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REVIEW ARTICLE

Cardiology

Extracorporeal cardiopulmonary resuscitation for adults with shock-refractory cardiac arrest

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Abstract

Background: Veno-arterial extracorporeal membrane oxygenation has increasingly emerged as a feasible treatment to mitigate the progressive multiorgan dysfunction that occurs during cardiac arrest, in support of further resuscitation efforts.

Objectives: Because the recent systematic review commissioned in 2018 by the International Liaison Committee on Resuscitation Advanced Life Support task did not include studies without a control group, our objective was to conduct a review incorporating these studies to increase available evidence supporting the use of extracorporeal cardiopulmonary resuscitation (ECPR) for cardiac arrest patients, while waiting for high-quality evidence from randomized controlled trials (RCTs).

Methods: MEDLINE, Embase, and Science Citation Index (Web of Science) were searched for eligible studies from database inception to July 20, 2020. The population of interest was adult patients who had suffered cardiac arrest in any setting. We included all cohort studies with 1 exposure/1 group and descriptive studies (ie, case series studies). We excluded RCTs, non-RCTs, and observational analytic studies with a control group. Outcomes included short-term survival and favorable neurological outcome. Short-term outcomes (ie, hospital discharge, 30 days, and 1 month) were combined into a single category.

Results: Our searches of databases and other sources yielded a total of 4302 citations. Sixty-two eligible studies were included (including a combined total of 3638 participants). Six studies were of in-hospital cardiac arrest, 34 studies were of out-of-hospital cardiac arrest, and 22 studies included both in-hospital and out-of-hospital cardiac arrest. Seven hundred and sixty-eight patients of 3352 (23%) had short-term survival; whereas, 602 of 3366 (18%) survived with favorable neurological outcome, defined as a cerebral performance category score of 1 or 2.

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Conclusions: Current clinical evidence is mostly drawn from observational studies, with their potential for confounding selection bias. Although studies without controls cannot supplant case-control or cohort studies, several ECPR studies without a control group show successful resuscitation with impressive results that may provide valuable information to inform a comparison.

KEYWORDS
cardiopulmonary resuscitation, ECPR, extracorporeal cardiopulmonary resuscitation, extracorporeal membrane oxygenation, refractory ventricular fibrillation, resuscitation

1 | INTRODUCTION

Shock-refractory ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT) refers to VF or pVT that persists despite standard resuscitation and unsuccessful administration of at least 3 defibrillation attempts.[1,2] Shock-refractory cardiac arrest is associated with a poor prognosis, with favorable neurological outcome observed in <20% of survivors.[3] The likelihood of neurologically intact survival for shock-refractory cardiac arrest declines abruptly if return of spontaneous circulation (ROSC) is not achieved within 30 to 45 minutes of cardiopulmonary resuscitation (CPR).[4,5] Newer approaches, including hemodynamic support, are increasingly being used, changing the array of therapeutic approaches designed to restore and support ROSC in victims of refractory cardiac arrest.[1,2]

Two of the primary goals of the American Heart Association in-hospital and out-of-hospital chain of survival are providing immediate artificial circulation via high-quality CPR and rapid defibrillation in individuals presenting with cardiac arrest.[1,6] Efforts to optimize the entire chain of survival and the evolution of artificial circulation/advanced perfusion/reperfusion techniques are increasingly adding up to a paradigm change in resuscitation science, especially for individuals presenting with shock-refractory VF/pVT.[1,2,7]

Rapid emergency medical services transport facilitated by mechanical CPR devices designed to augment circulation and deployment of extracorporeal cardiopulmonary resuscitation (ECPR) using extracorporeal membrane oxygenation (ECMO) are increasingly being used in selected patients to mitigate the multiorgan dysfunction that accompanies cardiac arrest,[8,9] by providing access to immediate coronary angiography and percutaneous coronary intervention to release the blockage of the coronary artery(s) and lessen the progressive ischemia that occurs to the hearts of patients presenting with shock-refractory VF/pVT.[8,9] There is a growing body of literature suggesting that ECPR may have a role in the treatment of prolonged shock-refractory cardiac arrest failing conventional therapy.

A recent systematic review commissioned in 2018 by the International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support task force concluded that ECPR may be considered as a rescue therapy for selected patients with cardiac arrest when conventional CPR is failing in settings where this strategy can be implemented (weak recommendation, very-low certainty of evidence). Because this systematic review did not include studies without a control group, our objective was to conduct a review incorporating these studies to increase available evidence supporting the use of ECPR for cardiac arrest patients, while waiting for high-quality evidence from randomized controlled trials (RCTs).

2 | MATERIALS AND METHODS

2.1 | Criteria for considering studies for this review

2.1.1 | Types of studies

All cohort studies with 1 exposure/1 group (ie, studies with exposure-based sampling that enable calculating absolute effects measures for a risk of outcome) and descriptive studies (ie, case series studies) that used ECPR support for adult patients who had refractory cardiac arrest among those studies reporting survival or favorable neurological outcome at discharge, 30 days, and 1 month, defined as a cerebral performance category (CPC) score of 1 or 2 were eligible for inclusion in this review. For a study to be included in the review as an observational descriptive study, the methodology had to explicitly use observations on a series of individuals, usually all receiving advanced cardiovascular life support (ACLS) before receiving ECPR but with no control group. Studies with ≤ 5 patients receiving ECPR or studies that did not report either survival or favorable neurological outcome were excluded. We excluded RCTs, non-RCTs, and observational analytic studies (ie, cohort studies, case-control studies, cross-sectional studies) with a control group. Reviews, case reports, letters to the editor, and studies published in abstract form also were excluded.

