Systematic Review and Meta-Analysis

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The treatment effect of Levofloxacin, Moxifloxacin, and Gatifloxacin contained in the conventional therapy regimen for pulmonary tuberculosis

Systematic review and network meta-analysis

Yiyue He, MM[a], Xiaofei Li, BA[b,*]

Abstract

Background: Tuberculosis (TB) is one of the serious epidemics that highly threaten the global public health. To explore the treatment effect of Levofloxacin, Moxifloxacin, and Gatifloxacin contained in the conventional therapy regimen for pulmonary tuberculosis.

Methods: Medline, PubMed, Embase, and Cochrane Library were searched with the keyword such as "Levofloxacin," "Moxifloxacin," "Gatifloxacin," and "tuberculosis", through June 1992 to 2017. According to the inclusion and exclusion criteria, 2 researchers independently screened the literature, extracted the data, and evaluated the quality of the included studies. The Cochrane system was evaluated by RevMan5.2 and the network meta-analysis was performed by Stata 15.

Results: A total of 891 studies were included, with a total of 6565 patients. The results of network meta-analysis showed that Moxifloxacin + conventional therapy (CT) regimen was superior to CT regimen only on the spectrum culture negative. Both Levofloxacin + CT and Moxifloxacin + CT were superior to the CT regimen in treatment success rate. For the adverse events, the Levofloxacin + CT showed much safer results than CT group, while Moxifloxacin + CT had more adverse events than CT group.

Conclusion: Levofloxacin, Moxifloxacin, and Gatifloxacin have different superiority, comparing to CT regimen in spectrum culture negative, treatment success rate, and adverse events. Hence, combined utilization of these quinolone is important on the clinical treatment for tuberculosis.

Abbreviations: CT = conventional therapy, MDR = multidrug-resistant, RR = risk ratios, TA = toxin-antitoxin, TB = tuberculosis, TM = translational medicine.

Keywords: Gatifloxacin, Levofloxacin, Moxifloxacin, pulmonary tuberculosis, treatment effects

1. Introduction

Tuberculosis (TB) is one of the serious epidemics that highly threaten the global public health for years. The global outbreak of TB in 1993 led the "World Health Organization (WHO)" to announce TB as a matter of high priority.[1] In the year 2017, WHO had estimated that around 10 million people was infected by the disease and about 6.4 million individuals were newly diagnosed with TB. It was further reported that around 1.3 million patients faced with TB-related fatality every year.[2] The morbidity and mortality of TB is stable on high level. In 2018, it was estimated that 10.1 million cases of TB were occurred, among which about 0.5 million were resistant to rifampicin, and 1.5 million patients died.[3] Alemu et al[4] found that the overall estimated pooled proportion of poor treatment outcomes among patients multidrug-resistant (MDR)/rifampicin-resistant-TB in Ethiopia was 17.86% (95% CI: 14.54, 21.18) and the pooled proportion of mortality was 15.13% (95% CI: 12.29, 17.97) (I^2; 83.1%, $P < .001$), based on the random effect model analysis. It is important to diagnosis TB at the latent stage, so that given medicines could intervene the development of TB as early as possible. And, the delay of diagnosis would complicate the treatment on TB. However, there is no gold standard test for latent TB infection. So far, intradermal tuberculin test and integrated global radiosonde archive are universally recognizable for latent TB infection diagnosis.[5]

For decades, drug-resistant variants of TB challenge the traditional anti-tuberculous drug. In 2012, about 45,000 cases of

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MDR-TB were identified, and an estimated 170,000 casualties occurred because of TB. HREZ (isoniazid, rifampin, ethambutol, pyrazinamide) or HRE (isoniazid, rifampin, ethambutol) used to be highly effective on TB patients as conventional therapy (CT) regimen. However, as the MDR-TB are prevailed in the world, the traditional regime contained with other antibiotics are becoming a necessity nowadays.

Mycobacterium tuberculosis accounts for the occurrence of TB, which is lethal. The mechanism of generation of *M tuberculosis* is varied. So far, 77 toxin-antitoxin modules, mycobacterial biofilms, stringent response, and sigma factors were found to be related to *M tuberculosis*.[6] Besides, the treatment duration for *M tuberculosis* is extremely long. One of the reasons underlying a long duration to eliminate the *M tuberculosis* from the organism was that it becomes tolerant to drugs or develops persisters being able to survive underneath extremely high drug concentrations in certain environmental conditions.[6] Most of the *M tuberculosis* toxin-antitoxin modules belong to type II, characterized by a toxin with endoribonuclease activity and an antitoxin that binds the toxin to neutralize its action. Specific environmental stimuli induce antitoxin degradation, allowing the toxin to exert its action on its specific target, such as the ribosome, specific tRNAs, or messenger RNAs.[7]

Quinolone are the effective treatments to cope with the drug-resistant TB. Gatifloxacin, Moxifloxacin, and Levofloxacin are clinically predominate quinolone combined with the standard regimen of isoniazid (H), rifampin (R), ethambutol (E), and pyrazinamide (Z) (HREZ) or other conventional regimens for TB treatment. There were numerous meta-analysis on the treatment of TB with quinolone. Guan and Liu[8] interpreted the effectiveness that Moxifloxacin regimen had a higher treatment success rate, compared with Levofloxacin or CT regimens (OR = 1.94; 95% CI = 1.16–3.25, P = .01), with no significant difference in sputum culture conversion rate. Hyun Woo Lee[9] 2016 indicated that Fluoroquinolone-containing regimens had a higher rate of sputum culture conversion at 2 months of treatment. However, Fluoroquinolone-containing regimens had less favorable outcomes (M-H fixed OR, 0.69; 95% CI, 0.59–0.82) and more frequent associated total adverse events (M-H fixed OR, 1.84; 95% CI, 1.46–2.31). Although Lee et al[9] already revealed the fact that HREZ combining with fluoroquinolone could rise the rate of sputum culture conversion, the treatment effect of single quinolone in the subset is unknown. In addition, traditional meta-analysis only compared 2 interventions in 1 study. Therefore, we aimed to use network meta-analysis to compare different quinolone combined with standard anti-tuberculous medicines.

