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Survival and neurological function in patients treated with extracorporeal membrane oxygenation and therapeutic hypothermia: a protocol for updating a systematic review

Pengfei Cheng,[1] Haizhen Wang,[1] Luyao Guo,[1] Meiling Wang,[1] He Xu,[1] Peipei Gu,[1] Jinjing Wu,[1] Minfei Yang[1]

***Corresponding author:**Minfei Yang; 2200056@zju.edu.cn

Author Affiliation

[1]Department of Nursing, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

Email

Pengfei Cheng:2522097@zju.edu.cn; Haizhen Wang:2508083@zju.edu.cn; Luyao Guo:guoluyao@zju.edu.cn; Meiling Wang:2522089@zju.edu.cn; He Xu:2522090@zju.edu.cn; Peipei Gu:gupeipei@zju.edu.cn; Jinjing Wu:2613357@zju.edu.cn

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ABSTRACT

Introduction The widespread application of extracorporeal membrane oxygenation (ECMO) has enhanced the outcome measures for patients experiencing cardiac arrest. However, the extent of its effectiveness remains limited and falls short of the desired level. Therapeutic hypothermia, an intervention aimed at maintaining body temperatures between 32°C and 36°C in cardiac arrest patients treated with ECMO, has been proposed as a potential means of neuroprotection and enhanced survival. Nevertheless, it remains a subject of controversy, with its impact on patient complications yet to be fully understood.

Method and analysis This protocol was developed in compliance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols 2015 (PRISMA-P). The following databases will be systematically searched: PubMed, Web of Science, Cochrane Library, Embase, Ovid, CNKI, Wanfang, and China Biology Medicine Disc. The database search strategy will utilize a combination of subject terms and free-text keywords. The search will encompass articles from the inception of each database up to 15 June 2023. Inclusion criteria encompass randomized controlled trials, cohort studies, case-control studies, and quasi-experimental studies. Two researchers will independently review articles and extract relevant data based on these criteria. Any disagreements will be resolved through discussion. Data analysis will be performed using Review Manager software.

Ethics and dissemination Since no patient data were collected in this study, ethical approval was not required. Research findings will be released in a

peerreviewed journal.

PROSPERO registration number CRD42023435353

Keywords heart arrest, extracorporeal membrane oxygenation, extracorporeal cardiopulmonary resuscitation, therapeutic hypothermia

STRENGTHS AND LIMITATIONS OF THIS STUDY

This review will use a rigorous methodology following the Preferred Reporting Items for Systematic Review and MetaAnalysis checklist.

This review will comprehensively and systematically search the English and Chinese literature to update the previous evidence.

The potential limitation is that the number of high-quality randomized controlled trials included may not be large, mainly due to the challenges of implementing strict randomization and blinding of ECPR patients in clinical studies.

INTRODUCTION

Cardiac arrest represents a significant global public health concern, given its high incidence, low survival rates, and poor neurological outcomes among survivors[1]. In 2022, the American Heart Association (AHA) reported that cardiac arrest affects over 88.8 per 100,000 adults in the United States annually. However, the overall survival rate is a mere 9.0%, with only 7% of survivors achieving good neurological function (defined as cerebral performance categories≤2)[2]. Across European countries, out-of-hospital cardiac arrest (OHCA) occurs at rates ranging from 67 to 170 per 100,000 adults annually, while in-hospital cardiac arrest (IHCA) affects 1.5 to 2.8 per 1000 hospital admissions. The average survival rate following OHCA discharge is 8%, and the survival rate within 30 days of IHCA discharge varies from 15% to 34%. In some countries, as many as 33% of survivors remain in a vegetative state after discharge[3 4]. The situation is even more challenging in China, where cardiac arrest impacts over half a million individuals annually, yet the survival rate is less than 2%, with only 2.5% of survivors experiencing a positive neurological outcome[5 6]. These statistics underscore the persistently grim survival rates and neurological prospects for patients experiencing cardiac arrest, with variations observed between different countries.

Extracorporeal membrane oxygenation (ECMO) was introduced for cardiopulmonary resuscitation (CPR) in the 1970s. This technique, known as extracorporeal cardiopulmonary resuscitation (ECPR), has shown success in cases where return of spontaneous circulation (ROSC) was not initially achieved[7]. With the continuous advancement and refinement of ECMO technology, ECPR has gained popularity in the clinical management of cardiac arrest patients, representing a significant breakthrough in improving survival rates and neurological outcomes. ECPR not only overcomes the limitations of

traditional CPR but also broadens the scope of clinical treatment options for cardiac arrest patients[8 9]. Even in cases of traumatic cardiac arrest, which carry a high mortality rate, and instances without ROSC, ECMO offers a lifeline by temporarily taking over cardiopulmonary function. It accomplishes this by diverting the patient's blood outside the body, oxygenating it through a membrane oxygenator, and then returning it to the body. This ensures vital organ perfusion and minimizes neurological damage, ultimately enhancing survival rates and neurological outcomes[10 11]. As of 2022, the Extracorporeal Life Support Organization (ELSO) annual report revealed that 42% of patients successfully weaned off ECMO, 44% were discharged from the hospital or awaiting organ transplantation, and over 14% of survivors achieved a favorable neurological status[12]. In summary, while ECPR has brought significant survival benefits to cardiac arrest patients, there remains a considerable gap in reaching the ideal survival rate and achieving favorable neurological outcomes. Further interventions and research are needed to optimize the impact of ECPR.

Therapeutic hypothermia is known to have a neuroprotective effect by reducing the brain's metabolic rate[13], inhibiting excitatory amino acids[14], reducing oxidative stress, preventing cytotoxic brain edema[15 16], and inhibiting cell apoptosis and necrosis[17]. In animal experiments, hypothermia has been observed to enhance mitochondrial calcium buffering capacity, reducing reperfusion injury and further demonstrating its neuroprotective potential[18]. Moreover, the adoption of therapeutic hypothermia in patients with cardiac arrest, involving the reduction of core body temperature to a range of 32°C to 36°C (89.6-96.8°F), is endorsed by both the American Heart Association (AHA) and the European Resuscitation Council (ERC). This intervention is considered to positively impact discharge survival rates and neurological outcomes for extracorporeal cardiopulmonary resuscitation (ECPR) patients[19]. Consequently, in the clinical management of ECPR patients, numerous countries have embraced the use of physical and chemical methods, such as surface cold compress technology, intravascular cooling technology, nasal cooling devices, and pharmaceutical agents, to swiftly achieve the target core temperature drop within intensive care units[20-24]. Nevertheless, in recent years, the implementation of therapeutic hypothermia in cardiac arrest patients undergoing ECPR has sparked some controversy. Recent studies have shown that survival rates and the likelihood of favorable neurological outcomes were comparable between normothermia and hypothermia groups[25]. In summary, significant controversies and uncertainties still surround the impact of therapeutic hypothermia on the prognosis of ECPR patients.

The clinical benefits of combining Extracorporeal Cardiopulmonary Resuscitation (ECPR) with therapeutic hypothermia in adults suffering from cardiac arrest remain unclear. Whether this combination yields a significant advantage in terms of survival and neurological function is a subject of considerable debate. The conclusions of previous original studies differ significantly, and remarkably, there are notable inconsistencies on this matter in

published systematic reviews and meta-analyses[26 27]. In 2020, Chen et al.[26] examined the relationship between therapeutic hypothermia and clinical outcomes in ECPR patients in a systematic review. Their meta-analysis suggested that therapeutic hypothermia was associated with improved neurological outcomes and survival in adult cardiac arrest patients undergoing ECPR. Another systematic review by Huang et al.[27], published in 2022, found that there was no significant difference in survival rates and neurological outcomes between the Targeted Temperature Management (TTM) group and the non-TTM group in ECPR patients. Notably, the Corona Virus Disease 2019 (COVID-19) pandemic has promoted the application and adoption of Extracorporeal Membrane Oxygenation (ECMO) technology in hospitals in developing countries and regions, including mainland China, Hong Kong, Taiwan, and others. This has led to an increase in the frequency of cardiac arrest patients treated with ECPR and mild hypothermia in hospitals. Consequently, numerous clinical studies have been conducted, with many research results published in Chinese and included in Chinese databases[28 29]. Therefore, it is essential to include systematic reviews and meta-analyses on the effects of ECPR and mild hypothermia on the survival and neurological function of cardiac arrest patients from Chinese studies. This approach can help increase the sample size, enhance the statistical power of the meta-analysis, boost the credibility of conclusions, and address the inconsistencies observed in previous systematic reviews. In light of these considerations, we have devised a plan to conduct a systematic review to update and supplement existing evidence. Our aim is to offer a reliable reference for future clinical practices.

