Systematic Review and Meta-Analysis

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# Efficacy and safety of acupuncture for chemotherapy-induced leukopenia

## A systematic review and meta-analysis

Jiayun Nian, MD[a], Xu Sun, PhD[b], Wenjie Zhao, MD[a], Xiaomin Wang, PhD[a,*]

**Abstract**

**Background:** Leukopenia is one of most common types of myelosuppression secondary to chemotherapy. The main methods used to treat leukopenia after chemotherapy have various limitations. Several studies have reported the role of acupuncture in the prevention and treatment of leukopenia, but the quality of the study is uneven. Here, we used a systematic review and meta-analysis to evaluate the efficacy and safety of acupuncture in the treatment of leukopenia after chemotherapy.

**Methods:** We searched the databases of the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library, Medline (via PubMed), EMBASE (via embase.com), the China National Knowledge Infrastructure Database (CNKI), the Chinese Biomedical Literature Database (CBM), the Chinese Scientific Journal Database (VIP database) and the Wanfang database to collect randomized clinical trials (RCTs) on acupuncture in the treatment of leukopenia after chemotherapy. Cochrane systematic reviewer manual 5.2 was used for bias risk assessment. RevMan5.3 statistical software was applied for statistical analysis.

**Results:** Fifteen RCTs were included in this study, with a total of 1130 patients. Meta-analysis results showed that acupuncture can increase white blood cell (WBC) count after chemotherapy [MD = 1.18, 95% CI (0.80, 1.57), $P < .00001$], reduce the incidence of myelosuppression [RR = 0.38, 95% CI (0.23, 0.63), $P = .0002$], and improve the clinical treatment effectiveness [RR = 1.20, 95% CI (1.00, 1.43), $P = .05$]. The differences were statistically significant.

**Conclusion:** It is recommended to use acupuncture in the treatment of leukocytopenia after chemotherapy, but this result needs further research for verification.

**Abbreviations:** ANC = absolute neutrophil count, CBM = Chinese Biomedical Literature Database, CENTRAL = Cochrane Central Register of Controlled Trials, CI = confidence interval, CNKI = China National Knowledge Infrastructure Database, CTCAE = Common Terminology Criteria for Adverse Events, G-CSF = granulocyte colony-stimulating factor, GM-CSF = granulocyte macrophage colony stimulating factor, MD = mean difference, RCTs = randomized clinical trials, RR = relative risk, WBC = white blood cell.

**Keywords:** acupuncture, effectiveness, leukopenia after chemotherapy, myelosuppression, white blood cell count

## 1. Introduction

Chemotherapy is one of the main clinical methods for the treatment of malignant tumors. However, with the increase of cumulative exposure to chemotherapy drugs and the depletion of bone marrow reserve function, the incidence of chemotherapy-related myelosuppression has gradually increased. Myelosuppression is the main dose-limiting toxicity of cytotoxic chemotherapy drugs. Most cancer patients have experienced myelosuppression during chemotherapy, which may induce complications of infection and bleeding, thus affecting the progress of chemotherapy and tumor treatment, and even leading to death of patients.[1,2] Leukopenia is a group of syndromes in which the number of white blood cells (WBC) in the peripheral blood is continuously lower than $4.0 \times 10^9$/L. It is one of the main types of myelosuppression, which is common in various chemotherapy. At present, granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony stimulating factor (GM-CSF) is mainly used in clinical treatment of chemotherapy-related leukopenia.[3] However, these drugs are expensive and can cause clinical symptoms such as fever and sore joints.[4] In addition, these drugs can promote

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*The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.*

*This paper contains data that support the results of this study.*

*The review does not need ethics approval because individuals cannot be identified.*

*Trial registration number: CRD42015027594.*

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the proliferation of bone marrow hematopoietic stem cells. Therefore, long-term use may induce hematopoietic tumors and cannot be used to treat leukemia patients with reduced WBC.[5] Considering the necessity of preventing and treating chemotherapy-related leukopenia and the problems of current treatment methods, it is very necessary to further explore more gentle, effective and cheap treatment methods.

Acupuncture is one of the main treatment methods of traditional Chinese medicine. It has been widely used in the world to treat tumors and related complications caused by treatment, including cancer pain, fatigue, nausea and vomiting, etc, and has good clinical efficacy.[6–9] In the past 20 years, several studies have also reported its role in the prevention and treatment of chemotherapy-related leukopenia, but the quality of the study is uneven, which reduces its argument strength and affects its further clinical use.[10] In order to better evaluate the clinical effect of acupuncture in preventing and treating chemotherapy-related leukopenia, this study used systematic reviews and meta-analysis to verify. The research protocol has been registered (registration number: CRD42015027594.) and published in advance.[11] The results were reported in the following.

## 2. Methods

### 2.1. Inclusion criteria for study selection

(1) Study types: Including RCT clinical studies, excluding semi-random clinical studies, cohort studies, one-arm clinical trials, animal studies, etc.
(2) Patient types: Leukopenia after chemotherapy in patients with solid tumors. The age must be greater than 18 years. No restriction on gender, ethnicity, tumor type and stage. Patients with hematopoietic diseases were excluded.
(3) Interventions: The experimental group: Acupuncture was used, including body acupuncture, abdominal acupuncture, electroacupuncture, and fire acupuncture, excluding acupoint stimulation (no needle), moxibustion, acupoint injection, percutaneous electrical stimulation, etc.

