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Left ventricular unloading during extracorporeal cardiopulmonary resuscitation: a target trial emulation of the ELSO registry

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Abstract

Background Patients who undergo extracorporeal cardiopulmonary resuscitation (ECPR) are at risk of left ventricular distention and complications. There is emerging evidence that concurrent mechanical left ventricular (LV) unloading (e.g. an intra-aortic balloon pump, or microaxial left ventricular assist device) may improve survival. Despite this, there are no large, well-conducted studies investigating the impact of LV unloading on outcomes in ECPR.

Methods We queried the Extracorporeal Life Support Organisation (ELSO) registry between 2020 and 2023, and used an emulated target trial framework to investigate the association between concurrent mechanical left ventricular unloading and outcomes in patients receiving ECPR. We imputed missing data using multiple imputation with chained equations, and identified potential confounders implicated in the causal pathway between ECPR and survival time up to 90 days (primary outcome). We used propensity score-matching to adjust for potential confounders, and analysed the primary outcome using a Cox proportional hazards model. We then emulated further target trials based on the inclusion criteria of prior ECPR RCTs to assess whether concurrent unloading was associated with better outcomes based on these criteria. Secondary outcomes included complications from ECPR as classified by ELSO, and survival with favourable functional outcome defined as a Cerebral Performance Category (CPC) 1–2.

Results Of the 3,215 patients included in our analysis, we matched 621 pairs of patients who did and did not receive LV unloading. There were no significant differences in survival time between both groups (HR 0.92, 95%-CI 0.79–1.08), nor survival with favourable functional outcomes (OR 1.15, 95%-CI 0.67–1.99). This was concordant across several sensitivity analyses. Of note, LV unloading was associated with a higher rate of renal (OR 1.55, 95%-CI 1.16–2.07) and cardiovascular (OR 1.60, 95%-CI 1.14–2.26) complications. LV unloading was also associated with central nervous system bleeding (OR 1.75, 95%-CI 1.03–2.96), arrhythmias (OR 1.56, 95%-CI 1.04–2.36), and haemolysis (OR 1.85, 95%-CI 1.10–3.09).

Conclusions Left ventricular unloading was not associated with improved survival in the context of ECPR and may increase complication rates. Randomised data are required to confirm these findings.

Keywords Extracorporeal membrane oxygenation, Cardiopulmonary resuscitation, Cardiac arrest, Left ventricle

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Introduction

Cardiac arrest imposes a major healthcare burden–approximately 600,000 people suffer from cardiac arrests annually in the United States of America alone, half of which are in-hospital cardiac arrests (IHCA) and the other half originate out-of-hospital [1, 2]. Globally, nearly 4 million people suffer from out-of-hospital cardiac arrest (OHCA) annually [3]. The risk-adjusted incidence of IHCA was 8.5 per 1,000 hospital admissions [4], the majority of which occur in intensive care units[5]. Survival rates have plateaued since 2014 [6], and more recently, decreased during the COVID-19 pandemic [7].

In refractory cardiac arrest, where conventional management with medications and cardiopulmonary resuscitation may be insufficient, the use of venoarterial extracorporeal membrane (VA ECMO) as extracorporeal cardiopulmonary resuscitation (ECPR) may improve outcomes. Meta-analyses of propensity score-matched studies and randomised controlled trials have found that ECPR is associated with lower mortality in both IHCA and OHCA [8–12]. However, given its retrograde aortic blood flow based on the femoral access of the perfusion cannula, peripheral VA ECMO may be associated with increased left ventricular afterload, leading to complications [13]. In the setting of cardiogenic shock, studies and meta-analyses have found that the use of a left ventricular (LV) unloading device may be associated with reductions in mortality [14, 15]. More recently, a meta-analysis of unadjusted observational studies on ECPR reported lower mortality in patients with a concurrent microaxial left ventricular assist device (mLVAD) [16] and intra-aortic balloon pump (IABP) [17]. However, adjusted analyses in studies using propensity score-matching did not report a significant reduction in mortality with mLVAD [16]; the meta-analysis on IABP did not conduct adjusted analyses. In addition, the studies recorded in the meta-analysis were mostly single-centre studies and of small sample size. On this backdrop, we analysed the Extracorporeal Life Support Organization (ELSO) registry – an international multicentre registry of patients supported on ECMO and used a target trial emulation framework to assess the association between LV unloading and mortality in patients receiving ECPR.

Methods

Study design and setting

In this cohort study, we harnessed the target trial emulation framework [18, 19] to assess the association of LV unloading in patients receiving ECPR with mortality. More information about target trial emulation is described in the Supplementary Methods. In this hypothetical target trial, we specified two arms. The first arm was assigned to receive ECPR during cardiac arrest (control arm), and the second arm was assigned to receive ECPR and mechanical LV unloading (intervention arm, either IABP or mLVAD). We then emulated the hypothetical target trial using observational data from the ELSO registry, which collects anonymised data on patients receiving ECMO from more than 300 active centres globally. All data entered into the ELSO registry are based on a standardised form by site managers who have been trained and certified for data entry. We received approval by the institutional review board of the National University Hospital, Singapore (NUH-RNR-2024–0024), and adhered to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement. We received approval for analysis by ELSO after external peer review by members of the ELSO Scientific Oversight Committee (ELSO request #2811).

