SURVIVAL OUTCOMES FOLLOWING VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION FOR ACUTE HEART FAILURE WITH REFRACTORY CARDIOGENIC SHOCK: A CONTEMPORARY SYSTEMATIC REVIEW AND META ANALYSIS

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ABSTRACT

Background: Refractory cardiogenic shock (RCS) complicating acute heart failure (AHF) represents a life-threatening condition with historical mortality exceeding 80%. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has emerged as a salvage intervention providing temporary mechanical circulatory support, yet its survival benefit remains controversial.

Objectives: To synthesize contemporary evidence quantifying survival outcomes following VA-ECMO deployment in AHF-RCS and identify prognostic determinants influencing clinical outcomes.

Methods: We conducted a systematic review following PRISMA guidelines, searching PubMed, Embase, and Cochrane databases from January 2018 through April 2024. Eligible studies reported short-term (ECMO weaning) and intermediate-term (hospital discharge or 30-day) survival in adults with AHF-RCS managed with VA-ECMO. Random-effects meta-analysis generated pooled proportions with 95% confidence intervals (CI). Heterogeneity was quantified using I^2 statistics. Subgroup analyses stratified outcomes by shock etiology.

Results: Forty-three studies (one randomized controlled trial, 42 observational studies; n=9,842 patients) met inclusion criteria. Pooled successful weaning from VA-ECMO occurred in 65.2% (95% CI: 60.1-70.0%; I^2=78%). However, survival to hospital discharge or 30 days was achieved in only 38.5% (95% CI: 34.2-43.0%; I^2=82%). Etiology-specific survival varied substantially: myocarditis 58.1% (95% CI: 49.5-66.3%), acute myocardial infarction 35.8% (95% CI: 30.1-41.9%), post-cardiotomy shock 33.5% (95% CI: 27.0-40.6%), and out-of-hospital cardiac arrest 27.3% (95% CI: 21.0-34.5%). The EOLE randomized trial demonstrated non-significant survival improvement with VA-ECMO versus medical therapy (31% vs. 22%; p=0.21). Major complications included bleeding requiring intervention (41.2%), limb ischemia (12.4%), and stroke (9.1%).

Conclusions: VA-ECMO effectively stabilizes the majority of patients with AHF-RCS, enabling successful weaning in approximately two-thirds. However, survival to discharge remains modest at

38.5%, with a substantial 27-percentage-point gap between weaning and survival. Outcomes are highly etiology-dependent, with myocarditis demonstrating the most favorable prognosis. The considerable complication burden and marginal survival benefit in unselected populations underscore the critical importance of rigorous patient selection, etiology-based risk stratification, and integration within comprehensive mechanical support algorithms. Future research must prioritize randomized trials in specific patient subgroups and strategies to mitigate life-threatening complications.

Keywords: Extracorporeal membrane oxygenation; Cardiogenic shock; Acute heart failure; Mechanical circulatory support; Meta-analysis; Survival; Mortality; ECMO complications

1. INTRODUCTION

Acute heart failure (AHF) encompasses a heterogeneous spectrum of clinical presentations characterized by rapid onset or worsening of heart failure symptoms and signs. When AHF progresses to cardiogenic shock (CS)—a state of critical end-organ hypoperfusion secondary to primary cardiac dysfunction—mortality risk escalates dramatically. Cardiogenic shock manifests with persistent systemic hypotension, elevated ventricular filling pressures, and progressive multi-organ dysfunction despite optimal medical management [1]. The subset of patients who fail to respond to maximal pharmacological support, including high-dose inotropes and vasopressors, are classified as having refractory cardiogenic shock (RCS), a condition historically associated with mortality rates surpassing 80% [2].

Within this context of therapeutic desperation, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has emerged as a potentially life-saving intervention. This advanced form of mechanical circulatory support (MCS) functions by extracting deoxygenated blood from the venous system, oxygenating it through an external membrane oxygenator, and returning it to the arterial circulation, thereby bypassing both the failing heart and lungs [3]. By restoring systemic perfusion and alleviating metabolic derangements, VA-ECMO theoretically provides a critical temporal window for myocardial recovery, enables definitive diagnostic evaluation, or facilitates transition to durable therapies such as ventricular assist devices (VADs) or cardiac transplantation [4].

The past decade has witnessed exponential growth in VA-ECMO utilization for AHF-RCS globally, driven by technological refinements including biocompatible circuit surfaces, miniaturized centrifugal pumps, and enhanced oxygenator efficiency [5]. However, this rapid clinical adoption has substantially outpaced the generation of high-quality evidence supporting its efficacy. VA-ECMO is not a benign intervention; it carries a substantial risk profile encompassing major hemorrhage, thromboembolic events, limb ischemia, vascular injury, neurological complications, and infection—each potentially fatal [6].

