Observational Cohort Study of a National Extracorporeal Membrane Oxygenation Service for Adults With Respiratory Failure: the NHS ECMO Study

NCT: NCT03979222

Statistical Analysis Plan

Authors: Yi-Da Chiu, Sofia S. Villar, Alex Warren, Alain Vuylsteke
Approved by NHS ECMO steering group.

SAP version: 25/02/2019

The aims of the project are:

- To describe the cohort of patients supported by the NHS England-commissioned Respiratory ECMO service from inception (Dec 2011) to now;
- To report the outcomes (morbidity and mortality) of patients supported by the NHS England-commissioned Respiratory ECMO service from inception (Dec 2011) to June 2018;
- To identify factors predictive of duration of stay, complications (to be specified) and survival.

To achieve this, we intend to perform a longitudinal observational cohort study of this patient group.

1. Identification of cohort

The national severe acute respiratory failure was commissioned in 2011 to provide extracorporeal membrane oxygenation (ECMO) for adult patients with severe acute respiratory failure. ECMO can be delivered in both VV (venovenous - supporting lungs only) and VA (venoarterial - supporting heart and lungs) modalities.

The eligibility criteria for this service is outlined in a commissioning document published in 2011.

Patients have been identified which meet the following inclusion criteria, as per the 2011 commissioning document:

- Admitted under the national commissioned service
- Age ≥16 years
- Admitted between 1st December 2011 and 31st December 2017.

For patients who have multiple runs during the same hospital admission, only the first run will be included in analysis. Those who have configuration changes during the same ECMO run will be counted as a single run for the purposes of analysis.

Patient data is contained in two databases – the Extracorporeal Life Support Organisation (ELSO) database, containing data from the ELSO runsheets of each patient having received ECMO, and the 'tracker' database kept by Public Health England to monitor the commissioned service.

The tracker identifies 1,317 patients who meet the above criteria, but only has basic data for these (date, centre and outcome). All patients with corresponding ELSO records will be entered into formal analysis.

2. Data checks

Data checks will follow the recommendations from Kirkwood and Sterne [1]. Outliers in continuous variables will be detected using ranges and plotting distributions within each treatment. Categorical variables will be tabulated and unexpected distributions further checked. Consistency checks between two or more variables will also be performed, e.g. plotting weight against age.

3. Descriptive statistics

The broad guidelines of descriptive statistics are as follows: (1) continuous data will be summarised with means and standard deviations if normally distributed, or with median and inter-quartile range if asymmetric or otherwise non-normal; (2) categorical data will be summarised by counts and percentage per level within factors; (3) missing count and proportion will also be reported. A table will be prepared with descriptive variables between survivors and non-survivors; 95% confidence intervals will be given.

The full list and data type of variables can be found in the appendix. Those which have been identified as having large numbers of missing data, unlikely to be suitable for inclusion in analysis, have been highlighted in yellow. A summary will be provided for these variables.

All statistical analysis and methodology will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [2].

3.1. Basic descriptive statistics on the patient cohort

- Number of patients
    - Both in total and per centre
- Number per calendar year (2012-2017, as full data allow)
    - Both in total and per centre
- Age
- Sex
- Weight

3.2. Clinical features of patients pre-ECMO

- Primary diagnosis
- Diagnostic category (bacterial pneumonia, viral pneumonia, aspiration pneumonitis, asthma, trauma, burns, other acute respiratory diagnosis, other non-respiratory diagnosis, unspecified)
- Pre-ECMO cardiac arrest (%)
- Time from admission to intubation
- Time from intubation to ECMO initiation

- Biochemical variables
    - pH
    - PaO2
    - PaCO2
    - FiO2
    - PaO2/FiO2 ratio
    - SaO

- Ventilator settings
    - Ventilation mode
    - PEEP
    - Ventilator rat

3.3. Features of ECMO treatment itself

- Which ECMO centre (can use numbers to anonymise)
- Initial ECMO modality (e.g. VV, VA, VV-CO2R, other)
- Transport on ECMO (%)
- Duration of ECMO therapy

- Repeat ECMO (several runs in same patient)
- Change of configuration during ECMO

3.4. Patient outcome data

The primary outcome of interest is the % of patients discharged alive from the ECMO ICU.

