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Effects of Tuina on newborns with jaundice

A meta-analysis

Huaying Yan, MD[a], Qiujun Zhou, MD[b], Haijia Zhu, MD[c], Huifeng Yang, MD[b], Hui Wang, MD[b], Jie Ling, MD[b], Jinhui Wang, MD[d], Yi Cao, PhD[e], Maocan Tao, PhD[e,*]

Abstract

Background: The impact of Tuina on neonatal jaundice is not yet comprehensively understood, and its clinical application is rather limited. This study systematically assessed the relevant literature and conducted a meta-analysis to study the influence of Tuina on neonatal jaundice and provide convincing clinical evidence for promoting its clinical application.

Methods: We searched Pubmed, Embase, Cochrane Library, CNKI, Wanfang, CQVIP, and CBM from the establishment of the database up to July 2021. Studies that are randomized controlled trials were included. However, duplicate publications; manuscripts with no full text, incomplete information, or inability to extract data; animal experiments; and reviews and systematic reviews were excluded. STATA 15.1 was used to analyze the data.

Results: The pooled results showed that compared with the treatment of neonatal jaundice solely with blue light, Tuina combined with blue light significantly improved the total effective rate and frequency of defecation on days 1, 2, 3, 4, and 5 and significantly decreased the traditional Chinese medicine syndrome score; the third serum total bilirubin on days 3, 4, and 7; and duration of jaundice. Moreover, the incidence of adverse events in neonatal jaundice treated with Tuina combined with blue light was significantly lower than that with blue light alone.

Conclusion: Tuina combined with blue light for treating neonatal jaundice can increase the effect of clinical treatment and reduce the adverse events caused by blue light therapy. Thus, the clinical application of traditional Chinese medicine Tuina in neonatal jaundice should be further promoted.

Abbreviations: LED = light-emitting diode, RCT = randomized controlled trial, RR = Ratio Rate, TCM = traditional Chinese medicine, WMD = weighted mean difference.

Keywords: jaundice, meta-analysis, newborn infants, Tuina

1. Introduction

Neonatal jaundice is a common disease in newborn babies. It is primarily caused by the abnormal bilirubin metabolism in the newborns, thereby causing yellow staining of the skin and sclera.[1] Neonatal jaundice is dangerous because excess bilirubin is toxic to the basal ganglia and various brainstem cell nuclei.[2] The clinical manifestation of bilirubin toxicity in the first few weeks is called acute bilirubin encephalopathy, and chronic or permanent damage to the brain is called kernicterus.[2] The underlying causes of neonatal jaundice are complex, and thus, it can be divided into physiological and pathological jaundice. Pathological jaundice can cause severe bilirubin encephalopathy, thereby leading to neurological sequelae (including cerebral palsy, hearing loss, and kernicterus) and even death.[3] At present, the treatment and nursing measures for neonatal jaundice primarily include phototherapy, plasma or albumin infusion, and liver protection.[4] Among them, phototherapy is presently the standard method for treating neonatal jaundice.[5] Light therapy uses a light source, typically a light-emitting diode, which emits blue and green spectra.[6] Lights of these wavelengths convert bilirubin to a less toxic water-soluble photoisomer, which is safely excreted from the body through bile and urine.[7] However, existing studies have also revealed that maculopapular rash, loose stools, and riboflavin deficiency on newborn skin are common adverse reactions following blue-light irradiation treatment.[8] In addition, blue light may damage the DNA molecules and retina of newborns and cause bronze syndrome.[9]

HY and QZ contributed equally to this work.

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The datasets are available from the corresponding author on reasonable request.

As this study did not involve patients or animals, no ethical approval was required.

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[a] *Yongkang Maternity and Child Care Hospital, Yongkang, China,* [b] *First Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, China,* [c] *Hangzhou Children's Hospital, Hangzhou, China,* [d] *Wenzhou City Hospital of Traditional Chinese Medicine and Western Medicine Combined, Wenzhou, China,* [e] *The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China.*

**Correspondence: Maocan Tao, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310000, China (e-mail: taomaocan@163.com).*

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According to traditional Chinese medicine (TCM) practice, neonatal jaundice belongs to the category of "fetal yellow" or "fetal jaundice." The concept of "Theories on the Sources of Diseases and Fetal Jaundice" describes the earliest records of the names, causes, and symptoms of fetal as "The child is in the fetus, and the mother's viscera is hot, fumigated in the fetus, until the child is born, the child's body is yellow".[10] Tuina, also named "Tui Na," implies "pushing (and) grasping" and has been used in China for thousands of years. It is a nonpharmacological manual therapy in TCM, which is primarily applied to the meridians or acupoints, which are pathways for the qi and blood of the human body, via pushing, grasping, pressing, and rubbing.[11] Clinical studies[12,13] have established that neonatal jaundice treatment by Tuina can promote the metabolism and excretion of bilirubin, reduce the intestinal and hepatic circulation of bilirubin, stimulate the meridian system in the body, and smoothen the operation of qi and blood. However, the impact of Tuina on neonatal jaundice is not comprehensively understood, and its clinical application is rather limited. Therefore, this study systematically assessed the relevant literature and conducted a meta-analysis to study the influence of Tuina treatment on neonatal jaundice and provide strong clinical evidence for promoting its clinical application.

2. Methods

2.1. Inclusion and exclusion criteria

Inclusion criteria: the study type is a randomized controlled trial; the intervention group underwent TCM Tuina combined with blue light therapy, and the control group only used blue light therapy; the language was limited to Chinese and English.

Exclusion criteria: duplicate publications; manuscripts with no full text, incomplete information, or inability to extract data; animal experiments; and reviews and systematic reviews.

2.2. Search strategy

We searched Pubmed, Embase, Cochrane Library, CNKI, Wanfang, CQVIP, and CBM from the establishment of the database up to July 2020. The Chinese search terms were primarily "Tuina" "massage" AND "baby" "newborn" "pediatric" "premature" AND "jaundice". The English search terms were as follows: "Tuina" "massage" AND "neonatal" "prematurity" "premature infant" "neonate" "pediatric" "pediatric" "newborn" "baby" "infant" AND "jaundice" "icterus" "hyperbilirubinemia" "serum bilirubin concentration".