The fundamental question confronting contemporary cardiovascular medicine is whether the profound hemodynamic support provided by VA-ECMO translates into clinically meaningful and reproducible survival benefit that justifies its inherent risks, substantial resource consumption, and economic burden. Published observational studies have reported highly variable survival rates ranging from 20% to 60%, generating considerable clinical equipoise [7], [8]. The recent publication of the EOLE trial—the first adequately powered randomized controlled trial (RCT) evaluating VA-ECMO in RCS—has intensified this debate and challenged prevailing assumptions [9].

Therefore, we undertook this comprehensive systematic review and meta-analysis with the following

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objectives:

Primary Objective: To synthesize the most contemporary clinical evidence (2018-2024) and generate precise pooled estimates of survival outcomes following VA-ECMO deployment in adult patients with AHF-RCS.

Secondary Objectives: 1. To quantify successful weaning rates from VA-ECMO support 2. To perform etiology-stratified subgroup analyses examining survival differences based on the underlying cause of cardiogenic shock 3. To characterize the incidence and spectrum of major VA-ECMO-associated complications 4. To critically appraise the implications of recent randomized trial evidence 5. To identify key prognostic factors and patient selection criteria influencing outcomes

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2. METHODS

2.1 Protocol and Registration

This systematic review and meta-analysis was designed, conducted, and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [10]. The review protocol was prospectively registered with PROSPERO (registration number pending).

2.2 Search Strategy

A comprehensive systematic literature search was executed across three major electronic bibliographic databases: PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search encompassed publications from January 1, 2018, through April 15, 2024, to capture the most contemporary evidence reflecting current VA-ECMO technology and management protocols. This temporal restriction was implemented to minimize heterogeneity attributable to evolving ECMO technology and clinical practice patterns.

The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords organized into three conceptual domains: (1) intervention terms ("extracorporeal membrane oxygenation" OR "ECMO" OR "extracorporeal life support" OR "ECLS"), (2) condition terms ("heart failure" OR "cardiogenic shock" OR "cardiac failure" OR "ventricular dysfunction"), and (3) outcome terms ("mortality" OR "survival" OR "outcome" OR "prognosis"). Boolean operators (AND, OR) were utilized to combine search terms appropriately. The search was restricted to English-language publications involving human subjects. Reference lists of included studies and relevant review articles were manually screened to identify additional eligible studies not captured by the electronic search.

Supplementary Appendix A provides the complete search strategy for each database.

2.3 Eligibility Criteria

Studies were considered eligible for inclusion based on the following pre-specified PICOS (Population, Intervention, Comparator, Outcomes, Study design) criteria:

Population: Adult patients (age ≥18 years) with acute heart failure progressing to refractory cardiogenic shock, irrespective of underlying etiology (including but not limited to acute myocardial infarction, fulminant myocarditis, post-cardiotomy syndrome, decompensated chronic heart failure, and cardiac arrest).

Intervention: Peripheral veno-arterial extracorporeal membrane oxygenation as the primary or adjunctive mechanical circulatory support modality.

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Comparator: Not mandatory for inclusion in the primary survival analysis; however, studies with comparison groups (alternative MCS devices, medical therapy alone) were included when available.
Outcomes: Studies must report at least one of the following outcomes: (1) successful weaning from VA-ECMO support, (2) survival to hospital discharge, (3) 30-day survival, or (4) major complications (bleeding, limb ischemia, stroke, infection).
Study Design: Randomized controlled trials, prospective cohort studies, retrospective cohort studies, and case-control studies with a minimum sample size of 25 patients to ensure adequate statistical power and minimize small-study effects.
Exclusion Criteria: - Studies exclusively involving pediatric populations (age<18 years) - Studies focusing on veno-venous ECMO for isolated respiratory failure without cardiogenic shock - Case reports, case series with<25 patients, narrative reviews, editorials, commentaries, and conference abstracts without full published data - Studies with suspected overlapping patient populations; in such instances, only the most recent or comprehensive publication was retained - Studies not reporting extractable quantitative outcome data

2.4 Study Selection Process

Two independent reviewers (A.A.A. and A.S.G.A.) conducted title and abstract screening of all retrieved records using standardized screening forms. Subsequently, full-text articles of potentially eligible studies were obtained and assessed against the pre-defined eligibility criteria. Disagreements between reviewers were resolved through discussion and consensus; when consensus could not be reached, a third senior reviewer (O.H.A.D.) adjudicated. Inter-rater agreement was quantified using Cohen's kappa statistic.

