

Supplementary material for the paper: Liberal or restrictive transfusion for veno-arterial Extracorporeal Membrane Oxygenation patients: a target trial emulation using the OBLEX study data, Thao et. al, 2025

Definition of confounders

Variable	Type	Definition	Confounder type
Age	Continuous	Age (years) at hospital admission	Time-fixed
Gender	Binary	Gender (male/female) at hospital admission	Time-fixed
Diagnosis group	Categorical	Diagnosis at hospital admission. Underlying conditions include: • Acute myocardial infarction (AMI) • Chronic cardiomyopathy • Pulmonary embolism • Myocarditis • Other acute cardiomyopathy such as: Acute decompensated heart failure not covered above, septic shock with myocardial depression, primary arrhythmia (Channelopathy) and toxic	Time-fixed
Renal replacement prior to ECMO	Binary	Renal replacement 24 hour prior to ECMO	Time-fixed
Extracorporeal cardiopulmonary resuscitation (ECPR)	Binary	Extracorporeal cardiopulmonary resuscitation 24 hour prior to ECMO	Time-fixed
Surgery	Binary	Any surgery prior to ECMO	Time-fixed
Renal replacement during ECMO	Binary	Renal replacement during ECMO	Time-varying
Severe bleeding	Binary	Severe bleeding during ECMO. Severe bleeding is defined as Bleeding academic research consortium (BARC) score >3	Time-varying
Any mechanical support	Binary	Mechanical support during ECMO. Types of mechanical support includes:	Time-varying

		• intra-aortic balloon pump (IABP) • right ventricular assist device (RVAD), • left ventricular assist device (LVAD), • total artificial heart, • impella device, • tandem heart, and • other mechanical circulatory support	
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Calculation of weights(1)

For individual i , let $L_{b,i}$ denote the set of time-fixed confounders, and $L_{k,i}$ denote the set of time-varying confounders recorded at time k with $\bar{L}_{k,i}$ denote the history of time-varying confounders prior to time k . From the assumed DAG (Figure S1), we have:

$$L_{b,i} = \{age_i, gender_i, diagnosis\ group_i, renal\ replacement\ prior\ to\ ECMO_i, ECPR_i, Surgery_i\}$$

$$L_{k,i} = \{severe\ bleeding_{k,i}, renal\ replacement_{k,i}, mechanical\ support_{k,i}\}$$

Denote $\bar{A}_{(k,j-1)} = \{A_k, A_{k+1}, \dots, A_{j-1}\}$ the treatment status from time k to time $j - 1$.

For individuals in the trial starting at time k , but do not initiate treatment at that time, the stabilized inverse probability of artificial-censoring weights (IPACW) at time $t - k$ from the start of the trial is:

$$SW_{i,k}^0(t - k) = \prod_{j=k+1}^{k+t} \frac{\Pr(A_j = 0 | \bar{L}_{k,i}, L_{b,i}, \bar{A}_{(k,j-1),i} = 0, T \geq k)}{\Pr(A_j = 0 | \bar{L}_{j,i}, \bar{A}_{(k,j-1),i} = 0, T \geq k)}$$

For individuals in the trial starting at time k , and initiate treatment at that time, the stabilized weights at time $t - k$ from the start of the trial is:

$$SW_{i,k}^1(t - k) = \prod_{j=k+1}^{k+t} \frac{\Pr(A_j = 1 | \bar{L}_{k,i}, L_{b,i}, \bar{A}_{k-1,i} = 0, \bar{A}_{(k,j-1),i} = 1, T \geq k)}{\Pr(A_j = 1 | \bar{L}_{j,i}, \bar{A}_{k-1,i} = 0, \bar{A}_{(k,j-1),i} = 1, T \geq k)}$$

We used logistic regression models to estimate the denominator and numerator of the weights, fitted to the combined data across 7 trials.

Reference:

1. Keogh RH, Gran JM, Seaman SR, Davies G, Vansteelandt S. Causal inference in survival analysis using longitudinal observational data: Sequential trials and marginal structural models. Stat Med. 2023 Jun 15;42(13):2191–225.

