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A Recommended Preclinical Extracorporeal Cardiopulmonary Resuscitation Model for Neurological Outcomes: A Scoping Review

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Review

A recommended preclinical extracorporeal cardiopulmonary resuscitation model for neurological outcomes: A scoping review

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Abstract

Background: Despite the high prevalence of neurological complications and mortality associated with extracorporeal cardiopulmonary resuscitation (ECPR), neurologically-focused animal models are scarce. Our objective is to review current ECPR models investigating neurological outcomes and identify key elements for a recommended model.

Methods: We searched PubMed and four other engines for animal ECPR studies examining neurological outcomes. Inclusion criteria were: animals experiencing cardiac arrest, ECPR/ECMO interventions, comparisons of short versus long cardiac arrest times, and neurological outcomes.

Results: Among 20 identified ECPR animal studies (n = 442), 13 pigs, 4 dogs, and 3 rats were used. Only 10% (2/20) included both sexes. Significant heterogeneity was observed in experimental protocols. 90% (18/20) employed peripheral VA-ECMO cannulation and 55% (11/20) were survival models (median survival = 168 hours; ECMO duration = 60 minutes). Ventricular fibrillation (18/20, 90%) was the most common method for inducing cardiac arrest with a median duration of 15 minutes (IQR = 6–20). In two studies, cardiac arrests exceeding 15 minutes led to considerable mortality and neurological impairment. Among seven studies utilizing neuromonitoring tools, only four employed multimodal devices to evaluate cerebral blood flow using Transcranial Doppler ultrasound and near-infrared spectroscopy, brain tissue oxygenation, and intracranial pressure. None examined cerebral autoregulation or neurovascular coupling.

Conclusions: The substantial heterogeneity in ECPR preclinical model protocols leads to limited reproducibility and multiple challenges. The recommended model includes large animals with both sexes, standardized pre-operative protocols, a cardiac arrest time between 10–15 minutes, use of multimodal methods to evaluate neurological outcomes, and the ability to survive animals after conducting experiments.

Keywords: ECPR, Neurological outcome, Preclinical, Animal models, ECMO, Cardiac arrest

Abbreviations: ABI, acute brain injury, ACT, activated clotting factor time, CePP, cerebral perfusion pressure, CBF, laser-Doppler-derived regional cerebral blood flow, CPB, cardiopulmonary bypass, CPR, cardiopulmonary resuscitation, DO_2, oxygen delivery, EEG, electroencephalogram, ECPR, extracorporeal cardiopulmonary resuscitation, ECLHA, extracorporeal lung and heart assistance, ECMO, extracorporeal membrane oxygenation, GFAP, glial fibrillary acidic protein, HO-1, heme oxygenase-1, Iba1, ionized calcium binding adapter molecule 1, ICP, intracranial pressure, IQR, interquartile range, MRI, magnetic resonance imaging, mSEEPs, median nerve somatosensory-evoked potentials, NIRS, near-infrared spectroscopy, NSE, neuron-specific enolase, OPC, Overall Performance Category, $PbtO_2$, brain tissue oxygenation, P-NGAL, plasma neutrophil gelatinase-associated lipocalin, ROSC, return of spontaneous circulation, S100B, calcium-binding protein B, UCHL1, ubiquitin C-terminal hydrolase L1, VA-ECMO, venoarterial ECMO, VO_2, oxygen consumption

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Introduction

Cardiac arrest, which can lead to sudden cardiac death, is a major global issue causing 15–20% of estimated deaths worldwide.[1,2] There have been over 350,000 out-of-hospital cardiac arrests and 475,000 cardiac arrests resulting in death annually.[3] Extracorporeal cardiopulmonary resuscitation (ECPR) is a rescue intervention for refractory cardiac arrest patients,[4,5] employing veno-arterial extracorporeal membrane oxygenation (VA-ECMO) to restore continuous circulation.[6] The lack of perfusion from refractory cardiac arrest leads to neurological dysfunction.[7] While there is emerging evidence that ECPR has benefits on survival and neurological outcomes,[8] ECPR has also been shown to lead to a variety of complications, including acute brain injury (ABI), which are all associated with significant morbidity and mortality.[9–12] Furthermore, presence of ABIs, such as ischemic stroke, intraparenchymal hemorrhage, and hypoxic-ischemic brain injury, results in a twofold increase in mortality.[13,14] Therefore, additional research is required to investigate the pathophysiology leading to ABIs and to develop optimal strategies to improve neurological outcomes in ECPR.

While there are numerous established neurological models for conventional CPR,[15–18] and some models that investigate the survival and organ function preservation in ECPR,[19–21] little is known regarding a mature and reproducible neurological ECPR model. Therefore, there is an urgent need for a translational ECPR model that can answer mechanistic questions and lead to intervention and monitoring strategies to ultimately improve neurological outcomes in ECPR.[22] Our objective was to scope the literature to comprehensively review and appraise available translational models that investigate neurological outcomes in ECPR. By identifying key features, we aimed to determine the recommended animal model in this field.

Methods

Primary aim

The primary aim was to comprehensively review existing preclinical models for studying neurological outcomes after ECPR and identify key features that constitute a recommended preclinical model.

Search strategy

This scoping review was performed following the method described in Arksey and O'Malley[23] and according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[24] We searched PubMed via NCBI, Embase via Elsevier, the Cochrane Library via Wiley, Web of Science Core Collection via Clarivate, and Scopus via Elsevier. The search included deliberate vocabulary and keywords pertaining to ECPR, translational animal models, cardiac arrest, and neurological outcomes from inception to 17th April 2022. Details regarding the search strategy are in the **Appendix**. The results were deduplicated and transmitted to Covidence.

Inclusion criteria

The population, intervention, comparator, outcome, and study design (PICOS)[24] approach was used to decide which articles to include in our study. We included (1) animal studies, (2) studies with ECPR or ECMO occurring after cardiac arrest, and (3) studies investigating neurological outcomes. The search included articles not in the English language, which were appropriately translated and screened for the study's eligibility.

Exclusion criteria

We excluded (1) research studies that did not use animal models, (2) non-original research articles (i.e., editorials, commentaries, and reviews), and (3) studies with cardiac arrest occurring after the implementation of ECPR.

Study selection and data extraction

Two reviewers (A.K., S.A.A.) independently reviewed the literature results for the study's eligibility. A third reviewer (A.M.) settled any disputes regarding inclusion/exclusion. Covidence was used for this study. Articles meeting the inclusion criteria were obtained, and the full text was perused. References of the included studies were also screened and were included if they met the inclusion criteria. An Excel spreadsheet was used to formally extract data from eligible articles (Microsoft, Redmond, WA). Extraction variables included authorship, article title, publication date, journal name, article type, objectives, methods, key results, sample size, animal characteristics, anesthesia surveillance pre-ECMO, cardiac arrest characteristics, use of CPR, timing of ECPR, ECMO/ECPR characteristics, primary and secondary outcomes of interest, survival, neurological scoring systems, brain histology results, neurological plasma biomarkers, invasive and non-invasive neuromonitoring devices, and imaging modalities.

