Table S2)

Statistical analysis

Continuous data are presented as median and interquartile range (IQR); categorical data are summarised by count and percentage. Descriptive data are presented both for the total population and split between survivors and non-survivors. In

addition, 95% confidence intervals (CIs) were calculated for comparison between groups. Data checks were performed[14] and missing data were checked using Little's test[15] and graphical inspection. Multiple imputation methods were performed for missing data analysis.

A combined and parsimonious logistic regression model-building strategy was used including clinical and statistical considerations. Variables were entered into the model if they met both clinical plausibility and statistical significance ($P<0.2$ in univariate analysis). Subsequently, possible interaction terms and non-linear terms (such as quadratic or square root) were included in the model. Variables were then excluded by using nested models by likelihood ratio test P-value (>0.05) and considering potentially confounding relationships (see Supplementary material for further details). Where significant co-linearity was identified between the initial included variables, the colinear variable with the strongest association with outcome was retained. In addition, the primary diagnosis was re-coded as a categorical variable (asthma *vs* non-asthma) based on the observed effects. Further details of the model-building strategy and multiple imputation analysis, including other models generated, are given in the Supplementary material, and the full statistical analysis plan is available on the trial registration website.

Results

Patient characteristics

A total of 1312 patients were identified on the NHS ECMO registry between December 1, 2011 and December 31, 2017 (Fig. 2). Overall, 1205 patients (median age: 44 yr [IQR, 33–55]; 676/1205 male, 55%) met the criteria for analysis, with a median Pao_2/Fio_2 ratio of 9.2 kPa (IQR, 7.5–12.3; Table 1). The median time from intubation to establishment of ECMO support was 48 h (IQR, 26–118). Viral pneumonia was the most common primary diagnosis (n=267; 22%), followed by bacterial pneumonia (n=233; 20%). The majority of patients received vv-ECMO (n=1149; 95%) and were retrieved on mobile ECMO (n=995; 80%).

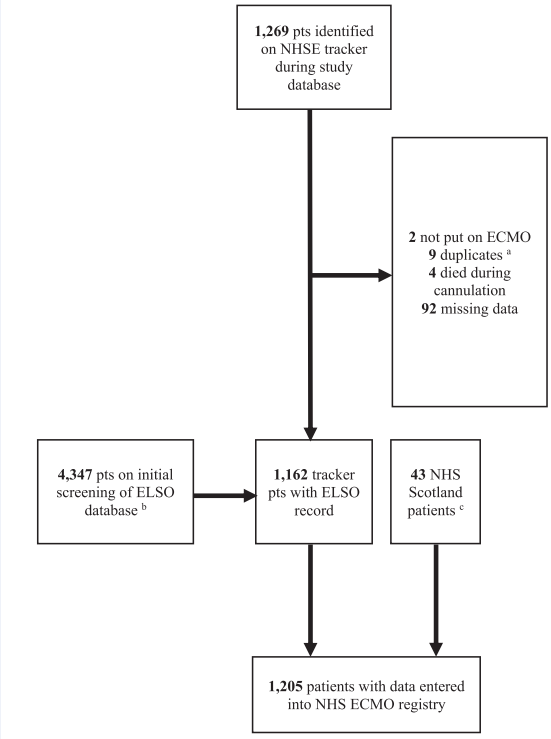

Fig 2. Flow diagram for the NHS ECMO study.

Primary outcome: survival to ECMO ICU discharge

Overall, 887/1205 (74%) patients survived to ECMO ICU discharge. One patient was transferred to another hospital on ECMO and was excluded from analysis of the primary outcome. Although activity increased year-on-year during the study period, there was no change in mortality over the same time interval (Supplementary Fig. S1).

Secondary outcomes

Duration of ECMO support/ICU stay

The median duration of ECMO support was 191 h (IQR, 111–356), with a median 16-day length of stay (IQR, 10–25) in the ECMO ICU. There was a trend towards lower survival with increasing duration of ECMO support (Fig. 3). Twenty-seven patients required multiple ECMO runs, with 23 receiving two separate periods of ECMO and four receiving three.

