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Traditional Chinese medicine injections for heart failure: a protocol for systematic review and network meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Heart failure (HF) has always been an important issue in global public health. The research and development of traditional Chinese medicine (TCM) provide more possibilities for improving the prognosis of HF patients. Because multiple traditional Chinese medicine injections (TCMIs) are being widely used clinically, it is important to choose the right TCMIs for HF patients. The purpose of this study is to assess and compare the effect of different TCMIs for HF using network meta-analysis (NMA) and further provide references for clinical decision-making.

Methods and analysis: The clinical randomized controlled trials (RCTs) and meta-analyses of TCMIs for treating HF will be searched in the relevant database, including PubMed, EMBASE, Cochrane Library (No.2 of 2020), Chinese BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Wan Fang database and VIP database from inception to February 29, 2020. The outcomes of interest include all-cause mortality, rehospitalization rate, left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), brain natriuretic peptide (BNP), cardiac output (CO), stroke volume (SV), 6 minutes walking distance, and adverse events. The risk of bias assessment of the included RCTs will be conducted according to the Cochrane Collaboration's tool for assessing the risk of bias. NMA will be performed in a Bayesian hierarchical framework using R (version 3.6.1) and STATA (version 16.0). Finally, we will rank the efficacy of these treatment programs according to the surface under the cumulative ranking curve (SUCRA), and perform quality assessment and recommendation grading of the evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Ethics and dissemination: This study will extract data from published literature and not involve private information from individuals or compromise their rights. Therefore, the study does not require ethical approval. The results will eventually be published in a peer-reviewed journal and disseminated at relevant conferences.

Strengths and limitations of this study

- Compared with traditional pairwise meta-analysis, NMA can comprehensively analyze direct and indirect comparison results of different TCMIs for HF to obtain more reliable conclusions.
- Compared with traditional pairwise meta-analysis, NMA can compare and rank the efficacy of different TCMIs for HF.
- This study can provide more comprehensive suggestions and references for clinical decision-making and guideline development.
- This study did not further explore the efficacy of drugs based on different TCM syndrome types.
- This study did not explore the economic benefits of these drugs, and further exploration can be done based on the results of this study.

INTRODUCTION

Heart failure (HF) is a complex set of clinical syndromes caused by abnormal changes in the structure and/or function of the heart that impair ventricular contraction and/or diastolic function.[1] HF is a severe end-stage of heart disease. Due to the high mortality rate, HF has become an important public health issue in global public health.[2] According to the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure, current treatment options for HF are diverse, generally including cardiotonic, diuretic, vasodilator, angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), β-blocker, and so on. Modern medicine has made great progress in the field of HF, but the prognosis of HF patients is still not satisfactory, resulting in a heavy global burden.[3, 4] The development of new therapeutic drugs is an inevitable trend of future medical development. The research and development of traditional Chinese medicine (TCM) provide more possibilities for improving the prognosis of HF patients. TCM has

the advantages of multi-target effect and bidirectional regulation, so it has received more and more attention in the global medical field.[5-7] With the development of modernization of TCM, more and more traditional Chinese medicine injections (TCMIs) for the treatment of HF have been developed and widely used in clinical practice. Many studies have shown that loading TCMIs based on conventional pharmacotherapy (CPT) can effectively improve the clinical symptoms, reduce the incidence of cardiovascular events and adverse reactions in HF patients.[8-17] However, due to the lack of direct comparison studies between TCMIs, the comparison results between TCMIs are unclear. Therefore, although the increasing variety of drugs has provided doctors and patients with more choices, it is also a new challenge to choose the best treatment scheme at the same time.

Meta-analysis is one of the highest levels of evidence in evidence-based research. However, it is difficult to compare the effects of multiple drugs at the same time by traditional pairwise meta-analysis. Network meta-analysis (NMA) is a further development based on the traditional pairwise meta-analysis. Based on the current clinical research data, NMA can complete direct and indirect comparisons between different TCMIs at the same time, and further comprehensively analyze the results of the direct and indirect comparison, to obtain the efficacy ranking of multiple drugs. At present, some researchers have performed the NMA on randomized controlled trials (RCTs) of TCMIs for HF.[18, 19] However, there are some shortcomings in the published literature: ①The types of TCMIs included are not comprehensive. Only a few commonly used drugs have been studied, which severely limits the development and utilization of other potentially effective drugs. ②Results of the most important clinical outcomes have not been reported, such as all-cause mortality and rehospitalization rate. ③The research data has not been updated in the past two years. Therefore, we conceived and designed this study to make up for the above shortcomings. We will comprehensively retrieve relevant data to assess and compare the effectiveness and safety of different TCMIs for the treatment of HF using NMA. The results of this study will provide more timely and comprehensive evidence for clinical decision-making.

OBJECTIVES

We will perform Bayesian reticulated meta-analysis of different TCMIs for HF based on clinical RCTs and meta-analysis.[20, 21] The purpose is to explore the efficacy and safety of TCMIs in the treatment of HF, and to rank the clinical efficacy of drugs.

METHODS AND ANALYSIS

Inclusion and exclusion criteria

Type of participants

The included studies must indicate that participants have been diagnosed with HF. And HF patients cannot suffer from serious complications or other organic diseases. There are no restrictions on gender, age, race, duration of disease, source of the case, and follow-up time.

Type of interventions and comparisons

The following forms of intervention will be included: conventional pharmacotherapy (CPT) + TCMI versus CPT alone, CPT + TCMI versus CPT + placebo, CPT + TCMI A versus CPT + TCMI B. CPTs include cardiotonic, diuretic, vasodilator, angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), β-blocker, and so on. CPTs in the two groups should be the same. These TCMIs must have been included in *the Pharmacopoeia of the People's Republic of China* or approved by *the China Food and Drug Administration*. Neither the treatment group nor the control group can be combined with other TCM treatment methods, such as TCM decoction, oral Chinese patent medicine, acupuncture, etc.

Outcomes

Only studies using at least one of the following outcomes may be included.

▸Primary outcomes

It is measured by the proportion of patients with endpoint outcome events, including all-cause mortality and rehospitalization rate;

▸Secondary outcomes

Outcomes related to the following indicators will be included, including ①left ventricular ejection fraction (LVEF); ②left ventricular end-diastolic diameter (LVEDD); ③left ventricular end-systolic diameter (LVESD); ④brain natriuretic peptide (BNP); ⑤cardiac output (CO); ⑥stroke volume (SV); ⑦6 minutes walking distance.

▸Adverse events

The adverse events that occurred during the study period include allergic reactions, bleeding events, gastrointestinal discomfort, liver and kidney damage, and others.

Type of study

Randomized controlled trials (RCTs) that investigated the effectiveness and safety of TCHI for HF will be included.

Exclusion criteria

▸Interventions include other TCM treatment methods, such as TCM decoctions, oral Chinese patent medicines, acupuncture, and so on.

▸The full text cannot be obtained after seeking help online or contacting the corresponding author via email.

▸Studies that do not provide data for synthesis will be excluded.

▸Unfinished protocol.

Methods of obtaining data and analyzing data

Search strategy

The clinical RCTs and meta-analyses of TCMIs for treating HF will be searched in the relevant database, including PubMed, EMBASE, Cochrane Library (No.2 of 2020), Chinese BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI)、Wan Fang database and VIP database without language restriction. The retrieval time is from inception to February 29, 2020. Search terms include heart failure, traditional Chinese medicine injection, names of TCMIs that have been used in the clinic, randomized controlled trial, systemic review, meta-analysis, and their synonyms. The search strategy adopts a combination of Medical Subject Heading and free-text terms, and adopts different search strategies according to the characteristics of each database. The synonyms in the group are connected by “or”, and the search terms between the groups are connected by “and”. At the same time, we will also retrieve conference papers and dissertations, search and browse and review references of meta-analyses, conduct search engines such as Google Scholar to avoid omissions. The development of the search strategy has been completed by the researcher SS Lin with clinical work experience and the researcher QY Shi with evidence-based work experience, and has been modified according to the Cochrane Handbook for Systematic Reviews.[22] Take PubMed as an example. The detailed search strategy is shown in Annex 1.

Literature screening

Records from databases will be managed by NoteExpress (V3.2.0) software. First, we will import all retrieved records into NoteExpress and exclude duplicate records. Second, by reading the title and abstract of each record, we will exclude records that do not meet the inclusion and exclusion criteria. Finally, we will download and read the full texts of potentially relevant studies to perform the second screening. At the same time, the reasons for excluding records after reading the full text will be reported in detail. Literature screening will be done independently and cross-checked by two researchers (SS Lin and QY Shi). Disagreement will be determined through discussion between the two investigators. When consensus cannot be reached, a third investigator (FW Yang) will assist in the judgment. The literature screening based on PRISMA is shown in Figure 1.[23] In the early stage of the study, we will train the evaluators and conduct pre-tests to ensure a standardized screening process.

