# Early mechanical reperfusion in high-risk pulmonary embolism supported by V-A ECMO: a multicenter international cohort study

David Levy[1,2] MD, Matthieu Petit[3], MD, Benjamin Assouline[4] MD, Alexander Dietl[5] MD, Guillaume Lebreton[6] MD, PhD, Raphaël Giraud[4] MD, PhD, Joshua Ihle[7] MD, Paul Masi[8] MD, Sally Newman[9] MD, Anna Condella[10] MD, Jordi Riera[11] MD, PhD, Marc Pierrot[12] MD, Alexandre Mansour[13] MD, PhD, Shinichiro Ohshimo[14] MD, Lise Thellier[15] MD, Dirk W Donker[16] MD, PhD, Celine Besnard[17] MD, Alice Vennier[18] MD, Hadrien Winiszewski[19] MD, PhD, Guido Tavazzi[20] MD, PhD, Jonathan Taylor[21] MD, Julien Dessajan[22] MD, Philipp M. Lepper[23] MD, PhD, Pauline Yeung Ng[24] MD, Juan I. Chico[25] MD, Christophe Guervilly[26] MD, Louis Pot[27] MD, Dieter Dauwe[28] MD, PhD, Philip Fortuna[29] MD, PhD, Fabio Silvio Taccone[30] MD, PhD, Baptiste Compagnon[31] MD, Jae-Seung Jung[32] MD, Zied Ltaief[33] MD, Roberto Roncon-Albuquerque[34] Jr MD, Pierre Denormandie[35] MD, Marco Giani[36] MD, Thibault Duburcq[37] MD, Giacomo Grasselli[38] MD, PhD, Hélène Nougué[39] MD PhD, Adrien Werquin[39] MD, Olivier Sanchez[40] MD, PhD, Antoine Beurton[41] MD, Martin Balik[42] MD, PhD, Marie Jungling [43] MD, Maria Heinrich[5] MD, Thomas Mueller[5] MD, PhD, Alain Combes[1,2] MD, PhD, Matthieu Schmidt[1,2] MD, PhD for the CATAPULTE Investigator Group*

[1] Service de Médecine Intensive-Réanimation, Institut de Cardiologie, Assistance Publique-Hôpitaux de Paris (AP-HP), Sorbonne Université, Hôpital Pitié–Salpêtrière, Paris, France.

[2] Sorbonne Université, INSERM, UMRS_1166-ICAN, Institute of Cardiometabolism and Nutrition, Paris, France.

[3]Medical Intensive Care Unit, Ambroise Paré Hospital, APHP, Boulogne-Billancourt, Inserm, U1018, CESP, University Versailles Saint Quentin - University Paris Saclay, Guyancourt, France.

[4]Intensive Care Unit, Geneva University Hospitals, 4, Rue Gabrielle Perret-Gentil, 1205, Geneva, Switzerland

[5]Department of Internal Medicine II, University Hospital Regensburg, Regensburg, Germany

[6]Service de Chirurgie Cardiaque et thoracique, Institut de Cardiologie, AP-HP, Sorbonne Université, Hôpital Pitié–Salpêtrière, Paris, France.

[7]Department of Intensive Care, The Alfred Hospital, Melbourne, Australia

[8]Service de Réanimation Médicale, DHU ATVB, Hôpitaux Universitaire Henri Mondor, Assistance Publique-Hôpitaux de Paris, 51 Av Mal de Lattre de Tassigny, 94010, Créteil Cedex, France

[9]Intensive Care Unit, St Vincent's Hospital, Darlinghurst, Sydney, Australia

[10]Department of Emergency Medicine, University of Washington, Seattle, Washington, United States
[11]Department of Intensive Care, Hospital Universitari Vall d'Hebron, Barcelona, Spain
[12]Département de Réanimation Médicale et de Médecine Hyperbare, Centre Hospitalier Universitaire, 4 rue Larrey, Cedex 9, 49933, Angers, France
[13]Department of Anesthesia and Critical Care, Pontchaillou, University Hospital of Rennes, Université de Rennes, Rennes, France
[14]Department of Emergency and Critical Care Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan
[15] Univ. Lille, CHU Lille, ULR 2694-METRICS: évaluation des technologies de santé et des pratiques médicales, Department of Anesthesia and Critical Care Medicine, F59000-Lille, France
[16]Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
[17]Service de Médecine Intensive Réanimation, Centre Hospitalier Universitaire d'Orléans, 45000 Orléans, France
[18]Service de Médecine Intensive Réanimation, Centre Hospitalier Universitaire de Nantes, Nantes, France; Université de Nantes, Nantes 44093, France
[19]Medical Intensive Care Unit, University Hospital, Besancon, France
[20]Anesthesia and Intensive Care, Fondazione Policlinico San Matteo Hospital IRCCS, VIale Golgi 19, Pavia 27100, Italy
[21]Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada
[22]Assistance Publique Hôpitaux de Paris (AP-HP), Medical and Infectious Diseases Intensive Care Unit, Bichat Claude-Bernard Hospital, Paris Cité University, 46 Rue Henri Huchard, 75018 Paris, France
[23]Department of Pneumology, Allergology and Critical Care Medicine/ECLS-Centre Saar, University Medical Centre, Saarland University, 66421 Homburg, Germany
[24]Critical Care Medicine Unit, School of Clinical Medicine, The University of Hong Kong, Hong Kong, Hong Kong SAR, China
[25]Critical Care Department, Hospital Álvaro Cunqueiro, Vigo, Spain
[26]Service de Médecine Intensive Réanimation, Hôpital Nord, Assistance Publique-Hôpitaux de Marseille, Marseille, France
[27]Réanimation des Urgences, Timone University Hospital APHM, 13005 Marseille, France
[28]Department of Intensive Care Medicine, University Hospitals Leuven, Leuven, Belgium
[29]Department of Emergency and Critical Care, Local Health Unit of São José, Lisbon, Portugal
[30]Department of Intensive Care, Hôpital Universitaire de Bruxelles (HUB), Université Libre de Bruxelles (ULB), Route de Lennik, 1070, 808, Brussels, Belgium
[31]Anaesthesiology and Intensive Care Unit, Centre Hospitalier Universitaire de Rangueil, Toulouse, France

[32] Department of Thoracic & Cardiovascular Surgery, Korea University Anam Hospital, Seoul, Republic of Korea
[33]Department of Intensive Care, Lausanne University Hospital (CHUV), Lausanne, Switzerland
[34]Department of Emergency and Intensive Care Medicine, Centro Hospitalar S. João, Porto, Portugal
[35]Service de Réanimation Adulte, Hôpital Marie Lannelongue, Le Plessis Robinson, France
[36] School of Medicine and Surgery, University of Milano Bicocca, Monza Italy
[37]Medical Intensive Care Unit, CHU Lille, 59000, Lille, France
[38]Department of Anesthesia, Critical Care and Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[39]Department of Anaesthesiology and Intensive Care, Hôpital Européen Georges Pompidou, AP-HP, 20 rue Leblanc, 75015, Paris, France
[40] Université Paris Cité ; Service de Pneumologie et de soins intensifs, hôpital Européen Georges-Pompidou, AP-HP ; INSERM PARCC, 75015 Paris ; FCRIN INNOVTE, St-Etienne, France
[41] CHU Bordeaux, Department of Cardiovascular Anaesthesia and Critical Care, 33000 Bordeaux, France
[42]Department of Anaesthesiology and Intensive Care, 1st Faculty of Medicine, Charles University and General University Hospital in Prague, U nemocnice 2, Prague 2, 12808, Czechia, EU
[43] Univ. Lille, CHU Lille, ULR 2694-METRICS: évaluation des technologies de santé et des pratiques médicales, Department of Cardiac Surgery, F59000-Lille, France

[*] CATAPULTE Investigators are listed in pp 23-25

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**Corresponding author:**

**Matthieu SCHMIDT, MD, PhD,**
Pitié-Salpêtrière Hospital**,** Medical Intensive Care Unit**,**
Sorbonne Université, INSERM, UMRS_1166-ICAN, Institute of Cardiometabolism and Nutrition
47-83 Boulevard de l'Hôpital,
F-75013 Paris, France**.**
matthieu.schmidt@aphp.fr

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**Abbreviations**

aPTT: activated partial thromboplastin time

CDT: Catheter-directed therapy

CPR: cardiopulmonary resuscitation

CTEPH: chronic thromboembolic pulmonary hypertension

ECPR: extracorporeal cardiopulmonary resuscitation

ESC: European Society of Cardiology

HR: Hazard ratio

IRB: Institutional Review Board

PE: Pulmonary embolism

RV: right ventricle

SAPS II: Simplified Acute Physiology Score

SOFA: Sequential Organ Failure Assessment

V-A ECMO: Veno-arterial extracorporeal membrane oxygenation

## Abstract

**Objectives**: To explore how early mechanical reperfusion impacts outcomes in high-risk pulmonary embolism (PE) patients supported by veno-arterial extracorporeal membrane oxygenation (V-A ECMO).

**Methods:** This retrospective international study included adult patients treated with V-A ECMO for high-risk PE at 39 ECMO centers (2014–2024). Early mechanical reperfusion was defined as catheter-directed therapy or surgical embolectomy within 48 hours of ECMO initiation. Patients dying within 12 hours or receiving delayed reperfusion were excluded. The primary outcome was 90-day mortality, assessed using propensity-matched groups.

**Measurements and Main Results**: Among 492 patients on V-A ECMO (median age 53), 69% had cardiac arrest, and 28% received early mechanical reperfusion. After propensity matching, 137 patients were compared in each group. Ninety-day mortality was 32% with early mechanical reperfusion on ECMO versus 39% with ECMO stand-alone (HR 0.68; 95% CI, 0.45–1.03; p=0.07). Overall, ECMO duration and weaning rates were similar; however, early mechanical reperfusion improved ECMO weaning in patients without prior thrombolysis (sHR 1.56; 95% CI, 1.03–2.36; p=0.04). Bleeding occurred in 50% of patients, with no significant difference between groups.

**Conclusion:** In this large international cohort of patients with high-risk PE on V-A ECMO, early mechanical reperfusion therapy was not associated with a reduction in 90-day mortality or ECMO duration. These findings may support a stepwise, individualized approach favoring initial ECMO stand-alone support, although a certain clinical benefit from early mechanical reperfusion in selected patients cannot be excluded.

