

Effect of acupoint application on T lymphocyte subsets in patients with chronic obstructive pulmonary disease

A meta-analysis

Jian-Jun Wu, PhD^a, Ying-Xue Zhang, MM^a, Hong-Ri Xu, PhD^a, Yi-Xuan Li, MM^a, Liang-Duo Jiang, PhD^b, Cheng-Xiang Wang, PhD^{a,*}, Mei Han, PhD^{c,*}

Abstract

Background: The development of chronic obstructive pulmonary disease (COPD) is related to the T lymphocyte mediated inflammatory immune response and immune imbalance. The purpose of this systematic review was to evaluate the clinical efficacy and safety of acupoint application on T lymphocyte subsets in patients with COPD.

Methods: We searched CNKI, Wan fang, Chongqing VIP, China Biology Medicine disc, PubMed, the Cochrane Library, and EMBASE for studies published as of Oct. 31, 2019. All randomized controlled trials of acupoint application on COPD patients that met the inclusion criteria were included. The Cochrane bias risk assessment tool was used for literature evaluation. RevMan5.3 software was used for meta-analysis.

Results: Eight studies (combined n=524) qualified based on the inclusion criteria. Compared with routine treatment alone, acupoint application combined with routine treatment can significantly increase the T lymphocyte CD4⁺/CD8⁺ ratio (MD 0.12, 95% CI 0.03-0.21, $P < .01$, $I^2 = 49\%$), reduce CD8⁺ T-cells (MD-0.99, 95% CI-1.70-0.28, $P < .001$, $I^2 = 37\%$), reduce the times of acute exacerbations (MD-0.28, 95% CI-0.35-0.21, $P < .001$, $I^2 = 0$), and improve the clinical efficacy (MD 1.30, 95% CI 1.14-1.48, $P < .001$, $I^2 = 39\%$).

Conclusion: Acupoint application can improve the CD4⁺/CD8⁺ ratio and CD8⁺ T-cells in patients with COPD and has an auxiliary effect in reducing the times of acute exacerbations and improving clinical efficacy.

Abbreviations: CAT = COPD assessment test score, CIs = confidence intervals, COPD = chronic obstructive pulmonary disease, FEV₁% pred = forced expiratory volume in one second pre prediction, FEV₁/FVC = forced expiratory volume in one second/forced vital capacity, FVC = forced vital capacity, MD = mean.

Keywords: acupoint application, CD4⁺ T-cells, CD8⁺ T-cells, chronic obstructive pulmonary disease, meta, RCT

Editor: Jianxun Ding.

This study is an analysis of published literature, which belongs to the second study. Therefore, this study does not require the approval of the ethics committee. The findings will be disseminated through a peer-reviewed journal publication or conference presentation.

WJ and ZY contributed equally to this work.

The work was supported by Beijing Municipal Natural Science Foundation (Project No. 7182100) and Famous Doctor Training Program of Beijing University of Traditional Chinese Medicine(2019).

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Supplemental Digital Content is available for this article.

The data used to support the findings of this study are included within the article [and its supplementary information files].

^a The Third Affiliated Hospital of Beijing University of Chinese Medicine, ^b Dongzhimen Hospital Beijing University of Chinese Medicine, Beijing, ^c Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China.

* Correspondence: Cheng-Xiang Wang, The Third Affiliated Hospital of Beijing University of Chinese Medicine, No. 51, Xiaoguan Street outside Anding Men, Chaoyang, Beijing 100029, P.R. China (e-mail: wang601@vip.sina.com); Mei Han, Center for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, 11 East Road North 3rd Ring Road, Beijing 100029, P.R. China (e-mail: hanmeizoujin@163.com).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Wu JJ, Zhang YX, Xu HR, Li YX, Jiang LD, Wang CX, Han M. Effect of acupoint application on T lymphocyte subsets in patients with chronic obstructive pulmonary disease: A meta-analysis. *Medicine* 2020;99:16(e19537).

Received: 2 December 2019 / Received in final form: 22 January 2020 / Accepted: 11 February 2020

<http://dx.doi.org/10.1097/MD.00000000000019537>

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common and frequent disease of the respiratory system. The mortality rate of COPD is increasing annually, which causes serious economic and social burdens.^[1-3]

The prevalence of COPD in adults aged 20 years and over, 40 years and over, and 60 years and over is 8.6%, 13.7%, and 27.4%, respectively. With increasing age, the prevalence of COPD increases gradually. In 2015, the total number of adults aged 20 and over with COPD in China was estimated to be 99.9 million, which constitutes a major burden of disease.^[1] According to statistics, the number of COPD deaths in China in 2013 was approximately 911,000, accounting for 1/3 of the world's COPD deaths,^[3] far higher than the annual number of lung cancer deaths in China. COPD is expected to become the third leading cause of death and the fifth largest economic burden of disease in the world by 2020.^[2]

The development of COPD is related to the T lymphocyte-mediated inflammatory immune response and immune imbalance.^[4] In COPD patients, abnormal acquired immune responses mediated by T-cells mainly include abnormal immune regulation mechanisms and abnormal autoimmune regulation.^[4] In COPD patients, macrophages, neutrophils and lymphocytes are the main participants in chronic immune inflammation. CD4⁺ and CD8⁺ T-cells, as well as Th17 cells, play an important role in the characteristic inflammation and emphysema of COPD.^[5] The study found that the number of CD8⁺ T-cells in the pulmonary parenchyma and pulmonary artery increased in smokers with COPD compared with the numbers in nonsmokers. Compared with smokers with normal pulmonary function, the number of CD8⁺ T-cells in the pulmonary artery of smokers with COPD also increased. CD8⁺ cytotoxic T-cells are important T-cells in patients with COPD, whether in the airway or in the alveoli, and the number of CD8⁺ T-cells in the lung increases significantly with airflow restriction and the increase in emphysema. At the same time, it was found that the expression of CD4⁺ T-cells increased in the airways and lungs of smokers with COPD.^[6] Moreover, the expression of CD8⁺ and CD4⁺ T-cells in the lungs of asymptomatic smokers was higher than that of nonsmokers. In the sputum of patients with moderately acute exacerbation of COPD, CD8⁺ T-cells increased significantly and the ratio of CD4⁺/CD8⁺ decreased. These changes were not related to smoking history, demographic characteristics or disease severity compared with patients in the stable stage.^[7]

