



Impact of Tai Chi on CRP, TNF-alpha and IL-6 in inflammation: a systematic review and meta-analysis

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Background: Previous studies have reported that C reactive protein (CRP), tumor necrosis factor-alpha (TNF-alpha), and interleukin-6 (IL-6) in Coronavirus disease 2019 (COVID-19) patients are significantly increased, and their progressive increases are clinical warning indicators of severe and critical severity. The purpose of this meta-analysis is to evaluate the efficacy of Tai Chi on CRP, TNF-alpha and IL-6, and provide a basis for complementary treatment of COVID-19.

Methods: Five English databases (PubMed, Web of Science, Physiotherapy Evidence Database, Cochrane Library and Embase) and four Chinese electronic databases (CNKI, Wanfang, China Science and Technology Journal Database and SinoMed) were searched from inception to April 1st, 2020. Combination MeSH and free text terms were used to make up search strategy. Interventions in RCTs were Tai Chi with or without comparison (usual care, health education, drug therapy, psychosocial therapy). Revman version 5.3 was used to analyze the extracted data. Continuous outcomes were described by SMD, and the I^2 test was used to assess heterogeneity. Revised Physiotherapy Evidence Database scale was used to assess methodological quality.

Results: Nine RCTs involving 571 participants met the inclusion criteria, and the sample size ranged from 19 to 100 per study. Tai Chi can significantly reduce TNF-alpha (Tai Chi intervention: SMD = -0.92, 95% CI: -1.32 to -0.53; Tai Chi plus drug treatment intervention: SMD = -0.63, 95% CI: -1.15 to -0.11), moreover, it could reduce the amount of IL-6 (Tai Chi intervention: SMD = -0.62, 95% CI: -1.00 to -0.23; Tai Chi plus drug treatment intervention: SMD = -2.17, 95% CI: -3.69 to -0.64) and CRP (Tai Chi plus drug treatment intervention: SMD = -1.98, 95% CI: -2.47 to -1.50) while with a high exercise amount. A low exercise amount of Tai Chi showed poor efficacy on CRP (Tai Chi intervention: SMD = -0.18, 95% CI: -0.61 to 0.25; Tai Chi plus drug treatment intervention: SMD = -0.15, 95% CI: -0.47 to 0.16) and IL-6 (Tai Chi intervention: SMD = 0.15, 95% CI: -0.24 to 0.55).

Discussion: The strength of evidence might be limited due to relatively low methodological quality, heterogeneity and indirectness. The overall results elucidate that Tai Chi could significantly reduce TNF-alpha while it did not show the same effects in IL-6 and CRP. After subgroup analysis, Tai Chi with a high exercise amount can reduce IL-6 and CRP. Tai Chi with a high exercise amount could be suggested as a complementary intervention for people with COVID-19.

Trial registration: PROSPERO CRD42020177655.

Keywords: Tai Chi; inflammation; meta-analysis

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Introduction

Coronavirus disease-2019 (COVID-19), known as a novel infectious disease, has caused worldwide spread currently (1-3). When preparing this manuscript, the World Health Organization (WHO) reported over 2.7 million new COVID-19 cases last week (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>). The severity and mortality rates of COVID-19 are higher in elderly patients than young and middle-aged people (4-6). Previous studies have reported that CRP, TNF-alpha, and IL-6 in COVID-19 patients are significantly increased, and their progressive increases are clinical warning indicators of severe and critical severity (7-12). The COVID-19 challenges the national healthcare system for every country, which may overwhelm the available medical resources (13-15).

Tai Chi, known as a form of traditional Chinese health-promoting martial art, is beneficial for preventing and complementary treating of diseases (16-20), and the training intensity is suitable for the elderly (16-22). Besides, Tai Chi has a significant effect on alleviating mental stress and anti-depression (23-25), which is common during the COVID-19 outbreak (26,27). At present, Tai Chi was adopted in the *Beijing New Coronavirus Pneumonia Traditional Chinese Medicine Prevention and Treatment Program* (<http://www.satcm.gov.cn/xinxifabu/gedidongtai/2020-03-08/13717.html>) and *New Coronary Pneumonia Discharge Rehabilitation Program* (<http://www.nhc.gov.cn/xcs/zhengcwj/202003/d4558d2cc35e44d5b9adba7c911e0b4c.shtml>). Elevated inflammatory markers are one of the main concerns in COVID-19. Tai Chi may have potential benefits in COVID-19 by reducing inflammatory markers level.

