Postprint: Current Status of Outcome Measures in Randomized Controlled Trials of Traditional Chinese Medicine for Peptic Ulcer

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Abstract

Background: Peptic ulcer disease (PUD) is a common disorder of the digestive system. Traditional Chinese medicine (TCM) treatment constitutes an effective therapeutic measure for PUD. However, randomized controlled trials (RCTs) investigating TCM treatment for PUD currently exhibit substantial limitations in methodological quality and outcome measure selection, posing certain challenges to efficacy evaluation and data integration analysis.

Objective: This study systematically reviews the application status of outcome measures and key aspects of trial design in RCTs of TCM interventions for PUD over the past 15 years, aiming to provide a reference basis for constructing a core outcome set for TCM treatment of PUD and optimizing clinical trial design.

Methods: A computerized search was conducted for RCTs literature on TCM treatment of PUD in Chinese databases including China National Knowledge Infrastructure, Wanfang Data Knowledge Service Platform, VIP Chinese Journal Database, and China Biology Medicine disc, as well as international authoritative databases: PubMed, Embase, Cochrane Library, and Web of Science; the search timeframe was set from 2010 to 2024. Cochrane risk of bias assessment was performed on included literature, and relevant outcome measures were statistically compiled, summarized, and analyzed.

Results: A total of 323 RCTs were included, involving 34,933 patients. The maximum sample size of a single study was 498 cases, the minimum was 40 cases, and the average sample size was 108 cases. TCM syndrome types were reported in 171 studies, among which the most frequently used was spleen-stomach deficiency-cold (31 studies, 18.13%). Pure TCM treatment was adopted in 47 studies, while integrated Chinese and Western medicine treatment was used in 276 studies. The treatment course was predominantly 4 weeks (119 instances,

36.84%). Outcome measures were categorized into 6 types according to functional attributes, with 170 different outcome measures reported for a total frequency of 1,962 instances. The outcome measures with higher usage frequencies were clinical total effective rate (233 instances, 11.88%), Helicobacter pylori eradication rate (165 instances, 8.41%), and adverse reactions (155 instances, 7.9%). The risk of bias assessment was largely unclear in the included literature.

Conclusion: RCTs on TCM treatment for PUD still exhibit issues including non-standardized TCM syndrome differentiation and disease staging, incomplete methodological design (blinding, allocation concealment), unclear distinction between primary and secondary outcome measures, non-unified clinical efficacy criteria, large variations in outcome measurement timing, diversified scoring standards for TCM syndrome/symptom scores, inadequate attention to ethical registration, and non-standardized reporting of safety indicators. It is recommended to actively develop research on core outcome sets for TCM treatment of PUD, optimize and improve methodological quality, and provide high-quality scientific, reliable, and practical evidence for clinical practice of TCM treatment of PUD.

Full Text

Preamble

Methodological Research: Current Status of Outcome Measures in Randomized Controlled Trials of Traditional Chinese Medicine for Peptic Ulcer Disease

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Abstract

Background: Peptic ulcer disease (PUD) is a common digestive system disorder. While traditional Chinese medicine (TCM) represents an effective therapeutic approach for PUD, randomized controlled trials (RCTs) investigating TCM treatments exhibit significant limitations in methodological quality and outcome measure selection, posing challenges for efficacy evaluation and data integration.

Objective: This study systematically reviews the application status and design characteristics of outcome measures in RCTs of TCM interventions for PUD over the past 15 years, aiming to provide reference for constructing a core outcome set for TCM treatment of PUD and optimizing clinical trial design.

Methods: We conducted comprehensive searches in Chinese databases (China National Knowledge Infrastructure, Wanfang Data, VIP Chinese Journal Database, China Biomedical Literature Service System) and international databases (PubMed, Embase, Cochrane Library, Web of Science) for RCTs on TCM treatment of PUD published between 2010 and 2024. Cochrane risk-of-bias assessment was performed, and outcome measures were systematically categorized and analyzed.