The control group: No acupuncture treatment was used. The blank control or sham acupuncture treatment can be used. In the same study, the basic treatment in the experimental group and the control group should be balanced. The basic treatment included G-CSF or GM-CSF and other treatments.

We will investigate following treatment comparisons:

1. Acupuncture versus no treatment or sham acupuncture.
2. Acupuncture versus other treatment.
3. Acupuncture with another treatment versus the same treatment without acupuncture.

### 2.2. Types of outcome measures

(1) Primary outcome indicators: WBC count after treatment.
(2) Secondary outcome indicators: absolute neutrophil count (ANC), incidence of myelosuppression, clinical effectiveness, and acupuncture-related side effects after treatment. Myelosuppression is graded according to Common Terminology Criteria for Adverse Events (CTCAE).[12]
(3) Criteria for clinical effectiveness evaluation: The criteria for determining the efficacy of leukocyte drugs based on the *Criteria for diagnosis and efficacy of hematopathy(Version3)*[13] include: markedly effects: clinical symptoms are significantly improved or disappeared. The number of WBC is greater than $4 \times 10^9$/L; effective: The WBC doesn't return to normal, but it increases by one times or more than $3 \times 10^9$/L, and the clinical symptoms are improved; and ineffective: the clinical symptoms did not improve. The number of WBC did not increase. Total treatment effectiveness = markedly effect + effective.

### 2.3. Search methods for identification of studies

We will electronically search the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library, Medline (via PubMed), EMBASE (via embase.com), the China National Knowledge Infrastructure Database (CNKI), the Chinese Biomedical Literature Database (CBM), the Chinese Scientific Journal Database (VIP database) and the Wanfang database for literature published from the establishment of the database to January 1, 2021. At the same time, we also manually searched references, gray databases, and clinical research registration systems for related studies to see if relevant studies were omitted. The search strategy was adjusted according to the database search requirements. Article language is limited to Chinese or English. For details, see the published protocol.[11] Search strategy for Medline (via PubMed) was as follows:

1. randomized controlled trial [Publication Type]
2. controlled clinical trial [Publication Type]
3. randomized [Title/Abstract]
4. placebo [Title/Abstract]
5. randomly [Title/Abstract]
6. trial [Title]
7. clinical trials [MeSH Major Topic]
8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. Leucopenia [MeSH Terms]
10. Leukopenia [Title/Abstract]
11. Aleucocytosis [Title/Abstract]
12. Aleukocytosis [Title/Abstract]
13. Hypoleucocytosis [Title/Abstract]
14. Hypoleukocytosis [Title/Abstract]
15. oligoleukocythemia [Title/Abstract]
16. Oligoleukocytosis [Title/Abstract]
17. Hypoleukia [Title/Abstract]
18. CSF [Title/Abstract]
19. G-CSF [Title/Abstract]
20. GM-CSF [Title/Abstract]
21. Granulocyte monocyte colony-stimulating factor [Title/Abstract]
22. myelosuppression [Title/Abstract]
23. bone marrow suppression [Title/Abstract]
24. Marrow depression [Title/Abstract]))
25. 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24
26. Acupuncture therapy [MeSH Terms]
27. Acupuncture [Title/Abstract]
28. Acupoints [Title/Abstract]
29. Body acupuncture [Title/Abstract]
30. Scalp acupuncture [Title/Abstract]
31. manual acupuncture [Title/Abstract]
32. Auricular acupuncture [Title/Abstract]
33. ear acupuncture [Title/Abstract]
34. Electroacupuncture [Title/Abstract]
35. Fire needling [Title/Abstract]
36. dermal needle [Title/Abstract]
37. plum blossom needle [Title/Abstract])
38. 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37
39. 8 AND 25 AND 38

### 2.4. Data extraction and management

EndnoteX7 was used as the document management tool for the research, and an Excel table designed in advance was used as a record table for data extraction. Two reviewers searched

according to the search strategy, read the title and abstract independently based on the search results, and conducted preliminary screening to exclude studies that obviously did not meet the inclusion criteria. Cross-comparison was performed. The first excluded studies and the reasons for exclusion were recorded. The reviewers read the full text of the studies that meet the inclusion criteria, and contact the author when the information is incomplete, and recorded the second excluded study and its cause. Information was extracted from the final included studies, including the author's name, year of publication, sample size, average age, tumor type, chemotherapy regimen, acupuncture site and course of treatment, and observation indicators. If the conclusions of the two reviewers are inconsistent, an agreement is reached through discussion or consultation with a third party. The authors of trial will be contacted for further details if necessary.

### 2.5. Assessment of risk of bias in included studies

Two reviewers independently evaluated the quality of all included studies in accordance with the bias risk assessment criteria provided by the Cochrane systematic reviewer's manual 5.2. The contents of the evaluation included randomization, whether to use allocation hiding, blinding implementation, research integrity, and existence of selective report, or other bias. According to the research content, the evaluation items were classified into low-risk, unclear, and high-risk, which correspond to A, B, and C grades, respectively. Finally, a risk assessment is performed on the overall situation, and the disagreement was resolved by the third evaluator.