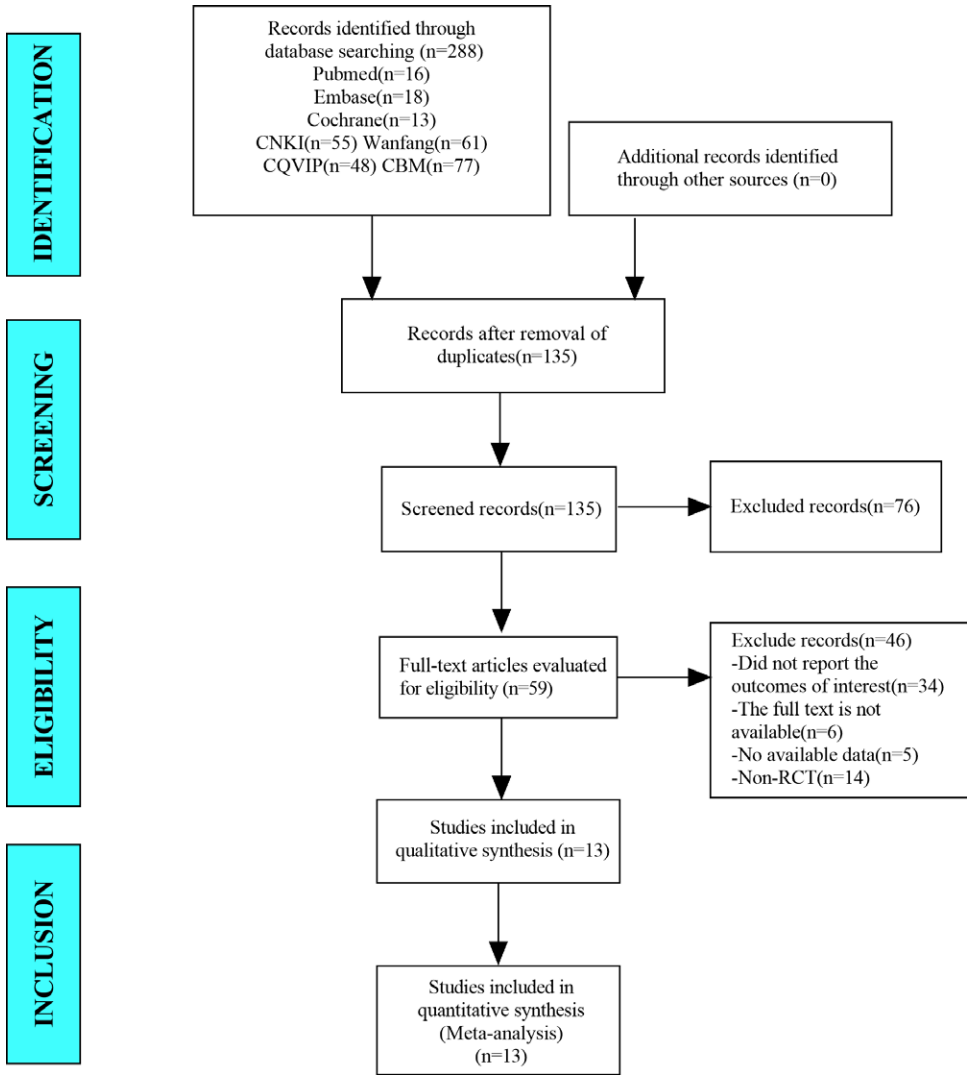

Figure 1. Flow diagram for selection of studies. RCT = randomized controlled trial.

Table 1

Baseline characteristics of the included studies.

				Number of cases		Gender (Male/Female)		Age (d)		Gestational age (week)		Weight (kg)		Measure	
Author	Year	Research type	Country	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group
Tang et al[14]	2020	RCT	China	34	34	19/15	18/16	–	–	38.22 ± 2.08	38.14 ± 2.16	–	–	Tuina and blue light	Blue light
Wang et al[15]	2018	RCT	China	40	40	–	–	–	–	38.61 ± 2.05	35.56 ± 2.12	–	–	Tuina and blue light	Blue light
Peng et al[16]	2018	RCT	China	40	40	19/21	22/18	8.6 ± 2.9	8.8 ± 2.5	–	–	–	–	Tuina and blue light	Blue light
Yu et al[17]	2019	RCT	China	34	33	17/17	15/18	12.15 ± 5.98	11.06 ± 5.36	38.15 ± 1.35	38.21 ± 1.45	–	–	Tuina and blue light	Blue light
Ma et al[18]	2014	RCT	China	55	52	34/21	29/23	21.31 ± 2.94	19.92 ± 3.01	–	–	–	–	Tuina and blue light	Blue light
Wu et al[19]	2021	RCT	China	75	75	36/39	33/42	27.18 ± 10.36	26.87 ± 10.34	37.52 ± 12.38	38.05 ± 12.41	3.58 ± 1.02	3.66 ± 1.07	Tuina and blue light	Blue light
Xu et al[20]	2019	RCT	China	75	75	39/36	40/35	7.52 ± 2.11	7.49 ± 2.06	39.42 ± 0.27	39.37 ± 0.25	3.16 ± 0.25	3.19 ± 0.21	Tuina and blue light	Blue light
Wang et al[21]	2016	RCT	China	41	39	23/18	26/13	–	–	–	–	3.24 ± 0.38	3.22 ± 0.35	Tuina and blue light	Blue light
Aimeti et al[22]	2017	RCT	China	43	43	46/40		14.5 ± 2.7		38.4 ± 2.5		4.8 ± 2.3		Tuina and blue light	Blue light
Ma et al[23]	2020	RCT	China	33	33	18/15	19/14	–	–	38.74 ± 2.01	38.64 ± 2.31	–	–	Tuina and blue light	Blue light
Wang et al[24]	2018	RCT	China	75	75	42/33	40/35	–	–	38.6 ± 3.8	38.7 ± 4.2	3.02 ± 0.033	3.02 ± 0.033	Tuina and blue light	Blue light
Chen et al[25]	2011	RCT	Japan	29	40	13/14	15/25	–	–	39.76 ± 1.13	39.66 ± 1.0	3.19 ± 0.21	3.16 ± 0.20	Tuina and blue light	Blue light
Eghbalian et al[26]	2017	RCT	Iran	67	67	37/30	29/38	–	–	38.61 ± 1.27	38.89 ± 1.6	3.04 ± 0.19	3.07 ± 0.19	Tuina and blue light	Blue light

RCT = randomized controlled trial.