Results: A total of 323 RCTs involving 34,933 patients were included. Individual study sample sizes ranged from 40 to 498 cases, with a mean of 108 cases. Among 171 studies reporting TCM syndrome patterns, spleen-stomach deficiency-cold was most frequent (31 studies, 18.13%). Forty-seven studies employed pure TCM treatment, while 276 used integrated Chinese-Western medicine approaches. The most common treatment duration was 4 weeks (119 studies, 36.84%). Outcome measures were classified into six functional categories, encompassing 170 distinct indicators with 1,962 total occurrences. The most frequently used outcomes were clinical total effective rate (233 occurrences, 11.88%), Helicobacter pylori eradication rate (165 occurrences, 8.41%), and adverse reactions (155 occurrences, 7.9%). Risk of bias assessment revealed predominantly unclear risk across domains.

Conclusion: RCTs of TCM for PUD exhibit multiple methodological deficiencies, including non-standardized TCM syndrome differentiation and disease staging, inadequate methodological design (blinding, allocation concealment), unclear distinction between primary and secondary outcomes, lack of unified clinical efficacy criteria, heterogeneous measurement timepoints, diverse TCM syndrome/symptom scoring systems, insufficient attention to trial registration, and non-standardized safety reporting. We recommend developing a core outcome set for TCM treatment of PUD and improving methodological quality to provide high-quality, reliable, and practical evidence for clinical practice.

Keywords: Peptic ulcer; Traditional Chinese medicine; Outcome index; Core indicator set; Randomized controlled trial

Introduction

Peptic ulcer disease (PUD) is a common digestive system condition characterized by inflammatory responses and necrotic shedding of gastrointestinal mucosa due to various pathogenic factors, forming lesions that typically involve the muscularis mucosae and may extend to the proper muscle layer or deeper [1]. PUD is closely associated with Helicobacter pylori infection and long-term use of

non-steroidal anti-inflammatory drugs, particularly aspirin. While most ulcers occur in the stomach and proximal duodenum, they may also develop in the esophagus, gastrojejunal anastomosis, and rarely in Meckel' s diverticulum [2-3]. Recent epidemiological surveys reported approximately 8.09 million PUD cases globally in 2019, with China' s prevalence reaching 101.27 per 100,000 population, making PUD a major disease burden worldwide [4-6]. Although PUD prevalence in China has declined significantly over the past 30 years due to widespread anti-Hp therapy, this trend has stabilized in the last decade [4].

In TCM, PUD falls under the categories of "stomach pain," "gastric ulcer," and "gastric discomfort," with pathological location in the stomach and close relationships to the liver and spleen [7]. Pathogenic factors include external pathogenic invasion, improper diet, emotional dysregulation, and drug toxicity. The disease nature involves mixed deficiency and excess patterns, with treatment principles focusing on strengthening the spleen and harmonizing the stomach, soothing the liver and regulating qi, clearing heat and eliminating dampness, and activating blood to resolve stasis [7-8]. TCM treatment offers unique advantages through multi-component, multi-target, and multi-pathway mechanisms with significant efficacy and high safety, emphasizing holistic syndrome differentiation and treatment. Numerous RCTs have demonstrated that TCM can significantly improve ulcer healing rates and Hp clearance while reducing recurrence, drug resistance, and adverse reactions when combined with conventional Western medicine [9-12].

Outcome measures serve as crucial benchmarks for evaluating treatment effectiveness, and their scientific selection is a key component of clinical trial design [13]. However, current clinical research suffers from non-standardized, arbitrary outcome measures with inconsistent measurement methods and excessive subjective indicators, posing significant challenges for data integration and efficacy assessment of TCM treatments [14-15]. Therefore, this study systematically reviews RCTs of TCM for PUD over the past 15 years to establish a foundation for developing a core outcome set and provide reference for high-quality research.

Methods

Study Design and Participants

We included patients with definitive diagnoses of peptic ulcer, gastric ulcer, or duodenal ulcer, without restrictions on baseline characteristics such as age, gender, disease duration, or disease stage.

