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Review Article

Effect of Bushen Tiansui Decoction on Delayed Fracture Healing: A Systematic Review and Meta-analysis

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Abstract

This review aimed to validate the therapeutic potential of Bushen Tiansui decoction (BSTSD), a traditional Chinese formulation, in treating delayed union of fractures. Comprehensive database searches identified randomized controlled trials up to September 13, 2022, assessing BSTSD's efficacy in delayed fracture healing. Outcomes were bone metabolism indexes and Harris hip scores. Quality and risk assessments were conducted using the Cochrane Collaboration's tools. Data were analyzed using RevMan software, with sensitivity analysis through Stata. BSTSD significantly improved bone GLA protein (SMD=1.76, P<0.00001) and alkaline phosphatase (SMD=1.31, P<0.00001). Additionally, Harris hip scores for pain, function, deformity, and motion showed marked improvement. BSTSD treatment also demonstrated enhanced clinical efficiency (RR=1.27, P<0.00001) with fewer complications. Sensitivity analyses indicated consistent results. BSTSD shows promise in treating delayed fracture unions, yet conclusions necessitate further high-quality research for validation.

Keywords: Bushen Tiansui Decoction, Chinese Medicine Compound, Delayed Fracture Healing, Meta-Analysis, Traditional Chinese Medicine Decoction

Introduction

Bone fractures are among the most frequent injuries to the musculoskeletal system, resulting from various causes and presenting in diverse forms[1]. Historically, fractures were predominantly due to traffic incidents, workplace mishaps, and sporting events[2]. However, recent trends indicate a rise in fracture-causing accidents[3]. Bone repair post-injury is intricate. Typically, the mended bone regains its original stability and robustness, resuming its standard anatomical shape[4]. While the majority of fractures heal promptly, 5–10% of cases manifest as non-union or delayed fracture healing (DFH)[5]. Contemporary statistics reveal that about 17% of open long bone fractures result in non-union, and roughly 8% undergo delayed union[6]. Delayed union often stems from the premature cessation of the initial intramembranous ossification post-fracture, halting before the bone fully reconnects[7]. Concurrently, non-union might arise due to halted ossification, with the bone tissue failing to form a solid link after the process ends[8]. Factors like scar tissue presence in the fracture gap, inadequate fracture end stability, and an overabundance of cartilage during callus formation notably contribute to delayed or non-union events[9].

According to the FDA, a non-union is characterized as a fracture that remains unhealed after a span of nine months and, notably, displays no progression towards healing over a continuous three-month period[10]. This definition underscores the importance of both duration and lack of progress in determining the non-union status of a fracture.

The authors have no conflict of interest.

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Antonova et al. retrospectively analyzed the case data of 853 tibial fractures and noted that about 12% of the patients experienced non-union one year after injury and emphasized that the cost of treatment for non-union of tibial fractures was about three times that of non-union[11]. Therefore, DFH is considered a severe fracture complication, and once it occurs, it imposes enormous physical, mental, and economic pressure on patients and families[12]. After trauma, various bone complications like delayed union, non-union, and fractures can arise, and among the available treatments, autologous cancellous bone grafts, harvested from the patient's own body, serve as the benchmark solution due to their compatibility advantages and proven effectiveness in clinical settings[13]. Even with advancements in surgical treatments and a deeper comprehension of DFH, there remains a risk of DFH recurrence post-surgery[14].

According to a unique theory about bone in traditional Chinese medicine (TCM), the bone tissue is closely related to the kidney[15]. The ancient medical classic "Huangdi-Neijing-Suwen" states that kidney governs bones and generates the marrow. TCM scholars believe in the healing of fractures[16]. The process includes "removal of blood stasis, regeneration, and osseointegration." They believe that the process of fracture healing is closely related to the strength of kidney function. The weakening of kidney *qi* is the main factor leading to DFH[17]. The kidney function can be repaired by TCM decoction. It helps fracture healing and reduces the incidence of DFH[18]. Bushen Tiansui decoction (BSTSD), a TCM decoction, has been widely used as adjuvant therapy for DFH and is reported to have good clinical efficacy[19-21]. As the clinical application of BSTSD as an adjuvant therapy for DFH grows, there's a pressing need to assess pertinent clinical studies. Our research delves into the therapeutic efficacy and safety of BSTSD for DFH using a rigorous meta-analysis and quantitative assessment. The goal is to offer robust evidence to support both clinical practices and foundational research.

Materials and Methods

Our manuscript was meticulously crafted, drawing insights from the 2020 version of the Preferred Reporting Project for Systematic Reviews and Meta-Analyses (Cochrane) Guidelines[22]. In essence, this work constitutes a systematic review and meta-analysis. Detailed characteristic data can be found in Supplementary Tables S1 and S2. For reference and transparency, the protocol for this systematic review has been registered on inplasy with registration number INPLASY202350060 and is available on https://doi.org/10.37766/inplasy2023.5.0060.

Data Source and Retrieval Strategy

Two researchers conducted extensive computer-based searches across various databases, including the China Knowledge Infrastructure (CNKI), China Biomedical Literature Database (CBM), Wanfang Database, Chinese Scientific Journals Database (CSJD-VIP), Web of Science, PubMed, Embase, and The Cochrane Library database. The retrieval time limit is from establishing each database to September 13, 2022. English search terms included "delay fracture healing," "delayed union of fracture," "Bushen Tiansui decoction," "Bushen Tiansui," and "traditional Chinese medicine." According to the usage of each database, the search formula was edited to search each database as comprehensively as possible and import the search results into the Citavi software (version 6.11.0). Specific search methodologies for each database are detailed in Supplementary Table S3.

Inclusion Criteria

The selection criteria encompassed the following parameters: 1) Study participants: All subjects had a confirmed diagnosis of delayed fracture union, with the diagnostic guidelines detailed within the respective studies. 2) Treatment modalities: In the experimental group (referred to as the BSTSD group), BSTST was employed either as the primary therapeutic intervention or as an adjunctive treatment. Conversely, the control group (designated as the conventional treatment group) underwent standard surgical procedures like autologous bone grafting, reaming surgery, among others, or received alternative drug treatments such as GS and NSAIDs. 3) Outcome measures: The studies explicitly defined clinical efficacy metrics or safety assessment indicators. 4) Study design: All selected research had a randomized controlled trial structure. 5) Language of publication: We maintained an inclusive approach, setting no language barriers for the considered literature. By adhering to these criteria, we aimed to ensure a comprehensive and unbiased evaluation of the available evidence.

Exclusion Criteria

Studies were excluded based on the following parameters: 1) Absence of comprehensive baseline statistical data. 2) Manuscripts that were purely review articles. 3) Clinical research not pertinent to BSTSD. 4) Investigations based solely on animal models. 5) Graduation thesis; 6) Papers presented exclusively at conferences. This exclusion framework was established to focus on the most rigorous and directly relevant research available.

