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Review Article

Effects of BCG-PSN on the Levels of Inflammatory Factors and Th1/Th2 Differentiation in Chronic Spontaneous Urticaria: Meta-Analysis and Systematic Review

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Background. Bacillus Calmette–Guerin polysaccharide nucleic acid (BCG-PSN), as an immune modulator, can effectively regulate the immune function of the body, control the release of histamine inflammatory substances, and achieve allergic effects against chronic spontaneous urticaria (CSU). This study aimed to evaluate the effectiveness of BCG-PSN on the levels of inflammatory factors and Th1/Th2 differentiation in CSU. *Methods*. A systemic literature search of BCG-PSN treatment of CSU was performed using the PubMed, Cochrane Library, Web of Science, CBM, and other databases. A quantitative meta-analysis was conducted according to the guidelines of the Cochrane Handbook. Review manager software 5.4 was used for meta-analysis. *Results*. Twenty-seven studies pertaining to 2840 patients were included. The duration of treatment was 4 to 12 weeks. BCG-PSN can increase CD3+T levels (MD = 6.06; 95% CI: 5.30 to 6.82; $p < 0.00001$; $I^2 = 31\%$), CD4+T levels (MD = 5.41; 95% CI: 4.82 to 6.01; $p < 0.00001$; $I^2 = 40\%$), and CD4+/CD8+(MD = 0.33; 95% CI: 0.28 to 0.38; $p < 0.00001$; $I^2 = 15\%$); at the same time, BCG-PSN can downregulate CD8+T levels (MD = −3.28; 95% CI: −3.82 to −2.74; $p < 0.00001$; $I^2 = 32\%$). Furthermore, BCG-PSN could downregulate IL-4 levels (MD = −4.06, 95% CI: −5.15 to −2.97, $p < 0.00001$; $I^2 = 0\%$), TNF-α levels (MD = −2.34; 95% CI: −3.01 to −1.66; $p < 0.00001$; $I^2 = 26\%$) and upregulate IL-10 levels (MD = 25.59, 95% CI: 23.50 to 27.69, $p < 0.00001$; $I^2 = 0\%$) and INF-γ levels (MD = 4.62, 95% CI: 3.79 to 5.45, $p < 0.00001$; $I^2 = 5\%$). *Conclusions*. BCG-PSN can regulate the levels of inflammatory factors and Th1/Th2 differentiation in CSU. However, the long-term effectiveness and more objective experimental indicators of BCG-PSN remain to be further studied. *Trial Registration*. This trial is registered with PROSPERO ID: CRD42022332475.

1. Introduction

CSU is characterized by transient wheal or vascular edema without obvious trigger factors, with recurrent symptoms for more than 6 weeks [1]. It affects about 1% of the global population of all ages, and more than 25% of cases do not respond to first-line and second-line treatments, while third-line and fourth-line therapies just can control two-thirds of antihistamine-resistant patients [2]. CSU impairs quality of life and affects productivity, and more than 30% of CSU patients have anxiety and depression [3, 4]. At present, it is believed that CSU is related to autoimmunity [5, 6], and mast cell activation is the key to CSU [7]. Degranulation of mast cells is considered the initial event that causes symptoms, and the release of histamine and a large number of mast cell-derived cytokines stimulate sensory nerves, causing vasodilation and extravasation of tissue fluid, which lead to pruritus, rubella, and angioedema. At the same time, chemokines secreted by mast cells cause T lymphocytes, eosinophils, monocytes, and basophils to migrate to the skin and form non-necrotizing cell infiltration in the blood vessels around skin venules [8].

These infiltrating cells are mainly Th2 cells, with a small amount of Th1 cells and related cytokines serving as proinflammatory effectors [9].

Currently, all guidelines recommend the use of a single conventional dose of sgAH as first-line treatment [10–12]. SgAH can antagonize histamine produced by mast cell, but it is not good at regulating the immune system of CSU patients, so sgAH can only control some mild symptoms and cannot effectively reduce the recurrence rate. Up to 50% of the patients are not responded to licensed doses of sgAH; even at higher doses, there is a subgroup of patients refractory to antihistamine treatment [13]. Although biologic drugs have emerged as a new therapeutic direction for CU [14], omalizumab and its biosimilar drugs such as remibrutinib, rilzabrutinib, and fenebrutinib have been studied; nevertheless, at least one-fifth is not sufficiently controlled by guideline-recommended treatment with sgAH and add-on therapy with omalizumab [15]. Therefore, returning to the nature of disease immune imbalance and regulating immune function are still worth studying. BCG-PSN is prepared by using thermophenol method to extract active components from BCG, in which polysaccharides account for 75% and nucleic acid accounts for 20%. As an immune regulator, BCG-PSN can regulate T cell differentiation and maturation of peripheral immune organs and central immune organs, maintaining the balance between T cell subsets and helper T cell subtypes.

Although BCG-PSN has been widely used in clinical allergic diseases and its clinical efficacy has been proved, there has been no systematic statistical analysis on the regulation of immune function and the level of inflammatory factors. Based on the analysis of clinical controlled trial data, this study systematically evaluated the regulation of BCG-PSN on serum inflammatory factors and immune cells in the treatment of CSU.

2. Materials and Methods

The protocol for the meta-analysis has been registered in the PROSPERO database (https://www.crd.York.ac.uk/PROSPERO) and the registration number is CRD42022332475.

2.1. Information Sources and Search Strategy. PubMed, Cochrane Library, Web of Science, Wan Fang (WF) Database, China Biology Medicine disc (CBM), China Science and Technology Journal Database (VIP), and China National Knowledge Infrastructure (CNKI) were searched and collected RCT studies of BCG-PSN in the treatment of CSU. The last search for all databases was updated on October 31, 2022. The search terms included "urticarial," "chronic urticarial," "chronic spontaneous urticarial," "Bacillus Calmette–Guerin polysaccharide nucleic acid," "BCG polysaccharide nucleic acid," "inflammatory factor," "Th1/Th2," and "clinical study."

(1) Study design: The study only included RCTs.

(2) Population: The study will consider participants given the diagnosis of CSU, irrespective of their gender, severity, education, and disease duration.

(3) Intervention: The intervention methods should be limited to use BCG-PSN; and in combination with sgAH, the combination drugs must be the same as the control group.

(4) Comparator: The control measure should be defined as sgAH, with clear reporting of the dosage and course of treatment.

(5) Outcomes: The outcome measures include the T cell levels and proportion, CD3+, CD4+, CD8+, and CD3+/CD8+; inflammatory factor levels, IL2, IL4, and IL10; INF-γ; TNF-α; histamine levels; clinical effective rate; recurrence rate; and adverse events.

2.2. Exclusion Criteria. Exclusion of course includes the following items: firstly, literature related to the same study, as well as duplicate publications. Secondly, it is not possible to obtain literature or full texts with data through various means. Finally, all outcome indicators were not counted according to the same evaluation criteria.

2.3. Study Selection and Data Management. Two researchers independently screened the literature and deleted the repeated articles by reading the abstracts. Then, by reading the full text, they excluded the literature that did not meet the inclusion criteria and recorded the reasons for the deletion. Last, the content of data extraction is recommended to include publication characteristics of the literature, basic characteristics of research objects, and methodological characteristics. The extracted data are cross checked; a third reviewer will be settled to consulting, if necessary [16].

2.4. Risk of Bias Assessment. Quality assessment was assessed according to the "risk of bias" tool based on the Cochrane Handbook. The evaluation includes seven items, random sequence generation, allocation concealment, blinding method, incomplete data assessment, selective reporting, and other bias. Evidence quality was divided into "low bias risk," "unclear bias risk," and "high bias risk." Then, the review manager 5.4 should be used for the display of the bias risk assessment chart drawn.

2.5. Data Synthesis and Analysis. Review manager 5.4 software was used to analyze the data. Binary variables were statistically analyzed by odds ratio (OR) and continuous variables were statistically analyzed by mean difference (MD). 95% confidence interval (95% CI) was used to evaluate each effect index. The heterogeneity of the study was evaluated according to the value of I^2. The random effects model was used for analysis if $I^2 \geq 50\%$; otherwise, the fixed effects model was used for analysis when $I^2 < 50\%$, and the evaluation results were shown in forest maps. When the results showed a high degree of heterogeneity, we used sensitivity analysis by excluding literature one by one to explore the stability of the results. Finally, a bias test was performed on the effective rate, and the results were displayed in a funnel chart.