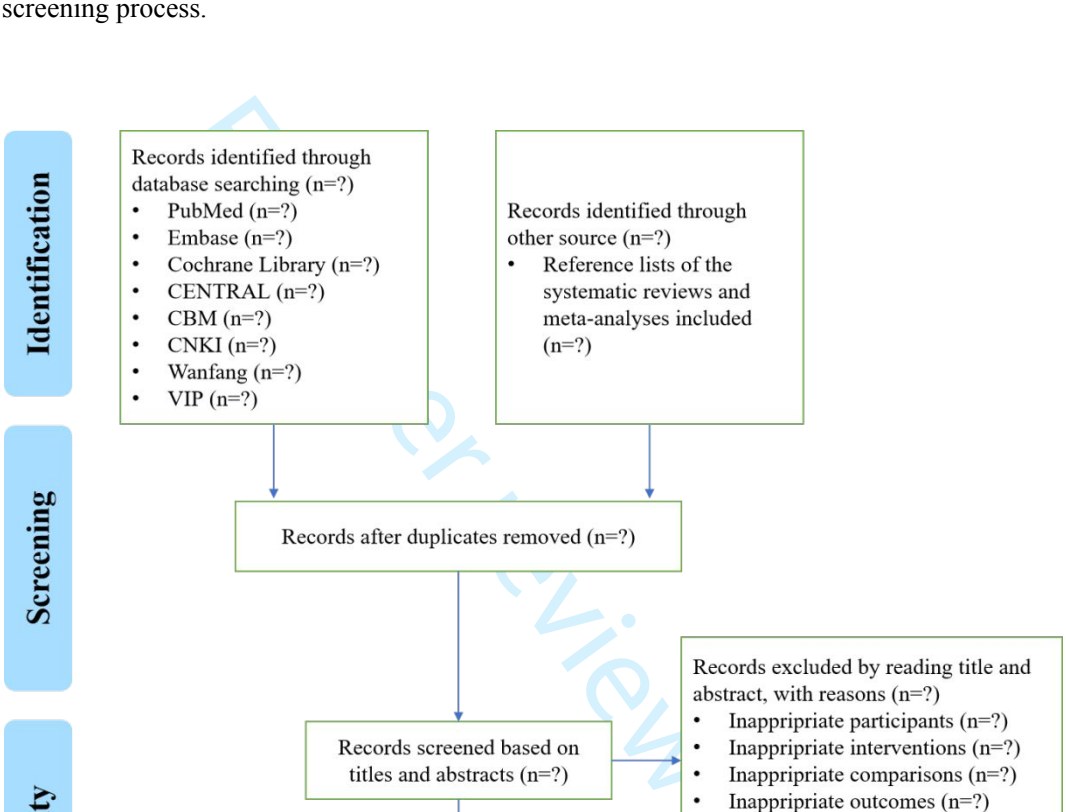

Figure 1 Proposed flowchart of the literature search process

Data extraction and management

Data extraction will be performed independently by two investigators (SS Lin and QY Shi) and cross-checked. Disagreement will be determined through discussion between the two investigators. When consensus cannot be reached, a third investigator (FW Yang) will assist in the judgment. The preset information extraction items are shown in Table 1.

Table 1 Information extraction items

Categories	Specific items
Study characteristics	title, first author, journal name, publication year, and type of study
Participants	diagnostic criteria, sample size, gender, age, ethnicity, case source, and baseline status
Intervention	drug name, medication route, drug dose, course of treatment, and patient compliance
Control	drug name, medication route, drug dose, course of treatment, and patient compliance
Outcomes	whether there is an intention-to-treat, loss to follow-up and withdrawal, outcomes
Risk of bias	random sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other bias
Others	author's main conclusions, funding, and others

Dealing with missing data

When data is missing, we will contact the original authors for complete data. If the missing value of outcomes cannot be obtained from the original author, we will delete the comparison results related to the missing data and fully consider the risk of bias. If baseline data cannot be obtained, multiple imputations will be used to handle missing values of the baseline data if necessary.

Assessment of risk of bias

According to the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials,[24] we will assess the risk of bias in the included literature from the following seven items: ①random sequence generation; ②allocation concealment; ③participant and personnel blinding; ④outcome assessment blinding; ⑤incomplete outcome data; ⑥selective reporting; and ⑦other bias. The results of the risk of bias assessment include the low risk of bias, the high risk of bias, and the unclear risk of bias. This process will be done independently by two investigators (SS Lin and QY Shi) and cross-checked. Disagreement will be determined through discussion between the two investigators. When consensus cannot be reached, a third investigator (FW Yang) will assist in the judgment. When there is a difference in the risk of bias between studies, we will try to analyze the impact of risk of bias. The risk of bias graph and the risk of bias summary will be generated by RevMan 5.3.

Data analysis

Pairwise meta-analysis and network meta-analysis

A Bayesian approach will be used to conduct pairwise meta-analyses and network meta-analyses according to the Markov chain Monte Carlo (MCMC) method.[21] In a Bayesian hierarchical framework, we will assume the vague prior distribution parameters for the between-study heterogeneity with uniform distribution in advance. The convergence of the model will be assessed using the Brooks-Gelman-Rubin plot.[25] Dichotomous variables will be presented as the relative risk (RR) or odds ratio (OR) with a 95% credible interval (CrI). Continuous variables will be presented as the weight mean difference (WMD) with a 95% CrI. The χ^2 test and I^2 test will be conducted to assess the potential heterogeneity. $P<0.05$ is considered statistically significant. To achieve the highest generalisability in the pooled treatment effects, a random-effects model will be used to synthesize the data for pairwise and network meta-analysis.[26] A pairwise meta-analysis will be conducted when at least two studies compared the same intervention and comparator. When the treatment nodes formed a network of evidence, we will do a TCMIs to compare different treatment programs using the common comparator or placebo. A network diagram of each outcome will be generated to visualize the connections between different treatment programs included. If direct evidence exists, NMA will conduct a comprehensive evaluation of direct and indirect comparative evidence. If direct comparison evidence is lacking, we will only make adjusted indirect comparisons. For each outcome, a contribution matrix will be performed to demonstrate the percentage contribution of each direct comparison to the whole evidence body. The efficacy of different treatment programs will be ranked according to the surface under the cumulative ranking curve (SUCRA).[27] The SUCRA is a value range from 0 to 1 and can be re-expressed as a percentage. The larger the SUCRA, the better the treatment regimen.

Examination of assumptions in network meta-analysis

Heterogeneity The Cochran Q statistics will be employed to assess heterogeneity.[28] If there is significant clinical heterogeneity or methodological heterogeneity ($P<0.1$, $I^2>50\%$), the subgroup analysis will be performed to explore sources of heterogeneity. To assess potential bias resulting from baseline risk, we will perform meta-regression with regressors which included age of participants, sample size, duration of disease, course of treatment, and so on. Besides, sensitivity analyses will be performed by excluding studies with a high risk of bias or poor-quality to judge the stability of the results.

Transitivity We will verify the transitivity of this network by plotting the central trends (eg, mean, median) of patient characteristics in each treatment comparison.

Consistency Node-splitting analysis will be used to split mixed evidence into direct evidence and indirect evidence to evaluate the inconsistency of the model. And then, we will compare the direct and indirect evidence. If there is no statistically significant difference between direct and indirect evidence, the study fits the consistency model. If the 95% CrI of the result does not include the invalid value, the inconsistency will be considered to exist.

Assessment of publication bias

The comparison-adjusted funnel plots will be obtained with the specific ranking order to detect small sample size study effects and publication bias.

All analyses will be conducted using R (version 3.6.1) and STATA (version 16.0).

Quality assessment and recommendation grading of the evidence

Two reviewers (SS Lin and QY Shi) will independently perform quality assessment and recommendation grading of the evidence of the direct, indirect and mixed estimates of all comparisons according to GRADE criteria. In particular, the GRADE system was used to rank the quality of evidence for direct comparison from four aspects: limitation, inconsistency, indirectness, and publication bias, but without imprecision.[31] The grading of the evidence quality includes four levels,

which are 'high', 'medium', 'low' or 'very low' according to the GRADE rating standards.[32, 33] High indicates that the authors are very confident that the real effect is close to the estimate of the effect. Moderate indicates that the authors are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low indicates that the authors` confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low indicates that the authors have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.[29] Cross-checking will be performed after the classification is completed. In case of disagreement, it will be decided by discussion between the two parties or judged by the third evaluator (FW Yang).

