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Efficacy and safety of hyperbaric oxygen therapy for moderate to severe ulcerative colitis: a protocol for a systematic review and meta-analysis of randomizsed controlled trials

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ABSTRACT

Introduction

Ulcerative colitis(UC) is a type of inflammatory bowel disease (IBD). 62% of UC patients felt that it is difficult for them to live a normal life.[1] Furthermore, some researches have shown that about 15% of patients with UC undergo at least one extreme clinical course in their lifetime, and 10%–30% of patients with UC oblige colectomy. Although HBO_2 has been demonstrated by many investigations to have an advantageous impact on the treatment of UC, a systematic review and meta-analysis are not available. Therefore, a meta-analysis is essential to assess the efficacy and safety of HBO_2 for the treatment of UC.

Methods and analysis

A systematic search plan will be performed in the following seven databases with a restriction of time from inception to September 2020 to filter the eligible studies: PubMed, Web of Science, Embase, Cochrane Library, CNKI (China National Knowledge Infrastructure), Chinese Scientific Journal Database(VIP), Chinese Biomedical Database WanFang. Other related resources will also be searched. Only randomized controlled trials (RCT) of HBO_2 to treat patients with UC will be involved. Two independent reviewers will choose the eligible researches, extract data. The risk of bias will be evaluated based on the Cochrane Collaboration's Risk of Bias tool. Eventually, a systematic review and meta-analysis will be performed via the Review Manager V.5.3 statistical software.

Ethics and dissemination

This study will not involve the individual patient and any ethical problems since its outcomes are based on the published data. Thus, no ethical review and approval are required in this study. We plan to publish the study in a peer-reviewed journal.

PROSPERO registration number

CRD42020210244.

Strengths and limitations of this study

- ► This will be the first Preferred Reporting Items for Systematic Reviews and Meta-Analyses compliant systematic review to assess the effectiveness and safety of hyperbaric oxygen therapy for moderate to severe ulcerative colitis.
- ► This meta-analysis may contribute to offering reliable and objective evidence for the application of HBO_2 in patients with UC.
- ►The related original studies will be included because we developed a comprehensive search plan.
- ►Language bias may exist in this meta-analysis as there are restrictions of language in English and Chinese in the search strategy.

INTRODUCTION

Description of the condition

Ulcerative colitis (UC) is a type of inflammatory bowel disease(IBD), which is characterized by idiopathic, diffuse inflammation of the colonic mucosa.[2] The peak age for UC occurrence is 30-40 years, with no sex difference. Some researches have covered that there is a second

peak onset at 60-70 years old, but this statement needs to be further demonstrated.[3] While the etiology and pathogenesis of UC still not yet completely clear, but it has been clear that multiple factors together contribute to the development of UC, mainly implicates environmental factors (changes in the intestinal microbiome result from some medications, diet, smoking), genetic susceptibility, aberrant host immune responses, disturbance of intestinal barrier equilibrium.[4, 5]The typical gastrointestinal disorders of UC mainly including diarrhea, bloody stool, abdominal pain, and rectal urgency. In addition to the above typical symptoms, some patients with ulcerative colitis may present other multiple extraintestinal manifestations, such as oral ulcer, skin disorders, osteoporosis, inflammation of the eye, and arthritis.[6] Recurrent episodes of colonic inflammation seriously affect the life and work of UC patients, as well as their psychological well being, and may also increase the danger of colorectal cancer probability. 62% of UC patients felt that it is difficult for them to live a normal life.[1] Besides, some researches have shown that about 15% of patients with UC undergo at least one extreme clinical course in their lifetime, and 10%–30% of patients with UC oblige colectomy. [7, 8] There are significant differences in the incidence of UC in different countries and regions. Specifically, the highest incidence of UC was in Europe (such as 0.505% in Norway) and North America (such as 0.286% in the USA), while UC has a low incidence in developing countries and regions. However, due to the development of industrialization, the incidence of UC in Asia, South America, and Africa has gradually increased over the last decades.[9] According to the recent epidemiological data, ulcerative colitis has become a global disease, which places a notable socioeconomic burden on the health-care system.[10] Burisch et al assessed the health care expenditures of UC in the first five years after being diagnosed in Europe by means of analyzing the Epi-IBD cohort and demonstrated that the mean health care expenditures for one patient with UC per year were 2088 € during follow-up.[11]

At present, the recommended treatment goals in UC are aimed at inducing and maintaining clinical remission which means the disappearance of bloody stool and normalization of stool frequency, and endoscopic remission which is defined as a Mayo endoscopic subscore (MES) of 0 or 1.[12, 13]The main conventional medications for UC include aminosalicylates, corticosteroids, immunomodulators such as azathioprine, methotrexate.[14] Nevertheless, approximately 20% to 40% of UC have a poor response to the above drugs.[15] The treatment and management of UC have made significant progress since the approval of biologic agents(such as anti-TNF, inhibitors of cytokines) in the late 1990s.[16]An investigation has shown that the rate of colectomy decreased as the utilization of biological agents increased.[17] However, there are many shortcomings with biologic therapies, such as low compliance and high expenditure. Wentworth et.al assessed vedolizumab in IBD patients, with an overall adherence rate of 83%.[18] As a new therapy, doctors, and patients need to be aware of the associated risks, such as malignancy, infections, infusion/injection site reactions, and others.[19]In addition, there are 30% of patients with UC don't respond to anti-TNF, and about a third eventually lose response to the drug.[20] Therefore, there is an urgent requirement for other safer and more efficient non-drugs treatment options for UC, such as hyperbaric oxygen therapy and fecal transplant.