## Introduction

According to recent guidelines from the European Society of Cardiology (ESC), high-risk pulmonary embolism (PE) is characterized by hemodynamic instability, which includes sustained hypotension, cardiogenic shock, or cardiac arrest, with mortality rates ranging from 25% to 65% (1, 2). Given the wide spectrum of hemodynamic presentations included in this definition, each associated with different prognoses, some experts prefer the term *catastrophic PE* to describe cases involving cardiac arrest or peri-arrest conditions that ultimately necessitate mechanical circulatory support (3, 4). Management in these situations focuses on stabilizing hemodynamics and gas exchanges, initiating anticoagulation with heparin, and implementing reperfusion strategies, such as systemic thrombolysis, surgical embolectomy, or catheter-directed therapy (CDT) (2).

With the growing use of mobile extracorporeal membrane oxygenation (ECMO) teams, this technique is increasingly deployed to provide rapid hemodynamic support as a bridge to recovery for the most critical PE patients (5). Veno-arterial ECMO (V-A ECMO) is considered either in cases of failed systemic thrombolysis or when systemic thrombolysis is formally contraindicated. The most recent guidelines from the ESC recommend considering V-A ECMO in combination with surgical embolectomy or CDT for patients experiencing PE with refractory circulatory collapse or cardiac arrest (1). Early implementation of reperfusion strategies, such as CDT or surgical embolectomy, may support weaning from V-A ECMO and enhance survival outcomes (6, 7). Nevertheless, compared to an ECMO stand-alone approach, the added value of these reperfusion interventions in cases of catastrophic PE requiring V-A ECMO remains unclear and is associated with potential risks. The existing understanding of a combination approach is supported by limited retrospective data, often involving mixed patient populations or small, unmatched V-A ECMO cohorts (6, 8, 9).

The present study aims to address this gap by evaluating the impact of early adjunctive reperfusion therapy on ECMO versus ECMO stand-alone, using data from a large, international cohort of patients with catastrophic PE managed with V-A ECMO.

## Methods

*Study design and patient population*.

The CATAPULTE study is an international, multicenter, retrospective cohort study conducted in 39 tertiary hospitals with prompt access to V-A ECMO across 15 countries. Centers were invited to participate if they averaged at least 20 V-A ECMO runs per year (see characteristics of the centers, eTable 1). We included all patients, regardless of whether they received systemic thrombolysis before ECMO, who were referred between January 2014 and June 2024 with suspected or confirmed high-risk PE requiring V-A ECMO support. Patients were excluded if they initially received venovenous or central ECMO, or if reperfusion therapy (either CDT or surgical embolectomy) was performed before ECMO initiation. To maintain a focus on early management strategies, minimize confounding from delayed interventions, and avoid immortality bias, we excluded patients who either died within 12 hours of ECMO initiation or received reperfusion therapy more than 48 hours afterward. PE was diagnosed according to the latest ESC guidelines (1). Indications for V-A ECMO included cardiac arrest or refractory cardiogenic shock due to right ventricular (RV) failure, defined by evidence of tissue hypoxia despite adequate intravascular volume status, low cardiac index (≤2.1 L/min/m²), and sustained hypotension despite high-dose catecholamines (epinephrine ≥1 γ/kg/min or dobutamine ≥15 γ/kg/min + norepinephrine ≥1 γ/kg/min) (10). Echocardiographic criteria for acute cor pulmonale included paradoxical septal motion and an RV end-diastolic area to left ventricular end-diastolic area ratio >0.6 (11). The primary

comparison was between patients receiving ECMO stand-alone and those undergoing ECMO with early mechanical reperfusion.

*Study exposure - Reperfusion strategy on ECMO.*

Following ECMO initiation, patients managed with the combination approach underwent additional reperfusion interventions such as CDT or surgical embolectomy, while others were managed with an ECMO stand-alone approach combined with systemic anticoagulation. Early mechanical reperfusion was defined as any CDT or surgical embolectomy performed within 48 hours after ECMO initiation. The choice of reperfusion strategy was determined by local protocols and the availability of resources. Likewise, the selection of CDT techniques was left to the discretion of the interventional radiologist (12). Continuous heparin infusion was administered to maintain activated partial thromboplastin time (aPTT) at 2–3 times the control value, aiming to treat PE and avoid ECMO circuit thrombosis. Heparin was temporarily halted in cases of bleeding at the clinician's discretion.

*ECMO management.*

V-A ECMO was established using femoral–femoral cannulation (23–29 F venous, 15–19 F arterial), with placement of an additional catheter in the superficial femoral artery to prevent limb ischemia, as previously described (13). For critically unstable patients, mobile ECMO teams initiated support at the bedside in referring hospitals before transfer to specialized centers. Cannulation techniques, whether percutaneous or surgical, were selected based on local protocols. Pump speed was modulated to ensure a blood flow between 2 and 4.5 L/min, tailored to the individual patient's physiological requirements.

*Data collection*.

We collected demographics data, Simplified Acute Physiology Score (SAPS) II, and Sequential Organ Failure Assessment (SOFA) scores, presence of venous-thromboembolic risk factors, occurrence of cardiac arrest before ECMO implantation with related "no-flow" and "low-flow" durations (14–17) (see details in the supplement). During the pre-ECMO period, the inotrope score, defined as dobutamine dose (γ/kg/min) + (norepinephrine dose [γ/kg/min] + epinephrine dose [γ/kg/min]) × 100; blood gas analyses, renal, hepatic, and hemostasis function were noted (18).

*Study Outcomes.*

The primary outcome was 90-day survival after ECMO start. Secondary outcomes included the number of ECMO-free days up to day 28, defined as the days between weaning from ECMO and day 28 (with patients who died before day 28 assigned zero ECMO-free days), as well as survival to hospital discharge, duration of ECMO support, and mechanical ventilation duration. Additionally, among ICU complications, severe hemorrhage, limb ischemia requiring surgical or catheter-based intervention, and stroke were collected. Bleeding complications were reported using the Global Utilization of Streptokinase and TPA for Occluded arteries (GUSTO) classification (19). Severe or life-threatening hemorrhage was characterized as intracerebral bleeding or the induction of significant hemodynamic compromise necessitating aggressive treatment, qualifying as a hemorrhagic shock (according to GUSTO 1 criteria). Brain damage was defined as the presence of brain hemorrhage, cerebral edema, or malignant stroke on imaging, confirmed by neurological examination and assessment of electrical activity after discontinuation of sedation (20).

*Statistical analysis*.

This study was conducted following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cohort studies (21). Institutional Review Board approval was secured at each participating center in compliance with local regulatory requirements. In France, the coordinating country, ethical approval was granted by the Comité d'Éthique de la Société de Réanimation de Langue Française (CE-SRLF-24-047). Continuous variables, expressed as median ($1^{st}$–$3^{rd}$ quartiles), were compared with the Student t-test or the Kruskall-Wallis rank sum test, as appropriate. Categorical variables, expressed as numbers (percentage), were compared with $\chi^2$ or Fisher exact tests, as needed.

The primary outcome and the effect of early mechanical reperfusion on ECMO were assessed using Kaplan–Meier overall survival curves and Cox proportional hazards models. For the secondary outcome, given the presence of a competing risk of death before ECMO weaning, a Fine and Gray sub-distribution hazard model was used to assess the cumulative incidence of ECMO weaning within the 90 days following ECMO cannulation. This analysis provided subdistribution hazard ratios (sHRs) for the effect of early mechanical reperfusion on the probability of experiencing the event of interest over time, while appropriately accounting for non-informative censoring. The cumulative incidence curves for these competing events were drawn for each strategy and compared with a gray test.

To account for confounding, we first constructed a propensity score (PS) for survival analysis by fitting a multivariable logistic regression model, using early mechanical reperfusion as the binary outcome. Covariates for the PS model were selected based on clinical expertise and prior literature identifying factors associated with both the likelihood of receiving early mechanical reperfusion and 90-day mortality (4, 6, 16, 22, 23) (eFigure 1). The model included the following potential confounders: age, sex, SAPS II score, SOFA score before ECMO, history of diabetes mellitus or ischemic cardiopathy, use of thrombolysis before ECMO cannulation, use of invasive mechanical ventilation before

ECMO cannulation, occurrence of cardiac arrest before ECMO cannulation, ECMO under external cardiopulmonary resuscitation (ECPR), and pH at the time of ECMO cannulation. No data were imputed to construct the PS. The percentage of missing data is provided in eTable 2.

ECMO stand-alone and ECMO + early mechanical reperfusion patients were then matched according to their PS, using 1:1 matching without replacement and a 0.2 caliper width, as recommended (24). The covariate balance between the two groups was assessed after matching, and we considered an absolute standardized mean difference of less than 0.1 as evidence of balance (25). The dot-plot of covariates included in the PS is given in eFigure 2 and 3. The survival analysis was then conducted in the whole cohort and the PS-matched cohort.

To evaluate the robustness of our result, sensitivity analyses were performed. Since treatment allocation was not randomized, we first used the estimated PS as weights to construct an inverse probability of treatment weighting (IPTW) model and generate a weighted cohort. Survival analysis was then performed in the weighted population, thereby estimating the Average Treatment effect on the Treated. To further account for potential residual confounding, we applied a "double-robust" approach by adjusting for all variables that remained unbalanced after IPTW within the weighted cohort. Subsequently, we performed a third method of adjustment to improve covariate balance between groups, performing a genetic matching procedure (26). The algorithm iteratively searches for the set of weights that minimizes differences in covariate distributions, as assessed by the Mahalanobis distance combined with the standardized mean differences. The same covariates used in the propensity score model were included. We then used the optimal weights obtained through genetic matching to match individuals between groups and conducted survival analysis in the matched cohort.

Then, we performed the primary analyses within predefined subgroups: patients who received thrombolysis before ECMO initiation, those with cardiac arrest before ECMO, according to the type of early mechanical reperfusion strategy, and the inclusion period (2014–2019 vs. 2020–2024). Lastly, to account for the risk of immortal time bias, since patients in the early mechanical reperfusion group had to survive long enough to receive the intervention, we performed a time-dependent survival model and a subgroup analysis based on the timing of reperfusion (<24 h vs. 24–48 h after ECMO cannulation).

Given the multicenter design and potential inter-center heterogeneity, all survival analyses and Cox proportional hazards models included a random effect for center, while Fine and Gray competing risk models were fitted with clustered standard errors at the center level.

All analyses were conducted at a two-sided α risk of 5% and were performed using R software (R Foundation for Statistical Computing, Vienna, Austria), version 4.1.3, notably with packages ‘Matchit’, ‘Matching’, ‘Survival’, and ‘Cmprsk’.