Quality assessment

We assessed the quality of reporting of each animal study based on the established "ARRIVE"[25] guidelines, which analyzes study design, sample size, inclusion and exclusion criteria, randomization, blinding, outcome measures, statistical methods, experimental procedures, and results.

Statistical analysis

All quantifiable data that was extracted from the studies, such as sample size, animal weight, and cardiac arrest time, were collected and reported as an overall median and interquartile range (IQR).

Results

Study selection

Our initial search yielded 5,512 total publications, of which 2,091 duplicates were removed, yielding a final total of 3,421 studies (PubMed 567, Embase 783, Cochrane 18, Web of Science 805, and Scopus 1,248). These 3,421 studies were imported into Covidence for screening. After removing an additional 344 duplicates, 3,077 studies were screened. 2,909 studies were excluded according to the aforementioned exclusion criteria, allowing 166 full studies to be assessed. An additional 146 studies were excluded to include 20 studies with animal models that studied neurological outcomes in our study (Fig. 1).[64–68 15,26–39,48].

Quality of reporting

Generally, the quality of reporting based on the ARRIVE 2.0 checklist was stronger regarding the results versus methods (Supplemental Tables 1 and 2). 16/20 studies did not report sufficient information regarding the location of where procedures were formed or acclimatization periods. 5/20 studies reported an *apriori* sample size calcula-

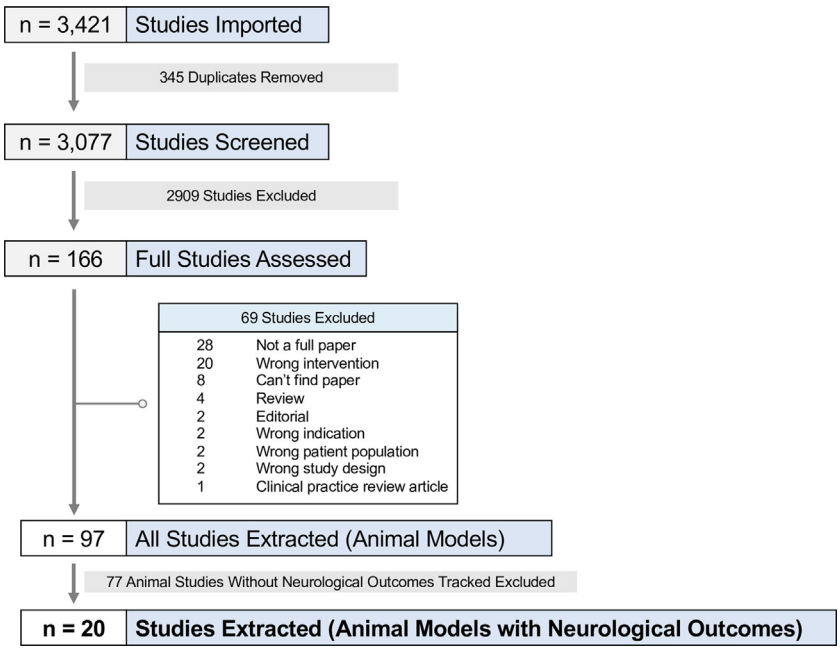

Fig. 1 – Flowchart depicting the inclusion process of the exemplified studies in this manuscript. The search strategy was performed from inception to 17th April 2022. Analysis was performed on all animal model studies that tracked neurological outcomes.

tion while 6/20 studies did not report specific information regarding species, strain, or sex of animals. In contrast, all 20 studies adequately reported baseline data and detailed main outcomes of interest. Overall, future ECPR animal studies should be more consistent with these important guidelines to report more reliable, high-quality findings, especially with their methodology.

General experimental overview

The experimental protocols in all 20 papers shared a similar structure. In studies that reported fasting protocols, animals were fasted one night before the experiment. On the day of the procedure, they were anesthetized and intubated, and baseline data and laboratory values were collected. Different monitoring strategies and devices were used according to the specific research focus. Then, cardiac arrest was induced. Efforts were made to attain return of spontaneous circulation (ROSC), with interventions including ECMO. Finally, outcomes were evaluated, including neurological outcomes (Fig. 2, Table 1).

Study characteristics

The total study population was 442 animals. The majority of studies utilized pigs (13/20, 65%), followed by dogs (4/20, 20%), and rats (3/20, 15%). 30% (6/20) studies did not report the sex of the animals and only two studies (10%) included both male and female animals. Seven studies used solely male (33%) animals while five studies included only females (25%). More than half of the studies did not report a fasting protocol. Anesthesia induction and maintenance were reported in all of the studies with various combinations among intravenous, intramuscular, and inhalational drugs. 90% (18/20) were considered interventional studies as they had several experimental

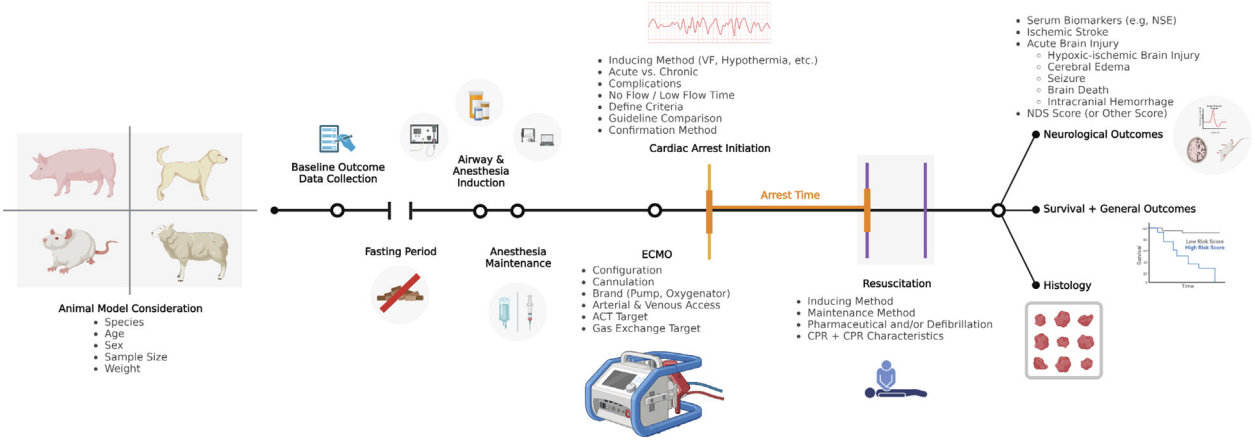

Fig. 2 – Timeline diagram depicting the common considerations when performing an ECPR experiment using an animal model for neurological outcome assessment. Created using BioRender (www.Biorender.com).

