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Ceftriaxone combination therapy versus respiratory fluoroquinolone monotherapy for community-acquired pneumonia: A meta-analysis

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ABSTRACT

Background: The goal of this study was to investigate whether ceftriaxone combination therapy is associated with better clinical outcomes than respiratory fluoroquinolone monotherapy for adults with community-acquired pneumonia (CAP). We conducted a meta-analysis of published studies.
Methods: Using the PubMed, EMBASE, and Cochrane Library databases, we performed a literature search of available randomized controlled trials (RCTs) published as original articles before September 2017.
Results: Nine RCTs, involving 1520 patients, were included in the meta-analysis. The pooled relative risks (RRs) for the efficacy of ceftriaxone combination therapy versus respiratory fluoroquinolones monotherapy were 0.96 (95% CI: 0.92–1.01), based on clinically evaluable populations, and 0.93 (95% CI: 0.88–0.99) based on intention-to-treat (ITT) populations. No statistically significant differences were observed in microbiological treatment success (pooled RR = 0.99, 95% CI: 0.90–1.09), although drug-related adverse events were significantly lower with ceftriaxone combination therapy than with respiratory fluoroquinolones monotherapy (pooled RR = 1.27, 95% CI: 1.04–1.55).
Conclusions: Current evidence showed that the efficacy of ceftriaxone combination therapy was similar to respiratory fluoroquinolone monotherapy for hospitalized CAP patients, and was associated with lower drug-related adverse events.

1. Introduction

Community-acquired pneumonia (CAP) is one of the leading causes of death and hospitalization for all age groups throughout the world [1,2]. Short-term mortality (in-hospital and 30-day mortality) for hospitalized patients with CAP ranges from 4.0% to 18.0% [3]. It is likewise the most frequent cause of community-acquired infections admitted to intensive care units (ICU) [4], and mortality can reach 50% for patients in the ICU [5]. The most common cause of CAP is *Streptococcus pneumoniae* [6-8]. However, it is a challenge to treat CAP due to increased incidence of antibiotic resistance [9,10] and the occurrence of other atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella species*). The treatment of CAP requires antibiotics, and inappropriate use of them in the community and hospitals has contributed to resistance. Thus, antibiotic therapy for CAP should be focused on the most efficient and effective antibiotic regimens.

Patients' outcomes from CAP depend on timely diagnosis and treatment, involving appropriate antimicrobial therapy directed at the most common possible respiratory pathogens. Beta-lactam-based therapy for CAP covers the most common possible pathogens involved in the pathogenesis of CAP and acts as one of the first-line standard treatments. It was suggested that patients be administered third-generation cephalosporin, such as cefotaxime or ceftriaxone, for high-severity CAP [11]. Ceftriaxone is a broad-spectrum antibiotic, most commonly used in the emergency department, particularly for patients with community-acquired pneumonia [12]. Fluoroquinolones have also been considered a possible regimen for CAP because of their effectiveness as a single agent [13], low spontaneous mutation rate for resistance, and cost-saving potential [14]. However, previous studies were not consistent and did not assess which was the better choice for CAP. We aimed to compare the efficacy, drug-related adverse events, and microbiological responses to ceftriaxone combination therapy with respiratory fluoroquinolone monotherapy for the treatment of CAP and conducted a meta-analysis of randomized controlled trials.

2. Methods

2.1. Search strategy

A systematic search was performed in the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (Cochrane Library Issue 1 of 9, 2017) databases to find studies published before September

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2017. Because several quinolones have been withdrawn from clinical use since the conduct of the trials, we used the keywords "levofloxacin", "moxifloxacin", "ceftriaxone" in combination with "community acquired pneumonia" and "CAP" to search the literature. There was no limitation on language or date of publication. We reviewed the reference lists of included articles for additional studies.

2.2. Selection criteria

Studies were included in the meta-analysis if they fulfilled the following criteria: (1) randomized controlled trials (RCTs) of adults aged >18 years with community acquired pneumonia (CAP); (2) comparison of the clinical efficacy and/or safety of ceftriaxone combination therapy versus respiratory fluoroquinolones monotherapy; (3) trials with blinded or unblinded design were included.

