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Chinese herbal medicine for epidermal growth factor receptor inhibitor-induced skin rash in patients with malignancy: An updated meta-analysis of 23 randomized controlled trials

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ABSTRACT

Objective: To systematically review and evaluate the effectiveness of Chinese herbal medicine (CHM) therapy for epidermal growth factor receptor inhibitor (EGFRI)-induced skin rash in patients with malignancy.

Methods: The electronic databases of Medline, PubMed, EMBASE, the Cochrane Library, China National Knowledge Infrastructure, VIP Chinese Sci-tech Journal, Wan Fang, and Chinese Biomedicine were searched from their inception to 31 st September 2018. Randomized controlled trials (RCTs) investigating the effectiveness of CHM in improving EGFRI-induced skin rash were analyzed by Review Manager 5.3.

Results: Twenty-three eligible RCTs with 1392 participants were identified and divided into four subgroups according to different treatment rules of Traditional Chinese Medicine (TCM) and different controls. CHM (dispel wind, clear heat, and eliminate dampness), the representative formula Xiao Feng San, is more effective than western medicine in improving and curing skin rash(RR,95%CI: 1.46,1.26–1.70 and 1.65,1.24–2.20); CHM (nourish yin, clear heat, and remove toxin for eliminating blood stasis), the representative formula Yang Fei Xiao Zhen Tang, is more effective than western medicine in improving skin rash(RR,95%CI: 1.45,1.10–1.92). CHM (clear lung and purge heat, cool blood, and remove toxic substance) is more effective in improving and curing skin rash, compared with the western medicine group (RR,95%CI: 1.42,1.21–1.67 and 2.43,1.23–4.81) or the blank control group(RR,95%CI:2.37,1.21–4.63 and 2.98,1.20–7.41). The side effects of CHM are all mild and tolerable. Sensitivity analysis indicates that the results of the study are stable. The asymmetry funnel plots described that publication bias of this research may exist.

Conclusion: The limited evidence suggests that CHM exhibits clinical effectiveness and good safety on the treatment of EGFRI-induced skin rash. Large-sample RCTs are required to further determine the effectiveness of CHM.

1. Introduction

Epidermal growth factor receptor inhibitors (EGFRIs) have been widely used in many types of cancers, which bring great survival benefit for selected cancer patients. Available drugs that inhibit EGFR signaling pathways include small-molecule tyrosine kinase inhibitors, such as gefitinib and erlotinib, and macromolecular monoclonal antibodies, such as cetuximab.[1] However, toxicities result in considerable physical and emotional discomfort.[2] The incidence of acne-like skin rash is up to 80% after receiving EGFRIs.[3] The rash caused by antagonists is mainly manifested as acne-like follicle, small pustule, or papule, often accompanied by pruritus, dry skin, and erythema. It mainly occurs in the skin parts of the face, head, and upper trunk with sebaceous distribution, which seriously affects the quality of life of patients.[4] When severe, it may to lead to dose modification or discontinuation by 36% and 72% of health care providers, respectively, which potentially compromise the clinical benefit of EGFRIs.[5,6]

Although most patients receiving EGFRIs experience these toxicities, few controlled studies have been conducted to determine the best practices for their management. Hydrocortisone, doxycycline, and cream containing urea are recommended based on randomized data.[3] However, the effect of these treatments is unsatisfactory in clinic setting. In recent years, clinical observation has shown that Chinese herbal medicine (CHM) might have advantage in improving rashes. Previous meta-analysis on CHM for EGFRI-induced rash also found a certain result.[7] However, the included trials tested different herbal compounds,

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and they cannot be pooled together. The evidence is very limited because of the few number of included trials. Thus, this meta-analysis aims to resolve the following clinical questions about CHM treatment for skin rash: whether CHM is more effective than the conventional therapies; whether the CHM-assisted therapy is more effective than using conventional therapies alone; whether CHM is more effective than blank control; and whether it is safe when CHM is used alone or combined with the conventional therapies.

2. Methods

2.1. Literature research

We searched the electronic databases, including PubMed, EMBASE, the Cochrane Library, Clinical Trials, China National Knowledge Infrastructure (CNKI), VIP Chinese sci-tech journal database (VIP), Wang Fang, and Chinese Biomedicine (CBM) from their inception to September 2018. Two reviewers independently searched articles in the databases using the following search terms: (1) "Chinese medicine," "Chinese drug," "herb," "Chinese herb," "Chinese herbology," "traditional Chinese medicine (TCM),"" TCM," and "herbal medicine," connected with "OR"; (2) "antagonists," "targeted medicine," "Epidermal growth factor receptor antagonist," "Epidermal growth factor receptor tyrosine kinase inhibitor," "Epidermal growth factor receptor monoclonal antibody," "Epidermal growth factor receptor antagonist,"" EGFR-TKI," "gefitinib," "erlotinib," "cetuximab," "iressa," "tarceva," "Erbitux," connected with "OR"; (3) "rash," "exanthema," "skin rash," "cutaneous toxicity," "dermatologic toxicity," "cutaneous side effect," "cutaneous adverse reaction," "dermatologic side effect," "dermatologic adverse reaction," connected with "OR"; (4) "randomized controlled" or "Clinical Trials." Then, the above search terms of (1), (2), (3), and (4) were connected with "AND." We manually searched the references of the original and review articles for possible related studies.

2.2. Inclusion criteria of the research

The inclusion criteria for this meta-analysis are as follows:

(1) Types of Studies. Type of study was randomized controlled trial (RCT). English and Chinese were applied as language restriction.
(2) Types of Participants. The patients were diagnosed as malignant tumor, received EGFRIs, and experienced skin rash; Age, race, nationality, and sex were not limited.
(3) Types of Interventions. The experimental group received Chinese herbal medicine or Chinese medicine plus western medicine. The control group received western medicine, blank control.
(4) Types of Outcomes. The study must have at least one of following outcomes: Effectiveness on skin rash; Improvement on symptoms of traditional Chinese medicine (TCM); and Adverse events.

2.3. Exclusion criteria of the research

Relevant clinical trials were manually removed if any of the following factors was identified:

(1) Rashes appeared before EGFR intervention.
(2) Patients suffered from severe infection before the trial began.
(3) CHM interventions were combined with other types of therapy, such as acupuncture;
(4) Duplicated articles.
(5) The design of the research was not clear, or the research method or data was not complete or wrong.

