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Original Article

Hospital-level volume in extracorporeal membrane oxygenation cases and death or disability at 6 months

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ABSTRACT

Objective: Extracorporeal membrane oxygenation (ECMO) is a high-risk procedure with significant morbidity and mortality and there is an uncertain volume-outcome relationship, especially regarding long-term functional outcomes. The aim of this study was to examine the association between ECMO centre volume and long-term death and disability outcomes.

Design, setting, and participants: This is a registry-embedded observational cohort study. Patients were included if they were enrolled in the binational ECMO registry (EXCEL). The exclusion criteria included patients on ECMO for heart/lung transplants. Data included demographics, clinical information on their first ECMO run, and six-month outcomes obtained by telephone interview. The primary outcome was death or new disability at six months. A multivariable analysis was conducted using hospitals' annual ECMO volume. High-volume centres were defined as having >30 ECMO cases annually, and analyses were run on ECMO subgroups of veno-venous (VV), veno-arterial (VA), and extracorporeal cardiopulmonary resuscitation (ECPR).

Results: Of 1232 patients, 663 patients were cared for on ECMO at high-volume centres and 569 patients at low-volume centres. There was no difference in six-month death or new disability between high- and

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Respiratory function
Oxygen delivery

low-volume ECMO centres in VV-ECMO [OR: 1.09 (0.65−1.83), p = 0.744], VA-ECMO [OR: 1.10 (0.66 −1.84), p = 0.708], and ECPR-ECMO [OR: 1.38 (0.37−5.08), p = 0.629]. This finding was persistent in all sensitivity analyses, including exclusion of patients who were transferred between high- and low-volume centres.

Conclusion: There was no difference in death or disability at six months between high- and low-volume centres in Australia and New Zealand, possibly due to the current model of coordinated care that includes patient transfers and training between high- and low-volume ECMO centres in our region.

Abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
BMI	body mass index
CI	confidence interval
COR	competing odds ratio
COVID	coronavirus disease
ECMO	extracorporeal membrane oxygenation
ECPR	extracorporeal cardiopulmonary resuscitation
ELSO	Extracorporeal Life Support Organization
HR	hazard ratio
ICU	intensive care unit
LOS	length of stay
MAP	mean arterial pressure
MD	median difference
OR	odds ratio
PBW	predicted body weight
PEEP	positive end-expiratory pressure
RESP	Respiratory ECMO Survival Prediction
REDCap	Research Electronic Data Capture
RRT	renal replacement therapy
SAVE	Survival after Veno-arterial-ECMO
SeRP	Secure e-Research Platform
SHR	subdistribution hazard ratio
SOFA	Sequential Organ Failure Assessment
US	United States
VA	veno-arterial
VV	veno-venous
WHODAS	World Health Organization Disability Assessment Schedule

1. Introduction

1.1. Background

Extracorporeal membrane oxygenation (ECMO) is one of the last lines of organ support used in reversible respiratory and/or cardiac disease when conventional management is insufficient. ECMO use has increased, with the international Extracorporeal Life Support Organization (ELSO) registry,[1] which collects data from >60 countries, reporting almost twice as many ECMO runs from 2015 to 2022. However, ECMO is associated with a significant risk of disability[2,3] and substantial costs,[4] therefore optimising its effectiveness is crucial.

ECMO as a complex procedure has a significant learning curve,[5,6] and whilst studies have explored ECMO's association with annual procedural volume in adult patients, results have been inconsistent[6–16] with variations between benefits of both high- and low-volume centres. It is unclear whether patients should be prioritised to centres with a greater annual volume, which could be critical in improving outcomes of a severely unwell population.

While there is no consensus on what defines a high-volume centre, several studies have used >30 cases per year as a cut-off.[7,10,13,14] ELSO also recommends that centres with <20 cases annually should have additional training, and new centres be in locations that can support a minimum of six ECMO cases per year as below this case-load, cost, and deskilling play a critical role in its effectiveness.[17]

Additionally, studies investigating volume-outcome relationships after ECMO have typically only assessed short-term in-hospital outcomes with a lack of longer-term or functional outcomes. Given the different healthcare structures internationally, previous studies of volume-outcome associations may be different in areas where ECMO is coordinated between sites.[9,10,15,16] As such, the primary aim of this study was to assess the association of annual ECMO volume against death or disability at six months in Australia and New Zealand. The secondary aims were to examine ECMO centre volumes against six-month mortality, in-hospital and ICU mortality, lengths of stay, total ventilation duration, and complication rates.

2. Patients and methods

This was a registry-embedded observational cohort study. The EXCEL registry is a binational ECMO registry that collects patient data prospectively from 31 hospitals across Australia and New Zealand.[3] Pre-existing data was used for this retrospective cohort study once patients completed their six-month follow-up. Ethics approval was obtained from the Alfred Ethics Committee (Project number: 43134, Local reference: 534/18) and Monash University Human Research Ethics Committee (Project number: 32373). Hospital data from the EXCEL registry are recorded under a waiver of consent, and follow-up phone interviews with the patient or their surrogate are conducted with an opt-out consent process.

Patient data were extracted from EXCEL with admission dates between 01/01/2019 and 29/12/2022, to ensure collection of six-month follow-up data. All ECMO patients were included. Patients were excluded if they had a missing ECMO mode, or were on ECMO for heart/lung transplants as transplants were only performed in high-volume centres and had significantly better outcomes. If patients had multiple ECMO runs, only their first run was counted. If patients were transferred within 24 h of ECMO initiation, they were considered part of the destination centre.