2.3. Data extraction and risk of bias

Data on study characteristics, treatment success, microbiological treatment success, and drug-related adverse events (AEs) were abstracted onto a standardized form by 2 authors independently and discrepancies were resolved by consensus in consultation with a third reviewer. The risk of bias for included studies was assessed by the Cochrane Collaboration's tool for evaluating study bias [15].

2.4. Analyzed outcomes

Treatment success was defined as primary outcome at the test-of-cure (TOC) visit based on clinically evaluable and ITT populations. The secondary outcomes included drug-related adverse events (AEs) and microbiological treatment success. Treatment success was defined as "clinical cure", which was the disappearance of all signs and symptoms related to infection.

2.5. Statistical analysis

The statistical heterogeneity among studies was tested with the Q statistic, and inconsistency was quantified with the I^2 statistic [16]. For the Q statistic, statistical significance was set at $P < 0.1$. When heterogeneity was detected, the random-effects model was used [17]. Analyses were performed with STATA 14.0 (StataCorp, College Station, TX, USA) and RevMan 5.3 (Cochrane Collaboration, Copenhagen, Denmark).

3. Results

3.1. Study characteristics and risk of bias

Six hundred sixty-eight potentially relevant articles were identified using the pre-defined search criteria by a primary computerized literature search. After screening titles and abstracts and reviewing the full-text articles, nine RCTs [18-27] were included (Fig. 1). Of these studies, six were in English, two were in Chinese, and one was in Spanish. The majority of participants included in the studies were the patients with moderate and/or severe CAP. The length of treatment was 7–14 days in most studies. The main characteristics of the studies that were included in the meta-analysis are summarized in Tables 1. The risk of bias summary for included studies is listed in Fig. 2.

3.2. Treatment success

All included trials reported the treatment success for clinically evaluable populations at the test-of-cure (TOC) visit. In Fig. 3, the analysis of all the studies revealed that there was no difference in treatment success between ceftriaxone combination therapy and respiratory fluoroquinolone monotherapy (pooled RR = 0.96, 95% CI: 0.92–1.01) based on clinically evaluable populations. Only five trials provided data about treatment success for ITT populations at the TOC visit. Ceftriaxone combination therapy was slightly more effective than respiratory fluoroquinolone monotherapy (pooled RR = 0.93, 95% CI: 0.88–0.99) based on ITT populations, as shown in Fig. 4.

3.3. Drug-related adverse effects

Data on drug-related AEs in the clinically evaluable populations were reported for six trials. The most common AEs were gastrointestinal disturbances, including diarrhea, vomiting, and other GI complaints. Fig. 5 shows that ceftriaxone combination therapy was associated with fewer adverse events (pooled RR = 1.27, 95% CI: 1.04–1.55).

3.4. Microbiological treatment success

Four of the nine relevant RCTs provided microbiological treatment success outcomes. No significant difference was observed between a ceftriaxone combination regimen and respiratory fluoroquinolone monotherapy (pooled RR = 0.99, 95% CI: 0.90–1.09), as shown in Fig. 6.

4. Discussion

To our knowledge, no meta-analysis comparing respiratory fluoroquinolone monotherapy to ceftriaxone combination therapy for community-acquired pneumonia has been published. A total of 1520 patients in 9 independent studies were identified in this meta-analysis. The results of this meta-analysis indicated that ceftriaxone combination therapy was similar to respiratory fluoroquinolone monotherapy, and the drug-related AEs were fewer in the ceftriaxone combination therapy regimen.

A meta-analysis conducted by Vardakas et al. [28] reported that respiratory fluoroquinolones were associated with higher clinical efficacy than combination therapy was. Similarly, a cohort from Querol-Ribelles JM et al. [29] also reported that levofloxacin was superior to the combination of ceftriaxone and clarithromycin in the treatment of community-acquired pneumonia that requires hospitalization. Furthermore, Fan H et al. [30] reported that in the treatment success rates, no significant differences were found between the respiratory fluoroquinolone monotherapy and the β-lactams plus macrolides combination therapy based on the data of intention-to-treat (ITT) and per-protocol (PP) analyses. Our meta-analysis demonstrated that the efficacy of ceftriaxone combination therapy was similar to respiratory fluoroquinolone monotherapy for hospitalized CAP patients, with higher treatment success rates based on ITT populations.