Ethics and dissemination This study will extract data from published literature and not involve private information from individuals or compromise their rights. Therefore, the study does not require ethical approval. The procedures of this systematic review and network meta-analysis will be conducted in accordance with the PRISMA guideline. Details of this study will be submitted to open access. The results will be published in a peer-reviewed journal and disseminated at relevant conferences.

Contributions SS Lin, JY Mao, and XL Wang conceived and designed the study together. SS Lin, QY Shi, and FW Yang developed the search strategy together. SS Lin drafted the protocol manuscript. All the authors have reviewed and approved the final manuscript.

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Competing interests None.

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Annex 1 Search Strategy in PubMed

Search	Query	Items found
#1	Heart Failure[MeSH Terms]	
#2	heart failure[Title/Abstract]	
#3	cardiac failure[Title/Abstract]	
#4	heart decompensation[Title/Abstract]	
#5	heart dysfunction[Title/Abstract]	
#6	cardiac dysfunction[Title/Abstract]	
#7	ventricular dysfunction[Title/Abstract]	
#8	heart dificiency[Title/Abstract]	
#9	cardiac dificiency[Title/Abstract]	
#10	heart insufficiency[Title/Abstract]	
#11	cardiac insufficiency[Title/Abstract]	
#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	
#13	Medicine, Chinese Traditional[Mesh]	
#14	traditional Chinese medicine[All Fields]	
#15	Chinese traditional medicine[All Fields]	
#16	Chinese medicine[All Fields]	
#17	Drugs, Chinese Herbal[Mesh]	
#18	Chinese herbal drug$[All Fields]	
#19	Chinese herbal medicine[All Fields]	
#20	Chinese patent drug$[All Fields]	
#21	Chinese patent medicine[All Fields]	
#22	Chinese proprietary drug[All Fields]	
#23	Chinese proprietary medicine[All Fields]	
#24	Chinese crude drug$[All Fields]	
#25	Chinese materia medica[All Fields]	
#26	traditional Chinese medicine patent prescription$[All Fields]	
#27	traditional Chinese patent medicines and simple preparations[All Fields]	

#28	traditional Chinese medicine injection$[All Fields]
#29	Chinese medicine injection$[All Fields]
#30	Complementary Therapies[MeSH]
#31	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
#32	Injections[MeSH]
#33	injection$[Title/Abstract]
#34	injectable$[Title/Abstract]
#35	#32 OR #33 OR #34
#36	Randomized Controlled Trials as Topic[Mesh]
#37	Randomized Controlled Trial[Publication Type]
#38	Controlled Clinical Trial[Publication Type]
#39	Equivalence Trial[Publication Type]
#40	randomized controlled trial[Title/Abstract]
#41	Random Allocation[Mesh]
#42	Double-Blind Method[Mesh]
#43	Single-Blind Method[Mesh]
#44	Clinical Trial[Publication Type]
#45	Research Design[Mesh]
#46	Placebos[Mesh]
#47	placebo$[Title/Abstract]
#48	random*[Title/Abstract]
#49	trial$[Title]
#50	#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR#43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49
#51	Systemic Review[Publication Type]
#52	systemic review[Title/Abstract]
#53	systemic literature review[Title/Abstract]
#54	Meta Analysis[Publication Type]
#55	Meta analysis[Title/Abstract]

#56	Meta-analysis[Publication Type]
#57	Meta-analysis[Title/Abstract]
#58	pooled analysis[Title/Abstract]
#59	Consensus Development Conference as Topic[Mesh]
#60	Consensus Development Conference[Publication Type]
#61	consensus development conference[Title/Abstract]
#62	expert consensus[Title/Abstract]
#63	Practice Guideline as Topic[Mesh]
#64	Practice Guideline[Publication Type]
#65	practice guideline[Title/Abstract]
#66	Cochrane database systemic review[Title/Abstract]
#67	Evidence-based Medicine[Mesh]
#68	evidence-based medicine[Title/Abstract]
#69	best practice[Title/Abstract]
#70	evidence synthesis[Title/Abstract]
#71	synthesis analysis[Title/Abstract]
#72	#51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71
#73	#12 AND #31 AND #35 AND #50 AND #72

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Traditional Chinese medicine injections for heart failure: a protocol for systematic review and network meta-analysis of randomized controlled trials

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Traditional Chinese medicine injections for heart failure: a protocol for systematic review and network meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Heart failure (HF) has always been an important issue in global public health. The research and development of traditional Chinese medicine (TCM) provide more possibilities for improving the prognosis of HF patients. Because multiple traditional Chinese medicine injections (TCMIs) are being widely applied in clinical work, it is important to choose the right TCMIs for HF patients. The purpose of this study is to assess and compare the effect of different TCMIs for HF using network meta-analysis (NMA) and further provide references for clinical decision-making.

Methods and analysis: The clinical randomized controlled trials (RCTs) and meta-analyses of TCMIs for treating HF will be searched in the relevant database, including PubMed, EMBASE, Cochrane Library (No.2 of 2020), Chinese BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Wan Fang database and VIP database from inception to February 29, 2020. The outcomes of interest include all-cause mortality, rehospitalization rate, left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), cardiac output (CO), stroke volume (SV), 6 minutes walking distance, and adverse events. The risk of bias assessment of the included RCTs will be conducted according to the Cochrane Collaboration's tool for assessing the risk of bias. NMA will be performed in a Bayesian hierarchical framework using R (version 3.6.1) with the *gemtc* package. Finally, we will rank the efficacy of these treatment programs according to the surface under the cumulative ranking curve (SUCRA), and perform quality assessment and recommendation grading of the evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Ethics and dissemination: This study will extract data from published literature and not involve private information from individuals or compromise their rights. Therefore, the study does not require ethical approval. The results will eventually be published in a peer-reviewed journal and disseminated at relevant conferences.

Strengths and limitations of this study

- Compared with traditional pairwise meta-analysis, NMA can comprehensively analyze direct and indirect comparison results of different TCMIs for HF to obtain more reliable conclusions.
- Compared with traditional pairwise meta-analysis, NMA can compare and rank the efficacy of different TCMIs for HF.
- This study can provide more comprehensive suggestions and references for clinical decision-making and guideline development.
- This study did not further explore the efficacy of drugs based on different TCM syndrome types.
- This study did not explore the economic benefits of these drugs, and further exploration can be done based on the results of this study.

INTRODUCTION

Heart failure (HF) is a complex set of clinical syndromes caused by abnormal changes in the structure and/or function of the heart that impair ventricular contraction and/or diastolic function.[1] HF is a severe end-stage of heart disease. Due to the high mortality rate, HF has become an important issue in global public health.[2] According to the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure, current treatment options for HF are diverse, generally including cardiotonic, diuretic, vasodilator, angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), β-blocker, and so on. Modern medicine has made great progress in the field of HF, but the prognosis of HF patients is still not satisfactory, resulting in a heavy global burden.[3, 4] The development of new therapeutic drugs is an inevitable trend of future medical development. The research and development of traditional

Chinese medicine (TCM) provide more possibilities for improving the prognosis of HF patients. TCM has the advantages of multi-target effect and bidirectional regulation, so there has been increasing attention in the global medical field.[5-7] With the development of modernization of TCM, more and more traditional Chinese medicine injections (TCMIs) for the treatment of HF have been developed and widely used in clinical practice. Many studies have shown that loading TCMIs based on conventional pharmacotherapy (CPT) can effectively improve the clinical symptoms and reduce the incidence of cardiovascular events and adverse reactions in HF patients.[8-17] However, due to the lack of direct comparison studies between TCMIs, the comparative results between TCMIs are unclear. Therefore, although the increasing variety of drugs has provided doctors and patients with more choices, meanwhile it is also a new challenge to choose the best treatment scheme at the same time.

Meta-analysis is one of the highest levels of evidence in evidence-based research. However, it is difficult to compare the effects of multiple drugs at the same time by traditional pairwise meta-analysis. Network meta-analysis (NMA) is a further development based on the traditional pairwise meta-analysis. Based on the current clinical research data, NMA can complete direct and indirect comparisons among different TCMIs at the same time, and further comprehensively analyze the results of the direct and indirect comparison, to obtain the efficacy ranking of multiple drugs. At present, some researchers have performed the NMA on randomized controlled trials (RCTs) of TCMIs for HF.[18, 19] However, there are some shortcomings in the published literature: ①The types of TCMIs included are not comprehensive. Only a few commonly used drugs have been studied, which severely limits the development and utilization of other potentially effective drugs. ②Results of the most important clinical outcomes have not been reported, such as all-cause mortality and rehospitalization rate. ③The research data has not been updated in the past two years. Therefore, we conceived and designed this study to make up for the above shortcomings. We will comprehensively retrieve relevant data to assess and compare the effectiveness and safety of different TCMIs for the treatment of HF using NMA. The results of this study will provide more updated comprehensive evidence for clinical decision-making.