METHODS

Registration and protocol amendment

We are committed to adhering rigorously to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines[30]. Our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 14 June 2023 and was last updated on 16 October, 2023 (registration number CRD42023435353). We have improved the title only by adding the primary outcome and highlighting the updated accreditation to make it more sensitive for future readers and to increase the transparency of the protocol.

Eligibility criteria

Types of studies

We prioritized the inclusion of Randomized Controlled Trials (RCTs) in our selection process. Additionally, we included cohort studies, case-control studies, and quasi-experimental studies with control groups because conducting comprehensive research on the care of patients with cardiac arrest in clinical practice can be challenging. We excluded animal studies, duplicate

publications, and studies with substantial missing data regarding outcome measures.

Population

We will include patients aged 18 years and older who underwent ECPR, encompassing both in-hospital and out-of-hospital cardiac arrest, with no restrictions based on the cause of cardiac arrest. This includes various etiologies such as cardiovascular-related diseases, severe arrhythmias, drowning, COVID-19 infection, drug poisoning, allergies, electric shock, extreme temperatures (low or high), hypoglycemia, acidosis, hypokalemia or hyperkalemia, severe trauma, pulmonary embolism, hypoxemia, and other factors.

Intervention

In the intervention group, ECPR patients were subjected to therapeutic hypothermia. This involved employing a variety of measures and methods to maintain the patient's body temperature within the range of 32°C to 36°C. The methods used to induce hypothermia included, but were not limited to, various physical cooling techniques and the administration of cooling medications.

Comparator

We will include studies that did not implement any specific targeted temperature management as the control.

Outcome indicators

The primary outcomes encompassed survival and neurological status. Survival was evaluated based on the discharge survival rate, 30-day survival rate, and long-term survival rate (beyond 6 months). Neurological function was assessed using the Cerebral Performance Category (CPC) score, with grade 1 and grade 2 indicating a favorable neurological prognosis, while other grades indicated a poorer prognosis. The secondary outcome focused on the occurrence of common complications in ECPR patients, which included bleeding, lower limb ischemia, renal injury, infection, ischemic hepatitis, and arrhythmia.

Language

Published in English or Chinese.

Information sources and search strategy

We will conduct our search in the following databases and trial registers: PubMed, Web of Science, Cochrane Library, Embase, Ovid, CNKI, Wanfang, and China Biology Medicine Disc. These databases will be searched from their respective inception dates to 15 June 2023. To ensure that this systematic review encompasses the entire body of relevant literature, we will also perform a comprehensive hand-search of reference lists from all included studies. Grey

literature will not be included in our search strategy, as the data we seek is predominantly published in peer-reviewed journals. The search strategy for PubMed is outlined as follows:

- #1 Search: (((((heart arrest[MeSH]) OR (cardiac arrest[Title/Abstract])) OR (out-of-hospital cardiac arrest[MeSH])) OR (in-hospital cardiac arrest[Title/Abstract])) OR (asystole [Title/Abstract])) OR (CA[Title/Abstract]) Filters: Abstract Sort by: Publication Date
- #2 Search: ((((((((((extracorporeal membrane oxygenation[MeSH]) OR (extracorporeal cardiopulmonary resuscitation[Title/Abstract])) OR (extracorporeal life support[Title/Abstract])) OR (mechanical circulation assistance[Title/Abstract])) OR (ECMO[Title/Abstract])) OR (ECPR[Title/Abstract])) OR (ECLS[Title/Abstract])) OR (cardiopulmonary resuscitation[MeSH])) OR (extracorporeal circulation[Title/Abstract])) OR (oxygenators, membrane[MeSH])) OR (life support, extracorporeal[Title/Abstract]) Sort by: Publication Date
- #3 Search: ((((((((((hypothermia, induced[MeSH]) OR (targeted temperature management [Title/Abstract])) OR (therapeutic hypothermia[Title/Abstract])) OR (moderate hypothermia[Title/Abstract])) OR (mild hypothermias[Title/Abstract])) OR (cryotherapy[Title/Abstract])) OR (cold therapy[Title/Abstract])) OR (TTM[MeSH])) OR (temperature monitoring[Title/Abstract])) OR (gastric hypothermia[MeSH])) OR (rewarming[Title/Abstract]) Sort by: Publication Date
- #4 Search: (((((randomized controlled trial[Title/Abstract]) OR (controlled clinical trial[Title/Abstract])) OR (RCT[Title/Abstract])) OR (cohort study[Title/Abstract])) OR (case-control study [Title/Abstract])) OR (quasi-experimental study[Title/Abstract]) Sort by: Publication Date
- #5 Search: #1 AND #2 AND #3 AND #4

Study selection

The results of the literature search will be imported into EndNote, a literature management software. The research team will conduct literature screening in accordance with predefined inclusion and exclusion criteria. Two independent reviewers will initially assess all retrieved citations. This initial assessment will involve screening based on the title and abstract to determine potential article eligibility. Importantly, each reviewer will remain unaware of the other's evaluation. The second phase of screening will involve downloading full texts, conducting a thorough reading, and performing a comprehensive review of each study that passes the initial screening. The final step will include a review of the reference lists of studies that meet all inclusion criteria, utilizing a snowball approach to identify additional studies that should be considered. In cases of ambiguity, the authors of the relevant studies will be contacted to seek clarification. Any disagreements between the two reviewers will be resolved by a third investigator. The screening and selection process is illustrated in Figure 1.

Data collection

Two researchers will independently utilize a data extraction form in Microsoft Excel to extract information from each eligible study. The following study details will be recorded: author, year of publication, country of study, study type, subjects, sample size, data source, temperature of therapeutic hypothermia, cooling measures, duration of therapeutic hypothermia, survival rates, neurological status, complications, measurement tools, and more. In cases of disagreement between the two reviewers, a third investigator will serve as a mediator. If a study includes multiple mild hypothermia groups, we will consolidate the groups from various studies. This approach helps prevent bias resulting from multiple statistical comparisons against a single control group. Additionally, we will standardize and unify the data units extracted for the same indicators before merging. Outcome data will be presented as mean±SD (M±SD). If the data are provided in alternative formats, such as median-range or median-IQR, we will employ appropriate statistical formulas for data transformation. If data are missing or unclear, we will make efforts to contact the authors for additional information to facilitate further analyses. Should we fail to obtain the required data, we will proceed with the analysis based on the available information.

Methodological appraisal and risk of bias

We utilized the critical appraisal tools provided by the Joanna Briggs Institute (JBI) for methodological assessments and to assess the risk of bias in all the studies included in our analysis. The Critical Appraisal Tool for Randomized Controlled Trials (RCTs) (version 2023) consisted of 13 items, and evaluators could respond with 'yes,' 'no,' 'unclear,' or 'not applicable,' depending on the study content[31]. For evaluating cohort studies, we employed the Cohort Studies Critical Appraisal Tool (version 2020), which included 11 items, and answers could be 'yes,' 'no,' 'unclear,' or 'not applicable' [32]. In a similar vein, the Case-Control Studies Critical Appraisal Tool [33] and the Critical Appraisal Tool for Quasi-Experimental Studies (experimental studies without random allocation)[34] released by the JBI in 2020 were used to assess the methodological quality and risk of bias in the included case-control and quasi-experimental studies. The former consisted of 10 items, while the latter comprised 9 items, with responses recorded as 'yes,' 'no,' 'unclear,' or 'not applicable.' The purpose of these assessments was to determine the extent to which the studies addressed the potential (or risk) of bias in their design, conduct, or analysis. All selected papers (i.e., those that met the eligibility criteria outlined in the protocol) underwent critical evaluation by two independent reviewers using the respective critical assessment tools mentioned above. Any discrepancies in bias classification were resolved through discussions between the two reviewers and, if necessary, in consultation with the study authors.

Assessing the quality of evidence

We will employ The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, as recommended by Cochrane, to assess the quality of evidence for all outcomes[35]. The evidence will be either upgraded or downgraded based on the evaluation results across various dimensions, including risk of bias, imprecision, inconsistency, indirectness, and publication bias. The final level of evidence will be categorized as high, moderate, low, or very low quality. The grading of evidence quality will be conducted using the online GRADEpro tool.

Data synthesis and statistical analysis

Measures of treatment effect

The outcome measures investigated will ultimately be presented as the survival rate, rate of good neurological function, and the incidence of various complications, all of which are binary outcomes. We will calculate risk ratios (RR) with 95% confidence intervals (CI) for these binary outcomes.

Assessment of heterogeneity

The Chi-Squared test and I^2 value were employed to assess heterogeneity. According to the Cochrane Handbook, an I^2 value below 50% was classified as low heterogeneity, while a value above 50% indicated high heterogeneity[36].