2.1.2 | Types of participant

We included all studies with adult participants (≥ 16 years) who had sustained cardiac arrest in any setting (in-hospital or out-of-hospital) and studies including both in-hospital and out-of-hospital cardiac arrest (mixed populations). We excluded all studies that exclusively assessed the use of ECPR for cardiac arrest in the context of

cardiogenic shock or respiratory failure. We excluded studies reporting the use of extracorporeal circulation for suspected traumatic origin or traumatic origin with uncontrolled bleeding of arrest, as well as studies comparing other forms of mechanical support.

2.2 | Search methods for identification of studies

2.2.1 | Electronic searches

We searched the following bibliographic databases to assess the literature: MEDLINE (Ovid interphase) (1946 to July 20, 2020) and Embase (Ovid interphase) (1947 to July 20, 2020). We used the Science Citation Index (Web of Science) to identify additional citations. Databases were searched for eligible studies from database inception to July 20, 2020. Google Scholar was used to search for relevant citations that may not have been indexed in traditional bibliographic databases. Our MEDLINE search strategy was adapted to the rest of the databases. We used a mixture of subject headings and keywords to perform a comprehensive search. The references of relevant papers were assessed for further citations. We updated our search to ensure that key references had not been published during the period up to September 28, 2020. The language was restricted to English. Our full MEDLINE search is included in Appendix A.

2.2.2 | Data collection

We used EndNote X9 software to identify and remove duplicate citations. Study selection was accomplished through 2 levels of study screening. The first level of screening was accomplished by one author who independently screened the titles and abstracts of all retrieved citations against the inclusion criteria. After the first level of screening, studies were categorized into 2 groups: studies that did not meet the inclusion criteria and studies that were eligible for inclusion and warranted full-text access. For the second level, one author independently reviewed all full-text articles against prespecified inclusion criteria.

2.2.3 | Data extraction and management

Data extraction was performed independently by 2 authors using a standardized Microsoft Excel form designed by one review author. The data extraction form includes information on the first author(s), year of publication, country of origin, sample participants (including demographic characteristics), study methods (intervention, method of delivery), rate of shockable initial cardiac rhythm (ie, VF/pVT instead of pulseless electrical activity or asystole), and outcomes of interest (including short-term survival and favorable neurological outcome). Short-term outcomes (ie, hospital discharge, 30 days, and 1 month) were combined into a single category. The studies that were included in the review were considered for a descriptive summary. To describe the gathered data, a descriptive statistic was used to present the mean and standard deviation or median and interquartile range for continuous variables and the number and percentage for categorical variables.

3 | RESULTS

3.1 | Results of the search

Our searches of databases and other sources yielded a total of 4302 citations (MEDLINE 1711, Embase 2132, Science Citation abstracts 447, Google Scholar 4, hand searching of references of included papers 8). After screening the titles/abstracts of studies identified by this search, we retrieved the full texts of 119 studies. Of the 119 articles that were analyzed for full-text review, we excluded 57, as they were found not to be eligible for inclusion, leaving 62 studies in the review (Figure 1).

3.2 | Included studies

We included data from 62 observational studies, some of which used multivariate and propensity score analyses (including a combined total of 3638 participants). Summaries of baseline characteristics and the critical outcomes of short-term survival and favorable neurological outcome of included studies are presented in Table 1.[10–71] All studies focused on adult participants who had sustained cardiac arrest and were refractory to the standard of care before receiving the intervention. The etiology of cardiac arrests was very heterogeneous. Acute coronary syndrome was the most prevalent etiology of all cases. The most common causes of cardiac arrest of non-cardiac origin for the use of extracorporeal circulation included overdoses, accidental hypothermia, and pulmonary embolism. The inclusion criteria for ECPR differed among the included studies. The most consistent criterion for inclusion was refractory cardiac arrest (no ROSC despite optimal CPR, usually by 30 minutes [as low as 10 minutes]). Another frequent criterion was the age, usually <75 years (low end: 10 years; high end: no upper age). Other significant inclusion criteria included witnessed cardiac arrest, shockable rhythm, no-flow time <5 or 10 minutes and low-flow time. The most frequently used exclusion criterion was the presence of major comorbidity.