Annual ECMO site volume was calculated using the average number of patients initiated on ECMO per site between 2020 and 2022 using EXCEL data. Disability was defined as a score ≥25% (moderate-to-complete disability) on the 12-item World Health

Organization Disability Assessment Schedule (WHODAS 2.0). New disability was defined using the minimum clinically important difference of a 10% increase.[18] These scores were measured via phone interview six months after ECMO initiation unless patients were still hospitalised. Hospitals were dichotomised into high- and low-volume, where high-volume was defined as >30 ECMO cases per year.[7,10,13,14]

The primary outcome was death or disability at six months (180 days) after ECMO initiation. Patients still in hospital at six months were classified as having disability. Both death and disability are patient-centred and have been prioritised by consumers and end-users.[19] Secondary outcomes included hospital and 180-day mortality, disability, new disability, complications of ECMO, and duration of ICU and hospital stay. Definitions of secondary outcomes can be seen in Supplemental Table 1.

Telephone interviews were conducted centrally at Monash by trained investigators. EXCEL data are stored on Research Electronic Data Capture (REDCap) tools hosted at Monash University, version 12.4.10.[20,21] Extracted data were stored on a secure drive and accessed through the Monash Secure e-Research Platform (SeRP).

We used convenience sampling including all patients who fulfilled the inclusion criteria (1232 patients) during the observed period (2019–2022).

This study was registered as part of the EXCEL study: CTG1819-03, NCT03793257.

2.1. Statistical analysis

Analyses were performed in subgroups of veno-venous (VV-ECMO), veno-arterial (VA)-ECMO, and extracorporeal cardiopulmonary resuscitation (ECPR)-ECMO as well as the entire patient population. As this was an exploratory study, no adjustments were made for multiple testing and a p-value <0.05 was considered significant. The analyses were performed using R.[22]

Rates of missing data were recorded. Patients with missing values in calculated scores had a default value of 0 assigned to that variable. Multiple imputations were used to impute missing data on endpoints and on predictors. Observed and imputed values were compared using density plots. Five multiple imputations and iterations were performed. Final parameters were computed as described by Rubin[23] and confidence intervals were fitted with bootstrap method. All missing data were imputed simultaneously.

Baseline characteristics were compared using Chi-square or Fisher exact tests for equal proportion, student *t*-tests for normally distributed continuous data, and Wilcoxon rank sum for non-normally distributed continuous data. Normality was checked with Shapiro tests. In addition to the univariable comparison between groups, multivariable comparisons were performed, adjusting for age, APACHE IV scores, occurrence of cardiac arrest pre-ECMO, Charlson comorbidity scores, need of renal replacement therapy pre-ECMO, lactate pre-ECMO, duration of mechanical ventilation pre-ECMO, and any transfer on ECMO. Furthermore, the model was adjusted for Respiratory ECMO Survival Prediction (RESP) scores in the VV-ECMO subgroup, and for SAVE scores in the VA-ECMO and ECPR subgroups. All variables were selected a priori and based on clinical relevance. For the WHODAS score, multivariate analysis was adjusted on scores at baseline. The main analyses were the analyses with imputed data. For ventilation duration, if the patient died within 24 h of extubation, they were considered deceased and not extubated. For all analyses, centres were considered as random effect.

Two sensitivity analyses were performed for all endpoints; a complete case analysis and an analysis excluding any patients who were transferred on ECMO. Additionally, a sensitivity analysis was performed on volume as a continuous variable, but only for the primary endpoint.

3. Results

The number of patients in the EXCEL Registry between 2019 and 2022 was 1377 from 28 hospitals across 5 states of Australia and New Zealand, where the organisation of ECMO services may differ from state to state. After exclusion of transplant patients (n = 143), patients with missing ECMO type (n = 1) and missing transplant information (n = 1), the study size was 1232 patients (Fig. 1), with 39 patients from New Zealand and 11 patients under 18 years of age.

Of the included ECMO patients, 433 were VV-ECMO, 534 were VA-ECMO, and 265 were ECPR-ECMO (Fig. 1). For rates of missing data by subgroup and volume, see Supplemental Table 2. There were five hospitals considered high-volume. Only one hospital was private (low-volume centre) while the rest were public. The number of patients per hospital is presented in Supplemental Table 3.

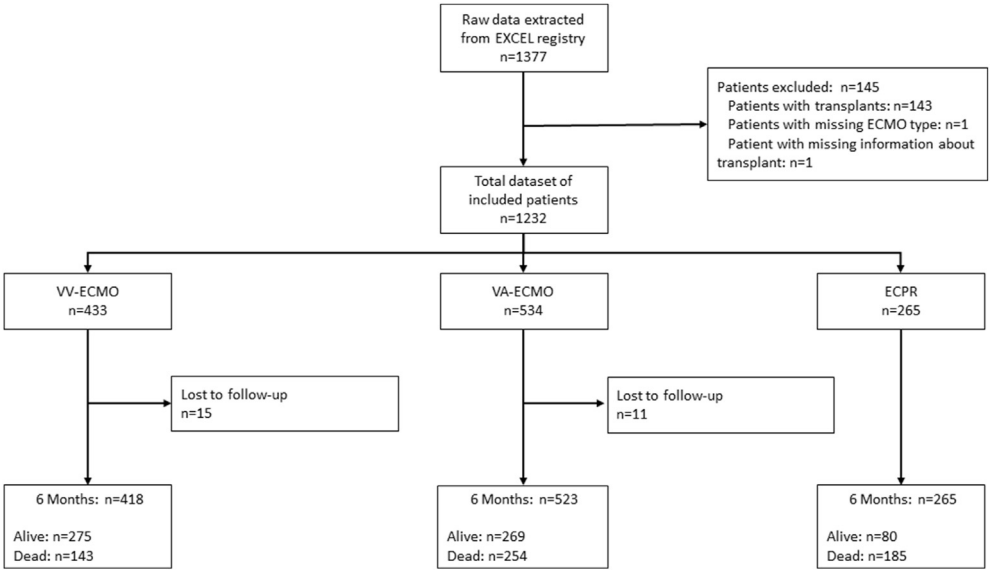

Fig. 1. Flow diagram of patient exclusion and ECMO mode split from raw data set.