Eligibility criteria

We included adults (≥18 years) who received ECPR for either IHCA or OHCA between 1/1/2020 through 31/12/2023; follow up data were last updated on 28/3/24. If patients received more than one run of ECMO, we used the data from their first run of ECMO. We excluded patients who received other modes of ECMO (including venoarterial ECMO in cardiogenic shock without cardiac arrest and venovenous ECMO).

Treatment strategy and assignment

We defined mechanical LV unloading using the appropriate Current Procedural Terminology (CPT®) codes, which are recorded by the ELSO registry (see Supplementary Methods). Patients were allocated into one of the two treatment strategies based on whether they received mechanical LV unloading during the ECPR run.

Follow-up and outcomes

Follow-up was started from initiation of ECPR, when patients were eligible to receive mechanical LV unloading. The primary outcome was survival time up to 90 days; patients who were alive beyond 90 days of follow-up were censored at 90 days. Secondary outcomes included the duration of ECMO, length of hospital stay, and complications after ECMO initiation. We defined complications broadly as classified by ELSO (see Supplementary Methods), and specifically looked at several mechanical (circuit change, circuit venous thromboembolism), neurological (central nervous system infarct/ischaemia, central nervous system bleeding), cardiovascular (cardiopulmonary resuscitation required, arrhythmia, tamponade), and metabolic (haemolysis) complications.

Data synthesis

We summarised participant demographics and clinical characteristics using descriptive statistics. We summarised continuous variables using the median and interquartile range (25–75th percentiles) and for categorical variables, we used counts and percentage.

In order to estimate the treatment effect of receiving LV unloading while receiving ECPR, we identified potential confounders which required adjustment in the analysis using a causal directed acyclic graph, and used a propensity score-matching analysis to adjust for these covariates (see Supplementary Methods). We then estimated survival time up to 90 days from initiation of ECPR using the Kaplan–Meier method, and compared survival time between both groups using a Cox proportional hazards model, and the log-rank test. In the presence of missing data, we used multiple imputation to propagate the uncertainty of the missingness (see Supplementary Methods) [20]. Assuming a two-tailed α value of 0.05, and a β value of 0.20, equal distribution of participants between both groups, and a conservative relative hazards of 0.8 (given that the literature suggests that unloading is associated with a 0.33 to 0.5 odds of mortality) [16], the minimum number of events (deaths) required is 158.

We conducted sensitivity analyses to assess the robustness of the primary analysis. First, we conducted the analysis using an inverse probability of treatment weighting method. Second, to reduce the amount of residual confounding, we assessed the standardised mean difference (SMD) of each covariate in the matched cohort, and reiterated the matching algorithm, including any covariates with an SMD > 0.10 [21]. Separately, we performed double-adjustment, repeating the primary analysis and adjusting for the covariates included in the original matching algorithm. Third, we conducted the analysis using a complete-case analysis, excluding patients who had missing data. Fourth, we conducted additional target trial emulations of previously published RCTs [8–10] investigating ECPR in cardiac arrest, with the aim of understanding whether LV unloading is associated with any benefits compared to ECPR in the context of these trials. Briefly, using multiple imputed data, we adopted the inclusion and exclusion criteria of each trial, matched patients using the propensity score model, and estimated the difference in survival time between patients who did and did not receive LV unloading (see Supplementary Methods).

We then conducted several subgroup analyses. We stratified the analysis based on the type of LV unloading (IABP or mLVAD), the aetiology of cardiac arrest (cardiac vs. non-cardiac), the initial presenting rhythm (shockable [pulseless ventricular tachycardia or fibrillation] or non-shockable [pulseless electrical activity, asystole]), and location of cardiac arrest (OHCA or IHCA). For continuous covariates of interest (age [for every increase by 10 years], centre volume [for every increase by 10 cases per year] and duration of cardiopulmonary resuscitation (CPR) prior to ECMO [for every increase by 10 min]), we introduced an interaction term to assess if each covariate altered the association between LV unloading and survival time. Given the increased risk of type 1 error with multiple testing, the results of the subgroup analyses should be viewed as exploratory and we did not adjust for multiplicity.

For secondary outcomes, we analysed continuous outcomes by estimating the absolute difference and 95% confidence intervals, and categorical outcomes using logistic regression and estimating the odds of each complication.

Protocol deviations

We did a post-hoc meta-analysis, summarising the literature and pooling the available data of propensity score-matched studies reporting on LV unloading during ECPR. Briefly, we conducted random-effects Mantel–Haenszel meta-analyses [22, 23], and reported the association between LV unloading and mortality using pooled odds ratios. As all the included studies reported 30-day mortality, we estimated the adjusted 30-day mortality rate from the propensity score-matched cohort, and included these results in the meta-analysis. More details on the meta-analysis are described in the Supplementary Methods.

We also conducted two additional post-hoc sensitivity analyses. First, we shortlisted a number of potential pre-existing conditions which may be deemed as contraindications to ECPR and LV unloading in accordance with previous RCTs and generally accepted practice (stroke/severe neurological impairment, severe bleeding, limb ischaemia, and vasoplegia); we did a sensitivity analysis excluding these patients. Second, we repeated the primary analysis, adding percutaneous coronary interventions (PCI) into the propensity score-matching algorithm.