Six studies were of in-hospital cardiac arrest,[10–15] 34 studies were of out-of-hospital cardiac arrest,[16–49] and 20 studies included both in-hospital and out-of-hospital cardiac arrest.[50–71] The bulk of evidence comes from 3 East Asian countries, Japan, Taiwan, and the Republic of Korea (n = 1706, 22 studies); European countries (Germany, France, Italy, Austria, Denmark, Poland, and Belgium, n = 1417, 28 studies); as well as Singapore (n = 79, 1 study), Australia (n = 130, 3 studies), Canada (n = 36, 2 studies), and the United States (n = 321, 7 studies). The years of inclusion ranged from 1997 to 2018 and the publication period ranged from 2001 to 2020. The mean age of included participants ranged from 40 to 63 and the proportion who were male ranged from 43% to 94%. The proportion of participants with initial shockable rhythms of VF/VT varied between studies from 11% to 89%. The

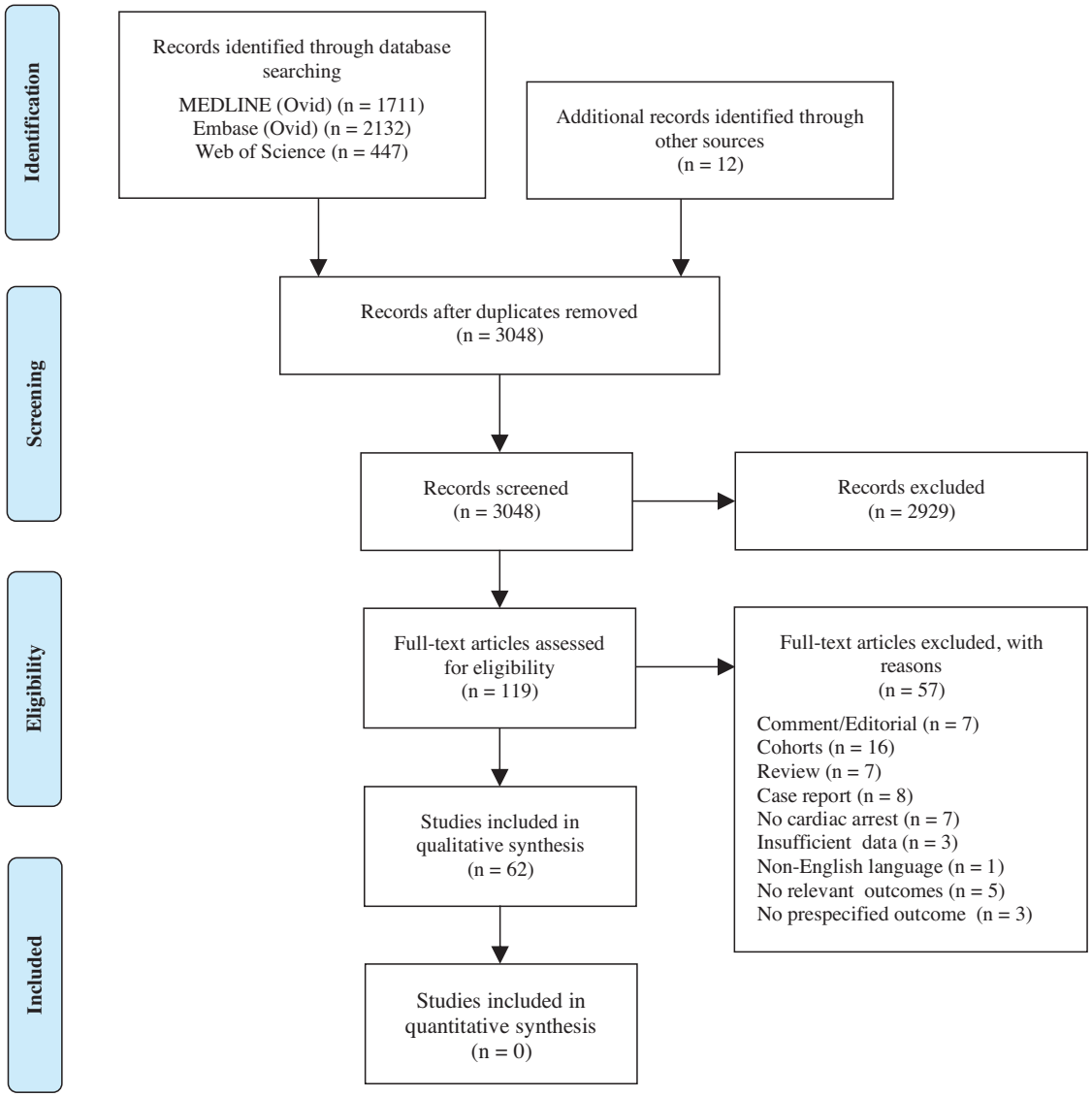

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the review process—search strategy *From*: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6: e1000097

no-flow time periods were generally <5 minutes (range from 0 to 7) for in-hospital cardiac arrest and the low-flow time periods were variable (range from 25 to 55 minutes for in-hospital cardiac arrest, and from 44 to 120 minutes for out-of-hospital cardiac arrest with no-flow time and low-flow time periods not included in many studies). Factors identified as favorable prognosis included initial shockable cardiac rhythms, time from cardiac arrest to the initiation of ECPR, and the identification of a potentially reversible cause of cardiac arrest. Many of the included studies did not address mortality beyond 30 days, duration of stay in the intensive care unit or stay in the hospital, major complications, quality of life, or cost effectiveness; few studies reported long-term patient-centered outcomes and health-related quality of life. There was substantial heterogeneity in the methodology, inclusion and exclusion criteria, intervention algorithms used, and reporting of results. Cumulative overall outcomes of short-term survival and favorable neurological outcome of each included study are provided in Figures 2–4.

3.3 | Short-term survival

Short-term survival outcomes (ie, hospital discharge, 30 days, and 1 month) were combined into a single category. Sixty studies (including 3352 participants) reported short-term survival.[10–45,48–71] Seven hundred sixty-eight of 3352 (23%) participants survived, although the proportion of participants with short-term survival varied from 1.5% to 70%. Cumulative overall survival rates of each included study are provided in Figure 2.