Data synthesis

We will employ Review Manager software version 5.3 for conducting the meta-analysis. In cases where there is significant statistical heterogeneity among the studies, we will utilize the random-effects model (RE) to analyze the statistical indicators. Conversely, if the statistical heterogeneity is low, we will use the fixed-effects model (FE) for analysis. If high heterogeneity is observed, we will explore the potential sources of heterogeneity through subgroup analysis, provided that the data allow for it. However, if the I^2 value exceeds 75%[36], we will forego the meta-analysis and opt for qualitative analysis instead. For sensitivity analysis and the Egger test, we will employ Stata version 17.0.

Subgroup analysis

If feasible, we intend to conduct subgroup analyses based on the location of cardiac arrest occurrence, primarily categorized into out-of-hospital cardiac arrest and in-hospital cardiac arrest.

Sensitivity analysis

We will assess the stability and reliability of the pooled results from our meta-analyses by employing two methods: changing the pooled model and using the leave-one-out technique. Initially, we can make a rough evaluation of the combined results by switching between the random-effects (RE) and fixed-effects (FE) models, with the consistency between these two models

indicating the stability of the outcomes. Furthermore, we will conduct sensitivity analysis using Stata version 17.0. This involves the systematic removal of each included study to examine the impact on the combined effect size. If the results do not exhibit significant changes, the original meta-analysis findings are considered stable.

Assessment of reporting biases

We will generate funnel plots and visually examine them to investigate potential publication bias. However, recognizing the inherent limitations of funnel plots, we will complement this analysis by performing the Egger test. This combination of methods will offer a more accurate assessment of publication bias.

Patient and public involvement

No patient involved.

Ethics and dissemination

Since no patient data were collected in this study, ethical approval was not required. Research findings will be released in a peerreviewed journal.

Future directions and clinical implications

Cardiac arrest has consistently been a major global public health concern and poses a significant challenge in the emergency and critical care domain. Research indicates that the widespread implementation of ECPR offers only limited improvements in the survival rates and neurological outcomes of these patients, falling short of satisfactory levels[37]. The combination of ECPR with therapeutic hypothermia, carefully regulated within the range of 32°C to 36°C, is considered a potential benefit. It is recognized by international guidelines as a neuroprotective intervention that enhances survival[38]. However, due to the generally low certainty of the available evidence, recent clinical research findings have raised doubts[39]. Furthermore, the impact of therapeutic hypothermia on the complications in ECPR patients remains uncertain[40].

We aim to enhance the robustness of this study by incorporating high-quality Chinese and English research within this domain. By doing so, we anticipate a substantial augmentation in the sample size available for meta-analysis, amplification of statistical power, and bolstering the credibility of our conclusions. This, in turn, will facilitate clinical practitioners in gaining better clarity regarding the risks and benefits associated with therapeutic hypothermia. Our aspiration is to bridge the existing gaps and disparities between available evidence and informed decision-making. In the process, we endeavor to furnish more dependable evidence concerning the impact of therapeutic hypothermia on the survival rates, neurological function, and complications in patients suffering from cardiac arrest.

Continuous monitoring of a patient's core body temperature, facilitated by temperature feedback devices, serves as a fundamental requirement for targeted

temperature management. Nevertheless, the exact protocols for cooling interventions remain somewhat indistinct. These include determining the optimal temperature and duration for therapeutic hypothermia, the choice of cooling techniques, cooling devices, and the specific strategies for rewarming. Consequently, several knowledge gaps persist on the path from evidence to effective decision-making. The future necessitates further exploration in this domain.

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Contributors PC, HW, LG and MW conceptualised and designed the study and drafted the manuscript. PC registered the review on the website of PROSPERO. HW developed the search criteria with input from LG and MW. HX ,PG and JW contributed to the design of the statistical methods. PC wrote the original draft of the manuscript, MY critically revised all study contents and ideas. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. The authors agree to take responsibility for the work.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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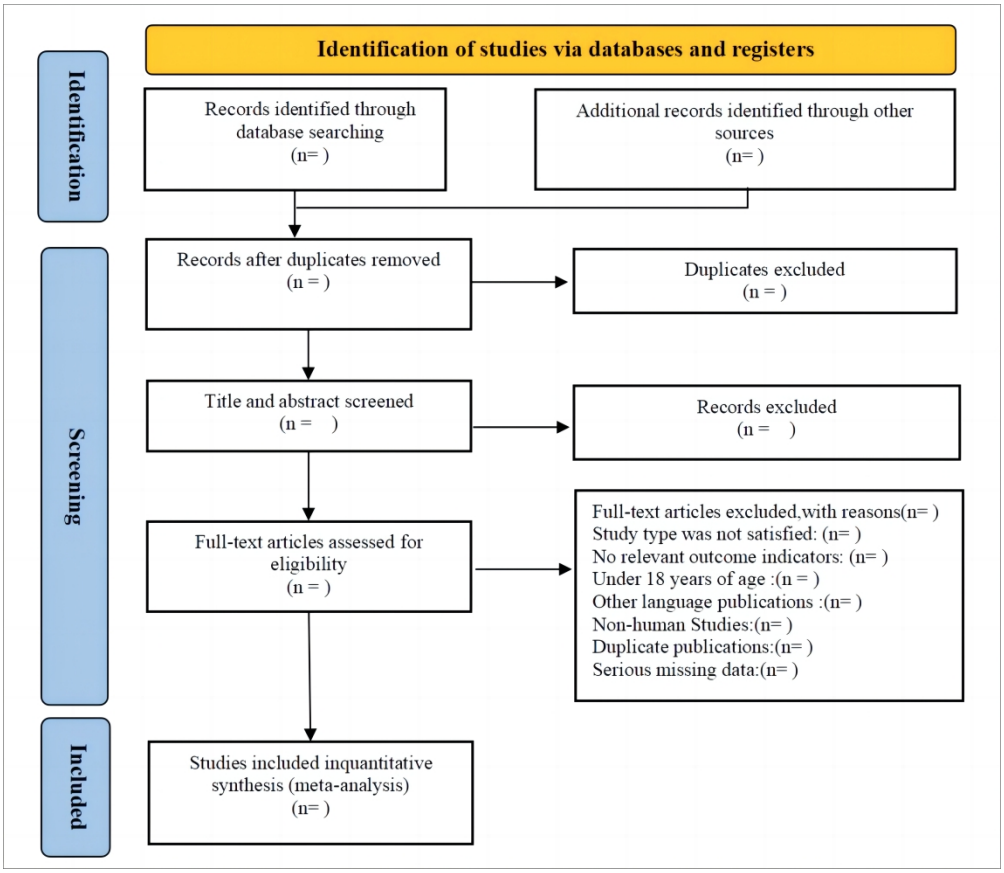

Figure 1. Flow diagram of the literature screening process and results.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Location where item is reported
ADMINISTRATIVE INFORMATION			
Title:			Page1/Line1-3
Identification	1a	Identify the report as a protocol of a systematic review	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Page1/Line1-3
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page4/Line155-159
Authors:			Page1/Line4-12
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page10/Line403-408
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Page4/Line159-163
Support:			Page10/Line409-410
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	Not applicable
Role of sponsor or funder	5c	Describe roles offunder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Not applicable
INTRODUCTION			

Rationale	6	Describe the rationale for the review in the context of what is already known	Page2-3/Line57-121
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page4/Line143-151
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page4-5/Line165-205
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page5-6/Line1207-217
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page6/Line217-242
Study records:			Page6-7/Line245-246,260-262
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page6/Line244-259
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page7/Line261-279
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page7/Line262-273
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page5/Line196-204
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page7/Line281-302
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page8/Line327-331
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration	Page8/Line314-335

		of consistency (such as I^2, Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page8-9/Line337-352
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page8/Line333-334
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page9/Line354-358
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page8/Line304-312

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the**
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Survival and neurological function in patients treated with extracorporeal membrane oxygenation and therapeutic hypothermia: a protocol for updating a systematic review

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Survival and neurological function in patients treated with extracorporeal membrane oxygenation and therapeutic hypothermia: a protocol for updating a systematic review

Pengfei Cheng,[1] Haizhen Wang,[1] Luyao Guo,[1] Meiling Wang,[1] He Xu,[1] Peipei Gu,[1] Jinjing Wu,[1] Minfei Yang[1]

***Corresponding author:**Minfei Yang; 2200056@zju.edu.cn

Author Affiliation

[1]Department of Nursing, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

Email

Pengfei Cheng:2522097@zju.edu.cn; Haizhen Wang:2508083@zju.edu.cn; Luyao Guo:guoluyao@zju.edu.cn; Meiling Wang:2522089@zju.edu.cn; He Xu:2522090@zju.edu.cn; Peipei Gu:gupeipei@zju.edu.cn; Jinjing Wu:2613357@zju.edu.cn

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ABSTRACT

Introduction The widespread application of extracorporeal membrane oxygenation (ECMO) has enhanced clinical outcomes for patients experiencing cardiac arrest. However, its effectiveness is still limited and falls short of the desired level. Therapeutic hypothermia, which maintains body temperatures between 32°C and 36°C in cardiac arrest patients treated with ECMO, has been proposed as a potential means of neuroprotection and increased survival rates. Nevertheless, it remains controversial, and its impact on patient complications has yet to be fully understood. Thus, this paper aims to update the protocol for a systematic review of patients treated with ECMO and therapeutic hypothermia, in order to explore its effects on survival and neurological function.