3.1. Baseline

The baseline characteristics and diagnoses for subgroups are presented in Supplemental Tables 4–5.

At baseline, VV-ECMO patients were similar between high-and low-volume centres, although diagnoses were different, with high-volume centres having a greater proportion of acute respiratory distress syndrome, and low-volume centres having a greater proportion of asthma and focal lung disease. The number of transferred patients also differed, with high-volume centres reporting more transfers.

At baseline for VA-ECMO, low-volume centre patients were older, with a higher severity of illness (greater APACHE IV scores, worse SAVE), with more comorbidities, and longer ventilation duration pre-ECMO. The number of transferred patients were higher at high-volume centres. However, diagnoses between centres were not significantly different.

ECPR patients at baseline had higher BMIs at low-volume centres, but no significant difference in age, severity scores, or comorbidities. There was no significant difference in diagnoses or transferred patients.

Baseline characteristics for the entire patient population are presented in Supplemental Table 6.

3.2. Primary analysis

In the primary adjusted analysis for VV-ECMO, there was no difference in the primary outcome of death or new disability at 6 months between high- and low-volume centres (adjusted OR: 1.09 [0.65–1.83], p = 0.74) (Table 1), or in other mortality, disability, or length of stay outcomes. The complications during ECMO until 1-week post decannulation were similar between high- and low-volume centres; however, patients at high-volume centres were more likely to have lung infections (adjusted OR: 1.79 [1.06–3.05], p = 0.03).

In the adjusted analysis for VA-ECMO, there was no difference in the primary outcome between high- and low-volume centres [adjusted OR: 1.1 (0.66–1.84), p = 0.71], or in other mortality, complication, and disability related outcomes (Table 2).

In the adjusted analysis for patients who received ECPR, there was no difference in the primary outcome between groups [adjusted OR: 1.38 (0.37–5.08), p = 0.63] (Table 3) or in other outcomes.

For the adjusted analysis of the entire patient population, there was no difference in the primary outcome [adjusted OR: 1.05 (0.76–1.45), p = 0.77]. There were greater odds of lung infection complications in high-volume centres compared with low-volume [adjusted OR: 1.8 (1.18–2.76), p = 0.007], but no differences in other factors (Supplemental Table 7).

3.3. Secondary outcomes

Of note, in unadjusted analyses, there was a greater risk of hospital and 180-day mortality in the overall population (Supplemental Table 7) and in VA-ECMO (Table 3) in low- versus high-volume centres, which was not significant in the adjusted analyses. There was no difference in the unadjusted hospital or 180-day mortality in VV- or ECPR-ECMO.

3.4. Sensitivity analyses

There were no differences in death or new disability at six months across all sensitivity analyses, including for volume as a continuous variable. When excluding transferred patients, outcomes were similar between high- and low-volume centres. For a summary of results, see Supplement pages 10–11. Tables of results for the case complete analysis are presented in Tables 1–3, exclusion of transferred patients presented in Supplemental Tables 8–10, and volume as a continuous variable presented in Supplemental Table 11.

4. Comment

4.1. Discussion

This study found no difference in incidence of death or disability at six months between high- and low-volume centres in patients receiving ECMO. Additionally, other than lung infections, complication rates were comparable. This is the first study to compare annual ECMO volume with six-month mortality and disability outcomes and the findings reflect positively on the functioning of the Australian and New Zealand healthcare system. This includes communication between ECMO centres within each state, patient transfers from low-volume to high-volume ECMO centres for complex cases, mentoring, and training between high- and low-volume centres.

Bailey and McCarthy have previously identified improved outcomes in low-volume centres.[8,13] They similarly found shorter lengths of stay in low-volume centres, but unlike their outcomes, we found reduced unadjusted mortality at high-volume centres. However, McCarthy had found no difference when volume was analysed as a continuous variable, similar to our findings.[13]

One unique aspect of Australia and New Zealand's ECMO system is the coordination of care and large number of transfers between centres. This differs from other regions internationally where ECMO is not coordinated between sites in the same region. Key aspects of such care include centralised communication and transfers, mentoring of low-volume centres, shared access to guidelines, and national education programs. Furthermore, standardisation of medical, nursing, and allied health training and accreditation, including an intensivist-led model of care across Australia and New Zealand ICUs may also contribute to outcomes in these critically unwell patients.[24] These may be factors that drive low-volume centres to be well supported, allowing them to achieve favourable outcomes for ECMO patients.

Even in low-volume centres in our region, mortality rates are similar or better than previously reported international cohorts.[8–11,14–16] For example, Barbaro et al.[7] reported mortality rates of 43%, 60%, and 71% for respiratory, cardiac, and ECPR, respectively. Conversely, patients in this study had lower mortality rates in both high-volume (VV 31%, VA 41%, ECPR 65%) and low-volume centres (VV 31%, VA 50%, ECPR 69%). This reflects possible differences in performance of ECMO use in Australia and New Zealand, which may imply differences in outcomes between regions across the world and inconsistent trends.

We did; however, find a difference in lung infections as a complication during ECMO, with high-volume centres having a greater rate in both VV- and VA-ECMO. The cause and significance of this is currently unclear, but may be related to longer length of stay, different diagnoses, sicker patients despite similar baseline scores, or other unknown factors.