TABLE 1 Baseline clinical characteristics and outcomes of in-hospital and out-of-hospital cardiac arrest patients treated with extracorporeal cardiopulmonary resuscitation

Study (author, year)	Country	Setting	Received ECPR, (n)	Age, (median [IQR] or mean [SD])	Male, (%)	Shockable rhythm, VF/VT, (%)	Survival, (%)[a]	CPC 1–2, (%)[a]
Avalli et al 2012	Italy	Mixed	18	46 (37–64)	94	89	5	5
Babatasi et al 2001	France	OHCA	6	34 (37–64)	94	0	66	NR
Bednarczyk et al 2014	Canada	IHCA	22	54.6 ± 11.4	65.6	46.8	45.4	45.4
Belle et al 2012	France	OHCA	17	50 ± 16	87.5	NR	4.2	4.2
Bellezzo et al 2012	United States	OHCA	18	55.7 ± 12.8	87.5	40	27.8	27.8
Chen et al 2003	Taiwan	IHCA	57	57.1 ± 15.6	59.6	47.4	31.6	NR
Christiansen et al 2015	Denmark	OHCA	13	Not specified	67	53	38.5	38.5
Darocha et al 2016	Poland	OHCA	10	48 ± 17	61.5	50	70	70
Debaty et al 2010	France	OHCA	40	47 (37–58)	61.5	65	12.5	NR
Debaty et al 2015	France	OHCA	21	46 (26–66[b]	58	NR	33.3	33.3
Dennis et al 2017	Australia	Mixed	37	54 (47–58)	73	51	35	35
Ellouze et al 2017	France	Mixed	65	56 (43–65)	69	34.4	24.6	23.1
Fagnoul et al 2013	Belgium	Mixed	24	48 (38–55)	58.3	46.6	25	25
Fjølner et al 2017	Denmark	OHCA	21	56 (19–73)	75	42	33	33
Goto et al 2018	United States	OHCA	144	63 (55–71)	84.7	61	19	7
Grunau et al 2017	Canada	OHCA	13	46 (35–61)	85	61.5	27.2	27.2
Ha et al 2016	Korea	OHCA	35	55 (45–64)	58.3	51.4	28.6	27.5
Han et al 2015	Korea	OHCA	37	Not specified	59.6	37.8	18.9	16.2
Han et al 2019	Korea	Mixed	100	Not specified	74	54	14	12
Haneya et al 2012	Germany	Mixed	85	59 ± 16	71,8	29.4	34.7	31.7
Hase et al 2005	Japan	OHCA	38	Not specified	Not specified	Not specified	34	21
Johnson et al 2014	United States	OHCA	26	40 ± 15	54	42	15	11.5
Jouffroy et al 2014	France	OHCA	15	52 (27–69)	80	NR	33.3	26.7
Jung et al 2016	Germany	Mixed	117	61 (51–74)	68	63	23	15
Kagawa et al 2010	Japan	Mixed	39[c]	56 (49–64)	85	49	10	8
Kagawa et al 2012	Japan	OHCA	42	63 (56–72)[d]	54	55	17	14
Kim et al 2018	Korea	Mixed	101	55 ± 16.7	68.3	44.6	46.5	33.7
Kuroki et al 2017	Japan	Mixed	119	63.2 ± 11.8	91	33	31.9	31.9
Lamhaut et al 2013	France	OHCA	7	42 ± 16	85.7	71.4	14.3	14.3
Lamhaut et al 2017	France	Mixed	156	55.5 ± 12.2	82	58	13.6	13.6[e]
Lamhaut et al 2018	France	OHCA	74	54.0 ± 12.2	81	66	32	31
Liu et al 2011	Taiwan	Mixed	10	55.9 (7.6)	81.8	36.4	36.4	36.4
Le Guen et al 2011	France	OHCA	51	42 ± 15	89	63	4	4
Lee JJ et al 2016	Korea	OHCA	23	55 ± 16	64	87	43.5	30.4
Lee YH et al 2016	Korea	OHCA	30	Not specified	80	73.3	26.6	16.6
Lee SW et al 2017	Korea	Mixed	111	55.9 ± 15.2	71.3	47.7	18.9	15.3
Leick et al 2013	Germany	OHCA	28	57 ± 13	74	29.4	39.3	28.6
Liem et al 2020	United States	IHCA	36	49 ± 13	62	NR	38.8	NR
Mair et al 2014	Austria	IHCA	28	Not specified	90	10.8	7.1	7.1
Mazzeffi et al 2016	United States	IHCA	23	57 ± 15	60.9	26.1	30.4	26.1
Mégarbane et al 2011	France	Mixed	66	46 (39–55)	77.3	45	1.5	1.5

(Continues)

TABLE 1 (Continued)