Acupoint application is one of the traditional Chinese medicine therapies. It is based on the theory of meridians and collaterals of traditional Chinese medicine. Acupoint application is a noninvasive and painless therapy for treating diseases by grinding Chinese medicine into fine powder and making a paste, ointment, pill or cake by specific methods, or boiling Chinese medicine decoctions into ointment, or dispersing the powder in the ointment and then pasting them on the acupoint.^[8-12] The mechanism may be related to the direct local effect of acupoint application, the synergistic amplification of meridian stimulation, the regulation of innate and specific immune responses, the regulation of biological enzymes and receptors, and the neuroendocrine regulation.^[13,14]

Studies have shown that acupoint application can improve the symptoms of COPD patients,^[15] reduce the number of acute

attacks,^[16,17] and delay the decline in lung function.^[17] Acupoint application can improve the score of St. George's questionnaire and the quality of life of COPD patients.^[18,19] However, the effect of acupoint application on T lymphocyte subsets in COPD patients is still unclear. Some studies have reported that acupoint application could increase CD4⁺ T-cells^[20,21] and the CD4⁺/CD8⁺ ratio^[20,21] and decrease CD8⁺ T-cells^[21] in COPD patients. Others reached the opposite conclusion.^[22] This study intends to conduct a meta-analysis of randomized controlled trials of acupoint application on the T lymphocyte subsets in COPD patients to provide evidence-based verification of the improvement in T lymphocyte subsets in COPD patients by acupoint application.

2. Research methods

This meta-analysis is carried out strictly in accordance with the recommendation of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for the systematic review items and meta-analysis priority reports, and the literature retrieval and screening schemes are predefined.

2.1. Search strategy

In this study, Chinese and English studies of public publications were retrieved. The retrieval databases include the China HowNet database, Wanfang database, Chongqing Weipu Chinese Science and Technology Journal database, China Biomedical Literature Database, PubMed, the Cochrane Library and EMBASE. The deadline was Oct. 31, 2019. The following key words or combinations were used to retrieve studies: "Chronic Obstructive Pulmonary Disease" or "COPD", merging "T-lymphocyte subsets" or "CD4⁺" or "CD8⁺", and "acupoint application" Or "Acupoint Application for Winter-Disease-Treated-in-Summer". To avoid omission, references for reviews and meta-analyses were manually screened.

2.2. Inclusion and exclusion criteria

Inclusion criteria:

- 1) patients in the stable stage of COPD;
- 2) treatment group: acupoint application or summer treatment of winter disease combined with routine treatment;
- 3) control group: routine treatment;
- 4) main outcome indicators: T lymphocyte subsets, mainly including CD4⁺ T-cells, CD8⁺ T-cells, and the CD4⁺/CD8⁺ ratio. Secondary outcome indicators: CD3⁺ T-cells, lung function, times of acute exacerbation, clinical efficacy (Reference to Traditional Chinese Medicine New Drug Clinical Instruction Principle^[23]), IgA, IgM, IgG, etc. It is required that at least one of the main outcome indicators listed in the study be reported; and
- 5) randomized controlled trials.

Exclusion criteria:

- 1) copied or plagiarized literature;
- 2) obvious inconsistencies in the data or suspicion of modification of data without authorization; and
- 3) studies with incomplete data or for which comprehensive information could not be obtained from the original author.

2.3. Data extraction and quality assessment

Two researchers independently performed literature screening and data extraction. Disagreements, if any, were resolved by consensus or by participation of a third coauthor (XH). The risk of bias (ROB) assessment tool of the Cochrane collaboration network was used to evaluate the quality of each item, and high risk, low risk and unclear risk were judged for each item.

2.4. Observation indicators

The extracted data mainly include the information of researchers (name, publication time, language, country/region, research type) and research information (sample size, average age, intervention and control measures, randomization scheme, allocation concealment, blinding method, drop-out, loss of interview, intention analysis, outcome indicators).

2.5. Publication bias assessment

If there were more than 10 studies included in the meta-analysis, the data were evaluated for publication bias. Publication bias was assessed by viewing the symmetry of the funnel plot and using the Begg^[24] rank correlation method and the Harbord^[25] modified linear regression method.

2.6. Data analysis

Rev Man 5.3 software was used for statistical analysis. Statistical heterogeneity among studies was evaluated by I^2 . In the event of no significant heterogeneity ($P > .1$ and $I^2 < 50\%$), the fixed effect model was used for meta-analysis. In cases of statistically significant heterogeneity ($P < .1$ and $I^2 > 50\%$), the random effect model was used for meta-analysis. Continuous variables were evaluated by the mean difference (MD). Dichotomous variables were evaluated by the relative risk (RR). The results are expressed with 95% confidence intervals (CIs). $P < .05$ was considered statistically significant.

3. Results

3.1. Literature search

According to the retrieval strategy, 338 articles were retrieved. After browsing the title and abstract, eliminating duplicate titles and screening, 17 articles were downloaded. By reading the full text and excluding 9 articles, 8 articles^[26–34] were finally included in the analysis. The process of literature retrieval is shown in Figure 1 and Supplementary materials Flow Diagram, PRISMA Checklist, S1, <http://links.lww.com/MD/D940>, <http://links.lww.com/MD/D938>.

3.2. Basic characteristics of the included studies

This study included 8 randomized controlled trials consisting of 524 cases, where 258 cases were in the treatment group and 266 cases in the control group. The average age of each group was 32 cases, with an average age of 65 years. No sample size was estimated in any of the studies. The basic features included in the study are shown in Table 1.

3.3. Quality evaluation

The studies were evaluated by the Cochrane bias risk assessment. The risk of bias in the selected studies is illustrated in Figures. 2 and 3.