2.3. Literature survey and data extraction

The literature survey, screening, and information extraction were independently completed by 2 researchers. When there were doubts or disagreements, the decision was made after discussion or consultation with a third expert. The data extraction included the author, year, research type, number of cases, and outcome indicators, such as total effect rate, TCM syndrome score, serum total bilirubin, defecation frequency, jaundice duration, and adverse events.

2.4. Assessment of literature quality

Two researchers independently evaluated the quality of literature using the Review manager 5.3 risk assessment tool, based on the Cochrane risk assessment scale. According to the random sequence generation, allocation hiding, blinding, whether the research results are blindly evaluated, and the result data are complete, the included studies were evaluated based on gender, choice of reporting research results, and other biases and discussed or consulted with a third expert when opinions were inconsistent. This meta-analysis was conducted based on the related items of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.

2.5. Data synthesis and statistical analysis

STATA 15.1 (Stata Corporation, College Station, TX, USA) was used to analyze the data. Ratio rate (RR) (95% Cl) was used as the binary variable, and weighted mean difference (WMD) (95% Cl) combined effect size was used as the continuous variable. I^2 is used to evaluate heterogeneity. The heterogeneity test of $P \geq .1$ and $I^2 \leq 50\%$ indicates homogeneity between studies, and the fixed effect model was used for combined analysis; $P < .1$ and $I^2 > 50\%$ indicates that the study is heterogeneous, and sensitivity analysis or subgroup analysis was then used to find heterogeneity source. If the heterogeneity is still large, the random effect model was used or the combination of results was rejected and descriptive analysis was used. Funnel plot was used to analyze the publication bias.

3. Results

3.1. Results of literature survey

In this study, 288 studies were retrieved from the database. After eliminating duplicate studies, 135 were obtained. After browsing titles and abstracts, 59 studies were obtained. Finally, 13 articles were included in the meta-analysis (Fig. 1).

3.2. Baseline characteristics and quality assessment of the included studies

3.2.1. Baseline characteristics. Thirteen randomized controlled trial studies were included in this meta-analysis. The sample size of patients was 1287, including 641 children who were treated with Tuina and 646 children who were treated with blue light. Patients in 10 studies were from China, and the patients in the other 2 studies were from Japan and India. The intervention group used TCM Tuina combined with blue light therapy, and the control group only used blue light therapy (Table 1).

3.2.2. Quality assessment of the included studies. The quality assessment of the included studies are shown in Figures 2 and 3. In this study, 10 manuscripts described the formation of random sequences, and only 2 manuscripts described the hiding method. Only 1 article used the blinding method, and the remaining studies did not use the blinding method.

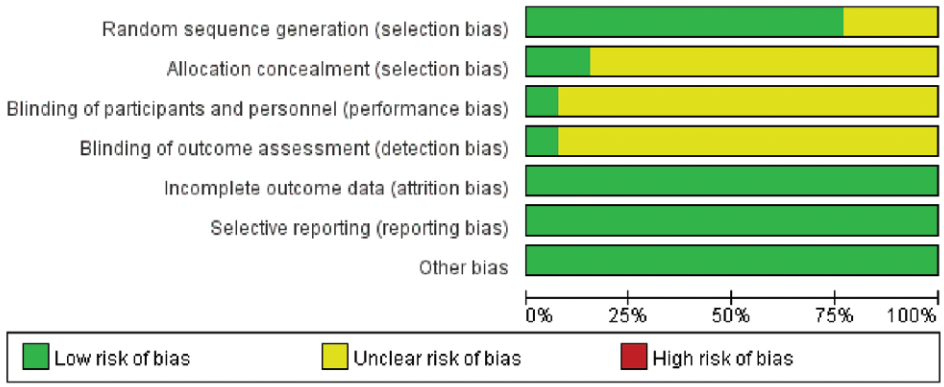

Figure 2. Risk of bias graph.

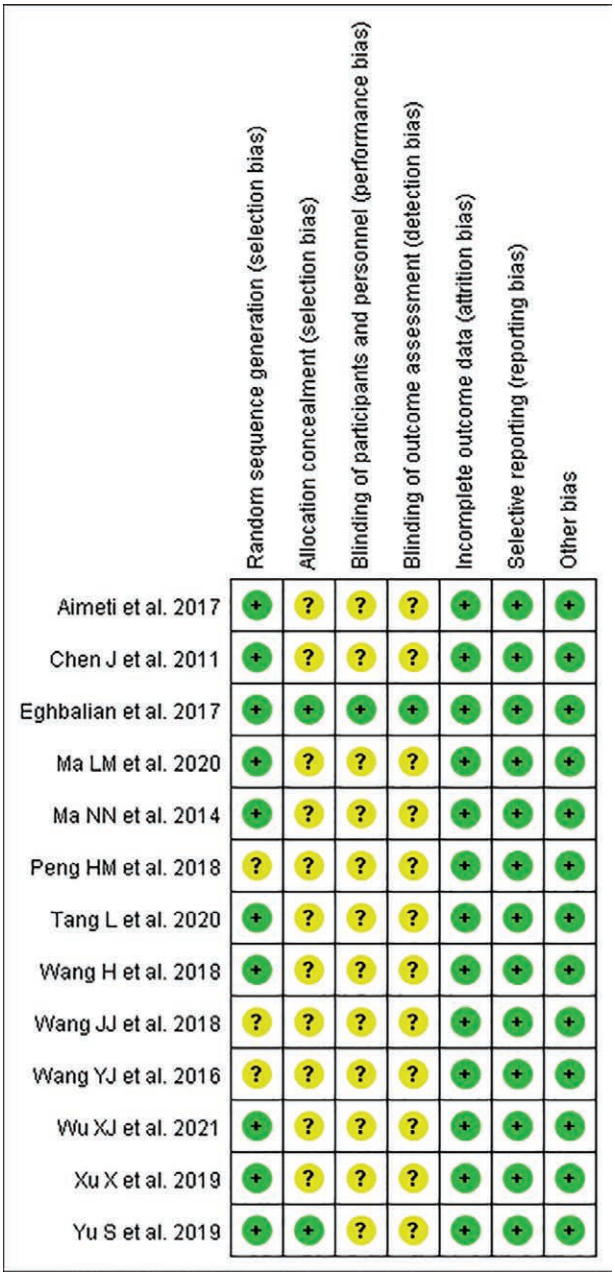

Figure 3. Risk of bias summary.