Complications

The most common patient-related complications were new culture-proven infection (n=184; 15%), arrhythmia (n=135; 11%), and pneumothorax (n=125, 10.4%; Table 2). The most common circuit-related complications were oxygenator failure (n=110; 9%) and cannula-related complications requiring adjustment, replacement (because of intraluminal clot, misplacement, or mechanical failure) (n=94; 8%), or both. Haemorrhagic complications occurred in <10% patients. Vascular complications occurred infrequently, with 38 patients (3%) developing limb ischaemia. Fifty patients (4%) experienced a cardiac arrest requiring cardiopulmonary resuscitation (CPR) while on ECMO, with 66% of these surviving. Renal replacement therapy (RRT), a therapy often used electively in ECMO patients for optimisation of fluid balance, was instituted in 495 patients (41%).

Multivariable analysis of factors associated with ECMO survival

In univariate analysis (Supplementary Fig. S2), survivors had a lower median age (43 *vs* 49 yr; 95% CI for median, 41–44 *vs* 47–52), and were more likely to have a primary diagnosis of asthma (12% *vs* 2%; 95% CI, 10–15% *vs* 0–3%). Patients with a

Table 1 Descriptive statistics of 1.205 patients treated with ECMO from the NHS ECMO registry. Categorical data are given as *n* (proportion); continuous data are given as median (interquartile range). Data derived from arterial blood gas samples and mechanical ventilation settings are derived from samples/settings closest to the decision-to-cannulate for ECMO. Column percentages may not sum to 100 for categorical variables because of rounding, missing data, or both. *Variables with statistically significant variation at the level of α=0.05. ECMO, extracorporeal membrane oxygenation; ICU LOS, ICU length of stay; LB, lower bound of 95% confidence interval; MV, mechanical ventilation; UB, upper bound of 95% confidence interval; va, veno-arterial; vv, veno-venous; vva, veno-veno-arterial; vv-ECCO$_2$R, veno-venous extracorporeal CO_2 removal.

	All patients	Discharged alive (*n*=887)			Died before discharge (*n*=317)		
			95% LB	95% UB		95% LB	95% UB
Age (yr)*	44 (33–55)	43 (32–52)	41	44	49 (39–60)	47	52
Weight (kg)	80 (69–98)	80 (70–100)	80	85	80 (69–90)	75	80
Male (*n*)	676 (56%)	490 (55%)	52%	59%	185 (58%)	53%	64%
Primary diagnosis							
Aspiration pneumonitis	53 (4%)	39 (4%)	3%	6%	14 (4%)	2%	7%
Asthma*	115 (10%)	109 (12%)	10%	15%	6 (2%)	0%	3%
Bacterial pneumonia	233 (20%)	175 (20%)	17%	23%	57 (18%)	14%	22%
Burns	10 (1%)	8 (1%)	0%	2%	2 (1%)	0%	2%
Postoperative	22 (2%)	16 (2%)	1%	3%	6 (2%)	0%	3%
Trauma	37 (3%)	32 (4%)	2%	5%	5 (2%)	0%	3%
Viral pneumonia	267 (22%)	183 (21%)	18%	24%	84 (27%)	22%	31%
Other respiratory	196 (16%)	138 (16%)	13%	18%	58 (18%)	14%	23%
Other non-respiratory	161 (14%)	111 (13%)	10%	15%	50 (16%)	12%	20%
Unspecified	193 (9%)	68 (8%)	6%	10%	35 (11%)	8%	14%
Intubation-to-time-on (h)	48 (26–116)	46 (21–107)	41	53	51 (22–128)	42	63
pH	7.2 (7.1–7.3)	7.2 (7.1–7.3)	7.18	7.2	7.2 (7.1–7.3)	7.17	7.21
Fio_2	1 (0.8–1)	1 (0.8–1)	1	1	1 (0.9–1)	1	1
Sao_2 (%)*	89 (83–93)	90 (84–93)	89	90	88 (80–92)	86	88
Pao_2 (kPa)*	8.5 (7.2–10.0)	8.7 (7.4–10.2)	8.5	8.8	8.0 (6.9–9.5)	7.8	8.2
$Paco_2$ (kPa)	9.0 (7.2–11.4)	8.9 (7.2–11.8)	8.6	9	9.1 (7.3–11.0)	8.7	9.4
Pao_2/Fio_2 ratio (kPa)*	9.2 (7.5–12.3)	9.4 (7.7–12.6)	9.2	9.7	8.5 (7.1–11.5)	8.1	8.8
PEEP (cm H_2O)	12 (10–15)	12 (9–15)	12	12	12 (10–15)	12	12
Ventilator rate	10 (10–14)	10 (10–14)	10	11	12 (10–14)	10	12
Initial ECMO mode							
vv	1149 (95%)	851 (96%)	95%	97%	297 (96%)	91%	96%
vv-ECCO$_2$R	18 (2%)	13 (2%)	1%	2%	5 (2%)	0%	3%
va	13 (1%)	7 (1%)	0%	1%	6 (2%)	0%	3%
vva	16 (1%)	11 (1%)	1%	2%	5 (1%)	0%	3%
Configuration change	9 (1%)	6 (1%)	0%	2%	3 (1%)	0%	1%
Repeat ECMO*	27 (2%)	13 (2%)	1%	2%	14 (4%)	2%	7%
Mobile ECMO	955 (80%)	714 (81%)	79%	84%	240 (77%)	73%	82%
Transport mode							
Air	45 (4%)	36 (4%)	3%	6%	9 (3%)	1%	5%
Road	1040 (90%)	769 (90%)	5%	8%	270 (89%)	5%	11%
Internal	77 (7%)	54 (6%)	87%	92%	23 (8%)	86%	93%
Hours of ECMO therapy	191 (111–356)	190 (119–324)	181	204	194 (68–497)	142	250
Hours of MV	49 (21–119)	47.2 (21.8–109.5)	42	54	52 (22–136)	43	65
ECMO ICU LOS (d)	16 (10–26)	16 (10–25)	15	17	17 (8–34)	12	21