### 2.6. Data synthesis and analysis

Statistical analysis was performed using Review Manager 5.3 statistical software. The relative risk (RR) was taken as the effect analysis statistic for dichotomous. The continuous variables used the mean difference (MD) as the effect analysis statistic. The interval estimates used the 95% confidence interval (CI). Cochran's $Q$ and the $I^2$ were used to test the heterogeneity of the included studies. If there was no statistical heterogeneity among the studies ($P > .1$ or $I^2 < 50\%$), the combined effect amount was analyzed using a fixed effect model. On the contrary, the random effect model was used for analysis. $P \leq .05$ was considered statistically significant. Where necessary, sensitivity analysis or subgroup analysis were used to assess the source of heterogeneity and the reliability of the research results, and inverted funnel charts were used to evaluate the publication bias of the included studies. GRADEprofiler software was used to grade the final results, and the quality of evidence was divided into four levels of high, moderate, low, and very low.

## 3. Results

### 3.1. Basic information of included studies

According to the corresponding search formula, a total of 1285 articles were detected, 726 was deducted after duplicate checking, with 559 remaining. After reading the title and abstract, 529 articles were removed. 15 articles were removed after reading the full text, and 15 RCTs were finally included, totaling 1130 patients.[14–28] There were 566 cases in the experimental group and 564 cases in the control group. The flow chart of article search was shown in Figure 1.The basic information of included studies was shown in Table 1

### 3.2. Bias risk assessment of included studies

The results of the risk assessment of the included studies were shown in Figure 2.

### 3.3. Meta-analysis results

***3.3.1. WBC count after chemotherapy.*** Ten studies (a total of 818 patients) reported WBC counts after chemotherapy, and there was a statistically significant difference in heterogeneity between the groups ($I^2 = 87\%$, $P < .00001$). Random effect