Literature Screening

The procedure for literature selection was as follows: 1) Utilizing Citavi software, two independent researchers undertook an initial screening of the available literature. 2) Redundant or duplicate studies were identified and excluded. 3) A preliminary scan was conducted by reviewing titles, bibliographies, abstracts, and other relevant sections based on the predetermined inclusion and exclusion guidelines. 4) If there was ambiguity regarding the eligibility of certain literature after an initial reading, the full text was reviewed twice for clarity. Only after this rigorous evaluation was the study considered for inclusion. 5) Both researchers

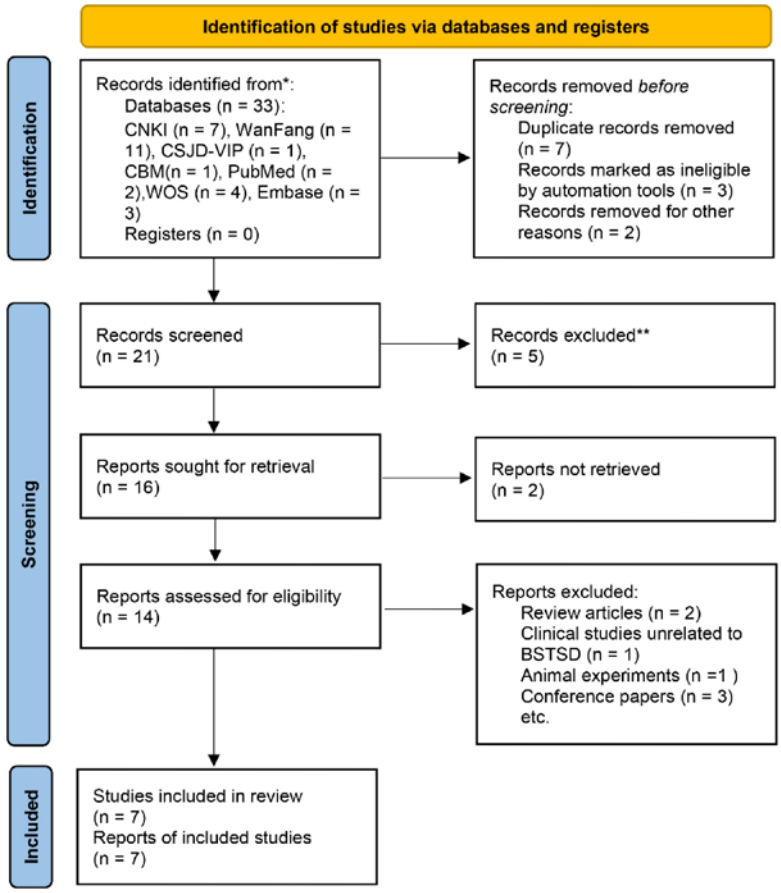

Figure 1. Flowchart of the selection of studies.

reviewed the selections made by the other. In instances of discrepancy, a third researcher was consulted to ensure a unanimous decision. By adhering to this meticulous procedure, we aimed to ensure the quality and relevance of the selected studies.

Data Extraction

The methodology for data extraction comprised the following steps: 1) A data extraction template was developed using Microsoft Excel (version 2204 Build 16.0.15128.20158). 2) A pair of researchers, working independently, populated this template with relevant data. 3) Essential information from the selected literature, such as the author's name, publication ID, date of publication, patient demographics, sample size, intervention, control procedures, and etc, was diligently recorded. 4) Outcome metrics from the literature, including benchmarks like bone GLA protein (BGP), alkaline phosphatase (ALP), scale scores, effectiveness rates, complication frequencies and etc, were captured. 5) To ensure accuracy and consistency, both researchers cross-verified the data extracted by their counterpart. In cases of divergence, collaborative discussions were held to arrive at a consensus. This rigorous approach was aimed at ensuring the precision and comprehensiveness of the data extracted from the studies.

Literature Quality Evaluation

We adhered to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.3 23 to evaluate the quality of the literature. The bias risk assessment for randomized controlled trials was conducted using a delineated bias assessment approach. Key factors evaluated included: the process of random cohort generation, the integrity of allocation concealment, the implementation of a double-blind methodology, the use of outcome result blinding, the thoroughness of outcome reporting, the potential for selective outcome reporting, and other considerations such as clear inclusion/exclusion criteria, baseline indicator comparability, and potential conflicts of interest. For each of the above options, if met, the risk of bias is low; if not met, the risk of bias is high, and items unclear in the literature indicate that the risk of bias is unclear. Two investigators completed

Table 1. Characteristics of included studies.

Author	year	Groups	Age	Gender: M/F	Number of participants	Time	Randomized treatments	Use time (in months)	Outcomes
Guo Z	2020	Control	42.7 ± 5.4	26/22	48	5.79 ± 1.37	Conventional surgery	2	①②③④⑤⑥⑦⑧
		Experimental	43.0 ± 5.6	29/20	49	5.82 ± 1.24	BSTSD + Conventional surgery	2	
Li L	2020	Control	34.08 ± 6.12	14/6	20	5.43 ± 3.27	Conventional surgery	N/A	①②⑦
		Experimental	34.13 ± 5.05	12/8	20	5.11 ± 3.18	BSTSD + Conventional surgery	N/A	
Bai HP	2019	Control	43.15 ± 10.44	27/17	44	N/A	Conventional surgery	4	①②③④⑤⑥⑦⑧
		Experimental	43.65 ± 10.59	28/16	44	N/A	BSTSD + Conventional surgery	4	
Chen LS	2018	Control	38.05 ± 6.12	39/21	60	5.12 ± 3.88	Conventional surgery	3	①②⑦⑧
		Experimental	38.21 ± 6.26	38/22	60	5.27 ± 3.19	BSTSD + Conventional surgery	3	
Xing HJ	2020	Control	40.12 ± 10.07	20/14	34	N/A	Conventional surgery	3	①②⑦
		Experimental	40.87 ± 10.71	19/15	34	N/A	BSTSD + Conventional surgery	3	
Zheng ZY	2017	Control	42.35 ± 5.58	22/12	34	N/A	Conventional surgery	3	①②⑦
		Experimental	43.14 ± 5.26	20/14	34	N/A	BSTSD + Conventional surgery	3	
Liu JH	2019	Control	36.36 ± 13.26	22/18	40	5.35 ± 3.16	Conventional surgery	3	①②③④⑤⑥⑦⑧
		Experimental	37.12 ± 13.37	25/15	40	6.11 ± 3.66	BSTSD + Conventional surgery	3	

M: male; F: female; ①: bone metabolism index BGP; ②: bone metabolism index ALP; ③: Harris hip score (pain); ④: Harris hip score (function); ⑤: Harris hip score (deformity); ⑥: Harris hip score (range of motion); ⑦: clinical efficiency ⑧: complication rate.

the evaluation independently and assessed the evaluation results. In case of inconsistency, they reached an agreement with the third investigator through discussion. The evaluation results were expressed using a risk of bias graph.