3. Results

3.1. Search Result. A total of 1366 studies were retrieved, and 425 remained after screening titles and abstracts. We read the full text of these 42 studies, and by excluding 15 studies, the 27 researches were included finally [17–43]. All trials were designed as clinical research and used the parallel group design. The screening process is shown in Figure 1.

3.2. The Characteristics of Included Trials. 27 RCTs were included with 2840 participants, 1433 in the experimental group and 1407 in the control group. Treatment ranges from 4 weeks to 12 weeks. The characteristics of the included trials are shown in Table 1.

3.3. Risk of Bias in Included Trials. Ten studies [19, 21, 24, 27, 33, 34, 36–38, 41] reported methods of randomizing participants by using random number tables, which were considered low risk of bias; 13 trials mentioned randomization but did not explain the randomization method in detailed [17, 18, 20, 23, 25, 26, 28, 30, 31, 35, 39, 40, 42]; these were considered unclear risk of bias; and 3 trials [29, 32, 43] were grouped by treatment approach and one study [22] by visit sequence; the four studies were identified as high-risk bias. None of the studies mentioned blindness and allocation hiding, which were considered unclear risk of bias. All of these studies have no patients fell off, and all studies reported test indicators as planned, and there was no selective reporting of research results. It is unclear whether there is other bias (Figure 2).

3.4. Primary Outcomes

3.4.1. The T Lymphocytes Levels and Proportions

(1) CD3+T Lymphocyte Levels. A total of 8 studies [18, 19, 24, 26, 29, 31, 40, 43] evaluated the CD3+T lymphocytes, comprising 777 patients, and we used random effects model for statistical analysis ($I^2 = 76\%$ and $p = 0.0001$). The results showed that the experimental group was significantly better than the control group in increasing CD3+T lymphocytes (MD = 6.38, 95% CI: 4.94 to 7.82, $p < 0.00001$). In order to decrease the heterogeneity, we eliminated the literature one by one and found that after removing ALMR [43] ($I^2 = 31\%$ and $p = 0.19$), the fixed effect model was used for subsequent statistical analysis. The results showed that the experimental group was more effective (MD: 6.06; 95% CI: 5.30 to 6.82; $p < 0.00001$) (Figure 3).

(2) CD4+T Lymphocytes Levels. Nine studies [18, 19, 22, 24, 26, 29, 31, 38, 43] evaluated the CD4+T lymphocytes, comprising 889 patients, and we used random effects model for statistical analysis ($I^2 = 98\%$ and $p < 0.00001$). The results showed that the experimental group was better than the control group in increasing CD4+T lymphocytes (MD = 7.79, 95% CI: 4.08 to 11.51, $p < 0.0001$). When we eliminated the Wang [18] and Ren et al. [19] ($I^2 = 40\%$ and $p = 0.12$), the fixed effect model was used for subsequent statistical analysis; the result was stable and reliable (MD: 5.41; 95% CI: 4.82 to 6.01; $p < 0.00001$) (Figure 4).

(3) CD8+T Lymphocytes Levels. A total of 8 studies [18, 19, 22, 24, 26, 29, 31, 38] evaluated the CD8+T lymphocytes, comprising 835 patients, and we used random effects model for statistical analysis ($I^2 = 85\%$ and $p < 0.00001$). The results showed that the experimental group was significantly better than the control group in downregulating CD8+T lymphocytes (MD = −2.98, 95% CI: −4.14 to −1.81, $p < 0.00001$); then, we eliminated the literature of Wang [18], Ren et al. [19], and Zhang et al. [26] ($I^2 = 32\%$ and $p = 0.21$); the fixed effect model was used for subsequent statistical analysis; the results showed that BCG-PSN was more effective (MD: −3.28; 95% CI: −3.82 to −2.74; $p < 0.00001$) (Figure 5).

(4) CD4+/CD8+ T Lymphocytes Proportions. A total of 8 studies [18, 19, 22, 24, 26, 29, 31, 38] evaluated the CD4+/CD8+T lymphocytes proportions, comprising 835 patients, and we used random effects model for statistical analysis ($I^2 = 89\%$ and $p < 0.00001$). The results showed that the experimental group was significantly better than the control group in upregulating CD4+/CD8+T lymphocytes proportions (MD = 0.33, 95% CI: 0.22 to 0.44, $p < 0.00001$). In order to test sensitivity, we eliminated the literature of Ren et al. [19] and Qian [29] ($I^2 = 15\%$ and $p = 0.32$); the results show that it is stable and reliable (MD: 0.33; 95% CI: 0.28 to 0.38; $p < 0.00001$) (Figure 6).

3.4.2. Inflammatory Factors Levels

(1) The IL-2 Levels. A total of 3 studies [17, 33, 39] evaluated the IL-2 levels, comprising 262 patients. The fixed effects model was used for meta-analysis ($I^2 = 0\%$ and $p = 0.60$); and the outcome showed that there was no statistical difference on the IL-2 levels (MD = 2.16, 95% CI: −0.88 to 5.20, $p = 0.16$) (Figure 7).

(2) The IL-4 Levels. A total of 4 studies [17, 23, 33, 34] evaluated the IL-4 levels, comprising 479 patients. The fixed effects model was used for meta-analysis ($I^2 = 0\%$ and $p = 0.90$). The results showed that the experimental group was significantly better than the control group in downregulating IL-4 levels (MD = −4.06, 95% CI: −5.15 to −2.97, $p < 0.00001$) (Figure 8).

(3) The TNF-α Levels. A total of 7 studies [23, 26, 27, 35, 37, 41, 42] evaluated the TNF-α levels, comprising 835 patients, and the random effects model was used for statistical analysis ($I^2 = 51\%$ and $p = 0.06$). The results showed that the experimental group was significantly better than the control group in downregulating TNF-α levels (MD = −2.80, 95% CI: −3.76 to −1.85, $p < 0.00001$). In order to test the sensitivity, we eliminated the literature of Li [23] ($I^2 = 26\%$ and $p = 0.24$); the results show that it is stable and reliable (MD: −2.34; 95% CI: −3.01 to −1.66; $p < 0.00001$) (Figure 9).

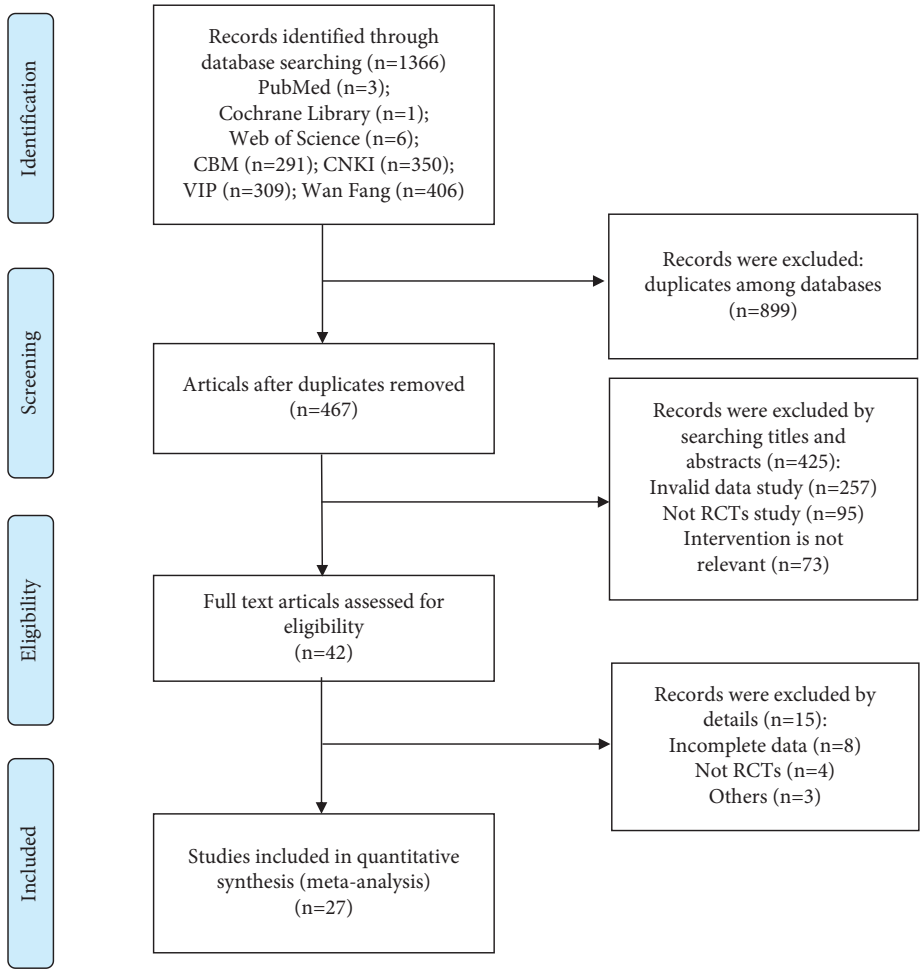


Figure 1: Flow diagram of study selection and identification.

