# Restrictive Versus Liberal Transfusion Strategy in Extracorporeal Membrane Oxygenation

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# Abstract

**Background:**

To compare the clinical outcomes of patients requiring extracorporeal membrane oxygenation (ECMO) support who had a restrictive red cell transfusion strategy with those who had a liberal transfusion strategy.

**Methods:**

We retrospectively reviewed all adult ECMO cases in Hong Kong from 2010 to 2019. Patients who received a minimum of one packed red blood cell (pRBC) during ECMO were included. Haemoglobin values before each episode of transfusion was retrieved. Restrictive transfusion strategy was defined as a transfusion threshold ≤ 8.5 g/dL in all transfusion episodes for a single patient, while liberal transfusion strategy was defined as a transfusion threshold > 8.5 g/dL in any transfusion episode. Mortality outcomes and other complications were compared.

**Results:**

The analysis included 763 patients, with 138 (18.1%) patients in the restrictive and 625 (81.9%) in the liberal transfusion strategy group, and median haemoglobin of 8.3 and 9.9 g/dL, respectively. The average units of pRBC received per day were 0.7 (0.3-1.8) and 1.2 (0.6-2.3) in the two groups. There were no significant differences in ICU mortality (adjusted odds ratio (OR), 0.86; 95% CI 0.56-1.30; P=0.47), hospital mortality (adjusted OR, 0.79; 95% CI 0.52 to 1.21; P=0.28), and 90-day mortality (adjusted OR, 0.84; 95% CI 0.55 to 1.28; P=0.42) between the two groups. Among patients receiving veno-venous ECMO, the ICU mortality was significantly lower with the restrictive transfusion strategy (adjusted OR, 0.36; 95% CI 0.17 - 0.73; P=0.005).

**Conclusions:**

Compared with a liberal transfusion strategy, a restrictive red blood cell transfusion threshold of 8.5 g/dL was not associated with worse outcomes in patients on ECMO, with better survival outcomes for patients on veno-venous ECMO.


# Background

Anaemia is a common problem encountered during extracorporeal membrane oxygenation (ECMO) support, contributed by a combination of circuit-related haemolysis, consumptive coagulopathy, thrombocytopenia, and the use of anticoagulants during ECMO [1]. About 90% of patients require at least one packed red blood cell (pRBC) transfusion and consume 17.7 units of pRBC during ECMO or 2.60 units per day [2]. The primary aims of red cell transfusion are to correct volume loss and to increase oxygen delivery. However, studies have shown that oxygen consumption is independent of oxygen delivery until a critical threshold [3]. While guidelines from the Extracorporeal Life Support Organisation

(ELSO) recommend maintaining the haematocrit over 40% to optimise oxygen delivery [4], which translates to an approximate transfusion threshold of 13 g/dL, no randomised controlled trials have been conducted in patients requiring ECMO and the most appropriate transfusion trigger is therefore unknown. Defining the transfusion threshold is important in order to balance the clinical benefits of transfusion against potential costs of transfusion-related complications.

A restrictive strategy of red cell transfusion threshold at haemoglobin of 7 g/dL has been shown to be as effective as a liberal transfusion threshold of 10 g/dL in the management of critically ill patients [5]. A number of retrospective and small prospective observational studies have attempted to determine the transfusion threshold during ECMO. However, the number of subjects in these individual studies is limited, and meta-analysis did not show concluding evidence as to transfusion management in ECMO [6]. Whether transfusion practices in broad categories of critically ill patients could be generalized to patients on ECMO, and if restrictive transfusion strategies may be associated with worse outcomes in this vulnerable population remains to be determined.

To address the uncertainty, we aimed to compare the clinical outcomes of patients who had a restrictive transfusion threshold against those who had a liberal transfusion threshold during ECMO. We retrospectively reviewed a large sample of data from a territory-wide electronic health system over a ten-year period. The hypothesis was that a restrictive transfusion strategy is associated with worse mortality compared with a liberal strategy.

# Methods

### Study Population

This was a retrospective cohort study including data from a territory-wide electronic health record system in Hong Kong from 1 January, 2010 to 31 December, 2019. Adult patients ≥ 18 years old who received ECMO and was admitted to mixed disciplinary intensive care units (ICU) at public hospitals under the Hospital Authority were identified. Episodes of ECMO were defined with the International Classification of Disease Clinical Modification (ICD-9-CM) procedure code for ECMO. Patients who received a minimum of 1 unit of pRBC during ECMO were included. Exclusion criteria were patients without a haemoglobin result within 12 hours before red blood cell transfusion, or had missing Acute Physiology and Chronic Health Evaluation IV (APCHE IV) scores. The study conforms with the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) (IRB Reference Number: UW 20-573) with a waiver of signed informed consent.

### Data Collection

ECMO data were retrieved from an administrative data registry which was managed by the Coordinating Committee in Intensive Care in Hong Kong, with information including ECMO configuration, time of initiation and discontinuation entered by qualified nurses at the corresponding ECMO centres. Patients'

baseline characteristics and clinical variables were collected using the Clinical Data Analysis and Reporting System (CDARS), a central de-identified data repository comprising electronic health records from all public hospitals in Hong Kong [7].

### Exposure

The transfusion threshold was defined as the haemoglobin level immediately preceding each episode of red cell transfusion during ECMO. Restrictive transfusion strategy was defined as a transfusion threshold of less than or equal to 8.5 g/dL in all transfusion episodes for a single patient. Liberal transfusion strategy was defined as a transfusion threshold of more than 8.5 g/dL in any transfusion episode for a single patient.