Description of the intervention

The application of hyperbaric air can date back to 1667. Hyperbaric oxygen (HBO_2) therapy, defined as breathing near 100% oxygen while inside a hyperbaric oxygen chamber that is

pressurized to greater than 1.4 atmospheres absolute (ATA).[21] HBO_2 therapy is performed in 2 to 3 absolute atmospheric pressure (ATA) chambers 2 to 3 times per day. As for the treatment duration, it depends on the distinct indication, but generally, it lasts about 1.5 to 2 hours.[22] After more than 300 years of development, it has been proved that HBO_2 therapy is safe and effective in the treatment of a variety of diseases, with few side effects. According to the Undersea and Hyperbaric Medical Society (UHMS), [23]recognized indications have been approved for the application of HBO_2, such as air or gas embolism, decompression sickness, severe anemia, intracranial abscess, and carbon monoxide poisoning. Also, there are some potential indications for HBO_2, without approval by the UHMS, include ulcerative colitis, Raynaud syndrome, otitis externa, etc. [24]A phase 2B randomized trial revealed that 85% of patients can avert second-line therapy (colectomy and biological agent) after receiving HBO_2 for patients who are hospitalized for acute flares. Furthermore, approximately 70% of patients can achieve remission or near-complete remission of rectal bleeding.[25] Therefore, HBO_2 brought survival benefits to patients with moderate-severe UC.

How the intervention might work

HBO_2 involves breathing 100% oxygen under increased atmospheric pressure, which significantly increases the oxygen levels in plasma and tissues to promote wound healing.[22] Although, high levels of oxygen produced by hyperbaric oxygen are only maintained when the patient is in the hyperbaric oxygen chamber and for a short time afterward, HBO_2 can also produce various biochemical effects, mainly include: (a) Inhibit the adhesion of neutrophils and the production of pro-inflammatory cytokines (IL-1, IL-6, TNF-a) ; (b) Up-regulation of hypoxia response pathway (HIF-1α, HO-1) ; (c) changes in host-microbiome metabolism; (d) increased growth factor synthesis and migration.[26-31]

OBJECTIVES

Some studies have demonstrated that HBO_2 can relieve a range of symptoms of patients who suffer from moderate-severe UC. On the contrary, Pagoldn et al conducted a prospective randomized study and indicated that HBO_2 is not beneficial for the treatment of UC.[32]To our best knowledge, there is no relevant systematic review or meta-analysis on the efficacy and safety of HBO2 in the treatment of UC patients. Therefore, we designed this study to fully assess evidence of HBO_2 in inducing and maintaining clinical remission in patients with UC. In summary, the result of our study will provide reliable reference information for patients and physicians when selecting treatment options.

METHODS AND ANALYSIS

Study design

The design of this protocol strictly follows the guidelines and recommendations of the systematic review and meta-analysis priority report item (PRISMA-P).[33] The methodology is preregistered on the International Prospective Register of Systematic Reviews (PROSPERO) with the registration ID of CRD42020210244.

Inclusion/ exclusion criteria for study selection

Types of studies

All randomized controlled trials (RCTs) of HBO_2 for UC will be eligible for inclusion. The experiments on animals, case reports, non-randomized clinical trials will be excluded. The language of the studies has a restriction of English or Chinese.

Types of participants

Inclusion criteria: studies of adult patients who suffer from moderate to severe UC will be considered. In other words, those patients with a full Mayo score ≥ of 6 and Mayo endoscopic subscore (MES) of 2 or 3 will be included, irrespective of gender, race, level of education.

Exclusion criteria: Pregnant women and those patients will be excluded if they have a clear contraindication to HBO_2 therapy, for example, cataract, age-related macular degeneration, pneumothorax.[34]In addition, patients who need urgent colectomy due to severe toxic megacolon will be eliminated too.

Types of interventions/controls

All studies evaluating hyperbaric oxygen therapy for moderate to severe UC will be included. Interventions mainly include the following two types: (a) HBO_2 therapy alone, without limiting the depth, duration, and frequency of hyperbaric oxygen; (b) HBO_2 therapy combined with the main conventional medications for UC, regardless of dose and route of administration, such as aminosalicylates, corticosteroids, immunomodulators, and biological agents. If the intervention is only involved in HBO_2 therapy, the control group can select sham HBO_2. Otherwise, the experimental group and the control group should use the same conventional drug treatment, except for HBO_2 therapy.

Types of outcome measures

Primary outcomes

Since our study aims at the systematic assessment of HBO_2 on moderate to severe UC, we will select the Mayo score and the Mayo endoscopic score (MES) as the primary outcomes, which can reflect the activity of UC to a certain extent. In addition to the above scores, it has been found that fecal calprotectin and serum inflammatory factors are also a reliable indicator of UC activity.[35]

Secondary outcomes

The secondary outcomes mainly include the safety, prevention of colectomy, clinical response from patients. The safety of HBO_2 is chiefly measured by the incidence of adverse effects and serious adverse events.

Patient and public involvement

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

Search resources

Electronic searches

A systematic search plan will be performed in the following seven databases with a restriction of time from inception to September 2020 to filter the eligible studies: PubMed, Web of Science, Embase, Cochrane Library, CNKI (China National Knowledge Infrastructure), Chinese Scientific Journal Database(VIP), Chinese Biomedical Database WanFang.

Clinical trial registers

The following two clinical trials registry platforms will be searched: (a) the US National Institutes of Health Ongoing Trials Register. (b) the International Clinical Trials Registry Platform.

Other sources

We will also search other related resources as far as possible by browsing the reference of

eligible studies and the other related grey literature (conference papers, journal articles).

Search strategies

We will use a combination of subject terms and free text terms for retrieval. Of course, there is a little difference in retrieval strategies in different databases. Therefore, we take the specific search strategy in PubMed as a typical example, and the specific steps of the retrieval are shown in Box 1.

