Application Analysis of Outcome Measures in Randomized Controlled Trials of Traditional Chinese Medicine for Coronary Microvascular Disease: A Postprint Study

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Abstract

Background Coronary microvascular disease (CMVD) is currently a focal point in cardiovascular research. Traditional Chinese Medicine (TCM) demonstrates unique advantages and significant efficacy in treating CMVD. However, existing clinical trials suffer from inconsistencies in diagnostic and efficacy criteria. Establishing a core outcome indicator set for TCM treatment of CMVD would facilitate the generation of high-quality evidence-based findings.

Objective To analyze the application of outcome indicators in randomized controlled trials (RCTs) of TCM interventions for CMVD and propose corresponding issues and recommendations.

Methods RCTs of TCM for CMVD were retrieved from China National Knowledge Infrastructure (CNKI), SinoMed, VIP, Wanfang Data, PubMed, Embase, and Cochrane Library from inception to February 9, 2023. Study characteristics, interventions, and outcome indicators were extracted. The Cochrane Handbook's risk-of-bias assessment tool was employed to evaluate methodological quality, while Excel was utilized for statistical analysis of outcome indicators.

Results Eighty-eight articles were included, comprising 2 clinical trial registration protocols and 1 English-language publication. The Corhrane bias risk tool assessment results showed that for the included literature, most evaluations were "unclear" for random sequence generation, allocation concealment, blinding of patients and trial personnel, blinding of outcome assessors, and other biases; most evaluations were "low risk" for completeness of outcome data and selective reporting. A total of 18 articles conducted TCM syndrome pattern analysis on included CMVD patients, including 6 articles on qi deficiency and blood stasis syndrome and 3 articles on phlegm-stasis intermingling syndrome. Statistical analysis of outcome indicators yielded a total of 115 distinct outcome indicators,

with a total frequency of 571, which could be divided into 7 categories: clinical efficacy, laboratory/physiological testing, symptoms and signs, TCM syndrome scores, quality of life, long-term prognosis, and safety monitoring. Overall clinical efficacy rate was the most frequently reported indicator (46 instances). The 3-month time point was most commonly used. The most frequent composite outcome indicator was clinical efficacy combined with laboratory/physiological testing (14 instances).

Conclusion The overall quality of RCTs on TCM for CMVD remains suboptimal. Outcome indicators lack standardized TCM syndrome diagnostic criteria and efficacy standards, with insufficient long-term prognosis monitoring. Future high-quality RCTs incorporating TCM therapeutic characteristics are warranted to establish a standardized core outcome indicator set for TCM treatment of coronary microvascular disease.

Full Text

Application Analysis of Outcome Measures in Randomized Controlled Trials of Traditional Chinese Medicine for Coronary Microvascular Disease

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Abstract

Background
Coronary microvascular disease (CMVD) represents a major focus of cardiovascular research. Traditional Chinese medicine (TCM) demonstrates unique advantages and significant efficacy in treating CMVD, yet current clinical trials suffer from inconsistent diagnostic and efficacy evaluation standards. Establishing a core outcome set for TCM treatment of CMVD would facilitate the generation of high-quality evidence-based findings in the future.

Objective
To analyze the application of outcome measures in randomized controlled trials (RCTs) of TCM interventions for CMVD and propose corresponding problems and recommendations.

Methods
We systematically searched CNKI, SinoMed, VIP, Wanfang, PubMed, Embase,

and Cochrane Library for RCTs of TCM treatment for CMVD from inception to February 9, 2023. Basic study information, interventions, and outcome measures were extracted. The Cochrane Handbook risk of bias assessment tool was used to evaluate bias risk, and Excel software was employed for statistical analysis of outcome measures.

Results
A total of 88 articles were included, comprising 2 clinical trial registration protocols and 1 English-language publication. Cochrane risk of bias assessment revealed that most included studies were rated as "unclear" for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, and other biases; outcome data completeness and selective reporting were mostly rated as "low risk." Eighteen studies analyzed TCM syndrome patterns in CMVD patients, including 6 studies on qi deficiency with blood stasis syndrome and 3 studies on phlegm-blood stasis intermingling syndrome. Statistical analysis identified 115 outcome measures with a total frequency of 571 occurrences, classified into 7 categories: clinical efficacy, physiochemical testing, symptoms and signs, TCM syndrome scores, quality of life, long-term prognosis, and safety monitoring. The most frequently reported measure was total clinical efficacy rate (46 occurrences), with 3 months being the most common intervention timepoint. The most frequent composite outcome measure combined clinical efficacy with physiochemical testing (14 occurrences).