4.2. Impacts on clinical practice

The rigorous training and education conducted in ECMO centres in our region, including simulations, wet-lab, and use of clinical practice guidelines shared across jurisdictions, may be one explanation for the similarity in outcomes between high- and low-volume centres. Our findings support the care of ECMO patients within our current health system at both high- and low-volume centres. Further research into the reason for this includes how low-volumes centres train their staff, develop internal guidelines

Table 1
VV-ECMO outcomes between high- and low-volume centres.

	High-volume (n = 262)	Low-volume (n = 171)	Univariate analysis	Adjusted analysis[a]	
			Effect estimate (95% CI)	Effect estimate (95% CI) Complete cases	Effect estimate (95% CI) Multiple imputations
New disability or death at six months-no. (%)	160/210 (76.2)	101/141 (71.6)	OR, 1.27 (0.78–2.06), p = 0.34	OR, 1.17 (0.61–2.23), p = 0.63	OR, 1.09 (0.65–1.83), p = 0.74
New disability at six months-no. (%)	73/123 (59.3)	45/85 (52.9)	OR, 1.30 (0.74–2.28), p = 0.37	OR, 1.11 (0.54–2.27), p = 0.78	OR, 0.94 (0.51–1.74), p = 0.84
WHODAS overall score (%)	22.9 [6.2, 45.8]	18.8 [6.2, 37.0]	MD, 4.17 (−5.16 to 13.49), p = 0.38	MD, 4.87 (−8.62 to 18.36), p = 0.48	MD, 3.90 (−10.58 to 18.37), p = 0.60
Disability at six months-no. (%)[b]	68/136 (50.0)	39/88 (44.3)	OR, 1.26 (0.73–2.15), p = 0.41	OR, 1.73 (0.80–3.75), p = 0.17	OR, 1.38 (0.7–2.72), p = 0.35
No disability	31/131 (23.7)	20/86 (23.3)	COR, 1.23 (−0.28 to 0.69), p = 0.40	COR, 1.32 (0.71–2.44), p = 0.38	COR, 1.29 (0.71–2.34), p = 0.40
Mild disability	37/131 (28.2)	29/86 (33.7)	COR, 1.23 (−0.28 to 0.69), p = 0.40	COR, 1.32 (0.71–2.44), p = 0.38	COR, 1.29 (0.71–2.34), p = 0.40
Moderate disability	33/131 (25.2)	24/86 (27.9)	COR, 1.23 (−0.28 to 0.69), p = 0.40	COR, 1.32 (0.71–2.44), p = 0.38	COR, 1.29 (0.71–2.34), p = 0.40
Severe disability	27/131 (20.6)	13/86 (15.1)	COR, 1.23 (−0.28 to 0.69), p = 0.40	COR, 1.32 (0.71–2.44), p = 0.38	COR, 1.29 (0.71–2.34), p = 0.40
Complete disability	3/131 (2.3)	0/86 (0.0)	COR, 1.23 (−0.28 to 0.69), p = 0.40	COR, 1.32 (0.71–2.44), p = 0.38	COR, 1.29 (0.71–2.34), p = 0.40
Hospital mortality-no. (%)	81/261 (31.0)	53 (31.0)	OR, 0.98 (0.62–1.56), p = 0.95	OR, 1.05 (0.59–1.86), p = 0.86	OR, 1.07 (0.65–1.76), p = 0.79
Complications during ECMO until 1 week post decannulation-no. (%)					
RRT under ECMO-no. (%)	104/247 (42.1)	57/160 (35.6)	OR, 1.36 (0.77–2.39), p = 0.29	OR, 1.00 (0.59–1.71), p = >0.99	OR, 1 (0.54–1.84), p = 0.99
Pneumothorax-no. (%)	20 (7.6)	10 (5.8)	OR, 1.13 (0.40–3.20), p = 0.81	OR, 1.09 (0.27–4.45), p = 0.90	OR, 1.17 (0.4–3.45), p = 0.78
Cardiac arrest-no. (%)	7 (2.7)	4 (2.3)	OR, 1.15 (0.33–3.98), p = 0.83	OR, 0.84 (0.17–4.19), p = 0.84	OR, 0.63 (0.15–2.65), p = 0.53
Major bleeding-no. (%)	42 (16.0)	20 (11.7)	OR, 1.48 (0.75–2.92), p = 0.26	OR, 1.86 (0.88–3.93), p = 0.10	OR, 1.6 (0.85–3), p = 0.14
Pulmonary embolism-no. (%)	16 (6.1)	8 (4.7)	OR, 1.33 (0.55–3.17), p = 0.53	OR, 0.81 (0.26–2.50), p = 0.71	OR, 1.14 (0.42–3.09), p = 0.80
Cerebral ischaemia-no. (%)	19 (7.3)	8 (4.7)	OR, 1.59 (0.68–3.73), p = 0.28	OR, 0.94 (0.32–2.75), p = 0.92	OR, 1.51 (0.59–3.86), p = 0.39
Cerebral haemorrhage-no. (%)	11 (4.2)	8 (4.7)	OR, 0.89 (0.35–2.27), p = 0.81	OR, 0.58 (0.18–1.89), p = 0.36	OR, 0.91 (0.31–2.67), p = 0.87
Lung infection-no. (%)	137 (52.3)	61 (35.7)	OR, 1.98 (1.20–3.27), p = 0.007	OR, 1.45 (0.88–2.40), p = 0.14	OR, 1.79 (1.06–3.05), p = 0.03
Thrombosis of ECMO circuit-no. (%)	7 (2.7)	6 (3.5)	OR, 0.75 (0.25–2.29), p = 0.62	OR, 0.68 (0.18–2.54), p = 0.56	OR, 0.82 (0.24–2.81), p = 0.76
Thrombosis of ECMO filter-no. (%)	4 (1.5)	0 (0.0)			
Total duration of invasive mechanical ventilation (days)	20.7 [10.0, 41.1]	19.5 [9.2, 44.6]	SHR, 0.92 (0.73–1.17), p = 0.51	SHR, 0.94 (0.72–1.21), p = 0.60	SHR, 0.91 (0.70–1.19), p = 0.51
ICU length of stay, days	25.7 [13.0, 44.9]	25.7 [12.7, 48.0]	SHR, 0.76 (0.59–0.98), p = 0.04	SHR, 0.80 (0.63–1.01), p = 0.06	SHR, 0.80 (0.62–1.04), p = 0.10
ICU LOS among discharged patients, days	24.9 [15.1, 49.6]	27.5 [13.8, 48.6]			
Hospital length of stay, days	36.4 [20.6, 61.1]	35.4 [19.7, 66.9]	SHR, 0.70 (0.45–1.07), p = 0.10	SHR, 0.87 (0.59–1.28), p = 0.49	SHR, 0.81 (0.58–1.14), p = 0.23
Hospital LOS among discharged patients, days	34.0 [19.7, 53.1]	29.8 [18.2, 57.9]			
180 days mortality-no. (%)	87/251 (34.7)	56/167 (33.5)	OR, 1.05 (0.70–1.59), p = 0.81	OR, 1.08 (0.61–1.93), p = 0.79	OR, 1.11 (0.68–1.81), p = 0.68