3.3. Meta-analysis results

Seven studies reported the total effective rate of Tuina on newborn infants with jaundice. As there was no significant heterogeneity (I^2 = 0.0%; P = .473), a meta-analysis was conducted through a fixed effect model. The pooled results showed that the total effective rate of Tuina combined with blue light therapy for neonatal jaundice is significantly higher than that of blue light therapy alone (RR, 1.18; 95% confidence interval [CI], 1.11–1.26; P = .000; Fig. 4).

Three studies reported the TCM syndrome score of Tuina on newborn infants with jaundice. As there was no significant heterogeneity (I^2 = 0.0%; P = .505), a meta-analysis was conducted through a fixed effect model. The pooled results showed that the TCM syndrome score of Tuina combined with blue light therapy for neonatal jaundice was significantly lower than that of blue light therapy alone (WMD, −6.05; 95% CI, −7.15 to −4.95; P = .000; Fig. 5).

We further explored the serum total bilirubin following Tuina treatment on newborns with jaundice. The pooled results showed that there was no statistically significant difference in the 1-day (d) serum total bilirubin between Tuina combined with blue light therapy and blue light treatment alone for neonatal jaundice (WMD, −6.94; 95% CI, −22.39 to 8.51; P = .379; I^2 = 87.1%, P = .005; in 2 studies). However, 3-d (WMD, −33.54; 95% CI, −40.51 to −26.57; P = .000; I^2 = 0.0%, P = .997; in 3 studies), 4-d (WMD, −40.88; 95% CI, −46.91 to −34.85; P = .000; I^2 = 0.0%, P = .547; in 2 studies), and 7-d (WMD, −34.84; 95% CI, 51.20 to −18.48; P = .000; I^2 = 85.9%; P = .001; in 3 studies) serum total bilirubin of Tuina combined with blue light therapy for neonatal jaundice was significantly lower than that of blue light therapy alone (Fig. 6). Additionally, 7 studies reported jaundice duration following Tuina treatment on newborns with jaundice. As there was no significant heterogeneity (I^2 = 86.5%; P = .000), a meta-analysis was conducted through a random effect model. The pooled results showed that jaundice duration following Tuina combined with blue light therapy for neonatal jaundice was significantly shorter than that of blue light therapy alone (WMD, −2.85; 95% CI, −3.26 to −2.43; P = .000; Fig. 7).

We also analyzed the defecation frequency of newborns at different times following Tuina treatment. The pooled results showed that 1-d (WMD, 1.43; 95% CI, 0.90–1.96; P = .000; I^2 = 0.0%, P = .721; in 2 studies), 2-d (WMD, 1.58; 95% CI, 0.99–2.16; P = .000; I^2 = 0.0%; P = .743; in 2 studies), 3-d (WMD, 1.46; 95% CI, 0.88–2.03; P = .000; I^2 = 62.0%; P = .072; in 3 studies), 4-d (WMD, 0.65; 95% CI, 0.06–1.23; P = .030; I^2 = 0.0%; P = .778; in 2 studies), and 5-d (WMD, 0.65; 95% CI, 0.08–1.34; P = .027; I^2 = 0.0%; P = .757; in 2 studies) defecation frequency of Tuina combined with blue light therapy for neonatal jaundice were all significantly higher than that of blue light therapy alone (Fig. 8).

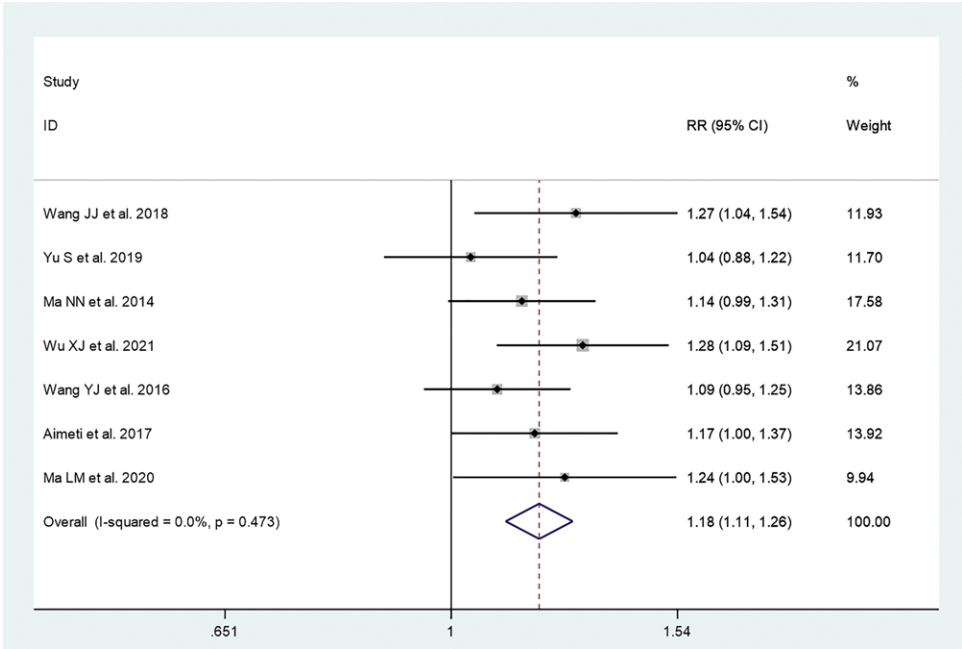

Figure 4. Total effective rate of Tuina on newborn infants with jaundice. CI = confidence interval; RR = ratio rate.