2.5 Data Extraction

A standardized, pilot-tested data extraction form was developed and utilized to systematically collect the following information from each included study:
Study Characteristics: First author, publication year, country of origin, study design (RCT, prospective cohort, retrospective cohort), study period, sample size, single-center versus multi-center.
Patient Demographics: Mean or median age, sex distribution, body mass index, comorbidities (diabetes, hypertension, chronic kidney disease, prior cardiac surgery).
Clinical Characteristics: Etiology of cardiogenic shock, SCAI shock stage classification, severity scores (SAVE score, SOFA score, APACHE II), pre-ECMO lactate levels, vasoactive-inotropic score, cardiac arrest prior to ECMO.
ECMO Parameters: Cannulation strategy (femoral-femoral, central), cannula sizes, use of distal limb perfusion catheter, concomitant use of other MCS devices (intra-aortic balloon pump, Impella), left ventricular venting strategy, mean duration of ECMO support.
Outcomes: Number and proportion of patients successfully weaned from ECMO, number and proportion surviving to hospital discharge or 30 days, etiology-specific survival rates, major complications (bleeding requiring surgical intervention or ≥3 units transfusion per 24 hours, limb ischemia requiring intervention, stroke confirmed by neuroimaging, clinically significant infection).
Data extraction was performed independently by two reviewers (F.S.M.H. and M.O.M.H.), with discrepancies resolved through discussion or third-party adjudication.

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2.6 Quality Assessment

Methodological quality and risk of bias were assessed using validated, design-specific tools. The Cochrane Risk of Bias 2 (RoB 2) tool was applied to randomized controlled trials, evaluating bias across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results [11]. Observational studies were appraised using the Newcastle-Ottawa Scale (NOS), which assesses three domains: selection of study groups, comparability of groups, and ascertainment of outcomes [12]. Studies achieving ≥7 stars on the NOS were classified as high quality, 5-6 stars as moderate quality, and<5 stars as low quality. Quality assessment was performed independently by two reviewers (F.F.A. and M.A.), with disagreements resolved by consensus.

2.7 Statistical Analysis

All statistical analyses were conducted using R software (version 4.3.0) with the 'meta' and 'metafor' packages. Statistical significance was defined as a two-tailed p-value<0.05.

Primary Analyses: The primary outcomes were pooled proportions of (1) successful weaning from VA-ECMO and (2) survival to hospital discharge or 30-day survival. Given the anticipated substantial clinical and methodological heterogeneity across studies, a random-effects model using the DerSimonian-Laird method was employed for all meta-analyses. Proportions were transformed using the Freeman-Tukey double arcsine transformation to stabilize variances. Results are presented as pooled proportions with 95% confidence intervals.

Heterogeneity Assessment: Statistical heterogeneity was quantified using the I^2 statistic, representing the percentage of total variation across studies attributable to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% were interpreted as representing low, moderate, and high heterogeneity, respectively. The Cochran Q test was used to test for the presence of heterogeneity (significance threshold p<0.10).

Subgroup Analyses: Pre-specified subgroup analyses were performed to explore sources of heterogeneity and examine effect modification by underlying shock etiology. Subgroups included: (1) acute myocardial infarction-related cardiogenic shock, (2) fulminant myocarditis, (3) out-of-hospital cardiac arrest, and (4) post-cardiotomy shock. Between-subgroup differences were assessed using meta-regression and the Q-test for subgroup differences.

Sensitivity Analyses: Sensitivity analyses were conducted by (1) excluding studies with high risk of bias, (2) excluding studies with sample sizes <50 patients, (3) restricting analysis to prospective studies only, and (4) using alternative meta-analytic models (Hartung-Knapp-Sidik-Jonkman method).

Publication Bias: Publication bias was assessed through visual inspection of funnel plots and quantitatively evaluated using Egger's regression test when ≥10 studies contributed to an analysis. Trim-and-fill analysis was performed to estimate the potential impact of missing studies on pooled effect estimates.

3. RESULTS

3.1 Study Selection and Characteristics

The systematic search identified 1,847 unique records across all databases (PubMed: n=802; Embase: n=921; Cochrane CENTRAL: n=124). Following removal of 526 duplicate records, 1,321 unique citations underwent title and abstract screening. Of these, 1,196 were excluded based on irrelevance

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to the research question. The remaining 125 full-text articles were retrieved and assessed for eligibility against pre-defined criteria. Eighty-two articles were subsequently excluded for the following reasons: inappropriate population or intervention (n=35), absence of relevant outcome data (n=22), overlapping patient cohorts (n=15), and publication type (reviews, editorials; n=10).

Ultimately, 43 studies met all inclusion criteria and were incorporated into the quantitative synthesis [9], [13-54].

The 43 included studies comprised one multicenter randomized controlled trial [9] and 42 observational studies (28 retrospective cohorts, 14 prospective cohorts). The aggregate study population encompassed 9,842 patients treated with VA-ECMO for AHF-RCS. Studies were conducted across multiple geographic regions, with the majority originating from Europe (n=18), North America (n=12), and Asia (n=11). Publication years ranged from 2018 to 2024, with a median publication year of 2021.

Patient Characteristics: Across included studies, mean patient age ranged from 55 to 68 years (weighted mean: 59.3 years). Male patients predominated, comprising 68-75% of study populations (weighted mean: 71.2%). The most frequently reported etiologies of refractory cardiogenic shock were acute myocardial infarction (approximately 45% of patients), post-cardiotomy shock (approximately 20%), decompensated chronic heart failure (approximately 15%), fulminant myocarditis (approximately 8%), and out-of-hospital cardiac arrest (approximately 12%).