Role of the funding source

There was no funding source for this study.

Results

Between 1 January, 2020, and 31 December, 2023, 7,911 patients receiving ECPR were reported to the ELSO registry, of which 3,736 patients had a valid ECPR addendum. After applying our inclusion and exclusion criteria, we included 3,215 patients in our study (median centre volume: 7, IQR: 3–13, Fig. 1). The median age was 57 years (IQR: 45–66), and 2,198 (68.4%) were males. 1,419 (44.1%) patients presented with a shockable rhythm, and

1,876 patients (74%) had an IHCA. The median duration of conventional CPR was 44 min (IQR: 22–58), and patients received ECMO for 67 h (IQR: 21–136). 344 patients received IABP, while 323 patients received mLVAD as the mechanical LV unloading device (Tables S1-S3). After applying propensity score-matching, we matched 621 pairs of patients who did and did not receive LV unloading. The baseline characteristics between both groups were well balanced (Table 1). The median age was 59 years (50–67), and 901 (72.5%) were male. 370 (30.0%) presented with a shockable rhythm. The median duration of conventional CPR was 36 min (20–55), and patients received ECMO for 76 h (29–144). 301 patients received IABP, while 320 patients received mLVAD as the

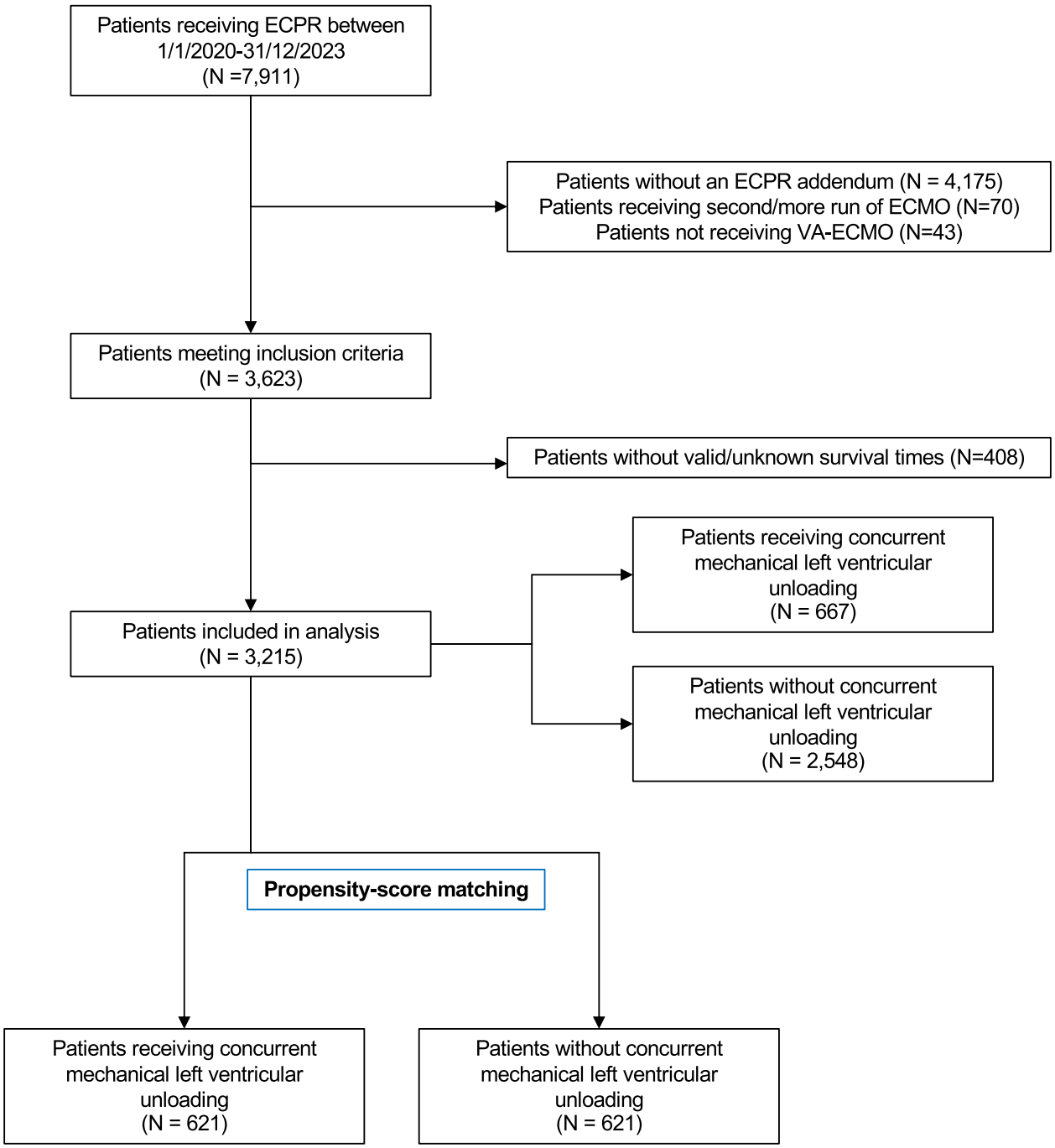

Fig. 1 STROBE patient inclusion flowchart

Table 1 Characteristics of cohort following propensity score matching

Characteristic	Overall N = 1,242	No LV unloading N = 621	LV unloading N = 621	SMD
Sex				
Female	339 (27%)	197 (32%)	142 (23%)	0.28
Male	901 (73%)	424 (68%)	477 (77%)	0.27
Age (Years)*	59 (50–67)	59 (50–67)	59 (49–67)	
BMI (kg/m^2)	29 (25–34)	28 (25–34)	29 (25–34)	0
Year of ECMO initiation*				
2020	204 (16%)	95 (15%)	109 (18%)	0.047
2021	238 (19%)	123 (20%)	115 (19%)	0.050
2022	370 (30%)	191 (31%)	179 (29%)	0.053
2023	430 (34%)	212 (34%)	218 (35%)	0.033
Presenting rhythm*				
Non-shockable	536 (43%)	267 (43%)	269 (43%)	0.026
Shockable	648 (52%)	326 (52%)	322 (52%)	0.028
Unknown	58 (4.7%)	28 (4.5%)	30 (4.8%)	0.014
Precipitating Event*				
Cardiac	1,095 (88%)	547 (88%)	548 (88%)	0.019
Non-Cardiac	56 (4.5%)	29 (4.7%)	27 (4.3%)	0.013
Unknown	91 (7.3%)	45 (7.2%)	46 (7.4%)	0.021
Time to ECPR*	36 (20–55)	36 (20–55)	37 (20–55)	0.081
Number of epinephrine doses	5.0 (3.0–8.0)	5.0 (3.0–8.0)	5.0 (3.0–8.0)	0
Type of LV unloading				
Nil	621 (50%)	621 (100%)	0 (0%)	NA
IABP	301 (24%)	0 (0%)	301 (48%)	
mLVAD	320 (26%)	0 (0%)	320 (52%)	
Number of ECPR cases per year*	9 (4–25)	9 (4–25)	9 (4–31)	0.031
High volume centre	492 (40%)	249 (40%)	243 (39%)	0.028
PCI	242 (20%)	58 (9.3%)	184 (29.6%)	0.53
Time of arrest*				
Morning	720 (58%)	362 (58%)	358 (58%)	0.033
Afternoon	369 (30%)	184 (30%)	185 (30%)	0.032
Night	153 (12%)	75 (12%)	78 (13%)	0.013
Location of cardiac arrest*				