### Study Outcomes

The primary outcome measure was ICU mortality. Secondary outcomes included hospital mortality and 90-day mortality. Patients with thrombotic complications, for instance of having cerebral thrombosis and arterial thrombosis, during hospital stay were recorded. Bacteraemia, defined as having positive bacterial or fungal blood culture results during ECMO was retrieved. New-onset end-stage renal failure (ESRF) was defined as requiring peritoneal dialysis or haemodialysis, or having a diagnosis of chronic kidney disease, or having a calculated eGFR using 2021 CKD-EPI [8] < 15 mL/min/1.73m$^2$ in the period between 28 days [9] and 90 days after ECMO initiation. The incidence of secondary myocardial infarction (MI), defined as having an elevated troponin T or troponin I result from 30 days to 90 days after ECMO termination was also recorded. All ICD-9-CM diagnostic codes used in defining study outcomes are included in the Additional file: Table S1.

### Statistical Analysis

All categorical variables were compared between the restrictive strategy group and liberal strategy group using the Fisher-exact test or Pearson's chi-squared test. The Shapiro-Wilk test was performed to test for normality of continuous variables. All continuous variables did not fulfil tests of normality and were analysed using the Mann-Whitney U test. Demographic and clinical variables with a P-value <0.1, and possible confounders based on biological plausibility such as age and type of ECMO configuration were subjected to a forward, stepwise logistic regression procedure. The duration of ECMO, total units of red cells transfused, and number of red cell transfusions were not included in the procedure due to their nature of being colliders. Five variables including APACHE IV score, age, type of ECMO, baseline international normalised ratio (INR), and baseline haemoglobin level were included in the final multivariable logistic regression model.

A priori designed subgroup analyses were performed for patients with a high APACHE IV score (>120), patients who were 55 years of age or older, patients who had a massive blood transfusion (defined as total units of transfusion >10 units within a 1-month period since the start of ECMO [10]), patients on different types of ECMO, and patients whose primary diagnosis was MI on veno-arterial (V-A) ECMO or

extracorporeal cardiopulmonary resuscitation (ECPR). Contingent upon observed heterogeneity between subgroups, interaction analyses were performed by including an interaction term in multivariable logistic regression, such as “restrictive strategy * type of ECMO”.

Sensitivity analyses included testing the exposure with transfusion threshold defined at 7.5 g/dL and 8 g/dL. Another multivariable logistic regression for the new-onset ESRF outcome adjusting for possible confounders specific to renal outcomes, including diabetes, hypertension, APACHE IV score, age, and type of ECMO configuration was performed. To address potential biases that were not considered in the multivariable logistic model, a logistic regression analysis was used to create a propensity score that estimated the likelihood of having a restrictive transfusion strategy, based on demographics and clinical variables. Propensity score matching was performed using a 1:1 matching ratio with nearest neighbour and sampling without replacement with a caliper of 0.15. The association of the transfusion strategy with ICU mortality was tested in the 1:1 propensity score–matched cohort.

All analyses were performed with two-tailed tests and a P-value of less than 0.05 was considered statistically significant. All analyses were done using STATA MP, version 16.1.

# Results

### Study Population

A total of 911 ECMO treatment episodes were recorded between 1 January, 2010 and 31 December, 2019 in mixed disciplinary ICUs in Hong Kong. After excluding 126 episodes without documented transfusion, 11 episodes with no available pre-transfusion haemoglobin, and 11 episodes with unknown APACHE IV score, a total of 763 episodes were included in the final analysis. By defining the transfusion threshold at 8.5 g/dL, 138 (18.1%) patients were included in the restrictive transfusion strategy group and 625 (81.9%) were included in the liberal transfusion strategy group. Fig.1 shows the study flow.

The baseline characteristics of the two groups are shown in Table 1. The median age was 55 (43-63) years. The median APACHE IV score was 101 (73-133). The median duration of ECMO was 5.9 (3.1-10.8) days. In terms of ECMO configuration, 253 (33.2%) were V-A ECMO, 382 (50.1%) were veno-venous (V-V) ECMO, and 128 (16.8%) were ECPR. A total of 161 (21.1%) and 137 (18.0%) patients were on antiplatelet or anticoagulation medication before admission, respectively. The major diagnoses necessitating V-A ECMO were MI in 58 (23.0%) patients and acute myocarditis in 41 (16.2%) patients. For patients on veno-venous (V-V) ECMO, 162 (42.4%) had bacterial pneumonia and 82 (21.5%) had viral pneumonia. For patients undergoing ECPR, 38 (29.7%) were due to MI and 9 (7.0%) were due to acute myocarditis.

Compared with the liberal strategy group, those who were in the restrictive strategy group had a higher APACHE IV score [109 (80-143) vs 99 (72-130), P=0.003], were less likely male [71 (51%) vs 198 (64%), P=0.008)], and had a shorter duration of ECMO [5.2 (2.1-9.7) vs 6.1 (3.2-10.9) days, P=0.020]. There were no significant differences in age [54 (42-63) vs 55 (44-63) years, P=0.54] or type of ECMO used [43 (31.2%) vs 210 (33.6%) for V-A ECMO, P=0.58; 65 (47.1%) vs 317 (50.7%) for V-V ECMO, P=0.44; 30

(21.7%) vs 98 (15.7%) for ECPR, P=0.09)]. Both groups had similar comorbidities, except the restrictive group which had more patients with malignancy [(18 (13.0%) vs 37 (5.9%), P=0.003]. The primary diagnoses were similar in both groups.