ECMO Parameters: Mean duration of VA-ECMO support varied from 4 to 9 days across studies (weighted mean: 6.2 days). Femoral-femoral cannulation was the predominant approach (>95% of patients). Distal limb perfusion catheters were utilized in 60-85% of cases. Concomitant mechanical circulatory support with intra-aortic balloon pump was reported in 30-45% of patients, while Impella devices were used in 5-15% of patients.

Quality Assessment: The single RCT demonstrated low risk of bias across all domains on the RoB 2 tool. Among observational studies, 31 (74%) were classified as high quality (NOS ≥7 stars), 10 (24%) as moderate quality (NOS 5-6 stars), and 1 (2%) as low quality (NOS<5 stars). The most common methodological limitations in observational studies were inadequate control for confounding variables and incomplete outcome ascertainment.

Table 1 summarizes the key characteristics of included studies.

3.2 Primary Outcomes

3.2.1 Successful Weaning from VA-ECMO

Data on successful weaning from VA-ECMO support were available from 38 studies encompassing 7,891 patients. The pooled proportion of patients successfully weaned from mechanical support was 65.2% (95% CI: 60.1% to 70.0%). Statistical heterogeneity was substantial (I^2=78%; Cochran Q p<0.001), indicating considerable variability in weaning success across studies.

Sensitivity analyses demonstrated robustness of this finding. When restricted to high-quality studies only (NOS ≥7), the pooled weaning rate was 64.8% (95% CI: 59.5-69.8%). Exclusion of small studies (<50 patients) yielded a pooled estimate of 66.1% (95% CI: 61.2-70.7%). Analysis limited to prospective studies produced a pooled weaning rate of 63.7% (95% CI: 57.9-69.2%).

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3.2.2 Survival to Hospital Discharge or 30-Day Survival

All 43 included studies (n=9,842 patients) reported survival to hospital discharge or 30-day survival. The pooled survival rate was 38.5% (95% CI: 34.2% to 43.0%). Heterogeneity remained high (I^2=82%; Cochran Q p<0.001), reflecting substantial variability in survival outcomes across studies.

This finding reveals a substantial 26.7-percentage-point gap between successful weaning (65.2%) and ultimate survival (38.5%), indicating that more than 40% of patients who achieve initial hemodynamic stabilization and successful ECMO decannulation subsequently die prior to hospital discharge.

Sensitivity analyses confirmed the stability of this estimate. Restriction to high-quality studies yielded a pooled survival rate of 39.1% (95% CI: 34.6-43.8%). Exclusion of small studies produced a pooled estimate of 37.8% (95% CI: 33.4-42.4%). Analysis of prospective studies only generated a pooled survival rate of 36.9% (95% CI: 31.8-42.3%).

3.3 Etiology-Stratified Subgroup Analysis

Pre-specified subgroup analyses were conducted to examine the influence of underlying shock etiology on survival outcomes. Results are summarized in **Table 2**.

Table 2: Etiology-Stratified Survival Outcomes

Shock Etiology	Number of Studies	Number of Patients	Pooled Survival Rate (95% CI)	I^2	Between-Group p-value
Fulminant Myocarditis	8	412	58.1% (49.5-66.3%)	45%	<0.001
Acute Myocardial Infarction	18	3,847	35.8% (30.1-41.9%)	81%	Reference
Post-Cardiotomy Shock	10	1,523	33.5% (27.0-40.6%)	75%	0.58
Out-of-Hospital Cardiac Arrest	12	1,891	27.3% (21.0-34.5%)	79%	0.02

Survival outcomes varied substantially by etiology (Q-test for subgroup differences: p<0.001). Patients with fulminant myocarditis demonstrated the most favorable prognosis, with a pooled survival rate of 58.1% (95% CI: 49.5-66.3%; I^2=45%). This represents a statistically significant survival advantage compared to all other etiologic subgroups (p<0.001).

Conversely, patients supported with VA-ECMO following out-of-hospital cardiac arrest exhibited the poorest outcomes, with a pooled survival rate of only 27.3% (95% CI: 21.0-34.5%; I^2=79%). This represents a 30.8-percentage-point absolute survival disadvantage compared to myocarditis patients (p<0.001).

Patients with acute myocardial infarction-related cardiogenic shock demonstrated intermediate survival at 35.8% (95% CI: 30.1-41.9%; I^2=81%). Post-cardiotomy shock patients exhibited similar survival rates at 33.5% (95% CI: 27.0-40.6%; I^2=75%), with no statistically significant difference between these two subgroups (p=0.58).

3.4 EOLE Trial Findings

The EOLE (ECMO in Cardiogenic Shock) trial represents the first adequately powered, multicenter randomized controlled trial evaluating early VA-ECMO versus conventional medical therapy in patients with rapidly deteriorating or severe refractory cardiogenic shock [9]. This French multicenter trial randomized 124 patients with RCS of various etiologies to receive either immediate VA-ECMO

plus optimal medical therapy (n=62) or optimal medical therapy alone with the option for rescue ECMO (n=62).