Table 1 – Methods to evaluate neurological outcomes in ECPR animal models[a].

Study	Objective	Groups	Methods to evaluate neurological outcomes
Wollborn et al. 2020	To investigate if ECPR with additional carbon monoxide application reduces neurological damage	Sham ($n = 5$) vs. conventional CPR ($n = 8$) vs. ECPR ($n = 8$) vs. ECPR with carbon monoxide application ($n = 8$)	• Biomarkers (caspase-3, HO-1, GFAP, Iba1) • Invasive neuromonitoring (rSO_2) • Non-invasive neuromonitoring (mSSEPs, Transcranial Doppler ultrasound) • Brain histopathology
Mandigers et al. 2021	To investigate if skin mitochondrial partial oxygen pressure measurements in cardiac arrest and ECPR are feasible and to investigate its course	N/A	• Scoring system (neurological deficit score)
Putzer et al. 2021	To investigate the effect of adrenaline on cerebral blood flow and oxygen delivery during low-flow ECPR	Group 1 (target MAP 40 mmHg, $n = 7$) vs. Group 2 (target MAP 60 mmHg, $n = 7$)	• Biomarkers (extracellular cerebral metabolites) • Invasive monitoring ($PbtO_2$, rSO_2, ICP, CePP)
Trummer et al. 2014	To investigate if pressure- and flow-controlled reperfusion conventional CPR vs ECPR improves neurological recovery and survival after 15 min of normothermic cardiac arrest	CPR ($n = 6$) vs. ECPR vs. no CPR ($n = 6$)	• Scoring system (neurological deficit score) • Biomarkers (neuron specific enolase) • Imaging (MRI)
Foerster et al. 2013	To investigate options for ECPR after an experimental 15 minutes normothermic cardiac arrest, with and without preceding anticoagulation	Group A without anticoagulation ($n = 6$) vs. Group B with anticoagulation ($n = 6$)	• Scoring system (neurological deficit score) • Biomarkers (neuron specific enolase) • Non-invasive neuromonitoring (EEG) • Imaging (MRI) • Brain histopathology
Foerster et al. 2018	To examine the role of immediate short-term blood cooling after cardiac arrest using a form of ECPR entitled the "controlled integrated resuscitation device" (CIRD) and its impact on both survival and neurological recovery	Hypothermia ($n = 10$) vs. Normothermia ($n = 11$)	• Scoring system (neurological deficit score) • Biomarkers (neuron specific enolase)
Mlcek et al. 2012	To examine early effects of ECMO after prolonged cardiac arrest	Survivors ($n = 12$) vs. Non-survivors ($n = 6$)	• Invasive monitoring (rSO_2) • Non-invasive neuromonitoring (EEG)
Pooth et al. 2022	To explore the plasma expander's role in the Controlled Automated Reperfusion of the whoLe body (CARL), a technique based off of ECLS, priming solution and examine its mechanism of action and effects on various physical properties	HHuman albumin treatment 20% ($n = 8$) vs. Gelatin polysuccinate 4% treatment ($n = 8$)	• Scoring system (neurological deficit score)
Spinelli et al. 2016	To examine the effects of the combination of ECPR and thrombolytic therapy on the recovery of vital organ function after prolonged cardiac arrest	ECPR group received Streptokinase 1.0 MU added to the pump prime ($n = 7$) vs. ECPR ($n = 6$) did not receive StreptoKinase ($n = 7$)	• Scoring system (neuropathologic damage score) • Non-invasive neuromonitoring (EEG) • Invasive monitoring ($PbtO_2$, ICP) • Brain histopathology
Casas et al. 2005	To trial a prototype CPB/ECMO system	Hypothermia ($n = 10$) vs. Normothermia ($n = 10$)	• Scoring system (level of consciousness, behavior, feeding, cranial nerves, motor/sensory functions, and coordination) • Brain histopathology
Ölander	To examine if the end-tidal carbon dioxide	Short CPR group with average of 11.6	• Scoring system (neuropathologic

Table 1 (continued)

Study	Objective	Groups	Methods to evaluate neurological outcomes
et al. 2022	could be used to guide commencement of ECPR	minutes (n = 6) vs. Long CPR with average of 35.5 minutes (n = 6)	damage score) • Biomarkers (P-S100B) • Invasive monitoring (ICP, CePP) • Brain histopathology
Zhang et al. 2019	To examine if how ECMO improves neurological outcomes of cardiac arrest patients compared with CPR	CPR (n = 8) vs. ECMO (n = 8)	• Biomarkers (IL-1, IL-1β, IL-6, TNFα, and TGFβ) • Non-invasive neuromonitoring (mSSEPs, Transcranial Doppler ultrasound) • Invasive monitoring (rSO_2) • Brain histopathology
Nilsen et al. 2021	To examine the effects of ECMO rewarming to restore oxygen delivery (DO_2) and organ blood flow after prolonged hypothermic cardiac arrest	N/A	• Biomarkers (S100B, UCHL1, GFAP, neuron specific enolase) • Non-invasive neuromonitoring (VO_2 and DO_2)
Taylor et al. 1995	To produce a hypothermic blood substitute that protects the brain and visceral organs during prolonged bloodless perfusion using extracorporeal circulation	Group 1 (n = 11): blood substituted with Hypothermosol purge solution (HTS-P) and Hypothermosol maintenance solution vs. Group 2 (n = 3): HTS-P only	• Scoring system (neurological deficit score)
Ichinose et al. 2006	To examine the neuroprotective effect of propofol under mild hypothermia with ECLHA	M group (n = 7) was infused with midazolam IV at a rate of 0.1 mg/(kg h), vs. P2 group (n = 7) with propofol at a rate of 2 mg/(kg h) as a small dose vs. P4 group (n = 7) with propofol at a rate of 4 mg/(kg h) as a moderate dose	• Scoring system (neurological deficit score) • Brain histopathology
Ichinose et al. 2006	To examine if the dose of heparin administered during the pre-arrest period affects outcomes in a dog model of cardiac arrest prompted by 15 min of normothermia followed by ECLHA	H-200 group (n = 6): given 200 U/kg heparin vs. H700 group (n = 6): given 700 U/kg heparin	• Scoring system (neurological deficit score)
Ao et al. 2001	To appraise the effects of long-term ECLHA with hypothermia (33 °C) in a dog model of prolonged cardiac arrest	Hypothermia (n = 7) vs. Normothermia (n = 8)	• Scoring system (neurological deficit score) • Brain histopathology
Janata et al. 2013	To examine if ECPR is possible after ventricular fibrillation cardiac arrest in rats and improves outcomes compared to conventional CPR	ECPR (n = 10), CPR (n = 10), ECPR with hypothermia (n = 10), CPR with hypothermia (n = 18), sham (n = 10)	• Scoring system (neurological deficit score, neuropathologic damage score) • Brain histopathology
Warenits et al. 2016	To detail observations and portray potential solutions to prevent future animal studies from adverse effects that may result from ECLS and CPB techniques	N/A	• Scoring system (neurological deficit score, overall performance category score)
Magnet et al. 2017	To examine if ECLS improves outcomes relative to conventional CPR in post-cardiac arrest rats	ECLS (n = 8) vs. CPR (n = 8) vs. Sham (n = 8)	• Scoring system (neurological deficit score, overall performance category score) • Brain histopathology