3.4. Evaluation of the therapeutic effect of acupoint

3.4.1. Evaluation of the therapeutic effect of acupoint application on T lymphocyte subsets in COPD patients

3.4.1. Evaluation of the therapeutic effect of acupoint application on CD4⁺ T-cells in COPD patients. Eight studies reported the CD4⁺ T-cell status after treatment. The heterogeneity among the samples was large, and only descriptive analysis was performed. Three studies^[29,30,33] reported that acupoint application combined with routine treatment could significantly increase the frequencies of CD4⁺ T-cells in COPD patients. Five studies^[26–28,31,32] reported that acupoint application combined with routine treatment could not increase the frequencies of CD4⁺ T-cells in COPD patients. Sensitivity analysis showed that heterogeneity originated from Gong and Mou,^[28] Aimaiti and Aizezi,^[31] Yang et al.^[33] After excluding this literature, meta analysis found that compared with conventional therapy alone, acupoint application combined with conventional therapy could significantly increase the frequencies of CD4⁺ T cells (MD 4.23, 95% CI 1.88–6.57, $P < .001$, $I^2 = 68\%$, 5 studies) in COPD patients (Supplementary materials Figure 15, <http://links.lww.com/MD/D939>).

3.4.2. Evaluation of the therapeutic effect of acupoint application on CD8⁺ T-cells in COPD patients.

Eight studies reported on CD8⁺ T-cells, and 1 study^[31] reported that acupoint application combined with routine treatment could improve CD8⁺ T-cells in COPD patients. Seven studies^[26–30,32,33] reported that acupoint application combined with routine treatment could not improve CD8⁺ T-cells in COPD patients. Meta-analysis showed that compared with conventional therapy alone, acupoint application combined with conventional therapy could significantly improve CD8⁺ T-cells (MD-0.99, 95% CI-1.70–0.28, $P < .001$, $I^2 = 37\%$) in COPD patients (Fig. 4).

3.4.3. Evaluation of the therapeutic effect of acupoint application on the CD4⁺/CD8⁺ ratio in COPD patients.

Eight studies reported the CD4⁺/CD8⁺ ratio, and 3 studies^[26,29,33] reported that acupoint application combined with conventional therapy could improve the CD4⁺/CD8⁺ ratio. Five studies^[27,28,30–32] reported that acupoint application combined with conventional therapy could not improve the CD4⁺/CD8⁺ ratio. Meta-analysis showed that compared with conventional therapy alone, acupoint application combined with conventional therapy could significantly improve the CD4⁺/CD8⁺ ratio (MD 0.12, 95% CI 0.03–0.21, $P < .01$, $I^2 = 49\%$) in COPD patients (Fig. 5).

3.5. Evaluation of the therapeutic effect of acupoint application on CD3⁺ T-cells, times of acute exacerbation, pulmonary function, clinical efficacy, immunoglobulin and CAT in COPD patients

All details of outcomes were found in Table 2 and Supplementary materials Figure 6-14, S2, <http://links.lww.com/MD/D941>, <http://links.lww.com/MD/D939>.

4. Discussion

This study found that acupoint application combined with routine treatment can increase the CD4⁺/CD8⁺ ratio, reduce CD8⁺ T-cells, reduce the times of acute exacerbations, and improve the clinical efficacy in COPD patients.