Study (author, year)	Country	Setting	Received ECPR, (n)	Age, (median [IQR] or mean [SD])	Male, (%)	Shockable rhythm, VF/VT, (%)	Survival, (%)[a]	CPC 1–2, (%)[a]
Mochizuki et al 2014	Japan	OHCA	50	51 ± 21	66	74	26	20
Murakami et al 2020	Japan	OHCA	85	57.7 ± 11.2	82.4	82,4	37.6	16.5
Okada et al 2020	Japan	OHCA	260	62.5 (49–71)	75.8	67.3	NR	15.8
Otani et al 2018	Japan	OHCA	137	65 (50–72)	85	64	25	16.3
Otani et al 2020	Japan	OHCA	156	64 (50–72)	82	66	25	15
Pang et al 2017	Singapore	Mixed	79	49.9 ± 12.4	78.5	41.8	26.6	20.3
Park et al 2019	Korea	OHCA	140	56 (46–63.5)	82.9	56.4	9.3	5
Peigh et al 2015	United States	IHCA	23	46 ± 10	65.2	43.5	30	30
Poppe et al 2020	Austria	Mixed	92	48 ± 14	78	64	15	8
Pozzi et al 2016	France	OHCA	68	43.7 48–63	79.2	47.1	8.8	4.4
Pozzi et al 2019	France	Mixed	131	43.2 ± 12.8	71.8	29	10.4	6.4
Rousse et al 2016	France	OHCA	32	43.2 ± 14.3	71.9	59.4	6.25	3.1
Sawamoto et al 2014	Japan	OHCA	26	50.5 (28.5–58.8)	69.6	NR	NR	38.5
Shinar et al 2019	United States	Mixed	43	56 ± 14	79.1	51.2	25.6	20.9
Spangenberg et al 2016	Germany	Mixed	35	59.4 ± 11.9)	77	57	31.4	28.6
Stub et al 2015	Australia	Mixed	26	52 (38–60)	77	73	54	54
Tazarourte et al 2012	France	OHCA	14	39 ± 10	43	28	7.1	7.1
Wang et al 2014	Taiwan	OHCA	31	50.7 ± 10	88.7	48.4	38.7	25.8
Wengenmayer et al 2017	Germany	Mixed	133	58.7 ± 2.6	74.4	NR	14.3	NR
Yukawa et al 2017	Japan	OHCA	79	59.0 (48.5–64.5)	82.3	73.4	22	14
Zakhary et al 2018	Australia	Mixed	75	50 (35–59)	81	57	31	29

CPC, cerebral performance category; ECPR, extracorporeal cardiopulmonary resuscitation; IHCA, in-hospital cardiac arrest; IQR, interquartile range; NR, not reported; OHCA, out-of-hospital cardiac arrest; VF, ventricular fibrillation; VT, ventricular tachycardia.

Note: There was some overlap between studies; some studies included the same patient population but reported different outcomes.

[a]Short-term outcomes with similar time frames (ie, hospital discharge, 30 days, and 1 month) were combined into a single category.

[b]Refers to the overall age of a total of 48 patients (58% male) that were included in the study.

[c]Refers to the OHCA subgroup. Thirty-eight patients had IHCA, 10 (26%) patients were discharged with neurologically intact survival.

[d]Refers to the overall age of 86 patients with acute coronary syndrome who were unresponsive to conventional cardiopulmonary resuscitation.

[e]This study includes all consecutive OHCA patients having received ECPR since 2011. A first protocol, including the use of prehospital ECPR, was applied from November 2011 to December 2014 (period 1). In January 2015, a new protocol was initiated (period 2). Compared to the initial period, when a less stringent protocol was used, survival increased from 9/114 (8%) to 12/42 (29%).

3.4 | Short-term survival with favorable neurological outcome

Short-term survival with favorable neurological outcome (ie, hospital discharge, 30 days, and 1 month) were combined into a single category. Fifty-seven studies (including 3366 participants) reported short-term survival with favorable neurological outcome.[12–47,50–70] Six hundred two of 3366 (18%) participants survived with favorable neurological outcomes, although the proportion of participants with short-term survival with favorable neurological outcome varied from 1.5% to 70%. Most studies defined favorable neurological outcome as a CPC score of 1 or 2. Cumulative overall survival with favorable neurological outcome rates of each included study is provided in Figure 3.

4 | LIMITATIONS

This review is subject to the following important limitations. In terms of methodology, this review was limited to 3 databases and articles published in English; therefore, it is possible that some studies were missed. These criteria may have biased the results. A critical aspect of the topic is the lack of uniformity in the inclusion and exclusion criteria of patients. Furthermore, outcomes varied widely across individual studies, which were mostly drawn from single-center observational case series; the larger studies of this type to date have used epidemiologic registry data that, although collected prospectively, may have limitations in describing associations. All included studies carry a high risk of bias; thus, possible selection and confounding bias cannot be ruled out, limiting our ability to draw any conclusions from the quality

