Chinese Medicine Decoctions for Post-Stroke Fatigue: A Systematic Review and Meta-Analysis

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Post-stroke fatigue is one of the concomitant symptoms of stroke. Despite the existence of various non-pharmacological interventions, there are no specific medications for patients with post-stroke fatigue because of its unclear mechanisms. This systematic review and meta-analysis aimed to summarize the role of Chinese medicine decoctions in managing post-stroke fatigue based on randomized controlled trials. This study used the Cochrane risk of bias tool to assess randomized controlled trials quality. The meta-analysis was conducted using RevMan 5.3. Eighteen randomized controlled trials met the study criteria, including 1478 patients with stroke. The control and experimental groups comprised 747 and 731 cases, respectively. The meta-analysis demonstrated that the Chinese medicine group experienced a greater level of fatigue relief compared to the control group, with improved fatigue severity scale scores (mean difference=-6.40; 95 % confidence interval=-8.12-4.68; p<0.00001) and fatigue impact scale scores (mean difference=-19.64; 95 % confidence interval=-25-14.29; p<0.00001). The quality of life and energy improvement in the Chinese medicine group were higher than those in the non-Chinese-medicine group, with improved stroke-specific quality of life scale scores (mean difference=19.80; 95 % confidence interval=12.59-27.01; p<0.00001) and stroke-specific quality of life scale-energy scores (mean difference=2.32; 95 % confidence interval=1.32-3.32; p<0.0001). The daily living activities of the Chinese medicine group were higher than those of the non-Chinese-medicine group, with improved modified Barthel index scores (mean difference=6.34; 95 % confidence interval=3.19-9.49; p<0.0001). The overall quality of evidence evaluated by the Cochrane system was not high. Three studies reported no adverse reactions in the patients. The effectiveness and safety of utilizing Chinese medicine decoctions in treating post-stroke fatigue were demonstrated. However, more rigorous studies with superior quality and expansive data are needed to further validate these findings.

Key words: Chinese medicine decoction, stroke, post-stroke fatigue, meta-analysis, ischemia

Stroke, an acute disorder of blood circulation in the brain, can be divided into ischemic and hemorrhagic stroke according to the broad lesion type. According to a report by the World Health Organization[1], stroke has emerged as the foremost cause of adult disability and ranks as the 2nd primary cause of mortality in humans, seriously jeopardizing human health. Stroke survivors usually experience cerebrovascular abnormalities and comorbidities that result in different types and degrees of structural dysfunction, severely affecting their daily living activities and ability to participate in society.

Post-Stroke Fatigue (PSF) is a pathological and persistent sensation of physical fatigue or lack of energy that occurs independently of previous activity levels and is characterized by a perception of inadequate energy during mental or physical tasks, as well as a lack of motivation or ability to sustain ongoing activities. It is usually not relieved by rest and often occurs during stroke[2]. The laziness, deficiency exhaustion and depression recorded in ancient Chinese medical tests are similar to the manifestations of PSF, including fatigue, weakness and lumbago, weakness of the legs, dizziness, and pulse weakness as the main clinical symptoms. This condition also embodies a fundamental imbalance between yin and yang energies, coupled with deficiencies in vital organs, specifically the liver,

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spleen, and kidneys[3]. Previous reports have shown that the incidence of PSF ranges from 23 % to 85 %[4]. PSF is common in the early and middle stages of stroke[5] and can last for >10 y[6]. It not only affects the neurological recovery of stroke survivors but also seriously reduces their quality of life. In recent years, research on this post-stroke symptom has gradually increased, and current rehabilitation treatments for PSF include respiratory training, noninvasive brain stimulation techniques, and cognitive-behavioral therapies[7]. Despite the existence of various non-pharmacological interventions, there are no specific medications for patients with PSF, and most medications are designed to relieve the effects of chronic pain and discomfort. Therefore, there is an urgent need for further research to recommend more effective medications in treating PSF[8].

The preventive and therapeutic approaches of Traditional Chinese Medicine (TCM) towards stroke and its associated complications have gained significant recognition globally[9]. It has been shown to be effective in the restoration of cortical function and functional reconstruction after brain injury[10] and can help with the restoration of the motor center and improvement of mood after stroke[11]. However, a comprehensive, objective and evidence-based examination summarizing the outcomes of Chinese medicine decoctions in treating PSF remains unexplored. Therefore, this systematic review and meta-analysis undertook an exhaustive search for Randomized Controlled Trials (RCTs) to rigorously assess the effectiveness and safety of these decoctions in managing PSF. The primary objective of this study is to provide a reliable reference for the clinical application of herbal medicines in PSF management, with the aspiration of laying a foundation for protocol development to enhance symptom relief and life quality after PSF.

MATERIALS AND METHODS

Search methods:

The search period was from the time of the construction of each library to June 2023. This study was officially registered on the PROSPERO platform, bearing the Registration No: CRD42023433638. This study searched the platforms of China Knowledge Network, Wanfang Database, Wipu Database of Chinese Scientific and Technical Journals and China Biomedical Literature Database for the terms Chinese medicine, stroke, cerebrovascular accident, ischemic stroke, PSF, fatigue and other keywords or subject terms. Moreover, this study also relied on the Cochrane central register of controlled trials, PubMed, among others, to collect keywords or subject terms such as stroke, apoplexy, ischemic stroke, TCM, Chinese medicine, Chinese herbal medicine, fatigue and PSF. This study screened RCTs using a strategy with an logical term. The Chinese search logic was as follows; (stroke or cerebrovascular accident or ischemic stroke) and (fatigue or PSF) and (Chinese medicine). The English search logic was as follows; (apoplexy or cerebrovascular accident or ischemic stroke) and (fatigue or PSF) and (TCM or Chinese medicine). Additionally, the reference lists of the included studies were meticulously scanned to supplement the literature search and facilitate further in-depth research based on the previously reviewed references.

Inclusion criteria:

Every participant in the study conformed to the established diagnostic standards of either Chinese or Western medicine for stroke, as well as the criteria set for the diagnosis of PSF[12].

The experimental group received a combination of Chinese medicine decoction and non-Chinese medicine general therapies, whereas the control group received only general therapies, other non-Chinese medicine modalities or a placebo.