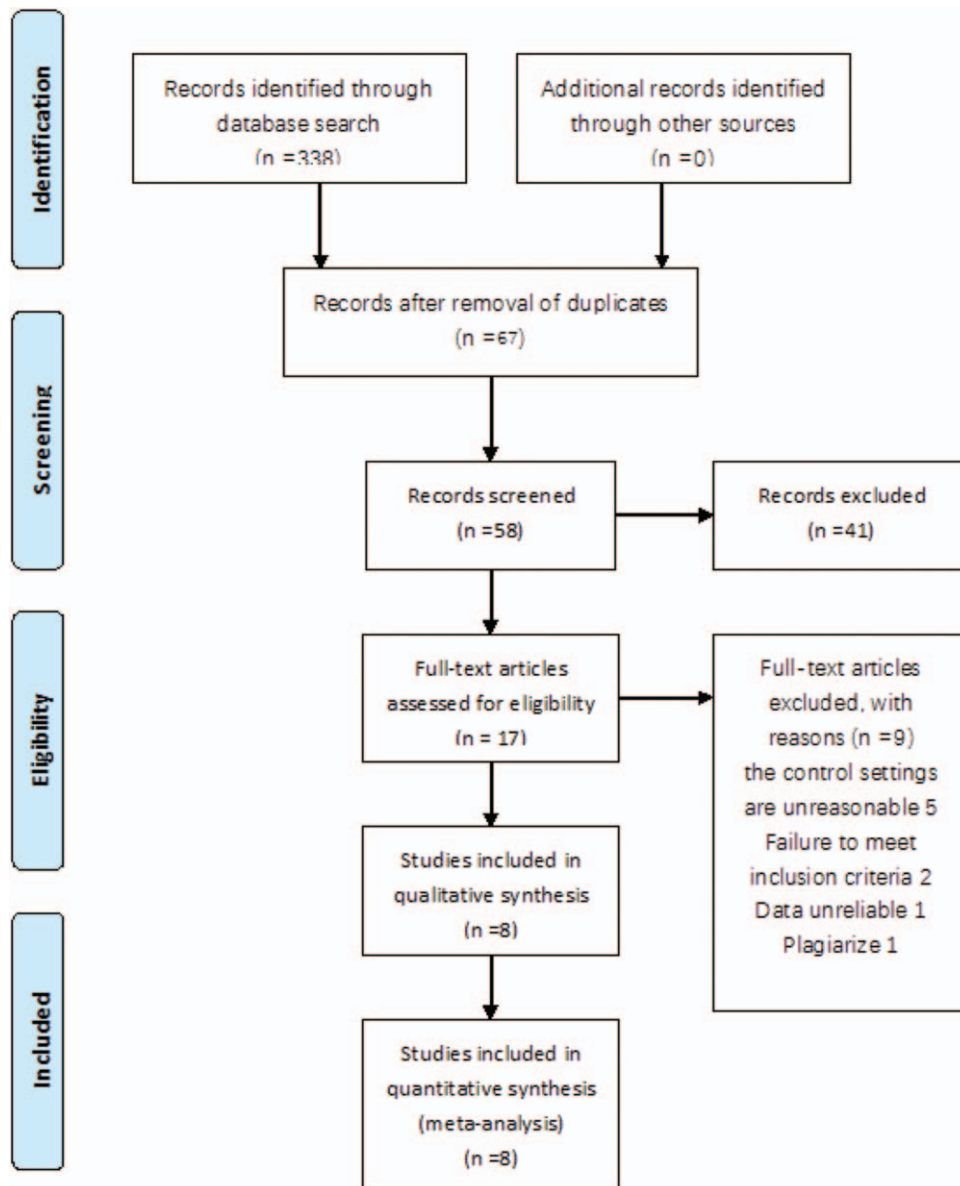


Figure 1. Literature included in flowchart.

Studies have shown that mature T-cells only express CD4 or CD8, that is, CD4⁺ T-cells or CD8⁺ T-cells. The main functions of CD4 and CD8 are to help T-cell receptors (TCRs) recognize antigens and participate in T-cell activation signal transduction, so they are also called common receptors of TCRs. CD4⁺ T-cells are restricted by their own major histocompatibility complex (MHC) II molecules. After activation, they differentiate into Th cells. However, a few CD4⁺ T-cell effector T-cells have cytotoxic and immunosuppressive effects. CD8⁺ T-cells are restricted by their own MHC I molecules. After activation, CD8⁺ T-cells differentiate into cytotoxic T-cells (CTLs), which have cytotoxic effects and can specifically kill target cells.^[34] In patients with COPD, the changes in T lymphocyte subsets involve three aspects:

1) CD8⁺ T-cells increase, and the proportion of the CD4⁺/CD8⁺ ratio decreases.

2) It is doubtful that CD4⁺ T-cells decrease or increase. Some studies have reported that CD4⁺ T-cells increased in the airway and lung parenchyma of COPD patients,^[35] while others reported that CD4⁺ T-cells decreased in the serum of COPD patients.^[36] The frequencies of CD4⁺ T-cells in the serum of COPD patients was inconsistent, which might be related to the following aspects: First, there had a difference in the level of CD4⁺ T-cells in the serum of COPD patients with different phenotypes. The absolute numbers of CD4⁺ T central memory cells in peripheral blood mononuclear cells of patients with frequent acute exacerbation phenotype of COPD was lower than that of patients with non frequent acute exacerbation phenotype of COPD.^[37] Second, after stimulated by different antigens, CD4⁺ T-cells could differentiate into different subtypes of T cells and perform different functions. The development of COPD was related to the mechanism of oxidative stress, inflammatory stimulation and airway

Table 1

Characteristics of the included studies.

Author	Year	Cases (T/C)	Age (years)	Country	Diagnosis	Intervention/Intervention	Acupoints	Formula	Course of treatment	Evaluation index	The source of specimen of T cells
Chen Qin	2010	30/31	77.2	China	stable COPD	T: Conventional treatment + acupoint application C: Conventional treatment + acupoint application	Feishu (BL13), Pishu (BL20), Shenshu (BL23), Dazhui (GV14), Gao Huang (BL43), Zusanli (ST36)	white mustard, asarum, corydalis, bomeol, et al	12 weeks	T-lymphocyte subsets (CD4 ⁺ , CD8 ⁺ , CD4 ⁺ /CD8 ⁺), CD3 ⁺ , lung function (FEV ₁ %pred), the number of the acute attack	Serum
Gong Xue	2018	35/35	T 62.3 ± 7.6	China	stable COPD	T: Conventional treatment + acupoint application C: Conventional treatment	Feishu (BL13), Shenshu (BL23), Dazhui (GV14), Danzhong (RN17), Tiantu (CV22), Dingchuan (EX-B1)	white mustard, asarum, kansui, corydalis, cinnamon, ephedra	1 month	T-lymphocyte subsets (CD4 ⁺ , CD8 ⁺ , CD4 ⁺ /CD8 ⁺), lung function (FEV ₁ %pred, FVC, FEV ₁ /FVC), curative effect	Serum
Juliati Aimati	2016	42/44	C 61.2 ± 8.3 T 69.25 ± 8.48	China	stable COPD	T: Conventional treatment + acupoint application C: Conventional treatment	Feishu (BL13), Shenshu (BL23), Pishu (BL20), Guanyuan (CV4)	white mustard seed, corydali s. kansui, asarum, earthworm, ginger	1 month	T-lymphocyte subsets (CD4 ⁺ , CD8 ⁺ , CD4 ⁺ /CD8 ⁺), CD3 ⁺ , lung function (FEV ₁ , FVC, FEV ₁ /FVC), the number of the acute attack, curative effect	Serum
Qin Xinxin	2019	20/19	C 69.02 ± 8.35 T 66.96 ± 6.10	China	stable COPD	T: Conventional treatment + acupoint application C: Conventional treatment	Feishu (BL13), Shenshu (BL23), Dingchuan (EX-B1)	white mustard, corydalis, kansui, asarum, astragalus, safflower, pinella	1 month	T-lymphocyte subsets (CD4 ⁺ , CD8 ⁺ , CD4 ⁺ /CD8 ⁺), CD3 ⁺ , the number of the acute attack, lung function (FEV ₁ %pred, FEV ₁ /FVC), CAT	Serum
Wang Haifeng	2011	43/42	C 65.74 ± 6.65 T 60.8 ± 10.6	China	stable COPD	T: Conventional treatment + acupoint application C: Conventional treatment + placebo	Feishu (BL13), Pishu (BL20), Shenshu (BL23), Danzhong (RN17), Gao Huang (BL43)	-	3 years	T-lymphocyte subsets (CD4 ⁺ , CD8 ⁺ , CD4 ⁺ /CD8 ⁺), CD3 ⁺ , the number of the acute attack, curative effect, IgA, IgM, IgG, IgM	Serum
Wang Peidong	2018	30/30	T 65.8 ± 2.7	China	stable COPD	T: Conventional treatment + acupoint application C: Conventional treatment	Feishu (BL13), Xinsu (BL15), Gesu (BL17)	white mustard, corydalis, asarum, aconite, radix aconiti, ephedra	1 month	T-lymphocyte subsets (CD4 ⁺ , CD8 ⁺ , CD4 ⁺ /CD8 ⁺), CD3 ⁺ , lung function (FEV ₁ , FEV ₁ %pred, FEV ₁ /FVC), IgA	Serum
Yang Jin	2019	30/30	C 65.2 ± 3.1 T 63.2 ± 9.2	China	stable COPD	T: Conventional treatment + acupoint application C: Conventional treatment	Different prescriptions at different times	white mustard, kansui, asarum, Corydalis, cinnamon	1 month	T-lymphocyte subsets (CD4 ⁺ , CD8 ⁺ , CD4 ⁺ /CD8 ⁺), lung function (FEV ₁ %pred, FEV ₁ /FVC), CAT, IgA, IgM, IgG	Serum
Zang Min	2016	28/36	C 62.4 ± 9.3 T 59.1 ± 11.6	China	stable COPD	T: Conventional treatment + acupoint application C: Conventional treatment	Tiantu (CV22), Dingchuan (EX-B1)	asarum, evodia, musk	6 month	T-lymphocyte subsets (CD4 ⁺ , CD8 ⁺ , CD4 ⁺ /CD8 ⁺), CD3 ⁺ , lung function (FEV ₁ , FVC, FEV ₁ /FVC), the number of the acute attack, IgA, IgM, IgG, CAT	Serum