The median transfusion threshold was lower in the restrictive strategy group [7.2 (6.8-7.7) vs 9.4 (8.7-10.2) g/dL, P<0.001]. Patients in the restrictive strategy group had a lower haemoglobin level [8.5 (7.3-11.2) vs 10.4 (8.7-12.3) g/dL, P<0.001], longer prothrombin time (PT) [18.5 (14.9-27.3) vs 16.6 (13.7-22.6) seconds, P=0.006] and INR [1.6 (1.3-2.4) vs 1.5 (1.2-1.9), P=0.004] upon ECMO initiation. Median values of haemoglobin during ECMO were lower in the restrictive strategy group [8.3 (7.7-9.0) vs 9.9 (9.2-10.8) g/dL, P<0.001], while PT [15.7 (13.7-24.6) vs 15.1 (13.3-18.0) seconds, P=0.008], INR [1.4 (1.2-2.2) vs 1.3 (1.2-1.6), P=0.006], and creatinine level [165 (104-247) vs 137 (86-201) μmol/L, P=0.003] were higher, compared with the liberal strategy group. There were no significant differences in activated partial thromboplastin time (aPTT) and platelet count between the two groups. Laboratory results are shown in Table 2.

### Blood product usage

The total units of red cell transfusion were lower in the restrictive group than in the liberal group [4 (2-7) vs 8 (4-16) units, P<0.001]. The average pRBC transfused per day was lower in the restrictive group (0.7 vs 1.2 packs per day, P<0.001). Patients in the restrictive group had fewer episodes of red cell transfusion (2 vs 5 times, P<0.001).

### Clinical Outcomes

The ICU mortality was 63 (46%) and 256 (41%) in the restrictive group and liberal group, respectively (P=0.31) (Table 3). Secondary outcomes such as hospital mortality were 68 (49%) in the restrictive group and 284 (45%) in the liberal group (P=0.41), and death at 90 days after ECMO initiation were 71 (51%) and 294 (47%), respectively (P=0.35). The unadjusted outcomes were not significantly different between the two groups.

After adjustment for confounders including APACHE IV score, age, type of ECMO performed, baseline haemoglobin, and baseline INR, there was no significant association between a restrictive transfusion strategy and ICU mortality (adjusted odds ratio [OR], 0.86; 95% CI 0.56-1.30; P=0.47). The model had good discriminatory performance and was well-calibrated (area under receiver operating characteristic curve, 0.73; 95% CI 0.69-0.76; Hosmer-Lemeshow test, P=0.97; Additional file: Fig. S1). There were no significant association between restrictive transfusion and hospital mortality (adjusted OR, 0.79; 95% CI 0.52-1.21; P=0.28), and 90-day mortality (adjusted OR, 0.84; 95% CI 0.55-1.28; P=0.42). Unadjusted and adjusted outcomes are shown in Table 3.

### Complications

The restrictive strategy group had fewer patients with new-onset ESRF [8 (6%) vs 83 (13%), P=0.014]. There were no significant differences in the number of patients with bacteraemia [7 (5%) vs 52 (8%),

P=0.20) and thrombotic complications [10 (7%) vs 53 (8%), P=0.63] from ECMO initiation to hospital discharge. The percentage of patients with secondary MI after discharge was similar [2 (1%) vs 30 (5%), P=0.01]. The results of adjusted analyses were similar (Table 3).

## Subgroup analyses

There was significant interaction between the transfusion strategy and the type of ECMO configuration. Restrictive strategy was associated with lower ICU mortality rates for the subgroup of patients who had V-V ECMO (adjusted OR, 0.36; 95% CI 0.17-0.73; P=0.005) (P for interaction “restrictive strategy * V-V ECMO” = 0.007). There were no significant differences in ICU mortality between the restrictive and liberal strategies in the V-A ECMO (adjusted OR, 1.53; 95% CI 0.74-3.15; P=0.25) and ECPR (adjusted OR, 1.59; 95% CI 0.55-4.59; P=0.39) subgroups.

Subgroup analyses were performed for patients with APACHE IV score (≤ 120 vs > 120), and age (≤ 55 years vs > 55 years). There were 57 (41%) patients with APACHE IV score > 120 in the restrictive group and 199 (32%) in the liberal group. There were no significant differences in ICU mortality between the restrictive and liberal groups in the subgroup of patients with an APACHE IV score of ≤120 (adjusted OR, 0.70; 95% CI 0.40-1.23; P=0.21) or APACHE IV score of >120 (adjusted OR, 1.27; 95% CI 0.65-2.48; P=0.48). There were 66 (48%) patients with age > 55 years in the restrictive group and 317 (51%) in the liberal group. There were similarly no effects of transfusion strategy on ICU mortality in the subgroup of age ≤ 55 years (adjusted OR, 0.80; 95% CI 0.42-1.50; P=0.48) and age >55 years (adjusted OR, 0.85; 95% CI 0.47-1.51; P=0.57)

A total of 13 (9%) and 200 (32%) patients had massive blood transfusion in the restrictive group and liberal group, respectively. There were no significant differences in ICU mortality between the two groups for patients with a massive blood transfusion (adjusted OR, 0.49; 95% CI 0.14-1.71; P=0.26) or without a massive blood transfusion (adjusted OR, 1.05; 95% CI 0.65-1.70; P=0.84).

For a subgroup of 58 (23%) patients who required V-A ECMO or ECPR for a diagnosis of MI, no differences in ICU mortality were found between the transfusion strategies (adjusted OR, 0.51; 95% CI 0.14-1.77; P=0.29).