We further analyzed the incidence of adverse events of Tuina treatment on newborn infants with jaundice. Five studies have reported the incidence of adverse events of Tuina treatment on newborn infants with jaundice. As there was no significant heterogeneity (I^2 = 0.0%; P = .478), a meta-analysis was conducted through a fixed effect model. The pooled results showed that the incidence of adverse events of Tuina combined with blue light therapy for neonatal jaundice was significantly lower than that of blue light therapy alone (RR, 0.29; 95% CI, 0.13–0.64; P = .002; Fig. 9).

3.4. Publication bias

The funnel plot is shown in Figure 10. Evidently, the funnel plot was basically symmetrical, and the P value of Egger's test was .215, indicating no evident publication bias in this study.

3.5. Sensitivity analysis

Sensitivity analysis eliminated each included study and performed a summary analysis of the remaining studies to assess

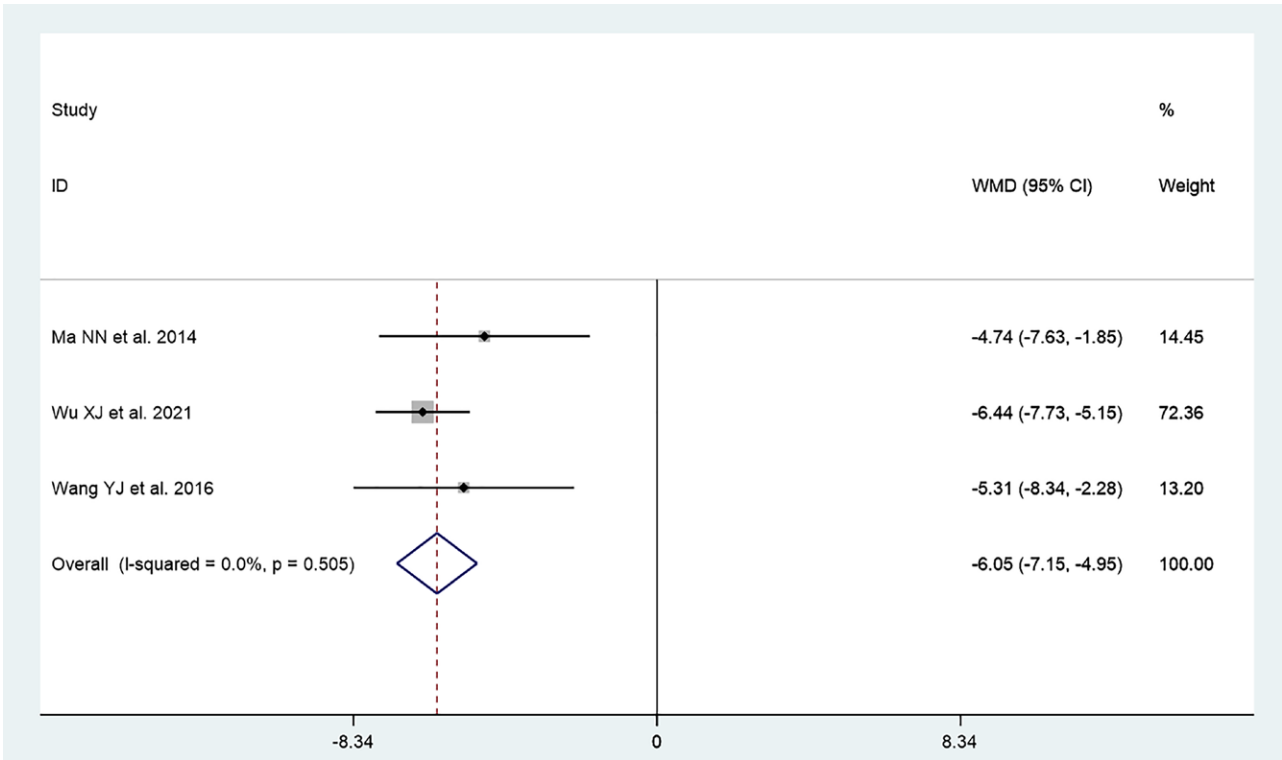

Figure 5. TCM Syndrome Score of Chinese Tuina on newborn infants with jaundice. CI = confidence interval; WMD = weighted mean difference.

