

Received 2025-10-21

Revised 2026-05-25

Accepted 2026-09-18

Efficacy and Safety of Xuebijing Injection in the Treatment of Septic Cardiomyopathy: Protocol for a Systematic Review and Meta-analysis

Short title: Xuebijing Injection for Septic Cardiomyopathy

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Abstract

Background: This protocol describes the planned evaluation of the efficacy and safety of Xuebijing injection (XBJI) as adjunctive therapy for septic cardiomyopathy (SCM). **Materials and Methods:** Eight databases will be searched from January 1, 2000 to October 1, 2026 to identify randomized controlled trials of XBJI plus conventional Western therapy for SCM. Risk of bias will be assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Review Manager Web (RevMan Web; Cochrane, London, UK) will be used for meta-analysis. Subgroup analysis, sensitivity analysis, publication bias assessment, trial sequential analysis, and certainty-of-evidence assessment using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach are prespecified. The primary outcomes are creatine kinase-MB (CK-MB) and cardiac troponin I (cTnI). Secondary outcomes include B-type natriuretic peptide (BNP), lactate dehydrogenase (LDH), high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), procalcitonin (PCT), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, intensive care unit length of stay, 28-day mortality, echocardiographic indices of cardiac function, and adverse events. **Discussion:** This protocol was designed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines to synthesize the available evidence on XBJI as adjunctive treatment for SCM. The findings will be reported after completion of the systematic review and meta-analysis. [GMJ.2026;15:e4138] DOI: [10.31661/gmj.v15i0.4138](https://doi.org/10.31661/gmj.v15i0.4138)

Keywords: Septic Cardiomyopathy; Xuebijing Injection; Meta-analysis; Systematic Review; Protocol

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Introduction

Septic cardiomyopathy (SCM) is a syndrome of sepsis-associated acute cardiac dysfunction affecting up to 30% of patients with sepsis [1,2]. It may manifest as arrhythmias and left- and/or right-ventricular systolic or diastolic dysfunction, with or without reduced cardiac output [1]. SCM is associated with markedly increased mortality; reported mortality may approach 70% in selected populations [3], and 28-day mortality remains approximately 42% despite advances in supportive care [4].

Currently, no evidence-based treatment recommendations are specific to SCM. Management primarily relies on correction of septic shock and general cardioprotective strategies, including antimicrobial therapy, fluid resuscitation, vasoactive agents, and supportive care [5,6]. However, these approaches do not directly target the underlying myocardial injury, highlighting the need for adjunctive therapies that provide myocardial protection.

Xuebijing injection (XBJI), an intravenous traditional Chinese medicine preparation, contains *Radix Salviae Miltiorrhizae*, *Flos Carthami*, *Radix Paeoniae Rubra*, *Radix Angelicae Sinensis*, and *Rhizoma Chuanxiong* [7-9]. It has been widely used as adjunctive therapy for SCM since 2004. Preclinical and clinical studies suggest that XBJI may exert cardioprotective effects by inhibiting inflammatory responses, improving microcirculation, attenuating oxidative stress, and regulating immune function [10,11]. Randomized controlled trials (RCTs) have reported associations between adjunctive XBJI and improvements in cardiac function indicators, including cTnI, CK-MB, BNP, NT-proBNP, LVEF, and CI [7,8]. Experimental studies in septic rats have further shown that XBJI may improve cardiac and endothelial function by reducing endothelial cell markers and pro-inflammatory cytokine release [12-14].

Several meta-analyses of XBJI have been published during the past decade [15-17]. However, these reviews did not specifically focus on SCM as a distinct clinical entity, and their inclusion criteria were not tailored to confirmed SCM populations. Findings from general sep-

sis-focused reviews cannot be directly extrapolated to SCM because SCM is characterized by specific myocardial injury patterns, cardiac biomarker profiles, and echocardiographic abnormalities. Patients with SCM may respond differently to adjunctive therapies, and pooled analyses of broader sepsis populations may dilute or obscure SCM-specific cardioprotective effects. In addition, previous reviews did not consistently include a GRADE assessment, comprehensive exploration of heterogeneity, or trial sequential analysis (TSA) to assess the risk of false-positive findings. These clinical and methodological gaps justify a rigorous evidence synthesis focused specifically on SCM.