IHCA	883 (71%)	439 (71%)	444 (71%)	0.013
OHCA	359 (29%)	182 (29%)	177 (29%)	

Abbreviations: BMI: body mass index, ECPR: extracorporeal cardiopulmonary resuscitation, ECMO: extracorporeal membrane oxygenation, IABP: intra-aortic balloon pump, IHCA: in-hospital cardiac arrest, LV: left ventricular, mLVAD: mechanical left ventricular assist device, OHCA: out-of-hospital cardiac arrest, PCI: percutaneous coronary intervention

* Included in propensity score model

mechanical LV unloading device. 839 patients had died at the end of follow-up.

Table 2 summarises the results with regards to survival time up to 90 days. In the matched cohort, there was no difference in survival time between patients who did and did not receive LV unloading (HR 0.92, 95%-CI 0.79–1.08, Fig. 2). This was concordant in several sensitivity analyses, including inverse probability of treatment weighting (OR 0.92, 95%-CI 0.82–1.03, Figure S1), and complete case analysis (HR 0.99, 95%-CI 0.86–1.15, Figure S2). As sex had an SMD > 0.1, we reiterated the matching algorithm, including it as a covariate. The point estimates did not substantially change with this (HR 0.92, 95%-CI 0.80–1.06) nor double-adjustment of the original propensity score matching algorithm (HR 0.94, 95%-CI 0.81–1.09). Post-hoc sensitivity analyses excluding patients with potential contraindications to ECPR and LV unloading (HR 0.93, 95%-CI 0.78–1.11), and including PCI as a covariate in the propensity score-matching

Table 2 Association between mechanical left ventricular unloading with survival time up to 90 days in patients receiving extracorporeal membrane resuscitation

Result	Hazards ratio (95%-CI)
Propensity score-matched cohort	0.92 (0.79–1.08)
Sensitivity analyses	
Inverse probability treatment weighting	0.92 (0.82–1.03)
Complete case analysis (propensity score matched)	0.99 (0.86–1.15)
Including sex in the propensity score-matching algorithm	0.92 (0.80–1.06)
Double adjustment on propensity score-matching algorithm	0.94 (0.81–1.09)
Target trial emulations	
ARREST trial	1.17 (0.84–1.63)
Prague OHCA trial	0.92 (0.77–1.10)
INCEPTION trial	1.05 (0.79–1.40)
Subgroup analyses	
Type of mechanical unloading device (p-interaction = 0.87)	
IABP	0.91 (0.74–1.12)
mLVAD	0.89 (0.68–1.16)
Aetiology of cardiac arrest (p = interaction = 0.97)	
Cardiac	0.92 (0.78–1.10)
Non-cardiac	0.91 (0.43–1.93)
Presenting rhythm (p-interaction = 0.067)	
Shockable	1.06 (0.84–1.33)
Nonshockable	0.79 (0.64–0.98)
Location of arrest (p-interaction = 0.88)	
Out-of-hospital cardiac arrest	0.91 (0.69–1.19)
In-hospital cardiac arrest	0.88 (0.73–1.06)
Interaction analyses	
Centre volume (per 10 cases per year)	1.03 (0.97–1.10)
Age (per 10 years)	0.99 (0.88–1.12)
Duration of CPR prior to ECMO (per 10 min)	0.95 (0.90–1.01)