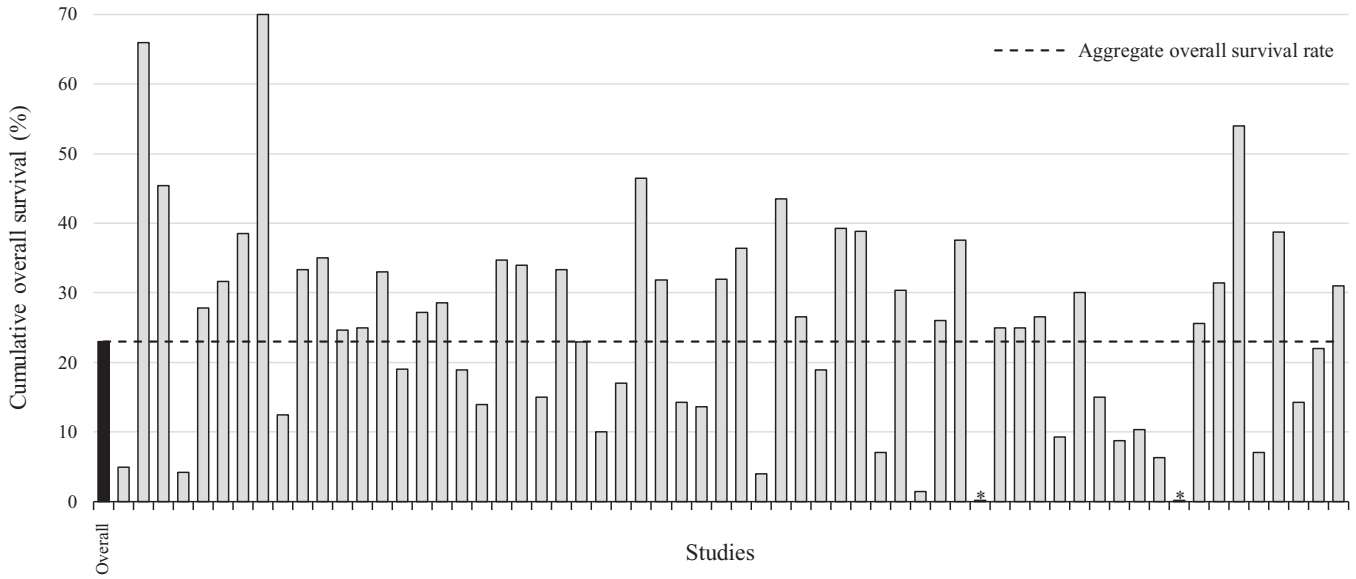

FIGURE 2 Cumulative overall short-term survival in each included study of cardiac arrest patients treated with extracorporeal cardiopulmonary resuscitation. Note: Studies are listed in alphabetical order regardless of the rate of cardiac arrest events in each study, as described in Table 1. *Data on survival rates were not reported by these studies

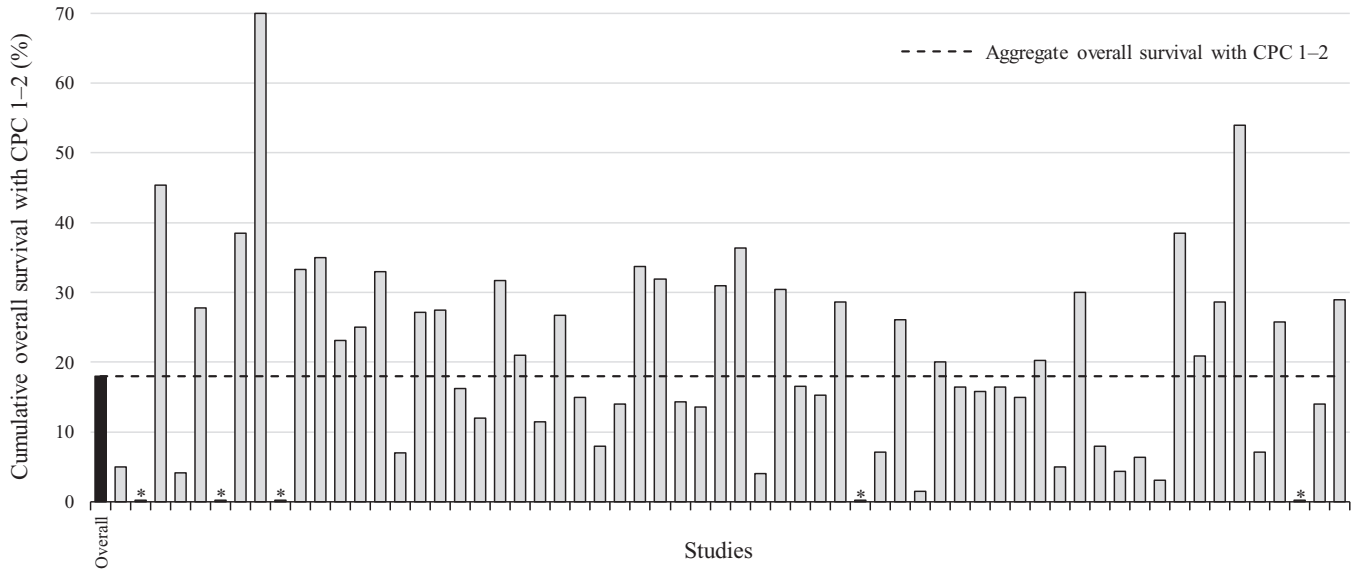

FIGURE 3 Cumulative overall short-term survival with favorable neurological outcome in each included study of cardiac arrest patients treated with extracorporeal cardiopulmonary resuscitation. Note: Studies are listed in alphabetical order regardless of the rate of cardiac arrest events in each study, as described in Table 1. *Data on survival with favorable neurological outcome rates were not reported by these studies. CPC, cerebral performance category

of the primary data. The well-recognized weaknesses of observational studies included mean that no reliable conclusions can be drawn from the primary data owing to the lack of a comparison group. A majority of the studies were principally based in East Asia and Europe, limiting the comparability and generalizability of results to different health care systems around the world. A limitation of this type of study is that reported outcomes include short-term outcomes (ie, the critical outcomes of survival and survival with favorable neurological outcome), yet it is an outcome of dubious clinical relevance for cardiac arrest, as a time-dependent evolution of the CPC score cannot be excluded. Limitations of the literature as a whole relate to the lack of high-quality studies, as well as the lack of reporting of long-term patient-centered outcomes and health-related quality of life in long-term follow-up.