2. Methods

2.1. Data extraction and quality evaluation

Using the term "pulmonary tuberculosis," "quinolone," "carbostyril," "random control trial" as keywords, and searching on PubMed, Medline, and Embase, a total of 891 results were found. The inclusion criteria were: the outcomes included "spectrum culture negative," "treatment success rate," and "adverse event"; and the regimen of quinolone contained "Levofloxacin," "Moxifloxacin," "Gatifloxacin," and/or "Ofloxacin." The exclusion criteria were: no detailed information on the subset of quinolone, patients relapsed for TB, included multi-drug resistant TB cases, and other forms of literature, such as review and case reports, which did not had a randomized control report.

Two reviewers (first and second authors) independently extracted data to a standardized template, which included the detailed baseline characteristics of the study, male rate, follow-up time, treatment regimens, and outcomes.

The primary outcome was the sputum culture conversion rate at 2 months of treatment after the initial stage treatment of fluoroquinolone-containing and standard regimens. Secondary outcomes were treatment success rate and any adverse events. Sputum culture conversion at 2 months of treatment was defined as a negative sputum mycobacterial culture at the end of intensive treatment during the initial 2 months. The cured and completed treatment categories were defined as the success of treatment. An adverse event was defined as any newly developed side effect associated with the treatment.

The risk of bias of each study was assessed by 7 factors according to the Cochrane risk of bias tool, including: selection bias by adequacy of random sequence generation and allocation concealment; performance bias by appropriate blinding of participants and researchers; attrition bias by knowing if missing data were absent, the reason of exclusion after randomization was not relevant to the study result, and the number and reason of missing data were similar between regimens; reporting bias by reviewing the study protocol and checking the funnel plot; and other biases. The risk of bias of each study was unanimously reviewed by 2 researchers. The procedure of the network meta-analysis was shown in Figure 1.

2.2. Data synthesis and analysis

We compared the main outcomes, including spectrum culture conversion, treatment success rate, and adverse events, using an NMA approach. R package ("meta," "grid," "netmeta," and "gemtc") was used to construct the NMA models. Node split analysis was used to testify the inconsistency of NMA models. Begg test was considered to calculate the publication bias, which visualized by funnel plot. The treatment effect between pairwise group included in the treatment was estimated by risk ratios (RRs).

3. Results

3.1. Data collection

We found 732 studies in Medline, 32 in Embase, 110 in Cochrane Library, and 47 in PubMed after searching the key terms in titles and abstracts, with 77 duplicated studies. After excluding 781 studies that were not suitable according to the study objectives, we reviewed the full text of 36 studies. Another 20 studies were excluded according to the inclusion/exclusion criteria. We finally selected 16 studies matching the inclusion and exclusion criteria.

3.2. Baseline characteristics of patients in the included studies

The 16 randomized clinical trials included a total of 6565 patients, who were enrolled from 1992 to 2017. Among all the studies, there were 3 types of anti-TB treatment durations, with 4, 6, or 9 months. We found several types of fluoroquinolones used as an intervention such as: Moxifloxacin in 14, Gatifloxacin in 3, Ofloxacin in 2, and Levofloxacin in 4 studies (Table 1). Control therapy was used as the conventional regimens for 6 months, except in 1 study that used an HRE regimen for 9 months. Lee and Jawahar included 2 arms, while Rustomjee included 3 arms in the studies. All the control standard regimens were administered for a longer duration. Most of the patients were men, ranging from 62% to 77% of the study subjects. Pulmonary cavity lesions were found in 3655 patients. CT regimen was defined as: ① HREZ; ② HREZ; ③ AMK/AMX/CLV/CM/CLR/CFZ/INH/EMB/LZD/PAS/PA/PTO/PZA/RFB/RE/; ④ AMK/CYC/EMB/KAN/LZD/RFB/PAS/PZA/PTO/STE; ⑤ AMK/CYC/EMB/KAN/LZD/RFB/PAS/PZA/PTO/STE; ⑥ AMK/DIP/EMB/RE; and ⑦ CM/KAN.