Statistical Analysis

We undertook a comprehensive synthesis and analysis of the acquired data. The analytical procedure encompassed: 1) Examination by dedicated data statisticians to ensure accuracy. 2) A meta-analysis was conducted using the Cochrane Collaboration's RevMan software (version 5.4.1). 3) For dichotomous variables, hazard ratio or relative risk (RR) was employed as the efficacy measure. Continuous variables relied on the weighted mean difference (WMD) when consistent units were presented across literature. In cases with inconsistent units, the standard mean difference (SMD) was preferred. 4) Each effect size was expressed with point estimates and 95% confidence intervals (95% CI). A $P<0.05$ was deemed statistically significant. 5) Heterogeneity was ascertained through the Q test. Its probability was gauged via the chi-square test, and quantified using I^2. Based on these

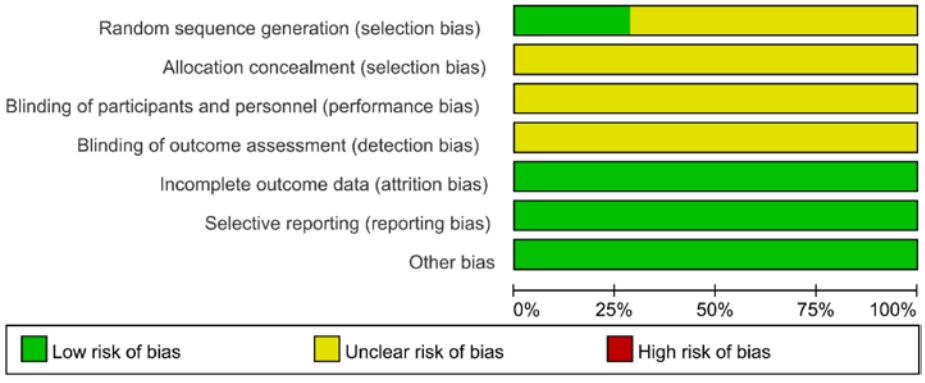

Figure 2. The risk of bias graph of included studies.

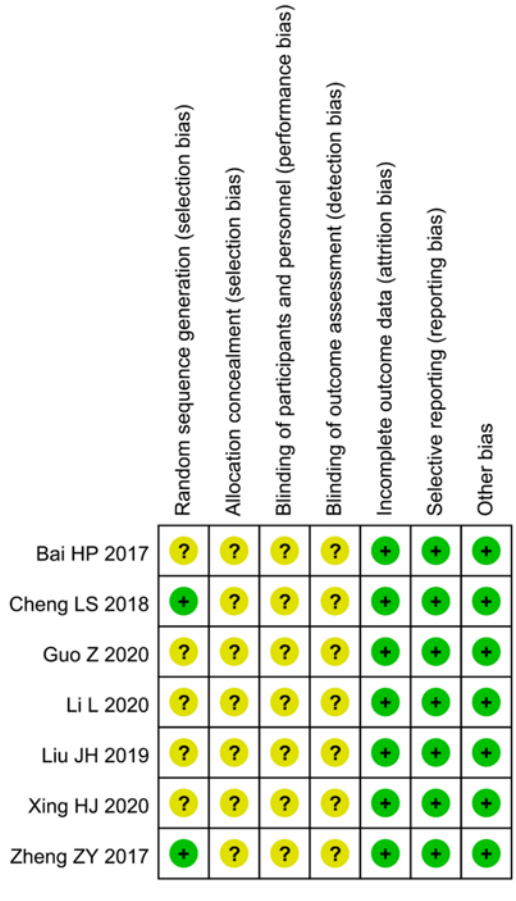

Figure 3. Risk of bias summary of included studies.

values, consistency was evaluated. For results displaying I^2<50% and P≥0.1, heterogeneity was considered minimal and a fixed-effect model was adopted. However, with I^2≥50% and P<0.1, substantial heterogeneity was inferred. Here, the random-effects model was applied. Persistent significant heterogeneity prompted a deeper dive into potential causes. Sensitivity analyses, facilitated by Stata software (version 16.0), were employed to pinpoint the sources of this heterogeneity. 6) to detect possible publication biases, a funnel plot was executed.

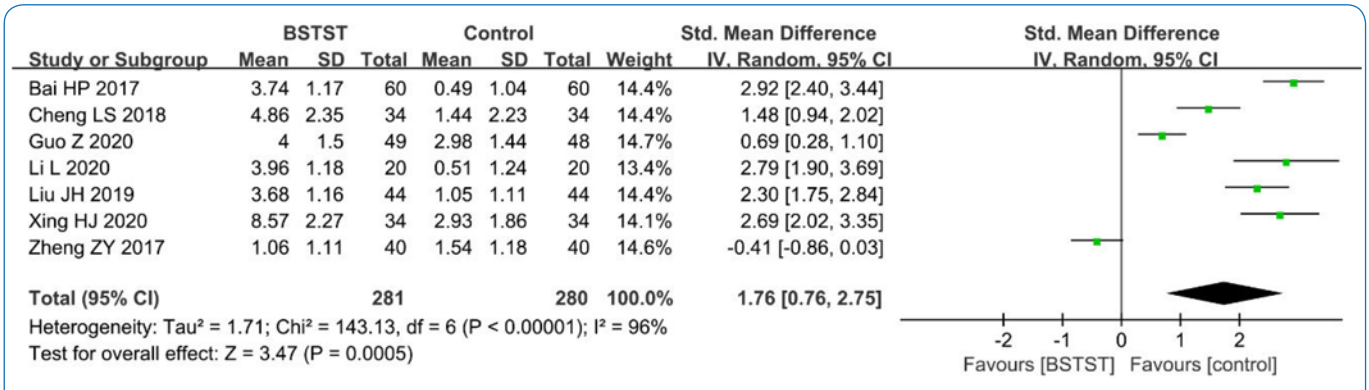

Figure 4. Forest plot of BGP.

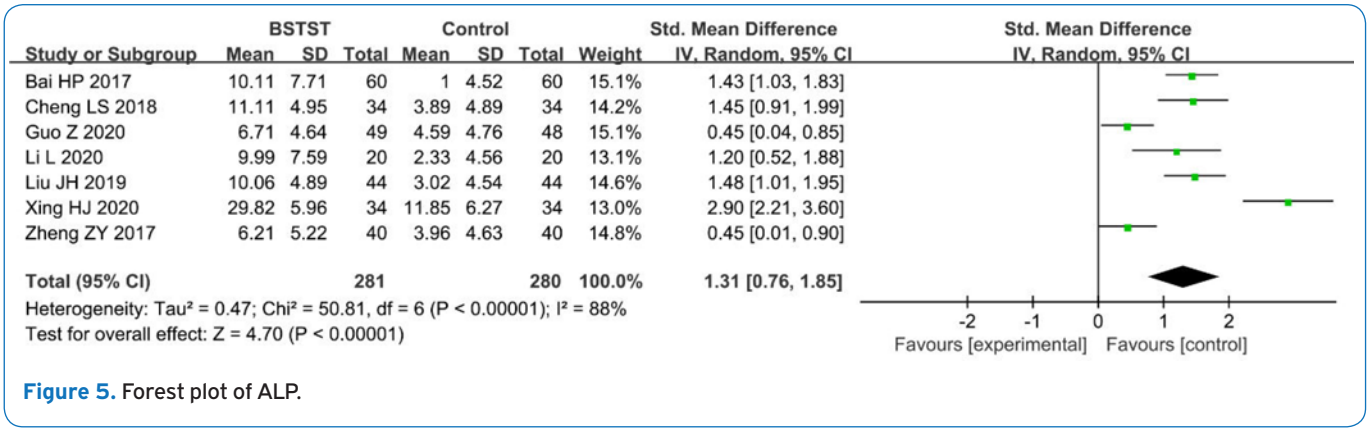

Figure 5. Forest plot of ALP.