Abbreviations: ARREST: Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation; CI: confidence interval; CPR: Cardiopulmonary resuscitation ECMO: Extracorporeal membrane oxygenation; IABP: Intra-aortic balloon pump; LVAD: Left ventricular assist device; INCEPTION: Early Initiation of Extracorporeal Life Support in Refractory Out-of-Hospital Cardiac Arrest

algorithm (HR 0.94, 95%-CI 0.81–1.09) did not substantially alter the point estimates either.

When emulating previously published RCTs, concurrent LV unloading when initiating ECPR based on the criteria in the ARREST (HR 0.89, 95%-CI 0.75–1.07, Figure S3), Prague-OHCA (HR 0.92, 95%-CI 0.77–1.10, Figure S4), and INCEPTION trials (HR 1.05, 95%-CI 0.79–1.08, Figure S5) was similarly not associated with any differences in survival time.

LV unloading was not associated with differences in survival time when stratified based on the type of LV unloading device (IABP 0.93, 95%-CI 0.74–1.17 mLVADs 0.90, 95%-CI 0.69–1.16, p-interaction = 0.87, Figure S6), aetiology of arrest (cardiac 0.92, 95%-CI 0.78–1.10, non-cardiac: 0.91, 95%-CI 0.43–1.93, p-interaction = 0.97, Figure S7), presenting rhythm (shockable 1.06, 95%-CI 0.84–1.33, non-shockable rhythm 0.79, 95%-CI 0.64–0.98, p-interaction = 0.067, Figure S8), or location of cardiac arrest (OHCA 0.91, 95%-CI 0.69–1.19, IHCA 0.88, 95%-CI 0.73–1.06, p-interaction = 0.88, Figure S9). Similarly, an increase in centre volume (interaction HR 1.03, 95%-CI 0.97–1.10, *p*-interaction = 0.36), age (interaction HR 0.99, 95%-CI 0.88–1.12, *p*-interaction = 0.88), and duration of CPR prior to ECMO (HR 0.95, 95%-CI 0.90–1.01, *p*-interaction = 0.11) did not alter the association between LV unloading and survival time.

Table 3 summarises the results of the secondary outcomes. Concurrent LV unloading was associated with an increase in renal (OR 1.55, 95%-CI 1.16–2.07) and cardiovascular (OR 1.60, 95%-CI 1.14–2.26) complications. When analysing specific complications, LV unloading was associated with an increase in central