Method and analysis This protocol has been developed in compliance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols 2015 (PRISMA-P). The following databases will be systematically searched: PubMed, Web of Science, Cochrane Library, Embase, Ovid, CNKI, Wanfang, and China Biology Medicine Disc. The database search strategy will utilize a combination of subject terms and free-text keywords. The search will encompass articles from the inception of each database up to 15 June 2023. Inclusion criteria encompass randomized controlled trials, cohort studies, case-control studies, and quasi-experimental studies. Two researchers will independently review articles and extract relevant data based on these criteria. Any disagreements will be resolved through discussion. Data analysis will be performed using Review Manager software.

Ethics and dissemination Since no patient data were collected in this study, ethical approval was not required. Research findings will be released in a peerreviewed journal.

PROSPERO registration number CRD42023435353
Keywords heart arrest, extracorporeal membrane oxygenation, extracorporeal cardiopulmonary resuscitation, therapeutic hypothermia

STRENGTHS AND LIMITATIONS OF THIS STUDY

This review will use a rigorous methodology following the Preferred Reporting Items for Systematic Review and MetaAnalysis checklist.
The systematic review will primarily focus on peer-reviewed articles, limiting the findings to those written in English or Chinese.
In order to obtain sufficient data and ensure adequate statistical power for meta-analysis, randomized clinical trials, cohort studies, case-control studies, and quasi-experimental studies will be included.
The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework will be employed to appraise the level of confidence in the presented evidence.
The variability in quality, sample size, and heterogeneity among the included studies may constrain the generalizability and precision in deducing the summarized results within this meta-analysis.

INTRODUCTION

Cardiac arrest is a major public health issue of global concern, given its high prevalence, low survival rates, and poor neurological outcomes among survivors. (1) According to the American Heart Association (AHA) report of 2022, more than 88.8 out of 100,000 adults in the United States are affected by cardiac arrest each year. However, the overall survival rate is a mere 9.0%, with only 7% of survivors achieving good neurological function (as defined by cerebral performance categories≤2).(2)
In European nations, the incidence of out-of-hospital cardiac arrest (OHCA) ranges from 67 to 170 cases per 100,000 adults each year, whereas in-hospital cardiac arrest (IHCA) impacts 1.5 to 2.8 per 1000 hospital admissions. The average post-discharge survival rate for OHCA stands at 8%, and the survival rate within 30 days following discharge from IHCA varies between 15% and 34%. Additionally, in certain countries, up to 33% of survivors experience a vegetative state after being discharged.(3,4) The situation is even more challenging in China, where cardiac arrest impacts over half a million individuals annually, yet the survival rate is less than 2%, with only 2.5% of survivors experiencing a positive neurological outcome.(5,6) These statistics underscore the persistently grim survival rates and neurological prospects for patients experiencing cardiac arrest, with variations observed across different countries.
Extracorporeal membrane oxygenation (ECMO) was first introduced for cardiopulmonary resuscitation (CPR) in the 1970s. This technique, known as extracorporeal cardiopulmonary resuscitation (ECPR), has demonstrated effectiveness

in cases where return of spontaneous circulation (ROSC) was not initially achieved.(7) With the continuous advancement and refinement of ECMO technology, ECPR has gained popularityfor managing cardiac arrest patients, representing a significant breakthrough in improving survival rates and neurological outcomes. Not only does ECPR overcome the limitations of traditional CPR, but it also broadens the scope of clinical treatment options for cardiac arrest patients.(8,9) In scenarios of traumatic cardiac arrest that have a high likelihood of mortality, as well as situations where ROSC is not achieved, ECMO serves as a lifeline by temporarily assuming control of cardiopulmonary function. This is achieved through rerouting the patient's blood outside the body, passing it through a membrane oxygenator for oxygenation, and then reintroducing it to the body. In doing so, vital organs are adequately perfused, and neurological harm is minimized, ultimately leading to increased survival rates and improved neurological outcomes.(10,11) As of 2022, the Extracorporeal Life Support Organization (ELSO) annual report revealed that 42% of patients successfully weaned off ECMO, 44% were discharged from the hospital or awaiting organ transplantation, and over 14% of survivors achieved a favorable neurological status.(12) In summary, while ECPR has brought significant survival benefits to cardiac arrest patients, there remains a considerable gap in reaching the ideal survival rate and achieving favorable neurological outcomes. Further interventions and research are needed to maximize the impact of ECPR.

Therapeutic hypothermia is recognized for its neuroprotective properties, attributed to its ability to decrease the brain's metabolic rate,(13) suppress excitatory amino acids(14), mitigate oxidative stress, prevent cytotoxic brain edema,(15,16) and inhibit cell apoptosis and necrosis.(17) In animal experiments, hypothermia has been observed to enhance mitochondrial calcium buffering capacity, reducing reperfusion injury and further demonstrating its neuroprotective potential.(18) Moreover, the adoption of therapeutic hypothermia in patients with cardiac arrest, involving the reduction of core body temperature to a range of 32°C to 36°C (89.6-96.8°F), is endorsed by both the American Heart Association (AHA) and the European Resuscitation Council (ERC). This intervention is considered to positively impact discharge survival rates and neurological outcomes for extracorporeal cardiopulmonary resuscitation (ECPR) patients.(19) Consequently, in the clinical management of ECPR patients, numerous countries have embraced the use of physical and chemical methods, such as surface cold compress technology, intravascular cooling technology, nasal cooling devices, and pharmaceutical agents, to swiftly achieve the target core temperature drop within intensive care units.(20-24) Nevertheless, in recent years, the implementation of therapeutic hypothermia in cardiac arrest patients undergoing ECPR has sparked some controversy. Recent studies have indicated that there were no marked differences in survival rates and the likelihood of favorable neurological outcomes between normothermia and hypothermia groups.(25) Overall, there are still significant debates and uncertainties regarding the effects of therapeutic hypothermia on the prognosis of ECPR patients.

The clinical benefits of combining Extracorporeal Cardiopulmonary Resuscitation (ECPR) with therapeutic hypothermia in adults suffering from cardiac arrest remain unclear. Whether this combination yields a significant advantage in terms of survival and neurological function is a subject of considerable debate. The conclusions of previous original studies differ significantly, and remarkably, there are notable inconsistencies on this matter in published systematic reviews and meta-analyses.(26,27) In 2020, Chen et al.(26) examined the relationship between therapeutic hypothermia and clinical outcomes in ECPR patients in a systematic review. Their meta-analysis suggested that therapeutic hypothermia was associated with improved neurological outcomes and higher survival rates in adult cardiac arrest patients undergoing ECPR. Another systematic review by Huang et al.(27) published in 2022, found that there was no significant differences in survival rates and neurological outcomes between the Targeted Temperature Management (TTM) group and the non-TTM group in ECPR patients. The meta-analysis, as presented in the systematic review by Chen et al.(26) exclusively incorporated data from studies conducted in select developed nations and regions, including Korea, Japan, Singapore, and Australia. Notably absent were pertinent investigations from eligible developing countries. Furthermore, a discernible publication bias was identified in the assessment of the correlation between hypothermia and neurological outcomes in patients undergoing ECPR. In light of the limited strength of evidence, these findings warrant a circumspect interpretation, indicative of the study's deficiency in encompassing a broader spectrum of data sources and a more expansive sample size. Similarly, the systematic review conducted by Huang et al.(27) is encumbered by several limitations that raise doubts about the reliability of the study outcomes. One of the foremost constraints is the significant heterogeneity in the characteristics of the included studies, demanding meticulous consideration when interpreting the results. Furthermore, the variability in the characteristics of the patients included in the studies, the lack of comprehensive comparisons of baseline demographic characteristics, a significant risk of bias in the conducted studies, and substantial gaps in data all limit the ability to definitively answer whether the combination of ECPR and targeted temperature management improves neurological outcomes in patients. As a result, the conflicting findings from previous studies, along with their inherent limitations, highlight the necessity for further extensive research on this topic.