Box 1 Search strategy in PubMed database

Search items

1. Ulcerative colitis.MeSh.
2. Colitis, Ulcerative. ti.ab.
3. UC.ti.ab.
4. IBD.ti.ab.
5. 1 or 2-4
6. Randomized Controlled Trial .MeSh.
7. RCT.ti.ab.
8. Controlled clinical trial.ti.ab.
9. Randomly.ti.ab.
10. Trial. ti.ab.
11. Randomized.ti.ab.
12. placebo.ti.ab.
13. 6 or 7-12
14. Hyperbaric oxygen.MeSh.
15. Hyperbaric Oxygenations. ti.ab.
16. Oxygenations, Hyperbaric. ti.ab.
17. Hyperbaric Oxygen Therapy . ti.ab.
18. Hyperbaric Oxygen Therapies. ti.ab.
19. Oxygenation, Hyperbari. ti.ab.
20. Oxygen Therapy, Hyperbaric. ti.ab.
21. Therapies, Hyperbaric Oxygen. ti.ab.
22. 14 or 15-21
23. 5 and 13 and 22

Data collection and analysis

Selection of studies

First, two independent reviewers(LHL, CJY) will respectively use the EndNote X9 software to read the titles, keywords, and abstracts of all the obtained studies. Then, the eligibility will be confirmed after screening the full text of potentially eligible studies. Any disagreements will be resolved through negotiation and consensus. Further controversy will be arbitrated by a third reviewer (LQ) if necessary. In summary, the entire selection process will be completed independently by at least two authors, and note the exclusion reasons for each excluded study. Figure 1 demonstrates the steps in the study screening process.

Data extraction and management

Two independent researchers (TLL, LQ) will apply a predesigned data collection form to extract data from included references. If there are any disagreements, the third reviewer (DYL)

will be consulted. The data items that we will extract mainly contain the following four parts:

1. Basic information of studies (year of publication, the first author, country sample size, follow-up time)
2. Participants (gender, age, area, duration and degree of UC, some blood biomarkers, Mayo endoscopic score [MES], and Ulcerative Colitis Endoscopic Index of Severity [UCEIS]).
3. Treatment (interventions, controls, type of HBO_2 chamber, HBO_2 protocol [depth, duration, prophylactic air breaks, frequency, the duration of treatment]).
4. Outcomes (mainly includes Mayo score, the Mayo endoscopic score, fecal calprotectin, adverse events).

Assessment of risk of bias

Three independent reviewers (YLL and DYL) evaluated the risk of bias of each included study by using the Cochrane Collaboration's Risk of Bias Tool. The assessed domains consist of the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. We will confirm each item from 3 levels of "high risk", "low risk", and "unclear". Any discrepancies will be arbitrated by negotiation with a four reviewer (PMF).

Assessment of reporting bias

Publication bias will be conducted if more than 10 studies are included through funnel plots.

Measures of treatment effect

According to the different types of data, we will apply diverse measures to assess the effect size of each included study. For continuous outcomes (including Mayo score, the Mayo endoscopic score, fecal calprotectin, serum inflammatory factors), the weighted mean difference (MD), or the standard mean difference (SMD) will be calculated for analysis. Dichotomous outcomes (colectomy, adverse events, serious adverse events, clinical response about remission of symptoms from patients) data will be expressed as the risk ratio (RR) with 95% confidence intervals (CIs).

Dealing with missing data

We will contact the corresponding authors via email as far as possible to obtain the missing data. In case of failure, we will eliminate this study from the analysis and give a rational explanation.

Assessment of heterogeneity

We will mainly adopt the following methods to evaluate the heterogeneity of the included studies: I^2 and the forest plot. This operation will be carried out by using the Review Manager (V.5.3.5). Statistical heterogeneity among studies will be evaluated with the I^2 statistic, with I^2 <25% indicating no heterogeneity, with I^2 <50% expressing low heterogeneity, I^2 <75% indicating moderate heterogeneity, with I^2 ≥75% expressing high heterogeneity.[36]

Data synthesis

We will use Review Manager V.5.3 software provided by the Cochrane Collaboration to implement the statistical analyses. If the eligible studies are sufficiently homogeneous, data from all studies will be pooled for a meta-analysis. If the included studies are low heterogeneity (I^2<50%), we will conduct the statistical combination via a fixed-effects model. On the contrary, we will choose the random-effects model, sensitivity analysis and subgroup analysis will also be carried out to explore potential sources of heterogeneity.[37] We will

perform descriptive summaries in the case of a meta-analysis without feasibility due to significant statistical heterogeneity.

Subgroup analysis

In case the data of the included studies are available and sufficient, a subgroup analysis will be performed to figure out the cause of heterogeneity. At present, we plan to conduct this implement according to characteristics of participants (age, gender, race, or stage of UC), types of HBO_2 protocol (depth, duration, break, frequency, the course of treatment), type of standard medical therapy (immunosuppressive drugs, 5-aminosalicylic acid (5-ASA) or steroids). However, during actual implementation, the subgroup analysis will not be restricted to the planned subgroup, and make some adjustments based on the extracted data.

Sensitivity analysis

To evaluate the robustness and reliability of each outcome, a sensitivity analysis will be carried out. We plan to repeat the meta-analysis based on the remaining data after removing each study one by one, and confirm whether the pooled results are robust and reliable via a comparison between the before and after results.

Evaluating the evidence

Two reviewers (LHL and LQ) will assess the quality of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE), which classifies the evidence into four levels: very low, low, moderate, and high levels.[38]

Ethics and dissemination

This study will not involve the individual patient and any ethical problems since its outcomes are based on the published data. Thus, no ethical review and approval are required in this study. We plan to publish the study in a peer-reviewed journal.