2.4. Literature screening

Two researchers independently excluded documents that did not meet the inclusion criteria by reading the titles and abstract. The full text of the remaining studies was read, and studies were assessed for inclusion in the meta-analysis based on the inclusion and exclusion criteria in accordance with the PRISMA recommendations.[8] Any disagreement was resolved by the third adjudicating author.

2.5. Assessment of outcomes

Effectiveness and Clinical Curative Efficiency on rash. It was evaluated in accordance with the common terminology criteria for adverse events(CTCAE) version 5.0,[9] the MASCC classification system.[10] Skin toxicity grading decreased by one grade or more is effective, including healing or marked reduction or from extensive to local distribution of the rash, relief or disappearance of subjective symptoms, and significant improvement in quality of life. No change in rash is invalid. Toxicity grading increased by one grade or more, including a marked increase in rash or a change from local to widespread distribution of the whole body, worsening of subjective symptoms or quality of life, is also invalid. Clinical curative efficiency is the ratio of the number of patients healed to the total number of the patients.

The improvement of TCM syndromes was in accordance with the standard of acne and eczema stipulated in the "Guiding Principles for Clinical Research of New Chinese Medicines".[11] The assessment criteria are as follows: Cured: skin rash completely subsided, symptoms disappeared, the TCM syndrome score reduced by more than 90%. Markedly effective: the area of skin lesions subsided more than 70% and less than 90% but not completely disappeared, the symptoms significantly reduced, and the TCM syndrome score reduced by more than 50% and less than 70%. Effective: skin lesions partially subsided, symptoms improved, and the TCM syndrome score decreased by no more than 50%. Ineffective: skin lesions did not recede, clinical symptoms did not improve or continue to aggravate, and the TCM syndrome score did not change or increase.

2.6. Data extraction

We extracted the following data from each selected study: the first author, year of publication, study location, sample size, intervention, course of treatment, and outcomes. The two researchers cross-checked their respective results, and any inconsistency was discussed with other reviewer authors who acted as arbiters. The lack of information was supplemented by contacting with the first author or correspondence author of the document. However, we did not receive correspondence. Thus, only available data were analyzed.

2.7. Quality assessment

Two researchers independently assessed the methodological quality of RCTs and then cross-checked the results of the quality evaluation according to Cochrane Risk Bias Assessment Tool 5.1.0. The methodological issues related to the quality of RCT were the generation of treatment allocation, concealment of treatment, blinding, the completeness of the resulting data, selective reporting of findings, and other potential risks of bias. Any disagreement on quality assessment was resolved by the third adjudicating author.

2.8. Statistical analysis

Meta-analysis was performed using Rev Man 5.3 software. The chi-squared test for heterogeneity was performed at first, and heterogeneity was presented as significant when I^2 was over 50% or $P < 0.1$. The random-effect model was used for the meta-analysis if significant heterogeneity was present, and the fixed-effect model was used when the heterogeneity was not significant. The effectiveness on rash and improvement of TCM syndromes were measured and presented with risk ratio (RR) and 95% corresponding confidential interval (CI).

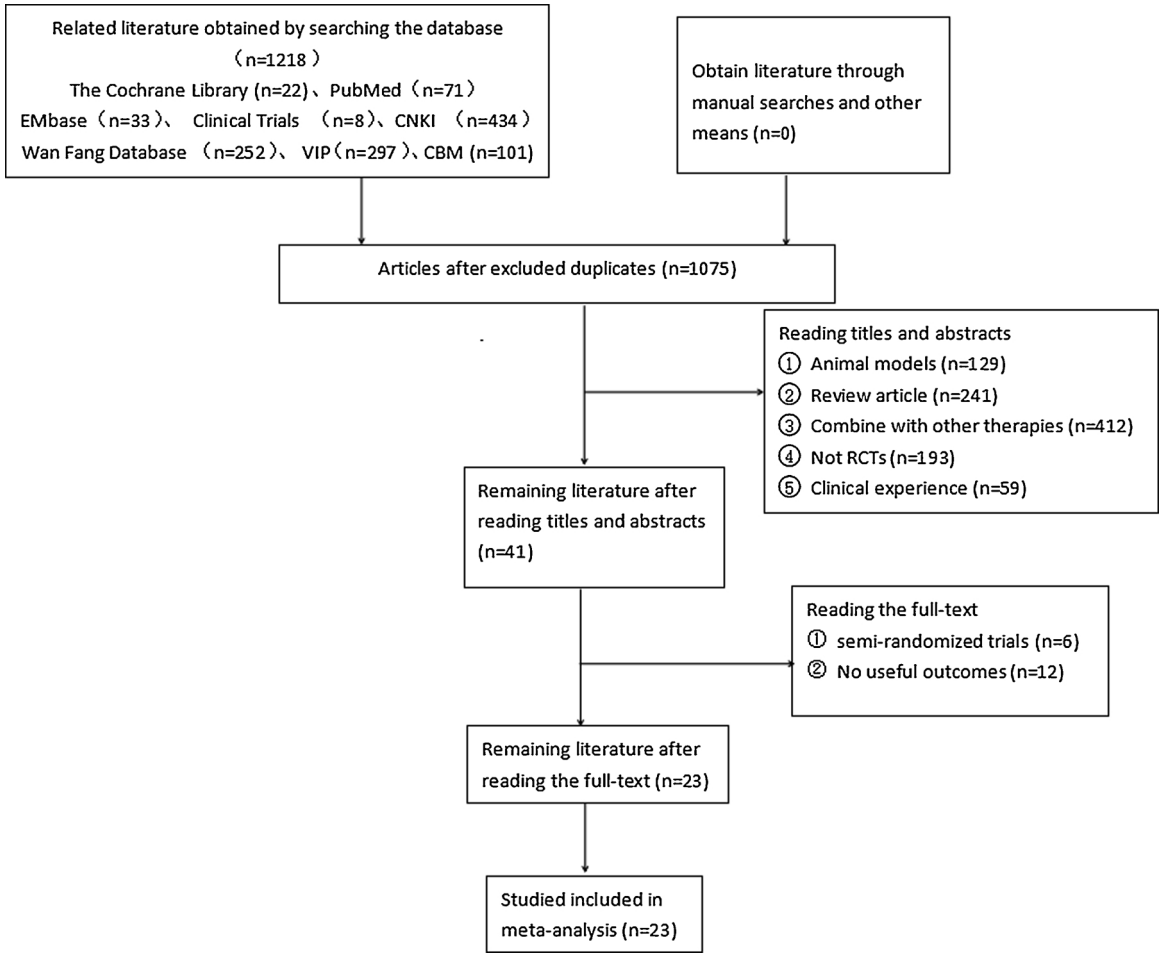

Fig. 1. Flow Chart of Study Searching and Selection.

