PROTOCOL

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Efficacy and safety of Chinese tonic medicines for treating sepsis or septic shock: a protocol for a systematic review and Bayesian network meta-analysis of randomized controlled trials

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Abstract

Background Sepsis is a life-threatening organ dysfunction with high morbidity and mortality. Various studies have demonstrated the effectiveness of Chinese tonic medicines (CTMs) in treating sepsis or septic shock. However, trials directly comparing the efficacy and safety of different CTMs for sepsis or septic shock are still lacking. To identify the most optimal CTM for treating sepsis or septic shock, we plan to perform a systematic review and network meta-analysis of various CTMs used for sepsis or septic shock patients.

Methods Randomized controlled trials (RCTs) that investigated the efficacy and safety of CTMs for patients with sepsis or septic shock will be systematically searched in Pubmed, Embase, Cochrane Central Register of Controlled Trials, Scopus, Web Of Science, CBM, CNKI, Wanfang, and VIP databases from inception to November 2023. The quality of the included studies will be assessed using the Cochrane Risk of Bias V.2.0. tool. The confidence of evidence will be evaluated through the CINeMA (Confidence in Network Meta-Analysis) web application. Primary outcomes include the delta Sequential Organ Failure Assessment (ΔSOFA) score at day 7 after interventions and 28-day mortality. Secondary outcomes comprise delta serum lactate levels (ΔLac) and delta mean arterial pressure (ΔMAP) at day 7 after interventions as well as total dose and duration of vasoactive drugs. Safety outcome includes adverse drug reactions or adverse drug events (ADRs/ADEs). The Bayesian network meta-analysis will be conducted using the "BUGSnet" package in R version 4.2.2. The surface under the cumulative ranking curve (SUCRA) values will be used to rank each treatment. Statistical inconsistency assessment, publication bias assessment, heterogeneity analysis, sensitivity analysis, and subgroup analysis will be performed.

Discussion This study will provide new insights into the efficacy and safety of various CTMs used in sepsis or septic shock patients, providing help for future clinical practice and research.

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Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. A subset of patients with sepsis may progress to septic shock, increasing the risk of mortality to 23.6% [2, 3]. Sepsis or septic shock is recognized as a primary health threat by the World Health Organization [4]. Despite substantial advances over the past two decades, the management of this disorder remains largely unchanged [5, 6]. Novel adjuvant therapies that are effective, safe, and economical for improving organ function, reducing mortality, and alleviating the financial burden of sepsis are urgently needed.

A new consensus termed Sepsis-3 requires the Sequential Organ Failure Assessment (SOFA) score to define sepsis [1]. Changes in SOFA score ($\triangle$SOFA) have been identified as an acceptable surrogate marker of efficacy in exploratory trials of novel therapeutic agents in sepsis [7, 8]. It is worth using the $\triangle$ SOFA score as the primary outcome to assess the performance of each adjuvant therapy.

In recent years, Chinese herbal medicines, especially Chinese tonic medicines (CTMs), have been widely used in China as adjuvant treatments for sepsis or septic shock, and have demonstrated efficacy in reducing mortality [9–14]. However, trials directly comparing the efficacy and safety of different CTMs for sepsis or septic shock are still lacking. Consequently, we plan to systematically search all randomized controlled trials (RCTs) of CTMs for treating sepsis or septic shock, perform a network meta-analysis, and, more importantly, use $\triangle$SOFA as a crucial evaluation index to assess the efficacy and safety of different CTMs, hoping to provide more evidence for clinical practice.

Methods

Study registration

This systematic review and network meta-analysis has been registered in the International Prospective Registry of Systematic Reviews (PROSPERO, CRD42023482572). The protocol followed the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol statement [15]. The PRISMA-P checklist is provided in Supplementary Table S1. Any modifications to this protocol will be reported in our full reviews if needed.

Eligibility criteria

Types of studies

We will include RCTs, whether placebo-controlled or head-to-head trials, without restrictions on language or publication date. Non-randomized trials, observational studies, reviews, meta-analysis commentary articles, and studies with unavailable full text will be excluded.