OBJECTIVES

We will systematically search all clinical RCTs on TCMIs for HF and perform a Bayesian network meta-analysis.[20, 21] The purpose is to explore the efficacy and safety of TCMIs in the treatment of HF, and to rank the clinical efficacy of drugs.

METHODS AND ANALYSIS

Patient and public involvement

No patient involved.

Inclusion and exclusion criteria for clinical RCTs

Type of participants

The included studies must indicate that participants meet the diagnostic criteria for HF in the "Guidelines for diagnosis and treatment of heart failure in China 2018" or "2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure".[1, 2] Primary diseases include coronary heart disease, hypertension, dilated cardiomyopathy, and rheumatic heart disease. There are no restrictions on gender, age, race, duration of disease, source of the case, and follow-up time.

Type of interventions and comparisons

The following forms of intervention will be included: conventional pharmacotherapy (CPT) + TCMI versus CPT alone, CPT + TCMI versus CPT + placebo, CPT + TCMI A versus CPT + TCMI B. CPTs include cardiotonic, diuretic, vasodilator, angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), β-blocker, and so on.

And CPTs in the two groups should be the same. TCMIs must have been included in *the Pharmacopoeia of the People's Republic of China* or approved by *the China Food and Drug Administration*. All retrieved eligible TCMIs may be included in the study, but TCMIs without literature support will not be compared and ranked.

Outcomes

Only studies using at least one of the following outcomes may be included.

▸Primary outcomes

①All-cause mortality during different follow-up periods - e.g. 3 months; 6 months; 1 year or other periods

②Rehospitalization rate during different follow-up periods - e.g. 3 months; 6 months; 1 year or other periods

▸Secondary outcomes

①Left ventricular ejection fraction (LVEF)

②Left ventricular end-diastolic diameter (LVEDD)

③Left ventricular end-systolic diameter (LVESD)

④Brain natriuretic peptide (BNP)

⑤N-terminal pro-brain natriuretic peptide (NT-proBNP)

⑥Cardiac output (CO)

⑦Stroke volume (SV)

⑧6-minute walking test (6MWT)

▸Adverse events

The adverse events that occurred during the study period include allergic reactions, bleeding events, gastrointestinal discomfort, liver and kidney damage, and others.

Type of study

Randomized controlled trials (RCTs) that investigated the effectiveness and safety of TCHI for HF will be included.

Exclusion criteria

▸Participants are any of the following: the primary disease is congenital heart disease, pulmonary heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, systemic invasive disease, hyperthyroid heart disease, alcoholic myocardium disease, perinatal cardiomyopathy, drug-induced cardiomyopathy, Keshan disease.

▸Participants are any of the following: heart failure with malignant arrhythmias, malignant tumors, hypothyroidism, severe liver and kidney dysfunction, or severe infections.

▸Studies on the mixed efficacy of TCHIs combined with other TCM treatments will be excluded. For example, interventions have combined TCM decoctions, oral Chinese patent medicines, acupuncture, etc.

▸None of the outcome indicators for this study.

- The full text cannot be obtained after seeking help online or contacting the corresponding author via email.
- The data are incomplete or incorrect, and the data cannot be used for synthesis.
- Studies with imbalanced or incomparable baseline data between the two groups.
- For duplicate literature, choose the one published earlier.
- Unfinished protocol.

Methods of obtaining data and analyzing data

Search strategy

The clinical RCTs and meta-analyses of TCMIs for treating HF will be searched in the relevant database, including PubMed, EMBASE, Cochrane Library (No.2 of 2020), Chinese BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI)、Wan Fang database and VIP database without language restriction. The retrieval time is from inception to February 29, 2020. Search terms include heart failure, traditional Chinese medicine injection, names of TCMIs that have been used in the clinic, randomized controlled trial, systemic review, meta-analysis, and their synonyms. The search strategy adopts a combination of Medical Subject Heading and free-text terms, and adopts different search strategies according to the characteristics of each database. The synonyms in the group are connected by "or", and the search terms between the groups are connected by "and". At the same time, we will also retrieve conference papers and dissertations, search and browse and review references of meta-analyses, conduct search engines such as Google Scholar to avoid omissions. The development of the search strategy has been completed by the researcher SS Lin with clinical work experience and the researcher QY Shi with evidence-based work experience, and has been modified according to the Cochrane Handbook for Systematic Reviews.[22] Take PubMed as an example. The detailed search strategy is shown in Annex 1.

Literature screening

Records from databases will be managed by NoteExpress (V3.2.0) software. First, we will import all retrieved records into NoteExpress and exclude duplicate records. Second, by reading the title and abstract of each record, we will exclude records that do not meet the inclusion and exclusion criteria. Finally, we will download and read the full texts of potentially relevant studies to perform the second screening. At the same time, the reasons for excluding records after reading the full text will be reported in detail. Literature screening will be done independently and cross-checked by two researchers (SS Lin and QY Shi). Disagreement will be determined through discussion between the two investigators. When consensus cannot be reached, a third investigator (FW Yang) will assist in the judgment. The literature screening based on PRISMA is shown in Figure 1.[23] In the early stage of the study, we will train the evaluators and conduct pre-tests to ensure a standardized screening process.

Data extraction and management

Data extraction will be performed independently by two investigators (SS Lin and QY Shi) and cross-checked. Disagreement will be determined through discussion between the two investigators. When consensus cannot be reached, a third investigator (FW Yang) will assist in the judgment. The preset information extraction items are shown in Table 1.

Table 1 Information extraction items

Categories	Specific items
Study characteristics	title, first author, journal name, publication year, and type of study
Participants	diagnostic criteria, sample size, gender, age, ethnicity, case source, and baseline status
Intervention	drug name, medication route, drug dose, course of treatment, and patient compliance
Control	drug name, medication route, drug dose, course of treatment, and patient compliance
Outcomes	whether there is an intention-to-treat, loss to follow-up and withdrawal, outcomes
Risk of bias	random sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other bias
Others	author's main conclusions, funding, and others

Dealing with missing data

When data is missing, we will contact the original authors for complete data. If the missing value of outcomes cannot be obtained from the original author, we will delete the comparison results related to the missing data and fully consider the risk of bias.

Assessment of risk of bias

According to the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials,[24] we will assess the risk of bias in the included literature from the following seven items: ①random sequence generation; ②allocation concealment; ③participant and personnel blinding; ④outcome assessment blinding; ⑤incomplete outcome data;

⑥selective reporting; and ⑦other bias. The results of the risk of bias assessment include the low risk of bias, the high risk of bias, and the unclear risk of bias. This process will be done independently by two investigators (SS Lin and QY Shi) and cross-checked. Disagreement will be determined through discussion between the two investigators. When consensus cannot be reached, a third investigator (FW Yang) will assist in the judgment. When there is a difference in the risk of bias between studies, we will try to analyze the impact of risk of bias. The risk of bias graph and the risk of bias summary will be generated by RevMan 5.3.

Data analysis

Pairwise meta-analysis and network meta-analysis

A Bayesian approach will be used to conduct pairwise meta-analyses and network meta-analyses according to the Markov chain Monte Carlo (MCMC) method.[21] In a Bayesian hierarchical framework, we will assume the vague prior distribution parameters for the between-study heterogeneity with uniform distribution in advance. The convergence of the model will be assessed using the Brooks-Gelman-Rubin plot.[25] Dichotomous variables will be presented as the relative risk (RR) or odds ratio (OR) with a 95% credible interval (CrI). Continuous variables will be presented as the weight mean difference (WMD) with a 95% CrI. The χ^2 test and I^2 test will be conducted to assess the potential heterogeneity. $P<0.05$ is considered statistically significant. To achieve the highest generalisability in the pooled treatment effects, a random-effects model will be used to synthesize the data for pairwise and network meta-analysis.[26] A pairwise meta-analysis will be conducted when at least two studies compared the same intervention and comparator. When the treatment nodes formed a network of evidence, we will do a TCMIs to compare different treatment programs using the common comparator or placebo. A network diagram of each outcome will be generated to visualize the connections between different treatment programs included. If direct evidence exists, NMA will conduct a comprehensive evaluation of direct and indirect comparative evidence. If direct comparison evidence is lacking, we will only make adjusted indirect comparisons. For each outcome, a contribution matrix will be performed to demonstrate the percentage contribution of each direct comparison to the whole evidence body. The efficacy of different treatment programs will be ranked according to the surface under the cumulative ranking curve (SUCRA).[27] The SUCRA is a value range from 0 to 1 and can be re-expressed as a percentage. The larger the SUCRA, the better the treatment regimen.