[a] CePP: cerebral perfusion pressure. CPB: cardiopulmonary bypass. CPR: cardiopulmonary resuscitation. DO_2: oxygen delivery. ECLHA: extracorporeal lung and heart assist. ECLS: extracorporeal life support. ECPR: extracorporeal cardiopulmonary resuscitation. ECMO: extracorporeal membrane oxygenation. EEG: electroencephalogram. GFAP: glial fibrillary acidic protein. HO-1: heme oxygenase-1. HTS-P: Hypothermosol purge solution. Iba1: ionized calcium binding adapter molecule 1. ICP: intracranial pressure. IV: intravenous. MRI: magnetic resonance imaging. mSEEPs: median nerve somatosensory-evoked potentials. N/A: not applicable as this information was not reported in the respective study. NDS: Neurological Deficit Scores. $PbtO_2$: brain tissue oxygenation. rSO_2: cerebral regional oxygen saturation. S100B: calcium-binding protien B. UCHL1: ubiquitin C-terminal hydrolase L1. VO_2: oxygen consumption.

groups. 55% (11/20) were survival models ranging from 48 to 504 hours with a median of 168 hours (IQR = 168–336) whereas 45% (9/20) were non-survival models wherein animals were euthanized after experiments.

Cardiac arrest characteristics

90% (18/20) studies utilized ventricular fibrillation to induce cardiac arrest. 85% (17/20) reported the duration of cardiac arrest with a median cardiac arrest duration of 15 minutes (IQR = 6–20). Foerster *et al* 2013 showed that all ECPR animals (n = 12) survived after 15 minutes of arrest under normothermia.[26] Similarly, Trummer *et al* showed that all ECPR animals (n = 6) survived after 15 minutes of arrest whereas five out of six animals (83%) in the conventional CPR group died.[27] Contrastingly, Mlcek *et al* adopted 20 minutes of arrest and showed 67% survival;[28] Spinelli *et al* employed 30 minutes of down time which led to five animals in the control group dying and one animal having severe left ventricular dysfunction despite ECPR.[29] Two studies reported 0 minutes of no flow time; one study maintained a low-flow time of 10 minutes using mechanical CPR whereas the other study restored low-flow circulation for 180 minutes using ECMO with acellular, aqueous blood substitute under hypothermia.[15,30] 7 out of 20 studies (35%) reported that CPR was performed. The resuscitation technique to achieve ROSC varied: the most common method was external defibrillation alone or with adjunct medication (16/20, 80%). Comprehensive description of study characteristics and procedural details is presented in Supplemental Table 3.

ECMO characteristics

The majority of studies (18/20, 90%) employed peripheral VA-ECMO cannulation. Two studies reported central cannulations (2/20, 10%). 40% (8/20) studies cannulated via surgical cut-down. 45% (9/20) used a percutaneous approach. The remaining four studies did not report a cannulation technique. Three studies using rats[31–33] employed arterial cannulas with gauges ranging from 14G to 22G and venous cannulas with gauges ranging from 14G to 20G, while in large animals, the median size of arterial and venous cannulas was 15 French and 19 French, respectively. Most of the studies did not report the length of the cannula. Nilsen *et al*—using pediatric pigs—reported an arterial cannula length of 18 centimeters and venous cannula length of 50 centimeters. The femoral artery was the preferred vessel for arterial access in 19 studies (95%), with the right femoral artery being the most commonly used site (50%).[34] ECMO flow rate, reported in 18 studies (90%), varied from 30-100 ml/kg/min. 95% (19/20) of studies reported an ECMO duration time with a median of 60 minutes (IQR = 30–360). No studies investigated the effect of ECMO duration on neurological outcomes. Of the seven studies that reported target activated clotting time (ACT) for monitoring intraoperative heparinization, six aimed for >300 seconds. A summary of key variables is found in Table 2. A detailed discussion of ECMO characteristics is found in Supplemental Table 4.

Neurological outcomes

Most studies (75%, 15/20) utilized neurological scoring systems for neurological evaluation, with 55% (11/20) studies using neurological

Table 2 – Summary of key variables.

Variables	Number of Studies
Animal Model	
Pigs	13/20 (65%)
Dogs	4/20 (20%)
Rats	3/20 (15%)
Cardiac Arrest Method	
Ventricular Fibrillation	18/20 (90%)
Others	2/20 (10%)
Survival Model	
Yes	11/20 (55%)
No	9/20 (45%)
Cardiopulmonary Resuscitation	
Yes	7/20 (35%)
No	12/20 (60%)
N/A	1/20 (5%)
Cannulation Technique	
Surgical	8/20 (40%)
Percutaneous	9/20 (45%)
N/A	3/20 (15%)
Arterial Access	
Femoral	19/20 (95%)
Aorta	1/20 (5%)
Activated Clotting Time Target	
>150	1/20 (5%)
250–350	1/20 (5%)
>300	5/20 (25%)
N/A[a]	13/20 (65%)

[a] N/A: not applicable as this information was not reported in the respective study.