Results

Literature Search and Screening Results

Based on our meticulously planned search strategy, we identified 33 pertinent articles. The distribution was as follows: two from PubMed, four via the Cochrane Library, three sourced from Embase, four from the Web of Science, seven from CNKI, 11 via Wanfang, one each from CSJD-VIP and CBM, with none being added from alternative resources. Leveraging the capabilities of Citavi software and adopting a hands-on approach to literature review - which entailed scrutinizing titles, bibliographies, full texts, and existing reviews - we ruled out 26 articles. Consequently, seven were deemed suitable for inclusion. This comprehensive literature review process is visually represented in Figure 1.

Basic Features of the Included Literature

A total of seven studies were included[19,24-29], and the study characteristics were as follows: 1) The language used in the study was all Chinese; 2) The study period was from 2017 to 2020; 3) No statistical difference was noted in the baseline indicators of all studies; 4) The experimental group of the study used BSTST as an adjuvant drug combined with autologous bone transplantation + bone marrow blood injection, and the control group used autologous bone transplantation + bone marrow blood injection; 5) The treatment duration was between 2–3 months. The main attributes of the selected studies can be found in Table 1.

Literature Quality Evaluation

Among all seven studies, one study applied the random number table method for randomization[21], one used random computer numbers[28], and the remaining five[19,24-27] did not assign specific groups. No study mentioned the allocation concealment method and specific implementation process. Furthermore, no study specified how blinding was implemented. Only blinding of outcome assessors was discussed. All included studies explained explicit inclusion and exclusion standards and described detailed baseline metrics and compared them. The associated risk of bias is depicted in Figures 2 and 3 and Supplementary Figure S1.

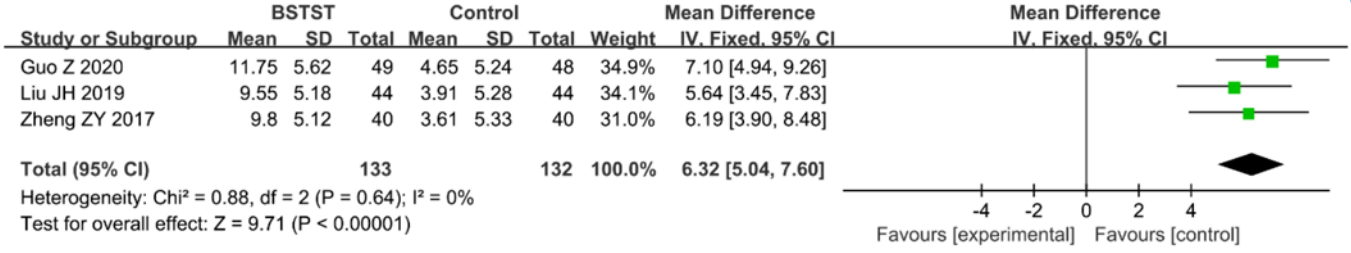

Figure 6. Forest plot of Harris hip score (pain).

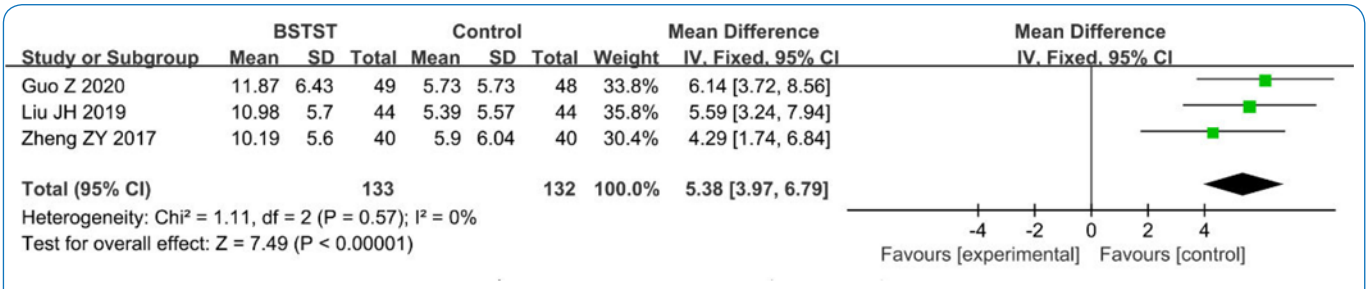

Figure 7. Forest plot of Harris hip score (function).

Meta-analysis

Bone metabolism index BGP

After the BGP indicators were combined, we found that the heterogeneity among studies was significant, and a random-effects model was selected for meta-analysis. After the random-effects model was combined, we found that the heterogeneity among the studies was significant (P<0.00001, I^2=96%). The results showed that the effect of BSTST on the bone metabolism index BGP was statistically significant between the experimental and control groups (SMD=1.76, 95% CI=[0.76, 2.75], P<0.00001), indicating that the use of BSTST can significantly increase the blood BGP content of patients. The selected documents have no obvious features, so the sub-group analysis could not be performed. We noted that Zheng's (2017) study was counterproductive, possibly due to irregular data entry[29]. The results are presented in Figure 4.

Bone metabolism index ALP

After the ALP indicators were combined, we found that the heterogeneity between studies was significant, and a random-effects model was selected for meta-analysis. After the random-effects model was combined, we found that the heterogeneity of the false research case was relatively significant (P<0.00001, I^2=88%; SMD=1.31, 95% CI=[0.76, 1.85], P<0.00001), indicating that the use of BSTST can significantly increase the blood ALP content of patients. The results are depicted in Figure 5.

Harris hip score (pain)

For the next assessment, only three studies were included[24,26,29], and the Harris hip scores for pain were combined and found to have good homogeneity (P=0.57, I^2=0%). A fixe d-effect model was selected for analysis. The difference between the experimental group and the control group was statistically significant (MD=6.32, 95% CI [5.04, 7.60], P<0.00001), and the results showed that BSTSD adjuvant treatment of DFH could significantly improve the symptoms of pain. The results are shown in Figure 6.

Harris hip score (function)

In this analysis, three studies were included[24,26,29]. Harris hip scores for function were combined and found to have good homogeneity (P=0.57, I^2=0%), and a fixed-effect model was selected for analysis. A statistically significant difference was observed between the experimental group and the control group (MD=5.38, 95% CI [3.97, 6.79], P<0.00001), and the results showed that BSTSD adjuvant therapy for DFH could significantly improve the patient's mobility. The results are shown in Figure 7.