Supplementary tables and figures

Table S1: Number of patients received transfusion over 7 days of ECMO

Characteristic	Day 1, N =	Day 2, N =	Day 3, N =	Day 4, N =	Day 5, N =	Day 6, N =	Day 7, N =
	534 ^I	495 ^I	475 ^I	417 ^I	342 ^I	267 ^I	215 ^I
Number of patients with at least 1 transfusion	291 (54%)	148 (30%)	197 (41%)	166 (40%)	129 (38%)	107 (40%)	90 (42%)
Number of patients with							
1 transfusion episode	115 (22%)	89 (18%)	136 (29%)	118 (28%)	96 (28%)	77 (29%)	61 (28%)
2 transfusion episodes	74 (14%)	33 (6.7%)	44 (9.3%)	34 (8.2%)	25 (7.4%)	19 (7.1%)	20 (9.3%)
3+ transfusion episodes	105 (20%)	27 (5.5%)	19 (4.0%)	15 (3.6%)	9 (2.6%)	11 (4.1%)	9 (4.2%)

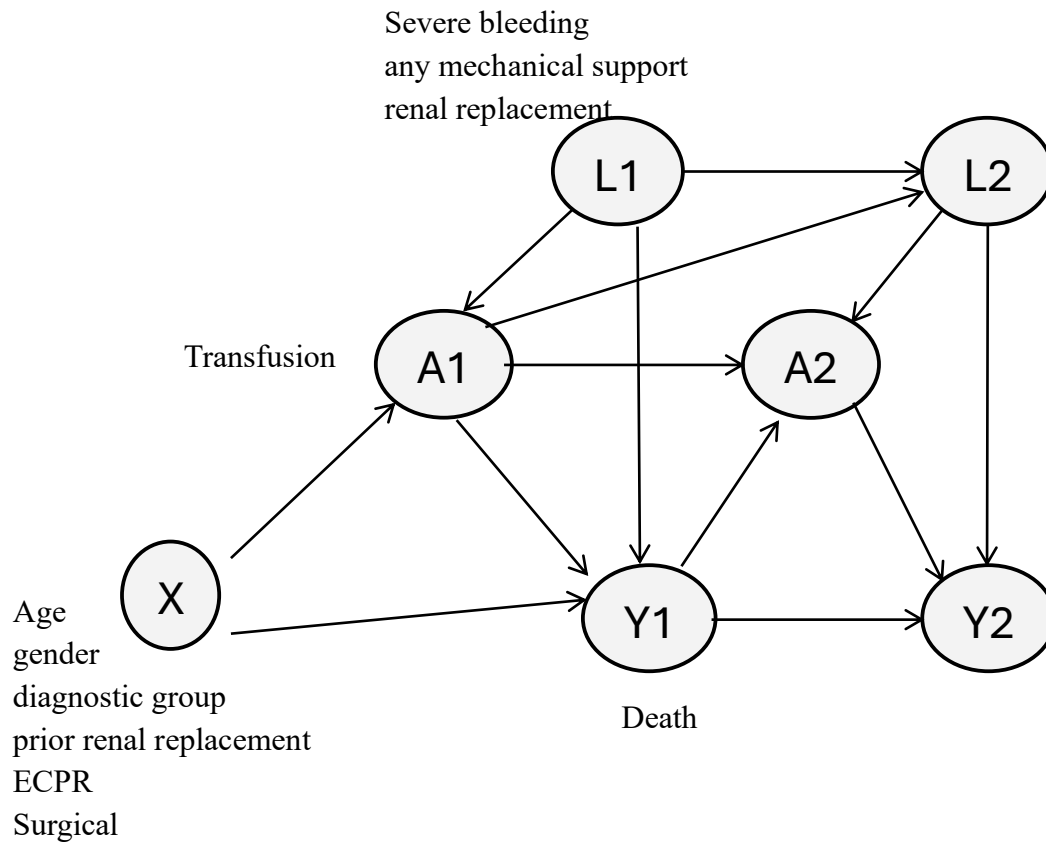
^I n (%)

Table S2: Number of events by treatment arm in the 7 sequential trials

Characteristic	N	Overall^I	Restrictive^I	Liberal^I	Intermediate^I	No transfusions^I
Trial 1	534	117/534 (22%)	16/48 (33%)	10/51 (20%)	69/192 (36%)	22/243 (9.1%)
Trial 2	233	38/233 (16%)	2/9 (22%)	1/8 (13%)	22/52 (42%)	13/164 (7.9%)
Trial 3	160	32/160 (20%)	2/8 (25%)	2/7 (29%)	15/46 (33%)	13/99 (13%)
Trial 4	89	13/89 (15%)	0/3 (0%)	1/3 (33%)	3/15 (20%)	9/68 (13%)
Trial 5	54	8/54 (15%)	0/2 (0%)	0/2 (0%)	2/10 (20%)	6/40 (15%)
Trial 6	26	6/26 (23%)	0/0	0/0	3/10 (30%)	3/16 (19%)
Trial 7	13	3/13 (23%)	0/0	0/0	2/4 (50%)	1/9 (11%)
Total	1,109	217/1,109 (20%)	20/70 (29%)	14/71 (20%)	116/329 (35%)	67/639 (10%)

^I n/N (%)

Figure S1: Directed acyclic graph (DAG) depicting the assumed confounding path of treatment-outcome association. A simplified version for two time points.