Conclusion
The overall quality of RCTs on TCM treatment for CMVD remains low, with outcome measures suffering from a lack of standardized TCM syndrome diagnostic criteria and efficacy standards, insufficient long-term prognosis monitoring, and other issues. Future high-quality RCTs incorporating TCM therapeutic characteristics are needed to construct a standardized core outcome set for CMVD treatment with TCM.

Keywords: Coronary artery disease; Coronary microvascular disease; Core outcome set of traditional Chinese medicine; Outcome measures; Traditional Chinese medicine; Randomized controlled trials

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1. Materials and Methods

1.1 Inclusion and Exclusion Criteria

Inclusion criteria: (1) Studies with participants definitively diagnosed with CMVD; (2) RCTs using Chinese patent medicines, herbal decoctions, herbal injections, acupuncture, massage, moxibustion, or other TCM therapies as interventions, with no restrictions on control group interventions; (3) No language restrictions.

Exclusion criteria: (1) Conference papers, master's theses, reviews, animal experiments, and case reports; (2) Studies without clear inclusion/exclusion criteria; (3) Studies with unreasonable design, duplicate publication, or incomplete data.

1.2 Search Strategy

We searched seven Chinese and English databases from inception to February 9, 2023: CNKI, Wanfang, VIP, SinoMed, PubMed, Embase, and Cochrane Library. Chinese search terms included: coronary microvascular disease, coronary microcirculation disorder, microvascular angina, cardiac syndrome X, coronary slow flow, no-reflow phenomenon, non-obstructive coronary artery disease, traditional Chinese medicine, Chinese patent medicine, herbal decoction, pill, granule, capsule, acupuncture, cupping, moxibustion, massage, scraping, qigong. English search terms included: Microvascular Angina, Syndrome X, coronary microvascular dysfunction, coronary microvascular disease, Slow-Flow Phenomenon, No-Reflow Phenomenon, CMD, CMVD, Chinese medicine, traditional Chinese medicine, Chinese and western medicine, acupuncture, cupping, Moxibustion, Chinese patent medicine, decoction, pill, granule, capsule, massage, scrapping, Qigong. We combined subject headings with title and keyword searches.

1.3 Literature Screening and Data Extraction

Two researchers independently screened literature according to inclusion and exclusion criteria, documenting the screening process in detail and cross-checking results. Disagreements were resolved through discussion or consultation with a third party. Excel software was used to extract literature information, including basic study characteristics, interventions, and outcome measures.

1.4 Risk of Bias Assessment

The Cochrane Handbook 5.1.0 risk of bias tool was used to assess literature quality, evaluating random sequence generation, allocation concealment, blinding of researchers and participants, blinding of outcome assessors, completeness of outcome data, selective reporting, and other potential biases.

1.5 Statistical Analysis

(1) Statistical analysis of TCM syndrome diagnosis and efficacy criteria in RCTs of TCM for CMVD; (2) Classification and frequency counting of outcome measures by type; (3) Frequency analysis of composite outcome measures based on different classification combinations; (4) Statistical analysis of intervention duration for high-frequency outcome measures.

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2. Results

2.1 Literature Screening Process and Results

The initial search yielded 2,025 articles. After removing duplicates (n=755), 1,270 articles remained. Title and abstract screening excluded 1,069 articles (reviews, experiments, dissertations, conference papers, case reports, and irrelevant studies), leaving 201 articles for full-text review. After excluding 95 studies with inappropriate study types, 10 non-RCT studies, and 8 studies with incomplete information, 88 articles were finally included (see Appendix A; scan the QR code on the article's first page for details), including 2 trial protocols and 1 English-language article [Figure 1: see original paper].