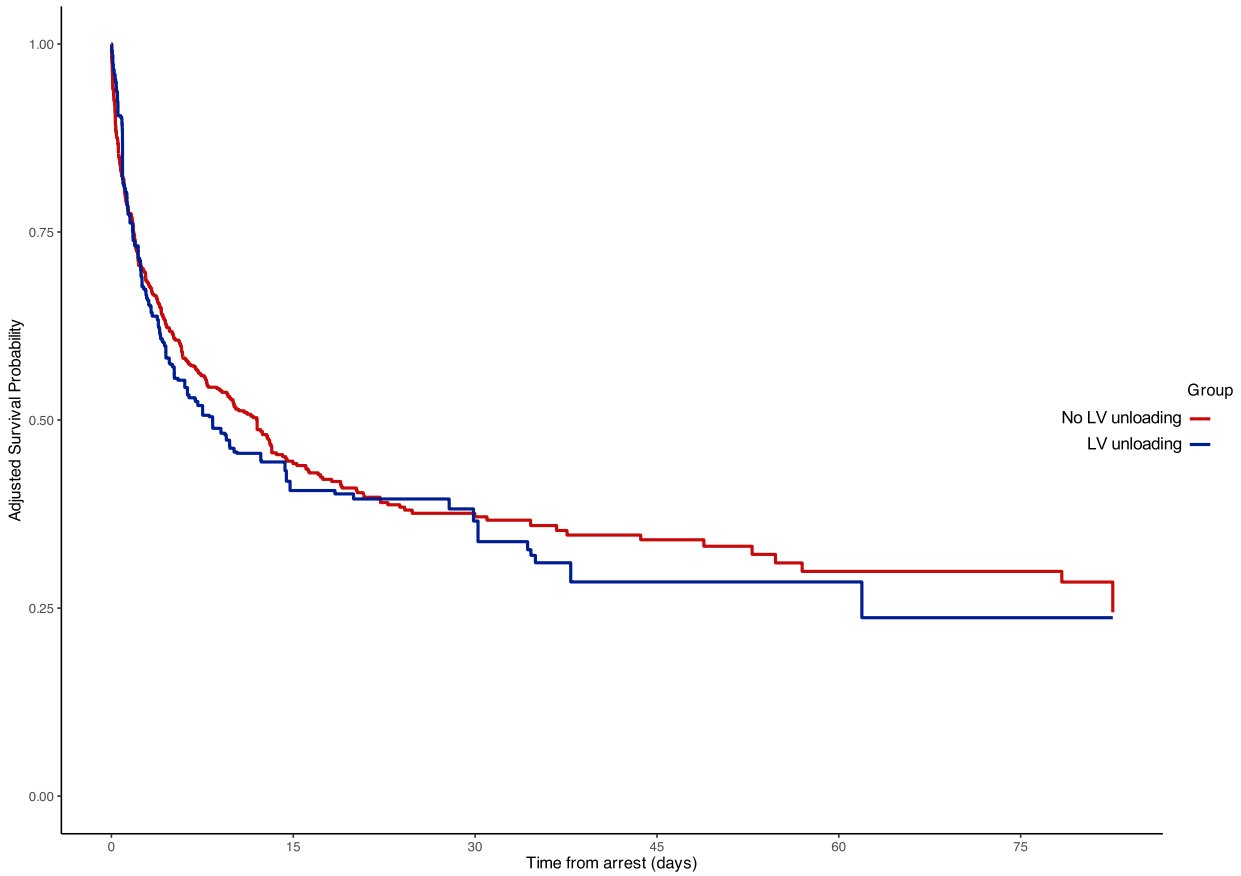

Fig. 2 Adjusted survival curves of the propensity score-matched cohort, comparing the surviving proportion of patients who received and did not receive mechanical left ventricular unloading during extracorporeal cardiopulmonary resuscitation

nervous system bleeding (OR 1.75, 95%-CI 1.03–2.96), arrhythmias (OR1.56, 95%-CI 1.04–2.36), and haemolysis (OR 1.85, 95%-CI 1.10–3.09). In addition, LV unloading was not associated with an increase in favourable functional outcomes (OR 1.15, 95%-CI 0.67–1.99). Patients receiving LV unloading had longer durations of ECMO (absolute difference: 23.3 h, 95%-CI 8.3–38.4), but there were no significant differences in hospital length of stay (absolute difference: 0.94, 95%-CI -2.05 to + 3.93).

Finally, our post-hoc meta-analysis yielded five other propensity score-matched studies [14, 24–27] with six cohorts for analysis (Figure S10, Table S4). There were no randomised controlled trials. When including our results in the meta-analysis, mechanical LV unloading may be associated with a lower 30-day mortality rate (OR 0.55, 95%-CI 0.35–0.87, low certainty), however, it was uncertain if IABP (OR 0.66, 95%-CI 0.37–1.17) or mLVAD (OR 0.51, 95%-CI 0.25–1.04) individually were associated with lower 30-day mortality (both very low certainty, Figures S11-13).

Discussion

In this international, multicentre cohort study of the ELSO registry, we found that mechanical LV unloading during ECPR was not associated with improved outcomes, and this was consistent across several subgroups and sensitivity analyses. More importantly, we found that concurrent unloading was associated with a higher risk of renal, neurological and cardiovascular complications.

Our study addresses an important aspect of ECPR in cardiac arrest. We harnessed observational data and propensity score-matching to emulate a theoretical RCT investigating the effect of LV unloading during ECPR, which allowed us to adjust for potential confounders at baseline. There are currently no RCTs investigating LV unloading during ECPR, and this is likely contributed to by challenges with patient enrolment, and ethical and logistical challenges in randomising and withholding

Table 3 Association between mechanical left ventricular unloading and complications after initiation of extracorporeal membrane resuscitation, favourable functional outcomes, and duration of ECMO and hospital stay

Result	Odds ratio (95%-CI)
Mechanical	0.92 (0.61–1.37)
Circuit change	0.90 (0.40–2.02)
Haemorrhagic	0.95 (0.70–1.29)
Neurological	1.37 (0.99–1.90)
Central nervous system infarct/ischaemia	1.27 (0.89–1.83)
Central nervous system bleeding	1.75 (1.03–2.96)*
Renal	1.57 (1.16–2.12)*
Cardiovascular	1.55 (1.06–2.26)*
Cardiopulmonary resuscitation required	1.57 (0.68–3.60)
Arrhythmia	1.56 (1.04–2.36)*
Tamponade	1.23 (0.58–2.62)
Pulmonary	1.10 (0.60–2.03)
Metabolic	1.46 (0.95–2.26)
Haemolysis	1.85 (1.10–3.09)*
Limb ischemia	1.15 (0.67–1.99)
Favourable functional outcome	0.77 (0.42–1.43)
Duration of ECMO	23.3 h longer (8.3–38.4)*
Duration of hospital stay	0.95 days longer (-2.05 to + 3.93)

Results which have crossed the threshold for statistical significance have been indicated with an asterisk. Complications have been classified based on the Extracorporeal Life Support Organisation Registry

what are believed to be potentially lifesaving therapies. Ultimately, evidence suggests that outcomes in patients receiving ECPR may be superior compared to patients receiving conventional CPR [8, 9, 11, 12]. In the absence of RCTs in the context of ECPR, our results represent the highest level of evidence investigating mechanical LV unloading during ECPR. Prior observational studies are limited by smaller sample sizes within a homogenous group of patients or centres, or unadjusted analyses. In fact, while a recent meta-analysis found that LV unloading was associated with reduced mortality during ECPR, it also found that certain patients (primarily acute coronary syndrome) were more likely to receive LV unloading than others (eg pulmonary embolism) during ECPR, underscoring the need to adjust for potential confounders [16]. In addition, our analysis is based on a large sample size across nearly 300 centres globally, which increases precision and the generalizability of our results.

