Efficacy of left ventricular unloading strategies during venoarterial extracorporeal membrane oxygenation in patients with cardiogenic shock: a protocol for a systematic review and Bayesian network meta-analysis

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Protocol

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Abstract

Background: Venoarterial extracorporeal membrane oxygenation (VA-ECMO) has been widely used for patients with refractory cardiogenic shock (CS). A common side-effect of this technic is the resultant increase in left ventricular (LV) afterload which could potentially aggravate myocardial ischemia, delay ventricular recovery, and increase the risk of pulmonary congestion. Several LV unloading strategies have been proposed and implemented to mitigate these complications. However, it is still indistinct that which one is the best choice for clinical application. The objective of this Bayesian network meta-analysis (NMA) is to summarize the evidence and compare the efficacy of different LV unloading strategies during VA-ECMO.

Methods: We will perform a systematic search to identify random controlled trials and cohort studies comparing different LV unloading strategies during VA-ECMO. PubMed, Embase, the Cochrane Library, and the International Clinical Trials Registry Platform (ICTRP) will be explored from their inception to 31 December 2020. The primary outcome will be in-hospital mortality. The secondary outcomes will include neurological complications, hemolysis, bleeding, limb ischemia, renal failure, gastrointestinal complications, sepsis, duration of mechanical ventilation, length of intensive care unit, and hospital stays. Pairwise and network meta-analysis will respectively be conducted using Stata (V.16, StataCorp) and Aggregate Data Drug Information System (ADDIS V.1.16.5), and the cumulative probability will be used to rank the included LV unloading strategies. The risk of bias will be conducted using the Cochrane Collaboration's tool or Newcastle-Ottawa Quality Assessment Scale (NOS) according to their study design. Subgroup analysis, sensitivity analysis, and publication bias assessment will be performed. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) will be conducted to explore the quality of evidence.

Discussion: This Bayesian network meta-analysis (NMA) will address the problem that which strategy could achieve left ventricular (LV) unloading most effectively during venoarterial extracorporeal membrane oxygenation and increase cardiogenic shock patient survival benefit, and will provide evidence for clinical decision-making.

Systematic review registration: PROSPERO registry number: CRD42020165093.

Background

Cardiogenic shock (CS) remains a challenging condition with about 40–50% mortality, despite significant advances that have been achieved in revascularization and heart failure pharmacotherapies [1–4]. Currently, venoarterial extracorporeal membrane oxygenation (VA-ECMO) has been widely used to provide life support for these refractory CS patients [5, 6]. VA-ECMO could be used as a bridge to myocardial recovery, durable mechanical circulatory support, or heart transplant for refractory CS patients [7]. Furthermore, VA-ECMO is associated with a significant mortality benefit [8], and has significantly improved outcomes of patients [9, 10].

Despite those benefits of VA-ECMO, it also has the potentially deleterious effects like the increased left ventricular (LV) afterload [6, 11]. VA-ECMO works relying on generating varying degrees of retrograde aortic flow, which will increase afterload in the aorta. The increased LV afterload could cause an increase in wall stress and oxygen demand, exacerbate myocardial ischemia, and delaying recovery from CS [12, 13]. Elevated LV pressure could further promote LV dilatation, trigger ventricular arrhythmias, and result in elevated left atrial (LA) pressure causing pulmonary edema [14]. Eventually, the reduced flow across the aortic valve and retrograde aortic flow can induce the LV or aortic root thrombus [15].

Several interventions have been used to unload LV afterload, thereby reducing the complications associated with increased LV afterload [16]. Recent meta-analyses had demonstrated that VA-ECMO concomitant with LV unloading was associated with higher short-term survival benefit as compared to VA-ECMO alone [17–19]. We previously demonstrated VA-ECMO plus IABP (intra-aortic balloon pump) was associated with decreased mortality [20]. Nevertheless, lacking direct randomized trials or studies comparing one with all other LV unloading strategies, it is still controversial that which strategy could achieve LV unloading and increase survival benefit most effectively for CS patients.

Network meta-analysis could combine all available evidence and compare the effectiveness of all available LV unloading strategies [21–23]. This NMA will combine all direct with indirect evidence within a Bayesian framework by Markov Chain Monte Carlo simulation. The aim of this NMA is to synthesize the available evidence on LV unloading strategies during VA-ECMO, and to address the problem that which strategy could achieve LV unloading during VA-ECMO and increase cardiogenic shock patient survival benefit most effectively. It is anticipated to be the first Bayesian NMA that evaluates the efficacy of different LV unloading strategies during VA-ECMO.