## Results

*Study population.*

Out of 683 patients who received V-A ECMO for high-risk pulmonary embolism, 24 were excluded due to either the absence of peripheral V-A ECMO or reperfusion therapy before ECMO initiation. Additionally, 157 patients who died within 12 hours of ECMO initiation and 10 patients who underwent surgical embolectomy or CDT more than 48 hours after ECMO start were also excluded (Figure 1). Characteristics of those patients are provided in eTables 3 and 4. As a result, 492 patients (15 [10-20] per center) were included in the final cohort. The median age was 53 years [41–61], and 235 (48%) were women (Table 1). The median SAPS II and SOFA scores were 74 [61–83] and 13 [11–15], respectively.

Before ECMO initiation, 340 patients (69%) had experienced cardiac arrest, and 191 (39%) underwent ECPR. Systemic thrombolysis was administered before ECMO in 209 patients (42%) and during ECMO in 18 patients (4%). A total of 330 patients (67%) were outpatients.

Early mechanical reperfusion therapy, defined as CDT or surgical embolectomy performed within 48 hours of ECMO initiation, was carried out in 139 patients (28%) (designated as the ECMO + early mechanical reperfusion group), with 66% undergoing CDT and 34% surgical embolectomy. The remaining 353 patients (72%) received only systemic anticoagulation (ECMO stand-alone group). Following PS matching, 137 patients were included in each group for comparative analysis (Table 1).

*Primary Outcome.*

Before PS matching, 90-day mortality was 43% overall (210 patients), with significantly higher mortality observed in the ECMO stand-alone group compared to the ECMO with early mechanical reperfusion group (47% vs. 32%, HR 0.61 [95%CI, 0.44-0.85]; $p$ <0.01; Table 2, Figure 2). However, after PS matching, this difference was no longer statistically significant (39% vs. 32%, HR 0.68 [95% CI, 0.45-1.03]; $p$ = 0.07; Table 2, Figure 2). Sensitivity analyses using IPTW and GenMatch approaches reported similar results (Figure 3, eFigure 4, eFigure 5). Likewise, ICU and hospital mortality rates were comparable between groups. Detailed causes of death are provided in eTable 5.

*Mechanical Ventilation and ECMO Duration.*

The number of mechanical ventilation–free days by day 28 did not differ significantly between the matched groups. The median ECMO duration was 4 days [3–7] in both cohorts, with no statistically significant difference observed before or after matching. Similarly,

ECMO-free days at day 28 were comparable (20 [0–24] vs. 22 [0–25] days, $p = 0.11$). A competing risk model, accounting for death as a competing event, further indicated that early mechanical reperfusion therapy did not significantly influence the likelihood of ECMO weaning over time (sHR = 1.24 [0.88–1.74], $p = 0.23$; see eFigure 6).

*Ischemic and Bleeding Events.*

Limb ischemia requiring surgical or catheter-based intervention occurred in 49 patients (10%), with no significant difference observed between groups either before (10% vs. 9%, p=0.8) or after matching (12% vs. 10%, $p = 0.6$; Table 2). Bleeding events were reported in 248 patients (50%), including 130 cases (26%) classified as severe. The incidence of bleeding did not differ significantly between groups before or after matching (Table 2). Likewise, bleeding rates were comparable across the ECMO stand-alone, ECMO + CDT, and ECMO + surgical embolectomy subgroups (46%, 46%, and 49%, respectively; $p > 0.9$; eTable 3).

*Subgroup Analyses.*

Baseline characteristics and clinical outcomes based on pre-ECMO cardiac arrest status and type of reperfusion therapy are detailed in eTables 6 and 7. Across all predefined subgroups, early mechanical reperfusion showed no significant impact on ECMO outcomes (Figure 3). Multiple matching strategies confirmed that neither 90-day mortality nor ECMO-free days differed significantly based on pre-ECMO cardiac arrest (eTable 6 and 7). No benefit of early mechanical reperfusion was observed when the 48-hour window was subdivided; however, in recent years, it was associated with an inconsistent trend toward lower 90-day mortality (eTable 8).

Among the 180 patients who did not receive systemic thrombolysis before ECMO, those who received early mechanical reperfusion had a lower 90-day mortality compared to

those managed with an ECMO stand-alone approach after PS matching (43% vs. 31%, HR 0.55 [95%CI, 0.33-0.92], p=0.02; Figure 3). Among survivors in this subgroup, the duration of ECMO was also shorter in the early mechanical reperfusion group (median 3 [2–5] vs. 4 [3–8] days, p=0.02; eTable 9). Notably, a competing risk analysis demonstrated that early mechanical reperfusion significantly increased the likelihood of ECMO weaning over time in patients who had not received pre-ECMO thrombolysis (sHR=1.56 [1.03–2.36], p=0.04; Figure 4).

## Discussion

This large, international cohort study evaluated the effect of early mechanical reperfusion therapy in patients receiving V-A ECMO for high-risk PE. Based on a propensity-matched analysis, the key findings are as follows: 1) early mechanical reperfusion within 48 hours of ECMO initiation did not significantly improve 90-day survival compared to an ECMO stand-alone approach; 2) the number of ECMO-free days by day 28 was comparable between both strategies; 3) among patients who had not received systemic thrombolysis before ECMO, early mechanical reperfusion could be associated with a faster weaning from ECMO and a significant trend for higher 90-day survival.

Mechanical reperfusion therapies for high-risk PE patients have been widely integrated into clinical routine, driven by advancements in percutaneous CDT technologies and an expanding body of literature (1, 2, 6, 27–30). The recent study by Staldbauer *et al.* showed in a large and unselected cohort of high-risk PE that advanced recanalization strategies, including systemic thrombolysis, CDT, and surgical embolectomy, resulted in better outcomes (in-hospital mortality of 48%, 43%, and 34%, respectively) compared to an ECMO stand-alone strategy (57%) (6). However, unmeasured confounders and indication

bias may have persisted despite sophisticated statistical models leading to premature conclusions (31).

V-A ECMO provides hemodynamic stabilization and may serve as a bridge for subsequent reperfusion interventions (2, 32). In a nationwide cohort study, Farmakis *et al.* found that combining ECMO with reperfusion therapy, particularly thrombolysis-based approaches, was linked to reduced in-hospital mortality (adjusted OR 0.55; 95% CI, 0.33–0.91) (7). However, their analysis did not differentiate between systemic and catheter-directed thrombolysis, nor did it consider the timing of reperfusion relative to ECMO initiation, factors that are critical for accurate interpretation. Likewise, another study reported lower mortality rates with surgical embolectomy (29%) in patients on V-A ECMO, compared to those receiving pre-ECMO systemic thrombolysis (77%) or an ECMO stand-alone strategy (78%) (8); yet, the absence of baseline severity adjustment in this cohort limited the strength of its conclusions. While these studies favor reperfusion therapy, Giraud *et al.* observed a survival rate of 80% in 36 patients treated with V-A ECMO as a stand-alone strategy along with others reporting a stepwise approach in which 52% of patients successfully recovered with this conservative strategy after waiting 3 to 7 days (33, 34). Additionally, differences in patient severity across studies may further complicate the identification of an optimal strategy for managing catastrophic PE requiring V-A ECMO. While our large cohort focuses on ECMO as a life-saving therapy (69% experiencing pre-ECMO cardiac arrest, 39% ECPR, median SAPS II score of 74), previous reports may have primarily included patients with less severe PE or those receiving ECMO as a bridge to reperfusion (6, 8, 34).

Mechanically removing the clot burden from the pulmonary artery is an appealing strategy, based on the premise that such interventions could provide immediate relief from hemodynamic compromise due to pulmonary hypertension and RV failure, thereby facilitating ECMO weaning. However, in our study, the median ECMO duration among

survivors in the ECMO stand-alone group was 4 days, comparable to the ECMO and early mechanical reperfusion group and similar to other studies, underscoring the effectiveness of heparin-induced and spontaneous thrombolysis (4, 33). Within just a few days, this intrinsic process often achieves sufficient clot resolution, lowering pulmonary hypertension below the threshold that impairs RV function and enabling ECMO separation.

Furthermore, survival in catastrophic PE patients is primarily driven by initial severity, especially the extent of multi-organ failure and the presence of cardiac arrest, rather than ECMO duration. This early period of hemodynamic support by ECMO is crucial for organ recovery, neurological assessment, and spontaneous thrombolysis (4, 33). Thus, initiating an early, resource-intensive procedure in patients with multi-organ failure or potentially irreversible brain damage is likely futile. As such, a stepwise, individualized approach, rather than a routine early mechanical reperfusion protocol, may be more appropriate for managing patients with life-threatening PE on ECMO (34). Interestingly, our subgroup analysis suggested that early mechanical reperfusion, facilitated by newer CDT techniques, may promote ECMO weaning in patients who had not received systemic thrombolysis before ECMO initiation and might be associated with improved 90-day survival. In this subgroup, early mechanical reperfusion could therefore be considered, unlike in patients placed on ECMO following failed systemic thrombolysis. However, the clinical relevance of a modest reduction in ECMO duration, approximately one day, remains debatable. Given the number of subgroup analyses performed, this result should be viewed as hypothesis-generating and warrants confirmation in larger cohorts.

Severe bleeding is a frequent complication in patients with catastrophic PE, likely due to factors such as ECMO support, prolonged cardiac arrest, and frequent administration of systemic thrombolysis before ECMO initiation. In our cohort, bleeding occurred in half of the patients, with the incidence of major bleeding aligning with that reported in another study

(35%) (7). Notably, there was no significant difference in bleeding rates between patients receiving ECMO with early mechanical reperfusion and those managed with ECMO stand-alone. Additionally, our findings revealed comparable bleeding rates between CDT and surgical embolectomy, echoing previous observations (7). Nonetheless, surgical embolectomy remains a highly invasive intervention, accompanied by procedural risks and logistical constraints. In contrast, modern percutaneous CDT techniques offer efficient thrombus removal with a more favorable safety profile. Thus, CDT may be considered a first-line reperfusion strategy, when needed, based on institutional experience and resource availability (27, 36).