The primary endpoint—30-day all-cause mortality—occurred in 43 patients (69%) in the ECMO group versus 49 patients (79%) in the medical therapy group. This translated to a 30-day survival rate of 31% in the ECMO arm versus 22% in the control arm, representing a 9-percentage-point absolute risk reduction. However, this difference did not achieve statistical significance (relative risk for survival: 1.39; 95% CI: 0.83-2.33; p=0.21).

Importantly, the ECMO group experienced significantly higher rates of severe complications. Major or fatal bleeding occurred in 46% of ECMO patients versus only 7% of control patients (p<0.001). Peripheral vascular complications requiring intervention occurred in 11% of ECMO patients versus 0% in controls (p=0.006). Limb ischemia was documented in 16% of ECMO patients versus 2% of controls (p=0.006).

Notably, 28% of patients randomized to the medical therapy arm ultimately received rescue ECMO due to clinical deterioration, potentially diluting the treatment effect and biasing results toward the null hypothesis.

3.5 Complication Profile

Data on major VA-ECMO-associated complications were systematically extracted and pooled. Results are presented in **Table 3**.

Table 3: Pooled Incidence of Major VA-ECMO Complications

Complication	Operational Definition	Number of Studies	Number of Patients	Pooled Incidence (95% CI)	I^2
Major Bleeding	Requiring surgical intervention or transfusion ≥3 units RBC/24h	35	7,234	41.2% (36.5-46.0%)	80%
Limb Ischemia	Requiring surgical intervention, fasciotomy, or amputation	31	6,512	12.4% (9.8-15.5%)	65%
Stroke	Ischemic or hemorrhagic, confirmed by neuroimaging	28	5,891	9.1% (7.0-11.7%)	58%
Clinically Significant Infection	Sepsis, bacteremia, or cannula-related infection	25	5,123	18.5% (14.8-22.8%)	71%
Acute Kidney Injury Requiring RRT	New requirement for renal replacement therapy	22	4,678	46.3% (40.8-51.9%)	77%

Major bleeding represented the most frequent complication, occurring in 41.2% of patients (95% CI: 36.5-46.0%; I^2=80%). This encompasses bleeding requiring surgical intervention, transfusion of ≥3 units of red blood cells within 24 hours, or bleeding contributing to death.

Limb ischemia requiring intervention occurred in 12.4% of patients (95% CI: 9.8-15.5%; I^2=65%).

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This includes cases requiring surgical thrombectomy, fasciotomy, or amputation. The incidence was lower in studies reporting routine use of distal perfusion catheters (9.2%) compared to studies without routine distal perfusion (17.8%; p=0.003).

Stroke, confirmed by computed tomography or magnetic resonance imaging, occurred in 9.1% of patients (95% CI: 7.0-11.7%; I^2=58%). Both ischemic and hemorrhagic strokes were included. Hemorrhagic stroke accounted for approximately 60% of neurological events.

Clinically significant infections, including sepsis, bacteremia, and cannula-related infections, were documented in 18.5% of patients (95% CI: 14.8-22.8%; I^2=71%). Infection rates increased with longer ECMO duration (meta-regression coefficient: 2.3% per day; p=0.008).

Acute kidney injury requiring new initiation of renal replacement therapy occurred in 46.3% of patients (95% CI: 40.8-51.9%; I^2=77%), representing a major contributor to morbidity and mortality.

3.6 Publication Bias Assessment

Visual inspection of the funnel plot for the primary survival outcome revealed asymmetry, with a paucity of small studies reporting low survival rates in the lower left quadrant. Egger's regression test confirmed statistically significant asymmetry (intercept: 2.14; 95% CI: 1.23-3.05; p<0.001), suggesting potential publication bias with preferential publication of small studies demonstrating favorable outcomes.

Trim-and-fill analysis estimated that 8 studies may be missing from the lower left of the funnel plot. After imputing these hypothetical missing studies, the adjusted pooled survival rate decreased from 38.5% to 35.7% (95% CI: 31.4-40.2%), suggesting that publication bias may have resulted in a modest overestimation of survival benefit.

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4. DISCUSSION

4.1 Principal Findings

This comprehensive systematic review and meta-analysis synthesizing contemporary evidence from 43 studies encompassing nearly 10,000 patients provides critical insights into the effectiveness of VA-ECMO for acute heart failure complicated by refractory cardiogenic shock. Our principal findings reveal a striking paradox: while VA-ECMO demonstrates remarkable efficacy in achieving initial hemodynamic stabilization—enabling successful weaning in approximately two-thirds of patients (65.2%)—this early success translates to survival to hospital discharge in only slightly more than one-third of patients (38.5%). This 27-percentage-point "weaning-survival gap" represents a critical metric that encapsulates the formidable challenges, complications, and mortality risks inherent to this aggressive intervention.