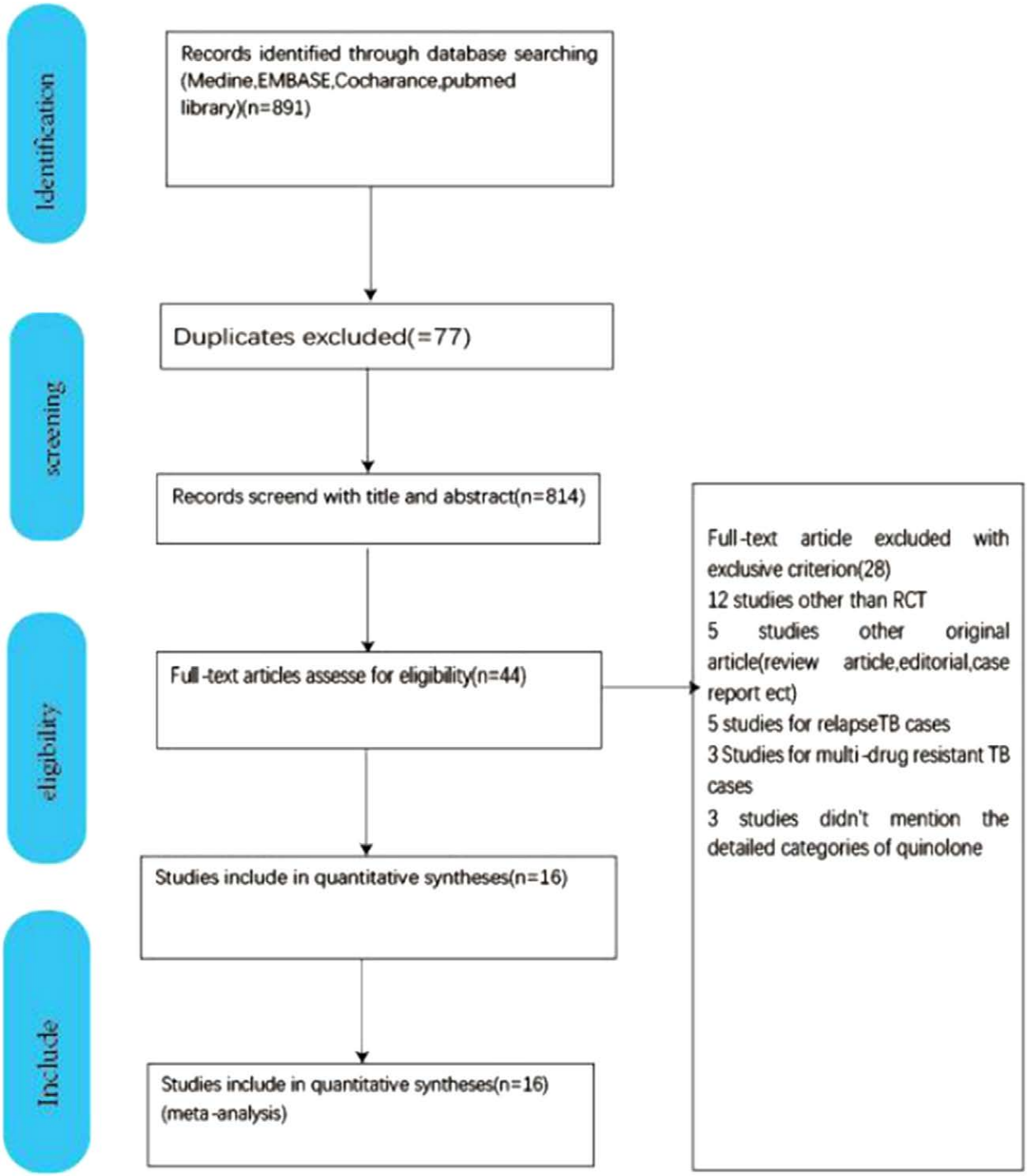

Figure 1. The procedure of network meta-analysis.

3.3. Risk of bias and quality assessment

Cochrane evaluation tools were used to evaluate the bias of risk of all the included articles, analyzed with Review Manager 5.3. Two studies had high risk of bias from random sequence generation. One literature had high risk of bias of blinding of outcome. One literature had high risk of incomplete bias, and 2 researches had high risk of selected reporting bias. And, 1 research had high risk of other bias. The results are shown in Figures 2 and 3.

3.4. Spectrum culture negative

3.4.1. Heterogeneity. The heterogeneity results showed that quantifying heterogeneity was $I^2 = 61.4\%$, 95% CI (23.0%, 80.6%)f. Hence, the random model was applied.

3.4.2. Network meta-analysis. The results showed that RR value of CT versus Moxifloxacin + CT was 0.9053, with 95% CI (0.8547, 0.9588), indicating that Moxifloxacin + CT had an advanced treatment effect than CT. Other pairwise of treatment

Table 1

Baseline characteristics of patients in the included studies.

Study	Male (%)	Type of fluoroquinolone used in the intervention	Standard regimen	Follow time	Outcome
Chien[10]	89	Moxifloxacin (400 mg) + CT	CT	8 mo	○2
Jiang[11]	42	CT + Moxifloxacin (400 mg) CT + LVO (500 mg/d)	CT	4–6 mo	○2
Kang[12]	68	CT + Moxifloxacin (400 mg) CT + LVO (500 mg/d)	CT	3 mo	○2
Koh[13]	67	CT + Moxifloxacin (400 mg) CT + LVO (500 mg/d)	CT	3 mo	○2
Jawahar[14]	74	Moxifloxacin (400 mg) + CT Gatifloxacin (400 mg) + CT	CT	9 mo	○1
Merle[15]	73	Gatifloxacin (400 mg) + CT	CT	4 mo	○1
Kohno[16]	69	Ofloxacin (400 mg) + CT	CT	6 mo	○2
El-Sadr[17]	77	Levofloxacin (500 mg/d) +CT	CT	6–9 mo	○1
Burman[18]	67	Moxifloxacin (400 mg)	CT	2 mo	○1
Rustomjee[19]	67	Gatifloxacin (400 mg) + CT, Moxifloxacin (400 mg) + CT Ofloxacin (400 mg) + CT	CT	6 mo	○1○3
Dorman[20]	72	Moxifloxacin (400 mg) + CT	CT	2 mo	○1
Conde[21]	62	Moxifloxacin (400 mg) + CT	CT	2 mo	○1○3
Gillespie[22]	70	Moxifloxacin (400 mg) + CT/Levofloxacin (500 mg/d) +CT	CT	4 mo	○1
Lee[23]	44	CT + MOX (400 mg) CT + LVO (500 mg/d)	CT	594[481, 772] d	○2
Heemskerk[24]	69	Levofloxacin (500 mg) + CT	CT	9 mo	○3
Kalita[25]	56	Levofloxacin + CT (500 mg)	CT	6 mo	○1○3

○1 Spectrum culture negative; ○2 treat success rate; ○3 any adverse event. HREZ = isoniazid, rifampin, ethambutol, and pyrazinamide (H = 5 mg/kg/d, R = 10 mg/kg/d, Z = 25 mg/kg/d, E = 15 mg/kg/d); HRE = isoniazid, rifampin, ethambutol conventional therapy regimen (CT): 1. HREZ; 2. HREZ; 3. AMK/AMX/CLV/CM,/CLR/CFZ/INH/EMB/LZD/PAS/PA/PTO/PZA/RFB/RE/; 4. AMK/CYC/EMB/KAN/LZD/RFB/PAS/PZA/PTO/STE; 5. AMK/CYC/EMB/KAN/LZD/RFB/PAS/PZA/PTO/STE; 6. AMK/DIP/EMB/RE; 7. CM/KAN.

AMI = aminoglycosides, AMK = amikacin, AMX/CLV = amoxicillin/clavulanic acid, CFZ = clofazimine, CLR = clarithromycin, CM = capreomycin, CYC = cycloserine, DIP = dipasic, EMB = ethambutol, INH = isoniazid, KAN = Kanamycin, LVO = Levofloxacin, LZD = linezolid, MOX = Moxifloxacin, PA = pasiniazide, PAS = para-aminosalicylic acid, PTO = protionamide, PZA = pyrazinamide, RE = rifapentine, RFB = rifabutin, STE = streptomycin, SUL = sulfamethoxazole, TRI = trimethoprim.

*M = moxifination, L = levoxifination, G = gaxifination, CT = conventional therapy regimen.

groups did not show significant differences, shown in Table 2. The network map and forest plot are shown in Figures 4 and 5, respectively.

3.4.3. Inconsistency analysis. The network showed no closed existed. Hence, inconsistency analysis was not necessary. And, the model could directly go through the consistency analysis.

3.4.4. Rank on the spectrum culture negative possibility based on SUCRA. The rank of the treatment effect of spectrum culture negative was that Gatifloxacin + CT regimen > Moxifloxacin + CT regimen > CT regimen > Levofloxacin + CT regimen. The SUCRA plot is shown in Figure 6.