Contrary to prior published observational studies and meta-analyses [14, 16, 17, 24–26], we found that mechanical LV unloading during ECPR was not associated with a significant reduction in mortality. While the meta-analysis suggested that mechanical LV unloading may be associated with lower 30-day mortality, this was based on low certainty as well. Several factors may account for these findings. First, prior studies were either single-centre or based on centres in countries or regions with substantial experience in ECPR, which may have well-defined protocols on initiating mechanical LV unloading in a highly specific subset of patients (three studies in the meta-analysis from Japan, one from Germany, one multinational study in Europe) [14, 24–26]. On the other hand, the ELSO registry amalgamates data across centres globally. Although centre experience may theoretically result in larger benefits [15], this was not observed in our interaction analysis based on centre volume. In addition, the variables utilised in estimating the propensity score were different. Previous studies used variables including demographics (age, sex), physiological variables (mean arterial pressure, heart rate), clinical variables (etiology of cardiogenic shock/cardiac arrest, previous cardiac arrest, time to ECMO), and biochemical tests (lactate, pH). In order to ensure a sufficient range and a robust variable selection process, we conducted a literature review prior to the analyses and based on this, used a causal directed acyclic graph to select variables when estimating the propensity score. Similar to our primary analysis, our sensitivity analysis investigating ECPR initiation based on the ARREST (40% of patients received LV unloading in the original trial), PRAGUE-OHCA and INCEPTION (30% of patients received unloading in the original trial) trial criteria did not reveal a significant benefit with concurrent mechanical LV unloading. Third, initiating VA-ECMO and LV unloading in the context of cardiac arrest (Society of Cardiovascular Angiography and Interventions [SCAI] E shock) versus cardiogenic shock (SCAI C-D shock) are fundamentally different [28, 29]. Though difficult to quantify and analyse, the severity of post-cardiac arrest syndrome may contribute to complications and potentially reduce the benefit of LV unloading.

Of note, LV unloading was associated with higher odds of renal and cardiovascular (primarily arrhythmias) complications, central nervous system haemorrhage, and haemolysis. These have been reported in prior studies in ECPR and in VA-ECMO for cardiogenic shock [15, 16, 30–32]. There are several potential explanations underlying this association. First, the introduction of an additional mechanical circulatory support device may increase wall shear stress on blood components, resulting in haemolysis [33]. Computational fluid dynamics studies have shown that at certain flows, the zone of "mixing" and turbulence occurs at the level of the renal arteries, which can cause acute kidney injury [34, 35]. Previous clinical studies have reported that mLVAD was associated with hemorrhagic strokes at durable LVAD implantation [36], and that an mLVAD was associated with

higher rates of hemorrhagic strokes than IABP in cardiogenic shock [30]. Our finding of a higher hemorrhagic stroke risk in patients with LV unloading may be driven by patients who received mLVAD.

Given that LV unloading was not associated with lower mortality, but was associated with complications, it is possible that some patients may benefit from unloading, and that these benefits were negated by increases in mortality due to complications in other patients. Ultimately, clearer indications and clinical criteria are needed for better patient selection and prognostic enrichment to better identify the potential benefits of LV unloading. Streamlining of ECPR services by including bundles of care that focusses on neuroprotection and downstream revascularization in addition to LV unloading might contribute to better outcomes in this cohort. Upcoming trials investigating LV unloading during VA-ECMO for cardiogenic shock (NCT06336655, NCT05577195, NCT05913622) may help better define these criteria, and pave the way for future trials in ECPR.

We recognise several limitations of our review. First, the use of propensity score-matching and weighting can adjust for potential confounders. However, this does not eliminate the possibility of residual unmeasured confounding. In addition, the use of matching may exclude certain patients who were eligible for analysis, reducing sample size and precision. We aimed to mitigate this using inverse probability of treatment weighting. Furthermore, the degree of cardiac dysfunction and indications for LV unloading in the context of ECPR were not recorded by the ELSO registry, though most patients receiving ECPR have moderate-to-severe degrees of cardiac dysfunction. Based on this, the analysis assumes that LV unloading is used systematically; this may not be true in all situations or institutions. Second, we did not have a group of patients who only received conventional CPR (standard care) in this cohort, and we cannot draw any associations between LV unloading and ECPR compared to conventional CPR alone. We also cannot exclude the possibility that a subset of patients were referred for VA ECMO for cardiogenic shock, but subsequently developed cardiac arrest just prior to cannulation and were recorded as receiving ECPR; such patients may have better prognosis. Third, in our emulation of prior RCTs, the ELSO registry did not record information regarding certain exclusion criteria and comorbidities (e.g. life-limiting comorbidities, treatment limitations, poor baseline functional status), and our study may have included these patients. In addition, the data available may have underestimated the severity of illness or unmeasured or unrecorded factors that contributed to a patient receiving LV unloading to begin with. Although there is a potential for bias, we believe that the impact is small, given that these patients form an especially small proportion of the population eligible for ECPR in routine clinical practice. Fourth, the sensitivity analysis adjusting for PCI may be limited by the fact that the ELSO registry does not record the timing nor indication for PCI. Fifth, there is a potential for immortal time bias, and that patients must first survive sufficiently long enough before receiving LV unloading (as has been described in prior studies investigating ECMO [37–39]); this may artificially inflate the potential benefit of LV unloading. Sixth, very few centres sufficiently recorded neurological outcomes at discharge. Finally, the exact timing of mechanical LV unloading vis-à-vis initiation of ECPR and duration of mechanical LV unloading is not recorded in the ELSO registry, and it is unclear if this is associated with divergent outcomes depending on the timing to unloading [14, 40, 41].