Harris hip score (deformity)

The same three studies as above were included in this analysis. Harris hip scores for deformity were combined and found to be more homogeneous (P=0.42, I^2=0%), and a fixed-effect model was selected for analysis. The difference

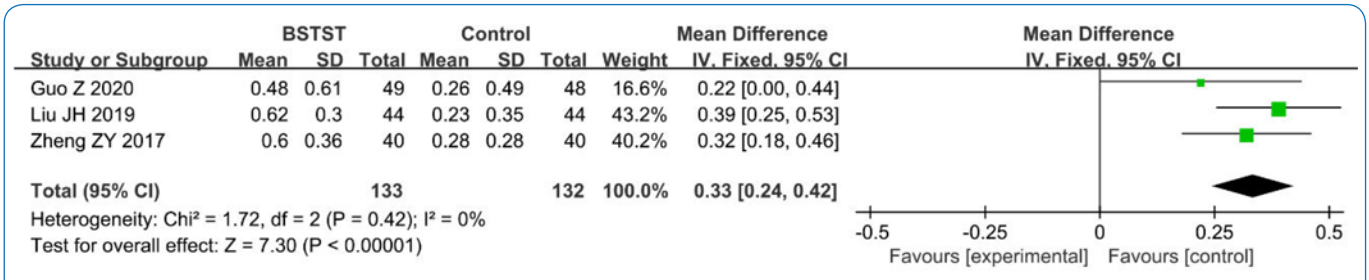

Figure 8. Forest plot of Harris hip score (deformity).

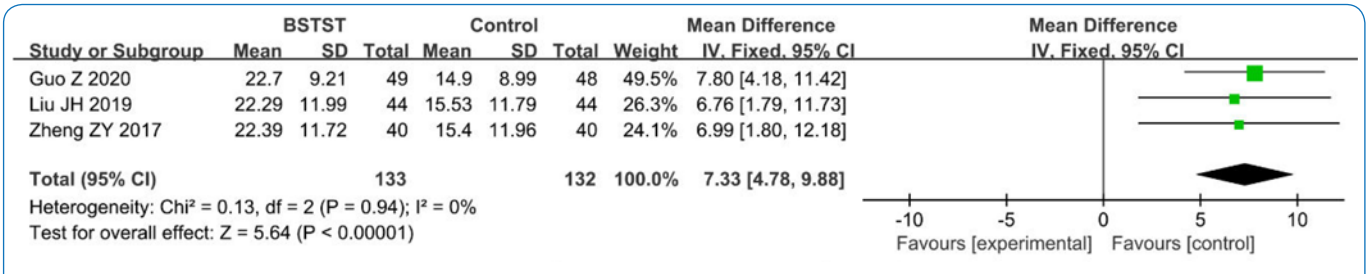

Figure 9. Forest plot of Harris hip score (range of motion).

between the experimental group and the control group was statistically significant (MD=0.33, 95% CI [0.24, 0.42], P<0.00001), and the results showed that BSTSD adjuvant treatment of DFH could significantly improve the deformity. The results are shown in Figure 8.

Harris (ROM) score

The same three studies were included for the next assessment, where Harris hip scores for range of motion were merged and found to have good homogeneity (P=0.94, I^2=0%), and a fixed-effect model was selected for analysis. The experimental group exhibited a notable difference compared to the control group (MD=7.33, 95% CI [4.78, 9.88], P<0.00001). This suggests that BSTSD adjunct therapy notably enhances the joint's range of motion in DFH cases. The results are depicted in Figure 9.

Clinical efficiency

All seven studies were included in this analysis, and the clinical response rate was combined and found to be more homogeneous (P=0.71, I^2=0%). A fixed-effect model was selected for analysis. In terms of efficiency (markedly practical, effective, and improved as effective), the difference between the experimental group and the control group was statistically significant (RR=1.27, 95% CI [1.17, 1.37], P<0.00001). The treated patients with DFH had a higher clinical cure rate (Figure 10).

Complication Rate

Five studies were included in this analysis[19,24,26,27,29], and the clinical complication rates were combined and found to be more homogeneous (P=0.40, I^2=0%). A fixed-effect model was selected for analysis. In terms of shortening and osteoarticular necrosis, which were regarded as complications, the difference between the experimental group and the control group was statistically significant (RR=0.81, 95% CI [0.52, 1.26], P<0.00001). Complication rates were lower in patients with DFH treated with adjuvant therapy, and the results are presented in Figure 11.

Publication bias analysis results

In the meta-analysis, the efficacy rate of BSTSD adjunct therapy for delayed fracture healing was represented by the standard error (SE) on the Y-axis, while the RR was plotted on the X-axis, producing the vulnerability diagram depicted in Figure 12. All data points fall within this diagram with a clustered distribution, suggesting minimal publication bias. Nonetheless, the limited number of studies included means potential bias cannot be entirely dismissed.

Sensitivity Analysis

The data for BGP and ALP underwent sensitivity analysis in R software due to their inherent heterogeneity. The findings revealed consistency across all studies, suggesting

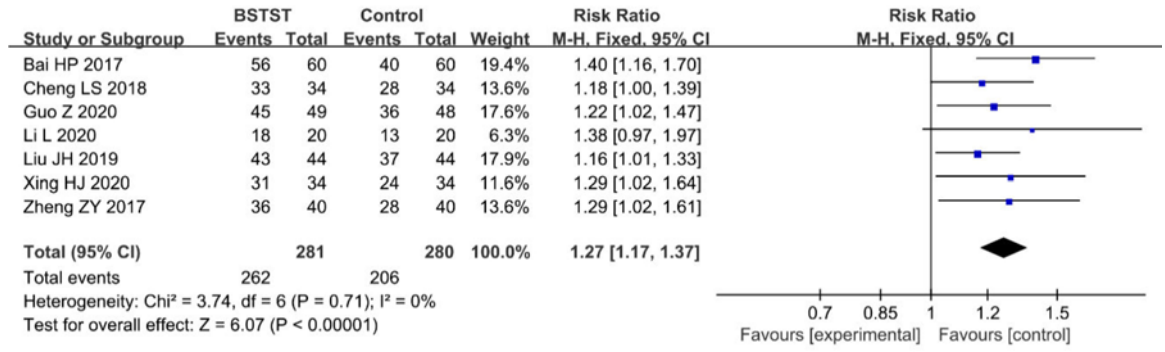

Figure 10. Forest plot of clinical efficiency.

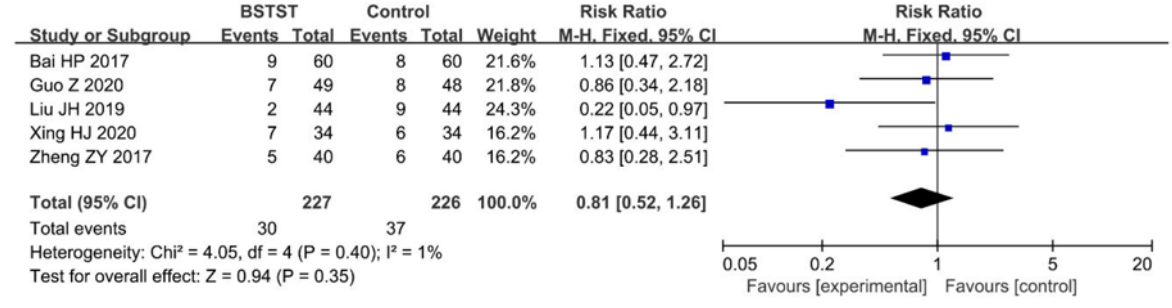

Figure 11. Forest plot of complication rate.