Description analysis was performed when quantitative data could not be pooled. Funnel plots were used to analyze potential publication bias, and sensitivity analysis was performed.

3. Results

3.1. Retrieval results

According to the retrieval strategy, 1218 articles were first detected, including 434 from CNKI, 252 from Wan Fang Data, 297 from VIP, 101 from CBM, 71 from Pubmed, 22 from the Cochrane Library, 33 from EMBASE, and 8 from Clinical Trials. A total of 143 duplicate articles were excluded after duplicate checking via literature management software. Through reading title and abstracts, 1034 articles were excluded due to failure to meet our inclusion criteria. In addition, 18 articles were excluded after reading the full text. Finally, 23 RCTs[12–34] involving 1392 patients were included (Fig. 1).

3.2. Research characteristics

A total of 23 RCT studies that met our criteria were included in the study (Table 1). These studies were published from 2009 to 2017 with 1392 patients involved, including 744 in the experimental group and 648 in the control group. The characteristics on baseline in each study were balanced according to the documents. The CHM was provided in the form of multiple compound formula, which can be divided into three categories according to the TCM treatment rules: the first treatment rule of TCM (dispel wind, clear heat, and eliminate dampness), the second treatment rule of TCM (nourish yin, clear heat, and remove toxin for eliminating blood stasis), the third treatment rule of TCM (clear lung and purge heat, cool blood, and remove toxic substance). The application of Chinese medicine is by oral administration or external washing. The course of treatment varied from 7 days to 30 days.

3.3. Quality assessment

The Cochrane risk of bias tool was used to assess the methodological quality of the included studies. The summarized results of quality and risk of bias of the included trials are shown in Figs. 2 and 3. Thirteen studies[13,15,17,21,22,26–31,33,34] described specific randomization methods, of which 12 studies[15,17,21,22,26–31,33,34] adopted the random number table method, one study[13] was randomized by lottery, whereas the rest of the literature claimed that the randomized method was used. All studies did not report allocated concealment. Except for the single-blinding of patients in the study of Zhang,[21] the use of blindness was not mentioned in the other studies. None of the included trials mentioned blinding of outcome assessment. Three studies[13,19,33] reported the cases of loss to follow-up or withdrawals with some reasons. Intention-to-treat analysis was not conducted in these studies. Seven studies[14,17,18,20,21,28,32] reported cases that strictly followed the treatment plan, contributing a high risk of attrition bias, which was deducted by an unbalanced sample between the groups. Pre-designed outcomes were all reported, indicating a low risk of reporting bias. No other bias was found in the included studies. In summary, the methodological quality of most included studies was generally poor.

Table 1
Characteristics of Included RCTs on CHM for EGFRIs Induced Skin Rash.

Study (Author,Year)	Sample Size	Sex(male/female)	Age		Treatment	Treatment rule of TCM	Control	Course of treatment (days)	Outcomes	Randomized method
			Treatment	Control						
Zhu Zhaocheng 2017	32/32	22/42	57.5	55.5	Xiao Feng San (po)	I	Hydrocortisone Cream (EA)	14	①②	Unclear
Chen Shuyi 2016	30/30	35/25	56.3 ± 3.8	55.3 ± 2.4	Xiao Feng San (po)	I	urea ointment (EA)	28	①②	Lottery
Deng Shanming 2013	40/36	53/23	59	61	Qing Fei Liang Xue Fang(po)	III	Hydrocortisone Cream (EA)	14	①②	Unclear
Zhang Yuhua 2016	40/40	NA	30-80		Yang Fei Xiao Zhen Fang(po + EA)	II	Hydrocortisone Cream (EA)	14	①②③	RNT
Li Yang 2016	45/45	49/41	50.1 ± 3.5	50.7 ± 3.7	Qing Re Jie Du Qu Shi Fang (EA)	III	Calamine Lotion(EA)	15	①②	Unclear
Chen Duanhong 2012	31/30	27/34	57.8 ± 10.1	53.9 ± 11.0	Pi Pa Qing Fei Yin(po)	III	Minocycline (po)	28	③	RNT
Shi Wenguang 2014	25/20	13/32	65.5	67.5	Yin Qiao San(po)	III	Routine anti-allery (po)	NA	①②	Unclear
Zhao Zhiwei 2015	21/21	20/22	57		Xiao Feng San (po)	I	Erythromycin Ointment(EA)	28	①②	Unclear
Wu Yiping 2013	15/11	3/23	56	60	Xiao Feng San (po)	I	Erythromycin Ointment(EA)	28	①②	Unclear
Zhang Hailin 2010	23/19	31/11	54		Jin Yin Hua (EA)	III	Blank control	7	①②	RNT
Chen Xuezhang 2014	20/20	26/14	52.3 ± 4.1		Xiao Feng San (po)	I	Hydrocortisone Cream(EA)	28	①②	RNT
Wang Jiaxiao 2010	21/21	31/11	46.3		Pu Xing Jie Du Tang(EA)	III	Body Lotion(EA)	7	①②	Unclear
Qiu Yumei 2012	32/32	33/31	46		Huang Bai San(EA)	III	dexamethasone acetate cream (EA)	28	①②	Unclear
Yin Jianli 2015	80/40	NA	NA		Jing Fang Bai Du San(po)	III	Blank control	28	①②	Unclear
Sun Tao 2013	25/25	NA	NA		Yang Fei Xiao Zhen Tang(po + EA)	II	Pirimosi ointment(EA)	30	①②③	RNT
Chen Chunxia 2015	30/30	NA	NA		LG09(po + EA)	III	Pirimosi ointment(EA)	30	①②	RNT
Jiang Xiaolin 2015	31/30	46/15	37.2		Jin Yin Hua(EA)	III	Blank control	7	①	Unclear
Wang Fuqiang 2013	30/30	34/26	NA		Pizen capsule(po)	III	Blank control	28	①②	RNT
Wang Hongyan 2013	80/40	74/46	60.81	62.5	Zhi Yang Fang(EA)	III	Erythromycin Ointment(EA)	14	①	RNT
Yang Jie 2013	25/25	21/29	60.7	58.3	Yang Fei Xiao Zhen Fang(po + EA)	III	Pirimosi ointment(EA)	30	③	Unclear
Zhang Yao 2009	18/17	22/13	42.4	38.6	Zhi Yang Fang(EA)	III	Calamine Lotion(EA)	30	②	Unclear
Wang Xueqian 2014	30/30	27/23	56.3 ± 11.3	59.7 ± 12.9	Pi Zhen Fang(po)	III	Silicone oil emulsion (EA)	14	③	RNT
Chen Xuewu 2016	30/30	27/33	51.69 ± 3.70	50.42 ± 4.55	Wu Wei Xiao Du Yin(po + EA)	III	urea ointment(EA)	14	③	RNT