Therefore, this protocol describes a systematic review and meta-analysis to be conducted in accordance with PRISMA-P guidelines. The primary objectives are to evaluate whether XBJI added to conventional Western therapy (CWT) improves myocardial injury biomarkers compared with CWT alone, to assess the anti-inflammatory effects of XBJI in patients with SCM, and to determine its safety profile. Secondary objectives include summarizing XBJI dosage and clinical use and evaluating effects on clinical outcomes such as 28-day mortality and ICU length of stay.

Materials and Methods

Search Strategy and Information Sources

Four English-language databases (PubMed, Web of Science, Embase, and the Cochrane Library) and four Chinese-language databases (Chinese Science and Technology Journal Database [VIP], China Biomedical Literature Database [CBM], Wanfang Database, and China National Knowledge Infrastructure [CNKI]) will be searched from January 1, 2000 to October 1, 2026 to identify eligible RCTs. No language restrictions will be applied during search or screening. Although the search is expected to retrieve mainly English- and Chinese-language studies, studies in other languages identified through database searches or reference screening will be eligible, and translation will be sought where necessary. The start date was selected because it predates the introduction of Xuebijing injection into

clinical practice in 2004, thereby allowing capture of all relevant studies since the drug became available.

Grey literature sources will also be searched, including clinical trial registries (ClinicalTrials.gov and the Chinese Clinical Trial Registry [ChiCTR]), conference proceedings of relevant international and Chinese societies (e.g., European Society of Intensive Care Medicine, Society of Critical Care Medicine, and the Chinese Medical Association Critical Care Medicine Branch), and dissertation databases (ProQuest Dissertations and Theses and CNKI Dissertations). Reference lists of included studies and relevant systematic reviews will be manually screened for additional eligible trials.

Eligibility Criteria

Participants

Patients aged ≥ 18 years diagnosed with septic cardiomyopathy (SCM) will be included. The diagnosis of sepsis or septic shock will be accepted according to Sepsis-1, Sepsis-2, Sepsis-3 criteria, or explicit criteria defined by the original investigators. To ensure specificity for SCM, eligible studies must report evidence of sepsis-associated cardiac dysfunction based on at least one of the following criteria: (1) echocardiographic evidence of cardiac dysfunction, including reduced left ventricular ejection fraction, ventricular dilatation, systolic dysfunction, diastolic dysfunction, impaired global longitudinal strain, or other investigator-defined echocardiographic abnormalities; (2) explicit diagnosis of SCM or sepsis-induced myocardial dysfunction by the original investigators using clearly described clinical, imaging, or functional criteria; (3) cardiac biomarkers (such as cTnI, cTnT, BNP, or NT-proBNP) combined with objective evidence of cardiac dysfunction. Studies reporting only isolated elevation of cardiac biomarkers without evidence of cardiac dysfunction will not be considered eligible. There will be no restrictions on race, gender, or country.

Interventions and Comparators

Control group: SCM patients in the control group will receive conventional Western

therapy (CWT). At a minimum, CWT must include antimicrobial therapy and hemodynamic support (i.e., fluid resuscitation and/or vasoactive agents), consistent with the Surviving Sepsis Campaign guidelines or equivalent contemporary standards. Additional components of CWT (e.g., oxygen therapy, mechanical ventilation, renal replacement therapy, glycemic control, nutritional support, or adjunctive pharmacologic agents) may vary across studies and will be accepted provided the minimum criteria are met. Intervention group: SCM patients in the intervention group will receive XBJI plus CWT. XBJI must be administered intravenously. Acceptable daily doses will range from 50 to 100 mL, and the treatment duration must be at least 7 days.

To explore the potential impact of variations in XBJI dosing and treatment duration, we will extract detailed information on the specific dose, frequency, and length of XBJI administration in each included trial. Similarly, to address the potential heterogeneity arising from variations in CWT components across included studies, we will extract detailed information on the specific CWT regimens used in each trial.