X: baseline confounders

{L1, L2}: time varying confounder at time 1 and 2, respectively,

{A1, A2}: Transfusion strategy at time 1 and 2, respectively

{Y1, Y2}: Outcome (in hospital death) at 1 and 2, respectively

Figure S2: Study design: illustration of 3 sequential trials

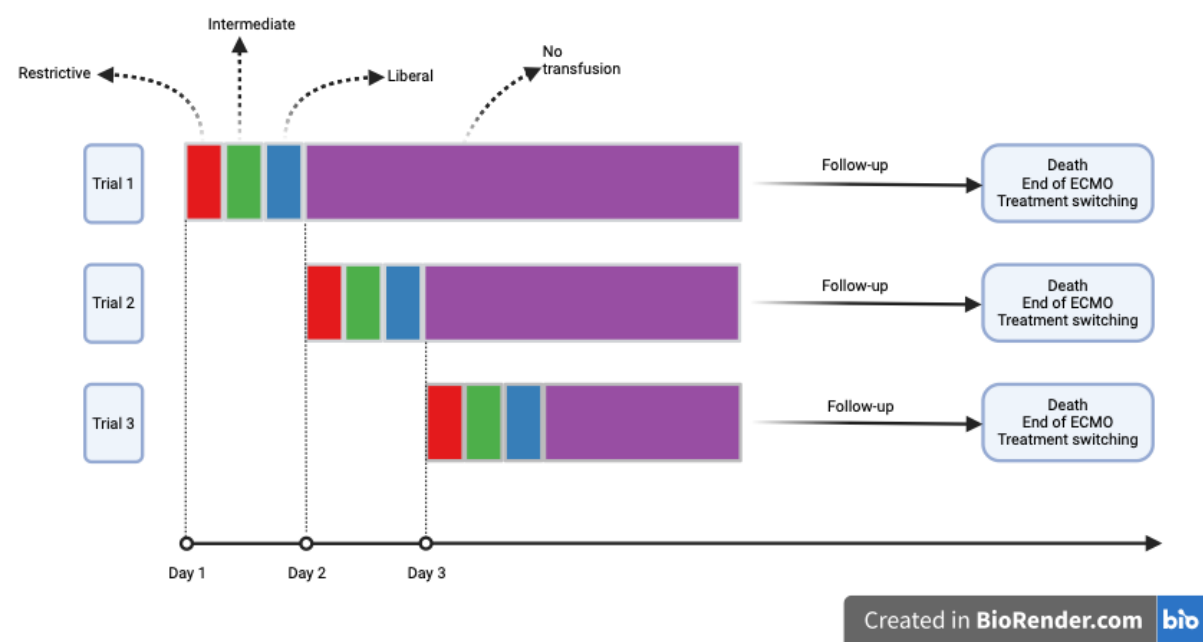


Figure S3: Transfusion pattern in the 7 sequential trials

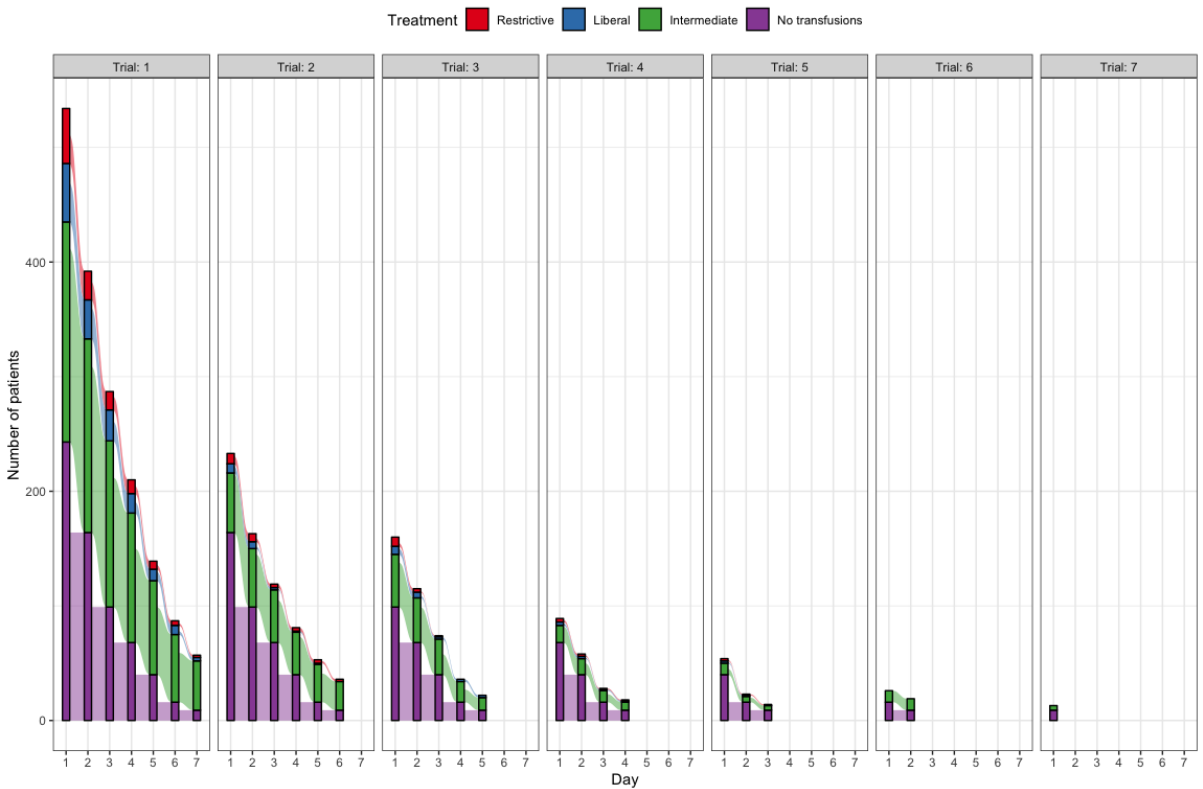


Figure S4: Distribution of the stabilised inverse probability weights for