Table 3 – Description of neurological outcomes in ECPR animal models.[a]

	Neurological Scoring Systems		Neurological Biomarkers		Neuromonitoring		Brain Histology	Imaging
Study	**Neurological Deficit Scores (NDS)**	**Other neurological scores**	**Neuron-Specific Enolase (NSE)**	**Other biomarkers**	**Non-invasive neuromonitoring**	**Invasive neuromonitoring**	**Histology findings**	**Magnetic resonance imaging (MRI)**
Wollborn et al. 2020	N/A	N/A	N/A	• ECPR: GFAP, Iba1, HO-1 •CPR: Iba1, HO-1 • ECPR + CO: lower HO-1	• mSSEPs: Faster recovery in ECPR + CO • Blood flow (Transcranial Doppler ultrasound): reduced in CPR & ECPR, unchanged in ECPR + CO	N/A	• ECPR: significant cordial injury • CPR: increased damage scores • ECPR + CO: significantly reduced injury	N/A
Mandigers et al. 2021	• Pig 1: NDS = 100 (Day 1), 60 (Day 2), 0 (Days 3–7) • Pig 2: NDS = 130 (Days 1–2), euthanized	N/A	N/A	N/A	N/A	N/A	N/A	N/A
*Putzer et al.*2021	N/A	N/A	N/A	N/A	N/A	Group 2 vs. Group 1: Improved ICP, CePP, CBF, rSO_2, $PbtO_2$, and extracellular cerebral metabolites	N/A	N/A
Trummer et al. 2014	• CPR: 1 survivor (score 10) at 24 hours • ECLS: 3 survivors (score 0), 1 survivor (score 20, then 0 at 48 hrs), 1 survivor (score 145)	N/A	7 days: • CPR: NSE increased (0.6 μg/l vs. 0.4 μg/l baseline) • ECLS: NSE stable at end of ECLS (0.3 μg/l ± 0.2 to 0.3 μg/l ± 0.1), increased at 7 days (2.3 μg/	N/A	N/A	N/A	N/A	Apparent diffusion coefficientdecreased in frontal lobe & cerebellum, no radiographic pathology in non-recovering CPR animals

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Table 3 (continued)

Study	Neurological Scoring Systems		Neurological Biomarkers		Neuromonitoring		Brain Histology	Imaging
	Neurological Deficit Scores (NDS)	**Other neurological scores**	**Neuron-Specific Enolase (NSE)**	**Other biomarkers**	**Non-invasive neuromonitoring**	**Invasive neuromonitoring**	**Histology findings**	**Magnetic resonance imaging (MRI)**
			l ± 1.5, $p < 0.05$)					
Foerster et al. 2013	24 hours mark: • Group A (with anticoagulation): 32 ± 39 • Group B (with anticoagulation): 35 ± 14	N/A	7 days post experiment: • Group A = 1.7 ± 1.4 • Group B = 1.3 ± 0.9	N/A	Group A showed • 10 sec post-ventricular fibrillation: Null EEG activity • Day 7: Responsive alpha activity	N/A	Moderate hypoxemic damage to both groups (no significant difference)	Difference in ADC between Group A and B, but no obvious infarction or ischemic changes
Foerster et al. 2018	At end of experiment: • Normothermia group: 37 ± 34 • Hypothermia group: 16 ± 13	N/A	At end of experiment: • Normothermia group: 4.3 ± 2.4 • Normothermic group: 1.5 ± 0.4	N/A	N/A	N/A	N/A	N/A
Mlcek et al. 2012	N/A	N/A	N/A	N/A	• Brain activity ceased within 2.1–4.1 min of cardiac arrest • 5 animals had EEG reappearance after ∼ 90 min post-cardiac arrest	N/A	N/A	N/A
Pooth et al. 2022	Day 7: • Human albumin 20% group: Median = 0 • Gelatin polysuccinate 4% group: Median = 5	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Spinelli et al. 2016	N/A	Histopathologic neurodegeneration score: • c-ECPR (no	N/A	N/A	Unchanged EEG activities in both groups	Thrombolytic addition: • c-ECPR: Improved cardiac	Intracerebral hemorrhages: • c-ECPR: 0.2 ± 0.2% (smaller	N/A

Table 3 (continued)

Study	Neurological Scoring Systems		Neurological Biomarkers		Neuromonitoring		Brain Histology	Imaging
	Neurological Deficit Scores (NDS)	Other neurological scores	Neuron-Specific Enolase (NSE)	Other biomarkers	Non-invasive neuromonitoring	Invasive neuromonitoring	Histology findings	Magnetic resonance imaging (MRI)
		streptokinase): 3.2 ± 0.9 • t-ECPR (streptokinase): 3.2 ± 1.1 (p = 0.97)				resuscitability, higher ICP • t-ECPR: Comparatively lower ICP	extent) • t-ECPR: 1.1 ± 0.7% (larger extent, $p < 0.05$)	
Casas et al. 2005	N/A	Neurological testing evaluating consciousness, behavior, feeding, cranial nerves, motor/sensory functions, and coordination (no specific score reported)	N/A	N/A	N/A	N/A	No neurological findings reported by histology, though it was performed	N/A
Ölander et al. 2022	N/A	No difference in levels in brain damage score between both groups at end of ECPR	N/A	No difference in levels of P-S100B between both groups at end of ECPR	N/A	ICP increase during ECPR, but no significant differences between two groups	No difference in histopathology of brain between both groups after ECPR	N/A
Zhang et al. 2019	N/A	N/A	N/A	• IL-1, IL-1β, IL-6, IL-10, TNFα, TGFβ, KL-6 levels detected • Ca2 + -ATPase, NA + -K + -ATPase detected	N/A	N/A	CPR group: Cell shrinkage, chromosome condensation, nuclear pyknosis, increased intercellular space, many inflammatory cells ECMO group: Much improved	N/A
Nilsen et al. 2021	N/A	N/A	N/A	S100B, UCHL1, GFAP detected	Cerebral VO_2 and DO_2 were calculated to measure cerebral blood flow	CePP (calculated as MAP - ICP) decreased with hypothermia and increased with rewarming	N/A	N/A
Taylor et al. 1995	1–2 days post-surgery: • Group 1	N/A	N/A	N/A	N/A	N/A	N/A	N/A

(*continued on next page*)

Table 3 (continued)

Study	Neurological Scoring Systems		Neurological Biomarkers		Neuromonitoring		Brain Histology	Imaging
	Neurological Deficit Scores (NDS)	Other neurological scores	Neuron-Specific Enolase (NSE)	Other biomarkers	Non-invasive neuromonitoring	Invasive neuromonitoring	Histology findings	Magnetic resonance imaging (MRI)
	(Hypothermosol purge): 0 ± 0 • Group 2 (Hypothermosol maintenance): 1.5 ± 0.5 3–7 days post-surgery: • Group 1: 0 ± 0 • Group 2: 1.0 ± 1.0							
Ichinose et al. 2006	N/A	168 hours of resuscitation: • M group (midazolam IV at a rate of 0.1 mg/kg h),: 20 ± 6 • P2 group (propofol at a rate of 2 mg/kg h): 10 ± 7 • P4 group (propofol at a rate of 4 mg/kg h): 4 ± 4	N/A	N/A	N/A	N/A	Greater intact pyramidal cells in hippocampal CA1: P2 & P4 groups > M group ($p < 0.05$)	N/A
Ichinose et al. 2006	120 hours of resuscitation: • H700 group: NDS = 18 ± 8%, • Most H700 animals died, 1 survivor: NDS = 24	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ao et al. 2001	96 hours post-resuscitation: • Hypothermia group: 29.8 ± 2.5% • Normothermia group: 60.5 ± 4.9%	N/A	N/A	N/A	N/A	N/A	Normothermia: CA1 subfield showed degeneration of pyramidal cells with nuclei condensation	N/A

