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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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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. 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 use 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 randomised 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 peer-reviewed journal.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review will use a rigorous methodology following the Preferred Reporting Items for Systematic Review and Meta-Analysis 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, randomised clinical trials, cohort studies, case–control studies and quasi-experimental studies will be included.
⇒ The Grading of Recommendations, Assessment, Development and Evaluation 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 generalisability and precision in deducing the summarised 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 USA 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 1.5–2.8 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 popularity for 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 minimised, ultimately leading to increased survival rates and improved neurological outcomes.[10 11] As of 2022, the Extracorporeal Life Support Organization 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 favourable 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 favourable neurological outcomes. Further interventions and research are needed to maximise the impact of ECPR.

Therapeutic hypothermia is recognised 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 oedema[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–36°C (89.6–96.8 °F), is endorsed by both the AHA and the European Resuscitation Council (ERC). This intervention is considered to positively impact discharge survival rates and neurological outcomes for 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 favourable 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 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 were 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 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 utilisation 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 geographical bias and better represent the global landscape of practices related to ECPR and its outcomes. This inclusivity not only broadens the generalisability 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 geographical 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 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 favourable 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 ischaemia, renal injury, infection, ischaemic 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.[32] Our systematic review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 14 June 2023. The protocol was last updated on 16 October 2023. We have made improvements to the title by incorporating the primary outcome and emphasising 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 prioritised the inclusion of randomised 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 randomised 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 Risk Of Bias In Nonrandomised Studies of Interventions (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 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 of 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), hypoglycaemia, acidosis, hypokalaemia or hyperkalaemia, severe trauma, pulmonary embolism, hypoxaemia 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–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: Favourable neurological 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 favourable neurological 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

ECMO-related complications: Occurrence of common complications in ECPR patients, including but not limited to bleeding, lower limb ischaemia, renal injury, infection, ischaemic 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 specialised grey literature repositories such as OpenGrey (www.opengrey.eu) and Grey Literature Report (www.greylit.org). In addition, we will use The WHO International Clinical Trials Platform Search Portal 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 population, intervention and outcomes, 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 online supplemental 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, using 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, the quality appraisal was undertaken by