Inclusion Criteria

Study type: RCTs published between 2010 and 2024 investigating clinical efficacy of TCM for PUD in core journals, both domestic and international. **Interventions:** Studies using Chinese herbal formulas, patent medicines, acupunc-

ture, moxibustion, or other TCM modalities, either as monotherapy or in combination with Western medicine, were eligible for inclusion.

Exclusion Criteria

We excluded studies involving patients with complications such as peptic ulcer bleeding or perforation; duplicate publications; literature with missing data or unobtainable full text; non-RCTs including reviews, meta-analyses, basic research, and theoretical studies; and studies not reporting treatment duration.

Literature Search Strategy

We searched Chinese databases (China National Knowledge Infrastructure, Wanfang Data Knowledge Service Platform, VIP Chinese Journal Database, China Biomedical Literature Service System) and international databases (PubMed, Embase, Cochrane Library, Web of Science) for literature published from 2010 to 2024. Chinese search terms included "peptic ulcer," "duodenal ulcer," "gastric ulcer,""traditional Chinese medicine,""Chinese patent medicine,""integrated Chinese and Western medicine," "acupuncture therapy," and related terms. English search terms included "peptic ulcer,""gastroduodenal ulcers,""ulcer,""traditional Chinese medicine," "traditional Chinese drug," and "acupuncture therapy." We employed a combination of subject headings and free-text terms, with search strategies adapted for each database.

Literature Screening and Data Extraction

We managed retrieved literature using Note Express software. After removing duplicates, two researchers independently screened titles and abstracts according to inclusion and exclusion criteria, with disagreements resolved through discussion or by a third researcher. Data extraction using Microsoft Excel included: (1) publication information (title, authors, year, journal); (2) study characteristics (PUD stage, diagnostic criteria, sample size, ethics review, TCM syndrome pattern, Hp infection status, treatment modality, treatment duration); and (3) outcome measures (laboratory tests, measurement tools, measurement timepoints, adverse reactions).

Risk of Bias Assessment

Two researchers assessed risk of bias using the Cochrane Collaboration' s tool [16] and RevMan 5.4 software, evaluating: (1) selection bias (random sequence generation and allocation concealment); (2) performance bias (blinding of participants and personnel); (3) detection bias (blinding of outcome assessors); (4) attrition bias (incomplete outcome data); (5) reporting bias (selective reporting); and (6) other biases. Studies were classified as "low risk," "high risk," or "unclear risk" for each domain.

Data Processing

We established a structured literature database using Microsoft Excel to record publication information, study characteristics, and outcome measures. Following the Technical Specification for Developing Core Outcome Sets for Clinical Trials of Traditional Chinese Medicine [15], we categorized all outcome measures into seven functional domains: TCM disease and syndrome, symptoms/signs, laboratory tests, quality of life, long-term prognosis, economic evaluation, and safety events. We then conducted frequency statistics and descriptive analysis of included indicators.

Results

Literature Screening Results

The initial database search yielded 14,786 articles. After preliminary screening with Note Express and applying inclusion/exclusion criteria, we included 323 RCTs (321 Chinese and 2 English) [Figure 1: see original paper]. The detailed screening process is illustrated in Figure 1.

Basic Characteristics of Included Studies

Over the past 15 years, 323 RCTs on TCM treatment of PUD were published, with the annual publication trend shown in Figure 2 [Figure 2: see original paper].

Sample Size The 323 RCTs included a total of 34,933 patients, with individual study sample sizes ranging from 40 to 498 cases (mean: 108 cases). Sample size distribution was: 40-80 cases in 96 studies (29.72%), 81-100 cases in 91 studies (28.17%), 101-150 cases in 93 studies (28.79%), and 151-200 cases in 43 studies (13.31%).

Treatment Duration and Follow-up Treatment duration ranged from 1 week to 6 months, with 4 weeks being the most common (119 studies, 36.84%) . Follow-up was reported in 114 studies (35.29%), with durations ranging from 1 month to 2 years, most frequently 1 year (44 studies, 38.60%) and 6 months (34 studies, 29.82%).