3.4.5. Publication bias. Begg test was used to testify the potential publication bias. The results showed no significant bias ($z = -1.32$, $P = .1885$). The funnel plot also showed no obvious bias, as shown in Figure 7.

3.5. Treatment success rate

3.5.1. Heterogeneity. The heterogeneity results showed that there were no heterogeneity ($I^2 = 38.8\%$, 95% CI [0.0%, 81.0%]). The fixed effects model was applied.

3.5.2. Network meta-analysis. The network analysis showed that RR for CT versus Moxifloxacin + CT, and CT versus Levofloxacin + CT were 0.7557 (95% CI [0.6240, 0.9151]) and 0.6940 (95% CI [0.5417, 0.8891]), respectively. The results revealed that both Moxifloxacin + CT and Levofloxacin + CT were superior to CT group. Other pairwise compared group did not have any significance differences. The detailed results were shown in Table 3. Network map results are shown in Figure 8 and the Forest plot is shown in Figure 9.

3.5.3. Rank on the spectrum culture negative possibility based on SUCRA. Levofloxacin + CT regimen > Moxifloxacin + CT regimen > CT regimen. The SUCRA graph is shown in Figure 10.

3.5.4. Inconsistency analysis. According to the network map, no closed loop existed. Hence, inconsistency analysis was not applied.

3.5.5. Publication bias. Less than 4 researches did not match the publication bias analysis threshold in this NMA model.

3.6. Adverse events

3.6.1. Quantifying heterogeneity. The results were as follows: $tau^2 = 0.1201$; $tau = 0.3466$; $I^2 = 72.3\%$ (43.1%, 86.5%]), indicating an obvious heterogeneity in the model. Hence, random effects model was applied.

3.6.2. Network meta-analysis. The results showed that RR of CT versus CT + LO was 1.3359, 95% CI (0.7769, 2.2971), and RR of CT versus CT + MO was 0.7110, 95% CI (0.5160, 0.9798), which indicated that CT + LO had less adverse events than CT, while CT + MO had more adverse events than CT (Table 4). The forest plot, network map, and sucra plot are shown in Figures 11–13, respectively.

Rank on the adverse event possibility based on SUCRA: rank of least adverse event was that CT + LO > CT > CT + MO.

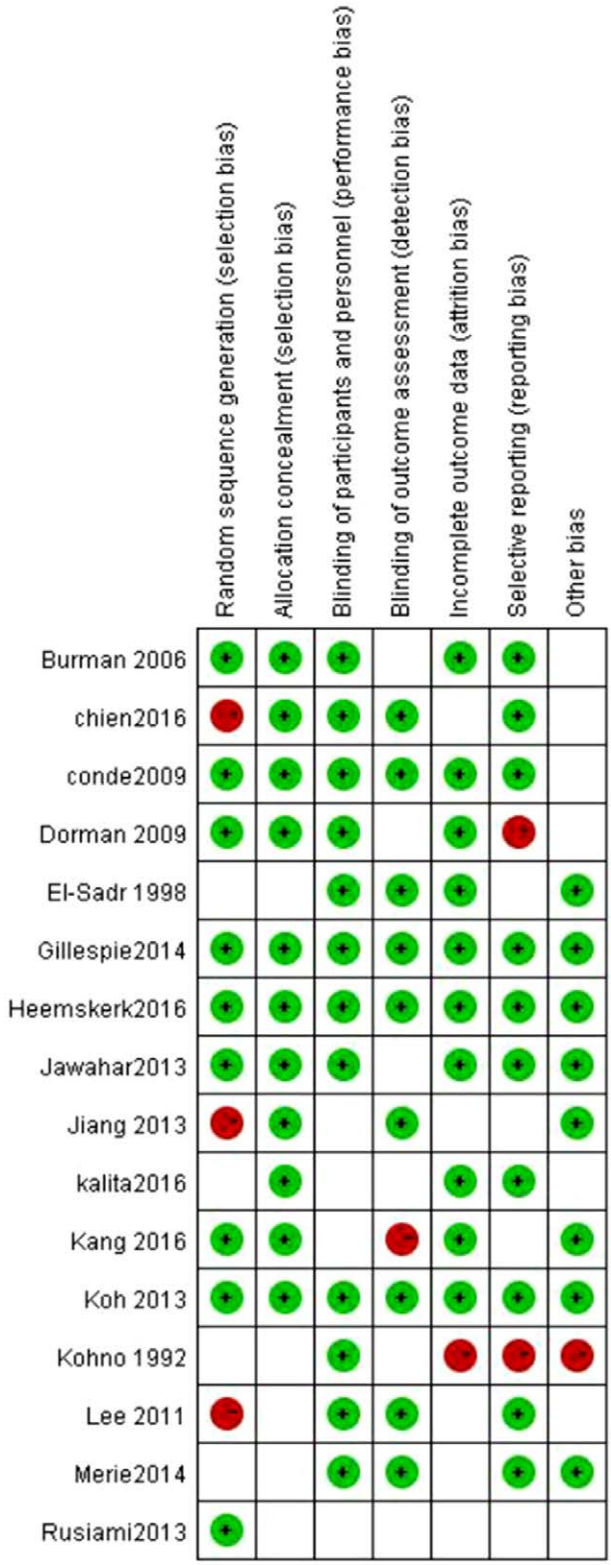

Figure 2 . The bias items of included studies.

3.6.3. Inconsistency analysis. The model did not have closed loop. Hence, inconsistency analysis was unnecessary.

3.6.4. Publication bias. Result from Begg algorithm was $z = 1.04$, $P = .2971$, which showed no obvious publication bias.

The funnel plot (Fig. 14) showed that most of studies were based on the quantity sample size, with ideal and high accuracy.

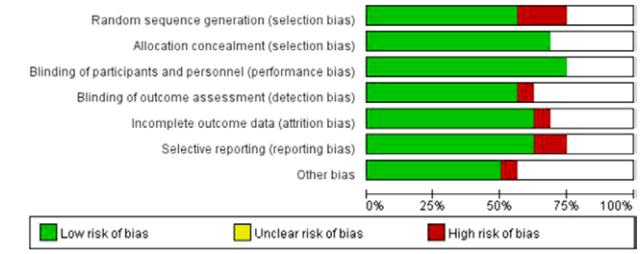

Figure 3. The proportion of 7 types of bias.