Table 3 (continued)

	Neurological Scoring Systems		Neurological Biomarkers		Neuromonitoring		Brain Histology	Imaging
Study	**Neurological Deficit Scores (NDS)**	**Other neurological scores**	**Neuron-Specific Enolase (NSE)**	**Other biomarkers**	**Non-invasive neuromonitoring**	**Invasive neuromonitoring**	**Histology findings**	**Magnetic resonance imaging (MRI)**
Janata et al. 2013	• ECPR group: 2 ± 3 • CPR group: 1 ± 1 • ECPR with hypothermia group: 1 ± 2 • CPR with hypothermia group: 1 ± 2 Sham group: 0 ± 0	Neuropathological Damage Scores: hypothermia significantly reduced neuropathological damage scores in all groups in the subiculum	N/A	N/A	N/A	N/A	• No reduced histological damage in ECPR groups • Damage more severe in CA1 • No significant difference between the ECPR vs. CPR groups	N/A
Warenits et al. 2016	NDS was assessed daily for 2 weeks, though no specific values are mentioned in the article itself.	Overall Performance Category (OPC) score was assessed daily for 2 weeks, though no specific values are mentioned in the article itself	N/A	N/A	N/A	N/A	N/A	N/A
Magnet et al. 2017	14 days: • ECLS group = 1 ± 2 • CPR group = 1.	14 days overall performance score (OPC): • ECLS group: 5 animals with OPC1, 2 with OPC2, 1 with OPC5 • CPR group: 1 awith OPC1, 4 with OPC5, 3 with no ROSC	N/A	N/A	N/A	N/A	• ECLS with lower # living neurons in CA1 • Damage neurons and microglial activity in 3 out of 7 ECLS group • 1 animal in CPR group survived with good functional neurological outcome with living neuron count	N/A

[a] CBF: laser-Doppler-derived regional cerebral blood flow. CePP: cerebral perfusion pressure. CO: carbon monoxide. CPB: cardiopulmonary bypass. CPR: cardiopulmonary resuscitation. DO_2: oxygen delivery. ECLHA: extracorporeal lung and heart assist. ECLS: extracorporeal life support. ECPR: extracorporeal cardiopulmonary resuscitation. ECMO: extracorporeal membrane oxygenation. EEG: electroencephalogram. GFAP: glial fibrillary acidic protein. HO-1: heme oxygenase-1. HTS-P: Hypothermosol purge solution. Iba1: ionized calcium binding adapter molecule 1. ICP: intracranial pressure. IV: intravenous. MRI: magnetic resonance imaging. mSEEPs: median nerve somatosensory-evoked potentials. N/A: not applicable as this information was not reported in the respective study. NDS: Neurological Deficit Scores. OPC: Overall Performance Category. $PbtO_2$: brain tissue oxygenation. rSO_2: cerebral regional oxygen saturation. S100B: calcium-binding protien B. UCHL1: ubiquitin C-terminal hydrolase L1. VO_2: oxygen consumption.

deficit scores. Histological analysis was carried out in 10 studies (50%), comprising eight large and two small animal studies. A summary of the histological findings can be found in Table 3. Among the eight large animal studies, two collected brain samples for histology on the seventh day of experiments,[26,35] while another one acquired brain samples 96 hours post-resuscitation.[36] Notably, 88% (7/8) of the histological examinations involving large animals included a detailed analysis of the hippocampus. All studies observed some degree of brain injury on histology in ECPR groups regardless of treatment. In the case of the two small animal models, brain histology was obtained on the 14th day, after the animals had survived for 14 days following experiments.[31,32]

Four studies (20%) examined neurological biomarkers including neuron-specific enolase (NSE). NSE expression was elevated seven days after experiments. A summary of all neurological biomarkers is presented in Table 3. Olander *et al* exclusively investigated S100B as a neurological biomarker, however, there were no significant differences in S100B levels between different durations of ECPR.[37] Zhang *et al* demonstrated that the ECPR group had elevated levels of various cerebral inflammatory markers.[15] Wollborn *et al*'s 2020 study showed an increased level of glial fibrillary acidic protein (GFAP), ionized calcium binding adapter molecule 1 (Iba1), and heme oxygenase-1 (HO-1).[38] Finally, Nilsen *et al* demonstrated that ubiquitin C-terminal hydrolase L1 (UCHL1) and GFAP, both highly selective for brain injury, were within normal limits in pigs that underwent rewarming via ECPR.[34]

Three studies (15%) utilized electroencephalogram (EEG) to monitor brain electrical activity.[26,28,29] Foerster *et al* demonstrated that EEG activity ceased after 10 seconds, while Mlcek *et al* showed that EEG activity stopped within two minutes of cardiac arrest.[26,28] In both cases, EEG activity resumed following the initiation of ECPR. Conversely, Spinelli *et* al observed that brain activity stopped after 30 minutes of arrest and did not return to normal despite the implementation of ECPR.[29]

Four studies (20%) employed neuromonitoring devices to monitor intracranial pressure (ICP) and brain tissue oxygenation to evaluate neurological outcomes. Putzer *et al* employed supplementary neuromonitoring tools to investigate the impact of adrenaline-induced vasoconstriction on cerebral blood flow and oxygenation during low-flow ECPR. These tools included a near-infrared spectroscopy (NIRS) probe for evaluating cerebral blood flow and a cerebral microdialysis catheter for examining extracellular cerebral metabolites.[39] Wollborn *et al* utilized non-invasive neurological monitoring—median nerve somatosensory-evoked potentials (mSSEPs) and Transcranial Doppler ultrasound of the middle cerebral artery—to compare neurological outcomes among CPR, ECPR, and ECPR with groups who were administered carbon monoxide.[38] Two studies (10%) used magnetic resonance imaging (MRI) to evaluate ABIs. Foerster *et al* 2013 reported that the apparent diffusion coefficient(ADC) differed between control and experimental groups of pigs but did not show obvious infarction or ischemic changes.[26] Similarly, in Trummer *et al*'s paper,[27] MRI showed decreased ADC in frontal lobe and cerebellum without any radiographic signs of pathology in control group animals that did not recover after conventional CPR (Tables 1 and 3).