Conclusions

In conclusion, our analysis of the ELSO registry found that LV unloading during ECPR was not associated with a reduction in mortality, regardless of the LV unloading device, aetiology of arrest, initial presenting rhythm, and demographic and centre characteristics. Emulating the criteria of prior RCTs also did not yield any significant benefits with LV unloading. Although our results are limited by their observational nature, they highlight an urgent need to re-examine LV unloading in the context of ECPR, and for randomised data to verify these findings.

Abbreviations

CPR	Cardiopulmonary resuscitation
ECPR	Extracorporeal cardiopulmonary resuscitation
ELSO	Extracorporeal life support organization
IABP	Intra-aortic balloon pump
IHCA	In hospital cardiac arrest
HR	Hazards ratio
mLVAD	Microaxial left ventricular assist device
LV	Left ventricle
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
RCT	Randomized clinical trial
SCAI	Society of cardiovascular angiography and interventions
STROBE	STrengthening the reporting of observational studies in epidemiology
SMD	Standardized mean difference
VA ECMO	Venoarterial extracorporeal membrane oxygenation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05345-3.

Additional file1 (DOCX 1356 KB)

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Author contributions
Study conception: RRL, KR Study design: RRL, KS, DB, GM, KR Data collection: RRL, KR Data analysis and interpretation: RRL, CJWL, YC, KR Tables and figures: RRL, CJWL, YC Writing of original draft: RRL, KR All authors provided critical conceptual input, interpreted the data analysis, read, and approved the final draft. RRL, YC, and KR have accessed and verified the data. RRL and KR were responsible for the final decision to submit the manuscript.

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Availability of data and materials
The ELSO registry data dictionary and policies are available online at https://www.elso.org/registry/datadefinitions,forms,instructions.aspx. The participant data collected for this study are available, as a limited dataset, to member centres conditional on approval from the ELSO Scientific Oversight Committee, but it is not publicly available.

Declarations

Ethics approval and consent to participate
This study received approval from the institutional review board of the National University Hospital, Singapore (NUH-RNR-2024–0024). The study data were received after review and approval by the Scientific Oversight Committee of the Extracorporeal Life Support Organisation (ELSO request #2811).

Consent for publication
Consent for publication was waived in view of the deidentified nature of the data.

Competing interests
RRL receives research support from the Clinician Scientist Development Unit, Yong Loo Lin School of Medicine, National University of Singapore. He serves as a fellow of the Extracorporeal Life Support Organisation (ELSO) Scientific Oversight Committee, and is an editorial board member of Critical Care. CA writes for UpToDate. SLL has received a Transitional Award from the National Medical Research Council Singapore. She has received research support for travel and conference meetings from the National University Heart Centre Singapore. She has been issued a patent for a "Novel Program and Biochemical Assays for Quantification of Single-Cell Secreted Biomolecules" (US Provisional Patent Application No. 63/676,851),serves as an Associate Editor for Resuscitation, and as an Editorial Board Member of Resuscitation Plus. RL received research support from Medtronic and LivaNova, is consultant for Medtronic and Livanova, Member of the Medical Advisory Board of Eurosets, Hemocue, and Xenios, and receives speaker fee from Abiomed. TM serves as a member of the board of the ELSO. YO has received a research grant from the ZOLL Foundation and an overseas scholarship from the FUKUDA Foundation for Medical Technology, International Medical Research Foundation, and the Khoo Postdoctoral Fellowship Award. JET is supported by the National Institutes of Health/ National Heart, Lung, and Blood Institute for a clinical trial investigating LV unloading during cardiogenic shock (R01HL168510) and is the Chair of the Registry Committee of ELSO. DB reports consulting for LivaNova. He has been on the medical advisory boards for Medtronic, Inspira, Cellenkos and HBOX Therapies. He participates on the Data Safety Monitoring Board for the Early mobilisation during extracorporeal membrane oxygenation (ECMO-PT) study. He is the President of ELSO and the Chair of the Board of ECMONet, and he writes for UpToDate. GM is the Past President of ELSO. KR is the chair of the ELSO Publications Committee, and serves as a member and the past-chair of the ELSO Scientific Oversight Committee. All other authors declare no competing interests.

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