Types of participants

We will include adults (aged $\geq$ 18 years) diagnosed with sepsis or septic shock [1, 16, 17] and exclude studies exclusively involving the elderly.

Types of interventions

We will include studies investigating the efficacy and safety of CTMs for treating sepsis or septic shock. The control groups received one of the following treatments: CTMs combined with Western medicine (WM), a placebo combined with WM, or only WM. The experimental groups were treated with different types of CTMs combined with WM. WM includes antibiotics, fluid resuscitation, vasopressors, mechanical ventilation, and other necessary therapies [5, 6, 18–20]. CTMs are defined as medicines aimed at reinforcing the body and preventing diseases. We specified that CTMs should be administered orally or intravenously, with no restriction on dosage, frequency, or course of intervention.

Types of outcome measures

Primary outcomes We chose the $\triangle$SOFA score at day 7 after interventions and 28-day mortality as the primary outcomes. The $\triangle$SOFA score is calculated by subtracting the SOFA score at enrollment from the corresponding value at day 7 after interventions.

Secondary outcomes 1. Delta serum lactate levels ($\triangle$Lac) at day 7 after interventions.

2. Delta mean arterial pressure ($\triangle$MAP) at day 7 after interventions.

3. Total dose and duration of vasoactive drugs.

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Safety outcome

Adverse drug reactions or adverse drug events (ADRs/ADEs).

Search strategy

There were no restrictions on language or publication date. The Pubmed, Embase (via Ovid), Cochrane Central Register of Controlled Trials (via Ovid), Scopus, Web Of Science, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang, and VIP databases will be searched by two investigators (Rui Yang and Cheng Hu). We will search the following MeSH terms, keywords, abstracts or titles: "sepsis", "septic shock", "traditional Chinese medicine", or "Chinese herbal medicine". The detailed search strategies are provided in Supplementary Table S2.

Selection process

Zotero 6.0.23 software will be used to collect citations and remove duplicate articles. Two investigators (Rui Yang and Cheng Hu) will independently screen based on the title and abstract first. The full text of all potentially relevant studies will be collected for subsequent assessment. In the presence of duplicate data, only studies with a larger sample size and longer follow-up time will be included. Any disagreements will be resolved by the third investigator (Lihui Deng). The process of study selection is shown in Supplementary Fig. S1.

Data collection process

Two investigators (Rui Yang and Cheng Hu) will independently extract the following data: study information (study design, first author name, publication year, study country), characteristics of participants (inclusion/exclusion criteria, size, age, sex), intervention and control (type of drug, administration, dose, frequency, and duration), outcomes (before and after the interventions). All the data will undergo cross-checking after extraction, and any disagreement will be resolved by the third investigator (Lihui Deng). In addition, we will send emails to researchers to obtain any missing data.

Assessment of risk of bias

The risk of bias for the included studies will be assessed by two investigators (Rui Yang and Cheng Hu) independently using the Cochrane Risk of Bias V.2.0. tool [21]. The assessments will be conducted across 5 domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in the measurement of the outcome and (5) bias in the selection of reported result. Each domain will be classified as high, moderate (some concerns), or low risk of bias, and studies will be given an overall classification of high, moderate (some concerns), or low risk of bias. Any disagreements will be resolved with the third investigator (Lihui Deng).

Data synthesis and analysis

If quantitative analysis is feasible, R version 4.2.2 and STATA 15.0 software will be used for statistical analysis. In case quantitative analysis cannot be conducted, the results will be described narratively. For binary outcomes, the pooled effects will be calculated as risk ratio (RR) with 95% confidence intervals (CIs). For continuous outcomes, if the scales of outcomes are uniform, mean difference (MD) with 95% CIs will be used, otherwise, standardized mean difference (SMD) with 95% CIs will be applied. Median and interquartile ranges (IQRs) will be transformed into mean and standard deviation (SD) [22].