Many corresponding randomized controlled trials (RCTs) have found that Tai Chi has a positive regulating effect on inflammatory markers (28-31), while the results are limited and inconclusive due to the small sample size of individual experiments. The purpose of this systematic review is to evaluate the effect of Tai Chi on C reactive protein (CRP), tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6).

We present the following article in accordance with the PRISMA reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-640>).

Methods

Trial registration

The study was prospectively registered in PROSPERO with

the number CRD42020177655.

Literature search

Five English (PubMed, Web of Science, Physiotherapy Evidence Database, Cochrane Library and Embase) and Four Chinese electronic databases (CNKI, Wanfang, China Science and Technology Journal Database and SinoMed) were searched from inception to April 1st, 2020. A search strategy in English electronic databases was composed using the Medical Subject Headings terms (MeSH) of 'tai ji', 'C-reactive Protein', 'Tumour Necrosis Factor-alpha', 'Interleukin-6', 'inflam*' and their free text terms. Moreover, the terms of 'baixibaojiesu6', 'baixibaojiesu-6', 'IL-6', 'IL6', 'zhongliuhuaisiyinziα', 'zhongliuhuaisiyinzi-α', 'TNF-α', 'TNFα', 'CRP', 'Cfanyingdanbai', 'yanzheng', 'taiji' were used to make up search strategy in Chinese electronic databases. No language restrictions were applied to all the databases searching.

Study selection

The following eligibility criteria were applied: (I) participants: human participants; (II) intervention: Tai Chi with or without usual care, health education, drug therapy, psychosocial therapy; (III) comparison: usual care or health education or drug therapy or psychosocial therapy; (IV) outcomes: C-reactive protein, tumor necrosis factor-alpha, interleukin-6; (V) study design: RCTs (length no less than 4 weeks).

Two reviewers (Cheng S. and Cui Q.) searched databases and selected articles independently. If any disagreement emerged between the two reviewers, the third person (Feng S.) participated in discussions and proposed solutions to reach an agreement.

Data extraction and quality assessment

Two reviewers extracted data from selected studies and assessed the methodological quality independently. If any disagreement emerged between the two investigators, the third person participated in discussions and proposed solutions to reach an agreement. Extracted information included study ID, participant characteristics, exercise frequency and time length, intervention measures of the experimental group and the control group, outcomes measured and adverse events. To calculate the effect size, quantitative data (mean, the standard deviation of the

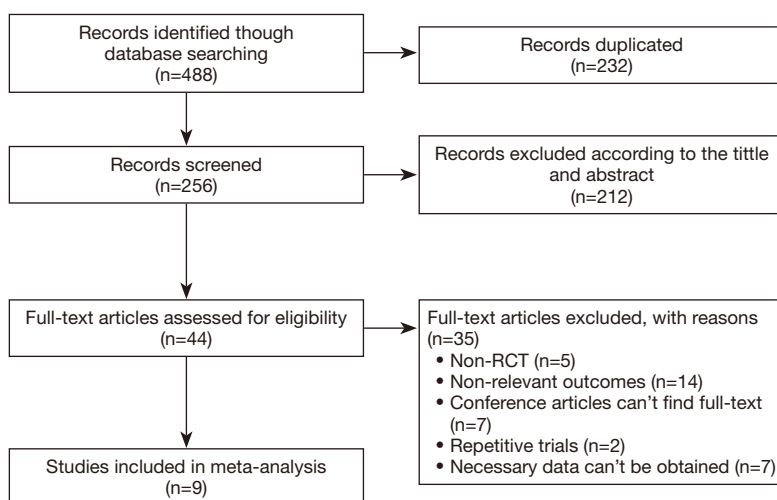


Figure 1 Flow chart of the study selection process.

outcomes and the number of participants) in each group were extracted by the same investigator.