DISCUSSION

UC has become a global disease, which places a significant socioeconomic burden on the health-care system.[10] However, as conventional medicine has some drawbacks (high price, poor efficacy, and low compliance), most patients with UC only receive limited benefits. Therefore, effective non-drug treatments appear extremely significant. In conclusion, if there is a combination of other non-drug therapies and traditional therapies, this may be a research direction with great potential.

Although HBO_2 has been demonstrated by many investigations to have an advantageous impact on the treatment of UC, a systematic review and meta-analysis are not available to assess the potential efficacy and safety of this therapeutic method. Therefore, we intend to provide reliable and objective evidence for HBO_2 at UC by conducting this study.

Some relevant studies in other languages might be omitted as restrictions of language in English and Chinese in our search strategy, which may lead to a language bias in this systematic review and meta-analysis. However, this study will still contribute to offering reliable and objective evidence for the application of HBO_2 in patients with UC.

Contributors LHL and LQ are joint first authors. LHL and QL initiated the idea and led the development of this protocol. CJY, DYL, YLL, TLLand PMF were involved in the planning and design process of this protocol. LHL and CJY conducted the selection of studies. Data extraction will be performed by TLL and QL. The assessment of the

risk of bias will be carried out by DYL and YLL. Any discrepancies will be resolved by discussion with a third PMF. PMF will monitor each procedure of the review. All authors read and approved the final manuscript.

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Box 1 Search strategy in PubMed database.

Figure 1 Flow chart diagram presenting the selection process for the studies. This figure shows the identification, screening, eligibility and included when we searching articles.

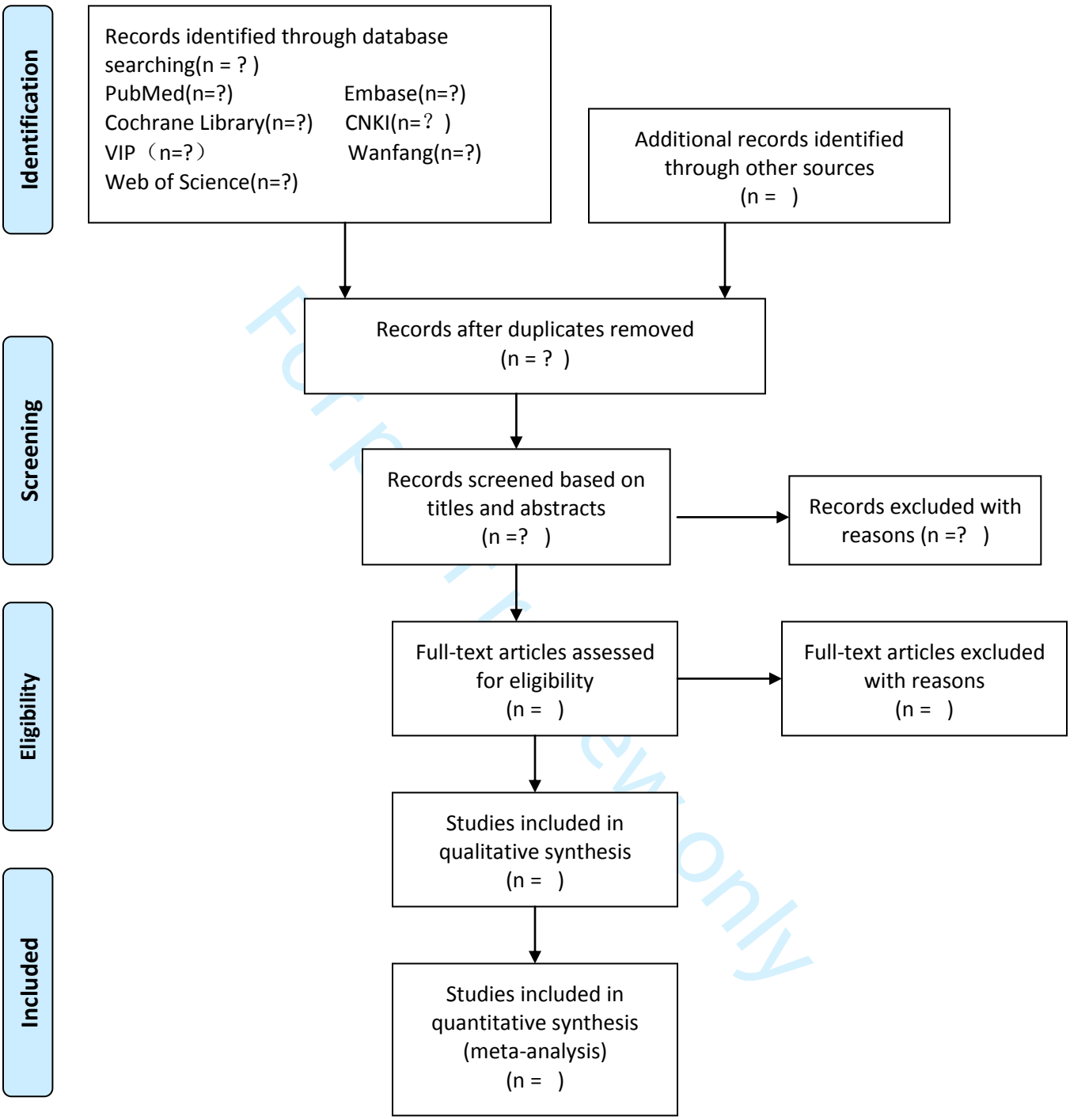

Figure 1 Flow chart diagram presenting the selection process for the studies. This figure shows the identification, screening, eligibility and included when we searching articles.

Reporting checklist for protocol of a systematic review.