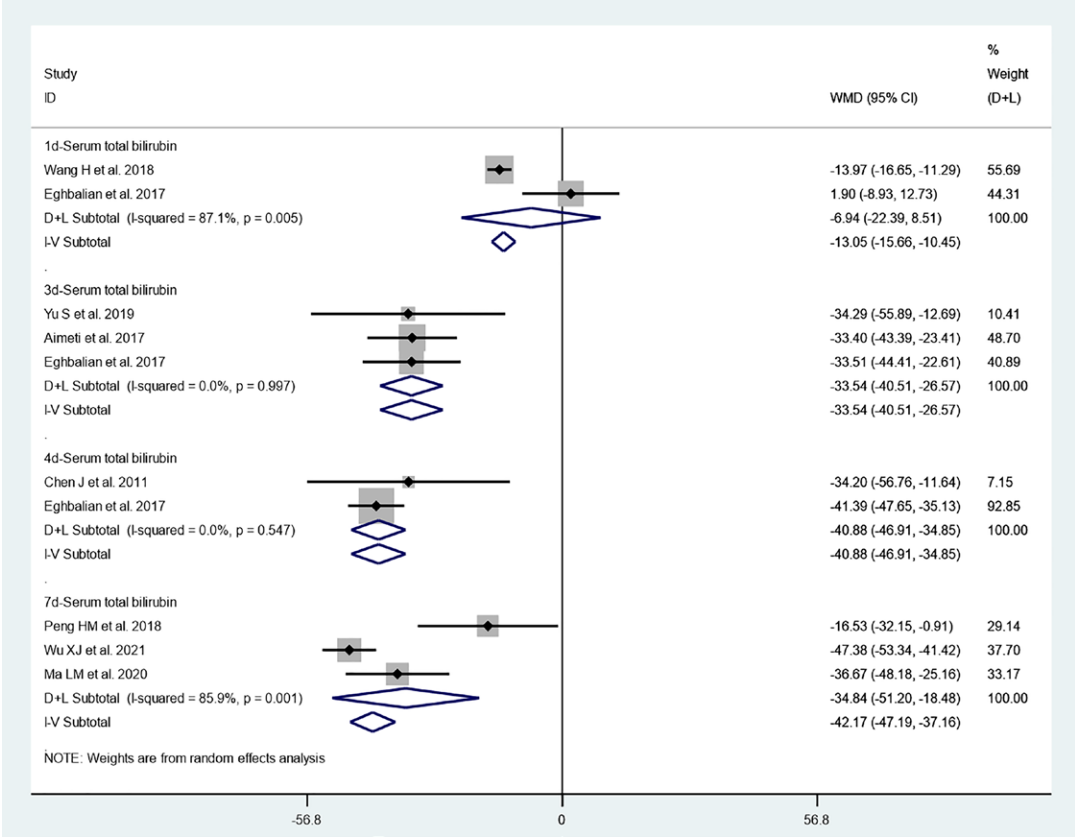

Figure 6. Serum total bilirubin of Tuina on newborn infants with jaundice. CI = confidence interval; WMD = weighted mean difference.

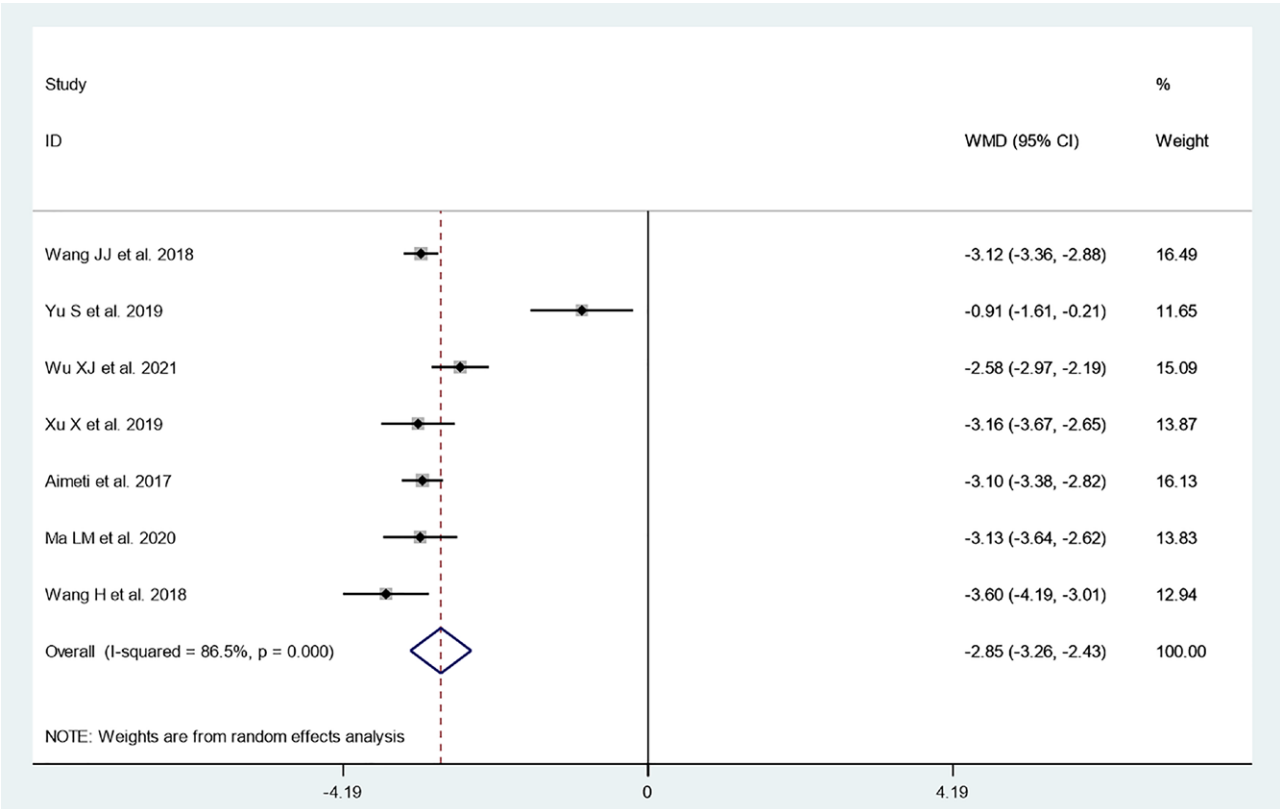

Figure 7. The duration of jaundice of Tuina on newborn infants with jaundice. CI = confidence interval; WMD = weighted mean difference.