Examination of assumptions in network meta-analysis

Heterogeneity The Cochran Q statistics will be employed to assess heterogeneity.[28] If there is significant clinical heterogeneity or methodological heterogeneity ($P<0.1$, $I^2>50\%$), the subgroup analysis will be performed to explore sources of heterogeneity. To assess potential bias resulting from baseline risk, we will perform meta-regression with regressors which included age of participants, sample size, duration of disease, course of treatment, and so on. Besides, sensitivity analyses will be performed by excluding studies with a high risk of bias or poor-quality to judge the stability of the results.

Transitivity We will verify the transitivity of this network by plotting the central trends (e.g. mean, median) of patient characteristics in each treatment comparison.

Consistency Node-splitting analysis will be used to split mixed evidence into direct evidence and indirect evidence to evaluate the inconsistency of the model. And then, we will compare the direct and indirect evidence. If there is no statistically significant difference between direct and indirect evidence, the study fits the consistency model. If the 95% CrI of the result does not include the invalid value, the inconsistency will be considered to exist.

Assessment of publication bias

The comparison-adjusted funnel plots will be obtained with the specific ranking order to detect small sample size study effects and publication bias.

All analyses will be conducted using R (version 3.6.1) with the *gemtc* package.

Quality assessment and recommendation grading of the evidence

Two reviewers (SS Lin and QY Shi) will independently perform quality assessment and recommendation grading of the evidence of the direct, indirect and mixed estimates of all comparisons according to GRADE criteria.[29, 30] In particular, the GRADE system was used to rank the quality of evidence for direct comparison from four aspects: limitation, inconsistency, indirectness, and publication bias, but without imprecision.[31] The grading of the evidence quality includes four levels, which are 'high', 'medium', 'low' or 'very low' according to the GRADE rating standards.[32, 33] High indicates that the authors are very confident that the real effect is close to the estimate of the effect. Moderate indicates that the authors are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low indicates that the authors` confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low indicates that the authors have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.[29] Cross-checking will be performed after the classification is completed. In case of disagreement, it will be decided by discussion between the two parties or judged by the third evaluator (FW Yang).

Ethics and dissemination This study will extract data from published literature and not involve private information from individuals or compromise their rights. Therefore, the study does not require ethical approval. The procedures of this systematic review and network meta-analysis will be conducted in accordance with the PRISMA guideline. Details of this study will be submitted to open access. The results will be published in a peer-reviewed journal and disseminated at relevant conferences.

Contributions SS Lin, JY Mao, and XL Wang conceived and designed the study together. SS Lin, QY Shi, and FW Yang developed the search strategy together. SS Lin drafted the protocol manuscript. All the authors have reviewed and approved the final manuscript.

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Competing interests None.

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Figure caption

Figure 1 Proposed flowchart of the literature search process

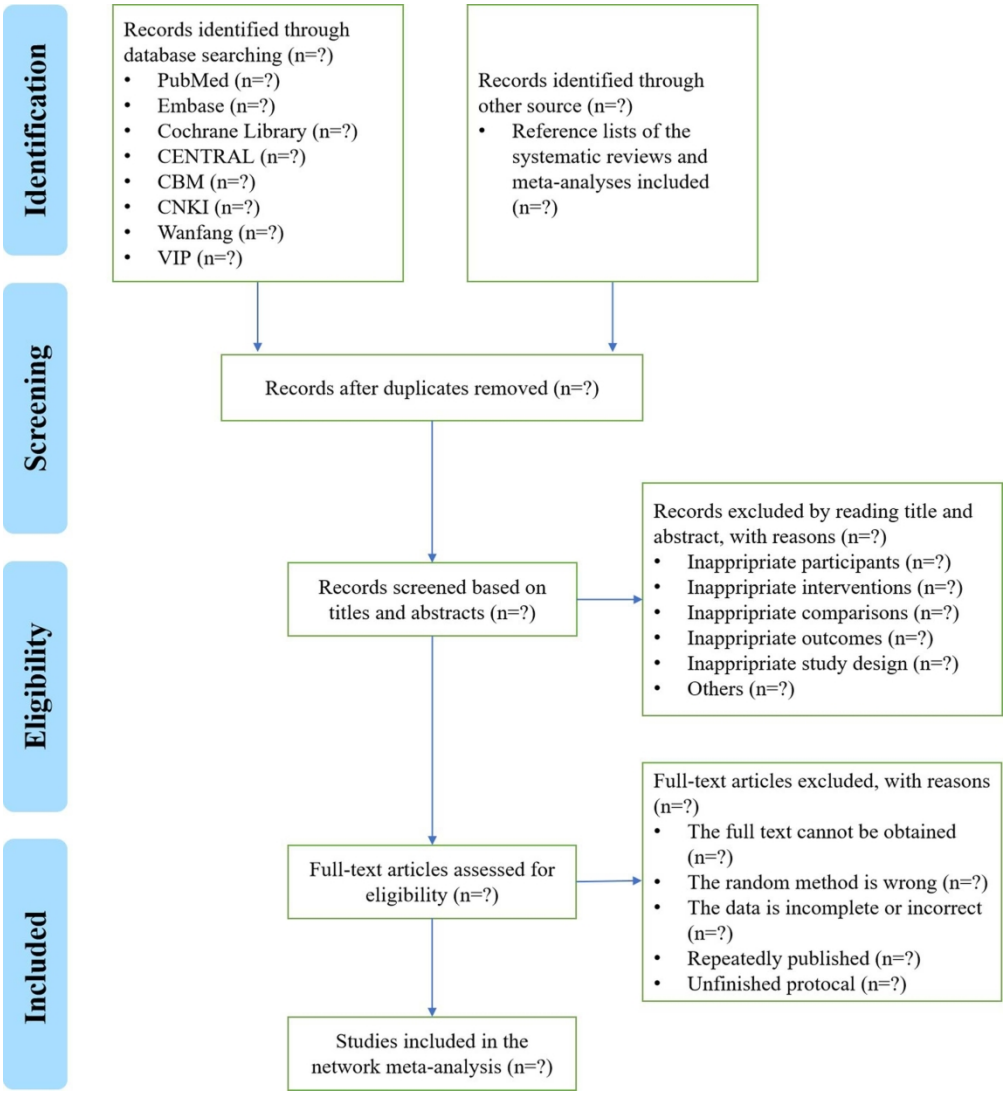

Figure 1 Proposed flowchart of the literature search process

234x254mm (300 x 300 DPI)

Annex 1 Search Strategy in PubMed

Search	Query	Items found
#1	Heart Failure[MeSH Terms]	
#2	heart failure[Title/Abstract]	
#3	cardiac failure[Title/Abstract]	
#4	heart decompensation[Title/Abstract]	
#5	heart dysfunction[Title/Abstract]	
#6	cardiac dysfunction[Title/Abstract]	
#7	ventricular dysfunction[Title/Abstract]	
#8	heart dificiency[Title/Abstract]	
#9	cardiac dificiency[Title/Abstract]	
#10	heart insufficiency[Title/Abstract]	
#11	cardiac insufficiency[Title/Abstract]	
#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	
#13	Medicine, Chinese Traditional[Mesh]	
#14	traditional Chinese medicine[All Fields]	
#15	Chinese traditional medicine[All Fields]	
#16	Chinese medicine[All Fields]	
#17	Drugs, Chinese Herbal[Mesh]	
#18	Chinese herbal drug$[All Fields]	
#19	Chinese herbal medicine[All Fields]	
#20	Chinese patent drug$[All Fields]	
#21	Chinese patent medicine[All Fields]	
#22	Chinese proprietary drug[All Fields]	
#23	Chinese proprietary medicine[All Fields]	
#24	Chinese crude drug$[All Fields]	
#25	Chinese materia medica[All Fields]	
#26	traditional Chinese medicine patent prescription$[All Fields]	
#27	traditional Chinese patent medicines and simple preparations[All Fields]	
#28	traditional Chinese medicine injection$[All Fields]	
#29	Chinese medicine injection$[All Fields]	
#30	Complementary Therapies[MeSH]	
#31	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	
#32	Injections[MeSH]	
#33	injection$[Title/Abstract]	
#34	injectable$[Title/Abstract]	
#35	#32 OR #33 OR #34	
#36	Randomized Controlled Trials as Topic[Mesh]	
#37	Randomized Controlled Trial[Publication Type]	
#38	Controlled Clinical Trial[Publication Type]	
#39	Equivalence Trial[Publication Type]	
#40	randomized controlled trial[Title/Abstract]	
#41	Random Allocation[Mesh]	
#42	Double-Blind Method[Mesh]	
#43	Single-Blind Method[Mesh]	
#44	Clinical Trial[Publication Type]	