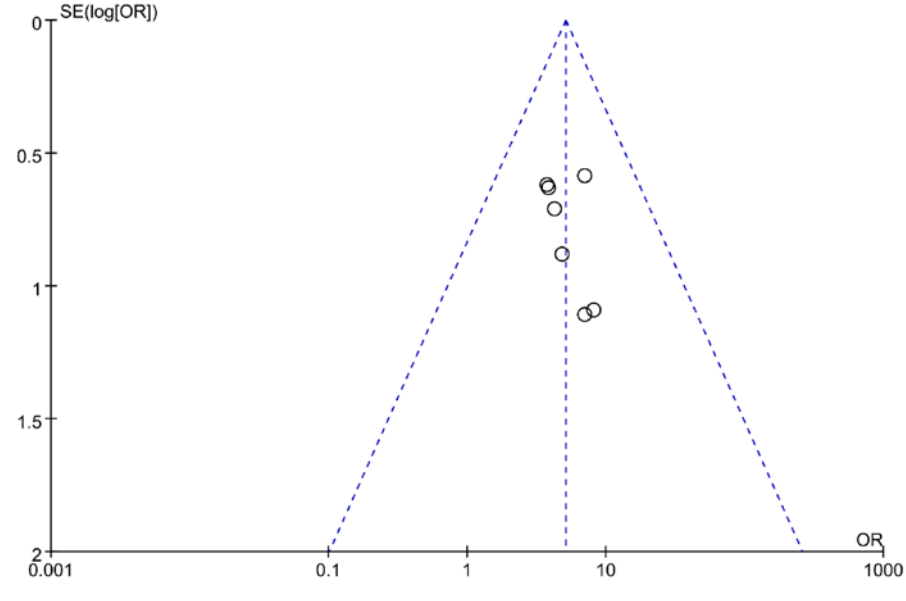

Figure 12. Funnel plot of clinical efficiency.

that these outcome measures were robust. Supplementary Figures S2 and S3 respectively detail the sensitivity analysis outcomes for BGP and ALP.

Discussion

It is well known that fracture healing is a complex and lengthy bone repair process that involves a series of changes in osteoblasts and osteoclasts[30]. In the early stage of a fracture, a subperiosteal hematoma forms in the subperiosteal of the fractured end, in the bone marrow cavity, and between the adjacent fascia, apoptotic cells, and necrotic bone tissue, inducing severe local reactions[31]. To produce the necessary biological environment for fracture healing, mesenchymal cells, lymphocytes, neutrophils, and different growth factors are abundant in fracture hematoma, and fractures heal under the combined effect of these factors[32].

In fracture healing, the tissue morphology and functional recovery of bone tissue are affected by a multitude of factors. A study found that infection, excessive fracture injury, unstable internal fixation, very old age, and unreasonable rehabilitation training could lead to delayed union or non-union of fractures[33]. When delayed fracture healing occurs, the number of bone marrow mesenchymal cells at the fractured end of the patient is significantly reduced, the growth of new blood vessels is lacking, the blood supply is reduced, and the bone tissue at the fractured end loses activity and cannot heal smoothly[34]. The occurrence of DFH imposes enormous physical, mental, and economic burdens on patients and their families, and the disease is challenging for clinicians[1-3]. At present, surgical re-fixation and autologous bone grafting are the mainstream treatment methods. However, there exists a possibility of DFH after surgery[35].

There was no record of the disease name of delayed union or non-union of fractures in ancient China. Generally, the disease can be classified into "kidney deficiency and bone wilting" and "bone arthralgia." The ancient medical classic "The Yellow Emperor's Classic of Internal Medicine Su Wen": "Kidney governs bone and marrow...Bone is the house of marrow..." They believed that kidney function is closely related to bone and marrow, so TCM often uses kidney-tonifying drugs to treat bone diseases. BSTSD comprises *Rhizoma Drynariae*, pyrite, turmeric, *Chuanxutan, Salvia*, Acacia bark, and *Astragalus*, among other drugs. It has the effect of invigorating the kidney, solidifying essence, and filling marrow. *Rhizoma Drynariae*, pyrite, and turmeric are the "three treasures of bone-setting," essential for bone-setting. *Salvia miltiorrhiza, Radix Glycyrrhizae,* and *Albizia Julibrissin* promote blood circulation, reduce swelling, remove blood stasis, and invigorate muscle. *Astragalus* has the effect of tonifying *qi*. This TCM decoction follows the theory of traditional Chinese medicine. It mainly treats DFH by tonifying the kidney, which can help patients recover after surgery and is feasible.

BGP and ALP are vital bone metabolism indexes. BGP refers to bone γ-carboxyglutamate protein, which is involved in and has an essential impact on bone remodeling. It is a specific marker produced during bone tissue remodeling. A decrease in its content indicates slow bone tissue remodeling[36]. ALP is a sensitive indicator for evaluating the degree of osteoblast differentiation and bone turnover. During fracture healing, osteoblasts increase ALP activity while the blood of patients with DFH increases[37]. Therefore, the detection of BGP and ALP helps judge fracture healing.

In this study, a meta-analysis was conducted on the application of BSTSD in the treatment of delayed fracture union. A total of seven studies with 561 subjects were included, of which 281 were in the experimental group (BSTSD + conventional surgery) and 280 were in the control group (conventional surgery). The analysis results showed that compared with conventional surgery alone, the cure rate of DFH after BSTSD treatment was significantly improved, the complication rate was significantly reduced, the indicators in Harris hip score were improved, and the bone metabolism index BGP was improved. ALP was significantly increased, indicating that BSTSD + conventional surgery has better clinical efficacy and a lower complication rate than conventional surgery alone for DFH.

This study evaluated the application of BSTSD as an adjuvant drug in DFH from the perspective of clinical effect and safety. The results showed that BSTSD has excellent potential in treating DFH. BSTSD may provide an evidence-based basis for orthopedic clinicians to formulate diagnosis and treatment plans. When fracture patients show signs of DFH in clinical work, clinicians can use BSTSD alone as an adjuvant drug or use BSTSD + conventional surgery as a treatment method if necessary. We believe that patients' bone healing ability may be enhanced after taking BSTSD.