Undoubtedly, the COVID-19 pandemic has spurred the application and adoption of Extracorporeal Membrane Oxygenation (ECMO) technology in hospitals across developing countries and regions, including mainland China, Hong Kong, Taiwan, and others. Consequently, there has been a notable increase in the utilization of ECPR and mild hypothermia for cardiac arrest patients within hospital settings. As a result, numerous clinical studies have been conducted, with many research findings published in Chinese and included in Chinese databases.(28,29) It is highly necessary to strengthen the reliability of the current body of evidence by including Chinese literature in the analysis. This inclusion will not only increase the sample size but also enhance the statistical power of the study, thereby reinforcing its overall validity.(30) The existing body of evidence, derived primarily from studies conducted in developed

countries and regions, provides a limited and potentially biased perspective on the subject matter. By excluding relevant studies from China, a country with a large population and a rapidly evolving healthcare system, the research fails to incorporate a vital source of diverse data that could contribute to a more comprehensive understanding of the phenomena being investigated.(29) By incorporating studies from China, the research could mitigate the current geographic bias and better represent the global landscape of practices related to ECPR and its outcomes. This inclusivity not only broadens the generalizability of the findings but also enhances the external validity of the study, enabling more robust conclusions applicable to a wider and more diverse patient population. Moreover, expanding the sample size through the inclusion of Chinese literature can greatly bolster the statistical power of the analysis.(31) A larger and more diverse sample provides a better chance of detecting meaningful associations and trends, reducing the risk of Type II errors. This, in turn, enhances the reliability and credibility of the study findings, fostering greater confidence in the conclusions drawn from the research.(30,31) In summary, the incorporation of Chinese literature into the research not only addresses the current limitations associated with the geographic scope of the evidence base but also strengthens the statistical power of the study, thereby reinforcing the quality and applicability of the findings.

Taking these factors into account, this systematic review seeks to provide a comprehensive evaluation of the advantages and potential risks of therapeutic hypothermia in patients undergoing extracorporeal cardiopulmonary resuscitation (ECPR). The review will include the most recent English and Chinese literature that meets the predefined inclusion criteria. The primary objective of this review is to assess survival rates, both in the mid-term and long-term, as well as favorable neurological outcomes over the same time frames. Additionally, the review will examine secondary outcome measures, such as complications associated with ECMO, which may include bleeding, lower limb ischemia, renal injury, infection, ischemic hepatitis, and arrhythmia.

METHODS

Registration and protocol amendment

We are dedicated to strictly following the guidelines set forth by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).(32) Our systematic review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 14 June 2023, and the registration number is CRD42023435353. The protocol was last updated on 16 October 2023. We have made improvements to the title by incorporating the primary outcome and emphasizing the updated accreditation. These modifications aim to enhance the sensitivity for future readers and enhance the transparency of the protocol.

Eligibility criteria

Types of studies

We prioritized the inclusion of Randomized Controlled Trials (RCTs) in our selection process. Additionally, we included cohort studies, case-control studies, and quasi-experimental studies with control groups because conducting rigorous randomized controlled studies of the treatment of patients with cardiac arrest in clinical practice can be challenging. We will only include non-randomised studies that meet the following criteria: At least two comparable groups, one receiving mild hypothermia and the control group not receiving targeted body temperature management, providing at least one outcome measure that we need. In addition, in order to avoid and reduce the inherent bias of non-randomised studies on the reality of meta analysis results, be ROBINS-I evaluation for "No information" or "Critical risk" study also will not be included. We excluded animal studies, duplicate publications, and studies with substantial missing data regarding outcome measures.

Population

This study will specifically focus on adults aged 18 years and above who have experienced cardiac arrest, whether it occurred in a hospital or outside of a hospital setting, and subsequently underwent extracorporeal cardiopulmonary resuscitation (ECPR). Cardiac arrest is defined as the sudden cessation of effective blood circulation, resulting in the absence of a detectable central pulse, loss of consciousness, and the cessation of normal breathing. The inclusion criteria for this study will encompass a broad range of underlying causes for cardiac arrest. These may include, but are not limited to, cardiovascular-related diseases, severe arrhythmias, drowning, COVID-19 infection, drug poisoning, allergies, electric shock, extreme temperatures (both low and high), hypoglycemia, acidosis, hypokalemia or hyperkalemia, severe trauma, pulmonary embolism, hypoxemia, and other relevant factors. Furthermore, there will be no restrictions regarding the mode of ECMO treatment for inclusion in this study.

Intervention

In the intervention group, patients who underwent ECPR were subjected to various temperature control measures, including therapeutic hypothermia, targeted temperature management, or induced hypothermia. These interventions aimed to maintain the patient's body temperature within the range of 32°C to 36°C. This controlled cooling can be achieved through different methods, such as surface cooling techniques like ice packs or cooling blankets, intravascular cooling devices, and the administration of cooling medications. There were no specific limitations regarding the type of temperature control method used or the duration of therapeutic hypothermia.

Outcome indicators

Primary Outcomes

1.Survival: Mid-term survival (survival at discharge or 28/30 days) and long-term survival (Survival for more than 6 months), We used the definition of survival outcomes for patients with cardiac arrest used by the International Liaison Committee on Resuscitation (ILCOR) advanced life support task force.(1)

2.Neurological Outcome: Favorable neurologic outcomes in the mid-term and long-term were included. Evaluated using the Cerebral Performance Category (CPC) score. Based on the category definition of CPC, CPC1 and CPC2 can be considered favorable neurologic outcomes.CPC1: be conscious, alert, and able to function normally, have normal brain function, and may have minor psychological or neurological deficits that do not significantly compromise brain or physical function. CPC2: conscious and alert, brain function in daily life activities, there may be hemiplegia, seizures, ataxia, dysarthria, language barriers or permanent memory or mental changes.(3)

Secondary Outcome

1. ECMO-related Complications： Occurrence of common complications in ECPR patients, including but not limited to bleeding, lower limb ischemia, renal injury, infection, ischemic hepatitis, and arrhythmia. (as defined by trialists).

Language

Published in English or Chinese.

Information sources and search strategy

We will conduct our search in the following databases and trial registers: PubMed, Web of Science, Cochrane Library, Embase, Ovid, CNKI, Wanfang, and China Biology Medicine Disc. These databases will be searched from their respective inception dates to 15 June 2023. To ensure that this systematic review encompasses the entire body of relevant literature, we will also perform a comprehensive hand-search of reference lists from all included studies. We will make every effort to conduct thorough searches using Google Scholar and specialized grey literature repositories such as OpenGrey (www.opengrey.eu) and Grey Literature Report (www.greylit.org). In addition, we will utilize The World Health Organization International Clinical Trials Platform Search Portal (ICTRP) and ClinicalTrials.gov to identify registered trials. We will also manually search the websites of renowned international associations and academic institutions in the field of cardiac arrest, such as AHA, ERC, and ILCOR, to locate relevant conference papers. Should the need arise, we will make efforts to reach out to authors to procure original articles and seek clarification on matters concerning study design, incomplete reporting of outcomes, and other related issues. In accordance with the PICO framework, the search terms employed encompass "heart arrest," "cardiac arrest," "asystole," "extracorporeal oxygenation," "extracorporeal cardiopulmonary resuscitation," "extracorporeal life support," "mechanical circulation assistance," "ECMO," "ECPR," "ECL," "cardiopulmonary resuscitation," "extracorporeal circulation," "hypothermia induced,"

"targeted temperature management," "therapeutic hypothermia," "moderate hypothermia," "mild hypothermia," "cryotherapy," and "TTM." Additionally, we will apply a filter (article type) to enhance retrieval accuracy. The exhaustive list of search items employed across all databases is detailed in Supplementary Material 1. Any necessary adjustments to the search terms used in the registry database will be made as required.

Study selection

The results of the literature search will be imported into EndNote, a literature management software. The research team will conduct literature screening in accordance with predefined inclusion and exclusion criteria. Two independent reviewers will initially assess all retrieved citations. This initial assessment will involve screening the title and abstract to determine potential article eligibility. Importantly, each reviewer will remain unaware of the other's evaluation. The second phase of screening will involve downloading full texts, conducting a thorough reading, and performing a comprehensive review of each study that passes the initial screening. The final step will include a review of the reference lists of studies that meet all inclusion criteria, utilizing a snowball approach to identify additional studies that should be considered. In cases of any ambiguity, the authors of the relevant studies will be contacted to seek clarification. Any disagreements between the two reviewers will be resolved by a third investigator. The screening and selection process is outlined in Figure 1.