primary diagnosis of asthma had a survival rate to ECMO ICU discharge of 95% (95% CI, 91–99%) compared with 71% of those with other diagnoses (95% CI, 69–74%). Severity of hypoxaemia at decision-to-cannulate was associated with a lower probability of survival: survivors had a median Sao_2 of 90 *vs* 88 (95% CI, 89–90 *vs* 86–88), a median Pao_2 of 8.7 *vs* 8.0 kPa (95% CI, 8.5–8.8 *vs* 7.8–8.2), and a median Pao_2/Fio_2 ratio of 9.4 *vs* 8.5 kPa (95% CI, 9.2–9.7 *vs* 8.1–8.8). Our multiple logistic regression model used eight variables meeting the pre-specified criteria (Table 3). Factors associated with survival included younger age (P<0.001), higher weight (P<0.001), primary diagnosis of asthma (P<0.001), and higher Sao_2 at the time for decision-to-cannulate (P=0.008). Further modelling was carried out including the use of imputed data to allow for missing-at-random data. These models did not differ from the complete case analysis (Supplementary Table S3).

Discussion

This study is the first report of a nationally organised ECMO service for undifferentiated acute respiratory failure in adults. The survival rate (74%) is the highest reported in contemporary cohorts of adult respiratory ECMO[7,16–18] and significantly higher than the 60% survival reported by the January 2020 ELSO international summary for adults treated for respiratory failure.[19] We speculate that this is multifactorial, but may be accounted for by the use of stringent network-wide patient selection criteria. The findings may also reflect a volume–outcome relationship related to centralisation of ECMO provision in a small number of specialist centres.[20] Younger patient age and higher patient weight were associated with better outcome. Although these analyses are exploratory, our findings are similar to those of the PRESERVE study, which observed that younger age and a higher BMI conferred a slight survival advantage.[18]