(4) The INF-γ Levels. A total of 6 studies [23, 26, 27, 33, 35, 39] evaluated the INF-γ levels, comprising 746 patients. The fixed effects model was used for meta-analysis ($I^2 = 5\%$ and $p = 0.39$), and the results showed that the experimental group was significantly better than the control group in upregulating INF-γ levels (MD = 4.62, 95% CI: 3.79 to 5.45, $p < 0.00001$) (Figure 10).

(5) The Histamine Levels. A total of 7 studies [20, 22, 25, 28, 30, 32, 36] evaluated the histamine levels, comprising 722 patients; 4 studies [20, 22, 25, 28] were measured in mmol/L, while 3 studies [30, 32, 36] were measured in ng/ml. The random effects model was used for meta-analysis, and the results showed that the experimental group was significantly better than the control group in downregulating histamine levels ($p < 0.01$) (Figure 11).

3.5. Secondary Outcomes

3.5.1. The Clinical Effective Rate. A total of 23 studies [17–20, 22, 24, 25, 28–43] evaluated the CER, comprising 2344 patients. The fixed effects model should be used for meta-analysis ($I^2 = 0\%$, $p = 0.84$). The results showed that the experimental group was significantly better than the control group in CER (OR = 5.56, 95% CI: 4.22 to 7.33, $p < 0.00001$) (Figure 12).

3.5.2. The Recurrence Rates. A total of 6 studies [20, 24, 29, 31, 33, 40] evaluated the recurrence rates, comprising 699 patients. The fixed effects model should be used for meta-analysis ($I^2 = 0\%$ and $p = 0.83$). The outcome showed that the experimental group was significantly superior in terms of total clinical effective rate (OR = 0.23, 95% CI: 0.14 to 0.36, $p < 0.00001$) (Figure 13).

3.5.3. The Adverse Events. 12 studies [17, 19, 20, 22–24, 26, 27, 29, 34, 35, 41] evaluated the adverse events, comprising 1372 patients. The fixed effects model should be used for meta-analysis ($I^2 = 0\%$ and $p = 0.63$). The outcome showed that there was no statistical difference in the adverse events (OR = 1.02, 95% CI: 0.69 to 1.53, $p = 0.91$) (Figure 14).

3.6. Evaluation of Publication Bias. We used review manager software 5.4 to evaluate publication bias based on the clinical efficacy rates, and the funnel plot indicated that the studies were approximately evenly and symmetrically

Table 1: The characteristics of the included trials.

Study ID	Country	Sample size (M/F)	Age (mean ± SD), years	Course of disease	Course of treatment	Intervention vs. control	Treatment frequency	Outcomes
De-Feng et al. [17]	China	T: 42 (21/21) C: 42 (25/17)	T: 37.14 ± 9.38 C: 38.61 ± 9.58	T: 3.06 ± 0.72, y C: 3.11 ± 0.88, y	8 w	BCG-PSN + olopatadine vs. olopatadine	5 mg, bid; 2 ml, qod	CER, AE, IgE, EOS, IL-2, TNF-α, IL-4, and IL-10
Wang [18]	China	T: 42 (23/19) C: 42 (22/20)	T: 42.39 ± 2.05 C: 41.26 ± 1.8	NR	4 w	BCG-PSN + desloratadine vs. desloratadine	5 mg, qd; 2 ml, qod	CER, CD3+, CD4+, CD8+, and CD4+/CD8+
Ren et al. [19]	China	T: 47 (22/25) C: 43 (21/22)	T: 35.87 ± 8.92 C: 37.93 ± 8.40	T: 43.51 ± 23.42, m C: 40.16 ± 21.35, m	12 w	BCG-PSN + olopatadine vs. olopatadine	5 mg, bid; 1 ml, qod	CER, AE, CD3+, CD4+, CD8+, and CD4+/CD8+
Li et al. [20]	China	T: 40 (23/17) C: 40 (22/18)	T: 17.40 ± 2.11 C: 17.33 ± 2.01	T: 8.92 ± 2.89, w C: 8.89 ± 2.90, w	12 w	BCG-PSN + setastine vs. setastine	1 mg, bid; 1 ml, qod	CER, AE, RR, and H
Fan [21]	China	T: 55 (28/27) C: 55 (30/25)	T: 34.61 ± 2.52 C: 34.50 ± 2.43	T: 2.24 ± 0.36, y C: 2.17 ± 0.22, y	12 w	BCG-PSN + fexofenadine vs. fexofenadine	30 mg, bid; 1 ml, qod	IL-10
Shen and Zhao [22]	China	T: 56 (26/30) C: 56 (24/32)	T: 41.65 ± 9.33 C: 42.16 ± 9.85	T: 11.54 ± 3.28, w C: 11.38 ± 3.46, w	6 w	BCG-PSN + ebastine vs. ebastine	10 mg, qd; 2 ml, qod	CER, AE, CD4+, CD8+, CD4+/CD8+, H, IgE, and H
Li [23]	China	T: 48 (20/28) C: 47 (21/26)	T: 37.0 ± 6.89 C: 36.9 ± 6.75	T: 4.01 ± 1.32, y C: 3.86 ± 1.25, y	4 w/8 w	BCG-PSN + cetirizine vs. cetirizine	5 mg, qd; 2 ml, qod	TNF-α, INF-γ, IL-4, and AE
Dong [24]	China	T: 43 (29/14) C: 43 (27/16)	T: 41.09 ± 8.53 C: 40.77 ± 7.99	T: 2.69 ± 0.86, y C: 2.73 ± 0.90, y	4 w	BCG-PSN + desloratadine vs. desloratadine	5 mg, qd; 2 ml, qod	CER, AE, RR, CD3+, CD4+, CD8+, and CD4+/CD8+
Wang [25]	China	T: 50 (NR/NR) C: 50 (NR/NR)	T: 18.5 ± 1.8 C: 17.4 ± 1.8	T: 9.2 ± 3.3, w C: 8.9 ± 2.9, w	4 w	BCG-PSN + ebastine vs. ebastine	20 mg, qd; 1 ml, qod	CER and H
Zhang [26]	China	T: 51 (29/22) C: 51 (27/24)	T: 35.3 ± 11.5 C: 36.4 ± 10.9	T: 2.3 ± 0.9, y C: 2.1 ± 0.7, y	6 w	BCG-PSN + cetirizine vs. cetirizine	10 mg, qd; 2 ml, qod	CD3+, CD4+, CD8+, CD4+/CD8+, TNF-α, INF-γ, IgE, and AE
Ji [27]	China	T: 95 (47/48) C: 94 (46/48)	T: 31.8 ± 2.0 C: 32.6 ± 2.1.6	T: 1.7 ± 0.6, y C: 1.6 ± 0.5, y	5 w	BCG-PSN + cetirizine vs. cetirizine	10 mg, qd; 1 ml, qod	TNF-α, INF-γ, and AE
Yang and Shen [28]	China	T: 75 (41/34) C: 75 (40/35)	T: 36.72 ± 1.83 C: 37.13 ± 1.22	T: 11.07 ± 1.46, w C: 10.31 ± 1.82, w	3 w	BCG-PSN + ebastine vs. ebastine	20 mg, qd; 1 ml, qod	CER and H
Qian [29]	China	T: 106 (48/58) C: 100 (50/50)	T: 36.7 ± 4.6 C: 38.1 ± 5.1	T: 2.2 ± 1.7, y C: 2.3 ± 1.4, y	4 w	BCG-PSN + desloratadine vs. desloratadine	5 mg, qd; 2 ml, qod	CER, AE, RR, CD3+, CD4+, CD8+, and CD4+/CD8+
Li [30]	China	T: 40 (30/10) C: 40 (28/12)	T: 36.12 ± 10.13 C: 36.24 ± 10.67	T: 6.35 ± 2.13, m C: 6.34 ± 2.15, m	4 w	BCG-PSN + ebastine vs. ebastine	10 mg, qd; 1 ml, qod	CER, IL-10, and H
Jiang [31]	China	T: 41 (24/17) C: 41 (21/20)	T: 40.3 ± 6.2 C: 39.7 ± 5.8	T: 2.0 ± 0.6, y C: 1.8 ± 0.5, y	4 w	BCG-PSN + desloratadine vs. desloratadine	5 mg, qd; 2 ml, qod	CER, RR, CD3+, CD4+, CD8+, and CD4+/CD8+
Lin [32]	China	T: 46 (22/24) C: 46 (23/23)	T: 32.29 ± 2.36 C: 32.61 ± 2.43	NR	12 w	BCG-PSN + fexofenadine vs. fexofenadine	30 mg, bid; 1 ml, qod	CER, H, IL-10, and H

Table 1: Continued.