We will construct a Bayesian network meta-analysis for each outcome to compare the individual CTMs used for sepsis or septic shock patients using the "BUGSnet" (Bayesian inference Using Gibbs Sampling to conduct a Network meta-analysis) package [23] in R. Both fixed-effects and random-effects model will be fitted, and we will use the more suitable model. Model fit will be assessed using the deviance information criterion (DIC) [24]. After selecting the appropriate model, we will evaluate model convergence using the trace and density plots, as well as Gelman-Rubin's potential scale reduction factor [25]. The network plot will be created to visualize direct and indirect comparisons between different treatments. League tables will be generated to estimate the relative effects of different treatments. Surface under the cumulative ranking curve (SUCRA) values will be utilized to rank each treatment [26]. A larger SUCRA value indicates a better rank of treatment.

Both global and local approaches will be used to assess inconsistency between direct and indirect evidence. We will use the Chi-square test to assess the global inconsistency. If closed loops exist, the node-splitting approach [27] will be used to examine the local inconsistency. Also, we will use a comparison-adjusted funnel plot to identify small study effects and assess potential publication bias in the outcomes with 10 or more RCTs. Heterogeneity will be assessed using the I^2. A sensitivity analysis will be performed to test the robustness of the results by eliminating each study. If feasible, subgroup analysis will be performed for the primary outcomes based on the severity of the disease and the diagnostic criteria.

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Certainty of evidence assessment

The quality of evidence for each outcome will be assessed using the CINeMA (Confidence in Network Meta-Analysis) web application [28, 29]. The CINeMA includes 6 domains: (1) within-study bias, (2) across-studies bias, (3) indirectness, (4) imprecision, (5) heterogeneity, and (6) incoherence. The certainty of evidence will be classified as high, moderate, low, or very low.

Discussion

Our study will be among the pioneering efforts to evaluate the △SOFA score for assessing various CTMs in the treatment of sepsis or septic shock. Furthermore, we will assess the protective effect of different CTMs on organ perfusion by examining △Lac, △MAP, total dose and duration of vasoactive drugs. We hope that the results of this network meta-analysis will provide additional insights into the efficacy and safety of various CTMs used in sepsis or septic shock patients, providing help for future clinical practice and research.

Dissemination

The results of the final analysis will be published and disseminated at the university and across various social media platforms. Additionally, the results will be presented at a conference, and the research findings will be submitted to a peer-reviewed journal.

Abbreviations

CTMs	Chinese tonic medicines
WM	Western medicine
RCTs	Randomized controlled trials
△SOFA	Delta Sequential Organ Failure Assessment
△Lac	Delta serum lactate levels
△MAP	Delta mean arterial pressure
ADRs/ADEs	Adverse drug reactions or adverse drug events
SUCRA	Surface under the cumulative ranking curve
CBM	Chinese Biomedical Literature Database
CNKI	China National Knowledge Infrastructure
RR	Risk ratio
CIs	Confidence intervals
MD	Mean difference
SMD	Standardized mean difference
IQRs	Interquartile ranges
SD	Standard deviation
BUGSnet	Bayesian inference Using Gibbs Sampling to conduct a Network meta-analysis
DIC	Deviance information criterion
CINeMA	Confidence in Network Meta-Analysis
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02736-5.

Supplementary Table S1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*. Supplementary

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Table S2. Search strategy. Supplementary Figure S1. PRISMA 2020 flow diagram of study selection. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Authors' contributions
Rui Yang and Cheng Hu contributed equally to this work and shared co-first authorship. Qing Xia and Lihui Deng defined the research topic and study design. Xin Sun, Wen Wang, and Kun Jiang provided advice on the statistical analysis. Rui Yang and Cheng Hu performed the protocol registration. Yuxin Zhuo, Yuxin Shen, and Qingyuan Tan elaborated on the search strategy. Rui Yang and Cheng Hu performed the literature search and wrote the manuscript. Qing Xia and Lihui Deng revised the manuscript. All authors read and approved the final manuscript.

Data availability
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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