#45	Research Design[Mesh]
#46	Placebos[Mesh]
#47	placebo$[Title/Abstract]
#48	random*[Title/Abstract]
#49	trial$[Title]
#50	#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR#43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49
#51	Systemic Review[Publication Type]
#52	systemic review[Title/Abstract]
#53	systemic literature review[Title/Abstract]
#54	Meta Analysis[Publication Type]
#55	Meta analysis[Title/Abstract]
#56	Meta-analysis[Publication Type]
#57	Meta-analysis[Title/Abstract]
#58	pooled analysis[Title/Abstract]
#59	Consensus Development Conference as Topic[Mesh]
#60	Consensus Development Conference[Publication Type]
#61	consensus development conference[Title/Abstract]
#62	expert consensus[Title/Abstract]
#63	Practice Guideline as Topic[Mesh]
#64	Practice Guideline[Publication Type]
#65	practice guideline[Title/Abstract]
#66	Cochrane database systemic review[Title/Abstract]
#67	Evidence-based Medicine[Mesh]
#68	evidence-based medicine[Title/Abstract]
#69	best practice[Title/Abstract]
#70	evidence synthesis[Title/Abstract]
#71	synthesis analysis[Title/Abstract]
#72	#51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71
#73	#12 AND #31 AND #35 AND #50 AND #72

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Traditional Chinese medicine injections for heart failure: a protocol for systematic review and network meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Heart failure (HF) has always been an important issue in global public health. The research and development of traditional Chinese medicine (TCM) provide more possibilities for improving the prognosis of HF patients. Because multiple traditional Chinese medicine injections (TCMIs) are being widely applied in clinical work, it is important to choose the right TCMIs for HF patients. The purpose of this study is to assess and compare the effect of different TCMIs for HF using network meta-analysis (NMA) and further provide references for clinical decision-making.

Methods and analysis: The clinical randomized controlled trials (RCTs) and meta-analyses of TCMIs for treating HF will be searched in the relevant database, including PubMed, EMBASE, Cochrane Library (No.2 of 2020), Chinese BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Wan Fang database and VIP database from inception to February 29, 2020. The outcomes of interest include all-cause mortality, rehospitalization rate, left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), cardiac output (CO), stroke volume (SV), 6 minutes walking distance, and adverse events. The risk of bias assessment of the included RCTs will be conducted according to the Cochrane Collaboration's tool for assessing the risk of bias. NMA will be performed in a Bayesian hierarchical framework using R (version 3.6.1) with the *gemtc* package. Finally, we will rank the efficacy of these treatment programs according to the surface under the cumulative ranking curve (SUCRA), and perform quality assessment and recommendation grading of the evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Ethics and dissemination: This study will extract data from published literature and not involve private information from individuals or compromise their rights. Therefore, the study does not require ethical approval. The results will eventually be published in a peer-reviewed journal and disseminated at relevant conferences.

PROSPERO registration number: CRD42020166900.

Strengths and limitations of this study

▪ Compared with traditional pairwise meta-analysis, NMA can comprehensively analyze direct and indirect comparison results of different TCMIs for HF to obtain more reliable conclusions.

▪ Compared with traditional pairwise meta-analysis, NMA can compare and rank the efficacy of different TCMIs for HF.

▪ This study can provide more comprehensive suggestions and references for clinical decision-making and guideline development.

▪ Since most TCMIs and clinical trials will come from China, the conclusion may have certain limitations.

▪ This study did not explore the economic benefits of these drugs, and further exploration can be done based on the results of this study.

INTRODUCTION

Heart failure (HF) is a complex set of clinical syndromes caused by abnormal changes in the structure and/or function of the heart that impair ventricular contraction and/or diastolic function.[1] HF is a severe end-stage of heart disease. Due to the high mortality rate, HF has become an important issue in global public health.[2] According to the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure, current treatment options for HF are diverse, generally including cardiotonic, diuretic, vasodilator, angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), β-blocker, and so on. Modern medicine has made great progress in the field of HF,

but the prognosis of HF patients is still not satisfactory, resulting in a heavy global burden.[3, 4] The development of new therapeutic drugs is an inevitable trend of future medical development. The research and development of traditional Chinese medicine (TCM) provide more possibilities for improving the prognosis of HF patients. TCM has the advantages of multi-target effect and bidirectional regulation, so there has been increasing attention in the global medical field.[5-7] With the development of modernization of TCM, more and more traditional Chinese medicine injections (TCMIs) for the treatment of HF have been developed and widely used in clinical practice. Many studies have shown that loading TCMIs based on conventional pharmacotherapy (CPT) can effectively improve the clinical symptoms and reduce the incidence of cardiovascular events and adverse reactions in HF patients.[8-17] However, due to the lack of direct comparison studies between TCMIs, the comparative results between TCMIs are unclear. Therefore, although the increasing variety of drugs has provided doctors and patients with more choices, meanwhile it is also a new challenge to choose the best treatment scheme at the same time.

Meta-analysis is one of the highest levels of evidence in evidence-based research. However, it is difficult to compare the effects of multiple drugs at the same time by traditional pairwise meta-analysis. Network meta-analysis (NMA) is a further development based on the traditional pairwise meta-analysis. Based on the current clinical research data, NMA can complete direct and indirect comparisons among different TCMIs at the same time, and further comprehensively analyze the results of the direct and indirect comparison, to obtain the efficacy ranking of multiple drugs. At present, some researchers have performed the NMA on randomized controlled trials (RCTs) of TCMIs for HF.[18, 19] However, there are some shortcomings in the published literature: ①The types of TCMIs included are not comprehensive. Only a few commonly used drugs have been studied, which severely limits the development and utilization of other potentially effective drugs. ②Results of the most important clinical outcomes have not been reported, such as all-cause mortality and rehospitalization rate. ③The research data has not been updated in the past two years. Therefore, we conceived and designed this study to make up for the above shortcomings. We will comprehensively retrieve relevant data to assess and compare the effectiveness and safety of different TCMIs for the treatment of HF using NMA. The results of this study will provide more updated comprehensive evidence for clinical decision-making.

OBJECTIVES

We will systematically search all clinical RCTs on TCMIs for HF and perform a Bayesian network meta-analysis.[20, 21] The purpose is to explore the efficacy and safety of TCMIs in the treatment of HF, and to rank the clinical efficacy of drugs.

METHODS AND ANALYSIS

Patient and public involvement

Patients and the public were not involved in the design or conduct of the study.

Inclusion and exclusion criteria for clinical RCTs

Type of participants

The included studies must indicate that participants meet the diagnostic criteria for HF in the "Guidelines for diagnosis and treatment of heart failure in China 2018" or "2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure".[1, 2] Primary diseases include coronary heart disease, hypertension, dilated cardiomyopathy, and rheumatic heart disease. There are no restrictions on gender, age, race, duration of disease, source of the case, and follow-up time.

Type of interventions and comparisons

The following forms of intervention will be included: conventional pharmacotherapy (CPT) + TCMI versus CPT alone,

CPT + TCMI versus CPT + placebo, CPT + TCMI A versus CPT + TCMI B. CPTs include cardiotonic, diuretic, vasodilator, angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), β-blocker, and so on. And CPTs in the two groups should be the same. TCMIs must have been included in *the Pharmacopoeia of the People's Republic of China* or approved by *the China Food and Drug Administration*. All retrieved eligible TCMIs may be included in the study, but TCMIs without literature support will not be compared and ranked.

Outcomes

Only studies using at least one of the following outcomes may be included.

▸Primary outcomes

①All-cause mortality during different follow-up periods - e.g. 3 months; 6 months; 1 year or other periods

②Rehospitalization rate during different follow-up periods - e.g. 3 months; 6 months; 1 year or other periods

▸Secondary outcomes

①Left ventricular ejection fraction (LVEF)

②Left ventricular end-diastolic diameter (LVEDD)

③Left ventricular end-systolic diameter (LVESD)

④Brain natriuretic peptide (BNP)

⑤N-terminal pro-brain natriuretic peptide (NT-proBNP)

⑥Cardiac output (CO)

⑦Stroke volume (SV)

⑧6-minute walking test (6MWT)

▸Adverse events

The adverse events that occurred during the study period include allergic reactions, bleeding events, gastrointestinal discomfort, liver and kidney damage, and others.