The results of subgroup analyses are shown in Table 4.

## Sensitivity analyses

Results remained similar for ICU mortality after separate adjustment of the definition of transfusion threshold to 7.5 g/dL (adjusted OR, 0.75; 95% CI 0.45-1.25; P=0.27) and 8 g/dL (adjusted OR, 0.98; 95% CI 0.51-1.88; P=0.95), respectively.

A further sensitivity analysis was performed for patients on V-V ECMO to explore the possible transfusion threshold. The restrictive group had a lower ICU mortality when the transfusion threshold was 8.0 g/dL

(adjusted OR, 0.38; 95% CI 0.16-0.91; P=0.030) and there was no difference in ICU mortality at a transfusion threshold of 7.5 g/dL (adjusted OR, 0.39; 95% CI 0.11-1.39; P=0.15).

After adjusting for confounders specific to renal outcomes including APACHE IV score, age, type of ECMO configuration, pre-ECMO hypertension and diabetes mellitus, restrictive strategy was still associated with lower risks of new-onset ESRF (adjusted OR, 0.39; 95% CI 0.18-0.84; P=0.015).

A total of 264 patients were successfully matched at a 1:1 ratio in propensity score matching. There was no significant association between a restrictive strategy and ICU mortality (adjusted OR, 0.86; 95% CI 0.53-1.39; P=0.54) in the propensity score–matched cohort.

The results of sensitivity analyses are shown in Table 4.

# Discussion

The principal finding of this territory-wide study was that a restrictive transfusion threshold of 8.5 g/dL was not associated with worse outcomes in patients on ECMO. ICU mortality, hospital mortality, and 90-day mortality were not significantly different between the restrictive and liberal transfusion strategy groups. Interaction analyses demonstrated restrictive transfusion strategy had 3-fold reduction in ICU mortality for patients on V-V ECMO, with non-inferior outcomes at transfusion thresholds as low as 7.5 g/dL. These data support that it is safe and potentially even beneficial to implement a protocol of restrictive transfusion in critically ill patients on ECMO.

The multicenter, randomised, controlled clinical trial of Transfusion Requirements in Critical Care (TRICC) study was the first study to provide robust evidence that a restrictive transfusion threshold at 7 g/dL was not associated with increased mortality in critically ill patients compared with a liberal threshold of 10 g/dL [5]. However, for patients requiring ECMO support, guidelines from the ELSO recommend maintaining the haematocrit over 40% to optimise oxygen delivery [4], which translates to an approximate transfusion threshold of 13 g/dL. The physiological derangement for V-A ECMO and ECPR patients is that they have impaired circulation and reduced cardiac output, while V-V ECMO patients have poor oxygenation, taken together ECMO patients are the ones who are most vulnerable to impaired oxygen delivery and resultant tissue hypoxia. A higher transfusion threshold is therefore suggested to increase serum haemoglobin concentration and oxygen delivery. At the same time, physiological studies have shown that oxygen consumption is able to adapt to a decrease in oxygen delivery until a critical threshold [3]. Whether this critical threshold is different between vulnerable ECMO patients and the wider population of critically ill patients, and whether a lower transfusion threshold in ECMO patients is safe and beneficial are unknown.

The red cell transfusion threshold in ECMO patients has only been evaluated in small case series. In a study including 38 patients receiving mostly V-V ECMO for acute respiratory distress syndrome, Agerstrand et al. showed, similar to what we did, that a restrictive transfusion strategy of 7.0 g/dL did not increase mortality at hospital discharge [11]. In the study by Cahill et al. comparing the outcome of 30

cardiac ECMO patients before and after implementation of a restrictive transfusion protocol, using a restrictive transfusion threshold of 8 g/dL was associated with reduced complications and improved survival [12]. In a meta-analysis, Abbasciano et al called for a randomised controlled trial of different transfusion thresholds in ECMO patients [6]. However, in most localities, the low annual number of ECMO episodes and the fact that cases are spread across different ECMO centres make conducting large randomised controlled trials in ECMO patients difficult if not impossible. Using territory-wide registry data, our study reflected real-life clinical practice across multiple ECMO centres over the past ten years and thus provided good evidence for the effect of a restrictive transfusion strategy across the broad groups of V-A, V-V, and ECPR ECMO patients.

The advantages of a restrictive transfusion strategy may be explained by the risks associated with red blood cell transfusion. A major cause of transfusion-related death is transfusion-associated circulatory overload (TACO). TACO has an incidence of 5.5% in critically ill patients [13], and is characterised by pulmonary edema and acute respiratory distress secondary to circulatory overload [14]. Another risk of transfusion is transfusion-related acute lung injury (TRALI), defined by pulmonary edema after circulatory overload or alternate acute respiratory distress syndrome risk factors are ruled out [15]. The exact pathophysiology of TRALI is unknown, but a “two-event” mechanism has been proposed. Red blood cell transfusion leads to transfusion-related immunomodulation (TRIM) which causes inflammatory and immunosuppressive effects as a first event [16], and the second event involves human leukocyte antigen (HLA) antigen-antibody interactions to induce lung injury [15, 17]. Furthermore, studies demonstrated a positive correlation between the amount of red cell transfused and hospital mortality [10]. For patients on V-V ECMO who already have respiratory failure, superimposed pulmonary edema caused by both TACO and TRALI can be potentially detrimental to clinical outcomes. Similarly, patients on V-A ECMO who already have profound circulatory failure may have heightened sensitivity to the volume effects of transfusion.