The revised Physiotherapy Evidence Database (PEDro) scale was used to assess the methodological quality, which is applicable to the assessment of physiotherapy. The original scale includes 11 items (32). Due to the blinded participants and instructors could not be achieved in selected studies, the revised PEDro scale contains the following 9 items: eligibility criteria, allocation randomly, allocation concealment, similar baseline, blinding assessor(s), retention rate of $\geq 85\%$, intention-to-treat analysis, between group statistical comparisons, point measures and measures of variability for at least one outcome. One point was awarded when a criterion was clearly satisfied. The higher score indicated better quality.

The authors of the studies which did not present the necessary data in their published papers were contacted by emails.

Statistical analysis

Revman version 5.3 was used to analyze the extracted data. Continuous outcomes were described by standardized mean difference (SMD). I^2 test was used to judge the heterogeneity of meta-analysis. $I^2 > 50\%$ was considered to have a significant heterogeneity. The random-effect model was adopted for high heterogeneity ($I^2 > 50\%$), and the fixed-effect model for low heterogeneity ($I^2 < 50\%$). Subgroup analysis was used to identify potential factors of high heterogeneity.

To investigate whether there was a dose-response relationship between Tai Chi and outcomes, a subgroup analysis was performed based on the total amount of exercise. Since the included studies did not report the intensity of Tai Chi exercise, considering all selected studies had the same exercise intensity. The exercise amount can be expressed as total exercise time (*TET*).

$$TET = ETPD \times DEPW \times TWE \quad [1]$$

Where, *TET* means total exercise time, *ETPD* means exercise time per day, *DEPW* means days of exercise per week and *TWE* means total weeks of exercise.

P values < 0.05 were considered statistically significant. Publication bias was not assessed due to the number of selected studies is less than 10 in each analysis.

Results

Search results

A total of 488 records (including duplicates) were found by searching the nine databases, of which 132 records were retrieved from Chinese electronic databases and 356 records from English. *Figure 1* shows the process of study selection. After removing 232 duplicated records, 256 records were assessed according to the titles and abstracts of articles, further excluding 212 irrelevant records. The remaining 44 full-text articles were assessed, 35 of which were excluded, and the reasons are presented in *Figure 1*. Eventually, 9 studies were selected for this meta-analysis (23,33-40).

Table 1 The characteristics of included studies

Study	Participants	No. of patients (M/F)	Mean age (years) (I/C)	Study group (n) (I/C)	Duration (weeks)/ exercise time (min)	Frequency	Intervention	Comparison	Outcomes	Adverse events
Janelins <i>et al.</i> 2011	Breast cancer survivors	19 (0/19)	54.33/52.70	9/10	12/60	Three times per week	Tai Chi	Psychosocial therapy	IL-6	No
Irwin <i>et al.</i> 2012	Older adults	83 (32/51)	70.7/71.4	46/37	16/40	Three times per week	Tai Chi	Health education	CRP, IL-6	No
Lavretsky <i>et al.</i> 2011	Depression	73 (28/45)	69.1/72.0	36/37	10/120	Once a week	Tai Chi + drug treatment	Drug treatment + health education	CRP	No
Chen <i>et al.</i> 2015	Ankylosing spondylitis	86 (61/25)	29.58/30.60	43/43	8/30	Once a day	Tai Chi + drug treatment	Drug treatment	CRP	No
Chen <i>et al.</i> 2019	Depression	36 (0/36)	not reported	18/18	16/60	Three times per week	Tai Chi	No treatment	TNF, IL-6	No
Du <i>et al.</i> 2014	Chronic obstructive pulmonary disease	74 (46/28)	65.24/64.48	36/38	12/60	Once a day	Tai Chi	No treatment	TNF, IL-6	No
Wu <i>et al.</i> 2010	Diabetes mellitus type 2	40 (15/25)	51.3/52.4	20/20	24/60	Three times per week	Tai Chi + drug treatment	Drug treatment	IL-6	No
Li <i>et al.</i> 2018	Stable Angina	100 (58/42)	65.07/65.08	50/50	24/30	Five times per week	Tai Chi + drug treatment	Drug treatment	CRP	No
Li 2013	Diabetes mellitus type 2	60 (36/24)	57.3	30/30	8/45	Once a day	Tai Chi + drug treatment	Drug treatment	TNF, IL-6	No

CRP, C reactive protein; TNF, tumor necrosis factor; IL-6, interleukin-6.