Secondary outcomes include:
- duration of ECMO therapy
- duration of mechanical ventilation
- ICU length of stay
- discharge destination

3.5. Complications
- Mechanical
    - Oxygenator failure
    - Pump failure
    - Raceway rupture
    - Other tubing rupture
    - Cannula problems
    - Circuit change
    - Heat exchanger malfunction
    - Thrombosis/clot
    - Clot haemofilter
    - Air in circuit
- Haemorrhage
    - GI haemorrhage
    - Peripheral cannula site bleeding
    - Mediastinal cannulation site bleeding
    - Surgical site bleeding
- Neurological
    - Brain death
    - Seizures
        - Clinically determined
        - EEG confirmed
    - Cerebral diffuse ischaemia
    - Cerebral infarction
    - Intracerebral haemorrahge
    - Neurosurgical intervention
- Renal
    - Renal replacement therapy required
- Cardiovascular
    - Cardiac arrest requiring CPR
    - Arrhythmia
    - Cardiac tamponade
    - Haemorrhagic tamponade
- Pulmonary
    - Pneumothorax
    - Pulmonary Haemorrhage
- Metabolic
    - Hyperbilirubinaemia
    - Moderate haemolysis
    - Severe haemolysis
- Limb-related
    - Fasciotomy
    - Amputation
    - Limb ischaemia requiring reperfusion cannula
- Infectious (culture proven)

Complication data will be summarised for the entire cohort, rather than entered into regression analysis.

4. Regression analysis

It would be useful to perform a regression analysis on the variables listed in 3.1 to 3.3 above, in order to identify factors independently associated with the primary outcome (mortality) and the secondary outcome (length of stay, complication).

The general modelling building strategies are: (1) clinical knowledge will decide which variables are important as potential predictors of outcomes and which should be accounted for in the models as potential confounders and/or effect modifiers (interactions); (2) in addition to clinical knowledge, univariate associations will be investigated between the primary outcome and exposure predictors. This will show which predictors are *a priori* associated with outcomes, and how those effects change when accounting for confounders and/or interactions; (3) in a multiple regression context, collinearity or high correlations between predictors can lead to unstable regression coefficients and extremely large standard errors. One way of avoiding collinearity is to select among a group of highly correlated predictors, the predictor most strongly associated with the response.

In addition, during modelling development (in a multiple regression context) suitable transformations (such as log, box-cox transformation) will be used if there is evidence of poor fit or influential measurements. Model selection will be achieved via likelihood ratio tests (LRT) and declaring statistical differences at p-values<0.05. Non-nested models will be compared using Akaike's information criterion (AIC), where a decrease in ≥10 units will indicate important statistical differences between models ([3]).

The specific regression analysis depends on the type of outcome variables. If the outcome is mortality or complication, logistic regression analysis will be performed; if the outcome is length of stay, Poisson regression or negative binomial regression will be used.

Predefined subgroup analysis will be undertaken on the following variables of clinical interest: age, diagnostic category, BMI, calendar year of ECMO run i.e. trend in outcome over time, and centre. It is important to stress that the centre comparative analysis is used here as a proxy for the underlying population, and may not be included in any data for publication.

5. Missing data analysis

All essential variables are expected to be complete or at least low missing percentage (less than 8%) before starting analysis. Variables with >25% missing data may not be used in modelling but will be summarised and reported.

Missing data patterns will be described, e.g. monotonic, intermittent, etc. Missing mechanism will be also identified as missing complete at random (MCAR), or missing at random (MAR), or missing not at random (MNAR) by using Little's test [4] and graphical inspection [5].

Sensitivity analysis will be performed based on complete case analysis and imputation data analysis. The latter will work on the imputed data using simple imputation or multiple imputation strategies depending on the identified missing mechanism. We will assess how much results change between the results of complete data and the ones using imputation data analysis with different imputation strategies.

6.. Summary of Changes to the Protocol
Additional or supplementary analyses not envisaged in this SAP or in the original protocol may be possible. This SAP will be updated and version-tracked to incorporate any new and potentially useful analysis.

Reference

[1] Kirkwood BR, Sterne J (2003) Essential Medical Statistics. Blackwell publishing.

[2] Vandenbroucke JP, Elm EV, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. Ann Intern Med. ;147:W–163–W–194. doi: 10.7326/0003-4819-147-8-200710160-00010-w1

[3] Burnham KP, Anderson DR (2002) Model selection and multi-model inference: a practical information-theoretic approach. Springer, New York.

[4] Taylor P, Little RJA. A Test of Missing Completely at Random for Multivariate Data with Missing Values A Test of Missing Completely at Random for Multivariate Data With Missing Values. *J Am Stat Assoc*. 2012;83(December 2014):37-41.

[5] Templ M, Alfons A, Kowarik A, Prantner B. VIM: Visualization and Imputation of Missing Values, 2011a. URL http://CRAN.R-project.org/package=VIM. R package version 3.0.0.

[6] Combes A, Hajage D, Capellier G, Demoule A, Lovoue S, Guervilly C, Silva DD, Zafrani L, Tirot P, Veber B, Maury E, Levy B, Cohen Y, Richard C, Kalfon P, Bouadma L, Mehdaoui H, Beduneau G, Lebreton G, Brochard L, Ferguson ND, Fan E, Slutsky AS, Brodie D, Mercat A. (2018) Extracorporeal membrance oxygenation for severe acute respiratory distress syndrome. The New England Journal of Medicine. Vol. 378, No. 21.