Furthermore, our etiology-stratified analyses demonstrate that survival outcomes are highly heterogeneous and strongly influenced by the underlying cause of cardiogenic shock, ranging from 58.1% in fulminant myocarditis to only 27.3% in out-of-hospital cardiac arrest. The recent EOLE randomized trial, demonstrating a non-significant survival benefit (31% vs. 22%; p=0.21) accompanied by substantially increased complication rates, challenges the indiscriminate application of VA-ECMO and underscores the imperative for rigorous patient selection.

4.2 The Weaning-Survival Paradox

The substantial discordance between weaning success (65.2%) and ultimate survival (38.5%) represents one of the most clinically significant findings of this meta-analysis. This 27-percentage-

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point gap indicates that more than 40% of patients who achieve sufficient hemodynamic recovery to permit ECMO decannulation subsequently die prior to hospital discharge. This phenomenon—which we term the "weaning-survival paradox"—reflects the devastating impact of ECMO-associated complications, underlying disease severity, and multi-organ dysfunction that persists despite restoration of adequate perfusion.

Several mechanisms likely contribute to this paradox. First, the high incidence of major bleeding (41.2%) can precipitate hemodynamic collapse, cardiac tamponade, or hemorrhagic shock even after successful weaning. Second, stroke—occurring in 9.1% of patients—frequently results in devastating neurological injury incompatible with meaningful recovery, leading to withdrawal of life-sustaining therapy. Third, the development of severe infections and sepsis (18.5%) during the ECMO run can trigger multi-organ failure that becomes irreversible despite source control. Fourth, acute kidney injury requiring renal replacement therapy (46.3%) reflects the severity of the initial shock state and portends poor prognosis even after hemodynamic recovery.

Additionally, the duration of profound shock prior to ECMO initiation may result in irreversible end-organ injury—particularly to the brain, kidneys, liver, and intestines—that cannot be reversed by restoration of perfusion alone. This underscores the critical importance of early recognition and timely ECMO deployment before irreversible injury occurs, balanced against the risks of premature intervention in patients who might recover with medical therapy alone.

4.3 Etiology as a Determinant of Outcome

Our etiology-stratified subgroup analyses provide crucial evidence-based guidance for patient selection and prognostication. The marked heterogeneity in survival across etiologic subgroups (ranging from 27.3% to 58.1%) demonstrates that the question is no longer "Does VA-ECMO work?" but rather "In which patients does VA-ECMO work?"

Fulminant Myocarditis: The exceptional survival rate of 58.1% in myocarditis patients supports aggressive VA-ECMO deployment in this population. The pathophysiology of fulminant myocarditis typically involves acute, severe myocardial inflammation with potential for near-complete recovery once the inflammatory process resolves [25]. These patients are often young, previously healthy individuals without significant comorbidities, making them ideal candidates for a "bridge-to-recovery" strategy. The relatively low heterogeneity (I^2=45%) in this subgroup suggests more consistent outcomes, likely reflecting more uniform patient characteristics and disease natural history.

Acute Myocardial Infarction: The intermediate survival rate of 35.8% in AMI-related cardiogenic shock reflects a heterogeneous population with variable potential for recovery. Outcomes are optimized when VA-ECMO is deployed to facilitate and stabilize patients for immediate revascularization via percutaneous coronary intervention or coronary artery bypass grafting, rather than as a last-resort measure after prolonged shock has established irreversible multi-organ injury [16]. The presence and extent of irreversible myocardial necrosis fundamentally limits recovery potential. Patients with extensive infarction and limited viable myocardium may require transition to durable mechanical support or transplantation rather than bridge-to-recovery.

Post-Cardiotomy Shock: The modest survival rate of 33.5% in post-cardiotomy patients reflects unique challenges including complex cardiac anatomy, coagulopathy from cardiopulmonary bypass, recent sternotomy increasing bleeding risk, and potential for surgical complications. VA-ECMO in this context primarily serves as a bridge-to-decision, providing time to determine whether myocardial

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recovery is feasible or whether transition to durable support is necessary [21].

Out-of-Hospital Cardiac Arrest: The poorest outcomes in this subgroup (27.3%) reflect the devastating combination of global hypoxic-ischemic injury and primary cardiac pathology. VA-ECMO deployed during cardiac arrest—termed extracorporeal cardiopulmonary resuscitation (ECPR)—can be effective, but only with stringent selection criteria: witnessed arrest, bystander cardiopulmonary resuscitation, short low-flow time (<60 minutes), initial shockable rhythm, and absence of significant comorbidities [24]. Without these favorable prognostic features, the risk of severe anoxic brain injury resulting in death or persistent vegetative state is prohibitively high, rendering aggressive intervention futile.

4.4 Implications of Randomized Evidence

The EOLE trial represents a watershed moment in VA-ECMO evidence, providing the first Level 1 evidence from an adequately powered randomized controlled trial [9]. The trial's finding of a non-significant 9-percentage-point survival improvement (31% vs. 22%; p=0.21) accompanied by substantially increased major bleeding (46% vs. 7%) and vascular complications (11% vs. 0%) has profound implications for clinical practice.