PUD Staging and H. pylori Infection Status PUD staging was reported in 136 RCTs, with 119 studies (87.5%) focusing on the active stage, 2 (1.47%) on the acute stage, and others including mixed stages. Hp infection status was reported in 221 RCTs (68.42%), with 213 studies (96.38%) including Hp-positive patients and 8 (3.62%) including Hp-negative patients; 102 studies (31.58%) did not mention Hp status.

TCM Syndrome Patterns Among 323 RCTs, 171 documented TCM syndrome patterns, with 24 studies including multiple patterns. Spleen-stomach deficiency-cold syndrome was most common (31 occurrences, 18.13%). Twenty patterns had $ $2 occurrences , with disease locations primarily involving the spleen, stomach, and liver.

Diagnostic Criteria TCM diagnostic criteria were mentioned in 185 RCTs (57.28%), with 20 studies (10.81%) using $ $2 standards, most frequently the *Guiding Principles for Clinical Research of New Chinese Medicines* [17] (63 occurrences, 34.05%) . Western medicine diagnostic criteria were reported in 227 RCTs (70.28%), with 19 studies (8.37%) using $ $2 standards, primarily the *Guiding Principles for Clinical Research of New Chinese Medicines* (33 occurrences, 14.54%) and *Practical Internal Medicine* (32 occurrences, 14.1%) .

Intervention Measures Of 323 studies, 47 (14.55%) used pure TCM treatment and 276 (85.45%) used integrated Chinese-Western medicine. TCM modalities included: oral Chinese herbal formulas/patent medicines (294 studies, 91.02%); oral formulas combined with external therapies (17 studies, 5.26%) such as moxibustion, acupoint application, acupuncture, auricular point pressing, acupoint injection, and combined techniques; and external therapies alone (12 studies, 3.72%) including acupuncture, warm acupuncture, moxibustion, and catgut implantation. Among 311 studies using oral formulas, the most frequently used were Huangqi Jianzhong Decoction modifications (21 occurrences, 6.75%), Banxia Xiexin Decoction modifications (18 occurrences, 5.79%), and Xiangsha Liujunzi Decoction modifications (8 occurrences, 2.57%) .

Risk of Bias Assessment

Using the Cochrane risk-of-bias tool for 323 RCTs: (1) Random sequence generation was low risk in 150 studies (46.44%), high risk in 16 (4.95%) using admission time or odd/even numbers, and unclear in 157 (48.61%). (2) Allocation concealment was low risk in 10 studies (3.1%) using sealed envelopes and unclear in 313 (96.9%). (3) Performance bias: 12 studies (3.72%) used blinding (low risk), while 311 (96.28%) were unclear. (4) Detection bias: 2 studies (0.62%) reported blinded outcome assessment (low risk), while 321 (99.38%) were unclear. (5) Attrition bias: 24 studies (7.43%) reported case attrition, with 21 rated low risk (<10% attrition) and 3 high risk (>10% attrition); 299 (92.57%) were unclear. (6) Reporting bias: 22 studies (6.81%) had missing outcome reports (high risk), while 301 (93.19%) were unclear. (7) Other biases were all rated as unclear risk [Figure 3: see original paper].

Outcome Measures

Classification of Outcome Measures Following the Technical Specification for Core Outcome Sets in TCM Clinical Trials, we categorized outcome

measures from 323 RCTs into six functional domains (no economic indicators were included): laboratory tests (134 types, 917 occurrences), symptoms/signs (11 types, 382 occurrences), safety events (10 types, 343 occurrences), TCM disease/syndrome (8 types, 210 occurrences), long-term prognosis (4 types, 68 occurrences), and quality of life (3 types, 22 occurrences) [Figure 4: see original paper].

Frequency of Outcome Measure Use The 323 studies reported 170 distinct outcome measures with 1,962 total occurrences. Most frequent were clinical total effective rate (233 occurrences, 11.88%), Hp eradication rate (165 occurrences, 8.41%), adverse reactions (155 occurrences, 7.9%), PUD/Hp recurrence rate (110 occurrences, 5.61%), gastroscopic efficacy (103 occurrences, 5.25%), TCM syndrome score (73 occurrences, 3.72%), gastrin (54 occurrences, 2.75%), and TCM syndrome efficacy (53 occurrences, 2.7%) .