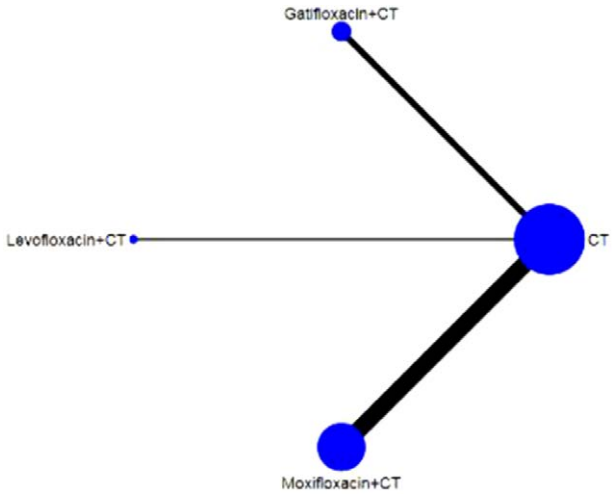

Figure 4. Network map.

4. Discussion

In this study, 16 randomized clinical trials were included, with a total of 6565 patients enrolled from the studies during from 1992 to 2018. The outcomes included spectrum culture negative (2 months), treatment success rate, and adverse events. The results showed that Moxifloxacin + CT regimen was superior to CT regimen only on the spectrum culture negative. Both Levofloxacin + CT and Moxifloxacin + CT were superior to the CT regimen in treatment success rate. For the adverse events, the Levofloxacin + CT showed much safer results than CT group, while Moxifloxacin + CT had more adverse events than CT group.

Pulmonary TB is a prevailed disease in the past decades. While, as the procession of treatments, the incidence of pulmonary TB has been reducing year by year. The predominate strategy for curing TB is antibiotic. Normally, CT regimen is the subset of HREZ (isoniazid, rifampin, ethambutol, and pyrazinamide) and other first-line anti-TB medicines. Furthermore, when the MDR-TB occurred, regimen contained quinolone have become an effect strategy to cure drug-resistant TB. The quinolone mainly includes Gatifloxaxin, Moxifloxacin, and Levofloxacin.

From the results of NMA model, Gatifloxacin + CT regimen showed the best treatment effects on the spectrum culture negative. Deshpande et al[26] recommended Gatifloxacin with doses of 800 and 1200 mg/day for pulmonary and meningeal MDR-TB treatment, respectively. From the perspective of treatment success rate, Levofloxacin + CT regimen had a better performance than other treatment groups. One study showed that new-generation fluoroquinolones (Levofloxacin and Moxifloxacin) showed faster time to culture conversion compared to the old generation (Ciprofloxacin and Ofloxacin).[27] Sgaragli et al[28] also

Table 2

The RR between different treatment with spectrum culture negative evaluation.

Treatment regimen	CT	Gatifloxacin + CT	Levofloxacin + CT	Moxifloxacin + CT
CT	1	0.9656 [0.8812, 1.0581]	0.9858 [0.8421, 1.1540]	0.9053 [0.8547, 0.9588]
Gatifloxacin + CT	1.0356 [0.9451, 1.1348]	1	1.0209 [0.8509, 1.2248]	0.9375 [0.8415, 1.0444]
Levofloxacin + CT	1.0144 [0.8666, 1.1875]	0.9795 [0.8164,1.1752]	1	0.9183 [0.7766,1.0859]
Moxifloxacin + CT	1.1047 [1.0430,1.1699]	1.0667 [0.9575,1.1883]	1.0890 [0.9209, 1.2877]	1

Treatment estimate (sm="RR").

CT = conventional therapy, RR = risk ratios.

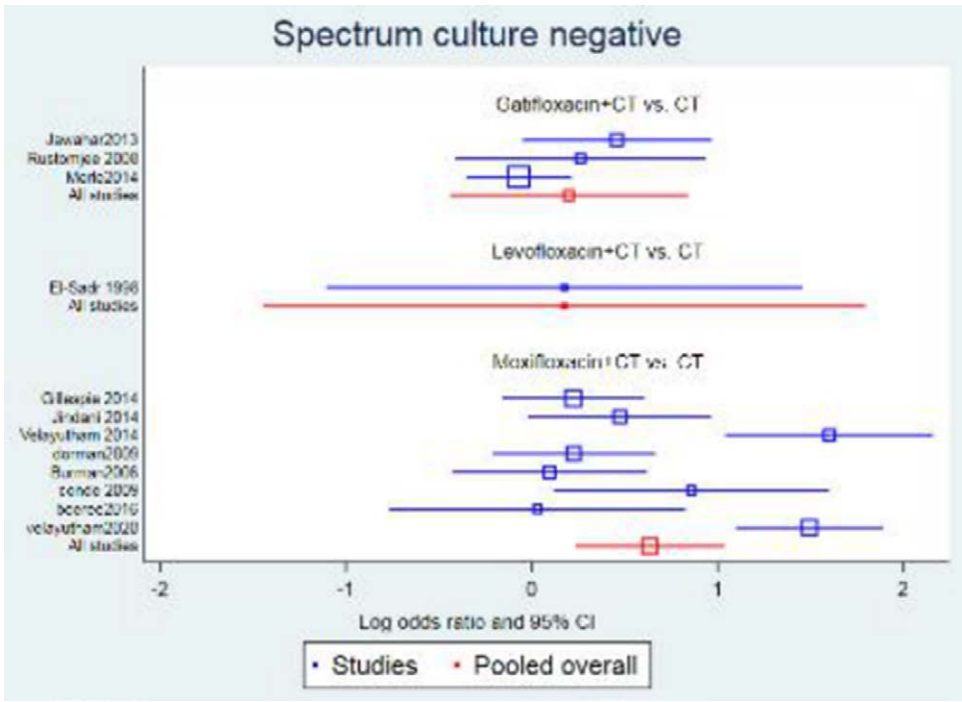

Figure 5. Forest plot.

found that fluoroquinolone-based therapies (Gatifloxacin and Moxifloxacin) were likely to be superior in culture conversion rates of spectrum at 2 months, although the relapse of TB was unclear. The rank of least adverse events was that Levofloxacin + CT > CT > Moxifloxacin + CT. Lan et al[29] indicated that Levofloxacin was safer than Moxifloxacin in treating translational medicine (TM) through a meta-analysis, and the former had fewer adverse events. While Guan and Liu[8] did not find the difference between Levofloxacin and Moxifloxacin in adverse events, and found out that Moxifloxacin had a superior treatment success rate, compared to conventional treatment. Pharmacologically, Pienaar et al[30] made a conclusion that MXF had a small clinically significant advantage over LVX, as well as LVX over GFX, partially due to a higher cellular accumulation ratio. All the ranks based on scrua did not indicate Moxifloxacin + CT as the best treatment. Nosova et al[31] indicated that mutations in gyrA, Asn538Asp, and Asp500His substitutions in gyrB were associated with cross-resistance of *M tuberculosis* to fluoroquinolones. This might explained the result of NMA model did not show any advantage of Moxifloxacin, although some prior evidence showed Moxifloxacin had a higher cellular accumulation ratio. The population distribution of gyrA mutation might be a factor to influence the results. In addition, the deviation to the true of the NMA itself might be a main factor to the explanation.