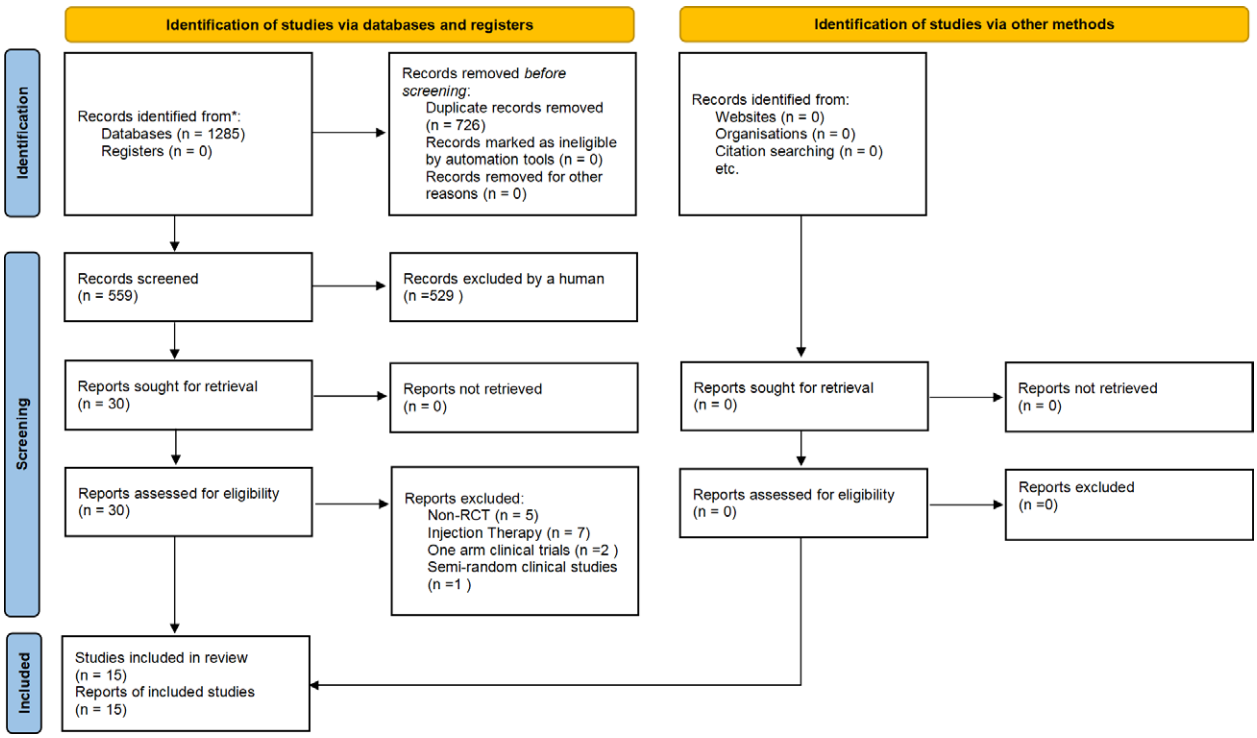


**Figure 1.** Flow chart of article search.

**Table 1**

**Basic information of included studies.**

| First author | Publication year | Country | Sample Size E/C | | Age E/C | | Cancer | Acupuncture type | Acupuncture points | Intensity | Frequency | Duration | Chemotherapy | Other treatments | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zhu DL | 2016 | China | 40 | 38 | 47 ± 16 | 46 ± 14 | BC | Routine Acupuncture | ST36, SP10, CV4, SP6, BL23, BL18 | 30min | QD | 5d | CAT/CET | G-CSF/Batilol Tablets | WBCs; Effective Rate |
| Chen C | 2004 | China | 28 | 28 | 46.2 | 49 | NC/NSCLC | Electroacupuncture | ST36 | 20min | QD | 20d | DDP + 5FU + CTX/ DDP + VP16 | NA | WBCs; |
| Wang LX | 2013 | China | 32 | 32 | 65.3 ± 12.0 | 66.4 ± 10.2 | NA | Routine acupuncture | LI4, CV6, CV4, ST36, SP6, SP9 | 30 min | QD | 10 d | NA | Leucogen tablets | Effective rate |
| Liu M | 2018 | China | 30 | 30 | 63.6 ± 8.0 | 63.2 ± 9.3 | CoC | Routine acupuncture | CV6, CV4, ST36, PC6 | 30 min | QD | 5 d | FOLFOX4 | NA | WBCs;ANC |
| Han YF | 2010 | China | 43 | 43 | 51.2 ± 4.3 | 50.8 ± 4.2 | EC | Routine acupuncture | TE6, LI11, LI4, SP10, SP9, ST36, KI3, LR3, SP6 | 20-30 min | QD | 14 d | AP | G-CSF | WBCs; effective rate |
| Li SY | 2019 | China | 25 | 25 | 59 ± 1.5 | | BC/LC/SC/ EC/CoC | Routine acupuncture | SP6, ST36, BL20, GV14, PC6, CV6, SP9 | 30min | QD | 14d | NA | Leucogen tablets | Effective rate |
| Fu YH | 2014 | China | 38 | 38 | 61.5 ± 8.9 | | NA | Routine acupuncture | GV14, BL20, PC6, SP9, CV4, CV6, SP10 | 30 min | QD | 14 d | NA | Leucogen tablets/ Batilol tablets | Effective rate |
| Wang F | 2017 | China | 30 | 30 | 55.8 ± 9.3 | 66.8 ± 3.0 | NA | Routine acupuncture | SP6, ST36, PC6, BL20, CV4, SP10, GV14, CV6, GB34 | 30tmin | QD | 14td | NA | Leucogen tablets/ Batilol tablets | WBCs; Effective rate |
| Wu GL | 2018 | China | 120 | 120 | 55.8 ± 13.4 | 56.7 ± 12.3 | BC/LC/SC/ LC,et al | Routine acupuncture | CV4, CV6, ST25, ST36, SP6, HT7, PC6, KI6, LR3, KI1, LU5, GV4, BL23, BL20 | 20-30 min | QD | 3-5 d | NA | G-CSF | WBCs;Myelosuppression rate |
| Ren JJ | 2013 | China | 29 | 29 | 62 | 61 | BC/LC/SC/ EC,et al | Routine acupuncture | ST36, SP6, GV14, BL20, BL17, SP10 | 30 min | QD | 14 d | NA | Leucogen tablets/ Batilol tablets | WBCs; Effective rate |
| Hu GW | 2016 | China | 30 | 30 | 51. 3 ± 9. 6 | 52. 0 ± 8. 9 | BC | Routine Acupuncture | ST36, SP6, SP10, BL23 | 30min | QD | 5d | TAC | G-CSF/Batilol Tablets | WBCs;ANC;Effective Rate |
| Zhang SQ | 2015 | China | 30 | 30 | 43.5 ± 6.5 | 42.8 ± 5.7 | LC | Routine acupuncture | BL13, ST40, LU1, LU9, LU5, BL15, SI11, CV17, BL43, LU5 | 15 min | QD | 56 d | DDP | NA | Myelosuppression rate |
| Zhang YL | 2017 | China | 31 | 31 | 53.6 ± 11.60 | | RC | Routine acupuncture | CV4, CV8, ST25, ST36 | 10 min | QD | 7 d | FOLFIRI | NA | Myelosuppression rate |
| Wang YH | 2014 | China | 30 | 30 | 57.7 ± 11.8 | 57.5 ± 8.2 | BC/LC/SC/ CC | Fire needling | BL17, BL19 | NA | QD | 7 d | DDP,GEM, et al | NA | WBCs;Myelosuppression rate |
| Lu S | 2016 | China | 30 | 30 | 51.1 ± 7.6 | 50.9 ± 7.3 | BC | Routine acupuncture | ST36, CV6 | 40 min | QD | 7 d | AC-T | G-CSF | WBCs;ANC |

ANC = absolute neutrophil count, BC = Breast Cancer, C = control group, CC = Colorectal Cancer, E = experimental group, EC = Endometrial Cancer, LC = Liver Cancer, LC = Lung Cancer, NA = Not Available, NC = Nasopharynx Cancer, NSCLC = Non Small Cell Lung Cancer, RC = Rectal Cancer, SC = Stomach Cancer.