Discussion

In order to better understand the field of ECPR and its associated outcomes, a variety of studies have been employed to investigate various research questions through different animal models, including pigs, dogs,[40,41] and sheep.[42] We conducted a scoping review of existing literature on neurological outcomes in preclinical ECPR models and identified 20 relevant studies. Subsequently, we pinpointed crucial elements that should be integrated into a recommended model.

Choice of animal

The majority of studies were done in large animals using pig and dog models. Large animals are generally more suitable for translational research in this area, as their physiology is comparable to humans after cardiac arrest and ECMO cannulation. Additionally, their size and weight allows for direct adaptation of ECMO cannula and circuits used in the clinical setting. Small animal models offer value by facilitating a greater number of experiments and enabling a wider range of molecular and immunochemical investigations,[31] but their use does not represent an ideal preclinical model for ECMO due to the inherent challenges of reproducing clinically relevant extracorporeal circulation in small-sized animals. Furthermore, small animal models have high complication rates, with nearly 50% related to ECMO cannulation, which can be fatal.[33] This makes them more prone to selection bias, as only animals with successful cannulation are likely to be included in studies. The reported methods used to evaluate neurological outcomes in these models are mainly limited to scoring systems and brain histology. The use of neuromonitoring tools is not well-established in small animals, restricting a detailed assessment of cerebral blood flow and autoregulation. Collectively, these factors contribute to the limited reproducibility of small animal models for studying neurological outcomes in ECPR. Therefore, we suggest using large animals in this field.

Peri-procedural details

We observed substantial variability in the preparation stage. Only two studies reported using both male and female species. Sex imbalance in animal experiments can introduce significant bias, making the research less reproducible, translatable, and overall generalizable.[43] Therefore, sex-sensitive design of ECPR models should be encouraged to improve the overall quality and efficacy of research. Additionally, feeding management was not reported in more than half of studies; this may influence the preoperative status of animals and lead to variability in intervention responses and potentially inconsistent neurological outcomes. Supplemental Table 3 summarizes the anesthetic induction methods used, which included intravenous, intramuscular, and inhaled agents. The role of different anesthetic agents on outcomes of interest should be considered when designing animal models. For instance, propofol is a very widely used anesthesia induction and maintenance drug in cardiac surgery, routinely used for sedation during ECMO.[44] However, if intravenous infusion is not slowly administered, propofol may induce significant hypotension and thus may not be the drug of choice when studying hemodynamics in ECMO.[45] Similarly, the use of inhalational agents like isoflurane should be discouraged, as they may offer neuroprotective effects that could potentially confound findings related to neurological outcomes.[46]

Cardiac arrest

The duration of cardiac arrest was reported in most studies, ranging from 0 to 30 minutes. Based on our review, we believe that the recommended duration of cardiac arrest under normothermia is 10–15 minutes. Studies by Spinelli *et al* and Mlcek *et al* saw significant mor-

bidity in animals with normothermic cardiac arrest longer than 20 minutes.[28,29] 30 minutes of cardiac arrest led to the cessation of electrical brain activity, which did not return even after 6 hours of continuous ECPR.[29] Conversely, Foerster *et al* 2013 and Trummer *et al* employed 15 minutes of cardiac arrest, which resulted in negligible differences in brain histopathology and good survival rates.[26,27] These results are corroborated by the three established phases of cardiac arrest. First, the electrical phase lasts 4–5 minutes, during which countershocks can achieve cardioversion without pre-shock CPR. Then, the circulatory phase lasts 5–10 minutes and requires interventions to restore circulation. After 10–15 minutes, the last stage (metabolic phase) begins and results in substantial organ damage and neurological impairment, even if cardioversion is achieved.[47] Therefore, we infer that a cardiac arrest time between 10–15 minutes but no more than 20 minutes would induce sufficient physiological and cerebral insult, as seen in clinical scenario, yet yield recoverable brain injuries and reasonable survival rates in animals with resuscitation and interventions. It is worth noting that several studies included in this review had longer than 15 minutes of cardiac arrest, but were under hypothermia. Understanding the complex interplay between different temperatures, hemodynamics, and oxygen and carbon dioxide levels is crucial for improving neurological outcomes in ECPR, yet these physiological variables have not been adequately studied in preclinical models.

Resuscitation method

The method of resuscitation used in each study varied substantially. For example, Foerster *et al* performed only external defibrillation of 300–360 joules to achieve ROSC.[48] Instead, Spinelli *et al* used pharmacological support with vasopressin and dobutamine in addition to external defibrillation to achieve ROSC.[29] Similarly, studies performed by Ichinose *et al*, Magnet *et al*, Mandigers *et al*, Putzer *et al*, Wollborn *et al*, Warenitis *et al,* and Zhang *et al*, used adjunct pharmacological agents to resuscitate the animals after cardiac arrest. Ultimately, the protocol for cardiac arrest should be thoughtfully designed based on the research question to eliminate any potential confounding factors while maintaining clinical relevance. For instance, if the objective is to investigate ECPR for out-of-hospital cardiac arrest, an animal model with solely mechanical CPR and external defibrillation would most closely resemble the clinical environment. Conversely, an experiment targeted towards ECPR for in-hospital cardiac arrest may involve more pharmacologic adjuncts, but must take into consideration the potential confounding effects of vasoactive agents on cerebral circulation.

ECMO details

The surgical approach for ECMO cannulation must also be considered. Most studies performed peripheral ECMO cannulation, likely due to its minimally invasive nature and lack of median sternotomy requirement. However, none investigated the impact of differential hypoxia on brain injury, a critical issue in peripherally-cannulated VA-ECMO patients in clinical settings.[49] Percutaneous cannulation was performed in more than half of the studies, likely because of its non-invasive nature as well as the lower incidence of infection and improved survival seen with this approach.[50–52] However, higher rates of vascular complications have been reported after decannulation with the percutaneous approach.[53] These risks and benefits must be weighed when considering the optimal surgical approach, particularly if designing a survival model. There is variation in cannula size, likely attributed to different animal sizes. We suggest that laboratories have multiple cannula sizes readily available and carefully choose the most appropriate size for each experiment to minimize complications and enhance the reliability of the study's results. Anticoagulation management and ACT target were reported in less than half of all studies. We believe this should be reported in all preclinical models as it provides a standardized approach of managing the ECMO circuit, especially when the ECPR model runs for a long duration. Furthermore, reporting additional ECMO details such as gas target and sweep flow should be considered.