The main outcome measured was the level of fatigue, while secondary outcomes encompassed life quality, daily activity levels and any adverse events. Assessment tools use include the Fatigue Severity Scale (FSS), Fatigue Impact Scale (FIS), Stroke-Specific Quality of Life (SS-QOL) scale, SS-QOL-Energy (SS-QOL-E), and the Modified Barthel Index (MBI). The types of studies included in the literature were RCTs.

Exclusion criteria:

Literature retrieved as duplicates; conference papers, application guides, and review literature; studies of other appropriate Chinese medicine techniques, such as combined acupuncture and tuina; studies in which the intervention modality was TCM fumigation or other non-oral Chinese medicines, such as Chinese patent medicine and literature for which complete data were unavailable or for which there were obvious misrepresentations of the data were excluded from this study.

Data extraction and risk assessment:

The literature was independently screened for compliance with the inclusion and exclusion criteria by two reviewers based on a search term strategy. Baseline and indicator data were entered into an information sheet. Disagreements were resolved by consensus or third-party means. The following data were extracted; authors, date of publication, study population and age, interventions (treatment and control), treatment duration, outcome indicators and adverse effects. The detailed process was illustrated in fig. 1.

The risk of bias was assessed in the included literature according to the risk of bias tool recommended in the Cochrane Reviews handbook 5.1, including the generation of random sequences, execution of random concealment, implementation of blinding, implementation of blinding of outcome measures, incomplete information, selective reporting and other biases. Based on these criteria, the risk was classified as low, high or unclear. RevMan 5.3 software was used to summarize and graphically depict the risk of bias determination results.

Statistical analysis:

Statistical analyses were conducted utilizing the Revman 5.3 software. Each outcome indicator was a continuous variable (FSS, FIS, MBI, SS-QOL and SS-QOL-E), and the Mean Difference (MD) and 95 % Confidence Interval (CI) were calculated separately. Heterogeneity between the results of the included studies was analyzed using the Chi-Square (χ^2) test (test level, Alpha (α)=0.1). The heterogeneity was then combined with the I^2 statistic; mild (I^2 0 %-50 %), moderate (I^2 30 %-60 %), large (I^2 50 %-90 %), or considerable (I^2 75 %–100 %). When I^2 was <50 %, the fixed effects model was used if there was literature homogeneity. When I^2 was >50 %, the heterogeneity was higher, and this study chose a random effects model or subgroups to re-conduct meta-analysis and analyze the source of heterogeneity, which could exclude some anomalous results. If the heterogeneity was still high after creating subgroups, this study performed sensitivity analysis and removed lower-quality studies to obtain robust results. The assessment of potential publication bias was conducted through a funnel plot. Symmetrical graph distributions in the funnel plot indicated an absence of publication bias in the study, while asymmetry suggested possible publication bias. $p<0.05$ is regarded statistically significant.

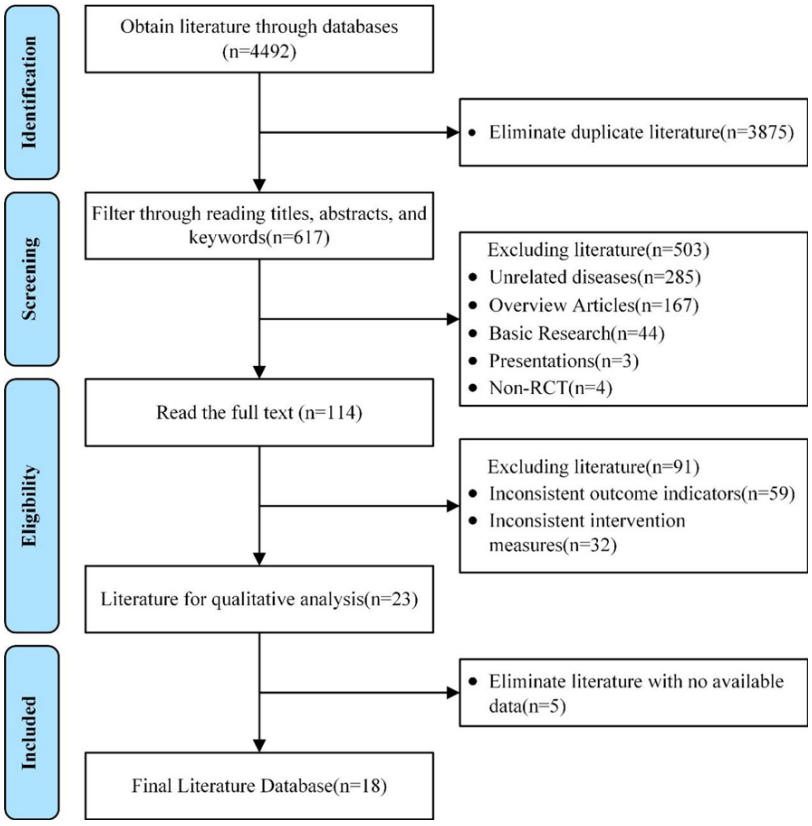

Fig. 1: Literature selection process

RESULTS AND DISCUSSION

Initially, 4492 relevant studies were identified through electronic search. Following a thorough review of article titles, abstracts, keywords and full texts, 18 papers met the inclusion and exclusion criteria and were selected for the systematic evaluation[13-30]. The total number of participants in these studies was 1478, with 731 in the experimental group and 747 in the control group.

Fourteen Chinese medicine decoctions were included; Peiyuan Huanwu Tang, Buyang Huanwu Tang, Buyang Huanwu Tang combined with Chaihu Shugan San, Buyang Huanwu Tang combined with Xiaoyao San, qi-tonifying fatigue-relieving decoction, modified middle-tonifying qi-replenishing decoction, formula for tonifying qi and reinforcing yang, formula for tonifying qi, minor life-prolonging decoction, self-formulated formula for cleansing phlegm and unblocking collaterals, Looseleaf *Millettia* fatigue-relieving decoction, major liver-tonifying decoction, three ingredients *Rehmannia* decoction, and compound Sini-wendang tang. The details of the studies included are summarized Table 1.