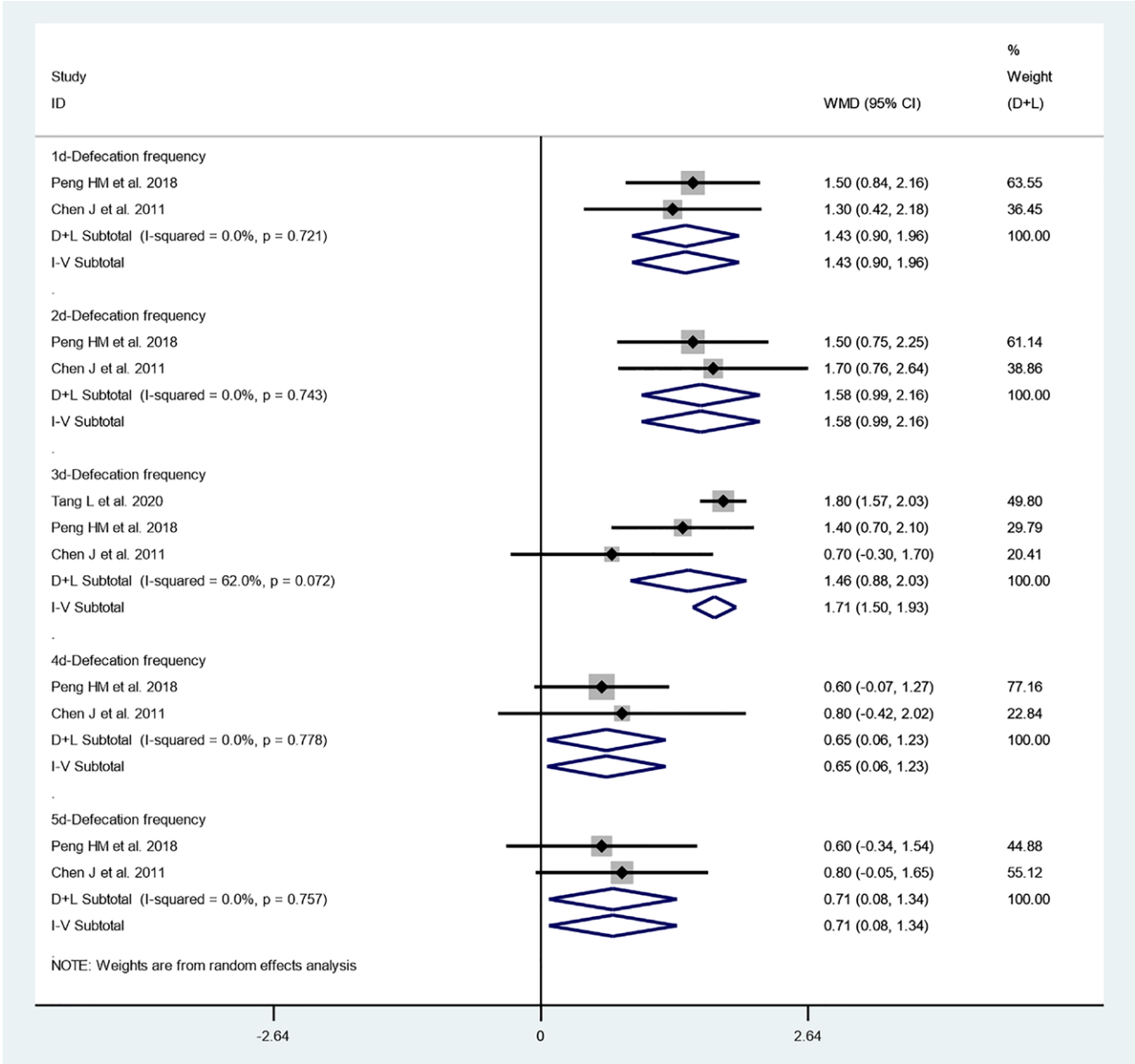

Figure 8. Defecation frequency of Tuina on newborn infants with jaundice. CI = confidence interval; WMD = weighted mean difference.

whether a single study had an excessive impact on the entire meta-analysis results. None of the studies had an excessive impact on the meta-analysis results, indicating that the results of the remaining studies are stable and reliable (Figs. S1–S7, Supplemental Digital Content, http://links.lww.com/MD/G928, which illustrates that none of the studies had an excessive impact on the meta-analysis results).

4. Discussion

TCM considers that the occurrence of neonatal jaundice belongs to the category of "fetal yellow." Moreover, the cause of the disease can be explained as that the body function of the newborn is not fully matured, and it is easily affected by damp and heat after birth, thereby causing the water to stop inward and then accumulate phlegm in the liver and gallbladder.[10] This will cause abnormal liver and gallbladder diarrhea in children and eventually develop the disease in the form of skin lesions.[27] TCM pediatric Tuina is a type of TCM Tuina, in which doctors perform Tuina on various acupoints of the patient to alleviate symptoms.[28] This meta-analysis included 13 related articles, including 641 children who were treated with Tuina and 646 children who were treated with blue light, to assess the influence of Tuina treatment on neonatal jaundice and provide strong clinical evidence for promoting its clinical application.

We first analyzed the total effective rate of Tuina on newborn infants with jaundice. Among the 7 included studies, 3 of the studies show that Tuina combined with blue light therapy does not increase the effective rate of neonatal jaundice, and the other 4 studies report that Tuina based on blue light therapy can significantly increase the total effective rate. The pooled results showed that total effective rate of Tuina combined with blue light therapy for neonatal jaundice was significantly higher than that of blue light therapy alone (RR, 1.18; 95% CI, 1.11–1.26). In addition, we analyzed the role of Tuina in neonatal jaundice from TCM perspective by analyzing the symptom scores of TCM. Observing neonatal jaundice syndrome is the direct way to diagnose the disease in TCM. It primarily observed and scored the 3 major symptoms of scleral yellow stain, yellow skin stain, and urine color and the 2 secondary symptoms of

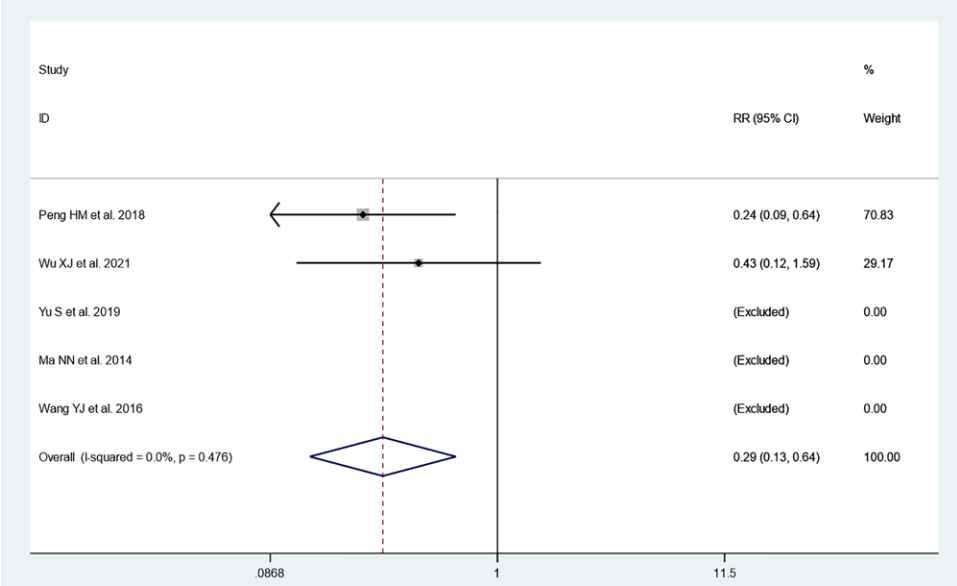

Figure 9. Adverse events of Tuina on newborn infants with jaundice. CI = confidence interval; RR = ratio rate.

stool color and urination frequency. We further analyzed and discussed the difference between the primary symptom, secondary symptom score, and total scores to obtain the efficacy results. The pooled results showed that the TCM syndrome score of Tuina combined with blue light therapy for neonatal jaundice was significantly lower than that of blue light therapy alone (WMD, –6.05; 95% CI, 7.15 to –4.95). The above results suggest that adding massage to the neonatal jaundice treatment based on conventional treatment can improve clinical treatment effect and effectively relieve the symptoms of children with yellow eyes, yellow body, and yellow urine.