This study has several limitations. First, it is an observational retrospective analysis. However, this large-scale, multicenter, international cohort provided a robust sample size and detailed data, enabling a well-balanced, propensity-matched comparison of the two strategies while minimizing selection and confounding bias. Nevertheless, residual confounding may persist, especially from factors influencing the decision to perform reperfusion that are difficult to measure, such as severe circulatory failure or the treating team's perception of salvageability early in the ECMO course. However, conducting randomized clinical trials in this setting is challenging given the rarity of such patients. Moreover, limited statistical power may have prevented the detection of a significant benefit from early mechanical reperfusion. Second, indications for ECMO and reperfusion, as well as their management, may vary depending on center volume and clinical experience. Although we limited inclusion to high-volume centers performing over 20 V-A ECMO cases annually, differences in radiologist and surgical expertise likely persist. Furthermore, decisions regarding withdrawal of life-sustaining therapies were not standardized across centers. Third, the study covers a 10-year period, which may introduce temporal bias related to evolving local protocols and therapy availability. Indeed, our findings suggest an inconsistent trend toward improved outcomes with early

mechanical reperfusion. Fourth, as the study focused on early management strategies, patients who died within 12 hours of ECMO initiation or required reperfusion beyond 48 hours were excluded. This selection may have influenced the cohort's characteristics and outcomes. Lastly, no long-term follow-up data were collected to assess the incidence of chronic thromboembolic pulmonary hypertension (CTEPH). However, existing long-term echocardiographic studies do not suggest an increased risk of CTEPH with an ECMO stand-alone strategy (4, 37).

## Conclusion

In this large international cohort of patients with life-threatening PE managed with V-A ECMO, the addition of early mechanical reperfusion therapy did not significantly reduce 90-day mortality or shorten ECMO duration compared to an ECMO stand-alone approach. Although early mechanical reperfusion using newer CDT techniques may provide advantages in selected patients by enabling earlier weaning, these findings require confirmation in larger cohorts. Until more definitive evidence becomes available, a pragmatic, stepwise, individualized approach favoring an initial ECMO stand-alone strategy may be preferable to routine early mechanical reperfusion.

**Author contributions**:

All authors were involved in data generation.

DL, MP, and MS had direct access to and verified the data.

DL, MP, and MS were involved in the analysis of the data.

DL, MP, and MS wrote the manuscript.

All authors contributed to the revision, read and approved the final version of the manuscript.

MS takes responsibility for the integrity of the work, from inception to publication of the article.

MS was responsible for the decision to submit the manuscript. All authors have seen and approved the final text.

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**Data sharing**

Individual patient data reported in this article will be shared after de-identification (text, tables, figures, and appendices), beginning 6 months and ending 2 years after Article publication, to researchers who provide a methodologically sound proposal and after approval

of the internal scientific committee. Proposals should be addressed to matthieu.schmidt@aphp.fr. To gain access, data requestors will need to sign a data access agreement.

## APPENDIX 1 :CATAPULTE Investigators

**- Assistance Publique—Hôpitaux de Paris, Pitié–Salpêtrière Hospital, Intensive Care Unit, Paris, France :** Juliette CHOMMELOUX, Alain COMBES, Guillaume HEKIMIAN, David LEVY, Charles-Edouard LUYT, Quentin MOYON, Grégoire DEL MARMOL, Marc PINETON DE CHAMBRUN, Ouriel SAURA, Matthieu SCHMIDT

**- Assistance Publique—Hôpitaux de Paris, Ambroise Paré Hospital, Intensive Care Unit, Boulogne-Billancourt, Inserm, U1018, CESP, University Versailles Saint Quentin - University Paris Saclay, Guyancourt, France:** Cyril CHARRON, Matthieu PETIT, Antoine VIEILLARD-BARON

**- Assistance Publique—Hôpitaux de Paris, Mondor Hospital, Intensive Care Unit, Créteil, France**: François BAGATE, Romain GALLET, Thierry FOLLIGUET, Paul MASI, Armand MEKONTSO DESSAP, Keyvan RAZAZI

**- Assistance Publique—Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Anaesthesiology and Intensive Care Unit, Paris, France:** Bernard CHOLLEY, Hélène NOUGUE, Adrien WERQUIN

**- Assistance Publique—Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Intensive Respiratory care Unit, Paris, France:** Olivier SANCHEZ

**- Assistance Publique—Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Radiology department, Paris, France:** Olivier PELLERIN

**- Assistance Publique—Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Cardiothoracic department, Paris, France:** Charles-Henri GAUTIER

**- Assistance Publique—Hôpitaux de Paris, Hôpital Bichat, Intensive care medicine Unit, Paris, France:** Lila BOUADMA, Julien DESSAJAN, Etienne DE MONTMOLLIN, Romain SONNEVILLE, Michael THY, Jean-François TIMSIT.

**- Centre Chirurgical Marie Lannelongue, Groupe Hospitalier Paris Saint-Joseph, Anaesthesiology and Intensive Care Unit, Le Plessis-Robinson, France :** Pierre DENORMANDIE, François STEPHAN

**- Assistance Publique–Hôpitaux de Marseille, CHU La Timone 2, Intensive Care Medicine Unit, Aix-Marseille Université :** Marc GAINNIER, Louis POT

**- Assistance Publique des Hôpitaux de Marseille, Hôpital Nord, Intensive care medicine Unit, Marseille :** Jean-Marie FOREL, Ines GRAGUEB-CHATTI, Christophe GUERVILLY, Sami HRAIECH, Laurent PAPAZIAN, Antoine ROCH

**- Centre Hospitalier Universitaire de Bordeaux, Hôpital Haut-Levêque, Anaesthesiology and Intensive Care Unit, Bordeaux, France :** Antoine BEURTON, Julien IMBAULT, Quentin LAJOYE, Alexandre OUATTARA

**- Centre Hospitalier Universitaire de Lille, Intensive Care medicine Unit, France :** Quentin DELFORGE, Nicolas DOGNON, Thibault DUBURCQ, Julien POISSY

**- Centre Hospitalier Universitaire de Lille, Cardiothoracic intensive care Unit, France :** Benoit BRASSARD, Oliver LUKOWIAK, Mouhamed DJAHOUM MOUSSA, Lise THELLIER, André VINCENTELLI

**- Centre Hospitalier Universitaire de Lille, Cardiac surgery, France :** Marie JUNGLING

**- University Hospital of Rennes, Anaesthesiology and Intensive Care Unit, France:** Erwan FLECHER, Yoann LAUNEY, Mathieu LESOUHAITIER, Lucie JANSEN, Alexandre MANSOUR, Nicolas NESSELER

**- Centre Hospitalier Universitaire de Rangueil, Anaesthesiology and Intensive Care Unit, Toulouse, France :** Baptiste COMPAGNON, Fanny VARDON

**- Centre Hospitalier Universitaire de Besançon, Cardiology department, France :** Nicolas MENEVEAU

**- Centre Hospitalier Universitaire de Besançon, Intensive care medicine Unit, France:** François BELON, Pierre-André PINEL, Gael PITON, Thibault VIEILLE, Hadrien WINISZEWSKI

**- Centre Hospitalier Universitaire d'Orléans, Intensive care medicine Unit, France :** Celine BESNARD, Gregoire MULLER, Kamel TOUFIK

**- Centre Hospitalier Universitaire de Nantes, Intensive care medicine Unit, France:** Emmanuel CANNET, Alice VENNIER

**- Centre Hospitalier Universitaire d'Angers, Intensive care medicine Unit, France :** Alain MERCAT, Pierre ASFAR, Satar MORTAZA, Pierre-Yves OLIVIER, Paul JAUBERT.

**- University hospital Leuven, Intensive Care medicine Unit, Belgium:** Dieter DAUWE, Erwin DETROY, Bart JACOBS, Dirk VLASSELAERS

**- University hospital Leuven, Cardiac surgery department, Belgium:** Tom VERBELEN, Bart MEYNS

**- Hôpital Universitaire de Bruxelles, Université Libre de Bruxelles, Intensive care medicine Unit, Belgium :** Filippo ANNONI, Luca D'AMELIO, Katarina HALENAROVA, Vincent LABBE, Fabio Silvio TACCONE, Leda NOBILE

**- Department of Emergency and Critical Care, Local Health Unit of São José, Intensive Care Unit, Lisbon, Portugal**: Cleide BARRIGOTO, Laura SANTOS, Pedro COSTA, Philip FORTUNA

**- São João University Hospital, Intensive care medicine Unit, Porto, Portugal:** Roberto RONCON-ALBUQUERQUE Jr, Francisco SANTOS-DIAS

**- General University Hospital, Anaesthesiology and Intensive Care Unit, Prague, Czech Republic:** Martin BALIK, Ivana JURISINOVA, Jan PUDIL

**- Centre Hospitalo-Universitaire Vaudois, Intensive Care Medicine Unit, Lausanne, Switzerland :** Isabelle CRISTIANI, Zied LTAIEF

**- Centre Hospitalo-Universitaire Vaudois, Cardiothoracic Surgery Department, Lausanne, Switzerland :** Filip DULGUEROV, Ziyad GUNGA, Anna NOWACKA

**- Geneva University Hospitals, Intensive Care Unit, Geneva, Switzerland :** Benjamin ASSOULINE, Karim BENDJELID, Raphaël GIRAUD

**- LKS Faculty of Medicine, The University of Hong Kong, Critical Care Medicine Unit:** Tammy Sin Kwan MA, Pauline Yeung NG

**- Saarland University Medical Center and University of Saarland, Internal Medicine V – Pneumology, Allergology and Critical Care Medicine, Homburg, Germany:** Philipp M. LEPPER, Vitalie MAZURU

**- University Hospital Regensburg, Internal Medicine II and Intensive care medicine Unit, Germany :** Alexander DIETL, Maria HEINRICH, Thomas MUELLER, Anna SCHNOBRICH

**- Korea University Anam Hospital, Thoracic & Cardiovascular Surgery, South Korea:** Jae-Seung JUNG, Ji Eon KIM, Hee Jung KIM, Jun Ho LEE, Yonghoon SHIM

**- Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Anesthesia, Critical Care and Emergency, Milan, Italy:** Nicola BOTTINO, Alessio CACCIOPPOLA, Giacomo GRASSELLI, Giovanna PEDRAZZINI

**- IRCCS Policlinico San Matteo, Anaesthesiology and Intensive Care Unit, Pavia, Italy:** Mirko BELLIATO, Costanza COLOMBO, Antonella DEGANI, Tavazzi GUIDO, Carlo PELLEGRINI

**- University of Washington Medical Center (UWML) and Harborview Medical Center (HMC), Emergency department and Intensive Care medicine Unit, Washington, USA:** Jenelle BADULAK, Anna CONDELLA, Whitney KIKER.