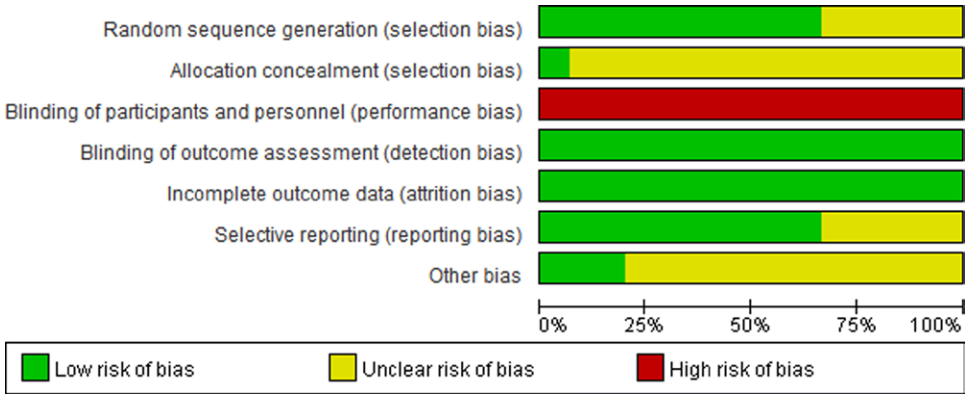


**Figure 2.** Risk assessment of the included studies.

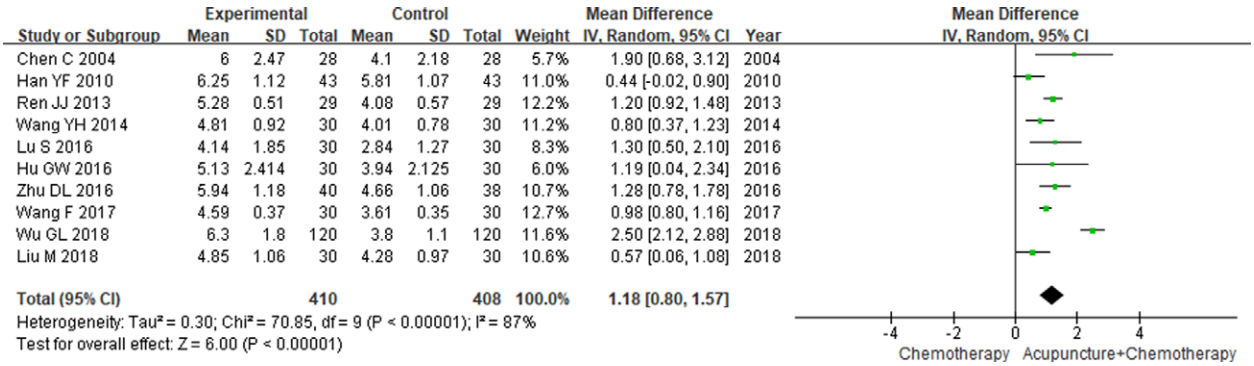


**Figure 3.** Forest chart of WBC count after chemotherapy. WBC = white blood cells.

model was used to synthesize the data, as shown in the Figure 3. Meta-analysis results showed that the WBC counts after chemotherapy in patients with acupuncture were significantly higher than those without acupuncture, and the difference was statistically significant [MD = 1.18, 95% CI (0.80, 1.57), $P < .00001$]. Considering the existence of greater heterogeneity after merging the above 10 studies, we conducted a sensitivity analysis. After manually eliminating the article, it was found that when the study of Wu 2018[22] was eliminated, the heterogeneity analysis result was $I^2 = 47\%$, suggesting that there was no significant heterogeneity between the groups. According to the analysis of fixed effect model, the differences of WBC count between the groups were still statistically significant [MD = 0.98, 95% CI (0.86, 1.11), $P < .00001$] (shown in Table 2).

***3.3.2. ANC count after chemotherapy.*** Three studies (a total of 180 patients) reported ANC counts after chemotherapy, and there was a statistically significant difference in heterogeneity between the groups ($I^2 = 71\%$, $P = .03$). Random effect model was used to synthesize the data, as shown in the Figure 4. Meta-analysis results showed that the ANC counts after chemotherapy in patients with acupuncture were not significantly higher than those without acupuncture [MD = 0.51, 95% CI (-0.14, 1.15), $P = .012$].

***3.3.3. Incidence of myelosuppression after chemotherapy.*** Four studies (a total of 422 patients) reported incidence of myelosuppression after chemotherapy, and there was no statistically significant difference in heterogeneity between the groups ($I^2 = 0\%$, $P = .73$). Fixed effect model was used to synthesize the data, as shown in the Figure 5. Meta-analysis results showed that the incidence of myelosuppression after chemotherapy in patients with acupuncture were significantly lower than those without acupuncture [RR = 0.38, 95%CI (0.23, 0.63), $P = .0002$].

***3.3.4. Clinical effectiveness after chemotherapy.*** Eight studies (a total of 532 patients) reported clinical effectiveness after chemotherapy, and there was a statistically significant difference in heterogeneity between the groups ($I^2 = 88\%$, $P < .00001$). Random effect model was used to synthesize the data, as shown in the Figure 6. Meta-analysis results showed that the clinical effectiveness after chemotherapy in patients with acupuncture were significantly higher than those without acupuncture [RR = 1.20, 95% CI (1.00, 1.43), $P = .05$]. Considering the existence of greater heterogeneity after merging the above 8 studies, we conducted a sensitivity analysis by eliminating articles one by one. When the study of Han YF 2010[18] was eliminated, the heterogeneity significantly reduced ($I^2 = 5\%$, $P = .39$). Fixed effect model was used to synthesize the data and the differences of clinical effectiveness between the groups were still statistically significant [RR = 1.23, 95% CI (1.13, 1.35), $P < .00001$] (shown in Table 3).