Footnotes: ①Effectiveness on improving skin rash; ②Curative efficiency on skin rash; ③Improvement of skin rash according to TCM syndromes criteria; EA, external application; po, oral administration. RNT, random number table. NA, not available; I, the first treatment rule of TCM (dispel wind, clear heat, and eliminate dampness); II, the second treatment rule of TCM (nourish yin, clear heat, and remove toxin for eliminating blood stasis); III, the third treatment rule of TCM (clear lung and purge heat, cool blood, and remove toxic substance).

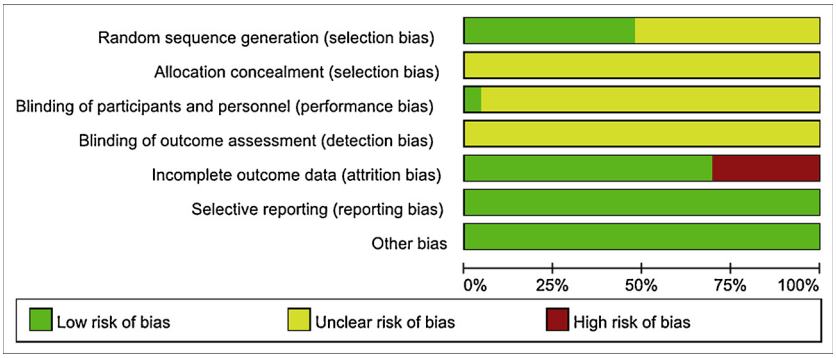

Fig. 2. Risk of bias summary.

3.4. Meta-analysis results

3.4.1. Effectiveness on improving skin rash

In clinical practice, we believed that the effect of CHM is similar when the treatment rule of TCM is the same. Thus, we analyzed the data according to different treatment rules of TCM and different controls. Twenty studies[12–16,18–30,33,34] included in the meta-analysis reported the effectiveness on improving skin rash, 5[12,13,19,20,22] of which adopted the first rule of TCM versus western medicine, 2[15,26] adopted the second rule of TCM versus western medicine, 9[14,16,18,23,24,27,30,33,34] adopted the third rule of TCM versus western medicine, and 4[21,25,28,29] adopted the third rule of TCM versus blank control (Fig. 4).

1) First rule of TCM versus western medicine. No heterogeneity was found in the included studies (P = 0.48, I^2 = 0%). The fixed-effect model was applied to calculate the combined RR and 95% CI as 1.46 (1.26–1.70), P < 0.01, indicating a significant difference between groups of the first rule of TCM and western medicine. This finding indicates that the first rule of TCM can improve skin rash more obviously when compared with western medicine alone.
2) Second rule of TCM versus western medicine. No heterogeneity existed in the two studies (P = 0.55, I^2 = 0%). The result analyzed by the fixed-effect model showed that the effectiveness on improving skin rash in the second rule of TCM is significantly higher than that of the western medicine group (RR = 1.45,95% CI:1.10-1.92, P < 0. 01).
3) Third rule of TCM versus western medicine. High heterogeneity existed in the included studies (P < 0.00001, I^2 = 83%). The random-effect model was applied to calculate the combined RR and 95% CI as 1.70 (1.31–2.19), P < 0.01, indicating a significant difference between groups of the third rule of TCM and western medicine. This results suggest that the effectiveness on improving skin rash in the third rule of TCM is higher than that of the western medicine group.
4) Third rule of TCM versus blank control. High heterogeneity existed in the included studies (P < 0.0001, I^2 = 89%). The meta-analysis by the random-effect model result revealed that the third rule of TCM can improve the EGFRI-induced skin rash compared with the blank control (RR = 2.37, 95% CI: 1.21–4.63, P = 0.01).

3.4.2. Clinical curative efficiency on skin rash

Seventeen studies [12,13,15,16,18–29,32] included in the meta-analysis reported the clinical curative efficiency on improving skin rash, 5[12,13,19,20,22] of which adopted the first rule of TCM versus western medicine, 2[15,26] adopted the second rule of TCM versus western medicine, 6[16,18,23,24,27,32] adopted the third rule of TCM versus western medicine, and 4[21,25,28,29] adopted the third rule of TCM versus placebo or observation. The comparation on curative efficiency is shown in Fig. 5.