**- Vall Hebron University Hospital, Intensive Care medicine Unit, Barcelona, Spain:** Luis S. CHISCANO CAMON, Jordi RIERA

**- Hospital Alvaro Cunqueiro de Vigo, Intensive Care medicine Unit, University Hospital, Galicia, Spain:** Cristina CARBAJALES, Juan I. CHICO, Dorian CIOBANU, Santiago FREITA, Vanesa GOMEZ, María D. RIVAS

**- Fondazione IRCCS San Gerardo dei Tintori, Emergency and Intensive Care Unit – Monza, Italy:** Giuseppe FOTI, Marco GIANI, Matteo POZZI, Michela RAVASI

**- Toronto General Hospital, Medical-Surgical Intensive Care Unit, University Health Network, Toronto, Canada:** Ghislaine DOUFLE, Eddy FAN, Jonathan TAYLOR

**- Hiroshima University, Department of Emergency and Critical Care Medicine Hiroshima, Japan:** Mitsuaki NISHIKIMI, Shinichiro OHSHIMO, Nobuaki SHIME

**- The Alfred Health, Cardiothoracic intensive care Unit, Melbourne, Australia:** Joshua IHLE, Eanna LOWNEY, Vincent PELLEGRINO

**- St Vincent's Hospital, Intensive Care medicine Unit, Sydney, Australia:** Hergen BUSCHER

**- University Medical Center Utrecht, Intensive Care medicine Unit Utrecht, the Netherlands :** Dirk W DONKER

## References


1. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing G-J, Harjola V-P, *et al.* 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *European Heart Journal* 2020;41:543–603.
2. Assouline B, Assouline-Reinmann M, Giraud R, Levy D, Saura O, Bendjelid K, *et al.* Management of High-Risk Pulmonary Embolism: What Is the Place of Extracorporeal Membrane Oxygenation? *Journal of Clinical Medicine* 2022;11:4734.
3. Kobayashi T, Pugliese S, Sethi SS, Parikh SA, Goldberg J, Alkhafan F, *et al.* Contemporary Management and Outcomes of Patients With High-Risk Pulmonary Embolism. *Journal of the American College of Cardiology* 2024;83:35–43.
4. Levy D, Saura O, Passarelli MT, Lucenteforte M, Lebreton G, Bougle A, *et al.* Thrombolysis before venoarterial ECMO for high-risk pulmonary embolism: a retrospective cohort study. *Intensive Care Med* 2024;50:1287–1297.
5. Lebreton G, Schmidt M, Ponnaiah M, Folliguet T, Para M, Guihaire J, *et al.* Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study. *The Lancet Respiratory Medicine* 2021;0:
6. Stadlbauer A, Verbelen T, Binzenhöfer L, Goslar T, Supady A, Spieth PM, *et al.* Management of high-risk acute pulmonary embolism: an emulated target trial analysis. *Intensive Care Med* 2025;doi:10.1007/s00134-025-07805-4.
7. Farmakis IT, Sagoschen I, Barco S, Keller K, Valerio L, Wild J, *et al.* Extracorporeal Membrane Oxygenation and Reperfusion Strategies in High-Risk Pulmonary Embolism Hospitalizations. *Critical Care Medicine* 2024;52:e512.

8. Meneveau N, Guillon B, Planquette B, Piton G, Kimmoun A, Gaide-Chevronnay L, *et al.* Outcomes after extracorporeal membrane oxygenation for the treatment of high-risk pulmonary embolism: a multicentre series of 52 cases. *European Heart Journal* 2018;39:4196–4204.
9. Rivers J, Pilcher D, Kim J, Bartos JA, Burrell A. Extracorporeal membrane oxygenation for the treatment of massive pulmonary embolism. An analysis of the ELSO database. *Resuscitation* 2023;191:109940.
10. Lüsebrink E, Binzenhöfer L, Adamo M, Lorusso R, Mebazaa A, Morrow DA, *et al.* Cardiogenic shock. *Lancet* 2024;404:2006–2020.
11. Vieillard-Baron A, Naeije R, Haddad F, Bogaard HJ, Bull TM, Fletcher N, *et al.* Diagnostic workup, etiologies and management of acute right ventricle failure : A state-of-the-art paper. *Intensive Care Med* 2018;44:774–790.
12. Giri J, Sista AK, Weinberg I, Kearon C, Kumbhani DJ, Desai ND, *et al.* Interventional Therapies for Acute Pulmonary Embolism: Current Status and Principles for the Development of Novel Evidence: A Scientific Statement From the American Heart Association. *Circulation* 2019;140:e774–e801.
13. Danial P, Hajage D, Nguyen LS, Mastroianni C, Demondion P, Schmidt M, *et al.* Percutaneous versus surgical femoro-femoral veno-arterial ECMO: a propensity score matched study. *Intensive Care Med* 2018;44:2153–2161.
14. McCABE WR, JACKSON GG. Gram-Negative Bacteremia: I. Etiology and Ecology. *Archives of Internal Medicine* 1962;110:847–855.
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.

16. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993;270:2957–2963.
17. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, *et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22:707–710.
18. Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, *et al.* Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med* 2010;11:234–238.
19. GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993;329:1615–1622.
20. Sharshar T, Citerio G, Andrews PJD, Chieregato A, Latronico N, Menon DK, *et al.* Neurological examination of critically ill patients: a pragmatic approach. Report of an ESICM expert panel. *Intensive Care Med* 2014;40:484–495.
21. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61:344–349.
22. Schmidt M, Burrell A, Roberts L, Bailey M, Sheldrake J, Rycus PT, *et al.* Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. *Eur Heart J* 2015;36:2246–2256.
23. Stephens AF, Šeman M, Diehl A, Pilcher D, Barbaro RP, Brodie D, *et al.* ECMO PAL: using deep neural networks for survival prediction in venoarterial extracorporeal membrane oxygenation. *Intensive Care Med* 2023;49:1090–1099.

24. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011;10:150–161.
25. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res* 2011;46:399–424.
26. Diamond A, Sekhon JS. Genetic Matching for Estimating Causal Effects: A General Multivariate Matching Method for Achieving Balance in Observational Studies. *The Review of Economics and Statistics* 2013;95:932–945.
27. Aggarwal V, Giri J, Nallamothu BK. Catheter-Based Therapies in Acute Pulmonary Embolism. *Circulation: Cardiovascular Interventions* 2020;13:e009353.
28. Kucher N, Ouda A, Voci D, Barco S, Micieli E, Münger M, *et al.* Percutaneous large-bore aspiration embolectomy with veno-arterial extracorporal membrane oxygenation support or standby in patients with high-risk pulmonary embolism and contraindications to thrombolysis: a preliminary single centre experience. *Eur Heart J Acute Cardiovasc Care* 2023;12:232–236.
29. Chopard R, Behr J, Vidoni C, Ecarnot F, Meneveau N. An Update on the Management of Acute High-Risk Pulmonary Embolism. *J Clin Med* 2022;11:4807.
30. Boey JJE, Dhundi U, Ling RR, Chiew JK, Fong NC-J, Chen Y, *et al.* Extracorporeal Membrane Oxygenation for Pulmonary Embolism: A Systematic Review and Meta-Analysis. *Journal of Clinical Medicine* 2024;13:64.
31. Petit M, Levy D, Schmidt M. Personalized strategies for high-risk acute pulmonary embolism: addressing the “catastrophic” subgroup. *Intensive Care Med* 2025;doi:10.1007/s00134-025-07885-2.

32. Elbadawi A, Mentias A, Elgendy IY, Mohamed AH, Syed MH, Ogunbayo GO, *et al.* National trends and outcomes for extra-corporeal membrane oxygenation use in high-risk pulmonary embolism. *Vasc Med* 2019;24:230–233.
33. Giraud R, Laurencet M, Assouline B, De Charrière A, Banfi C, Bendjelid K. Can VA-ECMO Be Used as an Adequate Treatment in Massive Pulmonary Embolism? *J Clin Med* 2021;10:3376.
34. Pasrija C, Shah A, George P, Kronfli A, Raithel M, Boulos F, *et al.* Triage and optimization: A new paradigm in the treatment of massive pulmonary embolism. *J Thorac Cardiovasc Surg* 2018;156:672–681.
35. Abdulaziz S, Kakar V, Kumar PG, Hassan IF, Combes A, Brodie D, *et al.* Mechanical Circulatory Support for Massive Pulmonary Embolism. *J Am Heart Assoc* 2025;14:e036101.
36. Silver MJ, Gibson CM, Giri J, Khandhar S, Jaber W, Toma C, *et al.* Outcomes in High-Risk Pulmonary Embolism Patients Undergoing FlowTriever Mechanical Thrombectomy or Other Contemporary Therapies: Results From the FLAME Study. *Circulation: Cardiovascular Interventions* 2023;16:e013406.
37. Stadlbauer A, Philipp A, Blecha S, Lubnow M, Lunz D, Li J, *et al.* Long-term follow-up and quality of life in patients receiving extracorporeal membrane oxygenation for pulmonary embolism and cardiogenic shock. *Annals of Intensive Care* 2021;11:181.