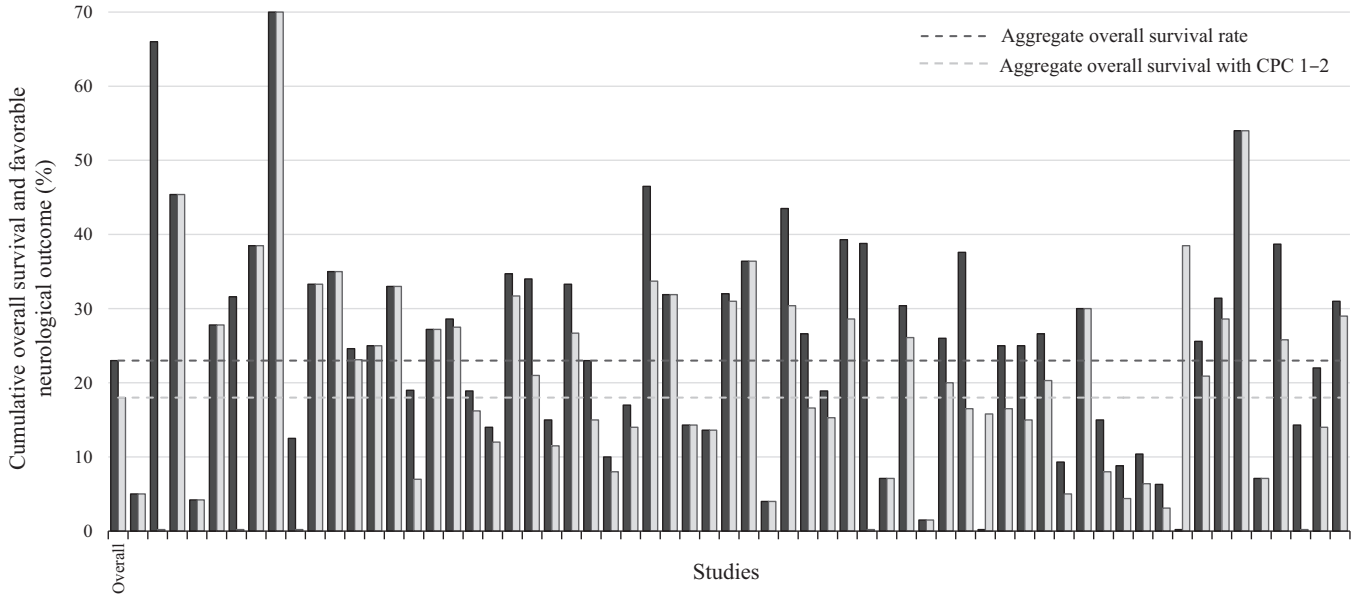

FIGURE 4 Cumulative overall short-term survival versus survival with favorable neurological outcome in each included study of cardiac arrest patients treated with extracorporeal cardiopulmonary resuscitation. Note: Studies are listed in alphabetical order regardless of the rate of cardiac arrest events in each study, as described in Table 1. CPC, cerebral performance category

Since completing this review, in July 2020, we searched for recent published studies on the topic. The 2CHEER trial, a prospective cohort study (included both in-hospital and out-of-hospital cardiac arrest of presumed cardiac origin), showed 44% of patients had survival to hospital discharge with a favorable neurological outcome (comparator not stated).[72] The ARREST trial (NCT3880565), a small phase 2 randomized trial was published showing significantly improved survival in the group that received early ECMO-facilitated resuscitation for refractory VF/VT out-of-hospital cardiac arrest.[73] This is the first RCT of ECMO-facilitated resuscitation versus standard ACLS treatment in patients with out-of-hospital cardiac arrest and refractory VF/VT and showed early initiation ECMO resulted in an impressive 43% survival to hospital discharge for refractory VF/VT out-of-hospital cardiac arrest. These either provide additional evidence of ECPR for refractory VF/VT cardiac arrest, or evidence supporting our conclusions that rigorous investigation in the form of RCTs is required to inform treatment guidelines and provide a bigger evidence base to inform practice, in order to optimize the entire chain of survival.