Outcomes

Primary outcomes: creatine kinase-MB (CK-MB) and cardiac troponin I (cTnI).

Secondary outcomes: B-type natriuretic peptide (BNP), lactate dehydrogenase (LDH), high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), procalcitonin (PCT), APACHE II score, ICU length of stay, 28-day mortality, and echocardiographic parameters of cardiac function, including left ventricular ejection fraction (LVEF), cardiac index (CI), and E/A or E/e' ratio, where reported in the included studies.

Safety outcomes will include any untoward medical occurrence during treatment, including allergic reactions, gastrointestinal disturbances, bleeding events, hepatic or renal function abnormalities, injection-site reactions, and other events reported by the original study authors. Adverse events will be categorized by system organ class and severity (mild, moderate, or severe) where available. For each in-

cluded study, the number of participants experiencing any adverse event, specific adverse events, and serious adverse events (SAEs) will be extracted. Safety data will be synthesized using risk ratios (RRs) with 95% confidence intervals for total adverse events and serious adverse events using Review Manager Web (RevMan Web; Cochrane, London, UK). Where sufficient studies report specific adverse events, separate meta-analyses will be performed for those events. If substantial heterogeneity is observed, potential sources will be explored through subgroup analyses based on XBJI dose and treatment duration.

CK-MB and cTnI were selected as primary outcomes because they are well-established, sensitive, and specific biomarkers of myocardial injury, which is the core pathological feature of septic cardiomyopathy. Directly quantifying the extent of cardiac damage allows for a focused evaluation of whether XBJI confers a cardioprotective effect. In contrast, clinical outcomes such as 28-day mortality and ICU length of stay, although clinically meaningful, are influenced by numerous confounding factors beyond myocardial protection (e.g., severity of sepsis, comorbidities, and institutional practices), which may dilute the ability to detect the specific myocardial effects of XBJI in the context of a pooled analysis. These clinical endpoints will therefore be evaluated as secondary outcomes, providing a more comprehensive assessment of the overall clinical benefit.

Study Designs

Only randomized controlled trials (RCTs) will be included. Quasi-randomized trials, defined as those using non-random allocation methods such as alternation, date of birth, or medical record number, will be excluded. Cluster RCTs and crossover trials will be considered for inclusion; however, for cluster RCTs, we will assess whether the study accounted for clustering in the analysis, and for crossover trials, we will only extract data from the first period prior to crossover to avoid carry-over effects.

Exclusion Criteria

1) duplicate literature, reviews, commentaries,

animal and cellular experiments; 2) unavailability of the full text of the study; 3) statistical flaws in the data of the article; 4) involvement of other specific drugs or interventions that are administered asymmetrically between the experimental or control groups in a manner that would confound the assessment of XBJI efficacy; 5) duplicate publications for similar authors and results.

Search Strategy

The search strategy will combine terms related to the population and intervention. The complete PubMed search strategy is provided as a supplementary file. Briefly, XBJI-related terms will include “Xuebijing injection,” “Xuebijing,” “Xue Bi Jing,” “Xuebijing injectable,” and related variants. SCM-related terms will include “septic cardiomyopathy,” “sepsis-induced cardiomyopathy,” “septic myocardial injury,” “sepsis-induced myocardial injury,” “sepsis-induced myocardial dysfunction,” “sepsis cardiomyopathy,” “sepsis-related cardiomyopathy,” “sepsis-associated cardiomyopathy,” “myocardial depression in sepsis,” “septic cardiac dysfunction,” and related terms. The MeSH terms “Sepsis” and “Cardiomyopathies” will be used to capture studies that may not explicitly name the condition in the title or abstract. These terms will be searched in titles and abstracts and combined using the Boolean operator AND. A randomized controlled trial search component will be applied to improve retrieval of potentially eligible studies. Corresponding Chinese-language terms for RCTs will be used in Chinese database searches. No study will be excluded solely based on the search filter, and final eligibility will be determined during screening. Searches will be limited to publications from January 1, 2000 to October 1, 2026.

Chinese-language database strategies will use corresponding terms for disease concepts, myocardial injury, cardiac dysfunction, and cardiac performance indicators. If the number of retrieved studies is too small, the search will be broadened using population and intervention terms only, followed by manual screening according to eligibility criteria.