In the included studies, in which drug-related adverse events were mentioned, the most common AEs for ceftriaxone were gastrointestinal disorders, such as diarrhea and vomiting; other AEs were phlebitis, nausea, rash, and so on. Macrolides were the most common combination drug regimen with ceftriaxone; six studies (azithromycin in three articles, clarithromycin in two articles, and erythromycin in two articles) used it. It was reported that *Clostridium difficile* infection, enterocolitis, central nervous system (CNS) effects, and digestive effects are common drug-related AEs in patients taking macrolide antibiotics [31]. For the compared regimens, fluoroquinolones can cause a range of serious drug-related adverse events. The drug-related adverse events that were reported in the included studies were gastrointestinal disorder (nausea, vomiting, diarrhea), rash, urticarial, phlebitis, dizziness, insomnia, paroniria, seizures, and headache. In addition, the Food and Drug Administration (FDA) recently advised restricting fluoroquinolone antibiotic use for its potential side effects [32]. All in all, there were fewer drug-related adverse events in CAP patients taking ceftriaxone combination therapy in our meta-analysis, which may make it a better choice for treating CAP.

The results of this meta-analysis indicated that there was no statistical difference between the two antibiotic regimens in microbiological treatment success. However, another meta-analysis reported that

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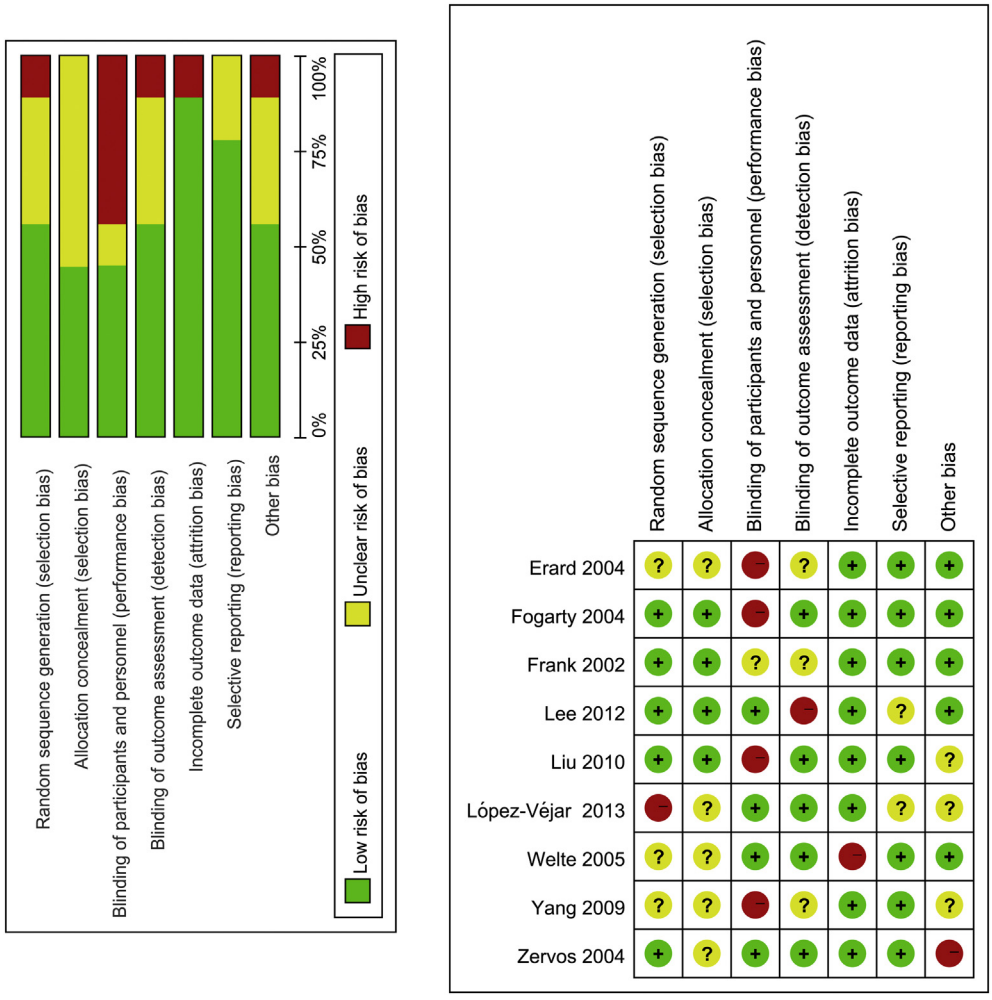

Fig. 1. Flow diagram of meta-analysis literature search results.