Efficacy Evaluation

Clinical Total Effective Rate Reported in 233 studies, this outcome showed 15 different evaluation forms. The most common classification was "clinical cure/healed, markedly effective, effective, ineffective"(143 occurrences), followed by "markedly effective, effective, ineffective" (29 occurrences) .

TCM Efficacy Evaluation TCM efficacy evaluation was used in 166 RCTs, with 133 reporting reference standards. The *Guiding Principles for Clinical Research of New Chinese Medicines* was most frequently used (84 occurrences, 63.16%) . TCM syndrome/symptom scoring criteria were detailed in 128 RCTs, showing 26 different forms, with the most common being 0-3 scoring for none, mild, moderate, severe symptoms .

Outcome Measurement Timepoints

Measurement timepoints were reported in 314 studies as pre- and post-treatment, and in 9 studies as pre-, mid-, and post-treatment. The most frequent timepoint was 0 and 4 weeks (98 occurrences, 30.34%) .

Discussion

Methodological Deficiencies in TCM RCTs for PUD

3.1.1 Non-standardized TCM Syndrome Patterns and Disease Staging Syndrome differentiation reflects the holistic perspective of traditional medicine and represents core clinical practice [18]. Among 323 RCTs, 171 reported TCM syndromes, with "spleen-stomach deficiency-cold" being most common. However, identical concepts appeared under different names (e.g., "liver-stomach

disharmony," "liver qi invading stomach," "liver-stomach qi stagnation," "spleen-stomach damp-heat," "damp-heat obstructing middle burner," "damp-heat obstructing stomach," "damp-heat and blood stasis obstruction," "blood stasis obstructing collaterals," "blood stasis"). This diversity, while demonstrating theoretical flexibility, affects diagnostic accuracy and may limit scientific objectivity [19]. PUD staging was reported in 136 RCTs, with 131 describing active stage using varied terminology including active stage, A1/A2 stage, acute stage, and one study using grade 2/3 classification. This non-standardization hinders cross-study comparisons and data synthesis, necessitating standardized disease staging and unified TCM syndrome criteria for PUD.

3.1.2 High Risk of Bias and Inadequate Methodological Design Risk-of-bias assessment revealed high overall risk across 323 RCTs. One hundred fifty-seven studies failed to describe random sequence generation methods, 313 did not mention allocation concealment, and 311 lacked blinding details. Most researchers focused solely on random sequence generation while neglecting allocation concealment and blinding—critical measures for ensuring validity. Poor methodological quality may exaggerate treatment effects and increase bias risk. Clinical trial registration enhances transparency and ensures quality [20], yet only 6 RCTs were registered on recognized platforms. Sample size estimation is crucial in RCT design; inadequate sample sizes compromise reliability, while excessive sizes waste resources. Included studies ranged from 40 to 489 participants, with only 2 conducting prospective sample size calculations. Future studies should prioritize allocation concealment, blinding, trial registration, and sample size estimation to provide high-level evidence.

3.1.3 Inadequate Attention to Ethics Registration Medical research requires ethics committee approval to protect participants' rights and welfare [21]. Only 94 RCTs (29.1%) mentioned ethics approval, with merely 25 (7.74%) providing specific ethics approval numbers. To better protect participants regarding informed consent, risk disclosure, and termination criteria [22], future studies should strengthen ethics systems and maintain transparent approval processes.

Outcome Measure Issues

3.2.1 Large Variation in Indicator Selection and Unclear Primary/Secondary Distinction Appropriate outcome selection reduces costs and efficiently reflects clinical efficacy [23]. This study identified 170 outcome measures with substantial variation: clinical total effective rate appeared 233 times, while 56 indicators appeared only once. This heterogeneity impedes cross-study comparisons and data synthesis. Researchers should consider eliminating low-relevance indicators (e.g., urinary D-xylose excretion, urinary mannitol, urinary lactulose) and prioritize representative, feasible measures such as TCM syndrome scores, gastric pain efficacy, pain duration/relief time, gastroscopic efficacy, ulcer healing extent (area/diameter), and Hp eradication rate.