TABLE 1: BASIC CHARACTERISTICS OF THE INCLUDED LITERATURE

Research	Number of cases (T/C)	T/C (M/F)	Age (T/C)	Interventions		Treatment of treatment group	Outcome indicators
				Treatment group	Control group		
Han *et al.*[13]	138 (69/69)	97/41	65.39±2.39/ 65.42±2.42	Qi-tonifying fatigue-relieving decoction	Conventional rehabilitation	One dose per day and 4 mo as a course of treatment	FSS and SS-QOL-E
Liu *et al.*[14]	60 (30/30)	30/30	54±8.4/ 49±8.4	Qi-tonifying fatigue-relieving decoction	Conventional rehabilitation	One dose per day and 4 mo as a course of treatment	FSS and SS-QOL-E
Shen *et al.*[15]	90 (45/45)	49/41	61.5±8.9/ 60.1±8.7	Three ingredients rehmannia decoction	Conventional rehabilitation	150 ml each time, twice a day and 4 mo as a course of treatment	FSS
Yu *et al.*[16]	74 (37/37)	48/26	63.7±9.4/ 63.9±8.6	Peiyuan huanwu tang	Conventional rehabilitation+ Chinese medicine placebo	One dose per day and 3 mo as a course of treatment	FSS; FIS and MBI
Liang *et al.*[17]	120 (60/60)	67/53	68.7±6.4/ 67.7±7.3	Looseleaf *Millettia* fatigue-relieving decoction	Western medicine	150 ml each time, twice a day and 4 mo as a course of treatment	FSS and SS-QOL-E
Tan *et al.*[18]	96 (48/48)	51/45	65±5.67/ 64±5.93	Looseleaf *Millettia* fatigue-relieving decoction	Conventional rehabilitation	150 ml each time, twice a day; 4 mo as a course of treatment	FSS
Yang *et al.*[19]	60 (30/30)	39/21	54±9/ 55±7	Formula for tonifying qi and reinforcing yang	Conventional rehabilitation	200 ml each time, twice a day and 4 mo as a course of treatment	FSS and MBI
Sun *et al.*[20]	83 (38/45)	45/38	55.6±8.8/ 54.8±9.1	Major liver-tonifying decoction	Conventional rehabilitation	100 ml each time, twice a day and 4 mo as a course of treatment	FSS and MBI
Zhang *et al.*[21]	111 (56/55)	81/30	59.16±8.24/ 58.96±8.22	Minor life-prolonging decoction	Conventional rehabilitation	One dose per day and 2 mo as a course of treatment	FSS; FIS and SS-QOL-E

Chen *et al.*[22]	60 (30/30)	32/28	64.59±11.29/ 65.20±10.00	Compound sini-wendang tang	Other medicine	300 ml each time, once a day and 1 mo as a course of treatment	FSS
Chen *et al.*[23]	80 (40/40)	38/42	69.7±5.1/ 70.4±2.95	Self-formulated formula for cleansing phlegm and unblocking collaterals	Conventional rehabilitation	One dose per day and 4 mo as a course of treatment	FSS and FIS
Liang *et al.*[24]	92 (46/46)	53/39	66.0±9.9/ 64.9±11.6	Buyang huanwu tang combined with xiaoyao san	Conventional rehabilitation	One dose per day and 4 mo as a course of treatment	FSS and SS-QOL
Yin *et al.*[25]	80 (40/40)	33/47	64.7±8.5/ 65.2±9.3	Buyang huanwu tang combined with chaihu shugan san	Conventional rehabilitation	One dose per day and 4 mo as a course of treatment	FSS and SS-QOL
Guo *et al.*[26]	90 (45/45)	70/20	56.1±4.6/ 57.2±5.7	Formula for tonifying qi	Conventional rehabilitation	150 ml each time, twice a day and 4 mo as a course of treatment	FSS and SS-QOL
Sima *et al.*[27]	80 (40/40)	48/32	65.9±7.57/ 65.45±8.22	Modified middle-tonifying qi-replenishing decoction	Conventional rehabilitation	One dose per day and 4 mo as a course of treatment	FSS
Duan *et al.*[28]	60 (27/33)	27/33	63.2±6.2/ 62.9±6.0	Modified buyang huanwu tang	Western medicine	One dose per day and 4 mo as a course of treatment	FSS
Guo *et al.*[29]	60 (30/30)	34/26	66.20±12.04/ 65.53±9.73	Modified buyang huanwu tang	Conventional rehabilitation+Chinese medicine placebo	100 ml each time, twice a day and 4 mo as a course of treatment	FSS and SS-QOL
Ye *et al.*[30]	44 (20/24)	23/21	62.55±5.85/ 64.79±4.22	Modified buyang huanwu tang	Conventional rehabilitation	One dose per day and 4 mo as a course of treatment	FSS

Nine studies clearly explicitly mentioned that their random sequence generation relied on the random number table method, marking them as low-risk for bias[16-19,21-23,25,29]. Two studies used the method of random assignment by sequential odd-even order admission to a hospital or group[13,30], presenting a high risk of bias. The remaining seven studies did not provide sufficient details on their random sequence generation[14,15,20,24,26-28], treading to an unclear bias risk assessment. Eighteen studies failed to identify the allocation concealment method in detail. Therefore, the risk of bias was judged to be unclear. Three papers pointed out that the control group implemented a Chinese medicine placebo intervention for trial participants and researchers[21,29,30], thus considered low-risk. The others did not specify blinding methods, heightening the risk due to potential recognition of treatment groups by participants and researchers. All eighteen studies reported complete data and systematic outcome measures, categorizing them as low-risk for incomplete data and selective reporting biases. Due to inadequate blinding of outcome assessments and insufficient details, the bias risk for some studies remained unclear. The risk of bias assessment was shown in fig. 2.

Eighteen papers reported changes in the FSS scores following the intervention. The FSS was applied as a measure of the results of the studies, which was found to have a high degree of heterogeneity among