Table 1
Characteristics of the included studies.

Study	Year	Type of study	Included population	Drug regimens		Enrolled population	Intention to treat
				Ceftriaxone combination	Respiratory quinolone monotherapy		
Frank	2002	Multicenter, randomized, open-label study	Patients ≥18 years old with a primary diagnosis of CAP	i.v. azithromycin 0.5 g OD + i.v. ceftriaxone 1 g OD	i.v./p.o.levofloxacin 0.5 g OD	236	121 vs. 115
Erard	2004	Randomized, open-label, controlled pilot observational study	Patients ≥18 years old admitted for the treatment of CAP	i.v. ceftriaxone 2 g OD ± i.v./p.o. clarithromycin 1 g OD	p.o. levofloxacin 1 g OD	129	37 vs. 79
Fogarty	2004	Randomized, open-label, comparative, study	Patients ≥18 years old with signs and symptoms of CAP	i.v/i.m. ceftriaxone sodium 1–2 g OD + i.v. erythromycin 0.5–1 g/6 h	p.o. levofloxacin 1 g OD	269	137 vs. 132
Zervos	2004	Multicenter randomized, open-label study	Patients ≥18 years old with a clinical diagnosis of CAP	i.v. ceftriaxone 1 g OD + i.v. azithromycin 0.5 g OD	i.v. levofloxacin 0.5 g OD	219	112 vs. 107
Welte	2005	Multicenter, randomized, controlled, nonblinded study	Patients ≥18 years old with a primary diagnosis of CAP	i.v. ceftriaxone 2 g OD ± i.v. erythromycin 1 g OD	i.v. moxifloxacin 0.4 g OD	397	197 vs. 200
Yang	2009	Randomized study	Elderly patients with moderate to severe CAP	i.v. ceftriaxone sodium 2 g OD+ i.v. azithromycin 0.5 g OD	i.v. moxifloxacin hydrochloride sodium chloride 0.4 g OD	100	50 vs. 50
Liu	2010	Randomized, controlled clinical study	Patients ≥18 years old with a primary diagnosis of CAP	i.v. ceftriaxone sodium 2 g OD + i.v. azithromycin 0.5 g OD	i.v. moxifloxacin sodium chloride OD	58	30 vs. 28
Lee	2012	Randomized, open-label study	Patients admitted to a hospital for CAP treatment	i.v. ceftriaxone 2 g OD + p.o. azithromycin 0.5 g OD	i.v. levofloxacin 0.75 g OD	40	20 vs. 20
López-Véjar	2013	Randomized, open-label, controlled study	Patients ≥18 years old with CAP with a severity index of pneumonia ≥ III	i.v. ceftriaxone 2 g b.i.d. + p.o. clarithromycin 0.5 g b.i.d.	i.v/p.o. levofloxacin 0.75 g OD	72	36 vs. 36

i.v.: intravenous, OD: once daily, b.i.d.: twice daily, p.o.: oral.