***3.3.5. Fungal chart of WBC count after chemotherapy.*** A funnel chart was drawn using the WBC count as an indicator after chemotherapy, as shown in Figure 7. The funnel chart had asymmetry on both sides, considering the possible publication bias.

***3.3.6. Acupuncture safety.*** No side effects of acupuncture treatment were reported in the included studies, including infection, broken needles, pain, and severe bleeding.

***3.3.7. GRADE classification.*** The GRADEprofiler software was used to grade the outcome indicators with statistical significance. The results showed that the quality of the evidence

**Table 2**

**Sensitivity analysis (WBC count).**

| Eliminating article | Effect model | Heterogeneity | | Pooled MD | |
|---|---|---|---|---|---|
| | | $I^2$ | *P* | MD (95% CI) | *P* |
| Chen 2004 | Fixed model | 88% | *P* < .00001 | 1.13 (1.01, 1.25) | *P* < .00001 |
| | Random model | 88% | *P* < .00001 | 1.14 (0.74, 1.54) | *P* < .00001 |
| Han 2010 | Fixed model | 87% | *P* < .00001 | 1.18 (1.06, 1.31) | *P* < .00001 |
| | Random model | 87% | *P* < .00001 | 1.28 (0.87, 1.68) | *P* < .00001 |
| Ren 2013 | Fixed model | 89% | *P* < .00001 | 1.12 (0.99, 1.25) | *P* < .00001 |
| | Random model | 89% | *P* < .00001 | 1.19 (0.72, 1.65) | *P* < .00001 |
| Wang 2014 | Fixed model | 88% | *P* < .00001 | 1.16 (1.04, 1.29) | *P* < .00001 |
| | Random model | 88% | *P* < .00001 | 1.23 (0.81, 1.66) | *P* < .00001 |
| Zhu 2016 | Fixed model | 89% | *P* < .00001 | 1.13 (1.00, 1.25) | *P* < .00001 |
| | Random model | 89% | *P* < .00001 | 1.17 (0.75, 1.60) | *P* < .00001 |
| Hu 2016 | Fixed model | 89% | *P* < .00001 | 1.13 (1.01, 1.25) | *P* < .00001 |
| | Random model | 89% | *P* < .00001 | 1.18 (0.78, 1.59) | *P* < .00001 |
| Lu 2016 | Fixed model | 89% | *P* < .00001 | 1.13 (1.01, 1.25) | *P* < .00001 |
| | Random model | 89% | *P* < .00001 | 1.17 (0.76, 1.59) | *P* < .00001 |
| Wang 2017 | Fixed model | 88% | *P* < .00001 | 1.25 (1.09, 1.41) | *P* < .00001 |
| | Random model | 88% | *P* < .00001 | 1.22 (0.73, 1.71) | *P* < .00001 |
| Liu 2018 | Fixed model | 88% | *P* < .00001 | 1.17 (1.04, 1.29) | *P* < .00001 |
| | Random model | 88% | *P* < .00001 | 1.26 (0.84, 1.67) | *P* < .00001 |
| Wu 2018 | Fixed model | 47% | *P* = .06 | 0.98 (0.86, 1.11) | *P* < .00001 |
| | Random model | 47% | *P* = .06 | 0.97 (0.76, 1.18) | *P* < .00001 |

CI = confidence intervals; MD = mean difference, WBC = white blood cell.

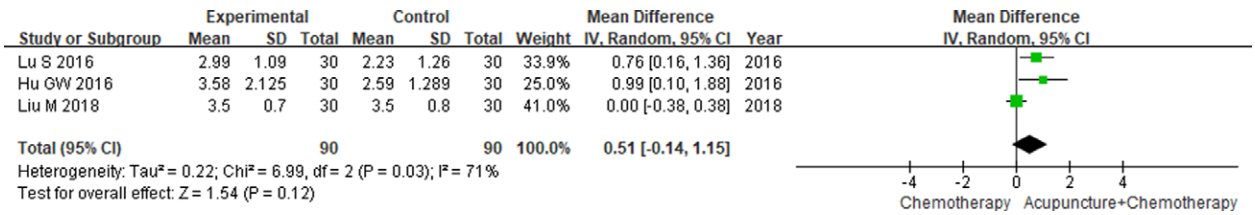


**Figure 4.** Forest chart of ANC count after chemotherapy. ANC = absolute neutrophil count.

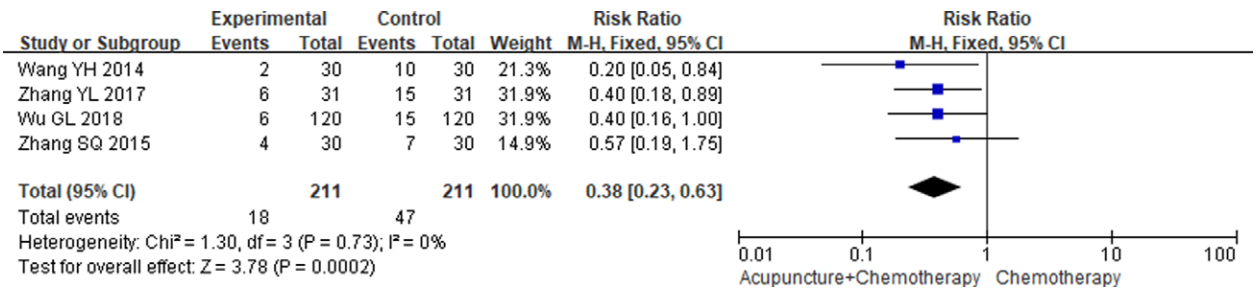


**Figure 5.** Forest chart of myelosuppression after chemotherapy.

for the reduction of WBC count after acupuncture treatment was "moderate" (shown in Table 4).