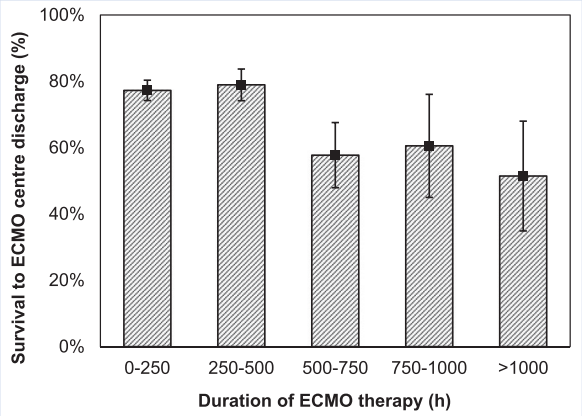

Fig 3. Observed survival by ECMO hours received (n=1167) with 95% confidence intervals.

The patients included in the study required ECMO owing to a broad range of aetiologies in contrast to much of the current literature, which derives its data entirely or partially from patients treated during the 2009 H1N1 influenza pandemic.[3–5,18] In this study, patients requiring ECMO because of asthma had a survival to discharge from the ICU at the ECMO centre of 95%. Although there are no reported RCTs of ECMO specifically in asthmatic patients, the mortality of near-fatal asthma treated with conventional management has been estimated at nearly 30%.[21] The last UK National Review of Asthma Deaths found that 59 patients died in 1 yr from asthma in UK hospitals.[22] The survival rate of 95% in our study should prompt clinicians treating asthmatic patients with refractory respiratory failure to make early contact with ECMO centres, as this therapy is likely to be life-saving in eligible patients.

Table 2 Frequency of complications observed in 1205 patients treated with ECMO for severe respiratory failure. CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation.

Complication	Frequency (n)	%
Patient complications		
Hyperbilirubinaemia	197	16.3
Culture-proven infection	184	15.3
Arrhythmia	135	11.2
Pneumothorax	125	10.4
Surgical-site bleeding	88	7.3
Intracerebral haemorrhage	81	6.7
Gastrointestinal haemorrhage	77	6.4
Cardiac arrest requiring CPR	50	4.1
Pulmonary haemorrhage	50	4.1
Limb ischaemia requiring reperfusion cannula	38	3.2
Cerebral infarction	29	2.4
Seizures	25	2.1
Brain death	20	1.7
Haemorrhagic tamponade	17	1.4
Cardiac tamponade	2	0.2
Circuit complications		
Oxygenator failure	110	9.1
Cannula-related complication	94	7.8
Pump failure	8	0.7
Air embolism	7	0.6
Haemofilter clot	5	0.4
Other tubing rupture	1	0.1
Circuit change	1	0.1
Heat exchanger malfunction	1	0.1

Table 3 Multivariate regression model of factors associated with survival to ECMO ICU discharge in 858 patients treated by the NHS ECMO service. *Age:weight is the interaction term of age and weight. Variables entered into modelling included age, weight, Fio_2, Pao_2, Pao_2/Fio_2 ratio, Sao_2, PEEP, and primary diagnostic category. Goodness-of-fit likelihood ratio P<0.001, c-statistic=0.684, pseudo r^2=0.115.

	Odds ratio	95% confidence interval	P-value
Age	0.966	0.953–0.977	<0.001
Weight	1.014	1.006–1.021	<0.001
Asthma	4.026	1.702–9.526	0.001
Sao_2	1.016	1.002–1.030	0.020
Age:weight*	0.999	0.999–0.999	0.021

Prior studies have demonstrated comparatively high survival in patients requiring ECMO because of viral pneumonia,[3–5,17,18] but this was not seen in our cohort. This may be attributable to the particularly favourable survival profile of the 2009 H1N1 influenza virus, or because we did not separate patients admitted with influenza from other causes of viral pneumonia. It is also possible that the favourable outcomes of influenza patients supported with ECMO during the 2009 pandemic led clinicians to support older and more comorbid patients who present with influenza. Notably, the average age of patients in the UK, Australia/New Zealand, and Italian H1N1 ECMO cohort studies were 36 (mean), 39, and 34 yr (median), respectively,[3–5] compared with a median of 44 in our study as a whole, and 46 for patients with viral pneumonia.