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Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	2
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol,	2

		identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	8
Sponsor	#5b	Provide name for the review funder and / or sponsor	8
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	8
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)	4
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	4,5
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4,5
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	5
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Study records - 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)	6
Study records - 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	6

		investigators	
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	6
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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
Data synthesis	#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 I2, Kendall's **T**)	6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

BMJ Open

Efficacy and safety of hyperbaric oxygen therapy for moderate to severe ulcerative colitis: a protocol for a systematic review and meta-analysis

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Efficacy and safety of hyperbaric oxygen therapy for moderate to severe ulcerative colitis: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD), and 62% of UC patients felt that it is difficult for them to live a normal life. Furthermore, some researches have shown that about 15% of UC patients undergo at least one extreme clinical course in their lifetime, and 10%–30% of UC patients oblige colectomy. Although many investigations have demonstrated that HBO_2 has a beneficial impact on UC treatment, a systematic review and meta-analysis are unavailable. Therefore, a meta-analysis is essential to assess the efficacy and safety of HBO_2 in treating UC.

Methods and analysis

A systematic search plan will be performed in the following seven databases with a restriction of time from inception to September 2020 to filter the eligible studies: PubMed, Web of Science, Embase, Cochrane Library, CNKI (China National Knowledge Infrastructure), Chinese Scientific Journal Database (VIP), and Chinese Biomedical Database WanFang. Other related resources will be also searched. Two independent reviewers will choose eligible researches and extract data. The risk of bias will be evaluated based on Cochrane Collaboration's Risk of Bias tool and Newcastle-Ottawa Scale (NOS). Eventually, a systematic review and meta-analysis will be performed via the Review Manager V.5.3 statistical software and Stata V.14.0 software.

Ethics and dissemination

This study will not involve the individual patient and any ethical problems since its outcomes are based on published data. Therefore, no ethical review and approval are required. We plan to publish the study in a peer-reviewed journal.

PROSPERO registration number

CRD42020210244.

Strengths and limitations of this study

► This systematic review and meta-analyses will be the latest report to answer the clinical question of whether HBO_2 should be promoted and applied in patients with moderate to severe ulcerative colitis.

► Screening of search citations, full-text screening, data extraction, risk of bias, and quality assessment will be completed independently by at least two reviewers and a third researcher as an arbitrator.

► However, since HBO_2 protocol types used in various studies may be different, the research conclusions may be biased to some extent.

► Studies published in languages other than English or Chinese may be omitted due to language limitations，which may lead to language bias.

INTRODUCTION

Description of the condition

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) characterized by idiopathic, diffuse inflammation of colonic mucosa.[1] The peak age for UC occurrence is 30-40 years,

without sex difference. Some researches have indicated that a second peak onset occurs at 60-70 years old, but this statement needs to be further demonstrated.[2] Although the etiology and pathogenesis of UC remain unknown, it has been established that several factors contribute to UC development. These factors include environmental factors (changes in the intestinal microbiome resulting from certain medications, diet, and smoking), genetic vulnerability, aberrant host immune responses, and disturbance of intestinal barrier equilibrium.[3, 4]The typical gastrointestinal disorders of UC mainly include diarrhea, bloody stool, abdominal pain, and rectal urgency. In addition to the above symptoms, some UC patients may present other multiple extraintestinal manifestations, such as oral ulcer, skin disorders, osteoporosis, eye inflammation, and arthritis.[5] Recurrent episodes of colonic inflammation seriously affect UC patients' lives and work, as well as their psychological well-being, and may also raise the risk of colorectal cancer. Among UC patients, 62% experienced a challenging normal life, [6]15% underwent at least one extreme clinical course in their lifetime, and 10%–30% of them obliged colectomy. [7, 8] UC incidence varies significantly between different countries and regions. Specifically, the highest UC incidence was in Europe (0.505% in Norway) and North America (0.286% in the USA), while UC has a low incidence in developing countries and regions. However, due to industrialization development, UC incidence in Asia, South America, and Africa has gradually increased over the last decades.[9] According to recent epidemiological data, UC has become a global disease, imposing a notable socioeconomic burden on the health-care system.[10] Burisch et al. assessed the health care expenditures of UC in the first five years after being diagnosed in Europe using Epi-IBD cohort and determined that the mean annual health care costs for one UC patient per year were 2088 € during follow-up.[11]

At present, the recommended treatment goals in UC are to induce and maintain clinical remission, which means bloody stool absence and stool frequency normalization, and endoscopic remission, which is defined as a Mayo endoscopic subscore (MES) of 0 or 1.[12, 13] The main conventional medications for UC include aminosalicylates, corticosteroids, and immunomodulators such as azathioprine and methotrexate.[14] Nevertheless, approximately 20% to 40% of UC patients poorly respond to these drugs.[15] Since the late 1990s, when biologic agents (such as anti-TNF, cytokine inhibitors) were approved, the treatment and management of UC have advanced significantly.[16] An investigation has shown that colectomy rates decreased as the utilization of biological agents increased.[17] However, many shortcomings with biologic therapies are present, such as low compliance and high expenditure. Wentworth et al. assessed vedolizumab in IBD patients, with an overall adherence rate of 83%.[18] As a new therapy, doctors and patients need to be aware of the associated risks, such as malignancy, infections, infusion/injection site reactions, etc.[19] In addition, 30% of UC patients do not respond to anti-TNF, and about a third eventually lose response to the drug.[20] Therefore, there is an urgent need for safer and more efficient non-drug treatment alternatives for UC, such as hyperbaric oxygen therapy and fecal transplant.