Study ID	Country	Sample size (M/F)	Age (mean ± SD), years	Course of disease	Course of treatment	Intervention vs. control	Treatment frequency	Outcomes
Mou and Zheng [33]	China	T: 80 (48/32) C: 80 (46/34)	T: 43.4 ± 3.4 C: 44.6 ± 3.7	T: 18.2 ± 1.8, m C: 18.5 ± 1.5, m	4 w	BCG-PSN + levocetirizine vs. levocetirizine	5 mg, qd; 2 ml, qod	CER, RR, INF-γ, IL-2, IL-4, and IL-10
Yang and Sun [34]	China	T: 70 (NR/NR) C: 70 (NR/NR)	53.6 ± 1.98	34.4 ± 26.9, m	8 w	BCG-PSN + mizolastine vs. mizolastine	10 mg, qd; 2 ml, qod	CER, AE, IL-4, and sVCAM-1
Pan [35]	China	T: 41 (241/19) C: 41 (23/18)	T: 32.0 ± 2.5 C: 31.5 ± 2.2	T: 1.7 ± 0.7, y C: 1.5 ± 0.6, y	6 w	BCG-PSN + cetirizine vs. cetirizine	10 mg, qd; 1 ml, qod	CER, AE, TNF-α, and INF-γ
Liu [36]	China	T: 54 (25/29) C: 54 (31/23)	T: 35.94 ± 8.16 C: 36.83 ± 10.06	NR	4 w	BCG-PSN + ebastine vs. ebastine	10 mg, qd; 1 ml, qod	CER and H
Congou and Chen [37]	China	T: 45 (27/18) C: 45 (29/16)	T: 33.28 ± 8.56 C: 34.06 ± 8.05	T: 2.75 ± 1.18, y C: 2.83 ± 1.23, y	60 d	BCG-PSN + cetirizine vs. cetirizine	10 mg, qd; 2 ml, qod	CER, TNF-α, C5α, LI-10, IL-18, and IgE
Li et al. [38]	China	T: 37 (17/20) C: 36 (25/11)	T: 36 ± 2 C: 28 ± 4	NR	36 d	BCG-PSN + mizolastine vs. mizolastine	10 mg, qd; 1 ml, qod	CER, CD3+, CD4+, CD8+, and CD4+/CD8+
An et al. [39]	China	T: 62 (NR/NR) C: 56 (NR/NR)	35.88 ± 17.28	NR	4 w	BCG-PSN + fexofenadine vs. fexofenadine	60 mg, bid; 2 ml, qod	CER, IL-2, IL-4, INF-γ, and IgE
Liu et al. [40]	China	T: 46 (20/26) C: 39 (18/21)	T: 19–68 C: 18–66	NR	36 d	BCG-PSN + fexofenadine vs. fexofenadine	60 mg, bid; 1 ml, qod	CER, RR, and IgE
Zhao [41]	China	T: 53 (31/22) C: 53 (30/23)	T: 33.96 ± 8.75 C: 33.76 ± 8.81	T: 2.39 ± 1.54, y C: 2.28 ± 1.61, y	8 w	BCG-PSN + cetirizine vs. cetirizine	10 mg, qd; 2 ml, qod	CER, AE, INF-γ, IgE, C5α, LI-10, and IL-18
Wu et al. [42]	China	T: 41 (23/18) C: 41 (24/19)	T: 31.52 ± 2.2 C: 32.0 ± 2.5	T: 0.5–8.5, y C: 0.6–8.8, y	6 w	BCG-PSN + cetirizine vs. cetirizine	10 mg, qd; 1 ml, qod	CER, TNF-α, and INF-γ
Alemige [43]	China	T: 27 (15/12) C: 27 (14/13)	T: 43.52 ± 1.22 C: 39.58 ± 1.24	T: 13.14 ± 0.12, w C: 13.18 ± 0.11, w	4 w	BCG-PSN + cetirizine vs. cetirizine	10 mg, qd; 1 ml, qd	CER, TNF-α, LI-6, CD3, and CD4

Note. NR, no report; y, year; w, week; CER, clinical effective rate; RR, the recurrence rate; AE, adverse events; H, histamine levels.

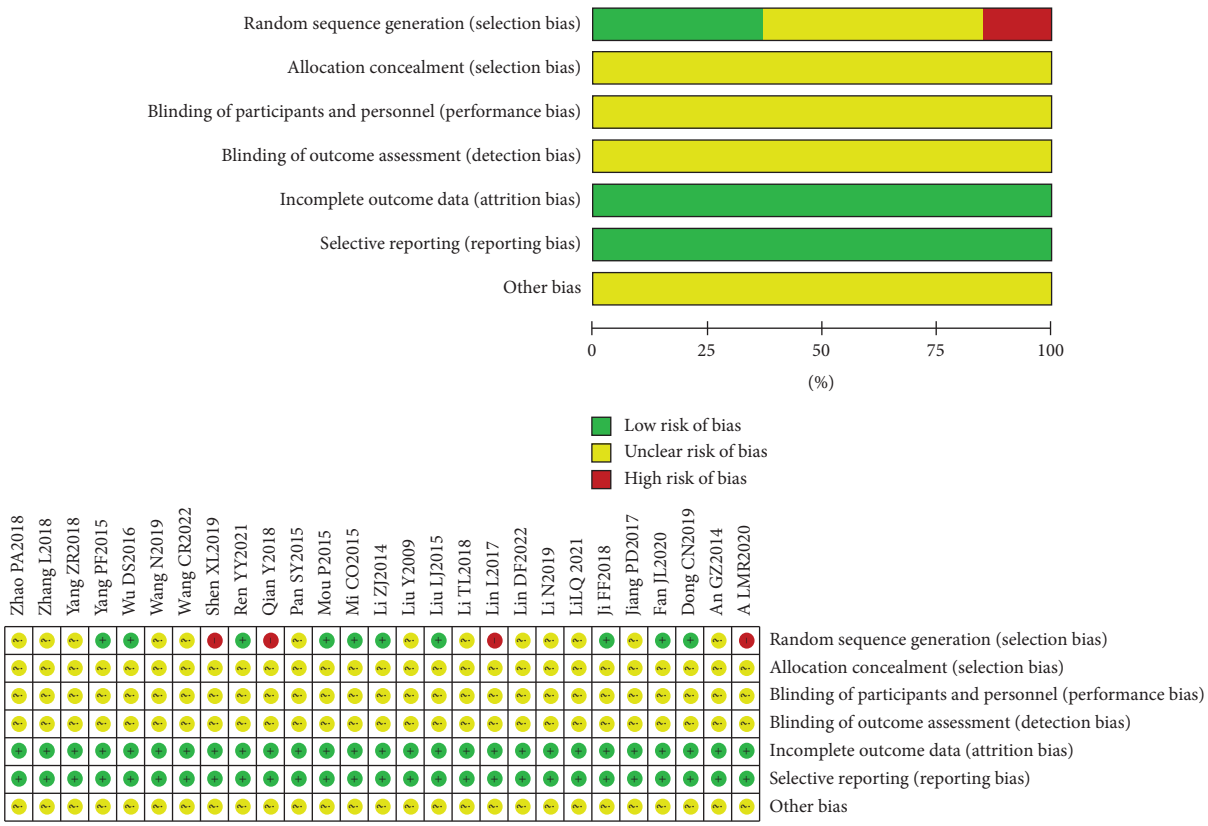
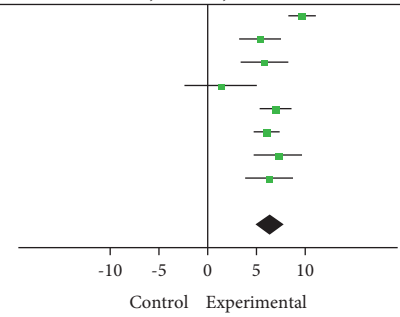