Data Collection and Analysis

Study Selection

All records retrieved from database and grey literature searches will be imported into NoteExpress (version 4.0.0.9855; Aegean Software, Beijing, China), and duplicate records will be identified and removed using the software duplicate-detection function. After deduplication, two reviewers will independently screen titles and abstracts according to the eligibility criteria. Full texts of potentially eligible studies will then be retrieved and independently assessed for final inclusion by the same two reviewers. Any disagreements during title/abstract screening or full-text review will be resolved through discussion; if consensus cannot be reached, a third reviewer will make the final decision.

Data Extraction and Management

Data from each eligible study will be extracted independently by two reviewers using a standardized form. Extracted items will include publication year, study setting (e.g., ICU, hospital, and country), baseline severity of illness (e.g., APACHE II score or SOFA score), SCM diagnostic criteria, sample size, participant age, intervention details (XBJI dose, frequency, route, and treatment duration), comparator details (CWT components), primary and secondary outcomes, follow-up duration, adverse events, and funding source. If essential data are missing or unclear, the corresponding author will be contacted by email, with one reminder sent after two weeks. If missing data cannot be obtained, the study will remain in the systematic review, but the specific outcome or variable will be reported as “not reported” and excluded from the relevant meta-analysis. For multi-arm studies, data from each eligible XBJI arm will be extracted separately, and shared control groups will be handled as described in the data synthesis section.

Risk of Bias Assessment

Two reviewers will assess risk of bias using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Because RoB 2 is outcome-specific, assessment will be performed separately for the two primary out-

comes (CK-MB and cTnI) and for the key secondary outcome of 28-day mortality. Domains will include the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result. Each outcome will be judged as “low risk of bias,” “some concerns,” or “high risk of bias.” Discrepancies will be resolved by consensus.

Data Synthesis and Statistical Analysis

Review Manager Web (RevMan Web; Cochrane, London, UK) will be used for meta-analysis. For continuous outcomes, mean difference (MD) with 95% confidence interval (CI) will be used when all studies report the same outcome using the same unit of measurement (e.g., CK-MB in U/L, cTnI in ng/mL, BNP in pg/mL, and IL-6 in pg/mL). Standardized mean difference (SMD) with 95% CI will be used when outcomes are reported on different scales or in different units. For dichotomous outcomes, risk ratio (RR) with 95% CI will be calculated.

Some outcomes, such as ICU length of stay and biomarker concentrations (e.g., CK-MB, cTnI, BNP, and IL-6), may have skewed distributions and may be reported as medians with interquartile ranges (IQRs) rather than means with standard deviations (SDs). If studies report only medians and IQRs, corresponding authors will first be contacted to request means and SDs. If these data cannot be obtained, means and SDs will be estimated using the methods described by Wan et al. [18] or Luo et al. [19], provided the sample size and distribution permit reasonable approximation. Studies for which means and SDs cannot be obtained or estimated will be excluded from the meta-analysis but retained in the qualitative synthesis.

A fixed-effect model assumes that all studies estimate the same true effect and accounts only for within-study variability. A random-effects model assumes that true effects may vary across studies and incorporates both within-study and between-study variability. Statistical heterogeneity will be assessed using the Chi-square test and I^2 statistic. If $P > 0.1$ and $I^2 \leq 50\%$, a fixed-effect model will be used; otherwise, a random-effects model will be applied. Clinical and methodological

heterogeneity will also be assessed by examining variation in study populations, SCM diagnostic criteria, XBJI dosing regimens, and CWT components. If important clinical heterogeneity is identified despite low statistical heterogeneity, a random-effects model will be considered to provide more conservative estimates. Subgroup and sensitivity analyses will be performed when $P \leq 0.1$ or $I^2 > 50\%$ suggests substantial heterogeneity.