Description of the intervention

The application of hyperbaric air dates back to 1667. Hyperbaric oxygen therapy (HBO_2) is defined as breathing close to 100% oxygen in a hyperbaric oxygen chamber where the pressure exceeds 1.4 absolute atmospheres (ATA).[21] HBO_2 therapy is performed in 2 to 3 absolute atmospheric pressure chambers 2 to 3 times daily. The length of treatment varies according to distinct indications but is usually between 1.5 and 2 hours.[22] After more than

300 years of development, HBO_2 therapy has been demonstrated to be safe and effective in treating various diseases, with few side effects. According to Undersea and Hyperbaric Medical Society (UHMS),[23] HBO_2 has been approved for use in recognized indications, such as air or gas embolism, decompression sickness, severe anemia, intracranial abscess, and carbon monoxide poisoning. In addition, without UHMS approval, HBO_2 has some potential indications, including UC, Raynaud syndrome, otitis externa, etc.[24] A phase 2B randomized trial revealed that, after receiving HBO_2, 85% of patients hospitalized for acute flares could avert second-line therapy (colectomy and biological agent). Furthermore, approximately 70% of patients can achieve remission or near-complete remission of rectal bleeding.[25] As a result, HBO_2 improved survival in patients with moderate-to-severe UC.

How the intervention might work

HBO_2 involves breathing 100% oxygen under increased atmospheric pressure, which significantly increases the oxygen levels in plasma and tissues to promote wound healing.[22] Although high oxygen levels produced by hyperbaric oxygen are only maintained when the patient is in the hyperbaric oxygen chamber, and for a short time afterward, HBO_2 can also produce various biochemical effects, including (a) inhibition of neutrophils' adhesion and production of pro-inflammatory cytokines (IL-1, IL-6, and TNF-a), (b) up-regulation of hypoxia response pathway (HIF-1 α , HO-1), (c) changes in host-microbiome metabolism, and (d) increased growth factor synthesis and migration.[26-31]

OBJECTIVES

Some studies have demonstrated that HBO_2 can relieve a range of symptoms of patients who suffer from moderate-to-severe UC. On the contrary, Pagoldn et al. conducted a prospective randomized study and indicated that HBO_2 is ineffective in treating UC.[32] Dulai et al. conducted a systematic review of safety and effectiveness of hyperbaric oxygen in treating IBD (including Crohn's disease and ulcerative colitis) in 2014, and they concluded that hyperbaric oxygen is a relatively safe and potentially effective option IBD treatment.[33]After careful assessment of this work, we found that the patients included in this systematic review had Crohn's disease and UC, and this systematic review did not separately investigate the safety of HBO_2 for UC. Therefore, we believe that this conclusion has limited guidance for gastroenterologists in treating UC. In addition, we also noted that there were some latest studies on hyperbaric oxygen therapy for UC patients after 2014. Consequently, we intend to perform a systematic review and meta-analysis to quantify the safety and efficacy of HBO_2 for UC. In summary, our study results will provide reliable reference information for patients and physicians when selecting treatment options for UC.

METHODS AND ANALYSIS

Study design

The design of this protocol strictly follows the guidelines and recommendations of the systematic review and meta-analysis priority report item (PRISMA-P).[34] The methodology is preregistered on the International Prospective Register of Systematic Reviews (PROSPERO) with a registration ID of CRD42020210244.

Inclusion/exclusion criteria for study selection

Types of studies

RCTs and observational studies (cohort and case-control) will be included. Articles including experimental animals, narrative reviews, cross-sectional studies, expert opinions, and editorials

will be excluded. The language of the studies has a restriction of English or Chinese.

Types of participants

Inclusion criteria: studies of adult patients who suffer from moderate to severe UC will be considered. In other words, those patients with a full Mayo score ⩾ 6 and Mayo endoscopic subscore (MES) of 2 or 3 will be included, irrespective of gender, race, and education level.

Exclusion criteria: pregnant women and those patients will be excluded if they have a clear contraindication to HBO_2 therapy, for example, cataract, age-related macular degeneration, or pneumothorax.[35] In addition, patients who need urgent colectomy due to severe toxic megacolon will be excluded.

Types of interventions/controls

All studies evaluating hyperbaric oxygen therapy for moderate to severe UC will be included. Interventions mainly include the following two types: (a) HBO_2 therapy alone, without limiting the depth, duration, and frequency of hyperbaric oxygen; (b) HBO_2 therapy combined with the main conventional medications for UC, regardless of dose and route of administration, such as aminosalicylates, corticosteroids, immunomodulators, and biological agents. If the intervention is only involved in HBO_2 therapy, the control group can select sham HBO_2. Otherwise, the experimental and control groups should use the same conventional drug treatment, except for HBO_2 therapy.

Types of outcome measures

Primary outcomes

Since our study aims to systematically assess HBO_2 on moderate-to-severe UC, we will select the Mayo score and the Mayo endoscopic score (MES) as the primary outcomes, which can reflect the activity of UC to a certain extent. In addition to the above scores, fecal calprotectin and serum inflammatory factors were found to be a reliable indicator of UC activity.[36]

Secondary outcomes

The secondary outcomes mainly include safety, prevention of colectomy, and clinical response from patients. The safety of HBO_2 is chiefly measured by the incidence of adverse effects and serious adverse events.

Patient and public involvement

Patients and/or public were not involved in design or conduct or reporting, or dissemination plans for this research.

Search resources

Electronic searches

A systematic search plan will be performed in the following seven databases with a restriction of time from inception to September 2020 to filter the eligible studies: PubMed, Web of Science, Embase, Cochrane Library, CNKI (China National Knowledge Infrastructure), Chinese Scientific Journal Database(VIP), and Chinese Biomedical Database WanFang.

Clinical trial registers

The following two clinical trials registry platforms were searched: (a) the US National Institutes of Health Ongoing Trials Register and (b) the International Clinical Trials Registry Platform.

Other sources

We will search other related resources as far as possible by browsing the reference of eligible

studies and the other related grey literature (conference, papers, and journal articles).

Search strategies

We will use a combination of subject terms and accessible text terms for retrieval. Indeed, there is a little difference in retrieval strategies in different databases. Therefore, we considered the specific search strategy in PubMed as a typical example, and the specific steps of the retrieval are shown in **Box 1**.