Type of study

Randomized controlled trials (RCTs) that investigated the effectiveness and safety of TCHI for HF will be included.

Exclusion criteria

▸Participants are any of the following: the primary disease is congenital heart disease, pulmonary heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, systemic invasive disease, hyperthyroid heart disease, alcoholic myocardium disease, perinatal cardiomyopathy, drug-induced cardiomyopathy, Keshan disease.

▸Participants are any of the following: heart failure with malignant arrhythmias, malignant tumors, hypothyroidism, severe liver and kidney dysfunction, or severe infections.

▸Studies on the mixed efficacy of TCHIs combined with other TCM treatments will be excluded. For example, interventions have combined TCM decoctions, oral Chinese patent medicines, acupuncture, etc.

- None of the outcome indicators for this study.
- The full text cannot be obtained after seeking help online or contacting the corresponding author via email.
- The data are incomplete or incorrect, and the data cannot be used for synthesis.
- Studies with imbalanced or incomparable baseline data between the two groups.
- For duplicate literature, choose the one published earlier.
- Unfinished protocol.

Methods of obtaining data and analyzing data

Search strategy

The clinical RCTs and meta-analyses of TCMIs for treating HF will be searched in the relevant database, including PubMed, EMBASE, Cochrane Library (No.2 of 2020), Chinese BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI)、Wan Fang database and VIP database without language restriction. The retrieval time is from inception to February 29, 2020. Search terms include heart failure, traditional Chinese medicine injection, names of TCMIs that have been used in the clinic, randomized controlled trial, systemic review, meta-analysis, and their synonyms. The search strategy adopts a combination of Medical Subject Heading and free-text terms, and adopts different search strategies according to the characteristics of each database. The synonyms in the group are connected by "or", and the search terms between the groups are connected by "and". At the same time, we will also retrieve conference papers and dissertations, search and browse and review references of meta-analyses, conduct search engines such as Google Scholar to avoid omissions. The development of the search strategy has been completed by the researcher SS Lin with clinical work experience and the researcher QY Shi with evidence-based work experience, and has been modified according to the Cochrane Handbook for Systematic Reviews.[22] Take PubMed as an example. The detailed search strategy is shown in Annex 1.

Literature screening

Records from databases will be managed by NoteExpress (V3.2.0) software. First, we will import all retrieved records into NoteExpress and exclude duplicate records. Second, by reading the title and abstract of each record, we will exclude records that do not meet the inclusion and exclusion criteria. Finally, we will download and read the full texts of potentially relevant studies to perform the second screening. At the same time, the reasons for excluding records after reading the full text will be reported in detail. Literature screening will be done independently and cross-checked by two researchers (SS Lin and QY Shi). Disagreement will be determined through discussion between the two investigators. When consensus cannot be reached, a third investigator (FW Yang) will assist in the judgment. The literature screening based on PRISMA is shown in Figure 1.[23] In the early stage of the study, we will train the evaluators and conduct pre-tests to ensure a standardized screening process.

Data extraction and management

Data extraction will be performed independently by two investigators (SS Lin and QY Shi) and cross-checked. Disagreement will be determined through discussion between the two investigators. When consensus cannot be reached, a third investigator (FW Yang) will assist in the judgment. The preset information extraction items are shown in Table 1.

Table 1 Information extraction items

Categories	Specific items
Study characteristics	title, first author, journal name, publication year, and type of study
Participants	diagnostic criteria, sample size, gender, age, ethnicity, case source, and baseline status
Intervention	drug name, medication route, drug dose, course of treatment, and patient compliance
Control	drug name, medication route, drug dose, course of treatment, and patient compliance
Outcomes	whether there is an intention-to-treat, loss to follow-up and withdrawal, outcomes
Risk of bias	random sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other bias
Others	author's main conclusions, funding, and others

Dealing with missing data

When data is missing, we will contact the original authors for complete data. If the missing value of outcomes cannot be obtained from the original author, we will delete the comparison results related to the missing data and fully consider the risk of bias. Besides, sensitivity analyses will be performed by repeating the main analysis with an imputed dataset using multiple imputation by chained equations.[24]

Assessment of risk of bias

According to the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials,[25] we will assess the risk of bias in the included literature from the following seven items: ①random sequence generation; ②allocation concealment; ③participant and personnel blinding; ④outcome assessment blinding; ⑤incomplete outcome data; ⑥selective reporting; and ⑦other bias. The results of the risk of bias assessment include the low risk of bias, the high risk of bias, and the unclear risk of bias. This process will be done independently by two investigators (SS Lin and QY Shi) and cross-checked. Disagreement will be determined through discussion between the two investigators. When consensus cannot be reached, a third investigator (FW Yang) will assist in the judgment. When there is a difference in the risk of bias between studies, we will try to analyze the impact of risk of bias. The risk of bias graph and the risk of bias summary will be generated by RevMan 5.3.

Data analysis

Pairwise meta-analysis and network meta-analysis

A Bayesian approach will be used to conduct pairwise meta-analyses and network meta-analyses according to the Markov chain Monte Carlo (MCMC) method.[21] In a Bayesian hierarchical framework, we will assume the vague prior distribution parameters for the between-study heterogeneity with uniform distribution in advance. The convergence of the model will be assessed using the Brooks-Gelman-Rubin plot.[26] Dichotomous variables will be presented as the relative risk (RR) or odds ratio (OR) with a 95% credible interval (CrI). Continuous variables will be presented as the weight mean difference (WMD) with a 95% CrI. The χ^2 test and I^2 test will be conducted to assess the potential heterogeneity. $P<0.05$ is considered statistically significant. To achieve the highest generalisability in the pooled treatment effects, a random-effects model will

be used to synthesize the data for pairwise and network meta-analysis.[27] A pairwise meta-analysis will be conducted when at least two studies compared the same intervention and comparator. When the treatment nodes formed a network of evidence, we will do a TCMIs to compare different treatment programs using the common comparator or placebo. A network diagram of each outcome will be generated to visualize the connections between different treatment programs included. If direct evidence exists, NMA will conduct a comprehensive evaluation of direct and indirect comparative evidence. If direct comparison evidence is lacking, we will only make adjusted indirect comparisons. For each outcome, a contribution matrix will be performed to demonstrate the percentage contribution of each direct comparison to the whole evidence body. The efficacy of different treatment programs will be ranked according to the surface under the cumulative ranking curve (SUCRA).[28] The SUCRA is a value range from 0 to 1 and can be re-expressed as a percentage. The larger the SUCRA, the better the treatment regimen.

Examination of assumptions in network meta-analysis

Heterogeneity The Cochran Q statistics will be employed to assess heterogeneity.[29] If there is significant clinical heterogeneity or methodological heterogeneity ($P<0.1$, $I^2>50\%$), the subgroup analysis will be performed to explore sources of heterogeneity. To assess potential bias resulting from baseline risk, we will perform meta-regression with regressors which included age of participants, sample size, duration of disease, course of treatment, and so on. Besides, sensitivity analyses will be performed by excluding studies with a high risk of bias or poor-quality to judge the stability of the results.

Transitivity We will verify the transitivity of this network by plotting the central trends (e.g. mean, median) of patient characteristics in each treatment comparison.

Consistency Node-splitting analysis will be used to split mixed evidence into direct evidence and indirect evidence to evaluate the inconsistency of the model. And then, we will compare the direct and indirect evidence. If there is no statistically significant difference between direct and indirect evidence, the study fits the consistency model. If the 95% CrI of the result does not include the invalid value, the inconsistency will be considered to exist.

Assessment of publication bias

The comparison-adjusted funnel plots will be obtained with the specific ranking order to detect small sample size study effects and publication bias.

All analyses will be conducted using R (version 3.6.1) with the *gemtc* package.

Quality assessment and recommendation grading of the evidence

Two reviewers (SS Lin and QY Shi) will independently perform quality assessment and recommendation grading of the evidence of the direct, indirect and mixed estimates of all comparisons according to GRADE criteria.[30, 31] In particular, the GRADE system was used to rank the quality of evidence for direct comparison from four aspects: limitation, inconsistency, indirectness, and publication bias, but without imprecision.[32] The grading of the evidence quality includes four levels, which are 'high', 'medium', 'low' or 'very low' according to the GRADE rating standards.[33, 34] High indicates that the authors are very confident that the real effect is close to the estimate of the effect. Moderate indicates that the authors are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low indicates that the authors` confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low indicates that the authors have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.[29] Cross-checking will be performed after the classification is completed. In case of disagreement, it will be decided by discussion between the two parties or judged by the third evaluator (FW Yang).