Methods

This NMA protocol has been registered on the PROSPERO international prospective register of systematic reviews (ID = CRD42020165093) [24]. This protocol is written following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines and the PRISMA checklist for Reporting Systematic Reviews incorporating Network Meta-analyses [25 - 27]. The PRISMA-P checklist for this study is included in Additional file 1.

Criteria for included studies

Participants

Adult patients (older than 18 years) with CS using VA-ECMO with or without LV unloading will be included. We will not apply restrictions about gender, ethnic origin, or other characteristics.

Interventions and comparators

We will include any LV unloading strategies adjunct to VA-ECMO covering surgical LV unloading strategy, IABP, Impella, and TandemHeart [12, 28 - 30]. Despite the common comparator is VA-ECMO alone, any LV

unloading technique adjunct to VA-ECMO could be intervention or comparator in pairwise and network meta-analyses. The network of all possible pairwise comparisons among the eligible interventions is shown in Fig 1. As the surgical techniques of LV venting could be achieved by many approaches, we define the surgical LV unloading strategy as follows: (1) implanting LV venting cannulation of the ventricle apex or through the mitral valve from the left atrium (LA); (2) implanting a catheter across the aortic valve percutaneously; (3) implanting LV venting surgical cannulation through the right superior pulmonary vein, LA roof or interatrial groove into LA; (4) transseptal LA cannula; (5) an interatrial septostomy (septostomy usually with ballooning or stent); (6) the surgical or percutaneous pulmonary artery cannulation; (7) simultaneous left and right atrial drainage with the multistage cannula coming from the femoral vein and positioned transeptally [12, 17, 28, 31].

Outcomes measures

Primary Outcome

The primary outcome was all-cause in-hospital mortality (death of ECMO withdrawal due to futility, of patients unable to be weaned off ECMO, and of patients who died before hospital discharge despite successful ECMO weaning).

Secondary outcomes

The secondary outcomes will be neurological complications, hemolysis, bleeding, limb ischemia, renal failure, gastrointestinal complications, sepsis, duration of mechanical ventilation, length of intensive care unit, and hospital stays.

Study design and publication types

All published clinical studies investigating VA-ECMO and reporting data on LV unloading strategies will be evaluated for inclusion in this meta-analysis. Random controlled trials and prospective or retrospective cohort studies, reporting at least 10 adult CS patients, that compare different LV unloading techniques during VA-ECMO will be included in this study. Case-control and cross-sectional studies, case series studies, reviews and meta-analyses, letters to the editor, case reports, expert opinions, and animal studies will be excluded.

Information source and search strategy

PubMed, Embase, the Cochrane Library, and the International Clinical Trials Registry Platform (ICTRP) will be explored from their inception to 31 December 2020. We will use a combination of MeSH, EMTREE and free-text terms: 'extracorporeal membrane oxygenation', 'extracorporeal life support', 'intra-aortic balloon pumping', 'counterpulsation', 'impella', 'TandemHeart' 'transaortic catheter', 'transseptal left atrial cannula', 'decompression', 'venting', 'unloading'. The search strategy will be implemented by two experienced scholars of information retrieval (D.B.L and Y.N.L). Any potentially-relevant article will be retrieved for review. Besides, references of included studies and narrative reviews and meta-analyses will be

considered for additional potential studies. There will be no restrictions on date limit, country, the language of publication, publication status, or year of publication. The search strategies are shown in Additional file 2.

Study screening and selection

All studies to be screened will be managed by Endnote X9 (Thomson-Reuters; 2018, New York, USA). Firstly, it will be used to classify and organize the preliminary literature and exclude repeated literature. Secondly, following the prespecified inclusion criteria, two independent reviewers (P.B.Z and S.L.W) will screen the title and abstract of each study independently and identify relevant studies. Thirdly, they will obtain and review the full text of all potential studies, then, they will make decisions independently and compare their selection of studies. Any discrepancies will be resolved by consensus. If consensus cannot be reached, the third authors (D.B.L and Y.N.L) will serve as an arbitrator. And if a discrepancy is caused by insufficient information of the literature, it is necessary to classify it into the category of waiting for evaluating and then decide whether it should be included after adding sufficient additional information. If studies have duplicate data, only the study with a larger sample size or longer follow-up time will be included. The proposed flow diagram of studies selection is illustrated in Fig 2.