Data are median (quartile 25th–quartile 75th) or N (%).
An odds ratio >1 indicates an increased odds of an event occurring at a high-volume centre, thus an odds ratio >1 means worse outcomes at high-volume centres and <1 means better outcomes at high-volume centres. For length of stay, a subdistribution hazard ratio <1 means that high-volume centres are associated with a decrease in rate of discharged patients at any timepoint. This may be interpreted as patients at high-volume centres are discharged later. For ventilation duration, <1 means high-volume centres are associated with a decreased rate of extubation at a given time, which may be interpreted as high-volume centre patients having longer ventilation duration. Abbreviations: ICU is intensive care unit, ECMO is extracorporeal membrane oxygenation, CI is confidence interval, COR is competing odds ratio, LOS is length of stay, OR is odds ratio, HR is hazard ratio, RRT is renal replacement therapy, SHR is subdistribution hazard ratio, MD is median difference, and WHODAS is World Health Organization Disability Assessment Schedule.

[a] All models adjusted for age, APACHE IV, occurrence of cardiac arrest pre-ECMO, Charlson comorbidity score, need of renal replacement therapy, lactate pre-ECMO, duration of mechanical ventilation pre-ECMO, and transfer status. VV-ECMO was also adjusted for RESP score. Site included as random effect.

[b] Unable to account for the centre for this outcome in each population. Model ran without random effect.

Table 2
VA-ECMO outcomes between high- and low-volume centres.