5 | DISCUSSION

In this review, we identified 62 observational studies, with data from 3638 participants, and excluded RCTs, non-RCTs, and observational analytic studies with a control group. The publication dates of these studies span 2 decades and the results demonstrate marked heterogeneity in selection of participants, etiology of cardiac arrest, timing of ECPR application (ie, immediate vs delayed), and patient-centered outcomes; nevertheless, many of them are well-designed clinical research studies, some of which report impressive outcomes following ECPR. We provide the readers with an up-to-date summary of these studies rather than inferring recommendations on meaningful clinical significance from our gathered data, which was beyond the scope of this paper. Furthermore, this review highlights an area of research that is adding up to a paradigm change in resuscitation that may contribute to improvements in neurologically favorable survival for patients following refractory VF/pVT. We included this type of study design and not studies with a control group, as the recent systematic review commissioned by the ILCOR Advanced Life Support task force in July 2018 excluded studies that lacked a comparator group.[74] It could be suggested that the studies included in our review yield a lower level of evidence than cohort studies and case-control studies with a control group; however, based on an extensive evidence review process, we argue that these studies could inform a comparison with data from conventional CPR studies (ie, Bartos et al [75] recently compared 2 groups of patients with refractory VF/VT out-of-hospital cardiac arrest from a cohort of 160 consecutive patients treated with the University of Minnesota refractory VF/VT ECPR protocol,[8,9] with a cohort of 654 patients who received standard CPR in the amiodarone arm of ALPS [Amiodarone, Lidocaine, or Placebo Study][3] in out-of-hospital cardiac arrest).

It is noteworthy that marked heterogeneity in the cause of cardiac arrest exists in the included studies. Although the proportion of participants with short-term survival and survival with favorable neurological outcome varied from 1.5% to 70%,[10–71] we would like to highlight a few points of caution in making such a generalized conclusion. Mégarbane et al reported 1.5% survival with favorable neurological outcome from witnessed refractory in-hospital or out-of-hospital cardiac arrest of presumed or confirmed cardiac arrest etiology, but they did not apply strict inclusion criteria.[63] Their study evaluated the usefulness of routine laboratory parameters in the decision to treat refractory cardiac arrest patients with ECPR. Darocha et al reported 70%

survival with favorable neurological outcome from hypothermic cardiac arrest,[19] yet the likelihood of surviving hypothermic cardiac arrest is higher than normothermic cardiac arrest, thus better outcomes can be obtained in hypothermic cardiac arrest as the management and prognosis are different than normothermic cardiac arrest. There were other interesting results in the context of cardiac arrest because of suspected cardiac etiology. The CHEER trial (which includes mechanical CPR, hypothermia, ECMO, and early perfusion/reperfusion) had only 26 patients who received ECPR; 14 (54%) survived with favorable neurological outcome. Fifteen patients had in-hospital and 11 patients had out-of-hospital cardiac arrest; nine (60%) and five (45%) survived with favorable neurological outcome, respectively.[69]

No-flow time is one of the most crucial predictive factors for survival.[76,77] To obtain the best results, ECPR is generally not performed in unwitnessed cardiac arrest because the no-flow time cannot be determined.[1,2] However, many of these studies included cardiac arrests that were unwitnessed, whereas others had mixed populations; thus we were unable to assess no-flow time and low-flow time in many in-hospital or out-of-hospital studies. Bystander CPR is thus essential for a favorable outcome.[1,2] However, there were many patients who did not receive bystander CPR. Furthermore, some studies reported delayed low-flow time (ie, up to 155 [120–180] minutes)[63] and others did not report collapse-to-ECPR times. An initial refractory rhythm of VF/pVT is a strong predictor of acute coronary occlusion or stenosis, and a short no-flow time is a good prognostic factor for neurologically favorable survival to discharge.[7–9] In these studies the proportion of participants with initial shockable rhythms of VF/VT varied between studies from 11% to 89%, but overall <55% of patients had a shockable rhythm. This means that overall these studies included many patients who would clearly not have benefited from the intervention, which could also explain the marked heterogeneity in outcomes.

Evidence from low-quality studies suggests that access to ECPR compared with no ECPR in patients resuscitated from refractory VF/pVT cardiac arrest is associated with a 2- to 4-fold increase in survival rates (10%–15% to 30%–45%).[78–81] As with many complex clinical interventions, the best results will be achieved by following a feasible and system-structural protocol with stringent patient selection. Because ECPR is a complex and resource-intensive intervention, it should be considered for selected cardiac arrest patients who have a potentially reversible illness with a high likelihood of benefit from it, and where it can be expeditiously deployed and supported,[1] even in a setting in which a patient is waiting for a cardiac transplant or organ donation following unsuccessful ECPR. The provision of prompt and optimal resuscitation is essential to survival. Following out-of-hospital cardiac arrest, if a pulse is not restored at the scene, additional efforts at the receiving hospital almost invariably fail.[82] Nonetheless, if shock-refractory VF/pVT is present, the risk/benefit ratio of this approach warrants continued assessment. Implementation of system-structural protocols, the generalizability of this approach, the availability of this intervention as part of a multifaceted approach, and cost-effectiveness all deserve to be investigated in a more robust manner by high-quality studies; however, we acknowledge that this therapy is complex and that it requires considerable resources not available to many systems of care in other regions of the world.

6 | CONCLUSIONS

Current clinical evidence is mostly drawn from observational studies, with their potential for confounding selection bias. Although studies without controls cannot supplant cohort studies or case-control studies, several ECPR studies without a control group show successful resuscitation with impressive results, which may provide valuable information to inform a comparison. Rigorous investigation in the form of RCTs is required to inform treatment guidelines surrounding the practice, in order to optimize the entire chain of survival.

AUTHOR CONTRIBUTIONS

DM and JEA provided substantial contributions to the conception or design of the study. DM and JEA were responsible for the acquisition and analysis data. DM drafted the original manuscript. All authors reviewed and approved the final version of the manuscript. DM takes responsibility for the paper as a whole.

CONFLICT OF INTEREST

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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