the studies (p<0.00001, I^2=99 %). The FSS scores of the experimental group were higher than the value of the change in the control group, and the difference between the two groups was statistically significant (MD=-6.40; 95 % CI -8.12-4.68; p<0.00001). The results are illustrated in fig. 3. Considering the high clinical heterogeneity among the studies, 18 studies were sub-grouped according to the different compositions of Chinese medicine prescriptions, as well as the differences in therapeutic principles. The results are presented in Table 2 and fig. 4. In four papers[13-16], the therapeutic principle was Tonify qi, nourish the spleen and kidney (p=0.61, I^2=0 %) with a statistically significant difference (MD=-5.66; 95 % CI -6.88-4.45; p<0.00001). In three papers[17-19], the therapeutic principle was Tonify qi, circulate blood and transform stasis (p=0.74, I^2=0 %) with a statistically significant difference (MD=-4.77; 95 % CI: -6.98–-2.57; p<0.0001). In two papers[20,21], the therapeutic principle was Tonify qi, disperse cold and promote warmth, and circulation (p=0.57, I^2=0 %) with a statistically significant difference (MD=10.75; 95 % CI -12.30-9.21; p<0.00001). In two papers[22,23], the therapeutic principle was Tonify qi and cleanse phlegm (p=0.32, I^2=0 %) with a statistically significant difference (MD=-5.27; 95 % CI -7.75-2.79; p<0.0001). In two papers[24,25], the therapeutic principle was move qi and relieve stagnation (p=0.81, I^2=0 %) with a statistically significant difference (MD=-2.13; 95 % CI -2.43-1.83; p<0.00001). In two papers[26,27], the therapeutic principle was to regulate qi movement and raise the drooping (p<0.0001, I^2=94 %) with a statistically significant difference (MD=-5.26; 95 % CI -11.87-1.35; p<0.0001). In three papers[28-30], the basic Chinese medicine prescription was Buyang Huanwu Tang (p<0.00001, I^2=100 %) with a statistically significant difference (MD=-10.89; 95 % CI -20.94-0.84; p=0.03). The high heterogeneity may arise from the fact that there were additions and subtractions of drugs or changes in the dosage of drugs based on Chinese medicine prescriptions.

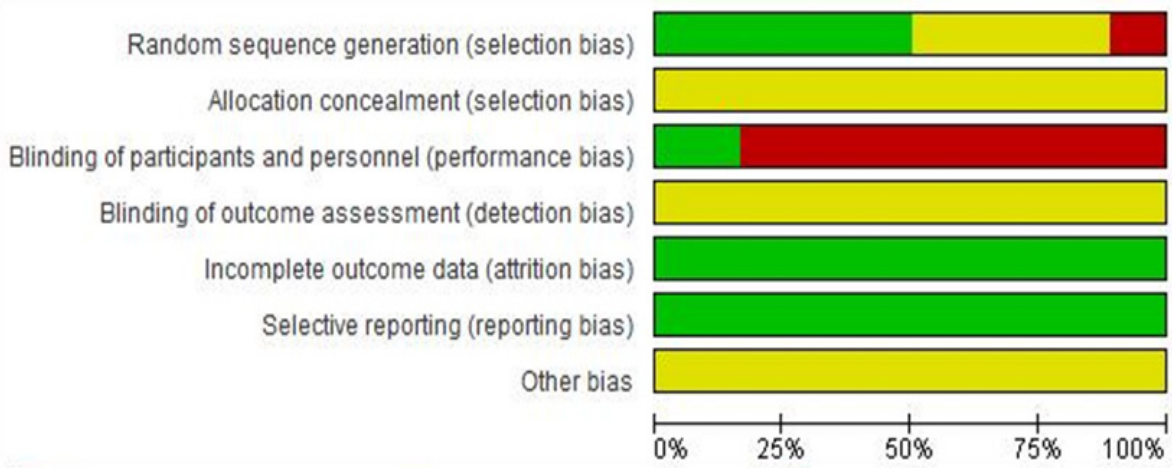

Fig. 2: The risk of bias assessment chart
Note: (■): Low risk of bias; (■): Unclear risk of bias and (■): High risk of bias