Data extraction and management

Microsoft Excel (V.2019; Microsoft Corporation, USA) will be used to extract data from the included studies by two reviewers (P.B.Z and S.L.W) independently, using a standardized data extraction form. Missing data will be requested from study authors. Any discrepancies will be resolved by consensus. If consensus cannot be reached, the third authors (D.B.L and Y.N.L) will serve as an arbitrator. The characteristics of the extracted data items are shown in Table 1.

Risk of bias assessment

The risk of bias will be assessed using the Cochrane risk of bias tool or Newcastle-Ottawa Quality Assessment Scale (NOS) for random controlled trials or observational studies separately [32, 33]. The Cochrane Collaboration's risk of bias assessment tool includes the following seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each item will be classified into one of three categories as follows: unclear, high or low risk. The NOS will be used to assess each included observational study using "star system". Each study will be judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest. A total score of 5 or less is considered low, 6 or 7 is considered moderate, and 8 or 9 is deemed of high quality. The judgments will be made by two review authors (P.B.Z and S.L.W) independently. Any discrepancies will be resolved by consensus. If consensus cannot be reached, the third authors (D.B.L and Y.N.L) will serve as an arbitrator.

Data synthesis and analysis

When quantitative analysis cannot be conducted, we will narratively describe the results. If the quantitative analysis is feasible, statistical analyses will be conducted using Stata (V.16, StataCorp, College Station, TX) and ADDIS (V.1.16.5 Aggregate Data Drug Information System, http://drugis.org/addis). The binary outcomes and continuous outcomes will be presented as risk ratios (RR) or mean difference (MD) with their 95% confidence intervals (CIs) respectively.

Pairwise meta-analyses

All the direct comparisons will be performed using Stata software and random-effects model if no less than two studies. Methodological and clinical diversity always exist in the pairwise meta-analysis, statistical heterogeneity is inevitable [34]. Cochran's Q tests, I-squared statistic, and visual inspection of forest plots will be used to assess heterogeneity levels. If significant heterogeneity existing (I-squared ≥ 50% or $p < 0.1$), subgroup or sensitivity analysis or meta-regression will be used to explain the source of heterogeneity. Moreover, if there is considerable heterogeneity, especially when the direction of the effect is inconsistent, we will do a general statistical description.

Indirect and mixed comparisons of interventions

A random-effects network meta-analysis within the Bayesian framework will be applied. Interactions among all included studies will be shown in the network geometry, and the contribution plot for the network will show the contributions of direct comparisons [35]. In the network diagram, the dots will represent every intervention, and the size of the dot will mean the number of participants. The lines will indicate direct comparisons between different interventions and the thickness of the line will mean the number of studies [36]. For each outcome, we will present the contribution plots, which exposit the contribution of each direct comparison to the entire network as well as for each network estimate [37]. The main characteristics of NMA are ranking analysis having the ability to rank the various treatments for each outcome. The cumulative probability will be used to rank the included LV unloading strategies.

Assessment of inconsistency

Inconsistency is the statistical manifestation of the violation of the transitivity assumption. It is the differences between indirect and direct effect estimates for the same comparison, includes loop inconsistency and design inconsistency [38]. We will use the node-splitting method to evaluate the inconsistency between direct and indirect evidence locally. If $p > 0.05$, it suggests consistency between direct and indirect evidence. We will also investigate possible sources of inconsistency using the inconsistency factor (IF) among studies in each closed loop. If the 95% CIs of IF values include zero, it indicates that there is no significant inconsistency.

Subgroup analysis and sensitivity analysis

If there are sufficient data, we will conduct prespecified subgroup analyses for outcomes based on following: (1) etiology of cardiogenic shock (postcardiotomy shock (PCS); acute myocardial infarction (AMI); myocarditis; mixed etiologies); (2) quality of study; (3) the time of LV unloading; (4) the mechanism

of LV decompression. Besides, the sensitivity analysis will also be conducted to validate the robustness of the results by excluding each study.

Assessment of publication bias

To assess small study effects and publication bias, a funnel plot will be used in pairwise meta-analyses when at least 10 studies would be analyzed. The comparison-adjusted funnel plot will be employed to identify possible small-study effects including publication bias at the network level [37]. And Egger's test will be used to assess the symmetry of the funnel plot [39].