We found a strong association between more severe hypoxaemia at the time of decision to cannulate and mortality, although the interpretation of this finding requires care. In the EOLIA trial, the mean Pao_2/Fio_2 ratio at randomisation was 9.7 kPa, compared with a median of 9.2 kPa at decision-to-cannulate in our cohort; the subgroup of EOLIA patients in the control arm who crossed over to ECMO had a median Pao_2/Fio_2 ratio of 6.8 kPa and a mortality of 57%. The nature of our observational data means, however, that we cannot know how many of these patients may have survived without ECMO. The optimal 'threshold' for institution of ECMO in an individual patient may also be affected by multiple variables not assessed in this study, including the response to other therapies such as prone positioning, neuromuscular block, or the speed of developing refractory hypoxaemia.

Infectious complications are common in patients receiving ECMO[1,4,12,17,18,23] but have not been shown to adversely impact mortality.[23] Haemorrhagic and neurological complications with long-term sequelae were observed, and these risks of ECMO should be made clear to referring clinicians and relatives when admission decisions are being discussed. Although cardiac arrest was relatively common during ECMO treatment (4%), the majority of patients (50/75; 66%) survived. The reasons underlying the two peaks characterising the duration of ECMO in non-survivors are unclear. The first early peak may

comprise the sickest patients who die within the first day of ECMO treatment, whereas the second peak represents the higher mortality of patients who require prolonged ECMO (>500 h/21 days). Although relatively few patients required ECMO for >1000 h (n=35), the survival of this group remained at approximately 50%. This suggests a nuanced approach is required for this complex group of patients, which, although small, will represent a disproportionate resource cost.

Our study was limited by the absence of routine data collection on outcomes in patients not accepted for ECMO. The aim of the national UK ECMO service is to ensure that all eligible patients who are appropriate for ECMO support receive it,[6] but there is no corresponding dataset for UK patients with similarly severe respiratory failure who do not receive ECMO. Another study reported 17% survival in patients declined for ECMO because of a perceived lack of benefit but 70% survival in patients who did not receive ECMO because they did not meet criteria for ECMO at the time of referral.[24] Another limitation is the choice of survival to ECMO ICU discharge as the primary outcome; in keeping with most cohort studies derived from data submitted to ELSO,[12,17,19] we were unable to assess long-term survival, quality of life, or functional outcomes. At the time of study conception, there were insufficient resources to fund formalised long-term follow-up of these patients, or to allow suitably anonymised data linkage to other data sources. Similarly, we lacked data on pre-ECMO treatment, such as tidal volume, driving pressure pre-ECMO, or both, or the use of prone positioning. The c-statistic and pseudo-r^2 values (0.68 and 0.12, respectively) in our multivariable analysis suggest the potential presence of significant unmeasured confounding. We could not determine the time, or cause, of death including the duration between cessation of ECMO support and death in patients who were successfully weaned from ECMO and died subsequently. We therefore could not perform Kaplan–Meier survival analysis or competitive risk analysis.

Conclusions

This study reports short-term outcomes from a nationally organised network providing ECMO in respiratory failure across a wide range of aetiologies. In 6 yr, no patient was denied ECMO because of lack of bed capacity. Younger patient age, higher patient weight, presenting diagnosis of asthma and less severe hypoxaemia at the time of decision-to-cannulate were associated with survival to ECMO ICU discharge in this cohort, but these factors alone are unlikely to account for all of the observed variability in patient outcomes.

Authors' contributions

The study was conceived by the NHS ECMO network from its conception.
Co-ordination of the study: AW
Registry creation: AW
Data cleaning and analysis: AW
Writing of statistical analysis plan: AW, YDC, SV
Expert input to the statistical analysis plan: YDC, SV
Statistical analysis: YDC, SV
Overall supervision of the entire study: AV
Collection and management of data: AV
Expert guidance on study design, data analysis, and interpretation: AV
Expert input on data cleaning and collection: JF
Oversight from NHS England: NS
Facilitation of access to the existing contract tracker data under the data sharing agreement: NS
Identification of the number of patients treated within the service: NS
ECMO directors of the six participating centres: JB, LC, CH, SL, IS, AV
Steering group for the study: JB, LC, CH, SL, IS, AV
Approval of all stages from data collection, study design, statistical analysis, and reporting on behalf of the NHS ECMO investigators: JB, LC, CH, SL, IS, AV
Writing of the first draft of the manuscript: AW
All authors have read, contributed to and approved the final manuscript.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.05.065.