Only 1 RCT clearly distinguished primary from secondary outcomes, while others simply listed all measures. Some relied solely on subjective indicators, reducing scientific rigor, while others used only objective measures, failing to capture TCM' s distinctive advantages. Future studies should incorporate both representative subjective and objective indicators, such as TCM efficacy (reflecting symptom improvement) and gastroscopic efficacy (demonstrating ulcer healing), to generate higher-quality evidence.

3.2.2 Lack of Unified Clinical Efficacy Criteria Clinical total effective rate was the most common outcome, yet evaluation criteria varied substantially. Some studies combined subjective and objective indicators (TCM syndrome efficacy, symptom efficacy, gastroscopic healing, Hp eradication), while others used only subjective or only objective measures. Subjective-only criteria lack scientific basis due to individual variability, while objective-only criteria inadequately reflect TCM' s holistic advantages. Future evaluations should integrate both representative subjective indicators (TCM efficacy) and objective measures (gastroscopic efficacy) to comprehensively assess TCM treatment effects.

3.2.3 Heterogeneous Measurement Timepoints and Diverse TCM Scoring Systems Outcome measurement timepoints showed substantial heterogeneity, with 47 different timepoints ranging from 1 week to 6 months. Short measurement periods cannot fully evaluate long-term efficacy or enable cross-study comparisons. Standardized timepoints are essential for efficacy observation and meta-analysis.

TCM syndrome/symptom scores reflect treatment improvement and represent a distinctive TCM evaluation feature. However, 128 RCTs used 26 different scoring systems, with 18 systems appearing only once and some studies creating self-defined criteria. This lack of standardization challenges result interpretation and comparability. Unified scoring criteria are needed to reduce heterogeneity and better reflect TCM efficacy.

3.2.4 Non-standardized Safety Reporting Safety indicators are crucial for evaluating TCM' s clinical safety profile. Among 343 safety event occurrences, adverse reactions were most frequent (155, 45.19%), followed by liver function (44, 12.83%) and kidney function (41, 11.95%). However, most studies simply listed adverse events without analyzing causality, frequency, or relationship to interventions. Three studies reported hemorrhage, and five reported hepatic/renal impairment during treatment. Although TCM showed lower adverse event rates than Western medicine, inadequate reporting limits safety evaluation. Future studies should emphasize systematic, continuous safety monitoring and standardized reporting to provide comprehensive evidence for clinical decision-making.

Recommendations

This comprehensive analysis of 323 RCTs over 15 years reveals significant methodological limitations in TCM research for PUD. Developing a unified core outcome set would address these deficiencies and enhance evidence quality. Future efforts should focus on: (1) standardizing disease staging and establishing universal TCM syndrome criteria for PUD; (2) improving methodological quality through allocation concealment, blinding, prospective sample size calculation, trial registration, and ethics approval; (3) selecting appropriate outcomes based on study objectives; (4) clearly defining primary and secondary outcomes; (5) standardizing clinical efficacy criteria, TCM scoring systems, and measurement timepoints; and (6) implementing rigorous safety reporting protocols.

Conclusion

This study systematically analyzed outcome measures in 323 RCTs of TCM for PUD over 15 years, identifying 170 distinct outcomes with 1,962 total occurrences across six domains. Current research suffers from non-standardized syndrome differentiation and disease staging, inadequate methodological design, unclear outcome hierarchies, heterogeneous efficacy criteria, diverse measurement timepoints, varied scoring systems, insufficient trial registration, and non-standardized safety reporting. Developing a core outcome set for TCM treatment of PUD and improving methodological rigor will provide high-quality, reliable, and practical evidence for clinical practice.

Author Contributions: Tian Rong conceptualized the study, performed data analysis, drafted the manuscript, and revised the final version, taking responsibility for the paper. Li Kaiyang and Zhang Fei verified data and performed statistical analysis and figure preparation. Yang Mei and Huang Jing guided framework development, manuscript drafting, and initial revisions. Zhao Qi supervised final revision and quality control. The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.