Figure 2: Assessment of risk of bias. (a) Risk of bias graph and (b) risk of bias summary.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Random, 95% CI
A LMR2020	75.53	2.82	27	65.85	2.28	27	15.1	9.68 [8.31, 11.05]
Dong CN2019	65.24	5.09	43	59.88	5.22	43	12.5	5.36 [3.18, 7.54]
Jiang PD2017	65.45	5.71	41	59.67	5.6	41	11.6	5.78 [3.33, 8.23]
Li ZJ2014	66.23	8.8	37	64.9	7.22	36	8.1	1.33 [-2.36, 5.02]
Qian Y2018	67.26	6.1	106	60.33	5.9	100	14.2	6.93 [5.29, 8.57]
Ren YY2021	70.6	3.09	47	64.56	3.28	43	15.2	6.04 [4.72, 7.36]
Wang CR2022	68.25	6.56	42	61.05	4.85	42	11.5	7.20 [4.73, 9.67]
Zhang L2018	63.68	6.34	51	57.39	6.19	51	11.7	6.29 [3.86, 8.72]
Total (95% CI)			*394*			*383*	*100.0*	*6.38 [4.94, 7.82]*

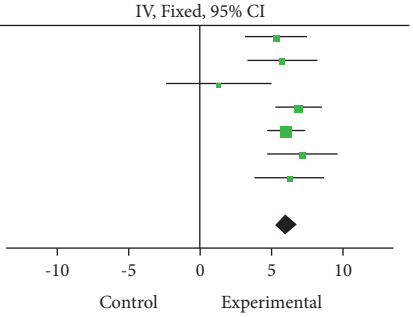
Heterogeneity: tau² = 3.10; chi² = 29.28, *df* = 7 (*P* = 0.0001); I^2 = 76%
Test for overall effect: *Z* = 8.68 (*P* < 0.00001)



(a)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Fixed, 95% CI
Dong CN2019	65.24	5.09	43	59.88	5.22	43	12.2	5.36 [3.18, 7.54]
Jiang PD2017	65.45	5.71	41	59.67	5.6	41	9.6	5.78 [3.33, 8.23]
Li ZJ2014	66.23	8.8	37	64.9	7.22	36	4.2	1.33 [-2.36, 5.02]
Qian Y2018	67.26	6.1	106	60.33	5.9	100	21.5	6.93 [5.29, 8.57]
Ren YY2021	70.6	3.09	47	64.56	3.28	43	33.2	6.04 [4.72, 7.36]
Wang CR2022	68.25	6.56	42	61.05	4.85	42	9.5	7.20 [4.73, 9.67]
Zhang L2018	63.68	6.34	51	57.39	6.19	51	9.8	6.29 [3.86, 8.72]
Total (95% CI)			*367*			*356*	*100.0*	*6.06 [5.30, 6.82]*

Heterogeneity: chi² = 8.70, *df* = 6 (*P* = 0.19); I^2 = 31%
Test for overall effect: *Z* = 15.62 (*P* < 0.00001)

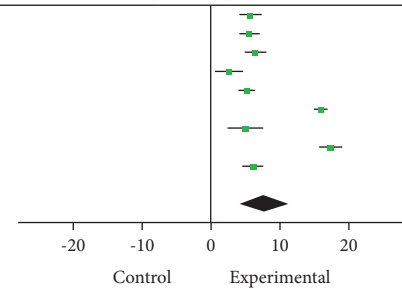


(b)

Figure 3: The outcome of the CD3+T lymphocytes. (a) All studies with the CD3+T lymphocytes and (b) without the heterogeneity studies.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Random, 95% CI
A LMR2020	45.23	2.48	27	39.51	3.48	27	11.1	5.72 [4.11, 7.33]
Dong CN2019	38.95	3.62	43	33.41	3.49	43	11.2	5.54 [4.04, 7.04]
Jiang PD2017	39.35	3.64	41	32.9	3.57	41	11.1	6.45 [4.89, 8.01]
Li ZJ2014	39.48	3.21	37	36.87	5.42	36	11.0	2.61 [0.56, 4.66]
Qian Y2018	41.46	4.8	106	36.27	3.6	100	11.2	5.19 [4.04, 6.34]
Ren YY2021	46.85	2.25	47	30.88	2.34	43	11.3	15.97 [15.02, 16.92]
Shen XL2019	40.14	7.52	56	35.11	6.23	56	10.8	5.03 [2.47, 7.59]
Wang CR2022	42.58	4.69	42	25.26	2.84	42	11.1	17.32 [15.66, 18.98]
Zhang L2018	40.39	3.92	51	34.28	4.01	51	11.1	6.11 [4.57, 7.65]
Total (95% CI)			*450*			*439*	*100.0*	*7.79 [4.08, 11.51]*

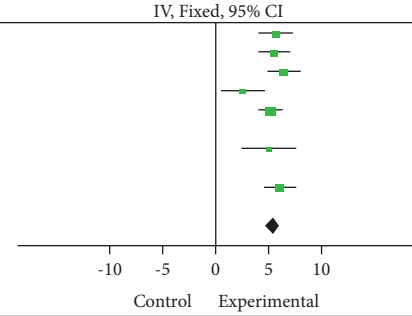
Heterogeneity: tau² = 31.69; chi² = 451.42, *df* = 8 (*P* < 0.00001); I^2 = 98%
Test for overall effect: *Z* = 4.11 (*P* < 0.0001)



(a)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Fixed, 95% CI
A LMR2020	45.23	2.48	27	39.51	3.48	27	13.7	5.72 [4.11, 7.33]
Dong CN2019	38.95	3.62	43	33.41	3.49	43	15.8	5.54 [4.04, 7.04]
Jiang PD2017	39.35	3.64	41	32.9	3.57	41	14.7	6.45 [4.89, 8.01]
Li ZJ2014	39.48	3.21	37	36.87	5.42	36	8.5	2.61 [0.56, 4.66]
Qian Y2018	41.46	4.8	106	36.27	3.6	100	26.8	5.19 [4.04, 6.34]
Ren YY2021	46.85	2.25	47	30.88	2.34	43		Not estimable
Shen XL2019	40.14	7.52	56	35.11	6.23	56	5.5	5.03 [2.47, 7.59]
Wang CR2022	42.58	4.69	42	25.26	2.84	42		Not estimable
Zhang L2018	40.39	3.92	51	34.28	4.01	51	15.1	6.11 [4.57, 7.65]
Total (95% CI)			*361*			*354*	*100.0*	*5.41 [4.82, 6.01]*

Heterogeneity: chi² = 10.06, *df* = 6 (*P* = 0.12); I^2 = 40%
Test for overall effect: *Z* = 17.76 (*P* < 0.00001)

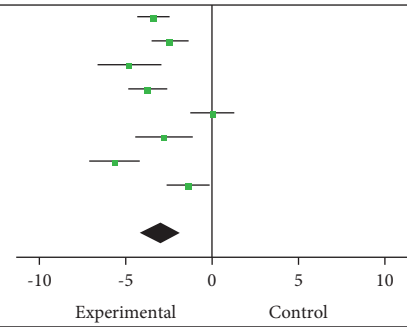


(b)

Figure 4: The outcome of the CD4+T lymphocytes. (a) All studies with the CD4+T lymphocytes and (b) without the heterogeneity studies.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Random, 95% CI
Dong CN2019	25.13	2.17	43	28.52	2.28	43	13.6	-3.39 [-4.33, -2.45]
Jiang PD2017	24.91	2.42	41	27.35	2.53	41	13.3	-2.44 [-3.51, -1.37]
Li ZJ2014	20.34	4.43	37	25.13	3.59	36	10.9	-4.79 [-6.64, -2.94]
Qian Y2018	22.82	4.6	106	26.54	3.7	100	13.1	-3.72 [-4.86, -2.58]
Ren YY2021	29.91	3	47	29.89	3.14	43	12.7	0.02 [-1.25, 1.29]
Shen XL2019	24.06	4.31	56	26.84	4.63	56	11.5	-2.78 [-4.44, -1.12]
Wang CR2022	21.98	3.85	42	27.63	2.89	42	12.1	-5.65 [-7.11, -4.19]
Zhang L2018	24.77	3.18	51	26.17	3.2	51	12.8	-1.40 [-2.64, -0.16]
Total (95% CI)			*423*			*412*	*100.0*	*-2.98 [-4.14, -1.81]*