References

1. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009; **374**: 1351–63
2. Peek GJ, Elbourne D, Mugford M, et al. Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR). *Health Technol Assess* 2010; **14**: 1–46
3. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA* 2011; **306**: 1659–68
4. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, Bailey M, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA* 2009; **302**: 1888–95
5. Patroniti N, Zangrillo A, Pappalardo F, et al. The Italian ECMO network experience during the 2009 influenza A(H1N1) pandemic: preparation for severe respiratory

emergency outbreaks. *Intensive Care Med* 2011; **37**: 1447–57
6. Group NESCC. *Adult ECMO service specification*. Available from: https://www.england.nhs.uk/wp-content/uploads/2019/02/Adult-ECMO-Service-Specification.pdf. [Accessed 13 May 2019]
7. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; **378**: 1965–75
8. Goligher EC, Tomlinson G, Hajage D, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc Bayesian analysis of a randomized clinical trial. *JAMA* 2018; **320**: 2251–9
9. Abrams D, Ferguson ND, Brochard L, et al. ECMO for ARDS: from salvage to standard of care? *Lancet Respir Med* 2019; **7**: 108–10
10. Combes A, Brodie D, Bartlett R, et al. Position paper for the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in adult patients. *Am J Respir Crit Care Med* 2014; **190**: 488–96
11. Gattinoni L, Vasques F, Quintel M. Use of ECMO in ARDS: does the EOLIA trial really help? *Crit Care BioMed Cent* 2018; **22**: 171
12. Elm von E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–7
13. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; **138**: 720–3
14. Kirkwood BR, Sterne JAC. *Essential medical statistics*. Malden, MA: John Wiley & Sons; 2010
15. Little RJA. A test of missing completely at random for multivariate data with missing values. *J Am Stat Assoc* 2012; **83**: 1198–202
16. Rozencwajg S, Pilcher D, Combes A, Schmidt M. Outcomes and survival prediction models for severe adult acute respiratory distress syndrome treated with extracorporeal membrane oxygenation. *Crit Care BioMed Cent* 2016; **20**: 392
17. 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**: 1374–82
18. Schmidt M, Zogheib E, Rozé H, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *Intensive Care Med* 2013; **39**: 1704–13
19. Extracorporeal Life Support Association. *International summary* 2020. Available from: https://www.elso.org/Registry/Statistics/InternationalSummary.aspx. [Accessed 7 March 2020]
20. Barbaro R, Odetola FO, Kidwell KM, et al. Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality. Analysis of the Extracorporeal Life Support Organisation Registry. *Am J Resp Crit Care Med* 2015; **191**: 894–901
21. Yeo HJ, Kim D, Jeon D, Kim YS, Rycus P, Cho WH. Extracorporeal membrane oxygenation for life-threatening asthma refractory to mechanical ventilation: analysis of the Extracorporeal Life Support Organization registry. *Crit Care BioMed Cent* 2017; **21**: 297
22. Levy M, Andrews R, Buckingham R, et al. *Why asthma still kills. The national Review of asthma deaths (NRAD) confidential enquiry report*. Royal College of Physicians; 2014 May. Available from: www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills
23. Aubron C, Cheng AC, Pilcher D, et al. Infectious acquired by adults who receive extracorporeal membrane oxygenation: risk factors and outcome. *Infect Control Hosp Epidemiol* 2013; **34**: 24–30
24. Gillon SA, Rowland K, Shankar-Hari M, et al. Acceptance and transfer to a regional severe respiratory failure and veno-venous extracorporeal membrane oxygenation (ECMO) service: predictors and outcomes. *Anaesthesia* 2018; **73**: 177–86

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