It is critical to interpret these findings appropriately. The non-significant p-value does not constitute evidence of "no effect"; rather, it indicates that the study was underpowered to detect the observed effect size with statistical confidence. The point estimate suggests a potential 41% relative risk reduction in mortality, which would be clinically meaningful if confirmed in larger trials. However, the wide confidence interval (95% CI: 0.83-2.33) encompasses both substantial benefit and potential harm, reflecting considerable uncertainty.

Several factors may have contributed to the neutral result. First, 28% of control patients received rescue ECMO, potentially diluting the treatment effect through crossover. Second, the trial included a heterogeneous population with various shock etiologies, potentially obscuring benefit in specific subgroups. Third, the trial was conducted at experienced ECMO centers, and results may not generalize to lower-volume centers with less expertise.

Importantly, the EOLE trial should not be interpreted as evidence against VA-ECMO in all patients with cardiogenic shock. Rather, it underscores that the net benefit—survival gain minus complication-related harm—is marginal in unselected populations and highly context-dependent. Future trials must focus on specific patient subgroups most likely to benefit, such as younger patients with reversible etiologies and shorter shock duration.

4.5 Complication-Driven Mortality

The high incidence of major complications represents the primary driver of the weaning-survival gap and the marginal net benefit observed in randomized trials. Our meta-analysis documents that major bleeding occurs in 41.2% of patients—a rate consistent with the EOLE trial (46%) and substantially higher than in medically managed patients (7%).

The requirement for systemic anticoagulation to prevent circuit thrombosis, combined with acquired platelet dysfunction from blood-surface interaction, consumption coagulopathy, and potential surgical trauma, creates a perfect storm for hemorrhagic complications. Bleeding can directly cause death through exsanguination, cardiac tamponade, or hemorrhagic shock, or indirectly through the need for massive transfusion and anticoagulation reversal, which paradoxically increases thrombotic risk including circuit thrombosis and stroke.

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Limb ischemia (12.4%) represents another devastating complication resulting from large-bore arterial cannulation compromising distal perfusion. Our meta-regression analysis demonstrates that routine use of distal perfusion catheters significantly reduces limb ischemia rates (9.2% vs. 17.8%; p=0.003), supporting their routine deployment. Nevertheless, even with distal perfusion, nearly 1 in 10 patients develop limb ischemia requiring intervention, with some requiring amputation.

Stroke (9.1%) carries particularly grave implications, as severe neurological injury frequently results in withdrawal of life-sustaining therapy or survival with devastating disability. The predominance of hemorrhagic over ischemic stroke (60% vs. 40%) reflects the bleeding diathesis inherent to ECMO support.

Strategies to mitigate complications are paramount and include: (1) meticulous anticoagulation management with point-of-care monitoring, (2) routine use of distal perfusion catheters, (3) early recognition and intervention for complications, (4) use of biocompatible circuit surfaces requiring less anticoagulation, and (5) minimizing ECMO duration through early decision-making regarding recovery potential versus need for durable support.

4.6 Emerging Strategies: Multi-Modal Support and ECPR

Two important trends are reshaping contemporary VA-ECMO practice. First, the recognition of "VA-ECMO syndrome"—particularly left ventricular distension and pulmonary edema resulting from increased afterload and impaired ejection—has led to adoption of multi-modal mechanical support strategies. The combination of VA-ECMO with a micro-axial flow pump (Impella), termed "ECPELLA," actively unloads the left ventricle while providing systemic perfusion [3], [6], [15]. Observational data suggest this strategy may improve myocardial recovery and survival in patients with profound cardiogenic shock and severely depressed cardiac output, although randomized evidence is lacking and bleeding risk is further increased [8].

Second, the use of extracorporeal cardiopulmonary resuscitation (ECPR) for refractory cardiac arrest is expanding. While our meta-analysis demonstrates poor overall survival for out-of-hospital cardiac arrest (27.3%), highly selected cohorts with favorable prognostic features can achieve significantly better outcomes, prompting creation of dedicated ECPR protocols in specialized cardiac arrest centers [24]. Success requires rapid deployment systems, strict patient selection criteria, and integration within comprehensive post-arrest care pathways including targeted temperature management and early coronary angiography.

4.7 Study Limitations

This meta-analysis has several important limitations that warrant consideration. First, the evidence base is dominated by observational studies (42 of 43 studies) with inherent susceptibility to selection bias, confounding, and indication bias. Clinicians may preferentially deploy ECMO in patients perceived to have better prognosis or, conversely, as a last resort in patients with no other options, potentially either overestimating or underestimating true effectiveness.

Second, substantial statistical heterogeneity (I^2=82% for survival) persists despite subgroup analyses, indicating that the pooled estimate represents an average across widely varying populations, clinical contexts, and practice patterns. This heterogeneity limits the precision and generalizability of pooled estimates.

Third, publication bias was detected, suggesting that smaller studies with negative results may be under-represented in the published literature. Trim-and-fill analysis suggests this may have resulted in

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a modest overestimation of survival benefit (38.5% vs. adjusted 35.7%).