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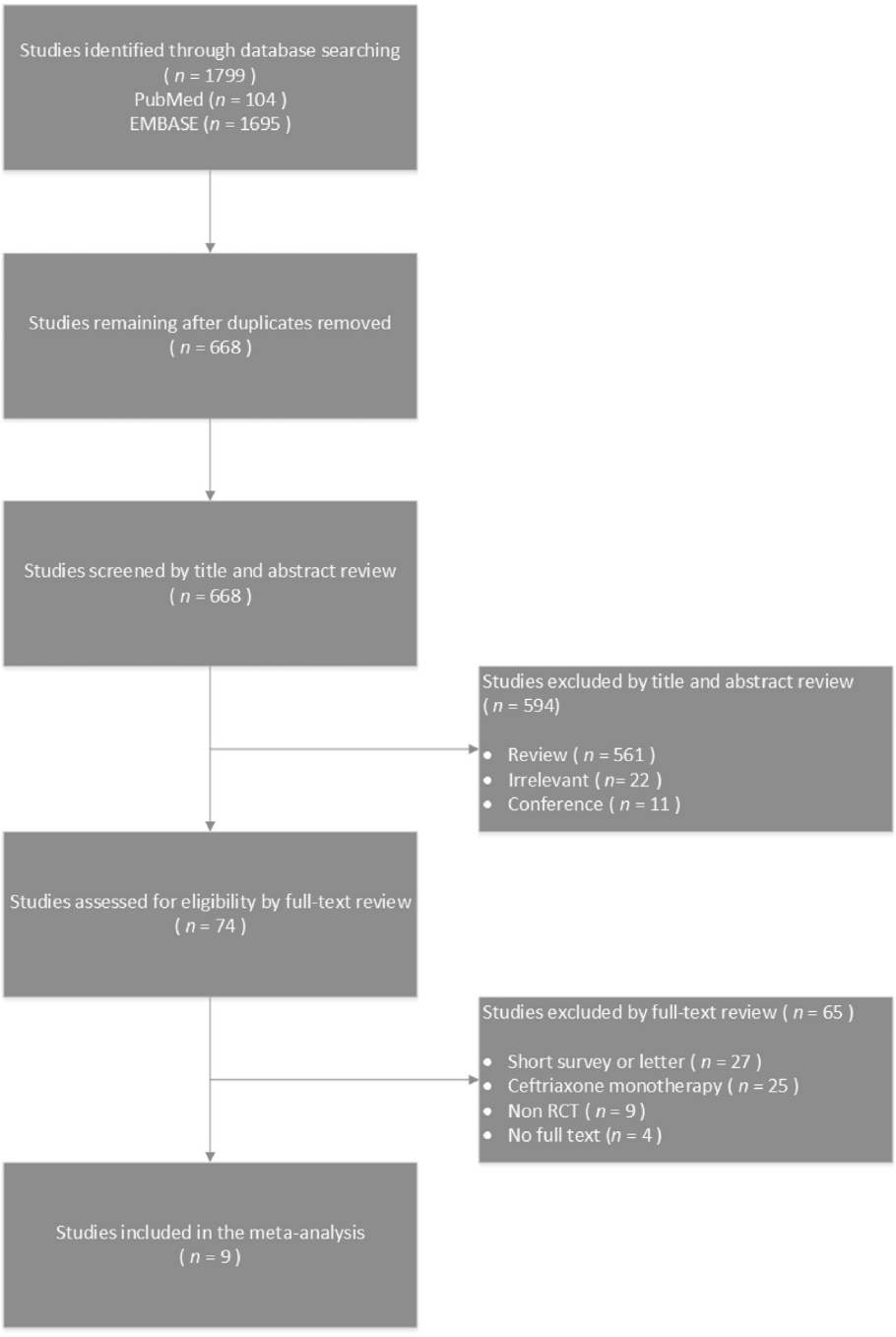

Fig. 2. Risk of bias graph and summary.

moxifloxacin had a favorable microbiological treatment success rate compared with β-lactam-based regimens [14]. It seemed that for microbiological treatment success, ceftriaxone combination therapy was not superior to respiratory fluoroquinolones monotherapy.

Several potential limitations of this meta-analysis should be noted. First, the included studies in this meta-analysis were open-label trials. Consequently, the relatively low quality of the included trials may affect our findings. Second, our meta-analysis was based on a small number of studies, and the results in this paper may also be affected. Third, one RCT [25] assessed the efficacy and safety in the elderly and one RCT [24] included only patients with mycoplasma pneumonia, making these results also less applicable to the general population.

The findings of this meta-analysis suggest that ceftriaxone combination therapy was as efficacious as respiratory fluoroquinolones monotherapy, but the drug-related AEs were lower in the ceftriaxone combination therapy regimen. Given the limitation of quantity and quality of these included studies, more high-quality RCTs are required to explore the conclusion further.

Conflicts of interest

The authors declare no conflicts of interest.