Table 2 Study quality of the included studies (revised PEDro scale)

Study	1	2	3	4	5	6	7	8	9	Score
Janelsins <i>et al.</i> , 2011, (34)	√	√	√	√		√		√	√	7
Irwin <i>et al.</i> , 2012, (33)	√	√		√		√		√	√	6
Lavretsky <i>et al.</i> , 2011, (23)	√	√	√	√	√	√	√	√	√	9
Chen <i>et al.</i> , 2015, (39)	√	√		√		√	√	√	√	7
Chen <i>et al.</i> , 2019, (40)	√	√		√		√	√	√	√	7
Du <i>et al.</i> , 2014, (38)	√	√		√		√	√	√	√	7
Wu <i>et al.</i> , 2010, (35)	√	√		√		√	√	√	√	7
Li <i>et al.</i> , 2018, (37)	√	√		√		√	√	√	√	7
Li, 2013, (36)	√	√		√		√	√	√	√	7

1, eligibility criteria; 2, allocation randomly; 3, allocation concealment; 4, similar baseline; 5, blinding assessors; 6, retention rate of ≥85%; 7, intent-to-treat analysis; 8, between group statistical comparison; 9, point measure and measures of variability for at least one outcome.

Table 3 The results of meta-analysis for primary outcome

Primary outcomes	Interventions with or without subgroup	Results
TNF-alpha	Tai Chi intervention	SMD =-0.92, 95% CI: -1.32 to -0.53, P<0.00001
	Tai Chi plus drug treatment intervention	SMD =-0.63, 95% CI: -1.15 to -0.11, P=0.02
IL-6	Tai Chi intervention with high exercise group	SMD =-0.62, 95% CI: -1.00 to -0.23, P=0.002
	Tai Chi intervention with low exercise group	SMD =0.15, 95% CI -0.24 to 0.55, P=0.44
	Tai Chi plus drug treatment intervention	SMD =-2.17, 95% CI: -3.69 to -0.64, P=0.005
CRP	Tai Chi intervention	SMD =-0.18, 95% CI: -0.61 to 0.25, P=0.41
	Tai Chi plus drug treatment intervention with high exercise group	SMD =-1.98, 95% CI: -2.47 to -1.50, P<0.00001
	Tai Chi plus drug treatment intervention with low exercise group	SMD =-0.15, 95% CI: -0.47 to 0.16, P=0.33

TNF, tumor necrosis factor; IL-6, interleukin-6; CRP, C reactive protein.

Characteristics of included studies

Table 1 shows the characteristics of the included studies. They were published between 2010 and 2019, and among them, 7 diseases were involved in the selected studies. The sample size ranged from 19 to 100 per study. Female percentages ranged from 29.1% to 100%. The mean age of participants ranged from 30 to 71 years, except one article did not mention the mean age (40). The duration of intervention ranged from 8 to 24 weeks. Weekly exercise frequency ranged from one to seven times, and each exercise time ranged from 30 to 120 minutes. Four trials adopted Tai Chi as the intervention group (33,34,38,40) and 5 trials adopted a combined intervention of Tai Chi and drug treatment (23,35-37,39). The comparison group included

psychosocial therapy, health education, drug treatment, and no treatment. Of the 9 studies, the outcome of TNF-alpha, IL-6 and CRP were reported in three (36,38,40), six (33-36,38,40), and four (23,33,37,39) articles, respectively. No adverse events occurred during studies.

Study quality assessment

Table 2 shows the study quality of each included article. Among them, sum scores ranged from 6 to 9, with a median of 7. Only two studies used allocation concealment (23,34), and one study adopted outcome assessment blinding (23). Two studies did not use intention-to-treat analysis (33,34).