2.2 Risk of Bias Assessment

The Cochrane risk of bias tool was used to assess 86 articles and 2 trial protocols. (1) Random sequence generation: 39 articles were rated as low risk [8,11-48], while 49 articles did not specify randomization methods and were rated as unclear risk; (2) Allocation concealment: 2 articles were rated as low risk [8,14], while 86 were rated as unclear risk; (3) Blinding of participants and personnel: 2 articles were rated as low risk [14,48], while 86 were rated as unclear risk; (4) Blinding of outcome assessors: 1 article was rated as low risk, 1 as high risk [14], and 86 as unclear risk; (5) Outcome data completeness: 2 articles were rated as unclear risk, while 86 were rated as low risk; (6) Selective reporting: 3 articles were rated as high risk [49-51], 2 as unclear risk, and 83 as low risk; (7) Other biases: All other trials lacked specific information for bias assessment or provided incomplete information, resulting in unclear risk ratings [Figure 2: see original paper].

2.3 Literature Analysis

Among the 88 included studies, interventions included Chinese patent medicines, injections, self-formulated prescriptions, auricular acupuncture, and other TCM treatments. The longest treatment duration was 12 months [37], the shortest was 7 days [44], the largest sample size was 577 cases [34], and the smallest was 27 cases [52], with an average sample size of 89 cases. Eighteen studies analyzed TCM syndrome patterns in CMVD patients, including 6 on qi deficiency with blood stasis syndrome, 3 on phlegm-blood stasis intermingling syndrome, 2 on

cold congealing in the heart meridian syndrome, 2 on qi-yin deficiency syndrome, 2 on qi deficiency with blood stasis and phlegm obstruction syndrome, 1 on heart blood stasis obstruction syndrome, 1 on qi stagnation with blood stasis syndrome, and 1 on qi stagnation with phlegm obstruction and blood stasis syndrome .

Twenty-three studies specified reference standards for total clinical efficacy evaluation, including: *Guidelines for Clinical Research of New Chinese Medicines* (12 studies) [16-17,21,23,27,31,35,41,53-54,59-60]; *Guidelines for Diagnosis and Treatment of Common Cardiovascular and Cerebrovascular Diseases in China* (4 studies) [51,61-63]; *Principles for Clinical Research Reporting of Cardiovascular Drugs* (2 studies) [14-15]; *Technical Guidelines for Clinical Research of Traditional Chinese Medicine and Natural Medicine in Treating Coronary Heart Disease and Angina* combined with *Guidelines for Clinical Research of New Chinese Medicines* (1 study) [13]; *Clinical Disease Diagnosis Basis and Cure/Improvement Standards* (1 study) [32]; *Expert Consensus on TCM Diagnosis and Treatment of Stable Angina Pectoris of Coronary Heart Disease* (1 study) [12]; *Criteria for Evaluating Therapeutic Efficacy of Coronary Heart Disease Angina* (1 study) [64]; and *Standards Revised at the Symposium on Prevention and Treatment of Coronary Heart Disease Angina and Arrhythmia with Integrated Traditional Chinese and Western Medicine* (1 study) [45]. The remaining studies did not specify relevant reference standards or used self-formulated efficacy criteria.

2.4 Outcome Measures Analysis

2.4.1 Classification of Outcome Measures Outcome measures were categorized into seven classes: clinical efficacy, physiochemical testing, symptoms and signs, TCM syndrome scores, quality of life, long-term prognosis, and safety monitoring.

2.4.2 Frequency Analysis of Outcome Measures A total of 115 outcome measures were identified with 571 total occurrences. The top five most frequent measures were: total clinical efficacy rate (46 occurrences), safety monitoring (39), endothelin-1 (ET-1) (38), angina attack frequency (32), and high-sensitivity C-reactive protein (hs-CRP) (31) [TABLE:2-3].

2.4.3 Analysis of Study Duration for High-Frequency Outcome Measures Analysis of intervention duration for the top 10 high-frequency outcome measures revealed that 1 month and 3 months were the primary measurement timepoints. Among measures using 1-month timepoints, total clinical effective rate appeared most frequently; among those using 3-month timepoints, ET-1 appeared most frequently [Figure 3: see original paper].

2.4.4 Evaluation of Composite Outcome Measures and Outcome Measure Set Analysis of composite outcome measure combinations showed: 24

studies used 2-item composites, 32 used 3-item composites, 16 used 4-item composites, 7 used 5-item composites, and 2 used 6-item composites; the remaining 7 studies used single outcome measures. The most frequent composite combined clinical efficacy with physiochemical testing (14 occurrences) .