There have been concerns regarding the use of a restrictive transfusion strategy in patients with diagnoses of cardiac diseases, especially MI. In the TRICC study, the potentially superior effect of a restrictive transfusion threshold of 7.0 g/dL was not observed in cardiac patients [5]. Myocardial oxygen extraction is high and dependent on haemoglobin even in its resting state. A low haemoglobin level may increase the propensity of myocardial ischemia and resultant mortality in these patients [18]. This could explain why a restrictive strategy was only found to be superior in V-V ECMO patients, while being equivocal for V-A ECMO and ECPR patients.

An important impact of a restrictive transfusion threshold is reduction in the use of packed red blood cells. In our study, the restrictive group required 0.7 units while the liberal group required 1.2 units of pRBC per day. The potential number of pRBC units saved locally in Hong Kong could be at least 225 units per year (0.5 units*median duration of ECMO in days*average number of ECMO patients per year). The significance of patient blood management has been magnified by the COVID-19 pandemic, when social activities were reduced and additional blood collection policies were implemented, causing drops in blood supply worldwide [19]. Locally in Hong Kong, more than 15 emergency appeals for blood donations had

been issued since the start of the pandemic in January 2020 [20]. Therefore, clearly-defined restrictive transfusion threshold facilitates evidence-based patient blood management, efficient stewardship of scarce red blood cells, and reduction of costs across the entire healthcare system.

The strength of this study was that it included patients with a broad range of primary diagnoses and different types of ECMO configurations. The large number of patients included allowed us to stratify and conduct subgroup analyses on primary diagnoses such as MI and the type of ECMO configuration. There were few exclusion criteria and nearly all patients who had at least one red cell transfusion during their ECMO episode in ICU were included. A large sample size of 763 ECMO episodes ensured adequate power to detect a significant difference if present.

One limitation was the retrospective and non-randomised nature of this study, which may lead to potential biases in other aspects of patient management. There were problems of confounding. For instance, the severity of patients' conditions was different and was reflected by the higher APACHE IV score in the restrictive strategy group, although if a restrictive strategy was harmful, this would have increased the likelihood of detecting a significant difference. Moreover, patients in the liberal strategy group included transfusion episodes with a restrictive threshold, although the median haemoglobin was significantly different in the two groups. In addition, the large sample of data made it difficult to undergo chart review for each individual ECMO episode to identify circumstances necessitating the transfusion. Lastly, the measurement of secondary outcomes such as new-onset ESRF, secondary MI, and bacteraemia was not prospectively recorded and may be subjected to errors in coding.

# Conclusions

A restrictive red cell transfusion threshold of 8.5 g/dL was not associated with worse outcomes in patients on ECMO and was shown to have better survival outcomes for patients on V-V ECMO compared to a liberal transfusion strategy.

# Abbreviations

APACHE IV - Acute Physiology and Chronic Health Evaluation IV

aPTT - activated partial thromboplastin time

CDARS - Clinical Data Analysis and Reporting System

ECMO - extracorporeal membrane oxygenation

ECPR - extracorporeal cardiopulmonary resuscitation

ELSO - Extracorporeal Life Support Organisation

ESRF - end-stage renal failure

HLA - human leukocyte antigen

ICD-9-CM - International Classification of Disease Clinical Modification

ICU - intensive care unit

INR - international normalised ratio

MI - myocardial infarction

pRBC - packed red blood cells

PT - prothrombin time

RBC - red blood cells

TACO - transfusion-associated circulatory overload

TRALI - transfusion-related acute lung injury

TRICC study - The multicenter, randomised, controlled clinical trial of Transfusion Requirements in Critical Care study

TRIM - transfusion-related immunomodulation

V-A - veno-arterial

V-V - veno-venous

# Declarations

### Ethical approval

This study was approved by the the Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) (IRB Reference Number: UW 20-573) with a waiver of signed finformed consent.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Conflicts of Interests

The authors declare that they have no competing interests.

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### Author Contributions

PYN and HCVC contributed to the study conception and design. HCVC and AI contributed to acquisition, analysis and interpretation of the data. PYN and HCVC contributed to drafting the manuscript and all authors contributed to critical revision of the article. PYN supervised the study. PYN and HCVC had full access to all of the data in the study and take responsibility for the integrity and accuracy of the data analysis. All authors read and approved the final manuscript.

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# Tables

**Table 1**

**Baseline characteristics**

| | Restrictive | Liberal | Total |
|---|---|---|---|
| | N=138 | N=625 | N=763 |
| Gender, Male | 71 (51%) | 398 (64%) | 469 (61%) |
| Age, years | 54 (42-63) | 55 (44-63) | 55 (43-63) |
| APACHE IV score | 109 (80-143) | 99 (72-130) | 101 (73-133) |
| ECMO duration, days | 5.2 (2.1-9.7) | 6.1 (3.2-10.9) | 5.9 (3.1-10.8) |
| | | | |
| **Type of ECMO** | | | |
| V-A | 43 (31.2%) | 210 (33.6%) | 253 (33.2%) |
| V-V | 65 (47.1%) | 317 (50.7%) | 382 (50.1%) |
| ECPR | 30 (15.7%) | 98 (21.7%) | 128 (16.8%) |
| | | | |
| **Premorbid medications** | | | |
| Antiplatelets[1] | 28 (20.3%) | 133 (21.3%) | 161 (21.1%) |
| Anticoagulants[2] | 26 (18.8%) | 111 (17.8%) | 137 (18.0%) |
| | | | |
| **Comorbidities**[3] | | | |
| Diabetes mellitus | 19 (13.8%) | 77 (12.3%) | 96 (12.6%) |
| Hypertension | 19 (13.8%) | 92 (14.7%) | 111 (14.5%) |
| Myocardial infarction | 13 (9.4%) | 35 (5.6%) | 48 (6.3%) |
| Heart failure | 13 (9.4%) | 69 (11.0%) | 82 (10.7%) |
| Cerebrovascular disease | 4 (2.9%) | 22 (3.5%) | 26 (3.4%) |
| Malignancy | 18 (13.0%) | 37 (5.9%) | 55 (7.2%) |
| Lung disease | 12 (8.7%) | 52 (8.3%) | 64 (8.4%) |
| Renal disease | 7 (5.1%) | 22 (3.5%) | 29 (3.8%) |
| Liver Disease | 8 (5.8%) | 40 (6.4%) | 48 (6.3%) |