Quality of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines will be used to assess the quality of direct and indirect evidence for the main outcomes [40]. Five factors can reduce the quality of evidence: study limitations (risk of bias), inconsistency, indirectness, publication bias, and imprecision. Correspondingly, three factors can improve the quality of evidence: residual confounding, dose-response gradient, and large magnitude of the effect. The quality of evidence will be graded in four levels: very low, low, moderate, high.

Discussion

VA-ECMO has become the preferred device for short-term hemodynamic support in CS patients as cost, ease, and rapidity of cannulation, and the ability to provide biventricular and respiratory support [5, 6, 41]. Despite the improvements in technology that have mitigated many adverse effects like the interaction between artificial surfaces of ECMO circuits and blood [42], the issue that a resultant increase in left ventricular afterload during VA-ECMO has not been solved. Several interventions have been used to achieve LV unloading, however, it remains controversial that which unloading strategy could achieve LV unloading and increase survival benefit most effectively.

In summary, this Bayesian network meta-analysis will provide evidence for the efficacy of different LV unloading strategies during VA-ECMO, and solve this thorny problem that which unloading strategy could achieve LV unloading and increase survival benefit most effectively during VA-ECMO for CS patients. As far as we know, this NMA is anticipated to be the first Bayesian NMA that assesses different LV unloading strategies during VA-ECMO. We expect that our findings will provide the best available evidence on LV unloading during VA-ECMO for clinicians, patients, cardiologists, and practice guideline developers. And this NMA will help both clinical practice and study design in the future. Based on this NMA, clinicians and perfusionists will make a more accurate and optimal intervention for LV overload for adults with VA-ECMO. We will publish the findings and results of this study in a peer-reviewed journal.

This NMA may have some limitations. Although LV overload has been reported in many studies, there are still no standardized diagnostic criteria for LV overload and no guidelines for the timing of intervention for it [12, 28]. We will not limit the time for LV unloading, so, the time of the intervention of LV overload in

different clinical studies maybe not unified absolutely. Besides, RCTs and cohort studies will be included in our study. All of the above will generate potential heterogeneity which may influence the results. There may exist inconsistency in this NMA, and the inconsistency will be reduced by setting subgroups or conducting meta-regression. However, it is also worth mentioning that if the scope of included studies is small, the ability to explore heterogeneity and conduct meta-regression could be limited.

Declarations

Ethics approval and consent to participate

This work synthesizes evidence from previously published studies, there are no ethical concerns nor informed consent required.

Consent for publication

Not applicable.

Availability of data and materials

All data generated and analyzed during this study will be included in the published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

P.B.Z, B.R.G, D.B.L and Y.N.L participated in the conception and design of the study. D.B.L and Y.N.L were responsible for search strategy development. P.B.Z, S.L.W, K.R.Z and J.H drafted the initial protocol. P.B.Z, X.D.C, Z.Z.T tested the feasibility of this protocol. All authors contributed to the development of the selection criteria. All authors read, provided feedback and approved the final manuscript as submitted.

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Abbreviations

VA-ECMO: Venoarterial extracorporeal membrane oxygenation; CS: cardiogenic shock; LV: left ventricular; NMA: network meta-analysis; ICTRP: the International Clinical Trials Registry Platform; ADDIS: Aggregate Data Drug Information System; LA: left atrial; IABP: intra-aortic balloon pump: PRISMA-P: Preferred Reporting Items for Systematic review and Meta-Analysis Protocols; PRISMA: the Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCTs: Random controlled trials; NOS: Newcastle-Ottawa Quality Assessment Scale; RR: risk ratios; MD: mean difference; CIs: confidence intervals: IF: inconsistency factor; PCS: postcardiotomy shock; AMI: acute myocardial infarction; GRADE: Grading of Recommendations, Assessment, Development and Evaluation.