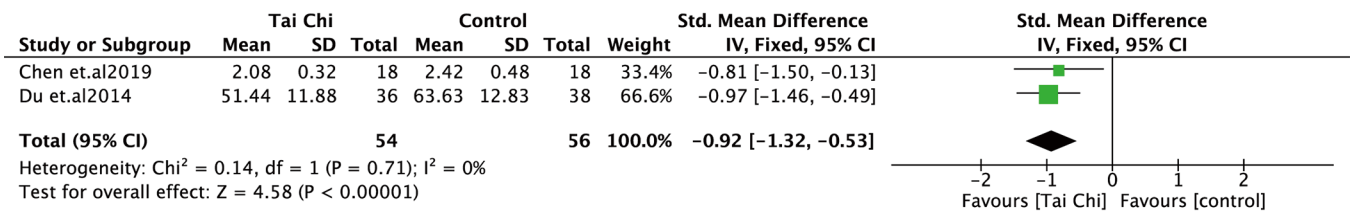


Figure 2 Forest plot of the comparison for the outcome TNF-alpha in Tai Chi intervention. TNF, tumor necrosis factor.

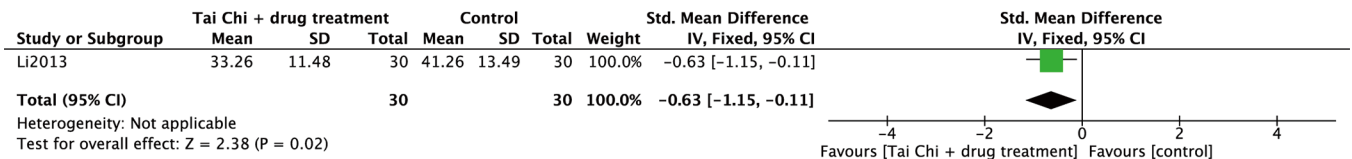


Figure 3 Forest plot of the comparison for the outcome TNF-alpha in Tai Chi + Drug treatment intervention. TNF, tumor necrosis factor.

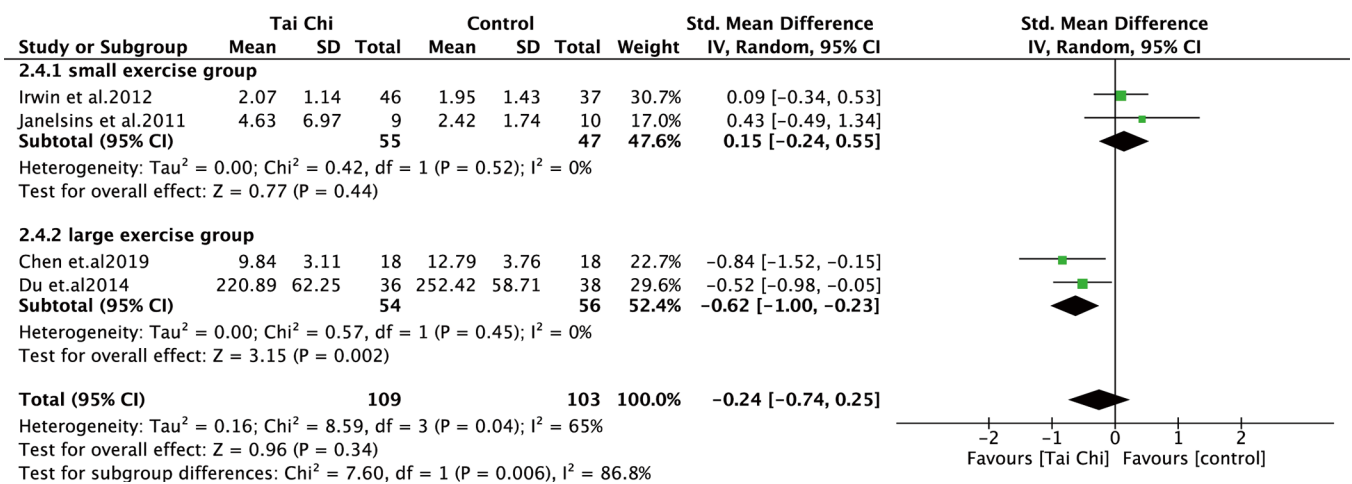


Figure 4 Forest plot of the comparison for the outcome IL-6 in Tai Chi intervention. IL-6, interleukin-6.

Primary outcomes

Table 3 presents the results of meta-analysis for primary outcomes. We found that high heterogeneity drops to 0 when using 2,500 min (exercise amount) as the cut-off value. Therefore, we further conducted subgroup analyses according to the exercise amount: low exercise group (exercise amount less than 2,500 min) and high exercise group (exercise amount more than 2,500 min).