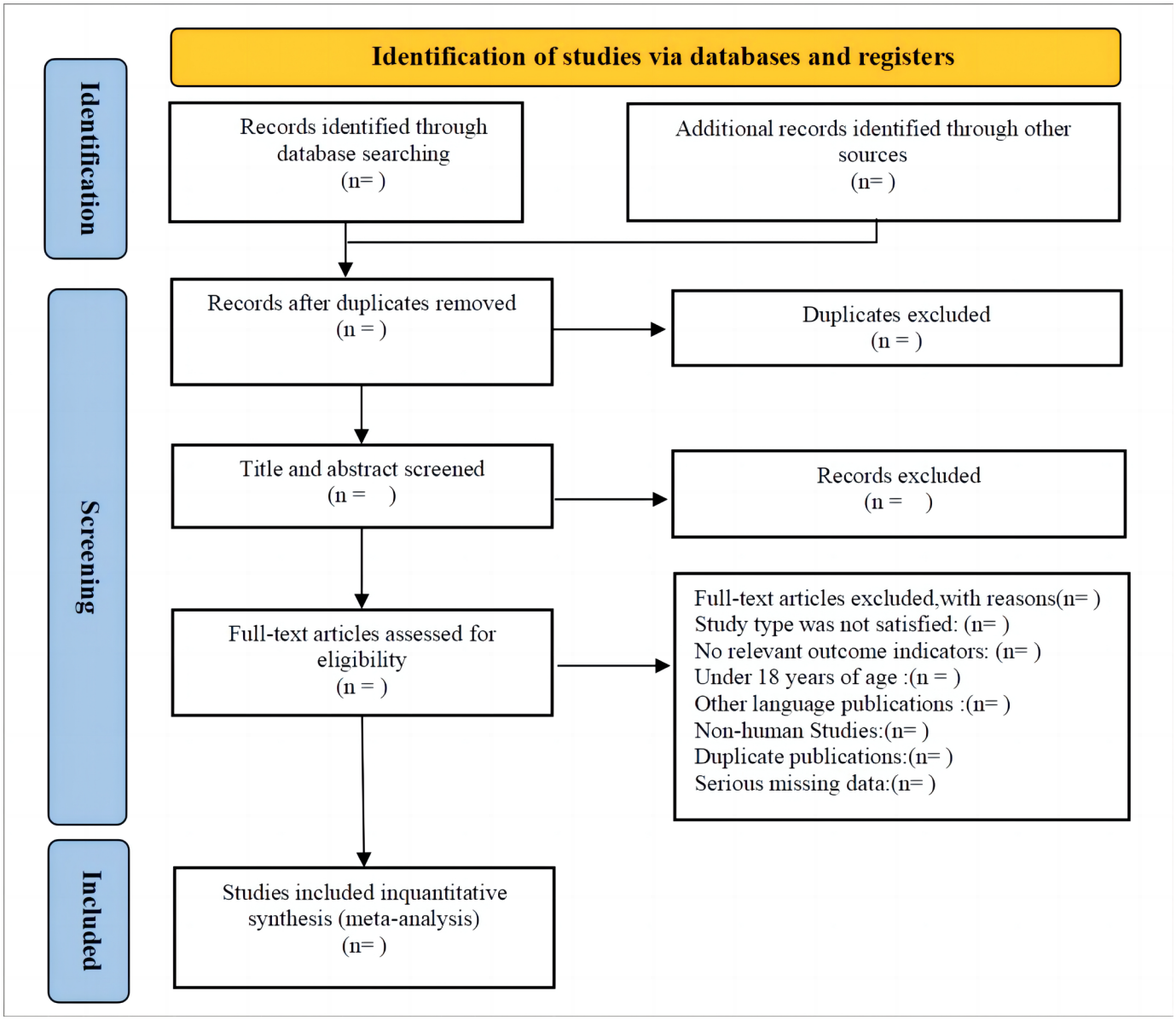

Figure 1 Flow diagram of the literature screening process and results.

two authors using the Risk of Bias 2 tool (RoB2) and ROBINS-I bias assessment tools.[33 34] In this meta-analysis, the assessment of the risk of bias in the included RCTs 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-randomised 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 (ie, 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 judgements 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 standardised forms produced by Microsoft Excel. Our piloted standardised forms were based on the standardised 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 standardised forms were 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 standardisation of data extraction. This approach helps prevent bias resulting from multiple statistical comparisons against a single control group. Additionally, we will standardise and unify the data units extracted for the same indicators before merging. Outcome data will be presented as mean±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 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 using 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 socio-demographic and baseline characteristics: age, gender, cardiac cause of arrest, bystander witness, bystander CPR, shockable rhythm, ECMO treatment mode, duration of Extracorporeal Life Support(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 (eg, bleeding, lower limb ischaemia, renal injury, infection, ischaemic hepatitis and arrhythmia).
- 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 prioritised 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 RCTs 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 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 incidence of various complications, all of which are binary outcomes. We will calculate risk ratios with 95% CIs for these binary outcomes.

Assessment of heterogeneity

The χ^2 test and I^2 value will be used to assess heterogeneity. χ^2 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^2 quantifies 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 generalisability 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 V.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 FE 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 RE model approach yields results congruent with the FE 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 categorised into OHCA and IHCA. 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 geographical 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 using the leave-one-out technique. Initially, we will evaluate the combined results by switching between the RE and 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 V.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 CIs and p values. If they do not 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, recognising 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 standardised 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 V.17.0.

Patient and public involvement

No patient is 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–36°C, is considered a potential benefit. It is recognised 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 endeavour to furnish more dependable evidence concerning the impact of therapeutic hypothermia on 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.

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