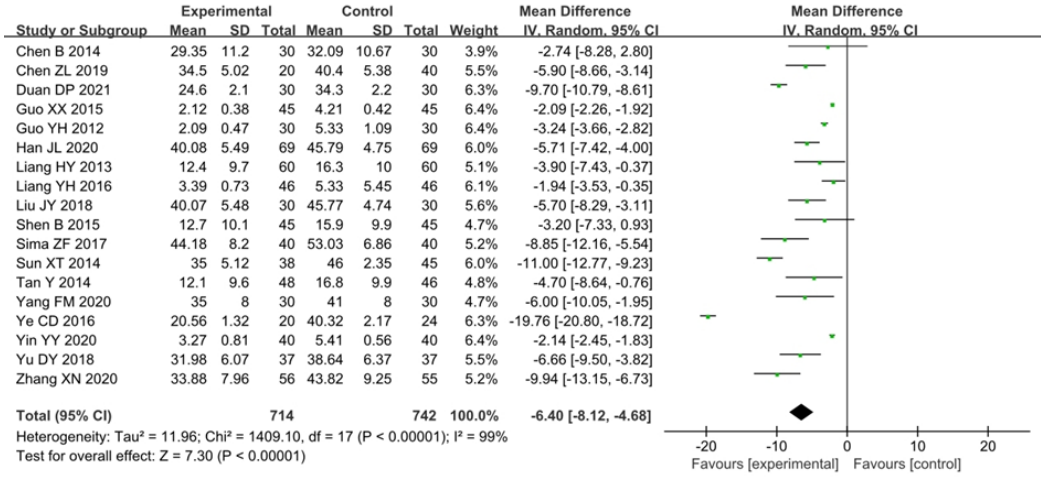

Fig. 3: Forest plot of FSS scores

TABLE 2: MAIN COMPOSITION AND THERAPEUTIC PRINCIPLE

Research	Interventions	Main composition	Therapeutic principle
Han *et al.*[13]	Qi-tonifying fatigue-relieving decoction	AM, RG1, RLW, An, Lu, CS, RAB, Po, FSC, RAT, CE, HT, RRP and RB	Tonify qi, relieve fatigue, nourish the spleen and kidney
Liu *et al.*[14]	Qi-tonifying fatigue-relieving decoction	AM, RG1, RLW, An, Lu, CS, RAB, Po, FSC, RAT, CE, HT, RRP and RB	Tonify qi, relieve fatigue, nourish the spleen and kidney
Shen *et al.*[15]	Three Ingredients rehmannia decoction	HA, HE1, Cu, RRR, FC1, HC, RMO, RALP, Ci, HD, RO, FSC, RAT, RP1, Po, Mi, ZRR and FJ	Tonify qi and excite kidney yang
Yu *et al.*[16]	Peiyuan huanwu tang	HS, AM, RP1, An, RAT, RLW, RC1, RPA, HC, RALP, RMO, RRP, RAB and FC1	Tonify qi, warm yang, nourish spleen and the kidney
Liang *et al.*[17]	Looseleaf *Millettia* fatigue-relieving decoction	AM, LM, RRR, SP, Lu, RAT, An, RPR, FC2 and RLW	Tonify qi, relieve fatigue, circulate blood and transform stasis
Tan *et al.*[18]	LM fatigue-relieving decoction	AM, LM, RRR, SP, Lu, RAT, An, RPR, FC2 and RLW	Tonify qi, relieve fatigue, circulate blood, and transform stasis
Yang *et al.*[19]	Formula for tonifying qi and reinforcing yang	HR, RMO, HE1, RG2, RB, RC2, An and Li	Tonify qi, reinforce yang, circulate blood and transform stasis
Sun *et al.*[20]	Major liver-tonifying decoction	RC1, RZ, FSC, FI, CMR, HL and RD	Tonify qi, disperse cold, promote warmth and circulation
Zhang *et al.*[21]	Minor life-prolonging decoction	HE2, RST, RG2, RC1, RPA, RLW, Li, SAA, RS1, RS2, FJ, RALP and ZRR	Assist yang, disperse cold, promote warmth and circulation
Chen *et al.*[22]	Compound sini-wendang tang	RB, RPA, FA, Po, PCR, RP2, BCIT, CB, CSF and Li	Tonify qi and cleanse phlegm
Chen *et al.*[23]	Self-formulated formula for cleansing phlegm and unblocking collaterals	RLW, CB, CSB, RPR, HD, HE1, HA, Hi and Lus	Tonify qi, cleanse phlegm and open the orifices
Liang *et al.*[24]	Buyang Huanwu Tang combined with Xiaoyao San	AM, RAS, RB, PCR, RLW, RPA, RAM, Po, SP, FC2, Li and ZRR	Move qi and relieve stagnation
Yin *et al.*[25]	Buyang Huanwu Tang combined with Chaihu Shugan San	AM, RAS, RB, PCR, RLW, RPA, RAM, Po, SP, FC2, Lus, Sc and ZRR	Move qi and relieve stagnation
Guo *et al.*[26]	Formula for tonifying qi	RLW, AM, RPR and RAB	Regulate qi movement and raise the drooping
Sima *et al.*[27]	Modified middle-tonifying qi-replenishing decoction	AM, RAM, RC3, Li, An, PCR, RC2, RB, RSM and RLW	Regulate qi movement and raise the drooping
Duan *et al.*[28]	Modified Buyang Huanwu Tang	AM, RPR, An, FC2, SP, Lu, RLW, SC, RA1, HE3, RT, HD, RUU, FC1, FSC, Sc, BB, RAT, CPM and SDS	Tonify qi, assist yang and regulate spirit
Guo *et al.*[29]	Modified Buyang Huanwu Tang	AM, RLW, RPR, RAB, RG1 and RO	Tonify qi, nourish yin and clam wind
Ye *et al.*[20]	Modified Buyang Huanwu Tang	AM, An, RLW, RPR, Lu, HE3, SC, RA1, HD, RT, BB, RAT, RG3, RUU, RP1 and RA2	Move qi, circulate blood and eliminate dampness

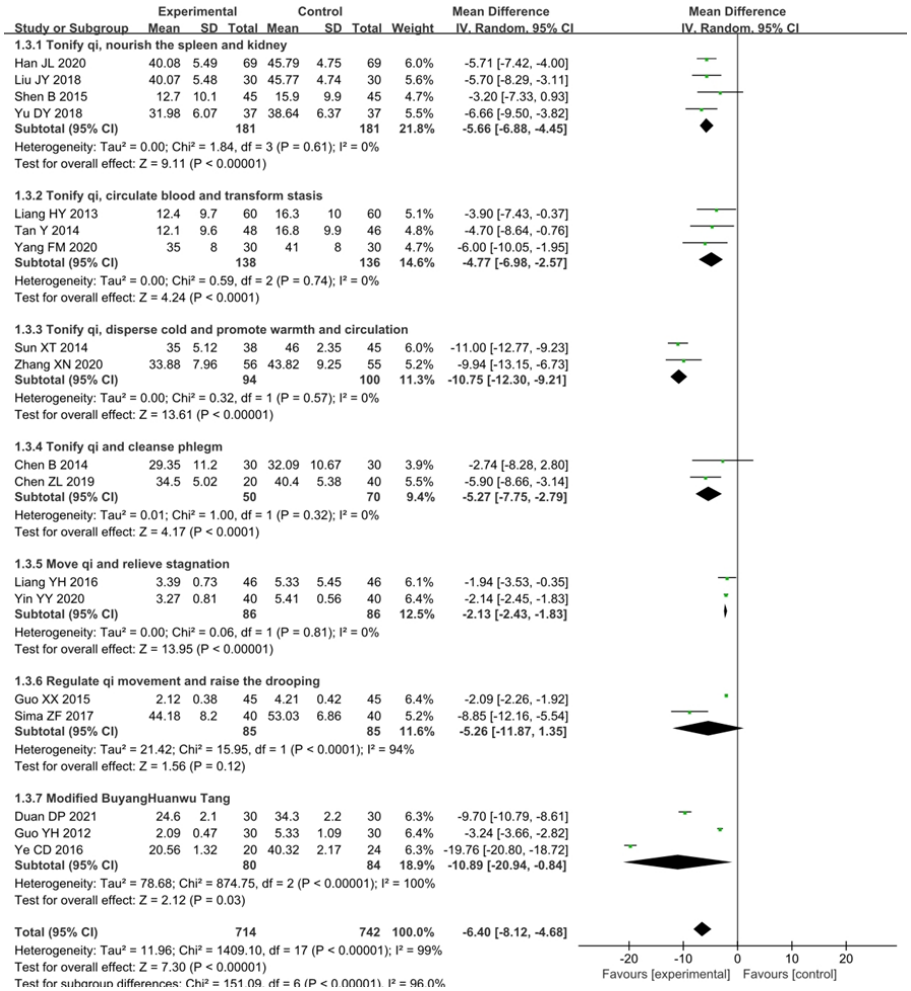

Fig. 4: Subgroup analysis of FSS scores

Three papers reported changes in the FIS scores after intervention[16,21,23]. Data analysis using the FIS as an outcome indicator showed moderate heterogeneity among the studies (p=0.05, I^2=67 %). The results showed that the change in FIS scores in the experimental group was better than that in the control group, and the difference between the two groups was statistically significant (MD=-19.64; 95 % CI: -25.00-14.29; p<0.00001). The results are illustrated in fig. 5. After eliminating Chen *et al.*[23] study, the FIS scores showed that there was a significant improvement in fatigue (p=0.62; I^2=0 %; MD=-16.76; 95 % CI -20.68-12.85; p<0.00001). The results are illustrated in fig. 6.