FEV₁ = forced expiratory volume in one second, FVC = forced vital capacity, CAT = COPD Assessment Test, T = treatment group, C = control group.

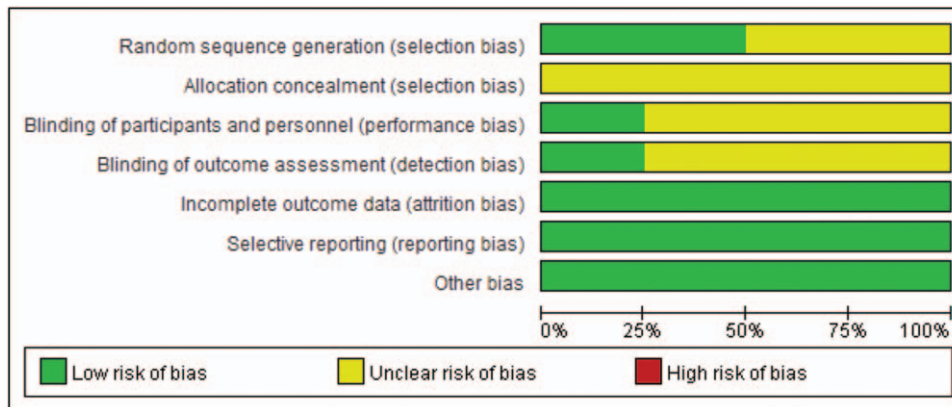


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

remodeling, which might have different effects on CD4⁺ T-cells. Third, the detection method of CD4⁺ T-cells and the surface markers versus intracellular cytokines may also have an impact on the results.^[38] Studies have shown that the prevalence of COPD in HIV-infected patients is higher than that in HIV-negative patients.^[39] CD4 is the receptor of

human HIV. The binding of HIV gp120 protein to CD4 is the mechanism by which HIV invades and infects CD4⁺ T-cells or CD4⁺ macrophages. It can be inferred whether the occurrence and development of COPD and HIV infection share the same immune mechanism. This needs further study.

3) T-cell failure is characterized by the loss of effector function due to the chronic binding of immune checkpoints on T-cells, a phenomenon often observed in chronic infections and autoimmune events. Although the accumulation mechanism of CD8⁺ and CD4⁺ T-cells in the lungs of COPD patients is still unclear, it is believed that the increase in the number of T-cells in the lungs is due to adhesion and selective chemotaxis.^[35] Over-recruitment of T-cells in the lungs may be a response to new antigens caused by cigarette smoke or only to viral infections (active or potential) common to the disease.^[35]

In this study, we found that the effect of acupoint application on CD4⁺ T-cells in COPD patients is still unclear, which is related to the heterogeneity of various research samples and needs to be further studied in large samples. At the same time, the study found that acupoint application can reduce CD8⁺ T-cells and increase the CD4⁺/CD8⁺ ratio in COPD patients, suggesting that acupoint application can improve the immune function of COPD patients.

CD3⁺ T-cells are important T lymphocytes. Their function is to transduce activated signals produced by TCR (T lymphocyte receptor) recognition antigens to T-cells.^[34] The significance of CD3⁺ T-cells in COPD is still unclear. Whether drugs can interfere with CD3-mediated signal transduction in COPD patients and thus have a positive effect on the prevention and treatment of COPD remains unclear and needs to be studied in the future. In this study, we found that the effect of acupoint application on CD3⁺ T-cells in COPD patients is still unclear, which is related to the heterogeneity of various research samples and requires further study in large samples.