	High-volume (n = 276)	Low-volume (n = 258)	Univariate analysis	Adjusted analysis[a]	
			Effect estimate (95% CI)	Effect estimate (95% CI) Complete cases	Effect estimate (95% CI) Multiple imputations
New disability or death at six months-no. (%)	162/224 (72.3)	174/234 (74.4)	OR, 0.89 (0.53−1.50), p = 0.66	OR, 1.46 (0.86−2.50), p = 0.16	OR, 1.1 (0.66−1.84), p = 0.71
New disability at six months-no. (%)	42/104 (40.4)	40/100 (40.0)	OR, 1.02 (0.47−2.23), p = 0.95	OR, 1.23 (0.51−2.98), p = 0.65	OR, 1.28 (0.69−2.37), p = 0.43
WHODAS overall score (%)	12.5 [4.2, 31.2]	15.6 [4.2, 31.8]	MD, −3.80 (−12.94 to 5.34), p = 0.42	MD, −2.81 (−14.15 to 8.54), p = 0.63	MD, 1.43 (−10.65 to 13.51), p = 0.82
Disability at six months-no. (%)	39/114 (34.2)	32/101 (31.7)	OR, 1.10 (0.57−2.12), p = 0.78	OR, 1.15 (0.53−2.52), p = 0.72	OR, 1.24 (0.64−2.37), p = 0.52
No disability	31/114 (27.2)	27/100 (27.0)	COR, 1.06 (−0.43 to 0.55), p = 0.82	COR, 0.87 (0.49−1.53), p = 0.63	COR, 4.56 (0.03−791.6), p = 0.48
Mild disability	44/114 (38.6)	42/100 (42.0)	COR, 1.06 (−0.43 to 0.55), p = 0.82	COR, 0.87 (0.49−1.53), p = 0.63	COR, 4.56 (0.03−791.6), p = 0.48
Moderate disability	27/114 (23.7)	20/100 (20.0)	COR, 1.06 (−0.43 to 0.55), p = 0.82	COR, 0.87 (0.49−1.53), p = 0.63	COR, 4.56 (0.03−791.6), p = 0.48
Severe disability	12/114 (10.5)	11/100 (11.0)	COR, 1.06 (−0.43 to 0.55), p = 0.82	COR, 0.87 (0.49−1.53), p = 0.63	COR, 4.56 (0.03−791.6), p = 0.48
Hospital mortality-no. (%)	113/275 (41.1)	130 (50.4)	OR, 0.69 (0.49−0.97), p = 0.03	OR, 1.21 (0.78−1.90), p = 0.39	OR, 0.96 (0.65−1.41), p = 0.84
Complications during ECMO until 1 week post decannulation-no. (%)					
RRT under ECMO-no. (%)	125/257 (48.6)	127/238 (53.4)	OR, 0.73 (0.38−1.40), p = 0.34	OR, 0.70 (0.37−1.32), p = 0.27	OR, 0.79 (0.45−1.39), p = 0.41
Pneumothorax-no. (%)	14 (5.1)	8 (3.1)	OR, 1.45 (0.41−5.14), p = 0.56	OR, 0.95 (0.29−3.15), p = 0.94	OR, 0.93 (0.24−3.57), p = 0.92
Cardiac arrest-no. (%)	11 (4.0)	11 (4.3)	OR, 0.93 (0.40−2.19), p = 0.87	OR, 0.90 (0.34−2.38), p = 0.84	OR, 1.2 (0.48−3.01), p = 0.70
Major bleeding-no. (%)	66 (23.9)	47 (18.2)	OR, 1.43 (0.68−3.02), p = 0.35	OR, 1.58 (0.87−2.88), p = 0.14	OR, 1.52 (0.69−3.37), p = 0.30
Pulmonary embolism-no. (%)	4 (1.4)	3 (1.2)	OR, 1.25 (0.28−5.64), p = 0.77	OR, 1.65 (0.33−8.27), p = 0.54	OR, 1.27 (0.26−6.26), p = 0.77
Cerebral ischaemia-no. (%)	37 (13.4)	22 (8.5)	OR, 1.63 (0.59−4.52), p = 0.35	OR, 1.26 (0.43−3.69), p = 0.67	OR, 1.36 (0.49−3.78), p = 0.56
Cerebral haemorrhage-no. (%)	4 (1.4)	7 (2.7)	OR, 0.49 (0.12−2.04), p = 0.33	OR, 0.60 (0.16−2.33), p = 0.46	OR, 0.42 (0.11−1.58), p = 0.20
Lung infection-no. (%)	102 (37.0)	59 (22.9)	OR, 2.14 (1.14−4.02), p = 0.02	OR, 2.02 (1.02−4.00), p = 0.05	OR, 2.01 (1.08−3.74), p = 0.03
Thrombosis of ECMO circuit-no. (%)	7 (2.5)	7 (2.7)	OR, 0.96 (0.21−4.37), p = 0.96	OR, 2.32 (0.35−15.58), p = 0.39	OR, 0.9 (0.19−4.3), p = 0.89
Thrombosis of ECMO filter-no. (%)	6 (2.2)	2 (0.8)	OR, 0.46 (0.00−90.91), p = 0.77	OR, 0.94 (0.01−58.82), p = 0.98	OR, 1.3 (0.02−93.51), p = 0.90
Total duration of invasive mechanical ventilation (days)	9.8 [5.0, 16.9]	8.9 [4.8, 16.7]	SHR, 1.39 (1.11−1.74), p = 0.005	SHR, 1.03 (0.81−1.32), p = 0.81	SHR, 1.16 (0.92−1.45), p = 0.21
ICU length of stay, days	15.7 [7.9, 27.1]	11.7 [5.6, 22.6]	SHR, 1.21 (0.94−1.56), p = 0.13	SHR, 0.88 (0.70−1.10), p = 0.25	SHR, 1.02 (0.80−1.28), p = 0.89
ICU LOS among discharged patients, days	18.5 [12.5, 31.3]	17.9 [10.9, 29.8]			
Hospital length of stay, days	28.0 [14.1, 48.0]	22.9 [9.0, 42.1]	SHR, 1.19 (0.79−1.79), p = 0.41	SHR, 0.84 (0.56−1.27), p = 0.41	SHR, 0.96 (0.67−1.40), p = 0.85
Hospital LOS among discharged patients, days	36.3 [20.6, 50.7]	35.6 [22.3, 55.0]			
180 days mortality-no. (%)	120/270 (44.4)	134/253 (53.0)	OR, 0.71 (0.50−1.00), p = 0.05	OR, 1.29 (0.83−2.02), p = 0.26	OR, 1.01 (0.69−1.48), p = 0.96

Data are median (quartile 25th−quartile 75th) or N (%).
An odds ratio >1 indicates an increased odds of an event occurring at a high-volume centre, thus an odds ratio >1 means worse outcomes at high-volume centres and <1 means better outcomes at high-volume centres. For length of stay, a subdistribution hazard ratio <1 means that high-volume centres are associated with a decrease in rate of discharged patients at any timepoint. This may be interpreted as patients at high-volume centres are discharged later. For ventilation duration, <1 means high-volume centres are associated with a decreased rate of extubation at a given time, which may be interpreted as high-volume centre patients having longer ventilation duration. Abbreviations: ICU is intensive care unit, ECMO is extracorporeal membrane oxygenation, CI is confidence interval, COR is competing odds ratio, LOS is length of stay, OR is odds ratio, HR is hazard ratio, RRT is renal replacement therapy, SHR is subdistribution hazard ratio, MD is median difference, and WHODAS is World Health Organization Disability Assessment Schedule.

[a] All models adjusted for age, APACHE IV, occurrence of cardiac arrest pre-ECMO, Charlson comorbidity score, need of renal replacement therapy, lactate pre-ECMO, duration of mechanical ventilation pre-ECMO, and transfer status. VV-ECMO was also adjusted for RESP score. Site included as random effect.

Table 3
ECPR-ECMO outcomes between high- and low-volume centres.