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Table

Table 1: Characteristics of the extracted data items

Characteristics	Data items
Study characteristics	title, first author, journal, publication year, study period, study type, country/district, ELSO center, funding information
Participants	sample size, gender, age, underlying diseases, duration of disease, left ventricular ejection fraction, etiology of cardiogenic shock, number of peripheral ECMO, average time on ECMO, number of survive to D/C, number of bridged to VAD / number of survive to D/C, number of bridged to HTP / number of survive to D/C, ECPR
Interventions	number of patients with LV unloading, the diagnose of LV overload, strategy of LV unloading, the time of LV unloading
Comparisons	number of patients without LV unloading
Outcomes	primary outcome: all-cause in-hospital mortality Secondary outcomes: neurological complications, hemolysis, bleeding, limb ischemia, renal failure, gastrointestinal complications, sepsis, duration of mechanical ventilation, length of intensive care unit and hospital stays

ELSO: Extracorporeal Life Support Organization; ECMO: extracorporeal membrane oxygenation; D/C: hospital discharge; VAD: ventricular assist device; HTP: heart transplant; ECPR: extracorporeal cardiopulmonary resuscitation.

Figures

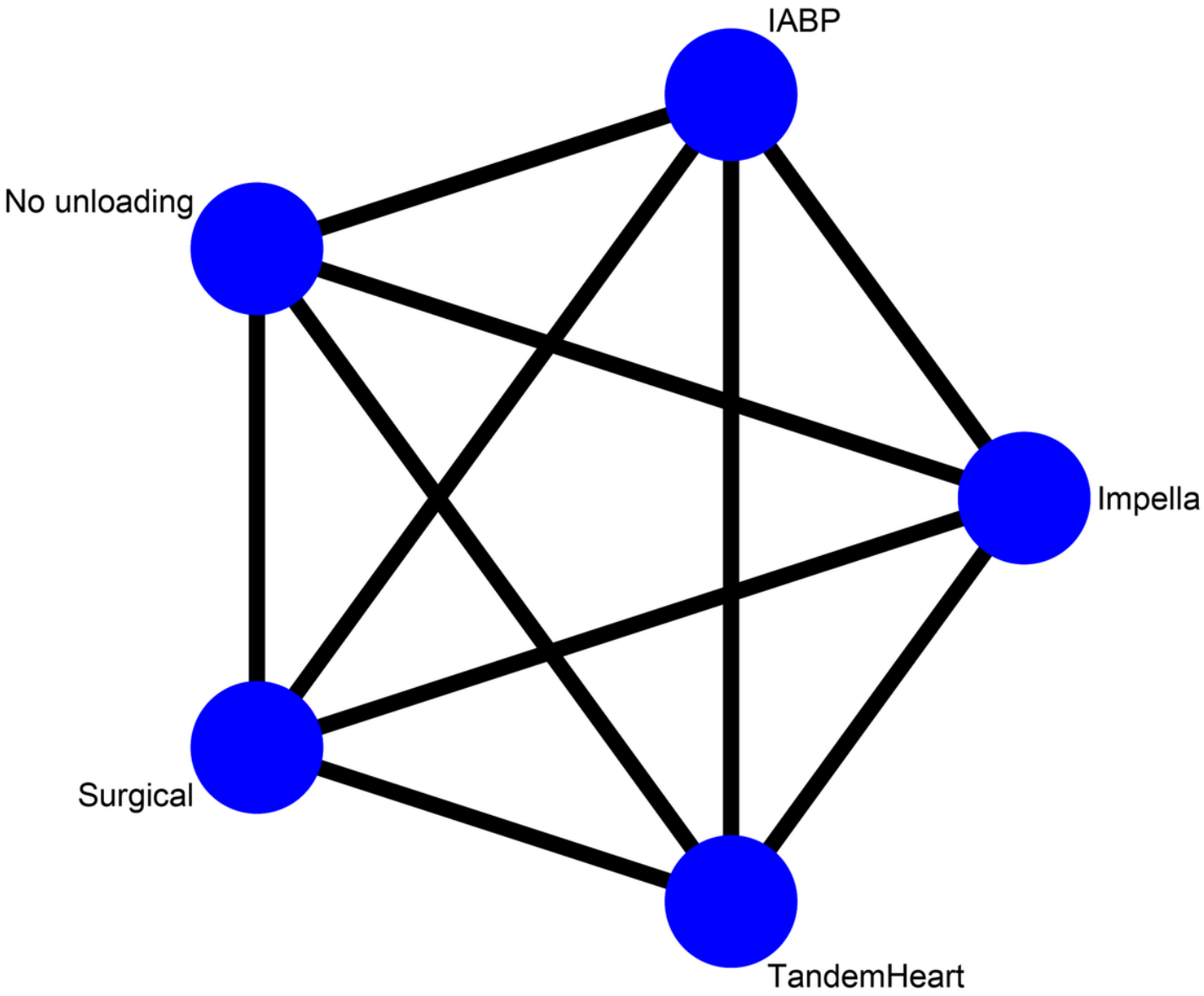

Figure 1

The network of all possible pairwise comparisons among the eligible interventions. Surgical: surgical LV unloading strategy; IABP: intra-aortic balloon pump.