Four studies reported changes in the SS-QOL scores after the intervention[24-26,29]. The SS-QOL was used as an outcome indicator for data analysis, which showed low heterogeneity among the studies (p=0.14, I^2=45 %). The results showed that the change in SS-QOL scores in the experimental group was higher than that in the control group, and the difference between the two groups was statistically significant (MD=19.80; 95 % CI 12.59-27.01; p<0.00001). The results are illustrated in fig. 7.

Four studies reported changes in the SS-QOL-E scores after the intervention[13,14,17,21]. Data were analyzed using the SS-QOL-E as an outcome indicator, showing a high degree of heterogeneity between the studies (p<0.0001, I^2=86 %). The results showed that the change in the SS-QOL-E score in the experimental group was higher than that in the control group, and the administration of Chinese medicine could improve the quality of life of patients with PSF. The difference between the two groups was statistically significant (MD=2.32; 95 % CI 1.32-3.32; p<0.00001). The results are illustrated in fig. 8. Two studies were sub-grouped according to the same Chinese medicine prescriptions. The SS-QOL-E scores showed that there was a significant improvement in the quality of life (p=0.98; I^2=0 %; MD=2.22; 95 % CI 1.75-2.70; p<0.00001). The results are illustrated in fig. 9.

Three studies reported changes in the MBI after intervention[16,17,20]. The MBI showed moderate heterogeneity among the studies (p=0.10, I^2=56 %), and the change in the MBI in the experimental group was higher than that in the control group. The difference between the two groups was statistically significant (MD=6.34; 95 % CI 3.19-9.49; p<0.0001). The results are illustrated in fig. 10. After eliminating Yu *et al.*[16] study, the MBI showed that there was a significant improvement in the activities of daily living (p=0.25; I^2=25 %; MD=5.68; 95 % CI 4.11-7.25; p<0.00001). The results are illustrated in fig. 11.