	High-volume (n = 125)	Low-volume (n = 140)	Univariate analysis	Adjusted analysis[a]	
			Effect estimate (95% CI)	Effect estimate (95% CI) Complete cases	Effect estimate (95% CI) Multiple imputations
New disability or death at 6 months-no. (%)	100/119 (84.0)	117/136 (86.0)	OR, 1.17 (0.36–3.80), p = 0.80	OR, 1.48 (0.42–5.24), p = 0.54	OR, 1.38 (0.37–5.08), p = 0.63
New disability at 6 months-no. (%)	16/35 (45.7)	16/35 (45.7)	OR, 1.68 (0.30–9.31), p = 0.55	OR, 1.61 (0.43–6.07), p = 0.48	OR, 0.85 (0.25–2.82), p = 0.79
WHODAS Overall Score (%)	12.5 [2.1, 27.1]	16.7 [4.2, 35.4]	MD, −4.17 (−21.55 to 13.22), p = 0.64	MD, 0.33 (−15.15 to 15.80), p = 0.97	MD, −9.48 (−24.26 to 5.30), p = 0.22
Disability at six months-no. (%)	10/37 (27.0)	16/35 (45.7)	OR, 0.68 (0.15–3.18), p = 0.62	OR, 0.95 (0.10–8.86), p = 0.96	OR, 0.43 (0.12–1.53), p = 0.19
No disability	12/37 (32.4)	11/35 (31.4)	COR, 0.61 (−1.35 to 0.35), p = 0.25	COR, 0.76 (0.24–2.47), p = 0.65	COR, 0.52 (0.21–1.25), p = 0.15
Mild disability	15/37 (40.5)	8/35 (22.9)	COR, 0.61 (−1.35 to 0.35), p = 0.25	COR, 0.76 (0.24–2.47), p = 0.65	COR, 0.52 (0.21–1.25), p = 0.15
Moderate disability	9/37 (24.3)	12/35 (34.3)	COR, 0.61 (−1.35 to 0.35), p = 0.25	COR, 0.76 (0.24–2.47), p = 0.65	COR, 0.52 (0.21–1.25), p = 0.15
Severe disability	0/37 (0.0)	4/35 (11.4)	COR, 0.61 (−1.35 to 0.35), p = 0.25	COR, 0.76 (0.24–2.47), p = 0.65	COR, 0.52 (0.21–1.25), p = 0.15
Complete disability	1/37 (2.7)	0/35 (0.0)	COR,0.61 (−1.35 to 0.35), p = 0.25	COR,0.76 (0.24–2.47), p = 0.65	COR,0.52 (0.21–1.25), p = 0.15
Hospital mortality-no. (%)	81 (64.8)	96/139 (69.1)	OR, 0.87 (0.47–1.61), p = 0.65	OR, 1.09 (0.42–2.84), p = 0.86	OR, 0.98 (0.45–2.13), p = 0.97
Complications during ECMO until 1 week post decannulation-no. (%)					
RRT under ECMO-no. (%)	57/116 (49.1)	64/137 (46.7)	OR, 1.15 (0.60–2.21), p = 0.68	OR, 1.23 (0.58–2.57), p = 0.59	OR, 1.19 (0.66–2.16), p = 0.56
Pneumothorax-no. (%)	5 (4.0)	4 (2.9)	OR, 1.42 (0.37–5.40), p = 0.61		OR, 1.5 (0.37–6.12), p = 0.58
Cardiac arrest-no. (%)	6 (4.8)	7 (5.0)	OR, 1.08 (0.27–4.27), p = 0.91	OR, 0.37 (0.04–3.03), p = 0.35	OR, 1.14 (0.35–3.71), p = 0.83
Major bleeding-no. (%)	23 (18.4)	23 (16.4)	OR, 1.12 (0.56–2.26), p = 0.75	OR, 1.63 (0.50–5.38), p = 0.42	OR, 1.13 (0.55–2.34), p = 0.73
Pulmonary embolism-no. (%)	1 (0.8)	1 (0.7)	OR, 1.12 (0.07–18.11), p = 0.94		OR, 0.78 (0.03–19.73), p = 0.88
Cerebral ischaemia-no. (%)	30 (24.0)	30 (21.4)	OR, 1.12 (0.58–2.14), p = 0.74	OR, 1.25 (0.55–2.83), p = 0.60	OR, 1.2 (0.58–2.48), p = 0.62
Cerebral haemorrhage-no. (%)[b]	2 (1.6)	4 (2.9)	OR, 1.45 (0.05–38.87), p = 0.82	OR, 1.66 (0.06–50.10), p = 0.77	OR, 1.15 (0.06–22.54), p = 0.93
Lung infection-no. (%)	36 (28.8)	33 (23.6)	OR, 1.31 (0.76–2.27), p = 0.33	OR, 1.43 (0.59–3.47), p = 0.42	OR, 1.24 (0.69–2.23), p = 0.46
Thrombosis of ECMO circuit-no. (%)	1 (0.8)	2 (1.4)	OR, 0.56 (0.05–6.21), p = 0.63		OR, 0.62 (0.04–9.56), p = 0.74
Thrombosis of ECMO filter-no. (%)	1 (0.8)	3 (2.1)	OR, 0.55 (0.03–10.01), p = 0.69		
Total duration of invasive mechanical ventilation (days)	4.9 [1.5, 11.1]	4.1 [1.1, 11.9]	SHR, 1.24 (0.73–2.10), p = 0.43	SHR, 1.29 (0.65–2.56), p = 0.46	SHR, 1.16 (0.62–2.15), p = 0.64
ICU length of stay, days	6.8 [1.5, 15.0]	6.2 [1.0, 14.7]	SHR, 1.24 (0.71–2.16), p = 0.46	SHR, 1.24 (0.69–2.23), p = 0.47	SHR, 1.16 (0.61–2.21), p = 0.65
ICU LOS among discharged patients, days	15.0 [8.8, 23.0]	16.0 [10.7, 21.7]			
Hospital length of stay, days	10.1 [2.1, 27.3]	7.7 [1.8, 22.9]	SHR, 1.55 (0.72–3.35), p = 0.27	SHR, 1.07 (0.55–2.11), p = 0.84	SHR, 1.57 (0.70–3.52), p = 0.27
Hospital LOS among discharged patients, days	29.7 [15.0, 40.1]	29.1 [20.6, 52.7]			
180 days mortality-no. (%)	84 (67.2)	101 (72.1)	OR, 0.85 (0.45–1.61), p = 0.61	OR, 0.78 (0.31–1.94), p = 0.59	OR, 0.95 (0.43–2.07), p = 0.89