Methodological appraisal and risk of bias

We explicitly state that our bias assessment is conducted at the study level. We evaluated potential sources of bias by considering factors such as study design, participant selection, and data collection procedures that may impact the validity of the study as a whole. Following the full-text screening, quality appraisal was undertaken by two authors using the RoB2 and ROBINS-I bias assessment tools.(33,34) In this meta-analysis, the assessment of the risk of bias in the included randomized controlled trials will be performed using the Cochrane revised tool for the separate analysis of bias risk (RoB2).(33) The comprehensive evaluation of the overall bias in each RCT was conducted by assessing the risk of bias across five domains. For practical implementation, the Cochrane website (https://www.riskofbias.info/) offers a downloadable Excel file, providing a standardised tool for bias risk assessment. To systematically appraise the risk of bias in five domains for each RCT, consideration is given to the following areas: bias arising from the randomisation process, bias due to deviations from intended interventions, bias associated with missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result. Each bias identified is then categorised as “low risk”, “high risk”, or “some concerns” based on their level of risk. The overall bias in each domain will then be determined through a comprehensive evaluation of the results. For non-randomized studies, the ROBINS-I bias assessment tool will be used to assess seven dimensions of bias, including

confounding, selection bias, measurement bias, intervention deviations, missing data, outcome measurement bias, and selection of reported results. These dimensions will be used to thoroughly evaluate the risk level of each study. Studies classified as "Low risk," "Moderate risk," and "Serious risk" will be considered for further data analysis. However, studies designated as "Critical risk" and those with "No information" will be excluded, aligning with the recommendations of the ROBINS-I tool development team.(34) All selected papers (i.e., those that met the eligibility criteria outlined in the protocol) underwent critical evaluation by two independent reviewers using the respective critical assessment tools mentioned above.This initial independent assessment allows each reviewer to formulate their individual judgments free from external influence. Conducting independent evaluations facilitates the identification of disparities, thus underscoring the necessity for in-depth discussion on specific issues. Subsequently, the two evaluators engage in a face-to-face dialogue to elucidate the fundamental principles underlying their respective assessments, aiming to reach a consensus through deliberation. In the event that differences persist, the inclusion of a third party as an independent arbiter is contemplated, serving to offer an impartial perspective for the resolution of divergent opinions.

Data collection Process

Two reviewers will independently extract information from each eligible study using piloted standardized forms produced by Microsoft Excel. Our piloted standardized forms were based on the standardized data extraction form provided by Cochrane Collaboration as a template, and were revised and extended to meet the needs of this study as a starting point.(35,36) Following independent extraction, the two reviewers conduct a comparative analysis of their findings, aiming to identify and meticulously document any discrepancies or variations in the extracted data. In instances where disparities emerge between the two reviewers, a third investigator assumes the role of mediator. To uphold consistency and accuracy, integrate routine checks and audits into the data extraction process. Additionally, piloted standardized forms mainly used in the top 10% of papers, according to the feedback of bidders, during timely correction and improvement to form a formal form used in the standardization of data extraction. This approach helps prevent bias resulting from multiple statistical comparisons against a single control group. Additionally, we will standardize and unify the data units extracted for the same indicators before merging. Outcome data will be presented as mean±SD (M±SD). In cases where the data are provided in alternative formats, such as median-range or median-IQR, we will employ appropriate statistical formulas for data transformation. In instances where data are either absent or ambiguous, diligent attempts will be made to communicate with the respective authors to solicit supplementary information, thereby enhancing the scope of subsequent analyses. In the event of unsuccessful data acquisition, the analysis will be conducted utilising the information at hand. In such circumstances, a sensitivity analysis will be undertaken as deemed necessary, aiming to assess the potential influence of missing data on the outcomes of the meta-analysis. In instances where data are either absent or ambiguous, diligent attempts will be made to communicate

with the respective authors to solicit supplementary information, thereby enhancing the scope of subsequent analyses. In the event of unsuccessful data acquisition, the analysis will be conducted utilising the information at hand. In such circumstances, two sensitivity analyses will be undertaken as deemed necessary, aiming to assess the potential influence of missing data on the outcomes of the meta-analysis.

Data items

We plan to extract the following information:

- Author name,year of publication and country of study.
- Study design, sample size, data source,and methodology.
- Participant sociodemographic and baseline characteristics: age, gender, cardiac cause of arrest, bystander witness,bystander CPR, shockable rhythm, ECMO treatment mode, duration of ECLS and location of cardiac arrest,
- Intervention and control group details:all aspects of temperature control including timing, temperature, duration, method of induction and maintenance, and rewarming.
- Outcome data will include time survival rates and neurological status (as measured by CPC score) at each follow-up node, as well as complications (bleeding, lower limb ischemia, renal injury, infection, ischemic hepatitis, and arrhythmia,e.g.)
- Duration of follow-up, point of data measurement,dropout rates and measurement tools.

If there was a discrepancy between the study follow-up date and our protocol, we prioritized extracting outcome measures at the time point we needed them. In cases where studies use multiple interventions, only data relevant to our research question will be extracted. The data will be extracted from the charts, text and table. If a study includes multiple mild hypothermia groups, we will consolidate the groups from various studies.

Assessing the quality of evidence

We will employ the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, endorsed by Cochrane, to appraise the evidence quality across all outcomes.(37) The evaluation results will guide the upgrading or downgrading of evidence based on various dimensions, ultimately categorising the final evidence level as high, moderate, low, or very low quality. The quality of evidence for individual outcomes in our study may be influenced by several factors, including a high risk of bias due to methodological limitations, inconsistent results across studies, indirect correlations among study populations, imprecision of effect estimates, and potential publication bias. For instance, unclear concealment of assignments or a lack of blinding in randomised controlled trials may necessitate downgrading. Conversely, escalation factors comprise large and clinically relevant effect sizes, the presence of dose-response gradients, the consistency of evidence

across studies, and endeavours to minimise publication bias. Consistency in positive outcomes observed in both RCTs and well-conducted observational studies may justify evidence upgrading. Publication bias, as evaluated through the examination of funnel plots and confidence intervals accounting for study sample size, is an additional factor that can affect the strength of evidence for each outcome. The grading of evidence quality will be conducted utilising the online GRADEpro tool.

Data synthesis and statistical analysis

Measures of treatment effect

The outcome measures investigated will ultimately be presented as the survival rate, rate of good neurological function, and the incidence of various complications, all of which are binary outcomes. We will calculate risk ratios (RR) with 95% confidence intervals (CI) for these binary outcomes.

Assessment of heterogeneity

The Chi-Squared test and I^2 value will be used to assess heterogeneity. Chi-Squared test assesses whether the observed variability in effect sizes is greater than expected by chance alone， a significant Q-statistic (P value < 0.1) indicates the presence of heterogeneity [38]. I^2quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. It is expressed as a percentage, with higher values indicating greater heterogeneity. According to the Cochrane Handbook, an I^2 value below 50% was classified as low heterogeneity, while a value above 50% indicated high heterogeneity.(38) Heterogeneity within systematic reviews is a common and unavoidable challenge, as it is often influenced by both clinical and methodological differences among the included studies. This heterogeneity can significantly impact the interpretation of meta-analysis results and the generalizability of the conclusions drawn. To address and understand the existing heterogeneity, several strategic approaches can be employed, including subgroup analysis, sensitivity analysis, narrative synthesis, and the use of a random effects model. These methods are selected to improve the reliability and interpretation of the meta-analysis findings, acknowledging the inherent variations across studies and ensuring a comprehensive and robust synthesis of evidence.

Data synthesis

We will employ Review Manager software version 5.3 for conducting the meta-analysis. Envisaging the adoption of a random-effects model (RE) for our meta-analysis, we recognise the model's consideration of potential true variability in effect sizes across studies. This approach integrates both within-study variability and between-study variability in the computation of the overall effect size. Conversely, the fixed-effects model (FE) assumes uniformity in the true effect size across all studies, engaging solely within-study variability in the overall effect size calculation.(38) Consequently, the fixed-effects model maintains a more stringent criterion for homogeneity, demanding no tolerance for heterogeneity between studies. Our systematic review, inherently accommodating diverse study designs, allows for

some degree of methodological heterogeneity. Ideally, in the absence of heterogeneity between studies, the random-effects model approach yields results congruent with the fixed-effects model approach.(38) If high heterogeneity is observed, we will explore the potential sources of heterogeneity through subgroup analysis, provided that the data allow for it. However, if the I^2 value exceeds 75%, we will opt for qualitative analysis instead of proceeding with the meta-analysis. Qualitative analysis serves to explore and elucidate the sources of variability. Moreover, challenges related to the availability or quality of quantitative data within the included studies may necessitate a shift towards qualitative analysis as a valuable supplement to enrich the overall research.(39) In instances encompassing, but not restricted to, incomplete result reporting, absence of effect sizes or essential parameters for data transformation, methodological disparities across studies, challenges in quantitatively summarising results due to divergent outcome definitions, and a limited number (fewer than 3) of studies reporting outcome measures, we will adhere to the SWiM reporting guidance.(39) In such cases, qualitative analysis will be undertaken.

Subgroup analysis

If feasible, we intend to perform subgroup analyses based on the location of cardiac arrest occurrence, primarily categorized into out-of-hospital cardiac arrest and in-hospital cardiac arrest. Given that there may be significant differences in cardiac arrest management systems across countries and regions, we will compare the differences in outcome measures across Asia, Europe, North America, South America, Africa and Oceania by geographic region. We also considered subgroup analyses of RCTS and non-rcts according to the type of study design.