Neurological scoring systems

Neurological scoring systems were used in 15/20 studies that investigated neurological outcomes, with neurological deficit scores being the most commonly used as pig (5/13), dog (3/4), and rat (3/3) models used this specific scoring system. Additional previous literature regarding cardiac arrest animal models confirms that neurological deficit scores are both a valid and reliable method for evaluating neurological outcomes,[54–56] especially for smaller animal models like rodents. Neurological deficit scores work by analyzing five different components of the animals: 1) consciousness and respiration, 2) cranial nerve function, 3) motor function, 4) sensory function, and 5) coordination, and were originally derived from canine experiments.[57] Given the comprehensive nature of its neurological assessment and its established validity, neurological deficit scores may be the recommended scoring system to evaluate neurological outcomes in preclinical ECMO models, and thus should be strongly considered.

Assessing neurological scores in survival experiments is also an important topic, as only animals who are successfully weaned from cardiac support can be woken up and then neurologically scored. Additionally, the more neurological parameters investigated during ECPR, including invasive brain monitoring techniques, the less likely animals are to survive and be successfully neurologically screened. Accordingly, in the five experiments that did not neurologically score animals, 4/5 used some form of invasive monitoring, which may explain why these animals did not survive and the corresponding absence of neurological scoring in these studies.

Neurological plasma biomarkers

Plasma biomarkers are another potential adjunct in assessing neurological outcomes. Biomarkers such as S100, NSE, and IL-6, which were used in multiple pig and canine models, have been demonstrated to be reliable markers of poor neurological outcomes, particularly with temperature management.[58] GFAP and UCH-L1 were also used in pig models and have shown high sensitivity for evaluating poor neurological outcomes.[59] Several studies suggest that NSE levels can peak 48–72 hours post-cardiac arrest and even up to day 7 post-ECPR.

For other cerebral biomarkers, Ölander *et al* suggested that the optimal peak time for P-NGAL (plasma neutrophil gelatinase-associated lipocalin) was around an ECPR time of 60 minutes in contrast to P-S100B which peaked around 30 minutes. Nilsen *et al* noted that GFAP increased significantly after rewarming of animals. Interestingly, previous literature has shown S100B peaks and better predicts neurological outcome at 24 hours post-cardiac arrest, compared to NSE, which is more accurate at time-points after 24 hours.[60] Furthermore, GFAP tends to peak 48–72 hours post-cardiac arrest, similar to NSE. Still, evidence regarding optimal peak and onset-time for such biomarkers was still limited in these studies, primarily due to lack of specific-time points for each day post-cardiac arrest, and thus warrants further investigation.

In summary, NSE and GFAP measurements can provide valuable information when obtained between 24 to 196 hours after cardiac arrest and ECPR initiation whereas P-NGAL and P-S100B can be used as intraoperative measurements within 24 hours.

Neuromonitoring and imaging modalities

Non-invasive neuromonitoring devices[61] were utilized in several studies. Foerster *et al,* Spinelli *et al,* and Mlcek *et al* monitored brain electrical activities using EEG during and after ECPR.[26,28,29] Wollborn *et al* 2020 is the only study to incorporate SSEPs and Transcranial Doppler ultrasound to measure cerebral blood flow in the middle cerebral artery.[20] Invasive neuromonitoring devices to monitor ICP and brain tissue oxygenation were utilized in four studies. For example, Putzer *et al* employed 3 additional tools—NIRS for measuring cerebral blood flow, brain tissue oxygenation ($PbtO_2$) catheter for assessing cerebral oxygenation, and cerebral microdialysis to measure metabolites seen in hypoxic-ischemic pattern.[39]

Invasive neuromonitoring devices, such as $PbtO_2$ and ICP monitoring devices, are also clinically employed to detect ABIs in non-ECMO patients.[62] These tools may not be feasible in ECMO patients due to inherent bleeding risk. However, as these tools provide real-time, continuous data on key physiological variables such as cerebral oxygen and carbon dioxide levels, and cerebral blood flow velocities, these monitoring devices should be strongly considered in preclinical models. Additionally, the inclusion of MRI and head Computed Tomography should be considered, given their widespread use in clinical settings for detecting ABIs.

In summary, it is crucial to perform a comprehensive investigation of ABIs using the aforementioned various tools. In addition to using neurological scoring systems, neurological biomarkers, and histological studies, multimodal monitoring strategies can offer novel approaches for objectively evaluating neurological outcomes in ECMO. These features help to understand and define (1) severity of the brain injury in ECPR based on arrest time and ECMO duration, (2) optimal cerebral blood flow and autoregulation function during and after ECPR, (3) real-time neurological biomarkers to predict ABI, and (4) neurovascular coupling in ECPR. Developing animal models utilizing these multimodal tools will provide more clinically relevant and better translatable research which will ultimately aid in improving clinical care in ECMO patients.

Limitations

Our scoping review has several limitations. First, the small number of studies using animal models to investigate neurological outcomes in ECPR should be noted. This paucity of literature emphasizes the need for additional studies in the area, which was the impetus for our review. Furthermore, our study offers an updated and more focused perspective relative to other review articles. For example, compared to Heinsar's 2020 systematic review[63] which analyzed 19 articles investigating preclinical animal VA-ECMO models and cardiac arrest, our study had a larger sample size (166 total animal studies, 20 neurologically-focused animal studies) and was able to focus specifically on neurological outcomes.

Conclusions

A limited number of preclinical models focus on neurological outcomes in ECPR, and there is vast heterogeneity in the research design and methodology among those studies. Based on our review, the recommended preclinical model for evaluating neurological outcomes in ECPR studies should include the following key components: (1) the use of large animals such as pigs or dogs, including both males and females in balanced number; (2) standardized preoperative protocols, such as overnight fasting before the experiment; (3) limited cardiac arrest duration of 10–15 minutes, but no greater than 20 minutes; (4) the use of multi-modal neuromonitoring strategies, in addition to neurological scoring systems, cerebral biomarkers, and histological studies, to ensure a comprehensive assessment of neurological outcomes; and (5) ability to survive the animals after experiments to observe outcomes beyond the acute setting. Standardizing the methodology in this manner can significantly enhance reproducibility between laboratories and result in better translation to the clinical environment.

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CRediT authorship contribution statement

Jin Kook Kang: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Andrew Kalra:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Syed Ameen Ahmad:** Methodology, Validation, Investigation, Data curation, Visualization, Investigation. **Arjun Kumar Menta:** Methodology, Validation, Investigation, Data curation, Visualization, Investigation. **Hannah Rando:** Validation, Writing – review & editing. **Ifeanyi Chinedozi:** Validation, Writing – review & editing. **Zachary Darby:** Validation, Writing – review & editing. **Marcus Spann:** Methodology. **Steven P. Keller:** Writing – review & editing, Supervision, Funding acquisition. **Glenn J. R. Whitman:** Writing – review & editing, Supervision. **Sung-Min Cho:** Conceptualization, Methodology, Resources, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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