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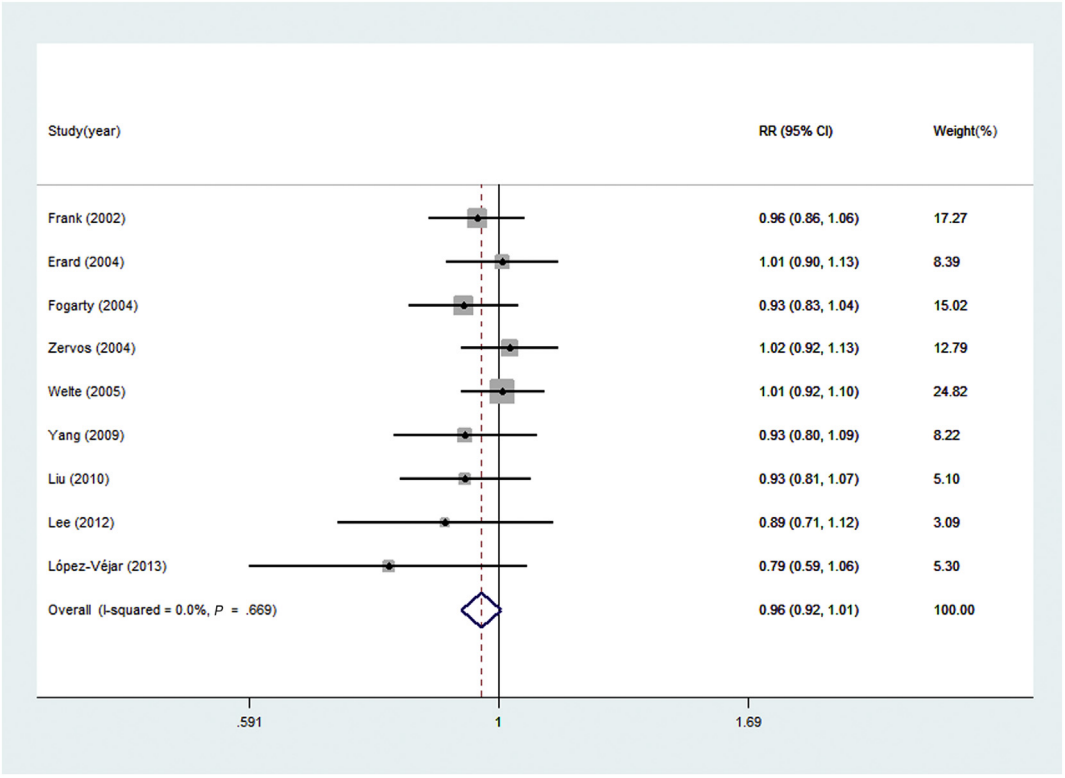

Fig. 3. Forest plots of treatment success, comparing respiratory ceftriaxone combination therapy with fluoroquinolone monotherapy for the treatment of CAP, based on the clinically evaluable population.