Box 1: Search strategy in PubMed database.

Search items

1. Ulcerative colitis.MeSh.
2. Colitis, Ulcerative.ti.ab.
3. UC.ti.ab.
4. IBD.ti.ab.
5. 1 or 2-4
6. Hyperbaric oxygen.MeSh.
7. Hyperbaric Oxygenations. ti.ab.
8. Oxygenations, Hyperbaric. ti.ab.
9. Hyperbaric Oxygen Therapy. ti.ab.
10. Hyperbaric Oxygen Therapies. ti.ab.
11. Oxygenation, Hyperbaric. ti.ab.
12. Oxygen Therapy, Hyperbaric. ti.ab.
13. Therapies, Hyperbaric Oxygen. ti.ab.
14. 6 or 7-13
15. 5 and 14

Data collection and analysis

Selection of studies

First, two independent reviewers (LHL and CJY) will use the EndNote X9 software to read the titles, keywords, and abstracts of all obtained studies. Subsequently, the eligibility will be confirmed after screening the full text of potentially eligible studies. Any disagreements will be resolved through negotiation and consensus. Further controversy will be arbitrated by a third reviewer (LQ) if necessary. In summary, the entire selection process will be completed independently by at least two authors, and the exclusion reasons for each excluded study will be noted. **Figure 1** demonstrates the steps in the study screening process.

Data extraction and management

Two independent researchers (TLL and LQ) will apply a predesigned data collection form to extract data from included references. If there are any disagreements, the third reviewer (DYL) will be consulted. The extracted data items mainly contain the following four parts:

1. Basic information of studies (year of publication, the first author, country ,sample size, and follow-up time)
2. Participants (gender, age, area, duration and degree of UC, some blood biomarkers, Mayo endoscopic score [MES], and Ulcerative Colitis Endoscopic Index of Severity [UCEIS]).
3. Treatment (interventions, controls, type of HBO_2 chamber, HBO_2 protocol [depth, duration, prophylactic air breaks, frequency, and treatment duration]).
4. Outcomes (Mayo score, the Mayo endoscopic score, fecal calprotectin, and adverse events).

Assessment of risk of bias

Two independent reviewers (YLL and DYL) evaluated the risk of bias of RCTs using the Cochrane Collaboration's Risk of Bias Tool. The assessed domains consist of the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. We will confirm each item from 3 levels of "high risk", "low risk", and "unclear". Any discrepancies will be arbitrated by negotiation with a four reviewer (PMF). As for the cohort studies and case-control studies, we intend to use the Newcastle-Ottawa Scale (NOS) to assess the risk of bias. NOS consist of the following items: selection, exposure, and comparability.

Assessment of publication biases

If more than ten studies are included, the publication bias will be conducted through a funnel plot. The funnel plot method can qualitatively identify publication bias, while Begg's rank correlation test and Egger's linear regression test can quantitatively judge whether there is publication bias by examining the P-value. We will use Begg's rank correlation test and Egger's linear regression test to examine the symmetry of funnel plots if sufficient studies are available. In the case of poor symmetry of the funnel plot, the trim and fill method will also be performed. Since the test power of the above methods is closely related to the number of included studies, we will make a careful selection based on the number of included studies in our specific analysis.

Measures of treatment effect

According to different data types, we will apply various measures to assess the effect size of each included study. For continuous outcomes (Mayo score, the Mayo endoscopic score, fecal calprotectin, and serum inflammatory factors), the weighted mean difference (MD) or the standard mean difference (SMD) will be calculated for analysis. Dichotomous outcomes (colectomy, adverse events, serious adverse events, and clinical response about remission of symptoms from patients) data will be expressed as the risk ratio (RR) with 95% confidence intervals (CIs).

Dealing with missing data

We will contact the corresponding authors via email as far as possible to obtain the missing data. In case of failure, we will eliminate this study from the analysis and give a rational explanation.

Assessment of heterogeneity

We will mainly adopt the following methods to evaluate the heterogeneity of the included studies: I^2 and the forest plot. This operation will be carried out using the Review Manager (V.5.3.5). Statistical heterogeneity among studies will be evaluated with I^2 statistic, with $I^2<25\%$ indicating no heterogeneity, with $I^2<50\%$ expressing low heterogeneity, $I^2<75\%$ indicating moderate heterogeneity, and with $I^2\geqslant75\%$ expressing high heterogeneity.[37]

Data synthesis

We will use Review Manager V.5.3 software provided by the Cochrane Collaboration to implement the statistical analyses. If necessary, STATA software V.14.0 (STATA Corporation) will also be used for statistical analyses. If the eligible studies are sufficiently homogeneous, data from all studies will be pooled for a meta-analysis. If the included studies exhibit low heterogeneity ($I^2<50\%$), we will conduct the statistical combination via a fixed-effects model.

On the contrary, we will choose the random-effects model. Subgroup analysis will also be carried out to explore potential sources of heterogeneity, while sensitivity analysis will be performed to evaluate the robustness and reliability of each outcome.[38] We will perform descriptive summaries in the case of a meta-analysis without feasibility due to significant statistical heterogeneity.

Subgroup analysis

If substantial heterogeneity exists between studies, a subgroup analysis will be performed to determine the cause of heterogeneity. Currently, we plan to conduct this analysis according to characteristics of participants (age, gender, race, or stage of UC), types of HBO_2 protocol (depth, duration, break, frequency, and the course of treatment), type of standard medical therapy (immunosuppressive drugs, 5-aminosalicylic acid (5-ASA) or steroids). In addition, we also intend to conduct subgroup analysis based on the level of evidence and risk of bias in the included literature, which can more accurately and comprehensively explore heterogeneity sources. However, during actual implementation, the subgroup analysis will not be restricted to the planned subgroup and incorporate some adjustments based on the extracted data. To further improve the subgroup analysis reliability, it will be evaluated based on the guidance for credible subgroup analysis. If the data of the included studies are available and sufficient, a meta-regression will be performed to determine heterogeneity.