**Table 1. Baseline characteristics at ECMO cannulation according to reperfusion strategy**

| | | Before PS-matching | | | After PS-matching | | |
|---|---|---|---|---|---|---|---|
| | **All patients (N=492)[1]** | **ECMO stand-alone (N=353)[1]** | **ECMO + early mechanical reperfusion (N=139)[1]** | **p[2]** | **ECMO stand-alone (N=137)[1]** | **ECMO + early mechanical reperfusion (N=137)[1]** | **SMD[3]** |
| Age, years | 53 [41; 61] | 53 [41; 61] | 53 [42; 62] | 0.7 | 52 [40; 60] | 53 [42; 61] | 0.08 |
| Female | 235 (48) | 176 (50) | 59 (42) | 0.14 | 54 (39) | 58 (42) | 0.06 |
| Body mass Index, kg/m² | 28 [24; 33] | 28 [25; 33] | 27 [24; 32] | 0.2 | 28 [24; 32] | 27 [24; 32] | 0.08 |
| Hypertension | 185 (38) | 137 (39) | 48 (35) | 0.4 | 40 (29) | 47 (34) | 0.11 |
| Diabetes mellitus | 81 (16) | 68 (19) | 13 (9) | <0.01 | 12 (9) | 13 (9) | 0.03 |
| Ischemic cardiopathy | 34 (7) | 27 (8) | 7 (5) | 0.3 | 3 (2) | 7 (5) | 0.16 |
| Chronic pulmonary disease | 68 (14) | 50 (14) | 18 (13) | 0.7 | 18 (13) | 18 (13) | >0.9 |
| Immunocompromised | 28 (6) | 20 (6) | 8 (6) | >0.9 | 6 (4) | 8 (6) | 0.07 |
| Cancer | 51 (10) | 35 (10) | 16 (12) | 0.6 | 13 (10) | 16 (12) | 0.07 |
| Previous PE | 51 (10) | 34 (1) | 17 (12) | 0.4 | 12 (9) | 17 (12) | 0.12 |
| Pregnancy | 18 (4) | 10 (3) | 8 (6) | 0.12 | 2 (1) | 8 (6 | 0.24 |
| Surgery within 7 days before ECMO | 131 (27) | 91 (26) | 40 (29) | 0.5 | 33 (24) | 40 (29) | 0.12 |
| Systemic thrombolysis before ECMO | 209 (42) | 160 (45) | 49 (35) | 0.04 | 45 (33) | 49 (36) | 0.06 |
| Pre ECMO cardiac arrest | 340 (69) | 251 (71) | 89 (64) | 0.13 | 90 (66) | 87 (64) | 0.05 |
| No-Flow | 0 [0; 0] | 0 [0; 0] | 0 [0; 0] | 0.08 | 0 [0; 0] | 0 [0; 0] | 0.20 |
| Low-Flow | 30 [12; 48] | 30 [12; 50] | 28 [10; 43] | 0.2 | 26 [11; 47] | 29 [10; 44] | 0.11 |
| Extracorporeal CPR | 191 (39) | 134 (38) | 57 (41) | 0.5 | 57 (42) | 55 (40) | 0.03 |
| At ECMO cannulation | | | | | | | |
| SAPS II | 74 [61; 83] | 75 [64; 85] | 68 [54; 77] | | 71 [52; 80] | 68 [54; 77] | 0.05 |
| SOFA | 13 [11; 15] | 14 [12; 15] | 12 [10; 14] | <0.01 | 12 [10; 14] | 12 [10; 14] | 0.07 |
| Vasoactive Inotropic score | 80 [29; 157] | 89 [30; 175] | 49 [25; 100] | 0.02 | 80 [15; 151] | 49 [25; 100] | 0.13 |
| IMV | 435 (88) | 321 (91) | 114 (82) | <0.01 | 116 (85) | 113 (82) | 0.06 |
| RRT | 21 (4) | 17 (5) | 4 (3) | 0.3 | 4 (2.9) | 4 (2.9) | >0.9 |
| pH | 7.14 [6.95 ; 7.29] | 7.11 [6.90 ; 7.25] | 7.25 [7.06; 7.36] | <0.01 | 7 .23 [7.08; 7.34] | 7.25 [7.06; 7.34] | 0.05 |
| Lactate, mmol/L | 8.5 [3.8; 13.8] | 10 [4.6; 15] | 5.8 [2.7; 11] | <0.01 | 7 [3; 12] | 6 [2.7; 11] | 0.17 |
| $PCO_2$, mmHg | 50 [38; 67] | 51 [41; 70] | 46 [33; 64] | 0.01 | 47 [36; 62] | 46 [34; 64] | 0.05 |
| Bilirubin, mg/L | 9 [5; 18] | 9 [5; 18] | 9 [4; 17] | 0.8 | 10 [5; 18] | 9 [4; 17] | 0.01 |
| ASAT, UI/L | 159 [48; 449] | 198 [53; 492] | 90 [40; 289] | <0.01 | 144 [50; 425] | 90 [40; 289] | 0.12 |
| ALAT, UI/L | 111 [39; 357] | 133 [44; 417] | 82 [35; 232] | 0.01 | 98 [34; 284] | 82 [34; 232] | 0.01 |
| INR | 1.5 [1.2; 2.3] | 1.50 [1.2; 2.3] | 1.4 [1.1; 2] | 0.05 | 1.4 [1.2; 2.1] | 1.4 [1.1; 2] | 0.05 |
| Fibrinogen, g/L | 2.1 [1; 3.9] | 2 [1; 3.2] | 2.9 [1.7; 4.8] | <0.01 | 2.3 [1.4; 4] | 3 [1.7; 4.8] | 0.24 |
| Platelet, G/L | 173 [120; 245] | 172 [117; 246] | 177 [126; 241] | 0.7 | 174 [123; 225] | 179 [126; 243] | 0.04 |
| Early mechanical reperfusion therapy on ECMO | | | | | | | |
| Catheter intervention | 92 (19) | 0 | 92 (66) | | 0 | 90 (66) | |
| Surgical embolectomy | 47 (10) | 0 | 47 (34) | | 0 | 47 (34) | |
| Time on ECMO before reperfusion, days | 0 [0; 1] | - | 0 [0; 1] | | - | 0 [0; 1] | |

*[1]Data are expressed as n (%) or median [Q1; Q3]*
*[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test*
*[3]Standardized Mean Difference*
*Definition of abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation; INR, international normalized ratio; PE, pulmonary embolism; RRT, renal replacement therapy; SAPS II, simplified acute physiology score; SOFA, Sequential organ failure assessment.*

**Table 2. ECMO-related complications and Outcomes**

| | | Before PS-matching | | | After PS-matching | | |
|---|---|---|---|---|---|---|---|
| | **All patients (N=492)[1]** | **ECMO Stand-alone (N=353)** | **ECMO + early mechanical reperfusion [1] (N=139)** | **p[2]** | **ECMO Stand-alone (N=137)** | **ECMO + early mechanical reperfusion [1] (N=137)** | **SMD[3]** |
| 90-Day mortality | 210 (43) | 165 (47) | 45 (32) | <0.01 | 54 (39) | 44 (32) | 0.2 |
| Death on ECMO | 153 (31) | 121 (34) | 32 (23) | 0.01 | 41 (30) | 31 (23) | 0.2 |
| ICU mortality | 206 (42) | 160 (45) | 46 (33) | 0.013 | 52 (38) | 45 (33) | 0.4 |
| Hospital mortality | 218 (44) | 170 (48) | 48 (35) | <0.01 | 55 (40) | 47 (34) | 0.3 |
| ECMO duration, days | 4 [3; 7] | 4 [3; 7] | 4 [3; 7] | 0.6 | 4 [3; 7] | 4 [3; 7] | 0.3 |
| ECMO duration among survivors, days | 4 [3; 7] | 4 [3; 7] | 4 [2; 7] | 0.3 | 4 [3; 7] | 4 [2; 7] | 0.2 |
| ECMO free days at day 28 | 19 [0; 24] | 17 [0; 24] | 22 [0; 25] | <0.01 | 20 [0; 24] | 22 [0; 25] | 0.11 |
| MV duration, days | 8 [4; 17] | 8 [4; 15] | 9 [4; 22] | 0.065 | 10 [4; 16] | 9 [4; 22] | 0.4 |
| MV duration among survivors, days | 11 [5; 22] | 10 [5; 21] | 11 [5; 25] | 0.6 | 13 [6; 20] | 11 [5; 25] | >0.9 |
| MV free days at day 28 | 0 [0; 19] | 0 [0; 18] | 4 [0; 20] | 0.5 | 4 [0; 18] | 4 [0; 20] | >0.9 |
| Tracheotomy | 72 (15) | 50 (14) | 22 (16) | 0.6 | 21 (15) | 22 (16) | 0.9 |
| Limb ischemia[4] | 49 (10) | 36 (10) | 13 (9) | 0.8 | 16 (12) | 13 (10) | 0.6 |
| Bleeding event | 248 (50) | 183 (52) | 65 (47) | 0.3 | 63 (46) | 64 (47) | >0.9 |
| Severe bleeding[5] | 130 (26) | 94 (27) | 36 (26) | 0.6 | 32 (23) | 36 (26) | 0.5 |
| Bleeding leading to intervention | 85 (17) | 59 (17) | 26 (19) | 0.2 | 23 (17) | 26 (19) | 0.6 |
| Ischemic stroke | 36 (7) | 26 (7) | 10 (7) | >0.9 | 5 (4) | 10 (7) | 0.2 |
| Hemorrhagic stroke | 23 (5) | 19 (5) | 4 (3) | 0.2 | 3 (2) | 4 (3) | >0.9 |

*[1]Data are expressed as n (%) or median [Q1; Q3]*
*[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test*
*[3]Standardized Mean Difference*
*[4] Defined as requiring catheter-directed procedure or surgery*
*[5]Defined as GUSTO 1 (18)*
*Definition of abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MV, mechanical ventilation*

# Figure Legends

**Figure 1: Study Flow Chart**

*Definition of abbreviations: PS, propensity score; V-A ECMO, venoarterial extracorporeal membrane oxygenation.*