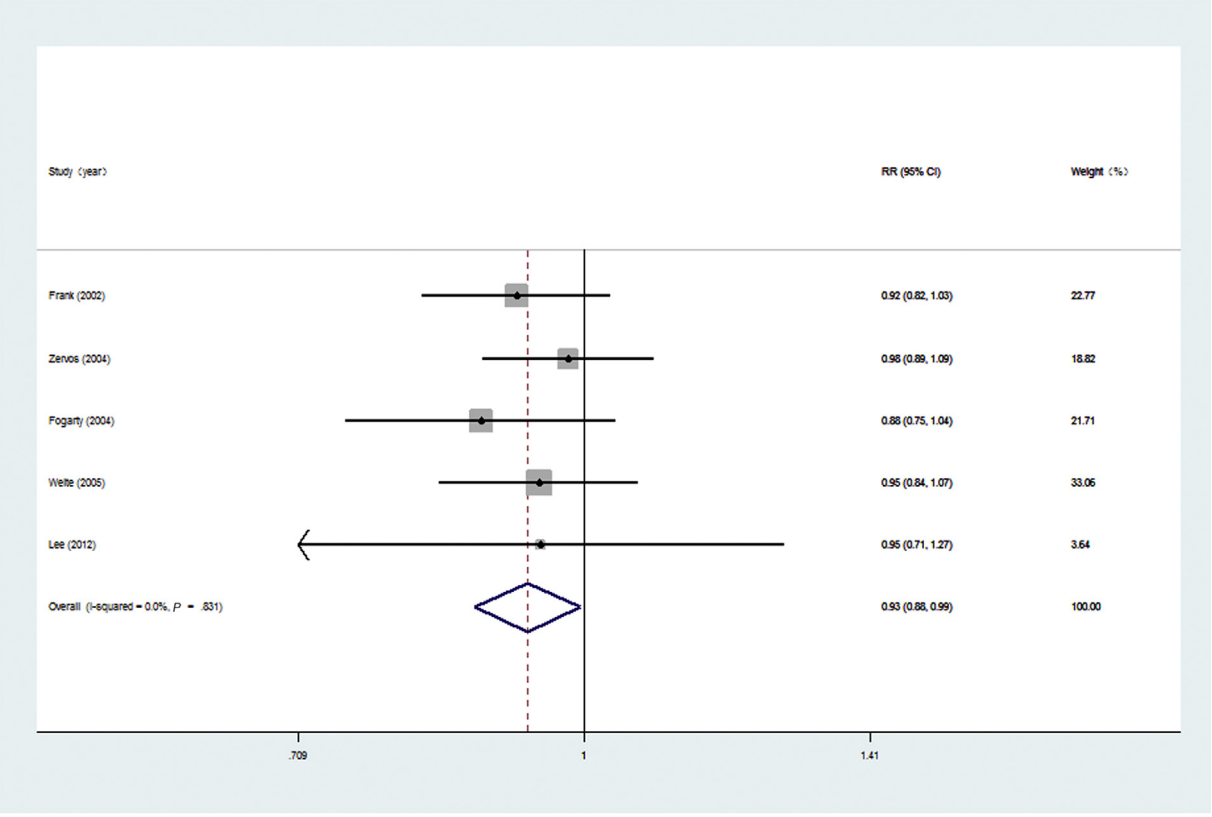

Fig. 4. Forest plots of treatment success, comparing respiratory ceftriaxone combination therapy with fluoroquinolones monotherapy for the treatment of CAP, based on the ITT population.

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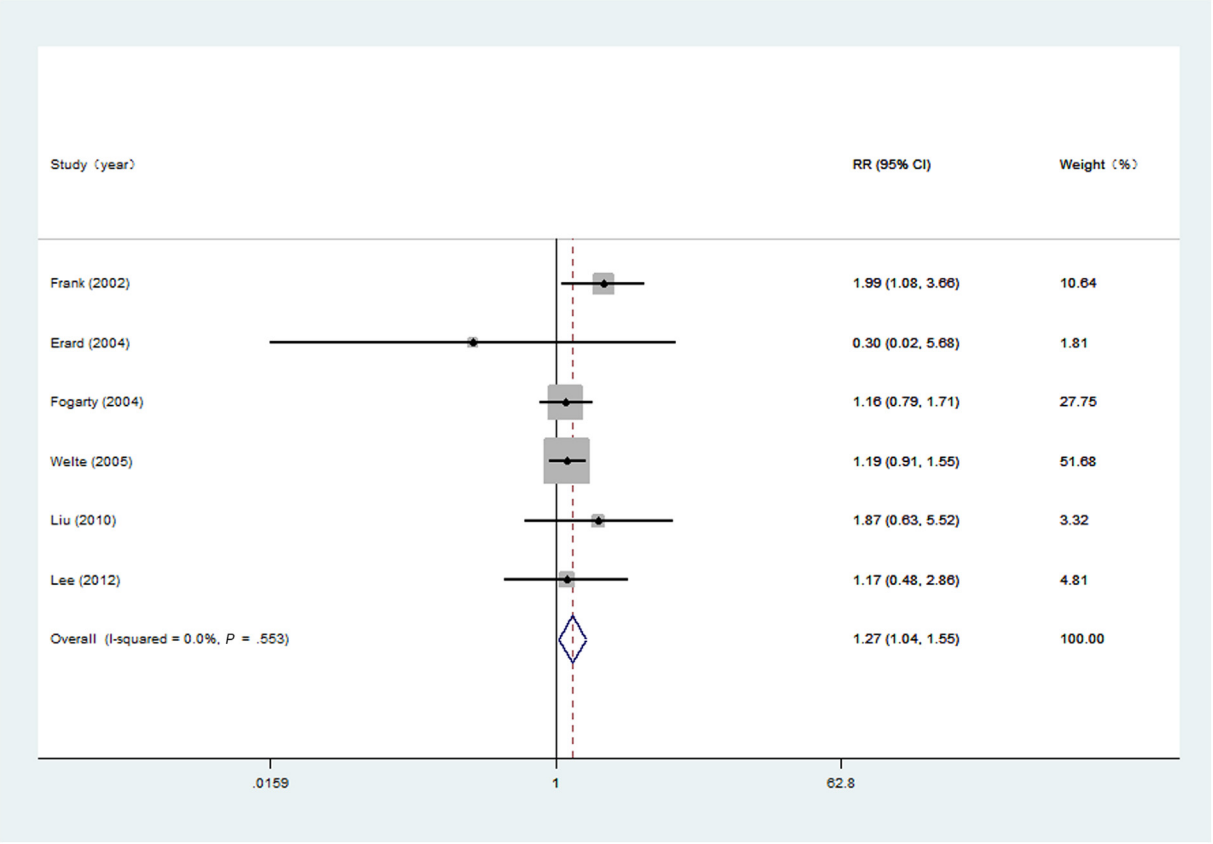