1) First rule of TCM versus western medicine. Low heterogeneity existed in the included studies (P = 0.37, I^2 = 7%). The fixed-effect model was applied in the analysis. The result showed that the curative efficiency in the first rule of TCM is higher than that of the western medicine group (RR = 1.65, 95% CI: 1.24–2.20, P < 0. 01).
2) Second rule of TCM versus western medicine. With good homogeneity in each study (P = 0.41, I^2 = 0%), the fixed-effect model was used for the analysis, and the results showed that the curative efficiency in the second rule of TCM is similar with that of the western medicine group (RR = 1.00,95% CI: 0.21–4.78, P = 1.00). These results indicate no statistical significance between the two groups.
3) Third rule of TCM versus western medicine. High heterogeneity existed in the included studies (P < 0.0001, I^2 = 83%). The random-effect model was applied to calculate the combined RR and

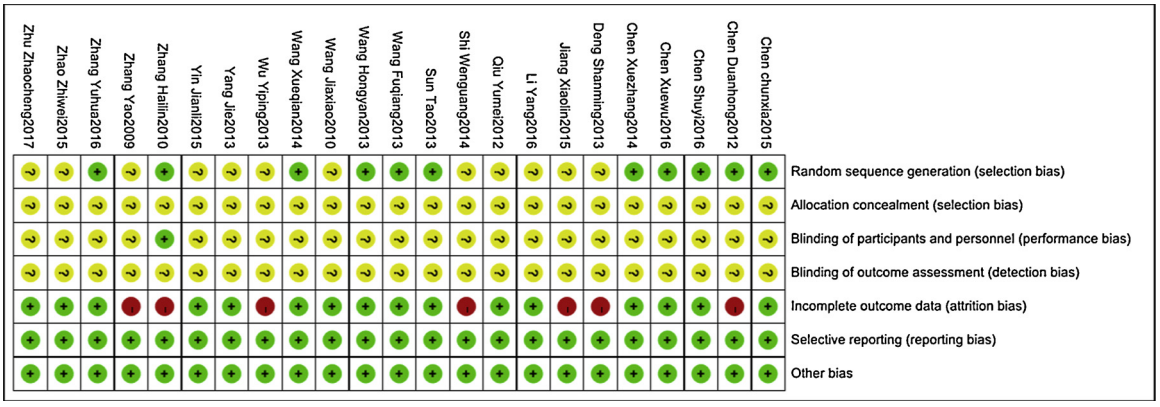

Fig. 3. Risk of bias graph.

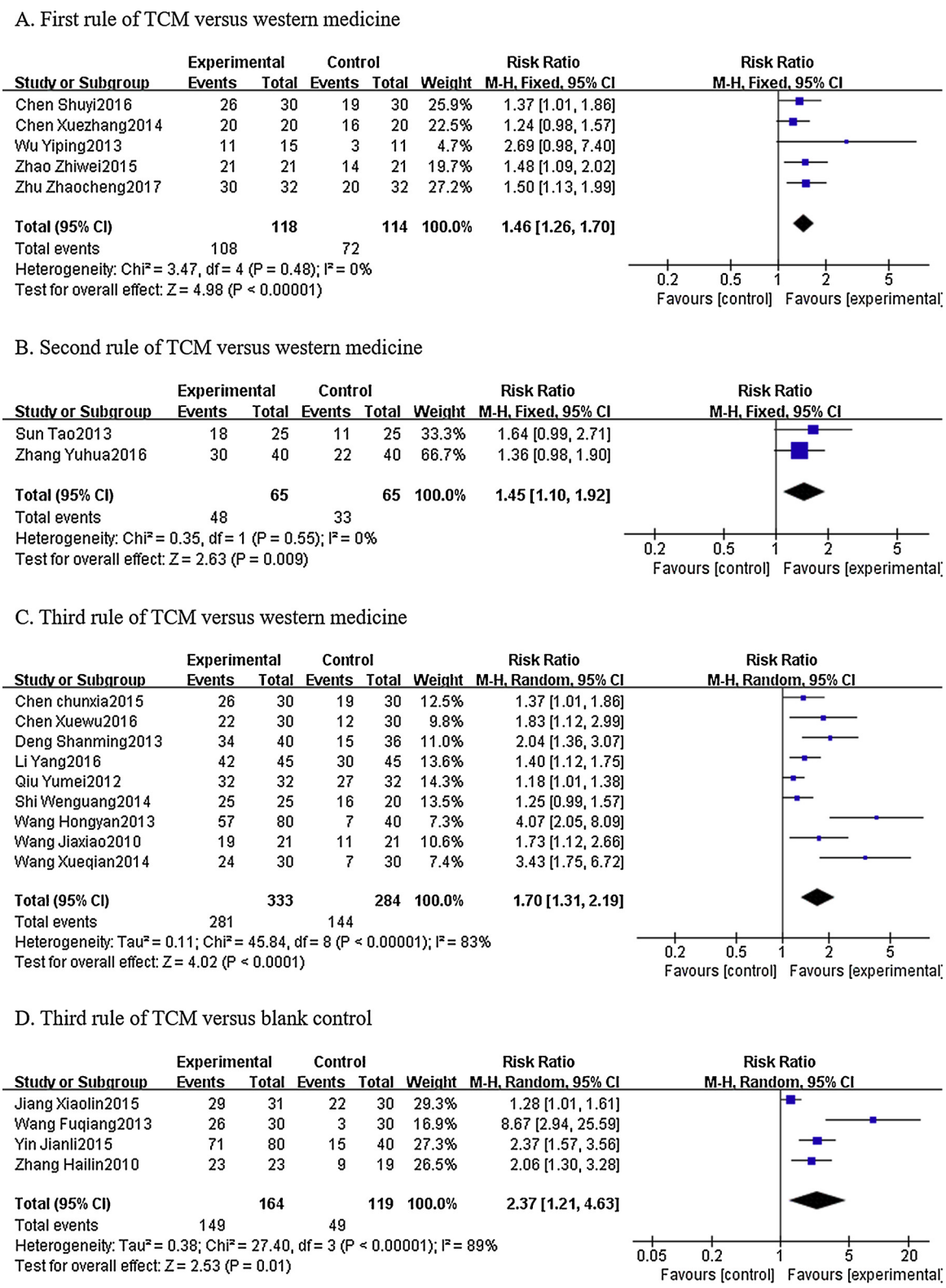

Fig. 4. Meta-analysis Result of Effectiveness on Improving Skin Rash.

95% CI as 2.43 (1.23–4.81), P = 0.01, indicating a significant difference between groups of the third rule of TCM and western medicine. This results suggest that the curative efficiency in the third rule of TCM is higher than that of the western medicine group.

4) Third rule of TCM versus blank control. No heterogeneity existed in the included studies (P = 0.91, I^2 = 0%). The result analyzed by the fixed-effect model showed that the curative efficiency in the third rule of TCM is higher than that of the blank control group (RR = 2.98,95% CI:1.20-7.41, P = 0.02).