TM is an emerging method and process to facilitate medical advances efficiently from the basic to the clinical sciences.[32] In China, patients often have to travel a great distance to prestigious/tertiary hospitals in search for medical diagnosis and solutions, especially for those with complex conditions. For patients with MDR-TB, TM might be beneficial to have an efficient diagnosis and obtain an individualized treatment regimen.

However, this study had several limitations. First, there might be a high risk of defined bias among 16 studies. The result of quality assessment indicated that the quality of the inclusive papers were various and limited. Second, 2 NMA models defined by treatment success rate and adverse events might had heterogeneity, with 2 potentially reasons that no subgroup analysis setting and including the articles with high risk of bias. Third, the period of follow-up was different, which might lead to bias on observed results. The following items of excluding the assays with high risk of bias, and subgroup analysis based on the component of conventional regimen, age, and follow up time could help improve the reliability and accuracy of the results.

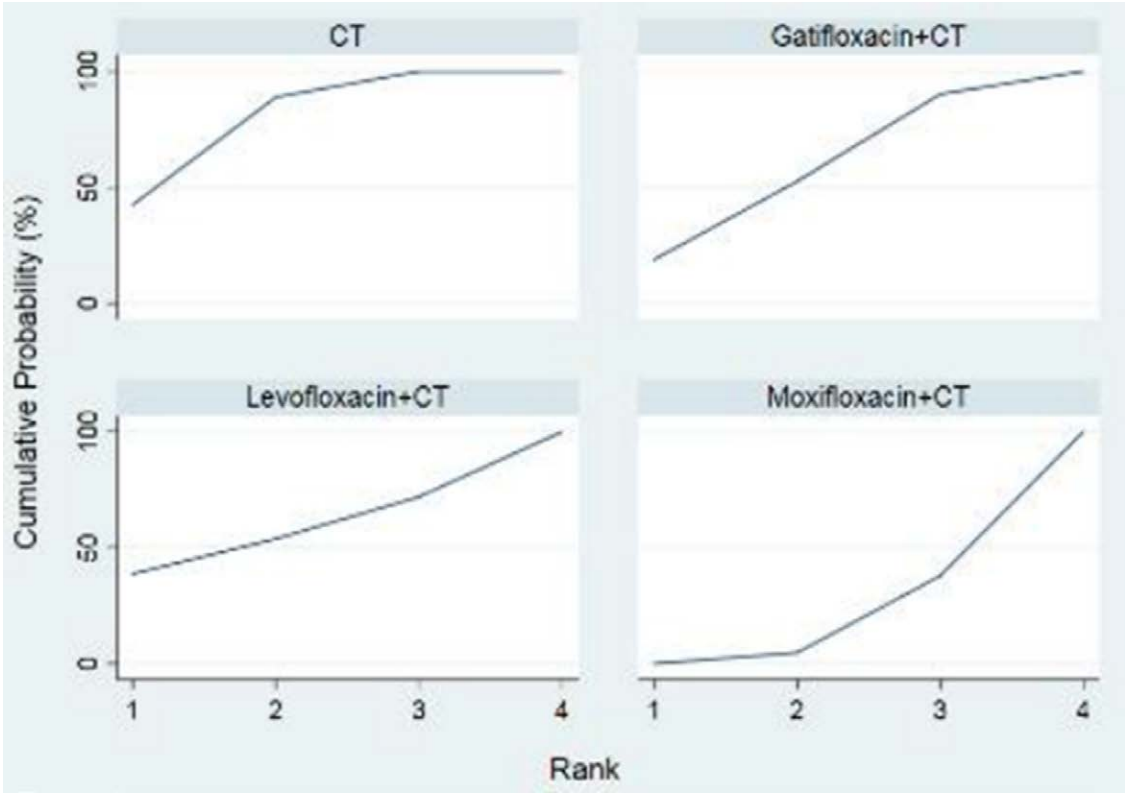

Figure 6. SUCRA plot.

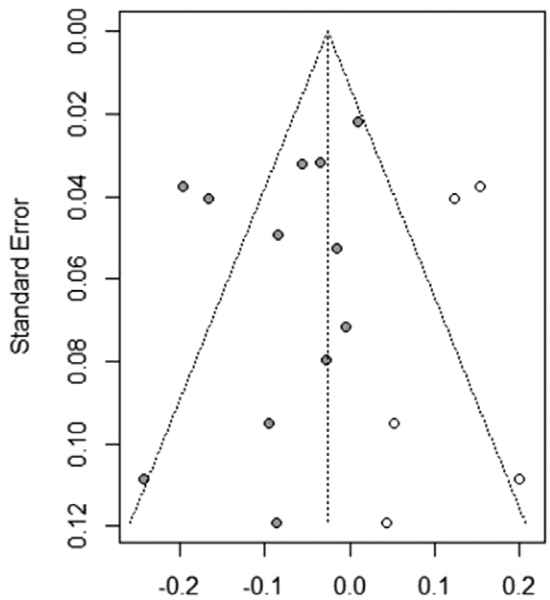

Figure 7. Funnel plot.