Fig. 5. Forest plots of drug-related adverse effects comparing ceftriaxone combination therapy with respiratory fluoroquinolone monotherapy.

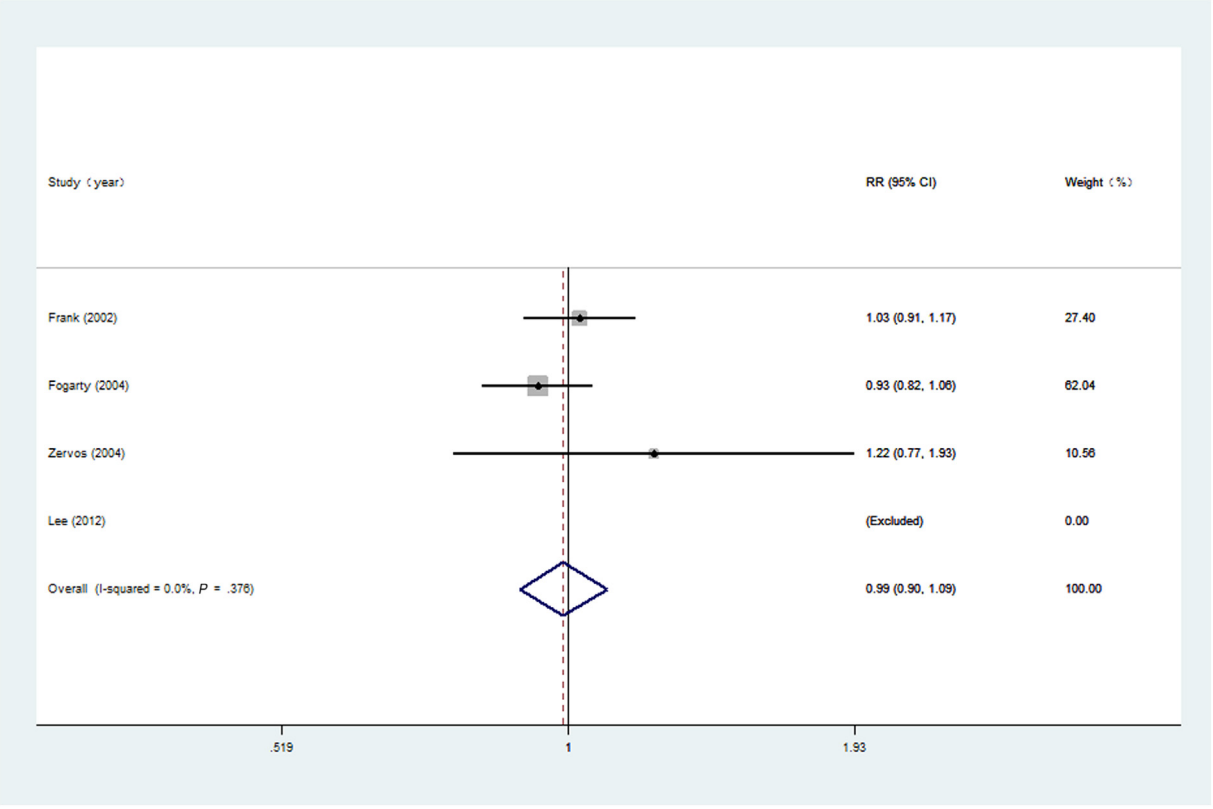

Fig. 6. Forest plots of microbiological treatment success comparing ceftriaxone combination therapy with respiratory fluoroquinolone monotherapy.

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