The following subgroup analyses are pre-planned to explore potential sources of heterogeneity and to assess whether the treatment effect of XBJI differs across clinically relevant subgroups: (1) XBJI dose: 50 mL/day versus 100 mL/day; (2) XBJI treatment duration: 7–13 days versus ≥ 14 days; (3) SCM diagnostic criteria: studies using Sepsis-3 definitions versus Sepsis-1 or Sepsis-2 definitions; (4) baseline sepsis severity: studies enrolling patients with a mean baseline APACHE II score < 20 versus ≥ 20 , or a similar validated severity score where available; (5) co-interventions: studies with versus without the concomitant use of ulinastatin or other specific adjunctive agents administered symmetrically to both arms. Subgroup analyses will only be conducted when at least three studies are available in each subgroup category to ensure meaningful comparisons.

If multi-arm studies (e.g., studies with two different XBJI dose groups compared with a single control group) are included, we will handle the shared control group to avoid double-counting of control participants in the meta-analysis. For continuous outcomes, the sample size of the shared control group will be divided by the number of intervention arms, and the means and standard deviations of the control group will remain unchanged. For dichotomous outcomes, both the number of events and the total number of participants in the shared control group will be divided by the number of intervention arms. This approach ensures that each control participant is counted only once across the pairwise comparisons, preserving the statistical independence of effect estimates. Where co-interventions such as ulinastatin are administered equally to both arms, we will record these regimens and, if a sufficient number of studies permit, perform

subgroup analyses to assess whether the presence of specific co-interventions modifies the estimated treatment effect of XBJI.

Publication bias will be assessed using funnel plots and Egger's regression test when at least 10 studies are available for a given outcome. For outcomes with fewer than 10 studies, funnel plots will not be generated, as the statistical power to detect asymmetry is insufficient, and potential publication bias will be discussed narratively in the final review based on clinical judgment and consideration of small-study effects.

Sensitivity Analysis

We will assess the robustness of the conclusions and explore potential sources of heterogeneity through the following prespecified sensitivity analyses: (1) exclusion of studies judged to be at high risk of bias by RoB 2 for the analyzed outcome; (2) exclusion of small studies, defined as those with fewer than 30 participants per arm; (3) exclusion of studies for which means and SDs were estimated from medians and IQRs; and (4) leave-one-out analysis to identify whether any single study disproportionately influences the pooled effect size or heterogeneity. These analyses will be conducted for CK-MB, cTnI, and 28-day mortality, provided that enough studies are available for meaningful comparison.

Trial Sequential Analysis

To control for the risk of type I and type II errors, trial sequential analysis (TSA) will be performed for the two primary outcomes (CK-MB and cTnI) and for the key secondary outcome of 28-day mortality, as these are the most clinically important endpoints for assessing the efficacy of XBJI in SCM. The following TSA parameters will be used: an overall type I error (α) of 5% and a type II error (β) of 20% (i.e., 80% statistical power). The anticipated intervention effect will be prespecified based on external evidence and established clinical judgment rather than estimated from the included studies after pooling. For the dichotomous outcome of 28-day mortality, we will assume a 20% relative risk reduction ($RR = 0.80$) and a control event proportion of approximately 42% [4], based on

previously published observational data for septic cardiomyopathy. For the continuous outcomes (CK-MB and cTnI), the anticipated intervention effect will be defined as an SMD of 0.4, representing a clinically meaningful moderate effect size. This threshold was selected based on conventional interpretation of standardized effects in clinical research [20] and will be interpreted cautiously considering the biological variability and clinical context of cardiac biomarkers.

The variance for continuous outcomes will be estimated from previously published data or external preliminary evidence, not solely from the included studies. Heterogeneity will be adjusted using a random-effects model with the diversity (D^2) statistic, as recommended for TSA. CIs will be adjusted for sparse data using TSA software (version 0.9.5.10beta), and the cumulative meta-analysis will be re-tested. If the cumulative Z-curve crosses the TSA monitoring boundary or the required information size (RIS) is reached before crossing the boundary, definitive conclusions can be drawn regarding the efficacy or futility of XBJI without further research. If neither condition is met, the results will be considered inconclusive, and further trials may be warranted [21].