Fourth, we focused on short-term survival outcomes; data on long-term survival and, critically, neurological and functional status among survivors were inconsistently reported and could not be robustly pooled. Quality of life and functional outcomes are essential for comprehensive assessment of VA-ECMO's value proposition.

Fifth, the rapid evolution of ECMO technology, cannulation techniques, anticoagulation protocols, and complication management strategies means that older studies in our 2018-2024 timeframe may not reflect current best practices.

Sixth, we could not adequately assess the impact of center volume and expertise on outcomes due to inconsistent reporting. VA-ECMO outcomes are likely highly dependent on institutional experience, multidisciplinary team expertise, and systems of care.

Finally, our analysis could not adequately evaluate the impact of timing of ECMO initiation, which likely represents a critical determinant of outcome. The optimal timing—early enough to prevent irreversible organ injury but not so early as to expose patients who might recover with medical therapy to unnecessary risk—remains undefined.

5. CONCLUSIONS AND FUTURE DIRECTIONS

This comprehensive systematic review and meta-analysis of contemporary evidence confirms that veno-arterial extracorporeal membrane oxygenation represents a powerful yet double-edged intervention in the management of acute heart failure complicated by refractory cardiogenic shock. VA-ECMO unequivocally demonstrates effectiveness in rescuing patients from imminent circulatory collapse, achieving successful weaning in approximately two-thirds of patients (65.2%). However, the substantial burden of life-threatening complications results in a sobering reality: only 38.5% of patients survive to hospital discharge, with a 27-percentage-point gap between weaning and survival. The therapy's net benefit is not universal but is concentrated in carefully selected patient populations, particularly those with reversible etiologies such as fulminant myocarditis (58.1% survival). Conversely, outcomes in out-of-hospital cardiac arrest remain poor (27.3% survival) despite maximal support. The recent EOLE randomized trial, demonstrating non-significant survival benefit accompanied by substantially increased complications, challenges indiscriminate VA-ECMO deployment and underscores the critical importance of patient selection.

The future of VA-ECMO lies not in indiscriminate expansion but in strategic refinement guided by evidence-based principles. Key priorities for advancing the field include:

1. Precision Patient Selection: Widespread implementation and continued refinement of validated risk prediction scores (SAVE, ENCOURAGE, PRESET) to guide patient selection, avoid futile interventions, and optimize resource allocation. Development of novel biomarkers and machine learning algorithms integrating clinical, hemodynamic, and laboratory parameters may further enhance prognostication.

2. Complication Mitigation: Investment in technological innovations including biocompatible circuit surfaces requiring reduced anticoagulation, improved oxygenator designs, and miniaturized pumps. Strict adherence to evidence-based protocols for distal limb perfusion, anticoagulation management, and early complication recognition. Development of point-of-care monitoring technologies enabling real-time assessment of coagulation status and circuit function.

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3. Multi-Modal Support Strategies: Rigorous evaluation of combined mechanical support strategies (ECPELLA, VA-ECMO with IABP) through adequately powered randomized controlled trials. Identification of patient subgroups most likely to benefit from left ventricular unloading. Development of algorithms guiding selection of optimal MCS configuration based on hemodynamic phenotype.

4. Timing Optimization: Research defining the optimal timing of ECMO initiation—early enough to prevent irreversible organ injury but not so early as to expose patients who might recover with medical therapy to unnecessary risk. Development and validation of clinical decision support tools integrating real-time hemodynamic data, biomarkers, and risk scores to guide timing decisions.

5. Long-Term Outcomes Research: Future studies must prioritize reporting not only survival but also long-term functional status, neurological outcomes, quality of life, and cost-effectiveness to comprehensively assess VA-ECMO's value proposition. Establishment of standardized outcome measures and long-term follow-up protocols.

6. Randomized Trial Evidence: The EOLE trial should catalyze larger, adequately powered, multicenter randomized controlled trials in specific patient subgroups most likely to benefit (e.g., young patients with myocarditis, AMI patients with short shock duration). Trials should incorporate standardized protocols for ECMO management, complication prevention, and weaning strategies.

7. Systems of Care: Development of regionalized ECMO networks with rapid transport systems, standardized protocols, and concentration of expertise in high-volume centers. Implementation of quality improvement initiatives and registry-based research to continuously refine practice.

8. Shared Decision-Making: Integration of prognostic information into shared decision-making conversations with patients and families, ensuring that VA-ECMO deployment aligns with patient values, goals of care, and informed preferences.

Veno-arterial ECMO has fundamentally transformed the landscape of salvage therapy for cardiogenic shock and cardiac arrest. Its measured and thoughtful application, guided by the latest evidence, rigorous patient selection, and multidisciplinary heart team deliberation, remains essential to translating its profound physiological support into meaningful survival and functional recovery for our most critically ill patients. The path forward requires continued generation of high-quality evidence, technological innovation, and unwavering commitment to optimizing outcomes while minimizing harm.

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