

Effects of propofol intravenous general anesthesia and inhalational anesthesia on T-lymphocyte activity after breast cancer surgery: A meta-analysis

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Background: Breast cancer is one of the most common cancers in women. General anesthesia is a commonly used anesthesia method for breast cancer surgery, and studies have confirmed that general anesthesia can induce immunosuppression in breast cancer patients and increase the metastasis rate of tumors. However, the difference between the effects of intravenous general anesthesia and inhalation anesthesia on the function of T-lymphocytes is still controversial, and it is necessary to explore reasonable anesthesia methods to reduce immunosuppression caused by surgery and anesthesia. **Materials and Methods:** Databases (Embase, PubMed, Cochrane Library, CBM, CNKI, and Wanfang) were searched (up to October 2022) for randomized controlled trials (RCTs) comparing intraoperative inhalation anesthesia and propofol intravenous anesthesia in breast cancer patients, with the outcome of T-lymphocyte subsets. The meta-analysis was performed by STATA 14.0. **Results:** Six RCTs with 352 patients were included in the study. Compared with inhalation anesthesia, there was no difference in T-lymphocyte subsets between the two groups immediately after surgery, but the activities of CD4⁺ T cells in patients with propofol anesthesia were higher (standard mean difference [SMD] = 0.234, 95% confidence interval [CI]: 0.003–0.466, $P = 0.047$, $I^2 = 44.1\%$) than those under inhalation anesthesia 1 day after surgery, and CD4⁺/CD8⁺ activities in patients with propofol anesthesia were higher (SMD = 304, 95% CI: 0.072–0.537, $P = 0.010$, $I^2 = 48.0\%$) than those under inhalation anesthesia 1 day after surgery. **Conclusion:** There were no differences in the effects of propofol and inhalation anesthetics on T-lymphocytes immediately after surgery, but the inhibitory effects of inhalation anesthetics on CD4⁺ and CD4⁺/CD8⁺ cells were stronger 1 day after surgery.

Key words: Anesthesia, breast cancer, propofol, T-lymphocytes

How to cite this article: Sun D, Li K, Chai Z, Wang L, Gu S, Sun N, *et al.* Effects of propofol intravenous general anesthesia and inhalational anesthesia on T-lymphocyte activity after breast cancer surgery: A meta-analysis. *J Res Med Sci* 2023;28:86.

INTRODUCTION

Breast cancer has the highest incidence in women, accounting for 30% of all cancers in the female population, and the incidence of infectious breast cancer in women increased slightly from 2007 to 2016, increasing by 0.3% per year.^[1] Surgical removal of solid tumors is the most common and effective form of treatment, and the usual anesthesia for breast surgery is general anesthesia, including intravenous propofol anesthesia and inhalation anesthesia. However,

surgery and anesthesia also pose several side risks to patients, which can produce intense stress responses, induce immunosuppression, and cause cancer to recur or metastasize. Immunocompromise has no benefits to the recovery of the disease and long-term survival in breast cancer patients, whereas anesthesia and surgery will lead to a 3–4 times increase in the rate of tumor metastasis in tumor patients.^[2] Therefore, it is very important to explore how to choose a reasonable anesthesia method to appropriately reduce the immune suppression caused by surgery and anesthesia.

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DOI:

10.4103/jrms.jrms_336_23

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Submitted: 28-May-2023; **Revised:** 20-Aug-2023; **Accepted:** 09-Oct-2023; **Published:** 23-Feb-2024

A controversial view is that propofol-based anesthesia seems to reduce perioperative immunosuppression compared to general anesthesia with volatile anesthetics.^[3] The results of existing clinical trials studying propofol, including laboratory studies, are inconsistent. More research supports that the beneficial effects of propofol on the immune system are largely restricted to NK cells.^[4] Among the immune cells, helper CD4⁺ Th1 cells and CD8⁺ cytotoxic T-lymphocytes (CTLs) are the major antitumor effector cells, which are implicated in postoperative cancer recurrence and metastasis.^[5] Some studies have proven that propofol can alleviate immunosuppression in breast cancer patients, preserve the activity of T-lymphocytes, and induce apoptosis of tumor cells, whereas inhalation anesthesia significantly reduces T-lymphocyte subsets, increasing tumor proliferation, migration, and invasion.^[6-10] Some studies also believe that the effect of propofol-based anesthesia on cancer cell and CTL functions does not differ from that of sevoflurane-based anesthesia in breast cancer surgery.^[11]

Therefore, in this meta-analysis, we pooled the results of prospective randomized controlled trials (RCTs) and attempted to determine the effect of propofol intravenous anesthesia and inhalation anesthesia on the activity of T-lymphocytes in patients immediately after breast cancer surgery and 1 day after surgery.

METHODS

This meta-analysis was conducted in accordance with the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. There was no registered protocol.

Inclusion and exclusion criteria

The inclusion criteria were as follows: RCTs of elective surgical inhalation anesthesia versus propofol-based intravenous anesthesia in adult female patients with primary breast cancer published at home and abroad and included the outcome measures in the trials. The exclusion criteria were as follows: Patients with a history of chronic pain or oral analgesia before surgery, patients with immune system disorders and other significant complications, and

studies comparing propofol combined with paravertebral or epidural block with inhalation anesthesia.