TNF-alpha

A total of 3 studies involving TNF-alpha (36,38,39). Considering the relatively low heterogeneity of the included

studies ($I^2=0\%$) in the Tai Chi intervention, we adopted a fixed-effect model.

Tai Chi showed a significant benefit on reducing TNF-alpha both in the Tai Chi intervention and the Tai Chi plus drug treatment intervention (SMD =-0.92, 95% CI: -1.32 to -0.53, $P<0.00001$) (see Figure 2) (SMD =-0.63, 95% CI: -1.15 to -0.11, $P=0.02$) (see Figure 3).

IL-6

A total of 6 studies involving IL-6 (33-36,38,40). The heterogeneity of the included studies was significantly high ($I^2=65\%$) in the Tai Chi intervention.

The results show that Tai Chi significantly reduced IL-6

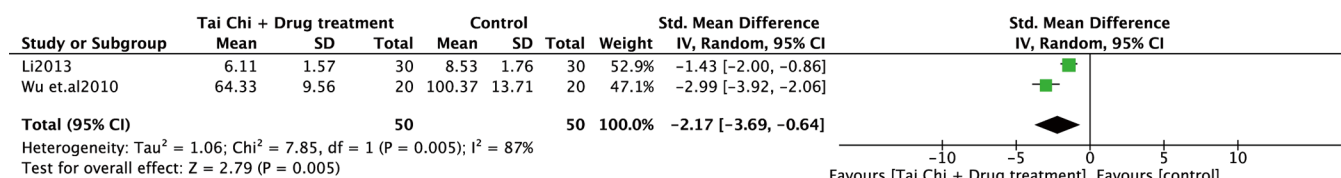


Figure 5 Forest plot of the comparison for the outcome IL-6 in Tai Chi + Drug treatment intervention. IL-6, interleukin-6.

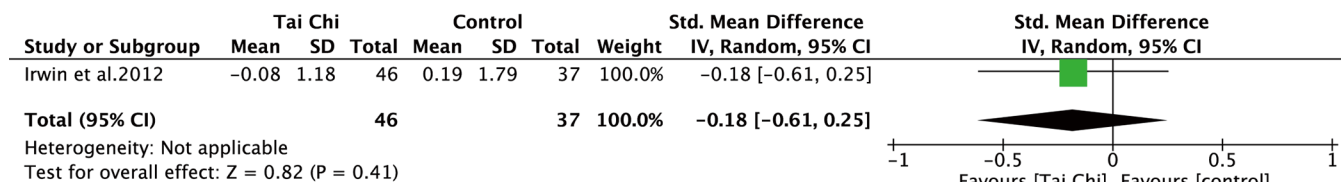


Figure 6 Forest plot of the comparison for the outcome CRP in Tai Chi intervention. CRP, C-reactive protein.