The treatment objectives of COPD in the stable stage are as follows:

- 1) alleviating current symptoms, including alleviating symptoms, improving exercise tolerance and improving health status; and
- 2) reducing future risks, including preventing disease progression, preventing and treating acute exacerbation and reducing mortality.^[39]

Studies have shown that acupoint application can improve symptoms such as shortness of breath, dyspnea, cough, and

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chen Qin2010	?	?	?	?	+	+	+
Gong Xue2017	?	?	?	?	+	+	+
Julaiti Aimaity2016	?	?	+	+	+	+	+
Qin Xinxin2019	?	?	?	?	+	+	+
Wang Haifeng2009	+	?	+	+	+	+	+
Wang Peidong2018	+	?	?	?	+	+	+
Yang Jin2019	+	?	?	?	+	+	+
Zang Min2016	+	?	?	?	+	+	+

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

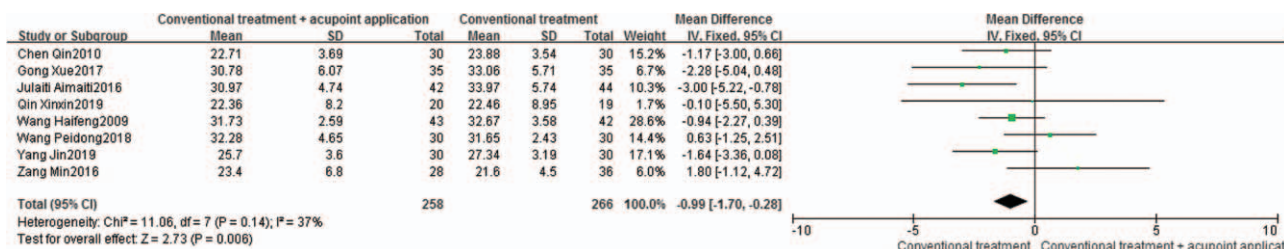


Figure 4. Evaluation of the therapeutic effect of Acupoint Application on CD8+ T-cells in COPD patients.

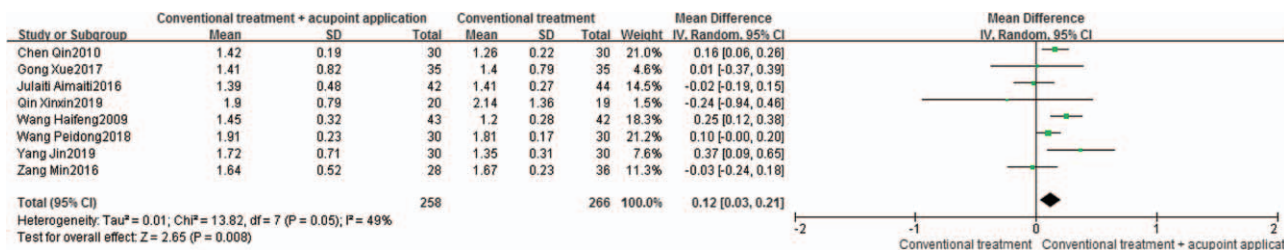


Figure 5. Evaluation of the therapeutic effect of Acupoint Application on CD4+/CD8+ ratio in COPD patients.

sputum expectoration in COPD patients;^[15,40] reduce the number of acute attacks;^[16,17] improve the lung function indicators FEV₁, FVC, and FEV₁/FVC;^[17] improve the St. George's questionnaire score of COPD patients; and improve the quality of life of patients.^[18,19] A meta-analysis of 14 studies in China shows that acupoint application combined with conventional treatment can improve the lung function indexes FEV₁% and FEV₁/FVC and reduce CAT, and the clinical efficacy is better than that of conventional treatment therapy.^[41] However, this study shows that acupoint application combined with conventional treatment cannot improve the lung function indexes FEV₁% pre and FEV₁ of COPD patients compared with that of conventional treatment. It may play a role in improving the effect of FEV₁/FVC, but the heterogeneity between samples is large. Sensitivity analysis suggests that the heterogeneity mainly comes from Gong Xue.^[28] Excluding this study, the results suggest that compared with conventional therapy alone, acupoint application combined with conventional treatment can improve FEV₁/FVC in COPD patients (MD 3.73, 95% CI 1.68–5.77, *P* < .001, *I*² = 0) (Supplementary materials Figure 16, <http://links.lww.com/MD/D939>). The reason may be related to the patient population in

Gong Xue's study, thereby requiring further large-scale samples and high-quality research.

Acupoint application may play a role in improving experiential immunity and CAT of COPD patients. However, due to the great heterogeneity among the samples, it is not yet possible to draw a definite conclusion, which needs to be further studied with large samples and high-quality data.

Only 1 study^[26] mentioned adverse events, while the other 7 trials did not. Due to insufficient information on the safety of acupoint application of COPD, more studies are needed to confirm its safety.

4.1. Limitations of this study

In this study, eight RCT studies were selected involving 524 patients. Because of the small sample size and heterogeneity among the studies, the effects of acupoint application on CD4+ T-cells, CD3+ T-cells, humoral immunity and lung function indexes of COPD patients in the stable stage have not yet been confirmed. Further large-sample and high-quality studies are needed in the future.

Table 2

Evaluation of the therapeutic effect of acupoint application on other indexes in COPD patients.

Secondary outcome	Inclusion study	MD	95% CI	<i>P</i>	<i>I</i> ² , <i>P</i>
CD3+	Six studies	1.64	(-1.33, 4.60)	.28	84%, <.001
Times of acute exacerbation	Four studies	-0.28	(-0.35, -0.21)	<.001	0, .48
Clinical efficacy	Three studies	1.30	(1.14, 1.48)	<.001	39%, .19
FEV ₁ %pre	Four studies	2.20	(-0.68, 5.07)	.13	47%, .13
FEV ₁	Three studies	0.20	(-0.04, 0.45)	.10	64%, .06
FEV ₁ /FVC	Five studies	4.80	(1.62, 7.97)	.003	76%, .002
IgA	Four studies	0.62	(0.16, 1.09)	.009	84%, .004
IgG	Three studies	1.96	(0.66, 3.26)	.003	75%, .02
IgM	Three studies	0.50	(-0.44, 1.45)	.30	95%, <.001
CAT	Three studies	-2.54	(-4.85, -0.24)	.03	73%, .03

This study takes COPD patients in the stable stage as the research object, regardless of their pulmonary function classification, and all of them are included in the study. Because of the small sample size, the stratified study cannot be carried out according to the classification, and there may be some defects. For the same reason, this study failed to refer to the comprehensive evaluation of Global Initiative for Chronic Obstructive Lung Disease (GOLD) and divided the patients into A, B, C, and D groups for research. There may be some drawbacks. Patients in different grades or groups may respond differently to treatment. Therefore, the conclusion of this study cannot fully reflect the therapeutic effect of acupoint application on different COPD patients. Moreover, studies have shown that with the decline in pulmonary function in COPD patients, the CD8⁺ T-cell index decreased more significantly. It is possible for patients with poor pulmonary function to benefit more from the improvement in CD8⁺ T-cells after acupoint application therapy. Further large-scale studies are needed in the future.