Sensitivity analysis

To evaluate the robustness and reliability of each outcome, a sensitivity analysis will be carried out. We plan to repeat the meta-analysis based on the remaining data after removing each study one by one and confirm whether the pooled results are robust and reliable via comparing the before and after results.

Evaluating the evidence

Two reviewers (LHL and LQ) will assess the quality of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE), which classifies the evidence into four levels: very low, low, moderate, and high levels.[39]

Ethics and dissemination

This study will not involve the individual patient and any ethical problems since its outcomes are based on published data. Therefore, no ethical review and approval are required in this study. We plan to publish the study in a peer-reviewed journal.

Contributors LHL and LQ are joint first authors. LHL and QL initiated the idea and led the development of this protocol. CJY, DYL, YLL, TLLand PMF were involved in the planning and design process of this protocol. LHL and CJY conducted the selection of studies. Data extraction will be performed by TLL and QL. The assessment of the risk of bias will be carried out by DYL and YLL. Any discrepancies will be resolved by discussion with a third PMF. PMF will monitor each procedure of the review. All authors read and approved the final manuscript.

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Figure 1 Flow chart diagram presenting the selection process for the studies. This figure shows the identification, screening, eligibility and included when we searching articles.

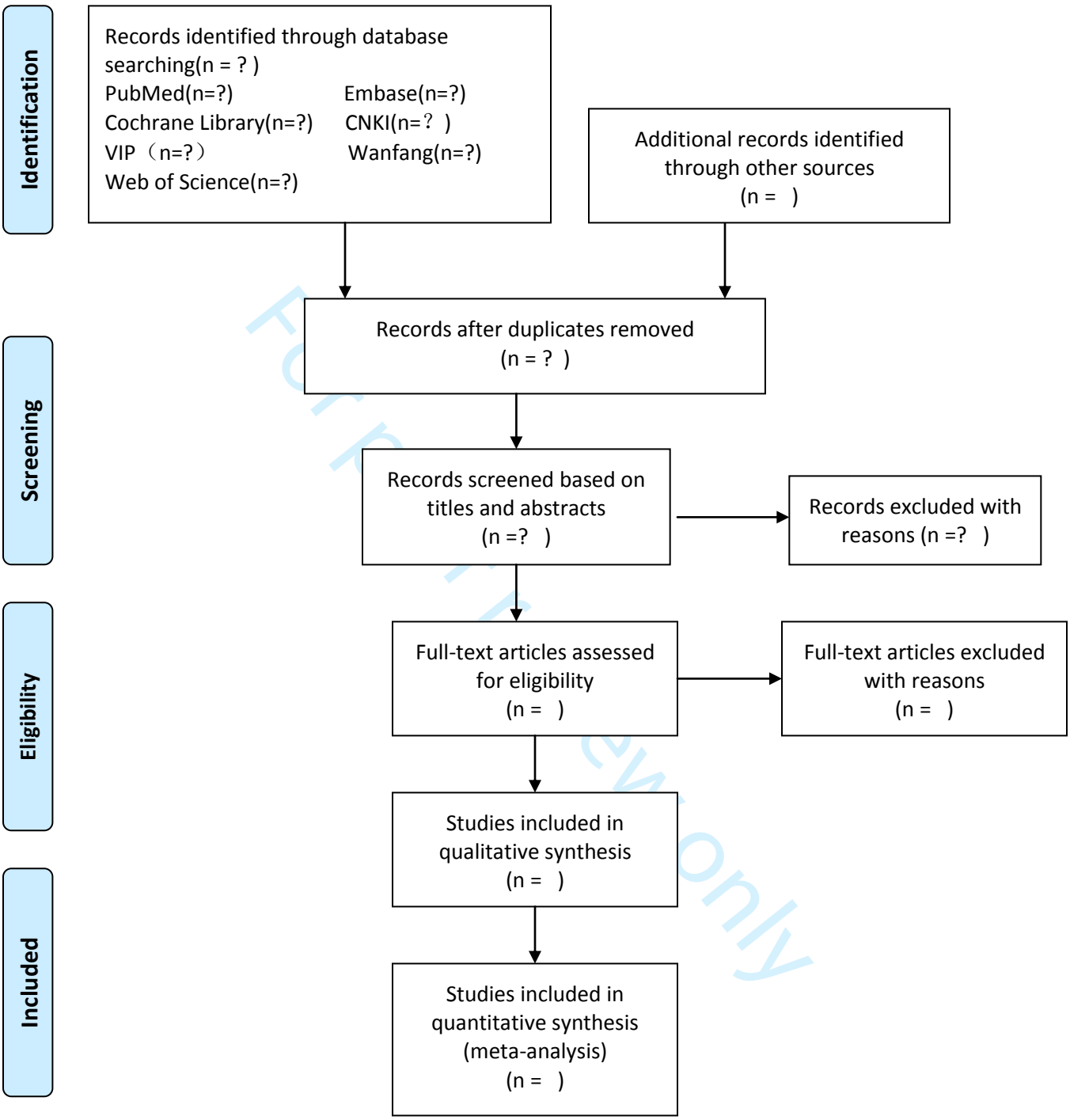

Figure 1 Flow chart diagram presenting the selection process for the studies. This figure shows the identification, screening, eligibility and included when we searching articles.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	2
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol,	2

		identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	8
Sponsor	#5b	Provide name for the review funder and / or sponsor	8
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	8
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)	4
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	4,5
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4,5
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	5
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Study records - 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)	6
Study records - 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	6

		investigators	
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	6
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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
Data synthesis	#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 I2, Kendall's **T**)	6
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7