Certainty of Evidence

The certainty of evidence for the meta-analysis results will be assessed using the GRADE approach. RCT evidence will initially be considered high certainty but may be downgraded for risk of bias, inconsistency, indirectness, imprecision, or publication bias. The final certainty of evidence will be categorized as high, moderate, low, or very low. A GRADE Summary of Findings table will be constructed using GRADEpro GDT software (McMaster University and Evidence Prime, Hamilton, Canada) to present the certainty of evidence for each outcome, anticipated absolute and relative effects, and reasons for downgrading decisions. <https://www.gradepro.org/>

Ethics Approval

This systematic review protocol has been registered in the Prospective Register of Sys-

tematic Reviews (PROSPERO) with this registration number: CRD420261480684 which is available here: www.crd.york.ac.uk/prosperto/. Because the review will use data from published studies, ethics approval and consent to participate are not required.

Discussion

Traditional Chinese medicine (TCM) has been explored as an adjunctive pharmacological approach in infectious diseases [22,23], including SCM. TCM combined with CWT has been investigated as a potential adjunctive approach for SCM; however, the magnitude and certainty of clinical benefit remain uncertain [24]. The efficacy and safety of XBJI for SCM therefore require rigorous evaluation using a transparent and prespecified systematic review methodology. This protocol was designed in accordance with PRISMA-P guidelines. The completed review will evaluate the efficacy and safety of XBJI combined with CWT for SCM and will assess whether XBJI may improve cardiac function, reduce inflammatory responses, shorten ICU stay, or reduce 28-day mortality.

SCM is characterized by impaired cardiac systolic function, diastolic dysfunction, and reduced cardiac index and ejection fraction [25]. XBJI has been investigated as adjunctive therapy for SCM in China, and some studies have reported potential therapeutic benefits and an acceptable safety profile [26]. Proposed mechanisms include inhibition of endogenous inflammatory mediators such as TNF- α and IL-6, reduction of malondialdehyde production, increased activity of antioxidant enzymes such as glutathione peroxidase, and modulation of immune-cell function, including neutrophils and mononuclear macrophages [27]. Some clinical studies have reported that XBJI may improve clinical outcomes and cardiac function, shorten disease duration, and reduce 28-day mortality in SCM [28,29]. Additional studies suggest that XBJI may exert cardioprotective effects by inhibiting inflammation, improving microcirculation, attenuating oxidative stress, and regulating immune function [10,11].

The planned meta-analysis will assess these

potential benefits systematically.

The planned methodology addresses key limitations of the existing evidence base, including methodological heterogeneity, inconsistent results, small sample sizes, and risk of bias. By applying RoB 2, prespecified subgroup and sensitivity analyses, TSA, and GRADE certainty assessment, this review aims to provide a more robust and transparent synthesis of evidence than previous reviews. Despite advances in sepsis management, SCM remains associated with substantial morbidity and mortality, underscoring the need for therapies that specifically target sepsis-associated cardiac dysfunction. The findings may help determine whether XBJI should be considered as a potential adjunctive treatment for patients with SCM, contingent on the certainty and consistency of the available evidence. The review will also summarize XBJI dose and treatment duration, which may inform future clinical trials and practice recommendations. Several potential limitations of this planned review should be acknowledged. First, included RCTs may have small sample sizes, limiting statistical power and increasing the risk of small-study effects. Second, although both English and Chinese databases will be searched, studies published in other languages or indexed in other regional databases may be missed, potentially introducing language

or database bias. Third, heterogeneity in SCM diagnostic criteria, sepsis definitions (Sepsis-1, Sepsis-2, and Sepsis-3), echocardiographic measures, and biomarker thresholds may limit comparability across study populations. Fourth, variation in CWT components and XBJI dose or duration may introduce additional heterogeneity, which will be explored through prespecified subgroup and sensitivity analyses. These limitations will be discussed in the completed review and considered when interpreting the findings.

Data Availability Statement

The full dataset will be generated from published literature. Data extracted and analyzed during the review will be available from the corresponding author upon reasonable request after completion of the study.

Conflict of Interest

The authors declare no conflict of interest.

AI Disclosure Statement

The author(s) declare that no artificial intelligence (AI)-assisted tools or services were used during the preparation of this work.

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