The outcome measure set for CMVD is illustrated in [Figure 4: see original paper]. The primary pathological mechanism of CMVD is endothelial dysfunction, which depends on four main effectors: inflammatory response, platelet activation, hemodynamics, and autonomic nervous system dysfunction [5,65]. Current outcome measures in TCM treatment for CMVD focus on endothelial function and inflammatory response, with ET-1 and hs-CRP being the two most frequently used physiochemical indicators. Modern basic medical research has identified ET-1 as an independent predictor of CMVD [66], while hs-CRP, as an important inflammatory factor, is closely associated with long-term prognosis in CMVD patients [67]. Integrated TCM and Western medicine demonstrates more significant efficacy than Western medicine alone in improving inflammatory response and endothelial function without increasing adverse events, offering good safety profiles and representing a promising new treatment strategy. However, current research directions and study quality require further improvement.

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3. Discussion

3.1 Problem Analysis

3.1.1 Low Literature Quality The overall quality of clinical trial literature on TCM interventions for CMVD is low, characterized by inconsistent diagnostic criteria, unclear randomization methods, and high risk of allocation concealment issues. Non-standardized clinical trial design, implementation, and analysis can introduce bias into study results [68]. Using the Cochrane risk of bias tool, we found most studies lacked specific information for bias assessment or provided incomplete details. Only a few studies described randomization methods, blinding, and allocation concealment. Future TCM clinical trials for CMVD should strictly adhere to clinical trial design standards to reduce relevant bias risks.

3.1.2 Non-uniform Standards for Clinical Efficacy Evaluation Among the 88 included studies, 46 reported total clinical efficacy, but only 23 specified reference standards for efficacy evaluation, which showed considerable diversity. The long-standing issues of non-unified evaluation indicators and arbitrary selection in TCM clinical efficacy assessment have severely constrained the internationalization of TCM [69]. Clinical efficacy evaluation is crucial for demonstrating TCM effectiveness in treating CMVD, and unified evaluation criteria should be established and referenced. The lack of standardized efficacy evaluation criteria represents a key issue that urgently needs resolution in establishing an outcome measure set.

3.1.3 Dispersed Surrogate Indicators, Lack of Quality of Life Assessment Outcome measures in TCM treatment for CMVD include numerous surrogate indicators, which offer advantages of convenient detection, short observation periods, and cost-effectiveness. However, inadequately validated surrogate indicators provide limited meaningful information and may produce contrary effects [70]. The pathogenesis of CMVD remains unclear, and surrogate indicators cannot comprehensively reflect disease progression. Under the TCM theoretical system of syndrome differentiation and treatment, TCM can improve patient symptoms through multiple mechanisms [71], playing a holistic regulatory role. Combining relevant quality of life scales to record and analyze patients' daily life quality can better demonstrate the significance of integrated TCM and Western medicine treatment.

3.1.4 Lack of Standardized TCM Syndrome Diagnosis and Efficacy Criteria Current TCM treatment for CMVD suffers from inconsistent reference standards for syndrome diagnosis and non-uniform syndrome nomenclature. Syndrome patterns represent a summary of pathological mechanisms at specific disease stages and constitute a unique theoretical system distinguishing TCM from other disciplines [72]. Syndrome differentiation and treatment form the core of TCM diagnosis and therapy, yet current reference standards for TCM syndrome differentiation remain incompletely unified. Different reference standards may produce different syndrome differentiation results for the same patient, introducing bias and affecting systematic evaluation of clinical trials.

3.1.5 Limitations of Composite Indicators Our analysis revealed that composite outcome measure combinations in CMVD clinical trials inadequately and subjectively evaluate the efficacy and safety of TCM treatment. Using TCM syndrome scores and angina symptoms as primary outcome measures, while reflecting subjective patient experiences to some extent, may produce false-positive results due to multiple influencing factors. The core of constructing a TCM efficacy evaluation index system lies in comprehensively, objectively, and scientifically reflecting TCM clinical intervention effectiveness, highlighting TCM treatment characteristics, and obtaining evidence support through evidence-based medicine validation [73]. Future studies should conduct comprehensive investigations incorporating TCM syndrome scores, total clinical efficacy, physiochemical testing, safety evaluation, and economic assessment to objectively and authentically reflect TCM effectiveness and safety in CMVD patients.