## 4. Discussion

Leukopenia after chemotherapy is a common but difficult side effect of malignant tumor patients during chemotherapy. It can reduce the quality of life of patients and greatly affect the normal chemotherapy plan. In view of this side effect, effective treatment methods are relatively limited, and new simple, convenient, inexpensive and effective treatment methods are urgently needed in clinical practice to enhance the treatment effect of existing methods and reduce the incidence and severity of the side effects.

This study performed a systematic review and meta-analysis of the clinical efficacy and safety of acupuncture for leukocytopenia after chemotherapy. The study included 15 RCTs with a total of 1130 patients. The results showed that acupuncture can increase the WBC count of patients after chemotherapy, reduce the incidence of myelosuppression after chemotherapy, and improve clinical effectiveness. The results suggest that acupuncture can be used as an effective auxiliary means to enhance the therapeutic effect of increasing WBC and reduce the incidence of myelosuppression. In order to further scientifically evaluate the strength of this study's verification, we graded GRADE on the primary outcome indicators of increasing WBC count, and the results showed "moderate". Due to the popularity of acupuncture, similar studies have not been conducted in other countries except China, so the included studies are all from China. A bias risk assessment of the included studies found that

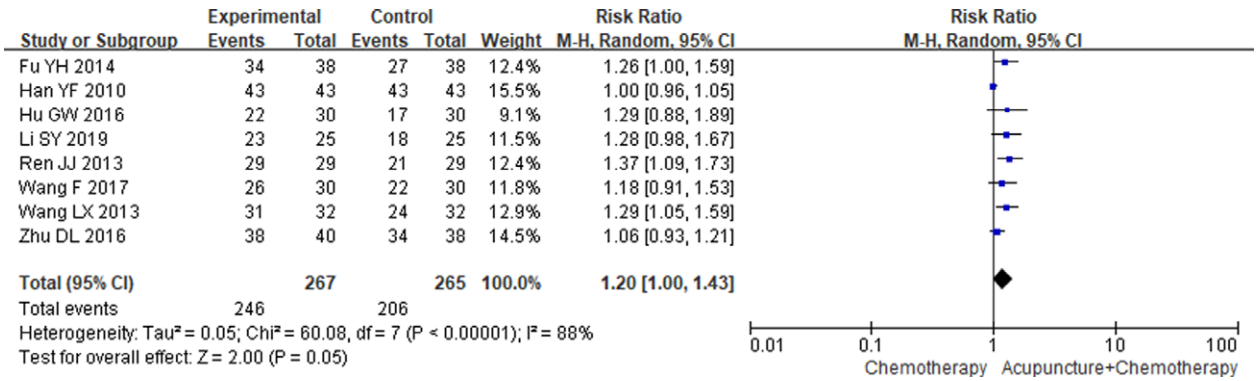


**Figure 6.** Forest chart of clinical effectiveness after chemotherapy.

**Table 3**

**Sensitivity analysis (clinical effectiveness).**

| | | Heterogeneity | | Pooled MD | |
|---|---|---|---|---|---|
| **Eliminating articleText?>** | **Effect modelText?>** | ***I²*** | ***P*** | **MD (95% CI)** | ***P*** |
| Fu 2014 | Fixed model | 89% | *P* < .00001 | 1.17 (1.09, 1.26) | *P* < .00001 |
| | Random model | 89% | *P* < .00001 | 1.19 (0.98, 1.44) | *P* < .00001 |
| Han 2010 | Fixed model | 5% | *P* = .39 | 1.23 (1.13, 1.35) | *P* < .00001 |
| | Random model | 5% | *P* = .39 | 1.20 (1.10, 1.30) | *P* < .0001 |
| Hu 2016 | Fixed model | 89% | *P* < .00001 | 1.17 (1.09, 1.26) | *P* < .00001 |
| | Random model | 89% | *P* < .00001 | 1.19 (0.99, 1.43) | *P* < .00001 |
| Li 2019 | Fixed model | 89% | *P* < .00001 | 1.17 (1.09, 1.26) | *P* < .0001 |
| | Random model | 89% | *P* < .00001 | 1.19 (0.98, 1.43) | *P* = .07 |
| Ren 2013 | Fixed model | 87% | *P* < .00001 | 1.16 (1.08, 1.25) | *P* < .00001 |
| | Random model | 87% | *P* < .00001 | 1.17 (0.98, 1.40) | *P* = .08 |
| Wang 2017 | Fixed model | 90% | *P* < .00001 | 1.18 (1.10, 1.27) | *P* < .00001 |
| | Random model | 90% | *P* < .00001 | 1.20 (0.99, 1.46) | *P* = .07 |
| Wang 2013 | Fixed model | 88% | *P* < .00001 | 1.17 (1.08, 1.26) | *P* < .00001 |
| | Random model | 88% | *P* < .00001 | 1.18 (0.98, 1.43) | *P* = .08 |
| Zhu 2016 | Fixed model | 91% | *P* < .00001 | 1.21 (1.11, 1.31) | *P* < .00001 |
| | Random model | 91% | *P* < .00001 | 1.23 (0.96, 1.57) | *P* < .10 |

CI = confidence intervals; MD = mean difference.