Of course, there are certain deficiencies in our research, and these deficiencies must be carefully considered when describing the results: 1) Among the seven studies included, the methodological explanations are generally lacking, and the researchers often mention randomization without a detailed description of the grouping process. The irregularity of the random process may lead to human subjective factors affecting the selection and grouping of research subjects; 2) all included studies describe the allocation concealment process, and it is unclear whether blinding is implemented or not, which could lead to bias from researchers and patients in the implementation of the intervention and the assessment of outcomes; 3) the included studies did not describe the conflict of interest related to the study; 4) the bone metabolism indicators BGP and ALP as outcome indicators displayed significant heterogeneity at the time of inclusion in this study, which may be due to differences caused by the index testing method of the research center and individual differences of patients; 5) the duration of drug use is inconsistent, which may also affect the statistical results of our research; 6) the included studies are few, which cannot fully reflect the advantages of BSTSD as a treatment plan and insufficient. From the above deficiencies, it can be seen that there are still incomplete considerations in the experimental design of randomized controlled trials in China, and more rigorous

design trials are needed. In addition, the results of this study should be viewed with caution, and further research into BSTSD and DFH should be pursued.

Conclusion

BSTSD exhibits strong clinical effectiveness as an adjunct therapy for DFH. Its integration with conventional surgical procedures in DFH treatment has shown to markedly enhance therapeutic outcomes, evident from improved bone metabolic markers such as BGP and ALP, a bettered Harris hip score, and a lowered rate of complications. To optimize the application of BSTSD for DFH, future endeavors might encompass high-quality, multi-center clinical studies, bioinformatics research[38,39], and in-depth laboratory investigations. These studies might elucidate its underlying pharmacological mechanism and potential targets, potentially refining the traditional Chinese medicine (TCM) formulation to amplify its therapeutic potency.

Authors' contribution

Ling Cheng: Conceptualization, methodology, software, investigation, formal analysis, and writing-original draft; Gao Wang: Data curation and writing-original draft; Hualong Lu: Resources and supervision; Song Li: Visualization and investigation; Wei Xiong: Conceptualization, funding acquisition, resources, supervision, writing-review & editing, Jun Wang: Software, validation visualization, and writing-review & editing, funding acquisition. All authors read and approved the final version of the manuscript.

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Supplementary Figures

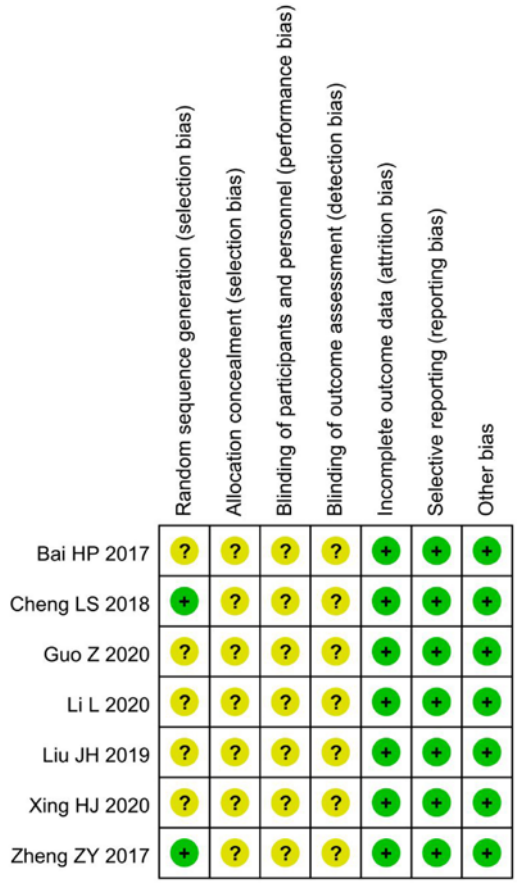

Figure S1. Risk of bias summary of included studies.

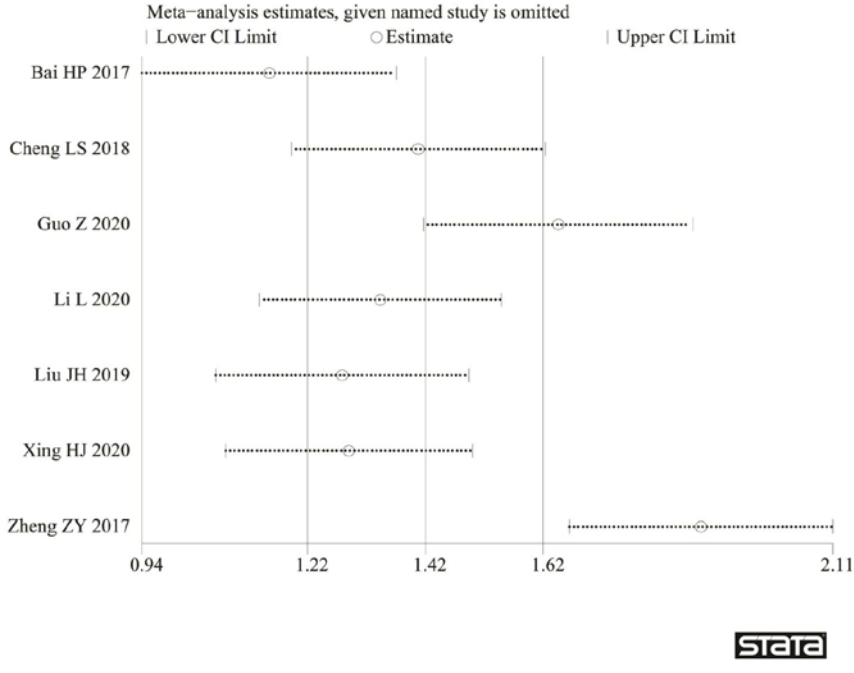

Figure S2. Sensitivity analysis of BGP.

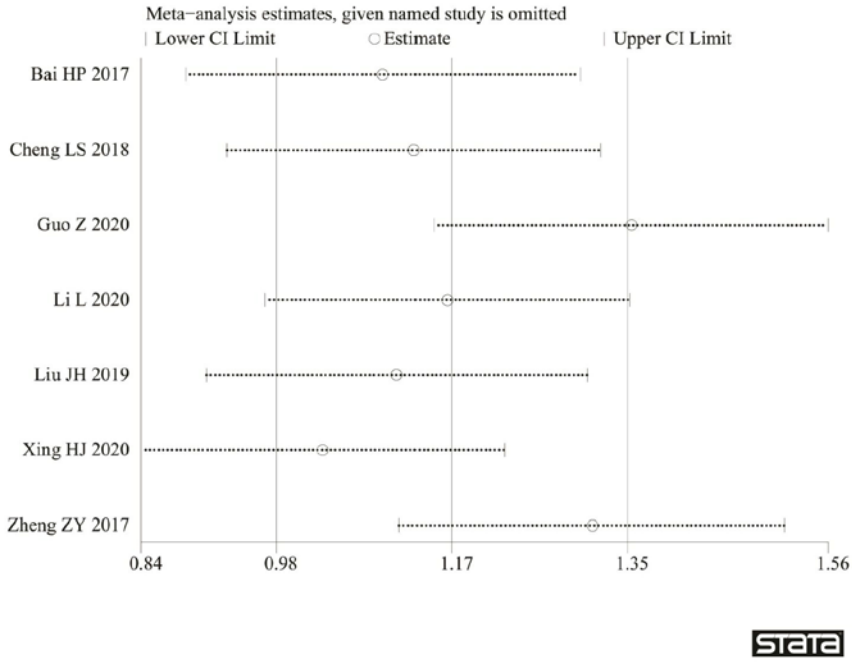

Figure S3. Sensitivity analysis of ALP.