Ethics and dissemination This study will extract data from published literature and not involve private information from individuals or compromise their rights. Therefore, the study does not require ethical approval. The procedures of this systematic review and network meta-analysis will be conducted in accordance with the PRISMA guideline. Details of this study will be submitted to open access. The results will be published in a peer-reviewed journal and disseminated at relevant conferences.

Acknowledgement We would like to thank Luo-Qian Liu for the language revision.

Contributions SS Lin, JY Mao, and XL Wang conceived and designed the study together. SS Lin, QY Shi, and FW Yang developed the search strategy together. SS Lin drafted the protocol manuscript. All the authors have reviewed and approved the final manuscript.

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Competing interests None.

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Figure caption

Figure 1 Proposed flowchart of the literature search process

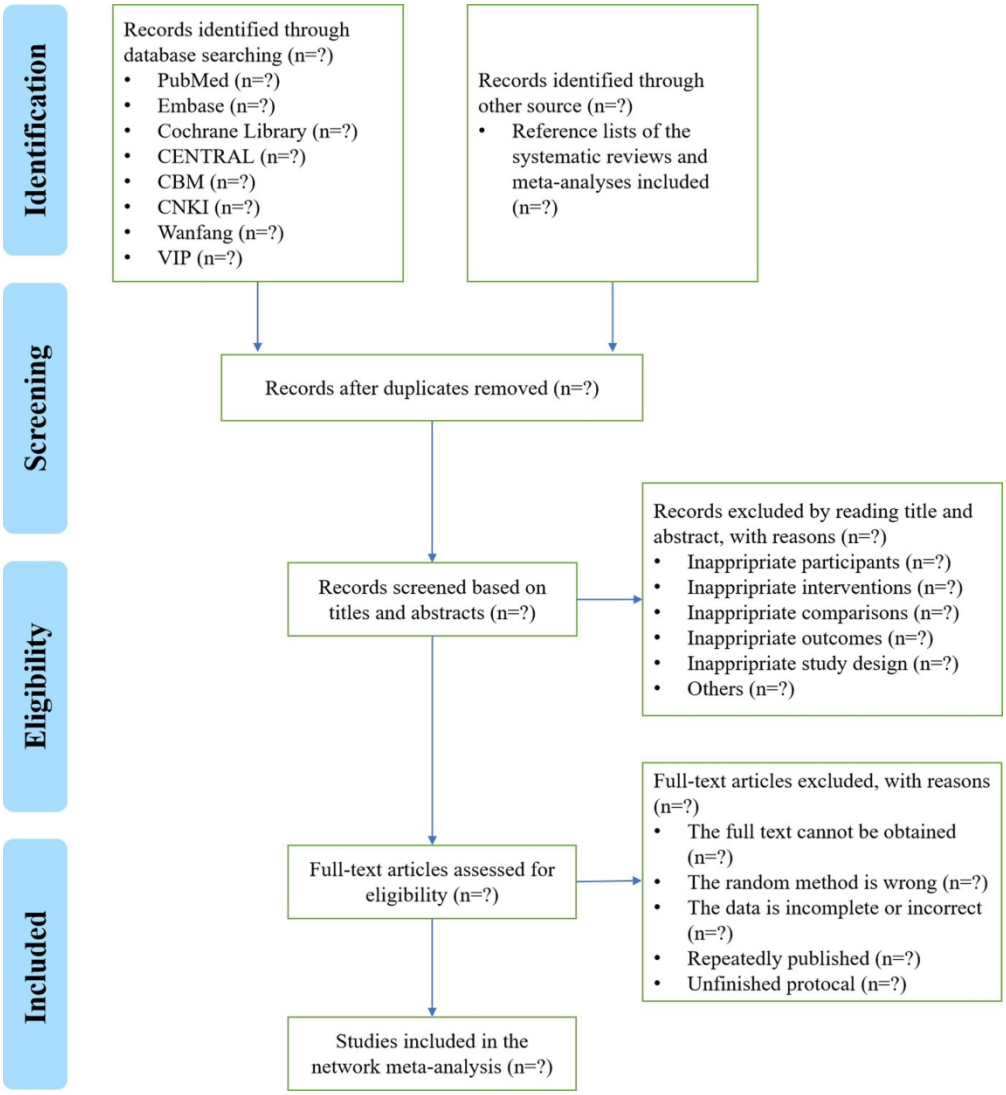

Figure 1 Proposed flowchart of the literature search process

234x254mm (300 x 300 DPI)

Annex 1 Search Strategy in PubMed

Search	Query	Items found
#1	Heart Failure[MeSH Terms]	
#2	heart failure[Title/Abstract]	
#3	cardiac failure[Title/Abstract]	
#4	heart decompensation[Title/Abstract]	
#5	heart dysfunction[Title/Abstract]	
#6	cardiac dysfunction[Title/Abstract]	
#7	ventricular dysfunction[Title/Abstract]	
#8	heart dificiency[Title/Abstract]	
#9	cardiac dificiency[Title/Abstract]	
#10	heart insufficiency[Title/Abstract]	
#11	cardiac insufficiency[Title/Abstract]	
#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	
#13	Medicine, Chinese Traditional[Mesh]	
#14	traditional Chinese medicine[All Fields]	
#15	Chinese traditional medicine[All Fields]	
#16	Chinese medicine[All Fields]	
#17	Drugs, Chinese Herbal[Mesh]	
#18	Chinese herbal drug$[All Fields]	
#19	Chinese herbal medicine[All Fields]	
#20	Chinese patent drug$[All Fields]	
#21	Chinese patent medicine[All Fields]	
#22	Chinese proprietary drug[All Fields]	
#23	Chinese proprietary medicine[All Fields]	
#24	Chinese crude drug$[All Fields]	
#25	Chinese materia medica[All Fields]	
#26	traditional Chinese medicine patent prescription$[All Fields]	
#27	traditional Chinese patent medicines and simple preparations[All Fields]	
#28	traditional Chinese medicine injection$[All Fields]	
#29	Chinese medicine injection$[All Fields]	
#30	Complementary Therapies[MeSH]	
#31	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	
#32	Injections[MeSH]	
#33	injection$[Title/Abstract]	
#34	injectable$[Title/Abstract]	
#35	#32 OR #33 OR #34	
#36	Randomized Controlled Trials as Topic[Mesh]	
#37	Randomized Controlled Trial[Publication Type]	
#38	Controlled Clinical Trial[Publication Type]	
#39	Equivalence Trial[Publication Type]	
#40	randomized controlled trial[Title/Abstract]	
#41	Random Allocation[Mesh]	
#42	Double-Blind Method[Mesh]	
#43	Single-Blind Method[Mesh]	
#44	Clinical Trial[Publication Type]	

#45	Research Design[Mesh]
#46	Placebos[Mesh]
#47	placebo$[Title/Abstract]
#48	random*[Title/Abstract]
#49	trial$[Title]
#50	#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR#43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49
#51	Systemic Review[Publication Type]
#52	systemic review[Title/Abstract]
#53	systemic literature review[Title/Abstract]
#54	Meta Analysis[Publication Type]
#55	Meta analysis[Title/Abstract]
#56	Meta-analysis[Publication Type]
#57	Meta-analysis[Title/Abstract]
#58	pooled analysis[Title/Abstract]
#59	Consensus Development Conference as Topic[Mesh]
#60	Consensus Development Conference[Publication Type]
#61	consensus development conference[Title/Abstract]
#62	expert consensus[Title/Abstract]
#63	Practice Guideline as Topic[Mesh]
#64	Practice Guideline[Publication Type]
#65	practice guideline[Title/Abstract]
#66	Cochrane database systemic review[Title/Abstract]
#67	Evidence-based Medicine[Mesh]
#68	evidence-based medicine[Title/Abstract]
#69	best practice[Title/Abstract]
#70	evidence synthesis[Title/Abstract]
#71	synthesis analysis[Title/Abstract]
#72	#51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71
#73	#12 AND #31 AND #35 AND #50 AND #72

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	Addressed on page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable.
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 Trial registration number: CRD42020166900
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7
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	Not applicable.
Support:			
Sources	5a	Indicate sources of financial or other support for the review	7
Sponsor	5b	Provide name for the review funder and/or sponsor	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	7
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2-3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
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	3-4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers	4-5

		or other grey literature sources) with planned dates of coverage	
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	4-5
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
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)	5
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	5
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	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
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	6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	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 of consistency (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (site 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 PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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