| Principal diagnoses for ECMO | | | |
|---|---|---|---|
| ***V-A ECMO*** | | | |
| Myocardial infarction | 9 (21%) | 49 (23%) | 58 (23%) |
| Acute myocarditis | 7 (16%) | 34 (16%) | 41 (16%) |
| ***V-V ECMO*** | | | |
| Bacterial pneumonia | 33 (51%) | 129 (41%) | 162 (42%) |
| Viral pneumonia | 13 (20%) | 69 (22%) | 82 (21%) |
| ***ECPR*** | | | |
| Myocardial infarction | 7 (23%) | 31 (32%) | 38 (30%) |
| Acute myocarditis | 3 (10%) | 6 (6%) | 9 (7%) |

All data were presented as frequency (percentage) or median (interquartile range (IQR)) unless specified.

[1] Antiplatelets included Aspirin, Clopidogrel, Dipyridamole, Prasugrel and Ticagrelor.

[2] Anticoagulants included Apixaban, Dabigatran, Edoxaban, Enoxaparin, Rivaroxaban, Tinzaparin and Warfarin.

[3] Defined according to Acute Physiology and Chronic Health Evaluation IV or Charlson Comorbidity Index.

**Abbreviation:** APACHE IV - Acute Physiology and Chronic Health Evaluation IV; ECMO - extracorporeal membrane oxygenation; ECPR - extracorporeal cardiopulmonary resuscitation; V-A - veno-arterial; V-V - veno-venous.

**Table 2**

**Laboratory results during ECMO support**

| | Restrictive | Liberal | Total | p-value |
|---|---|---|---|---|
| | N=138 | N=625 | N=763 | |
| Transfusion threshold, g/dL | 7.2 (6.8-7.7) | 9.4 (8.7-10.2) | 9.1 (8.2-10.0) | *<0.001* |
| **At time closest to ECMO initiation** | | | | |
| Haemoglobin, g/dL | 8.5 (7.3-11.2) | 10.4 (8.7-12.3) | 10.3 (8.4-12.1) | *<0.001* |
| PT, s | 18.5 (14.9-27.3) | 16.6 (13.7-22.6) | 16.7 (13.9-23.0) | *0.006* |
| INR | 1.6 (1.3-2.4) | 1.5 (1.2-1.9) | 1.5 (1.2-2.0) | *0.004* |
| aPTT, s | 59.2 (37.2-110.0) | 67.2 (38.2-120.0) | 65.3 (37.8-120.0) | 0.22 |
| Creatinine, µmol/L | 163.1 (111.4-250.0) | 146.0 (96.0-224.0) | 149.0 (98.0-230.0) | 0.057 |
| Platelet, $x10^9$/L | 121 (67-198) | 133 (85-196) | 132 (83-198) | 0.19 |
| **During ECMO**[1] | | | | |
| Haemoglobin, g/dL | 8.3 (7.7-9.0) | 9.9 (9.2-10.8) | 9.7 (8.9-10.6) | *<0.001* |
| PT, s | 15.7 (13.7-24.6) | 15.1 (13.3-18.0) | 15.3 (13.3-18.4) | *0.008* |
| INR | 1.4 (1.2-2.2) | 1.3 (1.2-1.6) | 1.3 (1.2-1.6) | *0.006* |
| aPTT, s | 50.9 (45.6-60.4) | 52.5 (45.0-61.2) | 52.2 (45.1-60.8) | 0.96 |
| Creatinine, µmol/L | 164.9 | 136.7 | 142.1 | *0.003* |

| | | | | |
|---|---|---|---|---|
| | (104.3-246.7) | (85.8-201.2) | (89.1-206.1) | |
| Platelet, $x10^9$/L | 95 (48-152) | 98 (76-132) | 97 (73-138) | 0.16 |

All data were presented as median (interquartile range (IQR)) unless specified.

[1]The weighted average of each patient during ECMO was calculated.

**Abbreviation:** aPTT - activated partial thromboplastin time; ECMO - extracorporeal membrane oxygenation; INR - international normalised ratio; PT - prothrombin time; s - second.