Supplementary Tables

Table S1. The reporting checklist of systematic reviews of animal experiments.

Heading	Subheading	Descriptor	Pages
Title		Identify the report as a meta-analysis [or systematic review] of animal toxicology experiments	471
Abstract	Objectives	Use a structured format	471
		Describe explicitly the scientific question/ hypothesis	
	Data sources	Describe the databases and other important information sources used	471
	Review methods	Describe the selection criteria (e.g. species, strain, intervention/exposure, outcome and study design): methods for validity assessment and data abstraction, the experiment characteristics, and quantitative data synthesis methods	471
	Results	Describe characteristics of the experiments included and excluded; qualitative and quantitative findings (e.g. point estimates and confidence intervals/standard errors), stating clearly what is estimated: dose-response curves, LD50 etc; and subgroup analyses	471
	Conclusion	State the main results and their implications	471
Introduction		Describe the scientific problem explicitly, biological rationale for the intervention/ exposure, and rationale for the review	471-472
Methods	Searching	Describe the information sources in detail (e.g. databases, registers, personal files, expert informants, agencies, hand-searching), including keywords, search strategy and any restrictions (years considered, publication status, language of publication) Describe special efforts to include all available data (e.g. contact with authors, searching the grey literature)	472
	Selection	Describe the inclusion and exclusion criteria (defining intervention/exposure, principal outcomes, and experimental design) List excluded experiments and reasons for exclusion	472-473
	Validity and quality assessment	Describe the criteria and process used (e.g. blind assessments, quality assessment, and their findings)	473-475
	Data abstraction	Describe the process or processes used (e.g. completed independently, in duplicate), including details on reproducibility, inter-rate agreement. Whether aggregate data or individual animal data are abstracted	473
	Study characteristics	Describe the type of study designs, animals' characteristics (e.g. species, strain, age, sex), details of intervention/exposure (including route of administration, dose and duration), outcome definitions	473
	Quantitative data synthesis	Describe the principal measures of effect, method of combining results (e.g. fixed- and random-effects; meta-regression), handling of missing data; how statistical heterogeneity was assessed; how data from different species and strains were dealt with; adjustment for possible confounding variables; rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias—all in enough detail to allow replication	473-475
Results	Flow chart	Provide a meta-analysis profile summarizing experiment flow giving total number of experiments in the meta-analysis	473
	Study characteristics	Present descriptive data for each experiment (e.g. species, strain, age, sex, sample size, intervention/exposure, dose, duration)	474
	Quantitative data synthesis	Report agreement on the selection and validity of assessment and relevance to the scientific question/hypothesis; present simple summary results (e.g. forest plot); present data needed to calculate effect sizes and confidence intervals; identify sources of heterogeneity, impact of study quality and publication bias	475-480
Discussion		Summarize key findings; discuss scientific/clinical inferences and generalizability based on internal and external validity; interpret the results in light of the totality of available evidence, including data from human studies; discuss rationale for use of animal data to help inform human health outcomes; critically appraise potential biases in the review process (e.g. publication bias); suggest a future research agenda	480-481

Table S2. The reporting checklist of systematic reviews and meta-analyses (PRISMA).

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	471
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	471
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	471
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	471
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	471
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	471
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary materials 488
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	472
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	473
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	473
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	473
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	473-475
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	474-475
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	474-475
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	473-475
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	473-475
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	473-475
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	473-475
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	473-475

Table S2. *(Cont. from previous page).*

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	476-478
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	476-478
Study characteristics	17	Cite each included study and present its characteristics.	474
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	475-476
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplementary materials 486
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	476-480
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	476-480
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	476-480
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	476-480
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	476-480
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	476-480
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	480-481
	23b	Discuss any limitations of the evidence included in the review.	480-481
	23c	Discuss any limitations of the review processes used.	480-481
	23d	Discuss implications of the results for practice, policy, and future research.	480-481
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	481
Competing interests	26	Declare any competing interests of review authors.	481
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	481

Table S3. Chinese and English search strategies.
***Comments**: In order for non-Chinese readers to understand the Chinese search strategy of this article, we translated the Chinese search terms in the search formula.*

CNKI	(SU%= Delay fracture healing OR SU%= Delayed fracture healing OR SU%= Delayed union) AND (SU%= Bushen TianSui Decoction OR SU%= Bushen TianSui)
WangFang Database	Subject:(" Delay fracture healing " OR " Dlayed fracture healing " OR " Delayed union ") AND Subject:(" Bushen TianSui Decoction " OR " Bushen TianSui ")
CSJD-VIP	M=(Delay fracture healing OR Delayed fracture healing OR Delayed union) AND M=(Bushen TianSui Decoction OR Bushen TianSui)
CBM	("Delay fracture healing "[Common Fields: Intelligent] OR " Delayed fracture healing "[Common Fields: Intelligent] OR " Delayed union "[Common Fields: Intelligent]) AND ("Bushen TianSui Decoction "[Common Fields: Intelligent] OR " Bushen TianSui "[Common Fields: Intelligent])
PubMed	((((delay fracture healing[Title/Abstract]) OR (delayed fracture healing[Title/Abstract])) OR (delayed union[Title/Abstract])) OR (delayed union of fracture[Title/Abstract])) AND ((((((Bushen TianSui Decoction[Title/Abstract]) OR (Bushen TianSui[Title/Abstract])) OR (traditional Chinese medicine[Title/Abstract])) OR (Chinese traditional medicine[Title/Abstract])) OR (Chinese patent medicine[Title/Abstract])) OR (herbal[Title/Abstract]))
Web of Science	#1 TS=(delay fracture healing OR delayed fracture healing OR delayed union OR delayed union of fracture)
	#2 TS=(Bushen TianSui Decoction OR Bushen TianSui OR traditional Chinese medicine OR Chinese traditional medicine OR Chinese patent medicine OR herbal)
	#3 #1 AND #2
Embase	#1'delay fracture healing':ab,ti OR 'delayed fracture healing':ab,ti OR 'delayed union':ab,ti OR 'delayed union of fracture':ab,ti
	#2'bushen tiansui decoction':ab OR 'bushen tiansui':ab OR 'traditional chinese medicine':ab OR 'chinese traditional medicine':ab OR 'chinese patent medicine':ab OR herbal:ab
	#1 AND #2
Corhrane	#1 (delay fracture healing):ti,ab,kw OR (delayed fracture healing):ti,ab,kw OR (delayed union):ti,ab,kw OR (delayed union of fracture):ti,ab,kw 421
	#2 (Bushen TianSui Decoction):ti,ab,kw OR (Bushen TianSui):ti,ab,kw OR (traditional Chinese medicine):ti,ab,kw OR (Chinese traditional medicine):ti,ab,kw OR (Chinese patent medicine):ti,ab,kw 8157
	#3 (herbal):ti,ab,kw 10088
	#4 #2 OR #3 16634
	#5 #1 AND #4 4