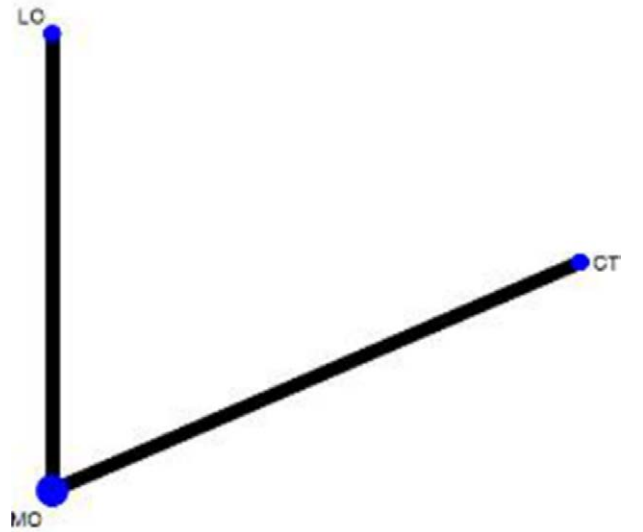

Figure 8. Network map.

Table 3

The RR between different treatment with treatment success rate evaluation.

Treatment group	CT	Levofloxacin + CT	Moxifloxacin + CT
CT	1	0.6940 [0.5417,0.8891]	0.7557 [0.6240,0.9151]
Levofloxacin + CT	1.4409 [1.1247,1.8461]	1	1.0889 [0.9303,1.2744]
Moxifloxacin + CT	1.3233 [1.0928,1.6025]	0.9184 [0.7847,1.0749}	1

Treatment estimate (sm="RR").

CT = conventional therapy, RR = risk ratios.

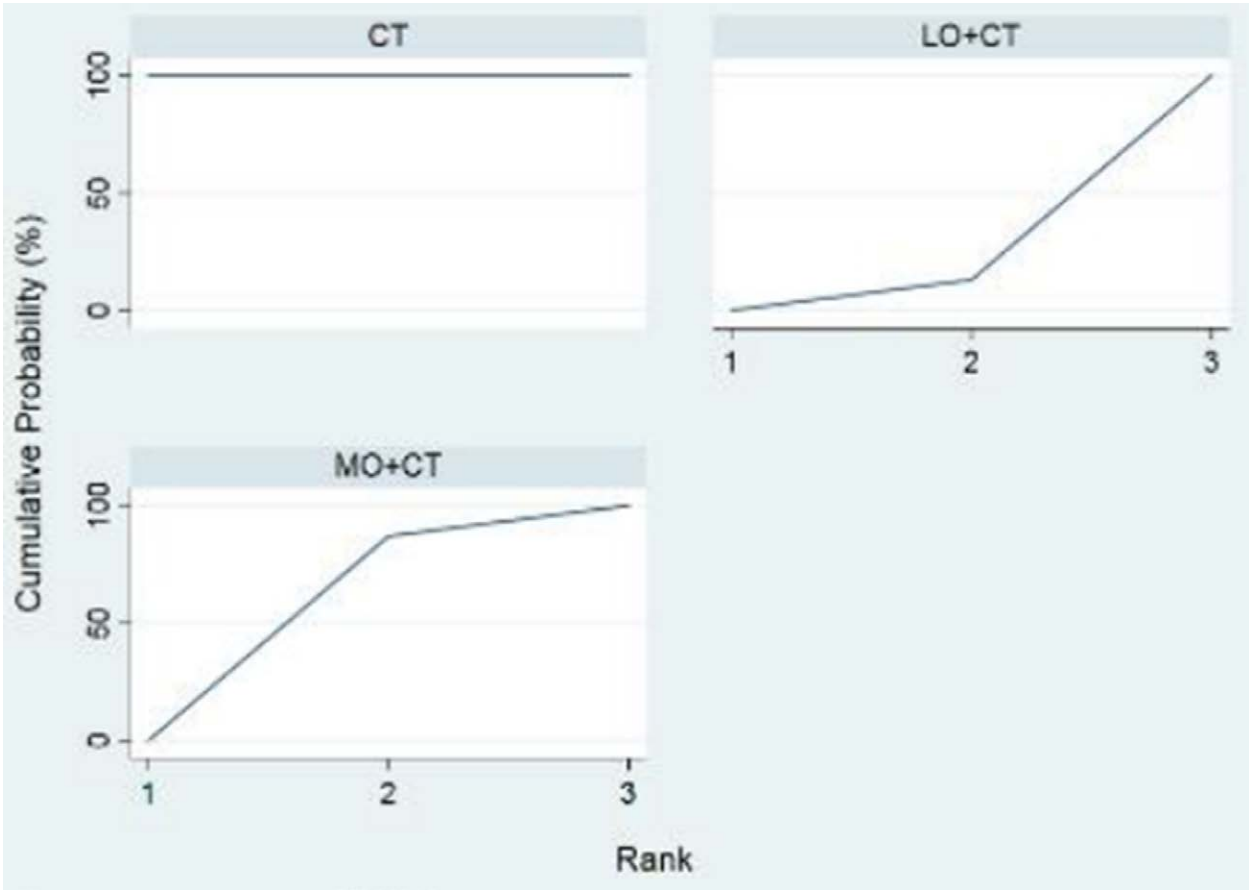

Figure 9. SUCRA plot.

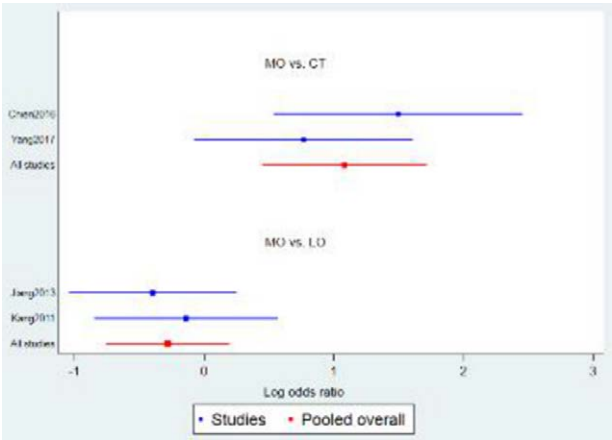

Figure 10. Forest plot.

5. Conclusion

We constructed NMA model to analysis the treatment effect and safety of Gatifloxacin, Moxifloxacin and Levofloxacin combined with CT regimens. The result showed that Levofloxacin + CT were safer in the adverse events than other groups, and also had the highest treatment success rate. In addition, Gatifloxacin + CT regimen had the best effects on spectrum culture negative. Since the quinolones had different performance when evaluated with different outcomes, combined utilization of quinolone may a potential treatment regimen for TB in clinical practice.

Author contributions

QYY focused on the study concepts, study design, clinical studies, and manuscript review; XFL carried out the literature research, data acquisition, data analysis, statistical analysis, and manuscript editing. All authors have read and approved this article.