## Table 3

## Clinical outcomes

| | Restrictive | Liberal | p-value | Unadjusted odds ratio (95% CI) | p-value | Adjusted odds ratio[1] (95% CI) | p-value |
|---|---|---|---|---|---|---|---|
| | N=138 | N=625 | | | | | |
| **Transfusion requirement** | | | | | | | |
| Total pRBC transfused | 4 (2-7) | 8 (4-16) | *<0.001* | | | | |
| PRBC transfused per day | 0.7 (0.3-1.8) | 1.2 (0.6-2.3) | *<0.001* | | | | |
| Number of RBC transfusion episodes | 2 (1-4) | 5 (2-9) | *<0.001* | | | | |
| **Mortality** | | | | | | | |
| ICU | 63 (46%) | 256 (41%) | 0.31 | 1.21 (0.84-1.75) | 0.31 | 0.86 (0.56-1.30) | 0.47 |
| Hospital | 68 (49%) | 284 (45%) | 0.41 | 1.17 (0.81-1.69) | 0.41 | 0.79 (0.52-1.21) | 0.28 |
| 90-day | 71 (51%) | 294 (47%) | 0.35 | 1.19 (0.82-1.73) | 0.35 | 0.84 (0.55-1.28) | 0.42 |
| **Complications** | | | | | | | |
| Thrombotic | 10 (7%) | 53 (8%) | 0.63 | 0.84 (0.42-1.70) | 0.63 | 0.85 (0.41-1.75) | 0.65 |
| Bacteraemia | 7 (5%) | 52 (8%) | 0.20 | 0.59 (0.26 -1.33) | 0.2 | 0.47 (0.19-1.14) | 0.09 |
| New-onset ESRF | 8 (6%) | 83 (13%) | *0.014* | 0.40 (0.19-0.85) | *0.017* | 0.39 (0.18-0.84) | *0.016* |
| Secondary MI | 2 | 30 | *0.014* | 0.29 | 0.09 | 0.26 | 0.08 |

| | | | | |
|---|---|---|---|---|
| | (1%) | (5%) | (0.07-1.24) | (0.06-1.14) |

**Abbreviation:** ESRF - end-stage renal failure; ICU - intensive care unit; MI - myocardial infarction; pRBC - packed red blood cells.

[1] Adjusted for APACHE IV score, age, type of ECMO performed, baseline haemoglobin results, and baseline INR results.

## Table 4

### Subgroup and sensitivity analyses for ICU mortality

| | Restrictive | Liberal | p-value | Unadjusted odds ratio (95% CI) | p-value | Adjusted odds ratio (95% CI) | p-value |
|---|---|---|---|---|---|---|---|
| *Subgroup analyses* | | | | | | | |
| **ECMO Type** | | | | | | | |
| V-A ECMO | 26/43 (60%) | 93/210 (44%) | 0.05 | 1.92 (0.99 - 3.75) | 0.06 | 1.53 (0.74 - 3.15) | 0.25 |
| V-V ECMO | 14/65 (22%) | 107/317 (34%) | 0.05 | 0.54 (0.29 - 1.02) | 0.06 | 0.36 (0.17 - 0.73) | *0.005* |
| ECPR | 23/30 (77%) | 56/98 (57%) | 0.05 | 2.46 (0.97 - 6.28) | 0.06 | 1.59 (0.55 - 4.59) | 0.39 |
| | | | | | | | |
| **APACHE IV score** | | | | | | | |
| ≤ 120 | 23/81 (28%) | 135/426 (32%) | 0.56 | 0.85 (0.51 - 1.44) | 0.56 | 0.70 (0.40 - 1.23) | 0.21 |
| >120 | 40/57 (70%) | 121/199 (61%) | 0.20 | 1.52 (0.80 - 2.86) | 0.20 | 1.27 (0.65 - 2.48) | 0.48 |
| | | | | | | | |
| **Age, years** | | | | | | | |
| ≤ 55 | 29/72 (40%) | 102/308 (33%) | 0.25 | 1.36 (0.80 - 2.30) | 0.25 | 0.80 (0.42 - 1.50) | 0.48 |
| > 55 | 34/66 (52%) | 154/317 (49%) | 0.66 | 1.12 (0.66 - 1.91) | 0.66 | 0.85 (0.47 - 1.51) | 0.57 |
| | | | | | | | |
| **Massive Blood Transfusion** | | | | | | | |
| No | 59/125 (47%) | 156/425 (37%) | *0.035* | 1.54 (1.03 - 2.31) | *0.035* | 1.05 (0.65 - 1.70) | 0.84 |
| Yes | 4/13 (31%) | 104/200 (49%) | 0.18 | 0.44 (0.13 - 1.49) | 0.19 | 0.49 (0.14 - 1.71) | 0.26 |
| | | | | | | | |
| **Diagnosis of MI** | 7/16 (44%) | 38/80 (48%) | 0.78 | 0.86 (0.29 - 2.53) | 0.78 | 0.51 (0.14 - 1.77) | 0.29 |
| | | | | | | | |
| *Sensitivity analyses* | | | | | | | |
| *Transfusion threshold* | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **7.5 g/dL** | 22/49 (45%) | 297/714 (42%) | 0.65 | 1.14 (0.64 - 2.05) | 0.65 | 0.75 (0.45 - 1.25) | 0.27 |
| **8.0 g/dL** | 38/88 (43%) | 281/675 (42%) | 0.78 | 1.07 (0.68 - 1.70) | 0.78 | 0.98 (0.51 - 1.88) | 0.95 |
| | | | | | | | |
| ***Transfusion threshold in V-V ECMO subgroup*** | | | | | | | |
| **7.5 g/dL** | 3/20 (15%) | 118/362 (33%) | 0.10 | 0.36 (0.10 - 1.27) | 0.11 | 0.39 (0.11 - 1.39) | 0.15 |
| **8.0 g/dL** | 9/41 (22%) | 112/341 (33%) | 0.16 | 0.28 (0.27 - 1.25) | 0.16 | 0.38 (0.16 - 0.91) | *0.030* |
| | | | | | | | |
| ***New-onset ESRF***[1] | 8 (6%) | 83 (13%) | *0.014* | 0.40 (0.19 - 0.85) | *0.017* | 0.015 (0.18 - 0.84) | *0.015* |

**Abbreviation:** APACHE IV - Acute Physiology and Chronic Health Evaluation IV; ECMO - extracorporeal membrane oxygenation; ECPR - extracorporeal cardiopulmonary resuscitation; ESRF – end-stage renal failure; ICU – intensive care unit; MI – myocardial infarction; V-A - veno-arterial; V-V - veno-venous.