3.4.3. *Efficiency on improvement of TCM syndromes*

Six studies[15,17,26,31,33,34] reported the efficiency on improving TCM syndromes, 2[15,26] of which adopted the second rule of TCM versus western medicine and 4[17,31,33,34] adopted the third rule of TCM versus

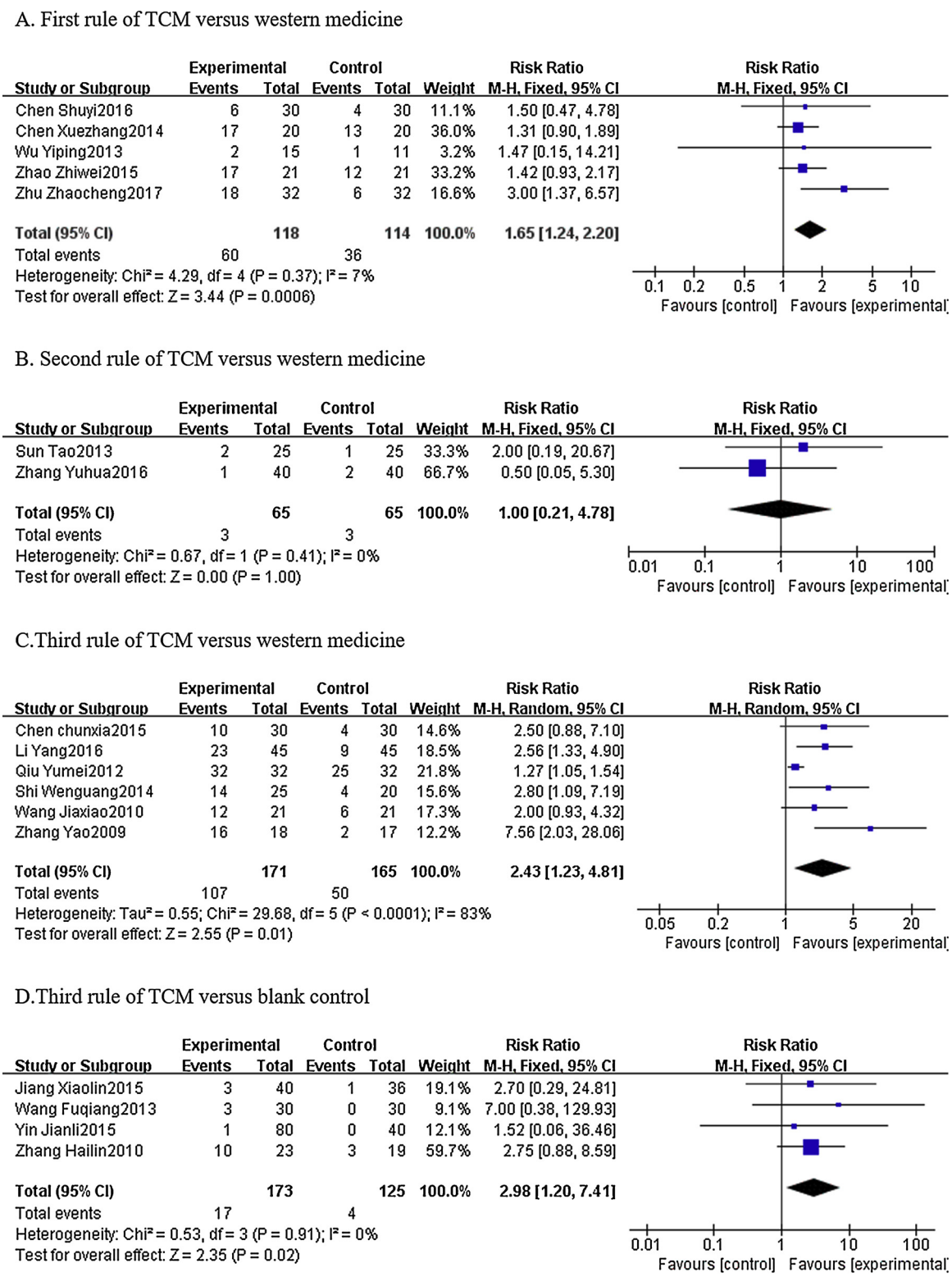

Fig. 5. Meta-analysis Result of Curative Efficiency on Skin Rash.

western medicine. The results are shown in Fig. 6.

1) Second rule of TCM versus western medicine. In consideration that a relatively high heterogeneity was detected (P = 0.12, I^2 = 58%), the random-effect model was used for analysis. The results showed that the rate of TCM syndrome improvement in the second rule of TCM is 1.91 times higher than that of the western medicine group (RR = 1.91, 95% CI: 1.19–3.08, P < 0. 01).

2) Third rule of TCM versus western medicine. Moderate heterogeneity was found in the included studies (P = 0.15, I^2 = 43%). The fixed-effect model was applied in the analysis. The result indicates that the rate of TCM syndrome improvement in third rule of TCM is higher than that of the western medicine group (RR = 1.58, 95% CI: 1.29–1.93, P < 0. 01).