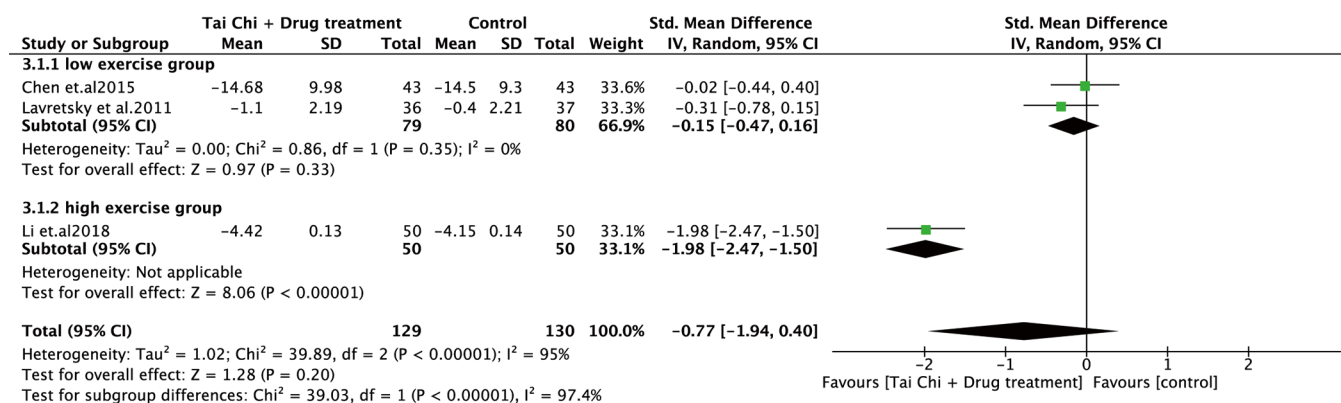


Figure 7 Forest plot of the comparison for the outcome CRP in Tai Chi + Drug treatment intervention. CRP, C-reactive protein.

in high exercise group (SMD = -0.62, 95% CI: -1.00 to -0.23, P=0.002) (Figure 4). However, it didn't have shown the efficacy in low exercise group (SMD = 0.15, 95% CI: -0.24 to 0.55, P=0.44) (see Figure 4).

In Tai Chi plus Drug treatment intervention, Tai Chi was associated with decreased IL-6 (SMD = -2.17, 95% CI: -3.69 to -0.64, P=0.005; I²=87%) (see Figure 5).

CRP

A total of 4 studies involving CRP (23,33,37,39). The heterogeneity of the included studies was significantly high (I²=94%) in Tai Chi plus Drug treatment intervention.

The results show that Tai Chi was not associated with an effect on reducing CRP in Tai Chi intervention (SMD = -0.18, 95% CI: -0.61 to 0.25, P=0.41) (see Figure 6).

The results show that Tai Chi significantly reduced CRP in high exercise group (SMD = -1.98, 95% CI: -2.47 to -1.50, P<0.00001), but not in the low exercise group (SMD = -0.15, 95% CI: -0.47 to 0.16, P=0.33) (see Figure 7).

Due to the imbalance of the CRP at baseline (37), we adopted differences in changes from baseline to analyze (41).

Discussion

Based on the analysis of existing data, the effects of Tai Chi on CRP, TNF-alpha and IL-6 are related to the exercise amount. Our quantitative analysis demonstrated that Tai Chi significantly reduce TNF-alpha in all selected studies (36,38,40) and all of them were the high amount of exercise. Except for the subgroup analysis showed that Tai Chi with

high exercise amount could reduce IL-6 and CRP but not with low exercise amount, Tai Chi was associated with decreased IL-6 (35,36) in Tai Chi plus Drug treatment intervention, and both interventions reached the standard of high exercise amount. Besides, the results showed that Tai Chi was not relevant in reducing CRP in Tai Chi intervention (33), and the exercise amount in this study was categorized as a low exercise amount.

In the clinical characteristics of COVID-19 patients, the average level of CRP is 23 mg/L (42), the average level of TNF-alpha and IL-6 is 8.3 ng/L and 34 ng/L respectively in moderate patients (43). Besides, the magnitude of the reduction of these inflammatory markers in Tai Chi are: TNF-alpha [40 (15.4%) to 36 (41%)]; IL-6 [33 (8%) to 36 (48.5%)]; CRP [33 (4.8%) to 37 (78.2%)]. According to these data, performing Tai Chi alone can hardly reduce the elevated inflammatory markers to the normal range. A previous study showed that Tai Chi had a better effect on reducing IL-6 in older adults with elevated IL-6 levels at baseline than the control group (33). Besides, another study also found that Tai Chi improved health function, especially in those who had the greatest impairments of health status at baseline (44). They are consistent with the actual situation of COVID-19 patients and provide evidence for Tai Chi as a complementary treatment for COVID-19 patients from another aspect.

Regarding the molecular mechanisms of Tai Chi's effect on inflammatory markers, a previous systematic review (45) indicated that mind-body interventions (including Tai Chi) are related to downregulate the nuclear factor kappa B pathway, and it suggested that mind-body interventions may reduce the risk of inflammation-related diseases.