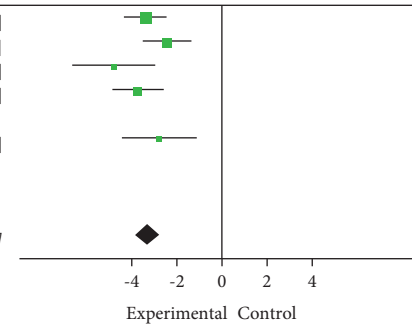
Heterogeneity: tau² = 2.38; chi² = 47.37, *df* = 7 (*P* < 0.00001); I^2 = 85%
Test for overall effect: *Z* = 4.99 (*P* < 0.00001)



(a)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Fixed, 95% CI
Dong CN2019	25.13	2.17	43	28.52	2.28	43	32.9	-3.39 [-4.33, -2.45]
Jiang PD2017	24.91	2.42	41	27.35	2.53	41	25.4	-2.44 [-3.51, -1.37]
Li ZJ2014	20.34	4.43	37	25.13	3.59	36	8.5	-4.79 [-6.64, -2.94]
Qian Y2018	22.82	4.6	106	26.54	3.7	100	22.5	-3.72 [-4.86, -2.58]
Ren YY2021	29.91	3	47	29.89	3.14	43		Not estimable
Shen XL2019	24.06	4.31	56	26.84	4.63	56	10.6	-2.78 [-4.44, -1.12]
Wang CR2022	21.98	3.85	42	27.63	2.89	42		Not estimable
Zhang L2018	24.77	3.18	51	26.17	3.2	51		Not estimable
Total (95% CI)			*283*			*276*	*100.0*	*-3.28 [-3.82, -2.74]*

Heterogeneity: chi² = 5.90, *df* = 4 (*P* = 0.21); I^2 = 32%
Test for overall effect: *Z* = 11.90 (*P* < 0.00001)



(b)

Figure 5: The outcome of the CD8+T lymphocytes. (a) All studies with the CD8+T lymphocytes and (b) without the heterogeneity studies.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Random, 95% CI
Dong CN2019	1.61	0.33	43	1.15	0.31	43	11.9	0.46 [0.32, 0.60]
Jiang PD2017	1.58	0.31	41	1.2	0.26	41	12.3	0.38 [0.26, 0.50]
Li ZJ2014	1.77	0.3	37	1.51	0.23	36	12.3	0.26 [0.14, 0.38]
Qian Y2018	1.54	0.27	106	1.45	0.33	100	13.4	0.09 [0.01, 0.17]
Ren YY2021	1.52	0.19	47	1.01	0.15	43	13.7	0.51 [0.44, 0.58]
Shen XL2019	1.67	0.25	56	1.36	0.21	56	13.3	0.31 [0.22, 0.40]
Wang CR2022	1.69	0.52	42	1.4	0.29	42	10.5	0.29 [0.11, 0.47]
Zhang L2018	1.63	0.28	51	1.31	0.29	51	12.7	0.32 [0.21, 0.43]
Total (95% CI)			*423*			*412*	*100.0*	*0.33 [0.22, 0.44]*

Heterogeneity: tau² = 0.02; chi² = 63.35, *df* = 7 (*P* < 0.00001); I^2 = 89%
Test for overall effect: *Z* = 5.76 (*P* < 0.00001)

Mean Difference IV, Random, 95% CI
-0.5 -0.25 0 0.25 0.5
Control Experimental

(a)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Fixed, 95% CI
Dong CN2019	1.61	0.33	43	1.15	0.31	43	12.5	0.46 [0.32, 0.60]
Jiang PD2017	1.58	0.31	41	1.2	0.26	41	15.0	0.38 [0.26, 0.50]
Li ZJ2014	1.77	0.3	37	1.51	0.23	36	15.3	0.26 [0.14, 0.38]
Qian Y2018	1.54	0.27	106	1.45	0.33	100		Not estimable
Ren YY2021	1.52	0.19	47	1.01	0.15	43		Not estimable
Shen XL2019	1.67	0.25	56	1.36	0.21	56	31.4	0.31 [0.22, 0.40]
Wang CR2022	1.69	0.52	42	1.4	0.29	42	7.1	0.29 [0.11, 0.47]
Zhang L2018	1.63	0.28	51	1.31	0.29	51	18.7	0.32 [0.21, 0.43]
Total (95% CI)			*270*			*269*	*100.0*	*0.33 [0.28, 0.38]*

Heterogeneity: chi² = 5.85, *df* = 5 (*P* = 0.32); I^2 = 15%
Test for overall effect: *Z* = 13.59 (*P* < 0.00001)

Mean Difference IV, Fixed, 95% CI
-0.5 -0.25 0 0.25 0.5
Control Experimental

(b)

Figure 6: The outcome of the CD4+/CD8+T lymphocytes proportions. (a) All studies with the CD4/CD8 T lymphocytes proportions and (b) without the heterogeneity studies.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Fixed, 95% CI
An GZ2014	39.31	21.65	62	37.14	15.72	56	20.1	2.17 [-4.61, 8.95]
Lin DF2022	51.64	8.05	42	49.9	8.31	42	75.6	1.74 [-1.76, 5.24]
Mou P2015	282.7	47.2	80	273.2	47.7	80	4.3	9.50 [-5.20, 24.20]
Total (95% CI)			*184*			*178*	*100.0*	*2.16 [-0.88, 5.20]*

Heterogeneity: chi² = 1.01, *df* = 2 (*P* = 0.60); I^2 = 0%
Test for overall effect: *Z* = 1.39 (*P* = 0.16)

Mean Difference IV, Fixed, 95% CI
-20 -10 0 10 20
Control Experimental

Figure 7: The outcome of the IL-2 levels.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Fixed, 95% CI
Li N2019	21.05	5.98	48	25.45	5.72	47	21.5	-4.40 [-6.75, -2.05]
Lin DF2022	25.71	6.03	42	30.23	9.61	42	10.1	-4.52 [-7.95, -1.09]
Mou P2015	22.8	4.6	80	26.6	4.1	80	65.3	-3.80 [-5.15, -2.45]
Yang PF2015	34.53	18.42	70	40.31	19.07	70	3.1	-5.78 [-11.99, 0.43]
Total (95% CI)			*240*			*239*	*100.0*	*-4.06 [-5.15, -2.97]*

Heterogeneity: chi² = 0.59, *df* = 3 (*P* = 0.90); I^2 = 0%
Test for overall effect: *Z* = 7.30 (*P* < 0.00001)

Mean Difference IV, Fixed, 95% CI
-20 -10 0 10 20
Experimental Control

Figure 8: The outcome of the IL-4 levels.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Random, 95% CI
Ji FF2018	24.4	5.4	95	27.1	5.1	94	17.0	-2.70 [-4.20, -1.20]
Li N2019	24.02	5.12	48	28.96	5.23	47	12.2	-4.94 [-7.02, -2.86]
Mi CO2015	15.25	3.21	45	16.88	3.46	45	18.2	-1.63 [-3.01, -0.25]
Pan SY2015	24.3	5.5	41	27	5.2	41	10.7	-2.70 [-5.02, -0.38]
Wu DS2016	15.13	3.19	53	16.79	3.5	53	19.2	-1.66 [-2.93, -0.39]
Zhang L2018	23.61	5.38	51	28.19	5.63	51	11.9	-4.58 [-6.72, -2.44]
Zhao PA2018	24.3	5.5	41	27	5.2	41	10.7	-2.70 [-5.02, -0.38]
Total (95% CI)			*374*			*372*	*100.0*	*-2.80 [-3.76, -1.85]*

Heterogeneity: tau² = 0.81; chi² = 12.17, *df* = 6 (*P* = 0.06); I^2 = 51%

Test for overall effect: *Z* = 5.76 (*P* < 0.00001)

Mean Difference IV, Random, 95% CI

-4 -2 0 2 4

Experimental Control

(a)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Fixed, 95% CI
Ji FF2018	24.4	5.4	95	27.1	5.1	94	20.5	-2.70 [-4.20, -1.20]
Li N2019	24.02	5.12	48	28.96	5.23	47		Not estimable
Mi CO2015	15.25	3.21	45	16.88	3.46	45	24.1	-1.63 [-3.01, -0.25]
Pan SY2015	24.3	5.5	41	27	5.2	41	8.6	-2.70 [-5.02, -0.38]
Wu DS2016	15.13	3.19	53	16.79	3.5	53	28.2	-1.66 [-2.93, -0.39]
Zhang L2018	23.61	5.38	51	28.19	5.63	51	10.0	-4.58 [-6.72, -2.44]
Zhao PA2018	24.3	5.5	41	27	5.2	41	8.6	-2.70 [-5.02, -0.38]
Total (95% CI)			*326*			*325*	*100.0*	*-2.34 [-3.01, -1.66]*