Table 4

The RR between different treatment with adverse event evaluation.

Treatment	CT	LO + CT	MO + CT
CT	1	1.3359 [0.7769, 2.2971]	0.7110 [0.5160, 0.9798]
LO + CT	0.7485 [0.4353, 1.2871]	1	0.5322 [0.2835, 0.9991]
MO + CT	1.4064 [1.0206,1.9381]	1.8789 [1.0009, 3.5270]	1

Treatment estimate (sm="RR").

CT = conventional therapy, RR = risk ratios.

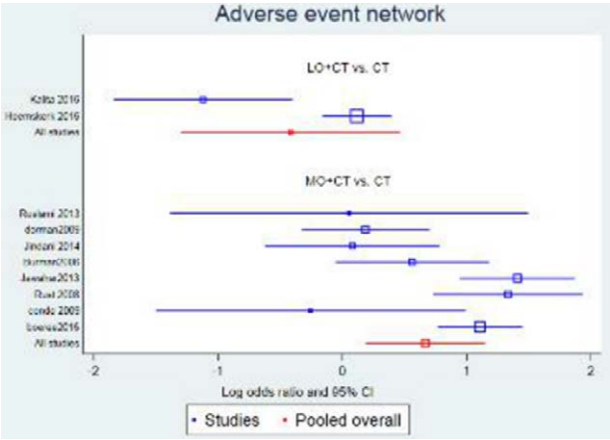

Figure 11. Forest plot.

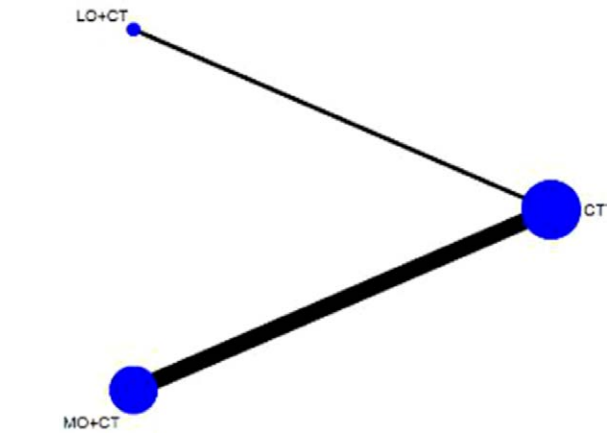

Figure 12. Network map.

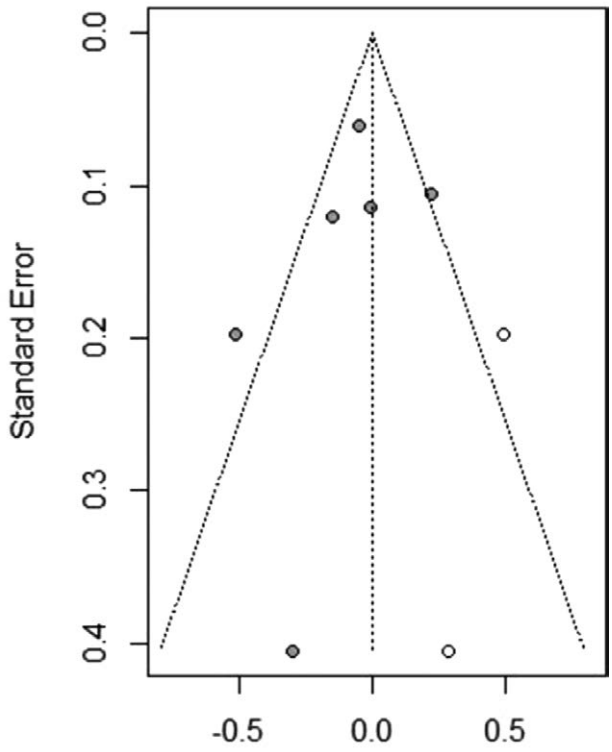

Figure 14. Funnel plot.

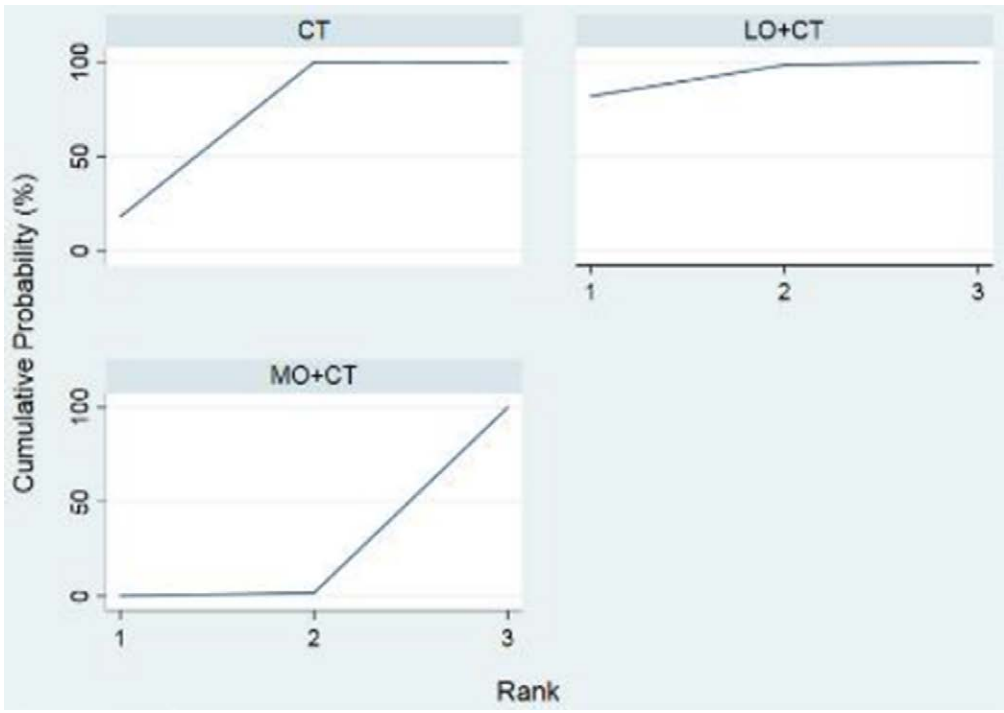

Figure 13. SUCRA plot.

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Formal analysis: Xiaofei Li, Yiyue He.
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