Studies have revealed that high bilirubin levels are present in meconium. If meconium accumulates in the intestines and is not excreted on time, bilirubin will be reabsorbed into the blood. Frequent excretion reduces bilirubin enterohepatic circulation and increases bilirubin excretion.[29] The pooled results showed that there was no statistically significant difference in serum total bilirubin on day 1 between Tuina combined with blue light therapy and blue light therapy alone in the treatment of neonatal jaundice, which may be related to the intervention time limit. However, serum total bilirubin on days 3, 4, and 7 of Tuina combined with blue light therapy for neonatal jaundice was significantly lower than that of blue light therapy alone. Moreover, we analyzed the influence of massaging on the neonatal jaundice duration. Our pooled results showed that jaundice duration following Tuina combined with blue light therapy was significantly shorter than that of blue light therapy alone. While treating neonatal jaundice with pediatric TCM Tuina combined with blue light therapy, the TCM Tuina promotes the patency

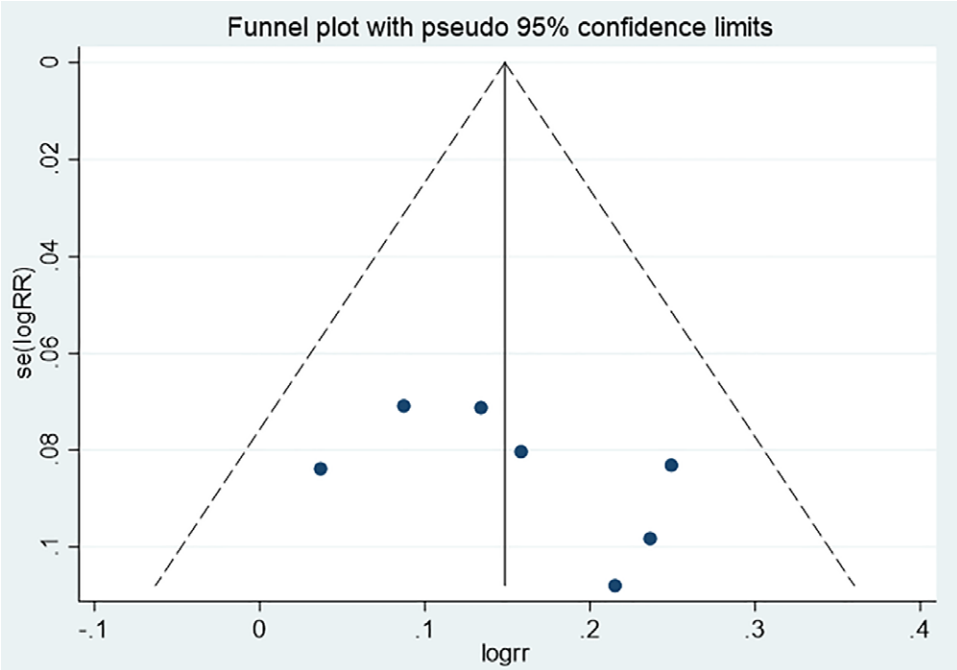

Figure 10. Funnel plot for assessing publication bias. RR = ratio rate.

of the meridian system and speeds up the body's blood circulation and simultaneously stimulates the various organs involved in bilirubin metabolism, enhances their functions, and speeds up bilirubin excretion in the blood.

Studies have revealed that the bilirubin in meconium is 5 to 10 times that of bilirubin produced every day. The meconium accumulation increases bilirubin reabsorption. Excretion reduces bilirubin enterohepatic circulation and serum bilirubin levels.[29] The pooled results showed that defecation frequencies on days 1, 2, 3, 4, and 5 of Tuina combined with blue light therapy were significantly higher than that of blue light therapy alone. These findings reveal that TCM Tuina can promote bilirubin excretion by promoting bowel movements in newborns. Notably, defecation conditions include not only defecation frequency but also defecation volume and meconium shape. However, owing to insufficient current research, we did not analyze the stool volume and meconium shape.

We further analyzed the incidence of adverse events of Tuina on newborn infants with jaundice. The pooled results showed that the incidence of adverse events of Tuina combined with blue light therapy for neonatal jaundice was significantly lower than that of blue light therapy alone (RR, 0.29; 95% CI, 0.13–0.64). The results show that TCM Tuina combined with blue light therapy can significantly reduce the occurrence of adverse events, improve the safety of treatment, and effectively reduce the side effects caused by blue light therapy alone, which thereby further enhances the reliability of massaging in neonatal jaundice treatment.

There are some limitations to this meta-analysis. First of all, high heterogeneity was observed among the studies and may be related to a few studies. In the future, researchers should conduct more studies on high-quality and large sample size studies. Second, the lack of included studies makes the investigation results be of low reliability, and there may be potential publication biases in the results of this study.

5. Conclusion

Tuina combined with blue light therapy for treating neonatal jaundice can increase the effect of clinical treatment and reduce the adverse events caused by blue light therapy. Therefore, the clinical application of TCM Tuina in neonatal jaundice should be further promoted.

Author contributions

Huaying Yan and Qiujunzhou conceived the article and wrote the initial draft. Haijia Zhu and Huifeng Yang participated in data collection. Hui Wang, Jie Ling, and Jinhui Wang participated in the revision of the article. Maocan Tao and Yi Cao read and approved the final article.

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