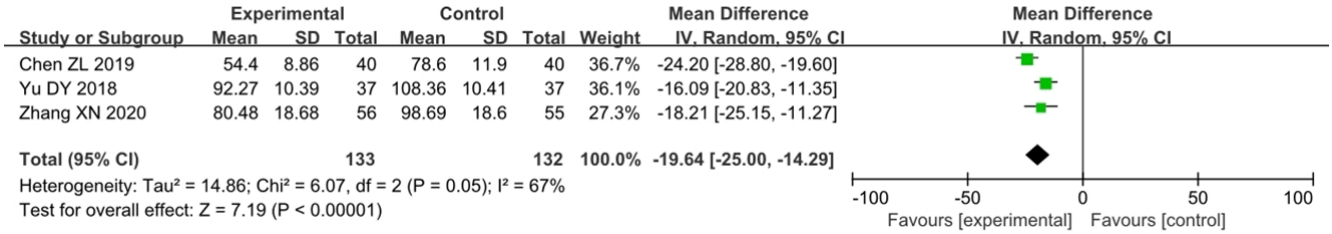

Fig. 5: Forest plot of FIS scores

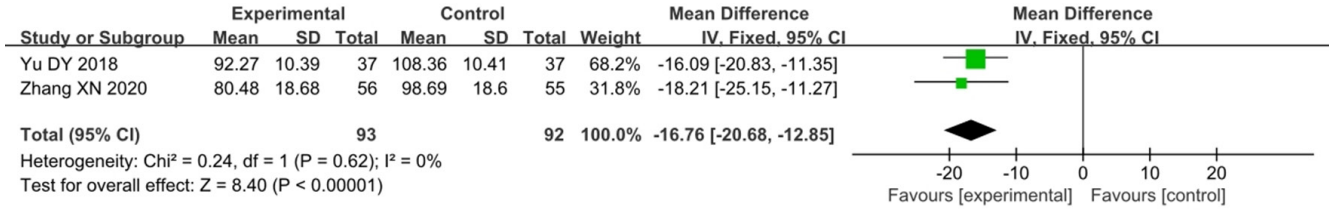

Fig. 6: Effective sensitivity analysis of FIS scores

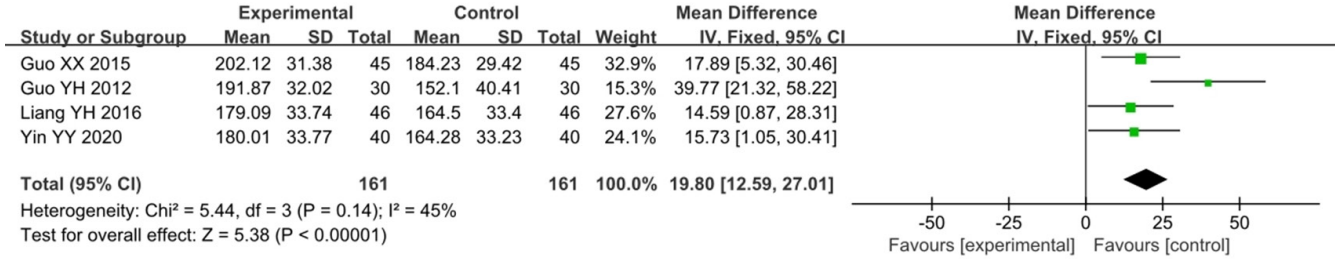

Fig. 7: Forest plot of SS-QOL scores

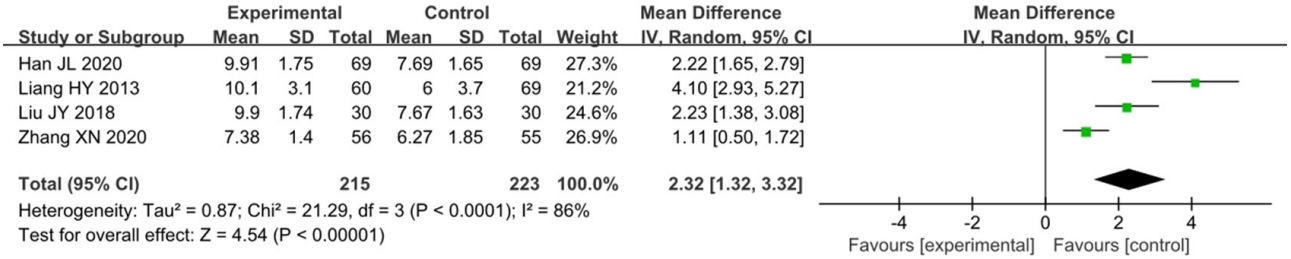

Fig. 8: Forest plot of SS-QOL-E scores

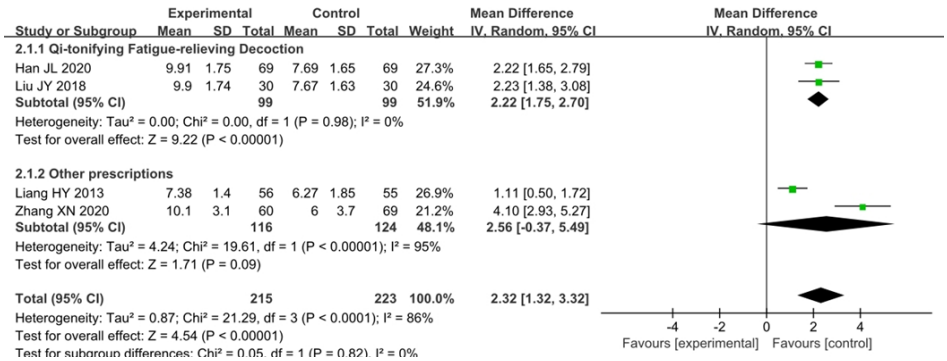

Fig. 9: Subgroup analysis of SS-QOL-E scores

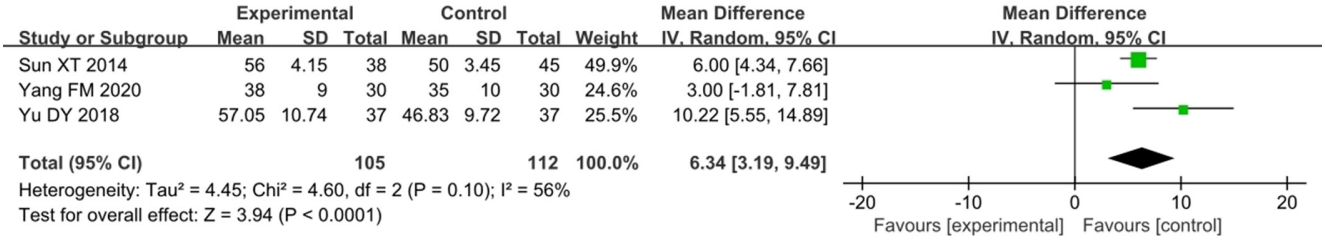

Fig. 10: Forest plot of MBI scores

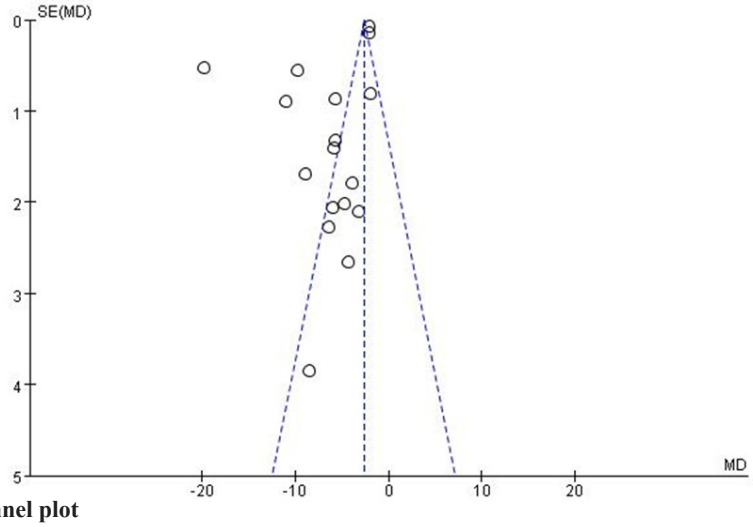

Fig. 11: Published offset funnel plot

Among the 20 included studies, one reported no adverse reactions during the study period[14], while the other studies did not make any mention of this.

This research involved the creation of a funnel plot to examine publication bias, specifically focusing on the 18 papers that utilized the FSS as an outcome measure. Fig. 11, shows that the selected papers were not evenly distributed on either side of the midline, and they had a higher likelihood of publication bias.

All formulas mentioned in the literature include the following Chinese medicines; *Astragalus membranaceus* (*A. membranaceus*) (67 %), Rhizoma *Ligustici wallichii* (78 %), *Angelica* (67 %), Rhizoma *Acori tatarinowii* (*A. tatarinowii*) (44 %), *Lumbricus* (44 %), Radix *Paeoniae rubra* (39 %), Radix Bupleuri (39 %), *ginseng* (28 %), Radix *Achyranthes bidentata* (28 %), *Carthami flos* (28 %), *Schisandrae chinensis* (28 %), Licorice (28 %), pericarpium citri reticulatae (22 %), *Ramulus cinnamomi* (17 %), *Herba epimedii* (17 %), Rhizoma *Arisaema cum* Bile (11 %), and Radix *Ophiopogon* is (11 %). PSF is primarily caused by a deficiency, with the liver, spleen and kidneys being the most affected organs. Statistics show that more than most of stroke cases demonstrate blood stasis patterns due to qi deficiency[31]. Therefore, TCM pathogenesis should prioritize addressing the root causes of qi deficiency and the associated blood stasis. Additionally, the impaired regulation of qi by the liver is a contributing factor to depression, which affects the patient's psychological state[32]. As a patient's ability to control muscles, store essence and store blood decreases, insufficient essence is produced to nourish the spirit, which consequently causes weakness and lethargy. This leads to a reduced initiative of the patient during rehabilitation exercises, thereby impeding recovery. The treatment principle of TCM frequently involves tonifying the qi, circulating the blood, unblocking collaterals, and warming and nourishing the liver and kidneys. Therefore, the highly utilized *A. membranaceus*, known as the supreme qi-tonifying medicine, is used to tonify yuan-primordial qi in the five zang organs. The combination with Rhizoma *Ligustici wallichii*, known as qi medicines within the blood, moves qi and nourishes the blood. The combination of *A. membranaceus* and Radix Bupleuri soothes the liver, elevates yang, moves qi, and resolves depression, as qi circulation ensures smooth blood flow. *Ginseng* and RG can benefit qi and nourish blood and are often used to treat dizziness caused by insufficient qi and blood. *Angelica* nourishes blood, circulates blood and transforms stasis without damaging the blood. Radix *Paeoniae rubra* and *Carthami flos* remove blood stasis and relieve pain. Radix *Achyranthes*

bidentata and *Lumbricus* nourish the liver and kidney, remove blood stasis, and unblock meridians. Radix *Ophiopogon* can alleviate fatigue and has a calming and hypnotic effect. *Ramulus cinnamomi* can reinforce yang to relieve exterior syndromes and benefit qi, dissipate cold and relieve pain.