Sensitivity analysis

To ensure the stability and reliability of the pooled results obtained from our meta-analyses, we will employ two methods: changing the pooled model and utilizing the leave-one-out technique. Initially, we will evaluate the combined results by switching between the random-effects (RE) and fixed-effects (FE) models. The consistency between these two models will provide a preliminary assessment of the stability of the outcomes. Furthermore, we will conduct sensitivity analysis using Stata version 17.0. This involves systematically removing each included study to examine the impact on the combined effect size. If the results show minimal changes or lack significant alterations, it indicates that the original meta-analysis findings are stable and reliable.

If there were missing values in our data analysis, we conducted extra sensitivity analyses to see how it might affect our main results for the key outcomes. In the first sensitivity analysis, we assumed that people lost to follow-up in the trial group had positive outcomes, like survival and good neurological status. In the control group, we assumed the opposite. In the second sensitivity analysis, we flipped these assumptions. These different scenarios (‘worst case’ and ‘best case’) help us understand the range of possibilities due to missing data. For our results to be reliable,

the main meta-analysis and sensitivity analyses should have similar confidence intervals and *P* values. If they don't match, it suggests a risk of biased results because of the missing data .(40)

Assessment of reporting biases

We will generate funnel plots and visually examine them to investigate potential publication bias. In the absence of publication bias, the plot should resemble an inverted funnel, with smaller studies scattered more widely at the bottom and larger studies clustering at the top. Asymmetry in the funnel plot may indicate publication bias. However, recognizing the inherent limitations of funnel plots, we will complement this analysis by performing the Egger's test. Egger's test is a statistical test to assess the funnel plot's asymmetry quantitatively. It regresses the standardized effect sizes against their precision. A significant intercept suggests publication bias. This combination of methods will offer a more accurate assessment of publication bias. For the Egger's test, we will employ Stata version 17.0.

Patient and public involvement

No patient involved.

Ethics and dissemination

Since no patient data were collected in this study, ethical approval was not required. Research findings will be released in a peer-reviewed journal.

Future directions and clinical implications

Cardiac arrest has consistently been a major global public health concern and poses a significant challenge in the emergency and critical care domain. Research indicates that the widespread implementation of ECPR offers only limited improvements in the survival rates and neurological outcomes of these patients, falling short of satisfactory levels.(41) The combination of ECPR with therapeutic hypothermia, carefully regulated within the range of 32°C to 36°C, is considered a potential benefit. It is recognized by international guidelines as a neuroprotective intervention that enhances survival.(42) However, due to the generally low certainty of the available evidence, recent clinical research findings have raised doubts.(43) Furthermore, the impact of therapeutic hypothermia on the complications in ECPR patients remains uncertain.(44)

We aim to enhance the robustness of this study by incorporating high-quality Chinese and English research within this domain. This inclusion of a diverse range of studies will result in a larger sample size available for meta-analysis, leading to an amplification of statistical power and bolstering the credibility of our conclusions. This, in turn, will facilitate clinical practitioners in gaining better clarity regarding the risks and benefits associated with therapeutic hypothermia. Our aspiration is to bridge the existing gaps and disparities between available evidence and informed decision-making. In the process, we endeavor to furnish more dependable evidence concerning the impact of therapeutic hypothermia on the survival rates, neurological

function, and complications in patients suffering from cardiac arrest.

Continuous monitoring of a patient's core body temperature is crucial for targeted temperature management in therapeutic hypothermia, but protocols for cooling interventions lack clarity. These include determining the optimal temperature and duration for therapeutic hypothermia, the choice of cooling techniques, cooling devices, and the specific strategies for rewarming. Further research is needed to fill knowledge gaps and develop evidence-based guidelines. This will improve patient outcomes and enable healthcare professionals to make informed decisions.

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Contributors PC, HW, LG and MW conceptualised and designed the study and drafted the manuscript. PC registered the review on the website of PROSPERO. HW developed the search criteria with input from LG and MW. HX ,PG and JW contributed to the design of the statistical methods. PC wrote the original draft of the manuscript, MY critically revised all study contents and ideas. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. The authors agree to take responsibility for the work.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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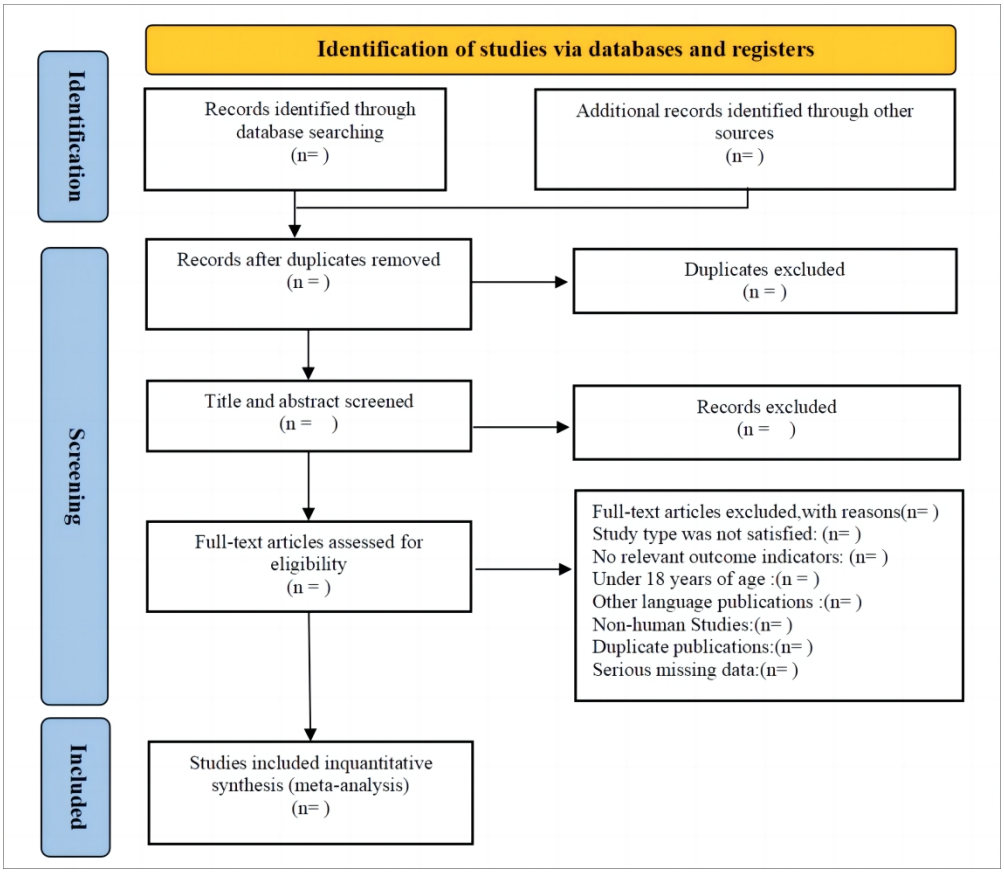

Figure 1. Flow diagram of the literature screening process and results.

977x846mm (144 x 144 DPI)

Supplemental material 1

Searched items for study selection based on different databases.

PubMed:

Order	Strategy
#1	(((((heart arrest[MeSH]) OR (cardiac arrest[Title/Abstract])) OR (out-of-hospital cardiac arrest[MeSH])) OR (in-hospital cardiac arrest[Title/Abstract])) OR (asystole [Title/Abstract])) OR (CA[Title/Abstract]) Filters: Abstract Sort by: Publication Date
#2	((((((((extracorporeal membrane oxygenation[MeSH]) OR (extracorporeal cardiopulmonary resuscitation[Title/Abstract])) OR (extracorporeal life support[Title/Abstract])) OR (mechanical circulation assistance[Title/Abstract])) OR (ECMO[Title/Abstract])) OR (ECPR[Title/Abstract])) OR (ECLS[Title/Abstract])) OR (cardiopulmonary resuscitation[MeSH])) OR (extracorporeal circulation[Title/Abstract])) OR (oxygenators, membrane[MeSH])) OR (life support, extracorporeal[Title/Abstract]) Sort by: Publication Date
#3	((((((((((hypothermia, induced[MeSH]) OR (targeted temperature management [Title/Abstract])) OR (therapeutic hypothermia[Title/Abstract])) OR (moderate hypothermia[Title/Abstract])) OR (mild hypothermias[Title/Abstract])) OR (cryotherapy[Title/Abstract])) OR (cold therapy[Title/Abstract])) OR (TTM[MeSH])) OR (temperature monitoring[Title/Abstract])) OR (gastric hypothermia[MeSH])) OR (rewarming[Title/Abstract]) Sort by: Publication Date
#4	(((((randomized controlled trial[Title/Abstract]) OR (controlled clinical trial[Title/Abstract])) OR (RCT[Title/Abstract])) OR (cohort study[Title/Abstract])) OR (case-control study [Title/Abstract])) OR (quasi-experimental study[Title/Abstract]) Sort by: Publication Date
#5	#1 AND #2 AND #3 AND #4