Data are median (quartile 25th–quartile 75th) or N (%).
An odds ratio >1 indicates an increased odds of an event occurring at a high-volume centre, thus an odds ratio >1 means worse outcomes at high-volume centres and <1 means better outcomes at high-volume centres. For length of stay, a subdistribution hazard ratio <1 means that high-volume centres are associated with a decrease in rate of discharged patients at any timepoint. This may be interpreted as patients at high-volume centres are discharged later. For ventilation duration, <1 means high-volume centres are associated with a decreased rate of extubation at a given time, which may be interpreted as high-volume centre patients having longer ventilation duration.
Abbreviations: ICU is intensive care unit, ECMO is extracorporeal membrane oxygenation, CI is confidence interval, COR is competing odds ratio, LOS is length of stay, OR is odds ratio, HR is hazard ratio, RRT is renal replacement therapy, SHR is subdistribution hazard ratio, MD is median difference, and WHODAS is World Health Organization Disability Assessment Schedule.

[a] All models adjusted for age, APACHE IV, occurrence of cardiac arrest pre-ECMO, Charlson comorbidity score, need of renal replacement therapy, lactate pre-ECMO, duration of mechanical ventilation pre-ECMO, and transfer status. VV-ECMO was also adjusted for RESP score. Site included as random effect.

[b] Unable to adjust for RRT on the endpoint.

and/or use external guidelines, or rely on high-volume centre expertise via referral.

4.3. Limitations

A significant challenge in this study was the transfer status of patients. Patients had frequent transfers for a variety of reasons. These high rates of transfer were a direct result of the coordination of care, and we attempted to account for this by adjusting for transfer status and performing a sensitivity analysis excluding these patients. Furthermore, missing data presents a major limitation, particularly in disability in VA-ECMO with differences in rates of missing data between high- and low-volume centres. There is a potential for recall bias, with patients or their families possibly over- or under-estimating their functional abilities at baseline. However, it is unclear whether data were missing due to potential bias or random effect. Also, New Zealand hospitals contributed to a very small proportion of cases (3%), which limits the applicability of these results to New Zealand.

While the WHODAS 12-level score provides a good overview of global disability, other outcome measures may provide greater detail into specific physical, psychological, and social engagement.

This study also included patients admitted during the COVID-19 pandemic, which may have affected the results, especially since ECMO mortality outcomes in COVID patients were high (54% at 90-days) and strongly related to hospital-volume.[25] In our cohort; however, rates of COVID were similar between high- and low-volume centres across subgroups, although we did not adjust for this in our analysis. Beyond direct impacts of COVID infections, Australia and New Zealand had significant restrictions and infection control measures in place, especially in the early years. These restrictions and re-allocation of resources (e.g. equipment, staffing) have the potential to indirectly affect VA-ECMO and ECPR outcomes.

The lack of a significant difference may be the result of this study being underpowered. The confidence intervals were wide and for mortality ranged from 35% harm to 83% benefit for high-volume centres. Small differences in outcomes may present more clearly and with greater power as the EXCEL registry increases in size over time. Given the high-risk and expensive nature of ECMO, such small differences are likely to be clinically relevant. In addition, given our analysis of numerous outcomes, there is a risk of type 1 errors from multiple testing which might further decrease our capacity to identify real differences.

Lastly, over 85% of high-volume cases came from the top three hospitals, which may limit generalisability beyond these few hospitals and introduce bias.

4.4. Future directions

While this study observed no difference in outcomes between high- and low-volume centres in Australia and New Zealand, ongoing monitoring is required to ensure these outcomes are maintained. It is unclear if this study can be extrapolated to other regions and further international studies are required with an emphasis on long-term and functional outcomes. Future directions should include an analysis of the cost-effectiveness of high vs low services to guide further government funding and resource allocation. Lastly, this study only addressed annual ECMO volume. Further work should investigate any potential benefit of centralised ECMO services (with all patients being transferred and managed by a small number of centres) versus allowing patients to be treated at their initial hospital. Overall, long-term and functional outcomes are crucial markers of success, and should be a greater focus in all future research.

4.5. Conclusion

In Australia and New Zealand, there was no difference in death or disability at six months between high- and low-volume centres, possibly due to the current model of coordinated care that includes patient transfers and training between high- and low-volume ECMO centres in our region. The certainty of this finding is limited by the EXCEL Registry size, leading to wide confidence intervals for most comparisons, and ongoing monitoring over time is required to confirm these findings.

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Conflict of interest

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Credit authorship contribution statement

CLH, ASN, ADE and AMH conceived of the study. BJF was project manager. MB and ACN analysed the data. ADE, CLH, ACN and AMH drafted the manuscript. All authors read and edited the final manuscript and contributed to final version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2024.08.006.

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