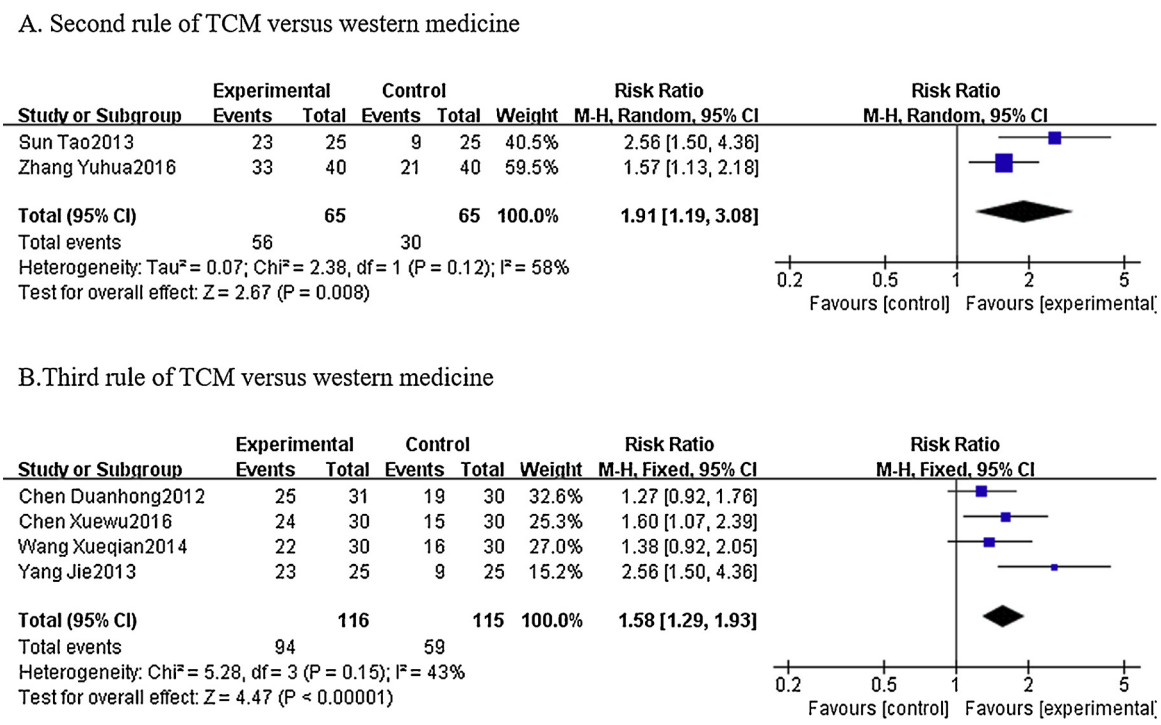

Fig. 6. Meta-analysis Result of Efficiency on Improvement of TCM Syndromes.

3.4.4. Safety

Among the 23 articles included, 12 studies[12,13,16,17,19,22,28,30,31,33,34] reported adverse reactions, 7 of which[12,16,17,28,31,32,34] reported no obvious adverse events during the treatment of both Chinese herbal medicine and western medicine. Chen's study[13] reported 2 cases of diarrhea and 3 cases of fatigue in the Chinese herbal medicine group and 6 cases of diarrhea, 2 cases of fatigue, 2 cases of granulocytopenia, and 2 cases of oral mucositis in the control group. Chen's study[22] reported that at the beginning of treatment, two patients in each group experienced diarrhea and recovered within 3 days without treatment, and no adverse events occurred in other patients. It was similar with Zhao's study[19], which also reported that two patients in the experimental group had diarrhea at the beginning of the treatment and all recovered within 2 days without corresponding treatment. Peng's study[29] found that 1 case of mild abnormal liver function (considered to be related to the side effects of antagonists) and 3 cases of skin allergy improved after topical treatment occurred in the Chinese herbal medicine group. Chen's study[34] Report: After treatment, 4 cases of abnormal blood test and 1 case of abnormal liver function were observed in the Chinese herbal medicine group, whereas 6 cases of abnormal blood test and 2 cases of abnormal liver function were observed in the control group. In total, the side effects of traditional Chinese medicine were all mild and tolerable.

3.5. Sensitivity analysis and publication Bias

We reperformed the meta-analysis with the random-effect model for the studies which no significant heterogeneity existed ($I^2 < 50\%$). The results were basically the same as those of the fixed-effect model (Table 2). After reperforming the meta-analysis with the fixed-effect model for the efficiency on improvement of TCM in the subgroup of Second rule of TCM versus western medicine, the result did not change obviously (Table 2).

For the included studies which have significant heterogeneity (third rule of TCM), by analyzing the patient, characteristics, the research method and the result of the included study, we found that the effect of the control group varies obviously and no obvious difference in the patient characteristic and research method. Thus, we exclude the studies in which the effect of the control group different obviously from the majority of the studies. The analysis of heterogeneity showed that the heterogeneity reduced in the subgroup of Third rule of TCM versus western medicine. By reperforming the meta-analysis with the fixed-effect model and random-effect model for the rest studies, the results still support the good efficacy of CHM for EGFRIs induced rash (Table 3). After excluding the corresponding studies, effectiveness on improving skin rash of the three CHM treatment method is similar (RR compared with western medicine: I, 1.46; II, 1.45; III,1.42).

Asymmetry of the funnel plot indicated that heterogeneity or publication bias in the included studies may affect the results of meta-analysis (Fig. 7).

4. Discussion

Including newer RCTs and analyzing the data according to the treatment rules of TCM, we updated the evidence on the effectiveness and safety of CHM for EGFRI-induced skin rash. After reviewing 23 RCTs, we found that CHM is effective for EGFRI-induced skin rash. It is safe and well tolerated.

The main finding is supported by the following results: 1) CHM according to the first rule of TCM (dispel wind, clear heat, and eliminate dampness), the representative formula Xiao Feng San, is more effective than western medicine in improving and curing skin rash; 2) CHM according to the second rule of TCM (nourish yin, clear heat, and remove toxin for eliminating blood stasis), the representative formula Yang Fei Xiao Zhen Tang, is more effective than western medicine in improving skin rash according to CTCAE criteria and TCM syndromes criteria; 3) CHM according to the third treatment rule of TCM (clear lung and purge heat, cool blood, and remove toxic substance) is more effective in improving and curing skin rash according to CTCAE criteria and TCM syndromes criteria, compared with the western medicine group or the blank control group; 4) the side effects of CHM are all mild and tolerable; and 5) the results of effectiveness on skin rash is relatively stable. Despite the apparently positive findings, the effectiveness and safety of CHM for the treatment of skin rash could not be fully

Table 2
Sensitivity analysis for the studies which low heterogeneity existed.

Subgroup	RR,95%CI (Fixed-effect Model)	RR,95%CI (random-effect Model)
Effectiveness on Improving Skin Rash		
First rule of TCM versus western medicine	1.46(1.26,1.70)	1.39(1.21,1.60)
Second rule of TCM versus western medicine	1.45(1.10,1.92)	1.44(1.09,1.90)
Clinical Curative Efficiency on Skin Rash		
First rule of TCM versus western medicine	1.65(1.24,2.20)	1.50(1.14,1.97)
Second rule of TCM versus western medicine	1.00(0.21,4.78)	1.01(0.19,5.30)
Third rule of TCM versus blank control	2.98(1.20,7.41)	2.86(1.15,7.16)
Efficiency on Improvement of TCM Syndromes		
Second rule of TCM versus western medicine	1.87(1.41, 2.47)	1.91(1.19,3.08)
Third rule of TCM versus western medicine	1.58(1.29,1.93)	1.55(1.19, 2.03)

confirmed and recommendations for clinical practice should be cautious because of the low quality of the included studies and small number of trials in the meta-analysis.