[1] Adjusted for APACHE IV score, age, type of ECMO performed, pre-ECMO hypertension and diabetes mellitus.

# Figures

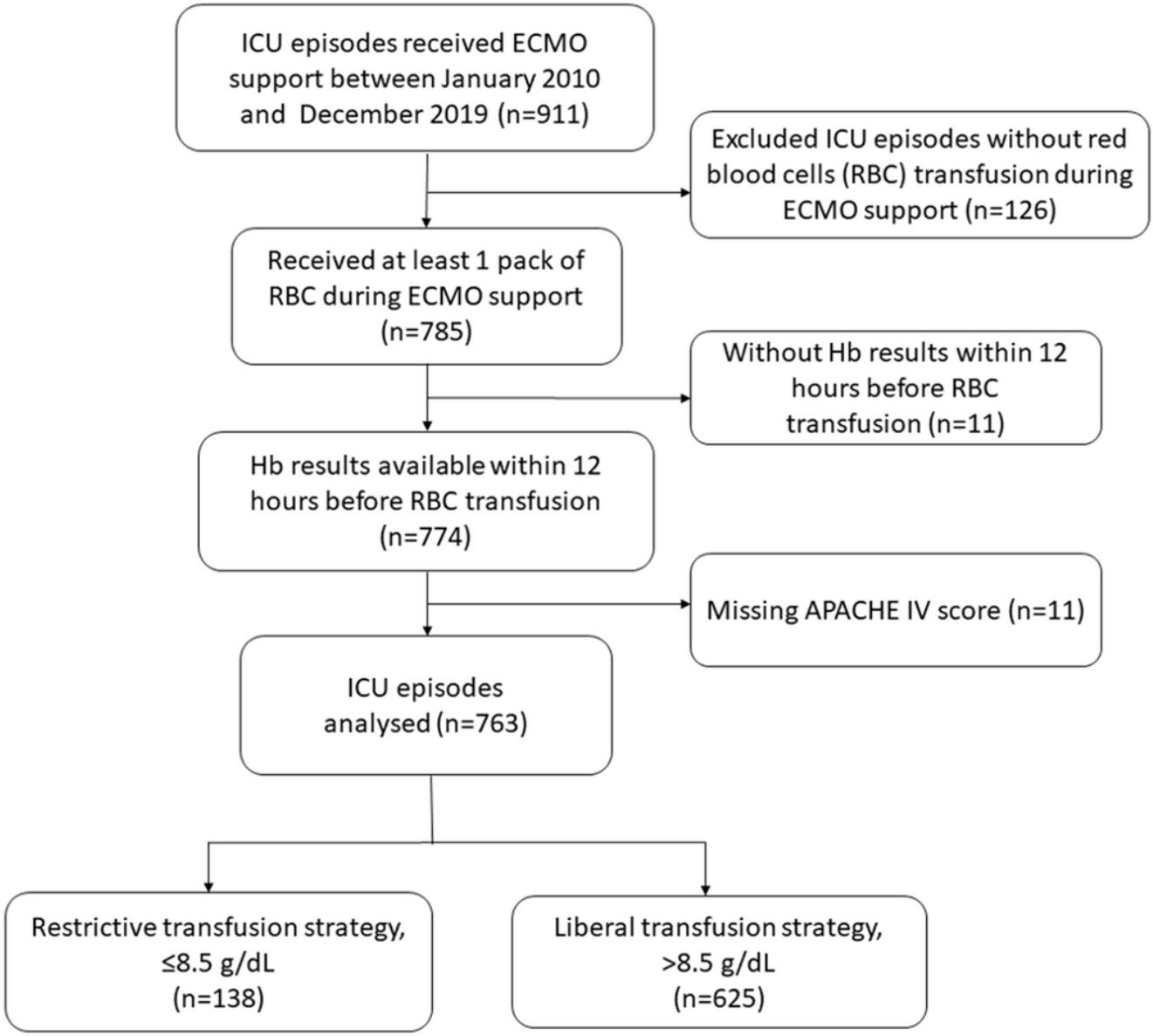


**Figure 1**

**Title:** Study flow

**Legend:** There was a total of 911 ECMO treatment episodes recorded between 1st January 2010 and 31st December 2019 in the mixed disciplinary intensive care units in Hong Kong. After excluding 126 episodes without documented red blood cells transfusion, 11 episodes without pre-transfusion haemoglobin results, and 11 episodes without APACHE IV score, a total of 763 episodes were included in the final analysis. Patients with a transfusion threshold ≤ 8.5 g/dL were assigned to the restrictive transfusion strategy group, and those with a transfusion threshold > 8.5 g/dL were assigned to the liberal transfusion strategy group.

**Abbreviation.** APACHE IV - Acute Physiology and Chronic Health Evaluation IV; ECMO - extracorporeal membrane oxygenation; Hb – haemoglobin; ICU – intensive care unit; RBC – red blood cells.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CriticalCareAdditionalFile1.docx
- ECMOTransfusionFigureS1.tif