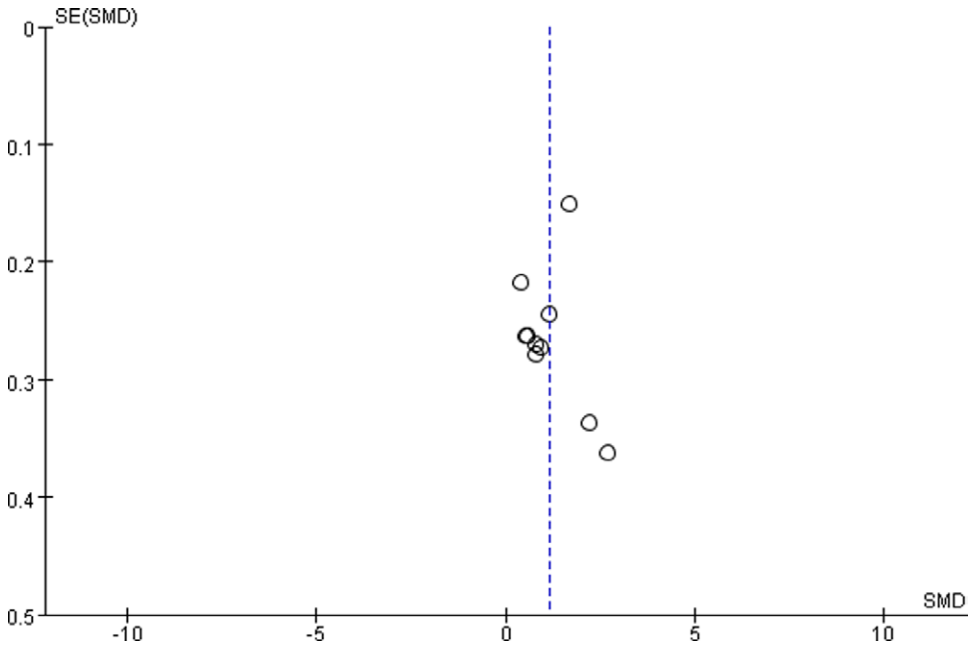


**Figure 7.** Funnel plot of WBC count. WBC = white blood cells.

**Table 4**

**GRADE classification.**

| **Acupuncture for chemotherapy-induced leukopenia**<br>**Patient or population:** patients with chemotherapy-induced leukopenia<br>**Settings:**<br>**Intervention:** acupuncture<br>**Outcomes** | | | | | | |
|---|---|---|---|---|---|---|
| | Assumed risk<br>**Control** | **Illustrative comparative risks* (95% CI)**<br>Corresponding risk<br>**Acupuncture** | **Relative effect (95% CI)** | **No of participants (studies)** | **Quality of the evidence (GRADE)** | **Comments** |
| **WBC counts after treatment**<br>Blood cell analyzer. Scale from: 0 to 10.<br>Follow-up: 5-45 days | | The mean wbc counts after treatment in the intervention groups was<br>**1.18 higher**<br>(0.8 to 1.57 higher) | | 818<br>(10 studies) | ⊕⊕⊕⊕<br>**moderate**[1] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

1 No explanation was provided.

all studies did not report the use of blinding methods, which may be related to the difficulty of blinding acupuncture (especially Chinese patients have extensive experience with true acupuncture treatment), but taking into account that the outcome indicators of the evaluation are objective and accurate values, we believe that non-blindness will not materially affect the credibility of the outcome evaluation. Therefore, we recommend acupuncture to treat leukopenia after chemotherapy.

In the evaluation of the heterogeneity of the two outcome indicators of leukopenia and clinical effectiveness, the results suggest that there is greater heterogeneity. Therefore, we adopt a sensitivity analysis method that is excluded from each study. After excluding Wu 2018[22] and Han 2010[18] studies in two meta-analysis, we found that both meta-analyses achieved higher homogeneity. Further analyzing the reasons, we found that in Wu 2018' study, the acupuncture group selected acupoints based on syndrome differentiation, that is, according to the method of syndrome differentiation and treatment of traditional Chinese medicine, acupuncture points were selected that are more likely to benefit according to the physical characteristics of patients for treatment, further improving the treatment effect. Not all patients choose unified acupuncture treatment, which leads to heterogeneity. Han YF 2010's follow-up time reached 45 days. According to the characteristics of the bone marrow's own hematopoietic cycle, most patients had WBC returned to normal at this time. Therefore, in his study, the experimental group and the control group reached 100% efficiency.

Due to the limitations of included studies, this article did not further analyze the information of optimal acupuncture point combination, operation technique and treatment course, etc. It is hoped that researchers can focus on in-depth research on these factors in the future.

The results of this study suggest that acupuncture can improve the WBC count in patients' peripheral blood after chemotherapy, reduce the incidence of myelosuppression and improve clinical treatment effectiveness. Clinical use of acupuncture is recommended for the treatment of leukopenia after chemotherapy (level of evidence: moderate). But limited to the current research quality, it is recommended to carry out large samples, multi-center, international research to further verify the above results.

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## Author contributions

**Data curation:** Xu Sun, Wenjie Zhao.
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