**Figure 2. Kaplan-Meier 90-day survival analysis before and after propensity score matching**

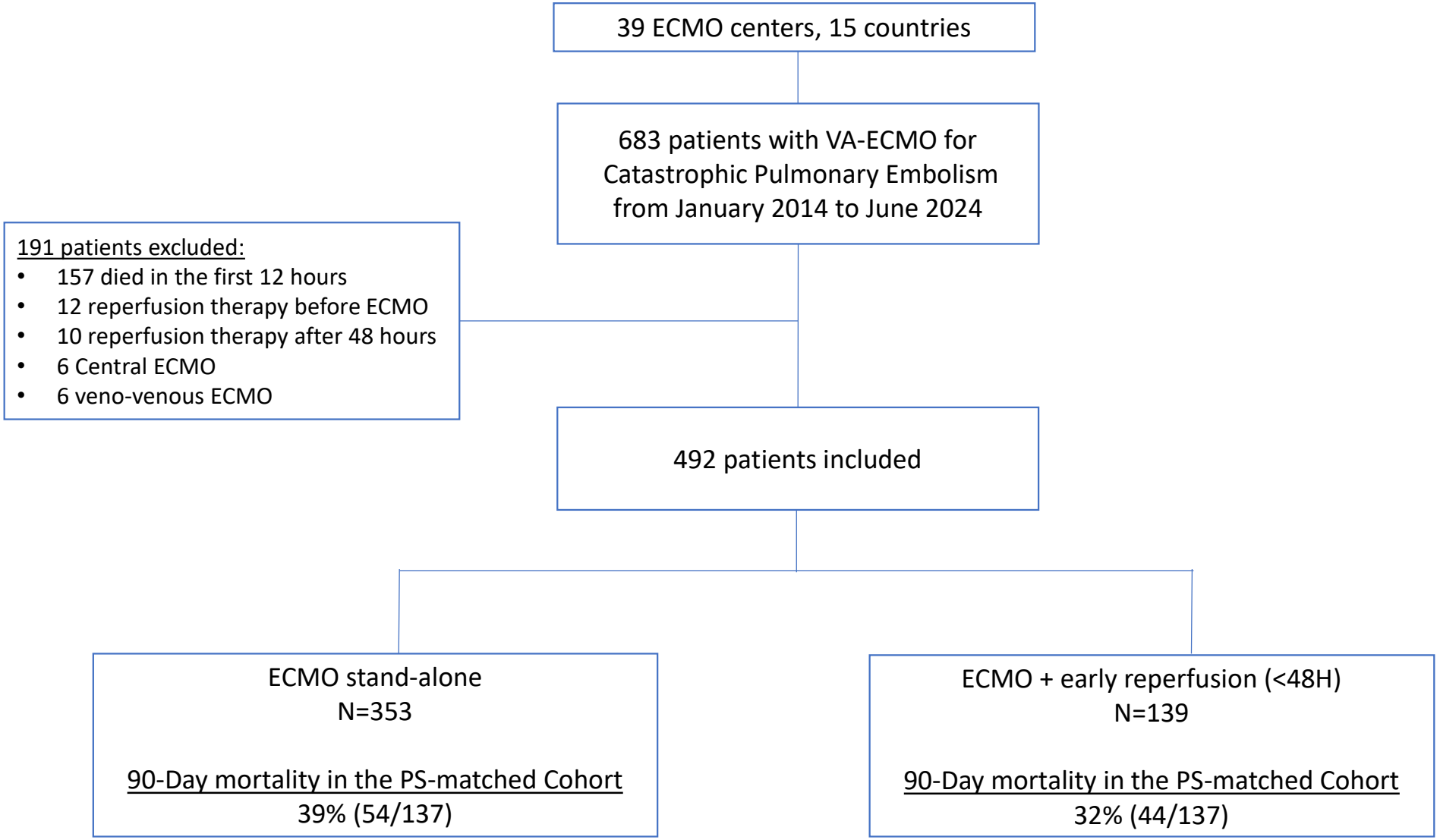
*Definition of abbreviations: ECMO, venoarterial extracorporeal membrane oxygenation; PS, propensity score*

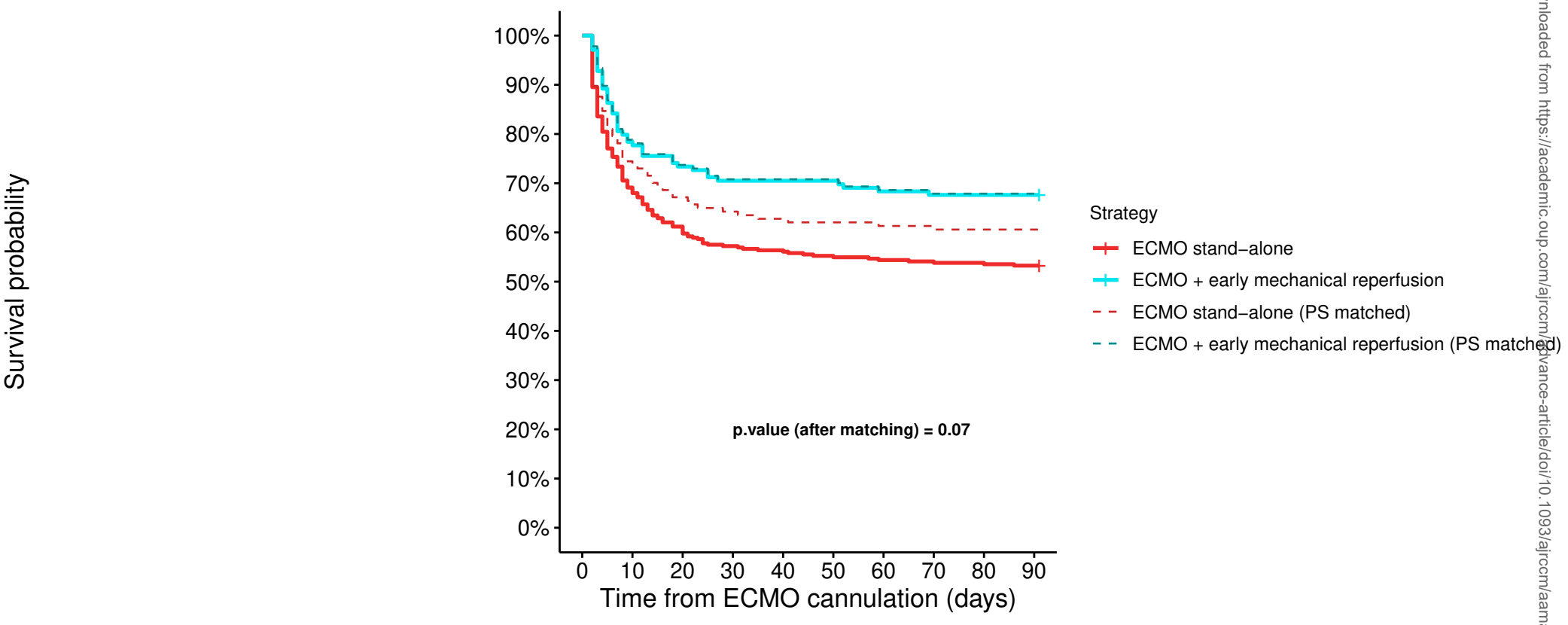
**Figure 3. Forest Plot of the matched cohort for 90-day mortality and subgroup analyses**

*Definition of abbreviations: ECMO, venoarterial extracorporeal membrane oxygenation; GenMatch, genetic matching; IPTW, inverse probability of treating weighting; PS, propensity score.*

**Figure 4. Cumulative incidence curves of ECMO weaning accounting for the risk of death according to pre-ECMO systemic thrombolysis**

*Definition of abbreviations: ECMO, extracorporeal membrane oxygenation; sHR, subdistribution hazard ratio.*



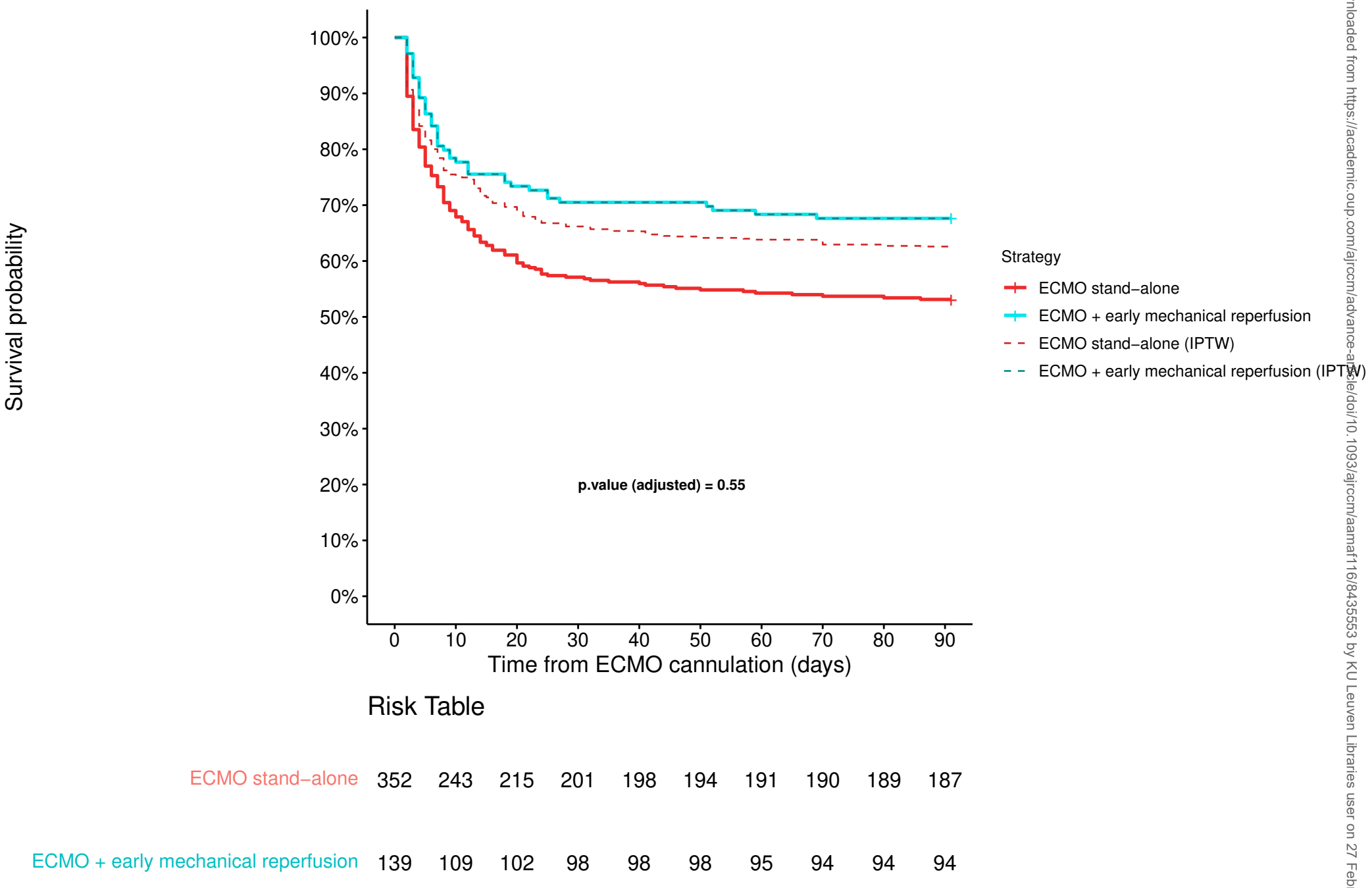



Risk Table: All Patients

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ECMO stand−alone | 353 | 244 | 216 | 202 | 199 | 195 | 192 | 191 | 190 | 188 |
| ECMO + early mechanical reperfusion | 139 | 109 | 102 | 98 | 98 | 98 | 95 | 94 | 94 | 94 |