Patients with PSF often also have phlegm, and Pericarpium *Citri reticulatae* can regulate the qi, moisten dryness, and eliminate phlegm. Licorice can relieve cough, eliminate phlegm, nourish the spleen, tonify qi and relieve pain. Rhizoma *A. tatarinowii* and Rhizoma *Arisaema cum* Bile open the orifices, resolve phlegm, calm the mind and arrest convulsion. The combined use of these medicines focuses on tonifying qi and reinforcing deficiency as the root while simultaneously resolving blood stasis, promoting warmth and circulation, and eliminating phlegm as the tip. They collectively contribute to relieving fatigue and revitalizing essence.

TCM may mitigate fatigue through mechanisms such as bolstering oxidation resistance, neutralizing free radicals, diminishing the accumulation of metabolites and ameliorating conditions like skeletal muscle cell ultrastructural damage or nervous system dysfunctions induced by fatigue[33]. For example, *A. membranaceus* may alleviate fatigue by boosting hypoxic tolerance and regulating the gut microbiota, oxidative stress and inflammation[34]. Research suggests that ginsenosides can safeguard the central nervous system and circumvent central fatigue as anti-inflammatory and anti-apoptotic molecules by influencing inhibitory amino acids, Acetylcholine (ACH)/NO amino acid metabolites, and apoptosis-regulating proteins[35]. Radix *Angelica sinensis* is classified as a neuroprotective because of its vasodilatory, anti-arteriosclerotic, anti-platelet aggregation, and anti-inflammatory effects[36]. Furthermore, Rhizoma *A. tatarinowii* has shown promise as an anti-fatigue agent, evidenced by its ability to decrease exercise-induced elevations in serotonin (5-Hydroxytryptamine (5-HT)) synthesis, along with reductions in Tryptophan Hydroxylase-2 (TPH2) messenger Ribonucleic Acid (mRNA) and protein expression, among other effects[37].

The TCM formulas included in this study have shown positive effects on the pathogenesis of qi deficiency, blood stasis, and liver and kidney undernourishment in patients with PSF. The meta-analysis results in this study showed that Chinese medicine decoctions could effectively improve the MBI and FSS, FIS, SS-QOL and SS-QOL-E scores of patients with PSF. This means that Chinese medicine decoctions can alleviate fatigue in patients with PSF to a certain extent, improving their quality of life and ability to perform daily living activities. Our study shows that the Chinese medicine decoctions had a positive effect on the patients.

This study had several limitations. First, this search encompassed both English and Chinese electronic databases, but all 18 trials included in this study were conducted in China, indicating a potential geographical limitation in the evidence.

The second limitation was the poor methodological quality of the evidence. Details on allocation concealment and blinding were often inadequately reported, raising concerns about selection, performance and detection biases. In addition, the limited number of included trials that were registered as RCTs made it challenging to evaluate publication bias risk. This concern was further supported by the asymmetry observed in the funnel plot, indicating possible bias.

The third limitation was the different versions of the fatigue measurement tools used. For the FSS, some studies used mean scores, whereas others used total scores or other metrics.

Further, there was a significant heterogeneity observed in the scores of FSS, SS-QOL-E and MBI. First, this may be attributed to the different basic characteristics of the participants, such as age, site of onset and disease duration. Second, it may be related to the composition and dosage of the drugs used in the different formulas. Regarding the FSS scores, this study discussed the heterogeneity in the seven subgroups according to the different efficacies presented by the formulas. Heterogeneity was eliminated when the drug compositions showed approximately the same efficacy. However, the heterogeneity remained high in the other two subgroups, probably because of the individualized herbal regimens developed for different patients. This study excluded Chen *et al.*[22] study to reduce the heterogeneity of the FIS score, considering that the pretreatment fatigue of the participants was less pronounced than that in the other two groups. Regarding the SS-QOL-E, the heterogeneity of the two studies with the same drug composition was low. Conversely, the heterogeneity of the two other formulas with different potencies was high. Further sensitivity analyses could not be performed because of the few studies that included the indicators.

In summary, this study evaluated the effectiveness and safety of Chinese medicine decoctions through various examination indices to comprehensively analyze their effects in treating PSF. The meta-analysis revealed that Chinese medicine decoctions were more effective than non-Chinese medicines or placebo in alleviating fatigue, enhancing quality of life, and improving the capacity for daily activities in the treatment of PSF. This also proves that Chinese medicine decoctions have obvious advantages and are safer for the treatment of PSF. However, the literature selected for this study was all in Chinese, with publication bias, low quality, and subjective and restrictive outcome indicators. Therefore, the above conclusions need to be further summarized in an evidence-based manner by including a sufficiently large sample size. Analyzing the etiology of PSF using TCM evidence-based thinking and applying individualized treatment plans has the advantage of macro-observation and management of the disease. In the future, we will deepen the study of the pathogenesis of PSF in TCM, refine the combination plan, and clarify the specific active ingredients in therapeutic formulas.

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Author's contributions:

Luye Feng done conception and design; Luye Feng, Jienuo Pan, Meiyi Luo done methodology and interpretation; Jienuo Pan, Meiyi Luo, Yilan Jin done data collection; Luye Feng, Jienuo Pan, Meiyi Luo done statistical analysis; Luye Feng have contributed in writing original draft and Jiqin Tang, Jienuo Pan, Meiyi Luo, Yilan Jin contributed in writing review and editing. All authors read and approved the final manuscript.

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The authors declared no conflict of interests.

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