Besides, a previous meta-analysis (46) evaluated the effects of mind-body therapies on inflammatory markers, which revealed the effects of Tai Chi/Qi Gong on CRP and IL-6 could be ignored. However, this meta-analysis only included articles in the English language and was published 6 years ago with much literature updating during this period. Moreover, Tai Chi is different from Qigong (47), that study merged Tai Chi and Qi Gong to analyze the effects which may cause high heterogeneity. Our research focused on the effects of Tai Chi more accurately and comprehensively. Besides, a previous systematic review (48) indicated non-conventional interventions such as Tai Chi, have shown significant associations with IL-6 and TNF- α decreasing, which supports our conclusions.

On the feasibility of COVID-19 patients to perform Tai Chi, a study from China CDC (49) showed that the

majority of COVID-19 patients (80.9%) were considered asymptomatic or mild infections. Among these patients, most of them can move freely. Besides, in Wuhan's first traditional Chinese medicine cabin hospital where Tai Chi was adopted as a complementary treatment, none of the patients turned into a severe case (<http://www.satcm.gov.cn/xinxifabu/gedidongtai/2020-02-27/13444.html>). Therefore, according to the specific conditions of the patients, it is feasible to perform Tai Chi for those who have the exercise ability with the guidance and assistance of professionals.

COVID-19 is caused by SARS-CoV-2, and the genome is similar to SARS-CoV which caused the outbreak of SARS in 2003 (50). A qualitative review (51) investigated five factors motivated SARS survivors in post-SARS Hong Kong to practice Tai Chi, including deterioration of health caused by SARS-associated sequelae, unpleasant experiences during follow-up biomedical treatment, regaining an active role in recovery and rehabilitation, overcoming SARS-associated stigmas, preparing for potential stigmatization and discrimination during future epidemics. The study concluded that practicing Tai Chi helped the participants improve health and played a vital role in social function. The phenomenon refracted by the above motivations may also occur in patients with COVID-19. Thus, the practice of Tai Chi could be maintained for a long time in COVID-19 patients, even as a way of life.

Although this study found that Tai Chi has a certain role in reducing these inflammatory indicators, the evidence itself has limitations. The strength of evidence might be limited from the following reasons: (I) with a small sample size, resulting in low precision; (II) risk of bias of the original studies and relatively low methodological quality; (III) heterogeneity, from the PICO aspects; (IV) indirectness, that means the outcome indicators could not be a direct verification of the clinical practice.

For clinical heterogeneity, the original studies included in this study differ in patient groups. But they have increased inflammatory indicators in common and the effect of inflammation on diseases is the same. This meta-analysis explored the effect of Tai Chi on three inflammatory indicators, so merging different patient groups is feasible. The results of the heterogeneity test support it. Although meta-analysis didn't include infectious disease patients, two controlled trials have assessed the effects of Tai Chi on clinically relevant immunity to varicella-zoster virus in the elderly and found Tai Chi can increase the specific cell-mediated immunity against the varicella-zoster virus (44,52).

A previous review (53) also showed that Tai Chi could improve the immunity of the elderly population at risk of herpes zoster to varicella-zoster virus. It provided potential evidence for Tai Chi as a complementary treatment to COVID-19 patients indirectly.

Clinical researchers should consider several points in the future: (I) improving methodology quality of studies, including reporting the detail of allocation concealment and assessors blinding, and recording the number and reasons of missing data; (II) in order to reduce selective reporting, all clinical trials should be registered in advance on the international platform; (III) future research should pay more attention to the relationship between the exercise amount of Tai Chi and outcomes.

Cytokine storm is essential for the progression of COVID-19, which may cause serious complications and even death (54,55). The elevated levels of proinflammatory cytokines such as TNF-alpha and IL-6 are closely related to cytokine storm (56). Besides, CRP is a sensitive biomarker of inflammation and infection, which is induced by IL-6 in the liver (57). Based on the data from our study, we cautiously recommend Tai Chi as a complementary intervention to deal with COVID-19 patients and defer the coming of the cytokine storm.

Conclusions

The overall results elucidate that Tai Chi could significantly reduce TNF-alpha while it did not show the same effects in IL-6 and CRP. After subgroup analysis, Tai Chi with a high exercise amount can reduce IL-6 and CRP. This may further indicate that Tai Chi with a high exercise amount could be suggested as a complementary intervention for people with COVID-19.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at <https://dx.doi.org/10.21037/apm-21-640>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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