Heterogeneity: chi² = 6.74, *df* = 5 (*P* = 0.24); I^2 = 26%

Test for overall effect: *Z* = 6.76 (*P* < 0.00001)

Mean Difference IV, Fixed, 95% CI

-4 -2 0 2 4

Experimental Control

(b)

Figure 9: The outcome of the TNF-α levels. (a) All studies with the TNF-α levels and (b) without the heterogeneity studies.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Fixed, 95% CI
An GZ2014	15.57	8.58	62	14.2	7.78	56	7.8	1.37 [-1.58, 4.32]
Ji FF2018	47.8	10.7	95	42.7	10.7	94	7.3	5.10 [2.05, 8.15]
Li N2019	46.36	8.24	48	41.02	7.69	47	6.7	5.34 [2.14, 8.54]
Mou P2015	31.46	3.32	80	26.55	3.9	80	54.2	4.91 [3.79, 6.03]
Pan SY2015	47.7	11.2	41	42.6	10.8	41	3.0	5.10 [0.34, 9.86]
Zhang L2018	45.7	4.82	51	41.08	4.49	51	20.9	4.62 [2.81, 6.43]
Total (95% CI)			*377*			*369*	*100.0*	*4.62 [3.79, 5.45]*

Heterogeneity: chi² = 5.24, *df* = 5 (*P* = 0.39); I^2 = 5%

Test for overall effect: *Z* = 10.95 (*P* < 0.00001)

Mean Difference IV, Fixed, 95% CI

-10 -5 0 5 10

Control Experimental

Figure 10: The outcome of the INF-γ levels.

distributed within the inverted funnel plot, indicating that the remaining studies may have less publication bias (Figure 15).

4. Discussion

At present, BCG-PSN is effective in the treatment of CU, but it is still not completely clear which cells and cytokines play a regulatory role in immune regulation, and some research results are also controversial, such as the regulation of IL-10. In this study, we further verified the effectiveness of BCG-PSN. Although we emphasized the randomized method, we still observed some defects in clinical studies, such as inappropriate selection of random method and defects in study design. According to recent studies, cytokines that initiate the Th2 immune response, such as IL-31, IL-33, IL-25, and IgG antithyroid peroxidase may be closely related to CU [44–47], and the C4 may be a potential biomarker of disease activity [48], but few studies have explored this indicator in clinical practice.

Our results showed that BCG-PSN can effectively regulate the immune function of the body, upregulating CD3+T and CD4+T levels and downregulating CD8+T levels. CD4+T cells can further differentiate into Th1 cells and Th2 cells; Th1/Th2 levels maintain a dynamic balance in normal organism, but in patients with CSU, the number and activity of Th1/Th2 cells are unbalanced and were shifted toward Th2. Abnormal levels of CD4+ and CD8+ are considered as

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Random, 95% CI
LiLQ 2021	1.56	0.22	40	2.45	0.21	40	26.8	-0.89 [-0.98, -0.80]
Shen XL2019	1.06	0.32	56	2.35	0.41	56	25.8	-1.29 [-1.43, -1.15]
Wang N2019	1.6	0.2	50	2.5	0.2	50	27.1	-0.90 [-0.98, -0.82]
Yang ZR2018	0.93	0.25	75	2.69	1.27	75	20.4	-1.76 [-2.05, -1.47]
Total (95% CI)			*221*			*221*	*100.0*	*-1.17 [-1.43, -0.92]*

Heterogeneity: tau² = 0.06; chi² = 54.55, *df* = 3 (*P* < 0.00001); I^2 = 95%
Test for overall effect: *Z* = 8.95 (*P* < 0.00001)

Mean Difference IV, Random, 95% CI
-2 -1 0 1 2
Experimental Control

(a)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean Difference IV, Random, 95% CI
Lin L2017	0.41	0.29	46	1.92	0.32	46	33.4	-1.51 [-1.63, -1.39]
Li TL2018	0.72	0.29	40	1.94	0.32	40	33.4	-1.22 [-1.35, -1.09]
Liu LJ2015	0.73	0.23	54	1.19	0.51	54	33.2	-0.46 [-0.61, -0.31]
Total (95% CI)			*140*			*140*	*100.0*	*-1.06 [-1.66, -0.47]*

Heterogeneity: tau² = 0.27; chi² = 114.79, *df* = 2 (*P* < 0.00001); I^2 = 98%
Test for overall effect: *Z* = 3.52 (*P* = 0.0004)

Mean Difference IV, Random, 95% CI
-2 -1 0 1 2
Experimental Control

(b)

Figure 11: The outcome of the histamine levels. (a) The 4 studies were measured in mmol/L and (b) 3 studies were measured in ng/ml.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds Ratio M-H, Fixed, 95% CI
A LMR2020	27	27	21	27	0.8	16.63 [0.89, 311.79]
An GZ2014	57	62	36	56	6.0	6.33 [2.18, 18.37]
Dong CN2019	37	43	27	43	7.4	3.65 [1.26, 10.56]
Jiang PD2017	35	41	26	41	7.5	3.37 [1.15, 9.85]
LiLQ 2021	39	40	32	40	1.6	9.75 [1.16, 82.11]
Lin DF2022	42	42	31	42	0.7	31.03 [1.76, 546.58]
Lin L2017	45	46	35	46	1.5	14.14 [1.74, 114.83]
Li TL2018	37	40	30	40	4.4	4.11 [1.04, 16.29]
Liu LJ2015	51	54	48	54	5.2	2.13 [0.50, 8.98]
Liu Y2009	39	46	20	39	6.5	5.29 [1.91, 14.69]
Li ZJ2014	34	37	26	36	4.2	4.36 [1.09, 17.46]
Mi CO2015	41	45	35	45	6.1	2.93 [0.84, 10.16]
Mou P2015	75	80	66	80	8.1	3.18 [1.09, 9.31]
Pan SY2015	40	41	31	41	1.5	12.90 [1.57, 106.26]
Qian Y2018	99	106	67	100	9.0	6.97 [2.91, 16.67]
Ren YY2021	41	47	30	43	7.9	2.96 [1.01, 8.68]
Shen XL2019	55	56	45	56	1.6	13.44 [1.67, 108.12]
Wang CR2022	41	42	33	42	1.5	11.18 [1.35, 92.81]
Wang N2019	49	50	36	50	1.4	19.06 [2.40, 151.60]
Wu DS2016	52	53	41	53	1.5	15.22 [1.90, 121.90]
Yang PF2015	65	70	55	70	7.7	3.55 [1.21, 10.38]
Yang ZR2018	71	75	60	75	6.3	4.44 [1.40, 14.09]
Zhao PA2018	40	41	31	41	1.5	12.90 [1.57, 106.26]
Total (95% CI)		*1184*		*1160*	*100.0*	*5.56 [4.22, 7.33]*
Total events	1112		862			

Heterogeneity: chi² = 15.51, *df* = 22 (*P* = 0.84); I^2 = 0%
Test for overall effect: *Z* = 12.18 (*P* < 0.00001)

Odds Ratio M-H, Fixed, 95% CI
0.005 0.1 1 10 200
Control Experimental

Figure 12: The outcome of the CER.

indicators of impaired immune function [49]. BCG-PSN could downregulate IL-4 and TNF-α levels and upregulate IL-10 and INF-γ levels. IL-2, TNF-α, and IFN-γ are secreted by Th1 cells; these cytokines have two functions, one is to mediate the cellular immune response, the other is to inhibit the activation of Th2; Th2 secretes IL-4, IL-6, and IL-10, which mediate humoral immune response [50, 51]. CSU patients' TNF-α is higher than the normal population, and

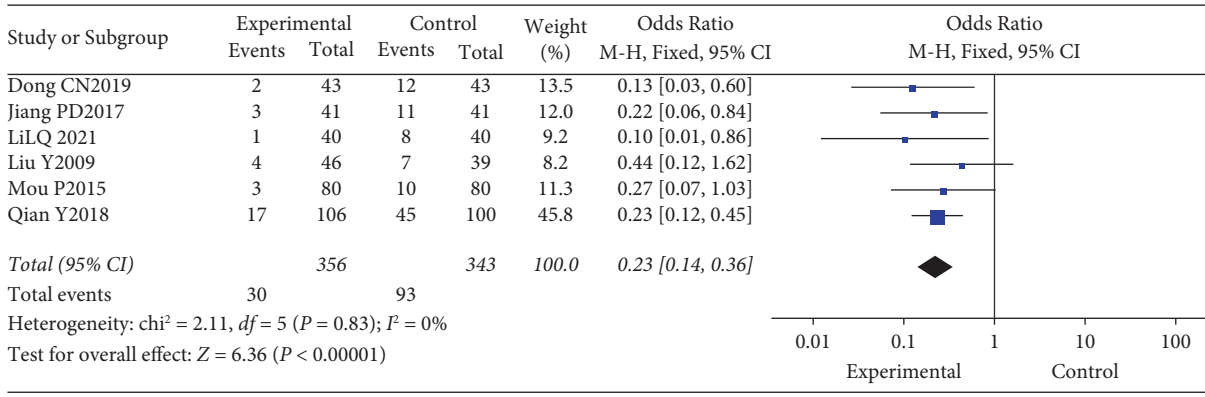


Figure 13: The outcome of the recurrence rates.