T cells can be divided into Th, CTL and regulatory T cells according to their functions. These cells are actually effector cells differentiated from initial CD4⁺ T-cells or initial CD8⁺ T-cells after activation. Th expresses CD4, which is commonly called CD4⁺ T cells. There are many subtypes of Th itself. This study has not yet explored the effect of Acupoint Application on Th in COPD patients, and needs further study.

In addition, acupoints and formula may affect the therapeutic effect. In this study, the acupoints used in the included studies were different. Among them, 5 studies^[26–29,31] selected acupoints contain Feishu and Shenshu acupoints, and 3 studies^[27,28,32] selected acupoints contain Dingchuan acupoints.

In this study, the selected drugs and proportion were different in the included studies, but most of them were based on the prescription of white mustard, corydalis tuber, kansui and asarum. This prescription originated from *Zhang's Yitong*,^[42] which had the effect of warming Yang and resolving phlegm. This study has not yet discussed this aspect, and needs further study.

The course of treatment may have an impact on the outcome. The course of treatment included in this study ranged from 1 month to 3 years, with a long time span. This may have an impact on the conclusions of the study, which needs to be examined in the future.

In addition to the level of CD4⁺ T-cells and CD8⁺ T-cells in serum of COPD patients, some studies reported the level of CD4⁺ T-cells and CD8⁺ T-cells in BAL and sputum of COPD patients. Regardless of smoking habits, CD8⁺ T-cells was activated in BAL of COPD patients. Compared with non-smokers, the percentage of CD8⁺ T-cells in BAL of smokers with normal lung function and COPD was increase, while the percentage of CD4⁺ T-cells was decrease.^[43] Compared with healthy controls, the amount of CD⁺ T-cells and CD8⁺ T-cells in sputum of COPD patients was normal.^[44] However, in this study, the source of T cells was all from the serum of COPD patients, and there were no T cells from BAL or sputum of COPD patients, which need further study in the future.

5. Conclusions

Acupoint application can improve CD8⁺ T-cells and the CD4⁺/CD8⁺ ratio in patients with COPD and has an auxiliary effect on reducing the number of acute exacerbations and improving clinical efficacy.

Author contributions

Conceptualization: Hong-Ri Xu, Liang-Duo Jiang, Cheng-Xiang Wang, Mei Han, Wu Jian-Jun.

Supervision: Yi-Xuan Li, Wu Jian-Jun.

Visualization: Yi-Xuan Li, Wu Jian-Jun.

Writing – original draft: Zhang Yingxue, Hong-Ri Xu, Wu Jian-Jun.

Writing – review & editing: Ying-Xue Zhang, Wu Jian-Jun.

References

- Wang C, Xu J, Yang L, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH]study): a national cross-sectional study. *Lancet* 2018;391:1706–17.
- Chinese Medical Association, Journal of Chinese Medical Association, General Medicine Association of Chinese Medical Association, et al. Guidelines for Primary Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease. *Chin J Gen Pract*. 2018;17:856–70.
- Yin P, Wang H, Vos T, et al. A subnational analysis of mortality and prevalence of COPD in China from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *Chest* 2016;150:1269–80.
- Yin S, Shijie H, Weige J, et al. Progress in immunopathogenesis of chronic obstructive pulmonary disease. *Medical Rev* 2019;25:2574–8.
- Chen Y, Bai P, Liu L, et al. Increased RANKL expression in peripheral T cells is associated with decreased bone mineral density in patients with COPD. *Int J Mol Med* 2016;38:585–93.
- Jackute J, Žemaitis M, Pranys D, et al. Distribution of CD4+ and CD8+ T cells in tumor islets and stroma from patients with non-small cell lung cancer in association with COPD and smoking [J]. *Medicina (Kaunas)* 2015;51:263–71.
- Makris D, Lazarou S, Alexandrakis M, et al. Tc2 response at the onset of COPD exacerbations. *Chest* 2008;134:483–8.
- Zhang R, Hu Y, Niu H. Rheumatoid arthritis treated with acupoint application of huiyao tongluo dingtong san:a rando-mized controlled trial. *Zhongguo Zhen Jiu* 2016;36:699–703.
- Zhang X, Zhong M, Yang J. Comparative study of acupoint sticking therapy with different application time in treatment of chronic obstructive pulmonary disease at stable stage. *Nurs Integr Trad Chin West Med* 2019;5:41–4.
- Zhu Y, Wang H, Zhao H, et al. Analysis of acupoint selection and medication regularity of acupoint application in the treatment of epigastric pain based on modern literature. *Jilin J Chin Med* 2017;37:757–60.
- Hu N, Xiong S, Liu S. Effect of Chinese medicine acupoint application on alleviating primary menstrual pain in students of one traditional chinese medicine college. *J Guangzhou Univ Trad Chin Med* 2016;33:817–22.
- Wan M, Wei D. Observation of therapeutic effect of Acupoint Application on hemiplegia after apoplexy. *Chin J Integr Med Cardio-Cerebrovasc Dis* 2019;17:2044–7.
- Liu J, Wu Y. Status quo of clinical application of acupoint plaster therapy and its mechanism. *Shanghai Med Pharmaceutical J* 2018;39:3–5.
- Liu Y. Summer acupoint application for winter disease in prevention and treatment of bronchial asthma. *J Trad Chin Med* 2015;56:1884–6.
- Zhang S, Zhang Z, Zhang X, et al. Curative effect observation and nursing care of winter disease cured in summer acupoint sticking therapy to treat stabilization COPD. *Chin J Gen Pract* 2017;15:2152–5.
- Zhang Y, Zhou Y, Liao X, et al. Observations on the efficacy of point application for stable chronic obstructive pulmonary disease. *Shanghai J Acu-Mox* 2016;35:1065–9.
- Xu M, Yang L, Liu S, et al. Clinical observation on treatment of stable COPD by point application. *Modern Trad Chin Med* 2017;37:21–6.
- Yu B, Hu H, Sun M, et al. Randomized controlled study on the treatment of chronic obstructive pulmonary disease with cold phlegm blocking pulmonary type by acupoint plaster of 'summer treatment for winter disease'. *China J Trad Chin Med Pharm* 2019;34:3818–20.
- Sun H, Wu ZL, Zhang C, et al. Clinical study on 60 cases of stable chronic obstructive pulmonary disease treated by kechuan plaster. *Chin Clin Doct* 2019;47:792–4.
- Ning L, Xu Y, Xu F, et al. Clinical observation on treating 44 cases of stable chronic obstructive pulmonary disease by four seasons acupoint external application. *J Pract Trad Chin Inter Med* 2011;25:3–5.