3.1.6 Lack of Adverse Cardiovascular Event Monitoring and Long-term Prognosis Follow-up Long-term follow-up studies have revealed that CMVD patients experience poor quality of life and high rates of adverse cardiovascular events, particularly hospitalization for unstable angina [74-75]. Adverse cardiovascular events represent the "hard endpoint" of greatest concern to patients and the optimal method for demonstrating TCM treatment effec-

tiveness. Current conventional Western medicine treatment strategies have not demonstrated significant impact on long-term adverse cardiovascular events in CMVD patients. Clarifying the effect of TCM on adverse cardiovascular events in CMVD patients can further leverage TCM advantages.

3.1.7 Lack of Safety Indicator Analysis and Economic Outcome Measures In TCM clinical research, combined use of Chinese and chemical medicines may raise safety concerns due to drug interactions [76]. TCM clinical trials should truthfully record adverse reactions occurring during combined TCM-Western medicine treatment and analyze their causes. Additionally, pharmacoeconomic advantage studies constitute an important component of TCM clinical efficacy evaluation and represent a major scientific issue facing current TCM inheritance and innovation [77]. However, none of the included studies assessed pharmacoeconomic indicators, suggesting that future TCM clinical trials should strengthen evaluation of pharmacoeconomics and safety indicators.

3.2 Reflections and Recommendations

3.2.1 Improving Trial Quality Future clinical trials should standardize the design of TCM treatment for CMVD, strictly following TCM clinical trial design standards with emphasis on key methodological items such as randomization methods, blinding, allocation concealment, and sample size estimation [78] to reduce relevant bias risks. Additionally, TCM clinical trials for CMVD should strengthen safety evaluation and pharmacoeconomic analysis, such as detailed recording and monitoring of adverse events (nausea, vomiting, gastrointestinal reactions, etc.) and safety indicators (liver function, kidney function, electrolytes, etc.), analyzing the causes of adverse events, and conducting statistical analysis of economic indicators such as readmission rates and medication costs.

3.2.2 Standardizing TCM Diagnosis and Treatment Standards The disease-syndrome combination model represents the main diagnostic and treatment paradigm for TCM prevention and treatment of various diseases. However, only a few studies have investigated CMVD syndrome distribution patterns, which remain unclear. Future research should strengthen investigation of CMVD syndrome distribution to establish diagnostic and efficacy criteria for different syndrome types and standardize and quantify them. Accurate syndrome differentiation and appropriate TCM intervention selection based on syndrome types can enhance TCM efficacy and demonstrate the characteristic TCM treatment approach of syndrome differentiation and treatment, highlighting TCM's unique advantages in effectively improving patient symptoms.

3.2.3 Selecting Appropriate Outcome Measures When selecting outcome measures, researchers should combine study objectives and interventions with domestic and international CMVD research to identify primary outcome

measures that are essentially related to study purposes and can accurately reflect intervention efficacy [69]. Appropriate secondary outcome measures should also be selected to comprehensively, truthfully, and objectively demonstrate TCM efficacy. For example, patient quality of life can reflect treatment effectiveness to some extent and can be assessed using scales such as SF-36 and SAQ. Clinical trials should also comprehensively consider factors such as sample size, research costs, and patient compliance to conduct long-term prognosis monitoring of TCM treatment for CMVD patients, including adverse cardiovascular events, readmission rates, and long-term survival rates.

3.2.4 Establishing a Core Outcome Set A core outcome set can standardize outcome measures and their measurement tools, reduce publication bias or selective outcome reporting, enable horizontal comparison of different interventions, and facilitate vertical meta-analysis across studies to form professional standards and promote systematic evaluation of relevant research [9]. We recommend summarizing outcome measures for TCM treatment of CMVD through expert interviews, questionnaires, and literature review, classifying them according to the 12 categories recommended in the COMET handbook (including mortality, physiochemical testing, pain, quality of life, mental health, treatment modifications, healthcare resource utilization, and adverse events). A standardized core outcome set for TCM treatment of CMD should be constructed through Delphi methods, consensus conferences, and other approaches, using internationally recognized methods to evaluate TCM effectiveness, safety, applicability, and cost-effectiveness.

Author Contributions: ZHU Mingjun conceived and designed the study and proposed the main research objectives. WANG Aolong was responsible for literature screening and data extraction, drafted the manuscript, performed data extraction and result analysis, and revised the article. WANG Aolong takes overall responsibility for the article and provided supervision and management. ZHU Mingjun was responsible for quality control and review.

Conflict of Interest: The authors declare no conflicts of interest.

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