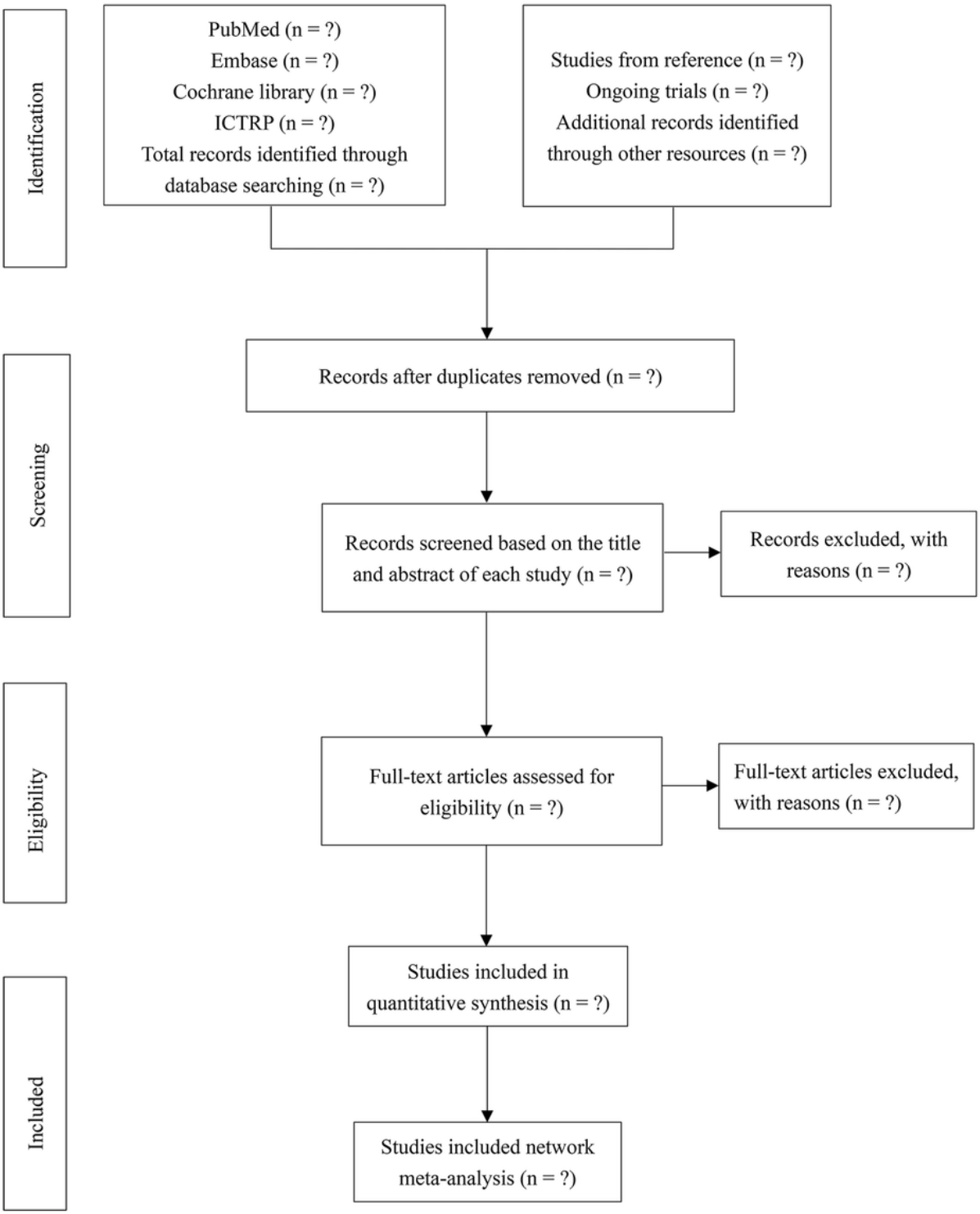

Figure 2

Hypothetic flow diagram of the study selection process. ICTRP: The International Clinical Trials Registry Platform.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalFile1.docx
- AdditionalFile2.docx