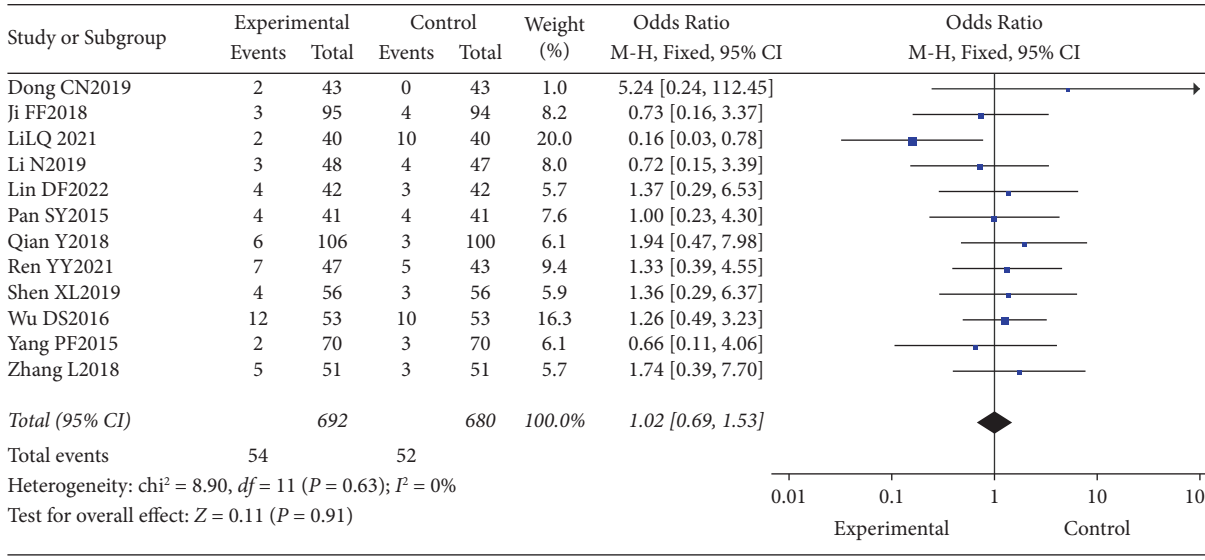


Figure 14: The outcome of the adverse events.

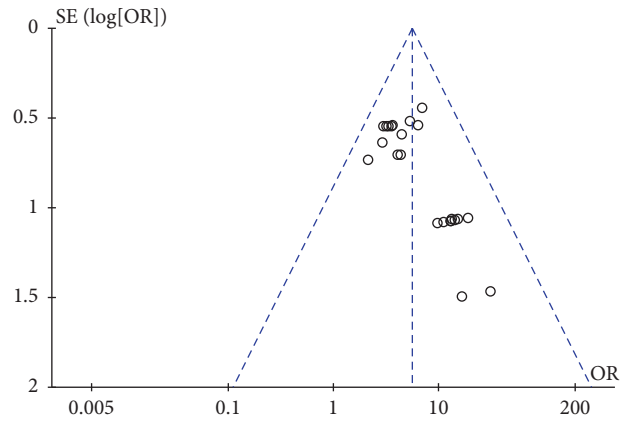


Figure 15: Funnel plot of the clinical efficacy rates.

TNF-α level is usually positively correlated with disease activity, due to TNF-α which can promote the destruction of the body's immune state and further aggravate the inflammatory response [52, 53]. In allergic diseases, IL-4 can promote B cell differentiation and transform Ig M into Ig E, thus increasing the level of Ig E and inhibiting the function of Th1. IFN-γ can inhibit IL-4 function, preventing the production of specific IgE, and Il-2 can promote the production of IFN-γ, which indirectly reduce the production of Ig E [54]. IL-10 can differentiate native Th cells into Th2 cells by inhibiting the secretion of IL-12 in antigen presenting cells [55]. However, another literature has reported that IL-10 can inhibit Th2-mediated inflammation and the release of proinflammatory cytokines and chemokines by Th1 cells and macrophages, maintaining tolerance to autoantigens, thereby preventing the development of autoimmune diseases [56].

BCG-PSN is a commonly used immunomodulator in clinical practice; it can effectively regulate the differentiation of CD4+ and CD8+T cells in peripheral and central immune organs, enhance Th1 cell proliferation, and inhibit Th2 cells. BCG-PSN stimulates the production of IFN-γ and IL-2, promote Th1 cell differentiation, enhance macrophage aggregation and activation, inhibit IL-4 production and Th2 cell differentiation, and maintain Th1/Th2

balance. The dose of BCG-PSN was correlated with the effect of regulating the secretion of Th1/Th2 related cytokines [57]. On the one hand, BCG-PSN may reduce β-hexosaminidase release rate and regulate IgE mediated mast cell activation through NF-κB pathway; on the other hand, BCG-PSN can synergistically enhance the inhibition effect of antihistamines on mast cell degranulation level. Therefore, although BCG-PSN cannot replace antihistamines as first-line drugs, it can be used in combination with antihistamines to play a synergistic role with antihistamines in the acute attack stage and regulate immunity to reduce recurrence in the stable stage [58]. Furthermore, BCG-PSN can increase EOS levels [16] and upregulate B-lymphocytes levels [59].

But at the same time, we also observed that there were contradictions in the literature included on IL-10. De-Feng et al. [17], Mou and Zheng [33], Congou and Chen [37], and Zhao [41] concluded that BCG-PSN could be downregulated IL-10, while Fan [21], Li et al. [30], and Lin [32] concluded that it could be upregulated IL-10. These disputes were also supported by other studies.

Our study also has some defects; some indicators have statistical heterogeneity, considering these heterogeneous sources are related to age, course of the disease, and patients with baseline differences; in order to explain the research that heterogeneity may exist, we use the random effect model to analyze the effect. At the same time, the literature was excluded one by one to verify its sensitivity, and heterogeneity could be reduced to a satisfactory degree after the exclusion of one study or up to three studies. In addition, especially for baseline symptom severity, some of the studies were poor and inconsistent, and therefore, meta-regression could not be properly performed. Finally, due to the inability to obtain the detailed design of some trials which makes it impossible to evaluate the literature quality, the quality of individual trials may affect the reliability of the study.

5. Conclusions

In this meta-analysis, we investigated the immune regulation of BCG-PSN in patients with CSU and found that BCG-PSN promoted CD3+T differentiation, increased CD4+T levels and CD4+/CD8+ ratio, and downregulated CD8T levels. Furthermore, BCG-PSN could downregulate IL-4 levels and TNF-α levels and upregulate INF-γ levels. Regardless of the heterogeneity observed between the included studies, we found that the addition of BCG-PSN significantly improved efficacy and controlled recurrence rates. This quantitative synthesis of observational studies confirms, complements, and extends the efficacy findings observed in randomized controlled trials of patients with CSU.

Data Availability

The original contributions presented in the study are included in the article; all data and materials are fully available without restriction.

Disclosure

This study is a systematic, meta-analysis which was used to conduct a second study on the published literature. The results will be reported in a peer-reviewed journal after the analysis is completed.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Qiang Fu and Lei Tang designed the study, analyzed the data, and drafted the manuscript. Zi-Wenyan Zhou, QI Zheng, Fu-Jun Huang, and Miao Zhang performed the experiments and contributed and collected data/analysis tools. Xun Zhou participated in the critical revision and final approval of the manuscript.

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