- [21] Wu H, Luo X, Chen Q, et al. Observation of the clinical efficacy on stable chronic obstructive pulmonary obstruction treated with festering moxibustion therapy. *World J Integr Trad West Med* 2014;9:263–5.
- [22] Hu F, Sun H, Wu Z, et al. Effect of Acupoint Application of traditional Chinese medicine on immune function of patients with stable chronic obstructive pulmonary disease. *Mod J Integr Trad Chin West Med* 2017;26: 2203–5+80.
- [23] State Administration of traditional Chinese medicine Traditional Chinese Medicine New Drug Clinical Instruction Principle (Trial). Beijing: China Medical Science and Technology Press; 2002. 361–390.
- [24] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–101.
- [25] Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006;25:3443–57.
- [26] Qin C. Effect of Acupoint Application of Buxu Pingchuan ointment on cellular immunity and BODE score index in COPD patients. *J Fuj Univ TCM* 2010;20:10–2.
- [27] Qin X. The effect of applying time of summer therapy for winter disease on stable COPD and T lymphocyte subsets [dissertation]. Beijing, China: School of clinical medicine, Beijing University of Traditional Chinese Medicine; 2019.
- [28] Gong X, Mou F. Effect of acupoint application therapy on immune function in patients with chronic obstructive pulmonary disease. *J Chin Med* 2018;33:2082–5.
- [29] Wang H, Li S, Wang M. Clinical effect and change of immunological function of patients with COPD by sticking acupuncture points with traditional Chinese medicine [J]. *Chin Arch Trad Chin Med* 2009;27: 1209–11.
- [30] Wang P. Effect of acupoint application therapy of shuangxi kechuan ointment on inflammatory factors in patients with stable chronic obstructive pulmonary disease. *J Chin Med* 2018;33:2086–9.
- [31] Aimaiti J, Aizezi N. Effect of Acupoint Application of traditional Chinese medicine combined with conventional western medicine on inflammatory factors and immune function in elderly patients with chronic obstructive pulmonary disease. *Mod J Integr Trad Chin West Med* 2016;25:3393–6.
- [32] Zang M, Chen X, Lin W, et al. Effect of external therapy of TCM on stable stage of chronic obstructive pulmonary disease and its effect on immune function. *Zhejiang J Integr Tradit Chin West Med* 2016;26:1006–8.
- [33] Yang J, Zhong M, Deng Q, et al. Effect of acupoint application duration of medicinal vesiculation therapy on immune function in patients with chronic obstructive pulmonary disease in stable phase. *J Guang Univ Chinese Med* 2019;22:10–4.
- [34] Cao Xue Tao. *Medical Immunology*. Beijing: People's Medical Publishing House; 2018. 86.
- [35] Jackute J, Žemaitis M, Pranys D, et al. Distribution of CD4+ and CD8+ T cells in tumor islets and stroma from patients with non-small cell lung cancer in association with COPD and smoking. *Medicina (Kaunas)* 2015;51:263–71.
- [36] Zhang M, Wan Y, Jin Y, et al. Cigarette smoking promotes inflammation in patients with COPD by affecting the polarization and survival of Th/Tregs through up-regulation of muscarinic receptor 3 and 5 expression. *PLoS One* 2014;9:e112350.
- [37] Geerdink JX, Simons SO, Pike R, et al. Differences in systemic adaptive immunity contribute to the 'frequent exacerbator' COPD phenotype. *Respir Res* 2016;17:140.
- [38] Roberts MEP, Higgs BW, Brohawn P, et al. CD4+ T-cell profiles and peripheral blood ex-vivo responses to T-cell directed stimulation delineate COPD phenotypes. *Chronic Obstr Pulm Dis* 2015;2:268–80.
- [39] Global Initiative for Chronic Obstructive Lung Disease [webpage on the internet]. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease [updated 2019; Accessed November 7, 2018 Available from <https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf>].
- [40] Li J. Effect of acupoint application of traditional chinese medicine on pulmonary function in patients with stable chronic obstructive pulmonary disease. *J Chin Med* 2016;31:787–90.
- [41] Hu H, Sun M, Zhu Z, et al. Systematic assessment and meta-analysis of acupoint application for stable chronic obstructive pulmonary disease. *Shanghai J Acu-mox* 2019;38:932–40.
- [42] Zhang L. *Zhang shiyitong*. Shanghai: Shanghai Science and Technology Press; 1990. 117.
- [43] Roos-Engstrand E, Ekstrand-Hammarström B, Pourazar J, et al. Influence of smoking cessation on airway T lymphocyte subsets in COPD. *COPD* 2009;6:112–20.
- [44] Leckie MJ, Jenkins GR, Khan JS, et al. T lymphocytes in asthma, COPD and healthy subjects have the phenotype of activated intraepithelial T cells (CD69+ CD103+). *Thorax* 2003;58:23–9.