[7] Williamson E. And Forbes A. (2014) Introduction to propensity scores. Respirology. 19(5):625-35. doi: 10.1111/resp.12312.

[8] Austin PC (2009) Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in Medicine; 28(25):3083-107. doi: 10.1002/sim.3697.

[9] Austin PC (2011) An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behavioral Research 46:399-424

[10] Leyrat C, Seaman SR, White IR, Douglas I, Smeeth L, Kim J, Resche-Rigon M, Carpenter JR and Williamson EJ. (2017) Propensity score analysis with partially observed covariates: How should multiple imputation be used? Statistical Methods in Medical Research. 962280217713032. https://doi.org/10.1177/0962280217713032

[11] Mitra R and Reiter JP (2012). A comparison of two methods of estimating propensity scores after multiple imputation. Statistical Methods in Medical Research; 0: 1–17.

Category	Variable	Data type
Demographics and general information	Center ID	CHARCTER / CATEGORICAL
	Patient ID	CHARCTER / CATEGORICAL
	Calendar year	CHARCTER / CATEGORICAL / ORDINAL
	Age	CONTINUOUS
	Sex	CATEGORICAL
	Weight	CONTINUOUS
Clinical feature	Primary diagnosis	CATEGORICAL
	Cardiac arrest	CATEGORICAL
	Time from admission to intubation	CONTINUOUS
	Time from intubation to ECMO initiation	CONTINUOUS
	pH	CONTINUOUS
	PaO2	CONTINUOUS
	PaCO2	CONTINUOUS
	FiO2	CONTINUOUS
	PaO2/FiO2 ratio	CONTINUOUS

s of patient before ECMO	SaO2	CONTINUOUS
	MAP	CONTINUOUS
	Cardiac index (CI)	CONTINUOUS
	Ventilation mode	CATEGORICAL
	PEEP	CONTINUOUS
	Ventilator rate	CONTINUOUS
	ΔP	CONTINUOUS
	Use of high-flow oscillatory ventilation (HFOV)	CATEGORICAL
Features of ECMO treatment	ECMO centre	CHARCTER / CATEGORICAL
	Site of cannulation	CATEGORICAL
	Initial ECMO modality	CATEGORICAL
	Type of cannula	CATEGORICAL
	Location of ECMO initiation	CATEGORICAL
	Transport on ECMO	CATEGORICAL
	Duration of ECMO therapy	CONTINUOUS
	Repeat ECMO	INTEGER
	Change of configuration during ECMO	CATEGORICAL

Patient outco	Discharge alive	CATEGORICAL
	Weaned off ECMO	CATEGORICAL
	Died on ECMO	CATEGORICAL
	Transplantation on ECMO	CATEGORICAL
	Duration of mechanical ventilation	CONTINUOUS
	Discharge destination	CHARTER / CATEGORICAL
	ICU length of stay	INTEGER

me		
Complication	Oxygenator failure	CATEGORICAL
	Pump failure	CATEGORICAL
	Raceway rupture	CATEGORICAL
	Other tubing rupture	CATEGORICAL
	Cannula problems	CATEGORICAL
	Circuit change	CATEGORICAL
	Heat exchanger malfunction	CATEGORICAL
	Thrombosis/clot	CATEGORICAL
	Clot haemofilter	CATEGORICAL
	Air in circuit	CATEGORICAL
	GI haemorrhage	CATEGORICAL
	Peripheral cannula site bleeding	CATEGORICAL
	Mediastinal cannulation site bleeding	CATEGORICAL
	Surgical site bleeding	CATEGORICAL
	Brain death	CATEGORICAL
	Seizures	CATEGORICAL
	Cerebral diffuse ischaemia	CATEGORICAL
	Cerebral infarction	CATEGORICAL
	Intracerebral haemorrahge	CATEGORICAL
	Intraventricular harmorrhage	CATEGORICAL
	Neurosurgical intervention	CATEGORICAL
	New AKI	CATEGORICAL
	Renal replacement therapy required	CATEGORICAL
	Cardiac arrest requiring CPR	CATEGORICAL
	Arrhythmia	CATEGORICAL
	Cardiac tamponade	CATEGORICAL
	Haemorrhagic tamponade	CATEGORICAL
	Pneumothorax	CATEGORICAL
	Pulmonary Haemorrhage	CATEGORICAL
	Hyperbilirubinaemia	CATEGORICAL
	Moderate haemolysis	CATEGORICAL
	Severe haemolysis	CATEGORICAL
	Fasciotomy	CATEGORICAL

	Amputation	CATEGORICAL
	Limb ischaemia requiring reperfusion cannula	CATEGORICAL
	Infectious	CATEGORICAL