Web of Science：

Strategy
((TS=('heart arrest' OR 'cardiac arrest' OR 'out-of-hospital cardiac arrest' OR 'in-hospital cardiac arrest' OR 'asystole' OR 'CA') AND TS=('extracorporeal be oxygenation' OR 'extracorporeal cardiopulmonary resuscitation' OR 'extracorporeal life support' OR 'mechanical circulation assistance' OR 'ECMO' OR 'ECPR' OR 'ECLS' OR 'cardiopulmonary resuscitation' OR 'extracorporeal circulation' OR 'oxygenators, membrane' OR 'life support, extracorporeal') AND TS=('hypothermia, induced' OR 'targeted temperature management' OR 'therapeutic hypothermia' OR 'moderate hypothermia' OR 'mild hypothermias' OR 'cryotherapy' OR 'cold therapy' OR 'TTM' OR 'temperature monitoring' OR 'gastric hypothermia' OR 'rewarming')) AND PY=(1637-2023) AND LANGUAGE=(Chinese OR English) AND DT=(Article)

Cochrane Library：

Order	Strategy
#1	(heart arrest OR cardiac arrest OR out-of-hospital cardiac arrest OR in-hospital cardiac arrest OR asystole OR CA):ti,ab,kw in Trials
#2	(extracorporeal be oxygenation OR extracorporeal cardiopulmonary resuscitation OR

	extracorporeal life support OR mechanical circulation assistance OR ECMO OR ECPR OR ECLS OR cardiopulmonary resuscitation OR extracorporeal circulation OR oxygenators, membrane OR life support, extracorporeal):ti,ab,kw in Trials
#3	(hypothermia, induced OR targeted temperature management OR therapeutic hypothermia OR moderate hypothermia OR mild hypothermias OR cryotherapy OR cold therapy OR TTM OR temperature monitoring OR gastric hypothermia OR rewarming):ti,ab,kw in Trials
#4	#1 AND #2 AND #3

Embase:

Order	Strategy
#1	'heart arrest'/exp
#2	'heart arrest':ab,ti,kw OR 'cardiac arrest':ab,ti,kw OR 'out-of-hospital cardiac arrest':ab,ti,kw OR 'in-hospital cardiac arrest':ab,ti,kw OR 'asystole':ab,ti,kw OR 'CA':ab,ti,kw
#3	#1 OR #2
#4	'extracorporeal be oxygenation'/exp
#5	'extracorporeal be oxygenation':ab,ti,kw OR 'extracorporeal cardiopulmonary resuscitation':ab,ti,kw OR 'extracorporeal life support':ab,ti,kw OR 'mechanical circulation assistance':ab,ti,kw OR 'ECMO':ab,ti,kw OR 'ECPR':ab,ti,kw OR 'ECLS':ab,ti,kw OR 'cardiopulmonary resuscitation':ab,ti,kw OR 'extracorporeal circulation':ab,ti,kw OR 'oxygenators, membrane':ab,ti,kw OR 'life support, extracorporeal':ab,ti,kw
#7	#3 OR #4
#8	'hypothermia, induced'/exp
#9	'hypothermia, induced':ab,ti,kw OR 'targeted temperature management':ab,ti,kw OR 'therapeutic hypothermia':ab,ti,kw OR 'moderate hypothermia':ab,ti,kw OR 'mild hypothermias':ab,ti,kw OR 'cryotherapy':ab,ti,kw OR 'cold therapy':ab,ti,kw OR 'TTM':ab,ti,kw OR 'temperature monitoring':ab,ti,kw OR 'gastric hypothermia':ab,ti,kw OR 'rewarming':ab,ti,kw
#10	#8 OR #9
#11	#3AND #7 AND #10

Ovid:

Strategy
heart arrest OR cardiac arrest OR "out-of-hospital cardiac arrest" OR "in-hospital cardiac arrest" OR asystole OR CA AND "extracorporeal membrane oxygenation" OR "extracorporeal cardiopulmonary resuscitation" OR "extracorporeal life support" OR "mechanical circulation assistance" OR ECMO OR ECPR OR ECLS OR "cardiopulmonary resuscitation" OR "extracorporeal circulation" OR "oxygenators, membrane" OR "life support, extracorporeal" AND hypothermia OR induced OR "targeted temperature management" OR "therapeutic hypothermia" OR "moderate hypothermia" OR "mild hypothermias" OR cryotherapy OR "cold therapy" OR TTM OR "temperature monitoring" OR "gastric hypothermia" OR rewarming AND ((English AND [embase]/py <= 20230615) OR (Chinese AND [embase]/py <= 20230615)) AND

[embase]/ti,ab,kw.

CNKI:

Strategy
(SU=('心脏骤停' +'呼吸心跳骤停' +'心搏骤停'+'心跳骤停' +'心脏停搏' +'猝死' +'SCA' +'CA') OR AB=('心脏骤停' +'呼吸心跳骤停' +'心搏骤停'+'心跳骤停' +'心脏停搏' +'猝死' +'SCA' +'CA')) AND (SU=('体外生命支持'+'体外心肺复苏'+'ECPR'+'ECMO') OR AB=('体外生命支持'+'体外心肺复苏'+'ECPR'+'ECMO')) AND (SU=('目标体温管理'+'亚体温'+'低温'+'治疗性低体温'+'保护性低体温'+'体温控制'+'体温监测'+'复温'+'冷疗') OR AB=('目标体温管理'+'亚体温'+'低温'+'治疗性低体温'+'保护性低体温'+'体温控制'+'体温监测'+'复温'+'冷疗'))
Filter by: synonym expansion

Wanfang:

Strategy
(题名或关键词:("心脏骤停"OR"呼吸心跳骤停"OR"心搏骤停"OR"心跳骤停"OR"心脏停搏"OR"猝死"OR"SCA"OR"CA") and 题名或关键词:("体外膜肺氧合"OR"机械循环辅助"OR"体外生命支持"OR"体外心肺复苏"OR"ECPR"OR"ECMO") and 题名或关键词:("目标体温管理"OR"亚体温"OR"低温"OR"治疗性低体温"OR"保护性低体温"OR"体温控制"OR"体温监测"OR"复温"OR"冷疗")) and 出版时间:[* TO 2023-06-15}

China Biology Medicine Disc.

Order	Strategy
#1	("心脏骤停"[全部字段:智能] OR "呼吸心跳骤停"[全部字段:智能] OR"心搏骤停"[全部字段:智能] OR"心跳骤停"[全部字段:智能] OR"心脏停搏"[全部字段:智能] OR"猝死"[全部字段:智能] OR"SCA"[全部字段:智能] OR"CA"[全部字段:智能])
#2	("体外膜肺氧合"[全部字段:智能] OR "机械循环辅助"[全部字段:智能] OR"体外生命支持"[全部字段:智能] OR"体外心肺复苏"[全部字段:智能] OR"ECPR"[全部字段:智能] OR"ECMO"[全部字段:智能]
#3	("目标体温管理"[全部字段:智能] OR "亚体温"[全部字段:智能] OR"低温"[全部字段:智能] OR"治疗性低体温"[全部字段:智能] OR"保护性低体温"[全部字段:智能] OR"体温控制"[全部字段:智能] OR"体温监测"[全部字段:智能] OR"复温"[全部字段:智能] OR"冷疗"[全部字段:智能])
#4	#1 AND #2 AND #3

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Location where item is reported
ADMINISTRATIVE INFORMATION			
Title:			Page1/Line1-3
Identification	1a	Identify the report as a protocol of a systematic review	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Page1/Line1-3
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page4/Line155-159
Authors:			Page1/Line4-12
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page10/Line403-408
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Page4/Line159-163
Support:			Page10/Line409-410
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	Not applicable
Role of sponsor or funder	5c	Describe roles offunder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Not applicable
INTRODUCTION			

Rationale	6	Describe the rationale for the review in the context of what is already known	Page2-3/Line57-121
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page4/Line143-151
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page4-5/Line165-205
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page5-6/Line1207-217
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page6/Line217-242
Study records:			Page6-7/Line245-246,260-262
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page6/Line244-259
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page7/Line261-279
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page7/Line262-273
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page5/Line196-204
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page7/Line281-302
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page8/Line327-331
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration	Page8/Line314-335

		of consistency (such as I^2, Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page8-9/Line337-352
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page8/Line333-334
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page9/Line354-358
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page8/Line304-312

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the**
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