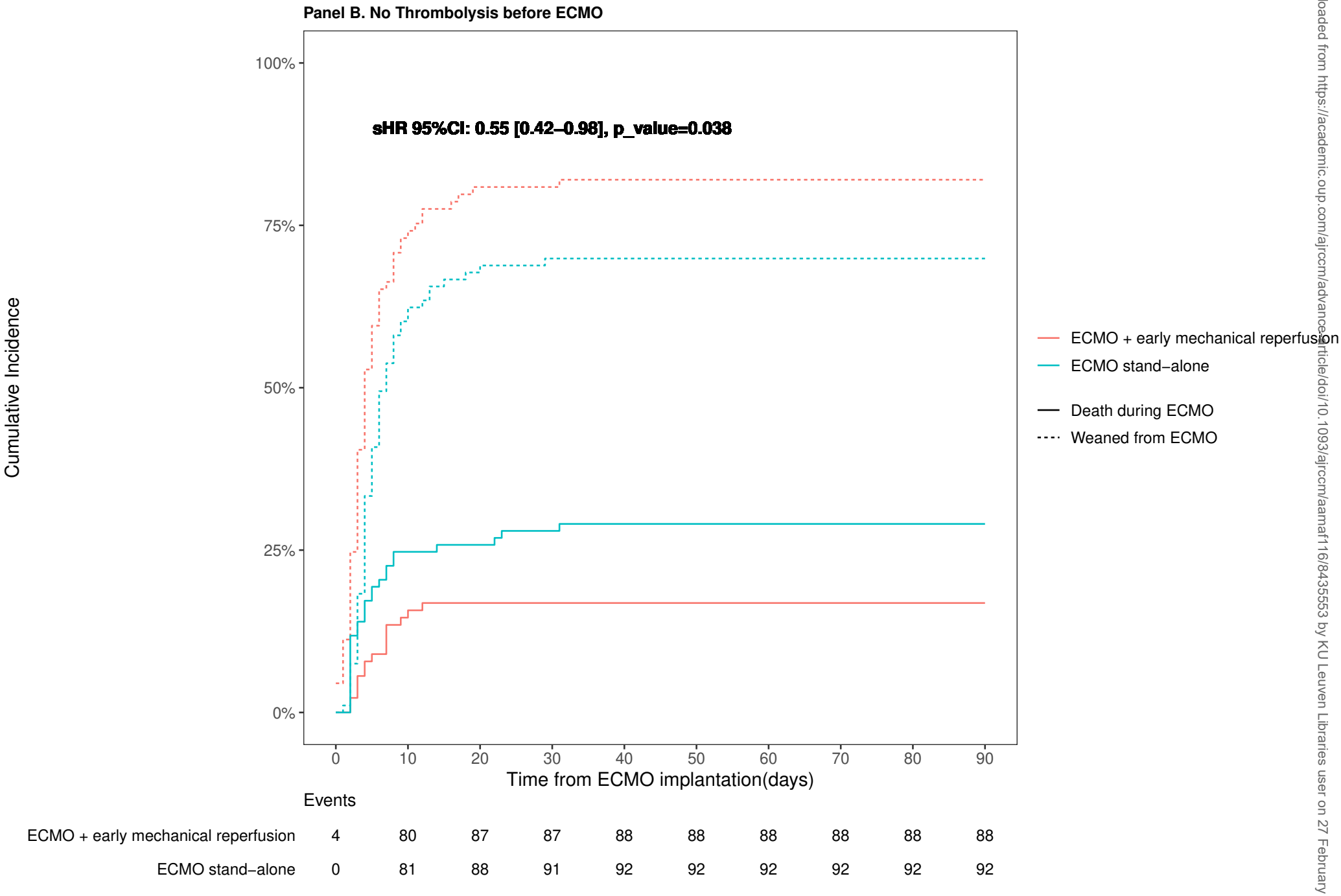
Risk Table: PS matched

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ECMO stand−alone (PS matched) | 137 | 102 | 92 | 88 | 86 | 85 | 84 | 84 | 83 | 83 |
| ECMO + early mechanical reperfusion (PS matched) | 137 | 108 | 101 | 97 | 97 | 97 | 94 | 93 | 93 | 93 |

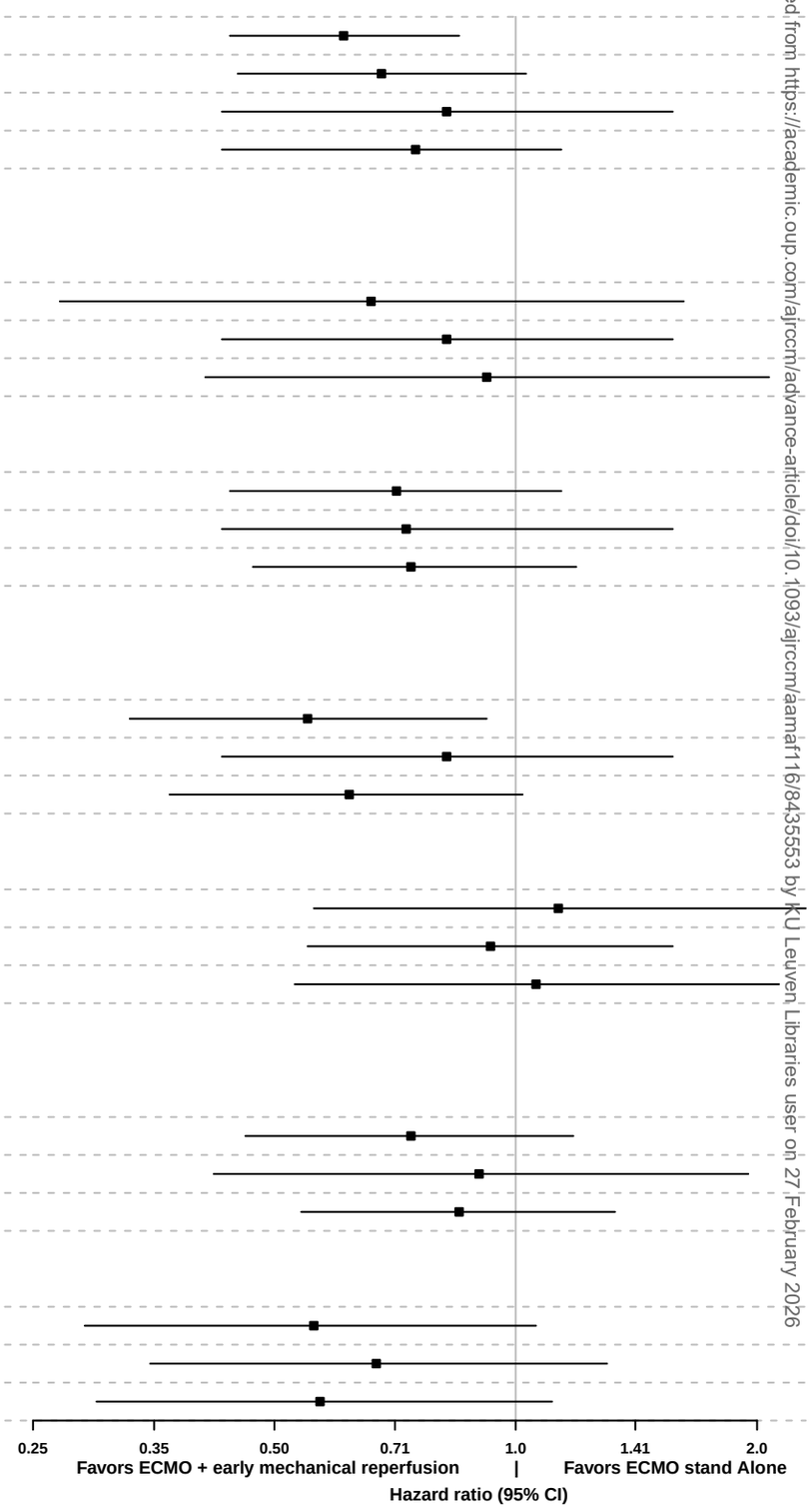



Risk Table

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ECMO stand−alone | 352 | 243 | 215 | 201 | 198 | 194 | 191 | 190 | 189 | 187 |
| ECMO + early mechanical reperfusion | 139 | 109 | 102 | 98 | 98 | 98 | 95 | 94 | 94 | 94 |



| Method | No./total No. ECMO + early mechanical reperfusion group | No./total No. ECMO stand−alone group | Hazard Ratio (95% CI) |
|---|---|---|---|
| **Primary analysis** | | | |
| Before adjustment | 45/139 | 165/353 | 0.61 (0.44 − 0.85) |
| PS Matching | 44/137 | 54/137 | 0.68 (0.45 − 1.03) |
| IPTW* | 45/139 | 54/143 | 0.82 (0.43 − 1.57) |
| GenMatch | 42/130 | 56/148 | 0.75 (0.43 − 1.14) |
| **Cardiac Arrest before ECMO** | | | |
| *No* | | | |
| PS Matching | 12/50 | 12/47 | 0.66 (0.27 − 1.62) |
| IPTW* | 12/50 | 13/56 | 0.82 (0.43 − 1.57) |
| GenMatch | 12/47 | 14/53 | 0.92 (0.41 − 2.07) |
| *Yes* | | | |
| PS Matching | 32/87 | 42/90 | 0.71 (0.44 − 1.14) |
| IPTW* | 33/89 | 41/87 | 0.73 (0.43 − 1.57) |
| GenMatch | 30/83 | 42/95 | 0.74 (0.47 − 1.19) |
| **Thrombolysis before ECMO** | | | |
| *No* | | | |
| PS Matching | 27/88 | 40/92 | 0.55 (0.33 − 0.92) |
| IPTW* | 28/90 | 35/93 | 0.82 (0.43 − 1.57) |
| GenMatch | 27/86 | 39/94 | 0.62 (0.37 − 1.02) |
| *Yes* | | | |
| PS Matching | 17/49 | 14/45 | 1.13 (0.56 − 2.3) |
| IPTW* | 17/49 | 19/50 | 0.93 (0.55 − 1.57) |
| GenMatch | 15/44 | 17/54 | 1.06 (0.53 − 2.13) |
| **Reperfusion strategy**** | | | |
| *Catheter intervention* | | | |
| PS Matching | 31/137 | 54/137 | 0.74 (0.46 − 1.18) |
| IPTW* | 32/92 | 54/143 | 0.9 (0.42 − 1.95) |
| GenMatch | 31/130 | 56/148 | 0.85 (0.54 − 1.33) |
| *Surgical embolectomy* | | | |
| PS Matching | 13/137 | 54/137 | 0.56 (0.29 − 1.06) |
| IPTW* | 13/47 | 54/143 | 0.67 (0.35 − 1.3) |
| GenMatch | 11/130 | 56/148 | 0.57 (0.3 − 1.11) |




** Weighted counts*

*** HRs are calculated without excluding any specific reperfusion strategy.*