Modern pharmacological studies have proven that the occurrence of skin rash is possibly associated with inhibitors of tyrosine kinase disrupting the normal function of keratinocytes and sebaceous glands in the skin and aggravated by inflammation.[35] The herbs might play their roles through anti-inflammation. For example, extracts from *Periostracum cicadae* (Chan Tui) can inhibit oxidative stress and inflammation on keratinocytes.[36] Matrine, the main ingredient of Ku Shen, exerts anti-inflammatory effects by inhibiting the activation of the JAK/STAT3 pathway.[37]

This meta-analysis summarizes evidence on the adverse events of CHM. In light of the previous report of the adverse reactions of target therapy, the adverse reactions (including diarrhea, fatigue, granulocytopenia, and oral mucositis) reported in the articles are mainly considered as side effects of EGFRIs.[38] The incidence of these adverse events shows no significant difference between groups. Skin allergy might be a side effect of CHM.

High heterogeneity existed in the subgroup 3, Third rule of TCM versus western medicine, and subgroup 4, Third rule of TCM versus blank control. In the sensitivity analysis, we excluded the studies which the efficiency of control group is lower than the rest studies. Thus, the bias favored the control group and the heterogeneity reduced. Correspondingly, the meta-analysis results are more reliable, which support the good role of CHM. After excluding Qiu's study in the sensitivity analysis for the curative effect, the heterogeneity reduced to 0%. The high curative efficiency of the CHM and control group in Qiu's study might be due to that the majority of enrolled patients suffered from mild skin rash.

These promising results should be interpreted with caution for the following reasons. First, the studies included were all written in Chinese, and all research was conducted in China. Publication bias may be demonstrated by the asymmetrical funnel plot. Second, the methodological quality of the included RCTs was generally low. Most of them did not describe allocation concealment and blinding, which limit the credibility of the results. These biases may affect the results of meta-analysis. Third, all the included studies did not explore the interaction between Chinese herbal medicine and target therapy. Given these limitations, additional well-controlled large studies are required to confirm these findings.

5. Conclusion

In summary, these limited results show that CHM might be safe and effective for EGFRI-induced skin rash. However, recommendations for clinical practice should be very cautious because of limited evidence.

Authors' contributions

Zhiqiang Chen, Zeyun Li, Caizhi Yang, Ruiting Lin, Lizhu Lin and Lingling Sun had full access to all study data and take responsibility for its integrity and the accuracy of the analysis. Lizhu Lin and Lingling Sun were responsible for the study concept and design. Zhiqiang Chen, Zeyun Li, Caizhi Yang and Ruiting Lin were responsible for data acquisition and extraction. The assessment of bias risk was performed by Zhiqiang Chen and Lingling Sun; data analysis and interpretation were performed by Zhiqiang Chen, Lizhu Lin, and Lingling Sun. Zhiqiang Chen drafted the paper, which was revised by Lizhu Lin and Lingling Sun. Statistical analyses were performed by Zhiqiang Chen and Lingling Sun. Lizhu Lin and Lingling Sun supervised the study.

Declaration of Competing Interest

The authors declare that there are no competing interests regarding the publication of this manuscript.

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Table 3
Sensitivity analysis for the studies which high heterogeneity existed.

Subgroup	Excluded Studies	I^2	RR,95%CI (Fixed-effect Model)	RR,95%CI (Fixed-effect Model)
Effectiveness on Improving Skin Rash				
Third rule of TCM versus Western medicine	Wang Hongyan 2013 Wang Xueqian 2014	56%	1.47(1.31,1.65)	1.42(1.21,1.67)
Third rule of TCM versus Blank control	Wang Fuqiang2013	82%	1.84(1.49,2.29)	1.80(1.10,2.95)
Clinical Curative Efficiency on Skin Rash				
Third rule of TCM versus Western medicine	Qiu Yumei2012	0%	2.86(1.94, 4.21)	2.67(1.81,3.94)

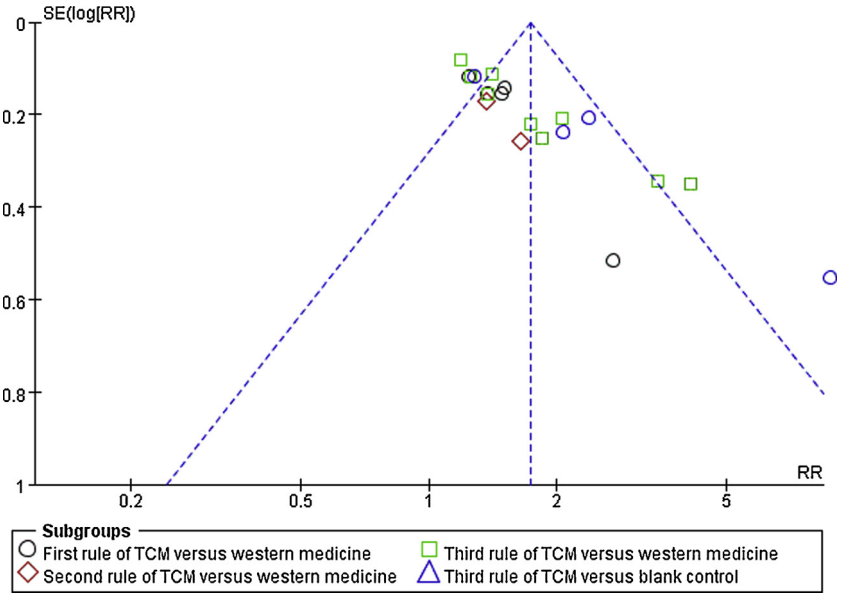

Fig. 7. Funnel Plot of Effectiveness on Improving Skin Rash.

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