artificial censoring. A) original weights; B) truncated weights at 95th percentiles

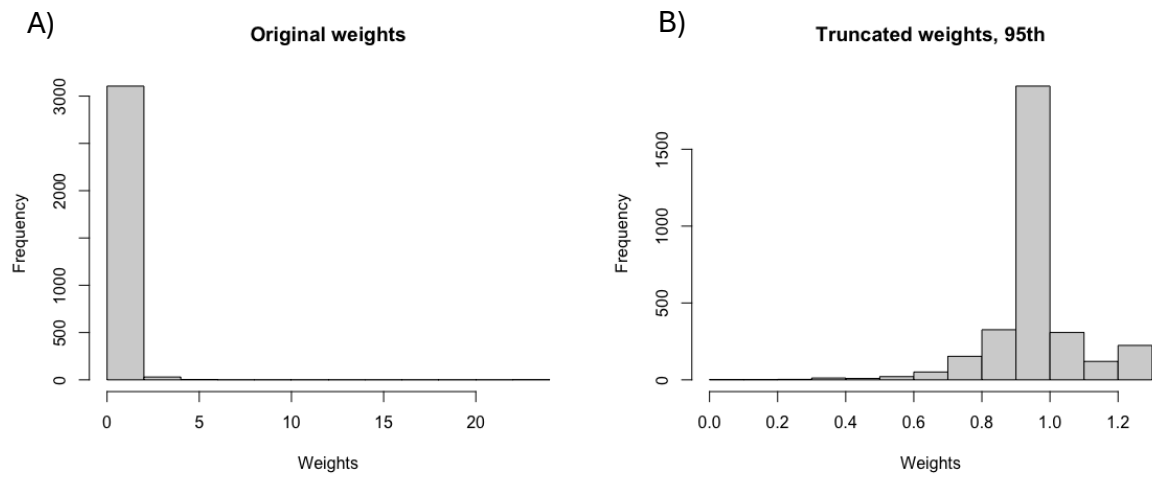


Figure S5: Estimated survival difference between the liberal and restrictive transfusion strategies A) with truncated weights; B) with massive transfusion prior to ECMO included as a confounder; C) restricted to patients with consistent treatment strategy. D) with patients with massive transfusion prior to ECMO excluded. The shaded areas show the 95% confidence intervals.