Literature search

The Embase, PubMed, Cochrane Library, CBM, CNKI, and Wanfang databases were searched. The searched terms were breast cancer, breast neoplasm, breast tumors, propofol, dispropofol, diprivan, RCT, randomized controlled, prognosis, and diagnosed. Clinical trial registries were searched for any further potentially eligible trials. The published languages included were English and Chinese. Search for articles from databases to October 2022.

Data extraction and quality assessment

Data were extracted by two researchers according to preset criteria, and if there were any differences and disagreements, it was again decided by the third researcher. The primary outcomes were as follows: activities of CD3⁺, CD4⁺, and CD8⁺ T-lymphocytes and CD4⁺/CD8⁺ T-lymphocytes before anesthesia (T₀), at the end of the operation (T₁), and 1 day after surgery (T₂). The results of the data extraction are shown in Table 1. The quality of the literature was assessed with reference to the Cochrane Manual for Systematic Reviewers, version 5.0 of the risk of bias assessment, which included the following seven evaluation indicators: (1) Random sequence generation (selection bias); (2) Allocation concealment (selection bias); (3) Blinding of participants and personnel (performance bias); (4) Blinding of outcome assessment (detection bias); (5) Incomplete outcome data (attrition bias); (6) Selective reporting (reporting bias); and (7) Other bias. For each study result, the above seven indicators were judged as "high risk," "low risk" and "unclear." Quality assessment was performed using Rev Man 5.4 (The cochrane collaboration, United kingdom).

Statistical analysis

Meta-analysis was performed using STATA 14.0 (Stata, United States). Pooled effect sizes for total T-lymphocytes (CD3⁺) and subgroups (CD4⁺, CD8⁺, CD4⁺/CD8⁺) included in the study were estimated using a fixed-effect or random-effect model. Standard mean differences (SMDs) and 95% confidence intervals (95% CIs) were used as pooled effect statistics. First, the pooled effect sizes of the preoperative

Table 1: Basic information and data extraction results of the included studies

Study	Number of examples/n		Interventions		Outcomes
	Experimental group	Control group	Experimental group	Control group	
Chen Ling 2018 ^[14]	20	20	Propofol	Sevoflurane	CD3 ⁺ CD4 ⁺ CD8 ⁺ CD4 ⁺ /CD8 ⁺ (T ₀ , T ₁ , T ₂)
Pihong Wei 2011 ^[13]	16	16	Propofol	Isoflurane	CD3 ⁺ CD4 ⁺ CD8 ⁺ CD4 ⁺ /CD8 ⁺ (T ₀ , T ₁ , T ₂)
Jianlong Du 2017 ^[15]	60	60	Propofol	Isoflurane	CD3 ⁺ CD4 ⁺ CD8 ⁺ CD4 ⁺ /CD8 ⁺ (T ₀ , T ₁ , T ₂)
Yue Cao 2021 ^[16]	30	30	Propofol	Desflurane	CD3 ⁺ CD4 ⁺ CD8 ⁺ CD4 ⁺ /CD8 ⁺ (T ₀ , T ₁ , T ₂)
Woo, JH 2015 ^[17]	20	20	Propofol	Desflurane	CD4 ⁺ CD8 ⁺ CD4 ⁺ /CD8 ⁺ (T ₀ , T ₁ , T ₂)
Qiaoyan Zhou 2016 ^[2]	30	30	Propofol	Sevoflurane	CD3 ⁺ CD4 ⁺ CD8 ⁺ CD4 ⁺ /CD8 ⁺ (T ₀ , T ₁)

T₀=The measurements before anesthesia; T₁=The measurements at the end of the operation; T₂=The measurements 1 day after surgery

baseline (T0) were calculated for each group, and if there was no difference between baselines, the pooled effect sizes for each subgroup were estimated for comparison immediately after surgery (T1) and 1 day after surgery (T2). The χ^2 test and the I^2 value were used to determine the level of heterogeneity. If $P > 0.1$ and $I^2 < 50\%$, no heterogeneity was considered, and data were pooled for meta-analysis using a fixed-effect model; if $P < 0.1$ and $I^2 > 50\%$ were considered heterogeneous, data were pooled using a random-effect model for meta-analysis.^[12] Pooled effect sizes were estimated by meta-analysis, and significance levels were determined at $P < 0.05$. Sensitivity analyses were performed for subgroups of high heterogeneity ($P < 0.1$ and $I^2 > 50\%$), and if there were data that had a clear impact on the results, they were excluded from the meta-analysis, and forest maps were drawn for each study. The pooled effect size is shown by the forest plot. Egger's test was performed, and $P > 0.05$ was considered free of publication bias.

RESULTS

Basic information from the included studies

According to the corresponding search formula, a total of

1221 articles were detected, 766 articles were excluded after removing duplicate articles, 651 articles were removed from the study by reading the titles, 38 articles were left after reading the abstracts, and the full text was read according to the inclusion criteria. Finally, six articles were included,^[2,13-17] with a total of 352 patients. Two of the studies compared propofol with sevoflurane, two compared propofol with desflurane, and two compared propofol with isoflurane. The literature screening procedure is shown in Figure 1, and the basic information of the included studies is shown in Table 2.

Quality assessment of the included studies

All six studies used a random allocation regimen and did not explicitly state allocation concealment or blinding, and all six studies had complete outcome measures. The results of the literature quality evaluation are shown in Figure 2.

Meta-analysis results

CD3⁺

Five studies (312 patients) reported CD3⁺ T-lymphocyte subsets with no statistical heterogeneity at T₀ between

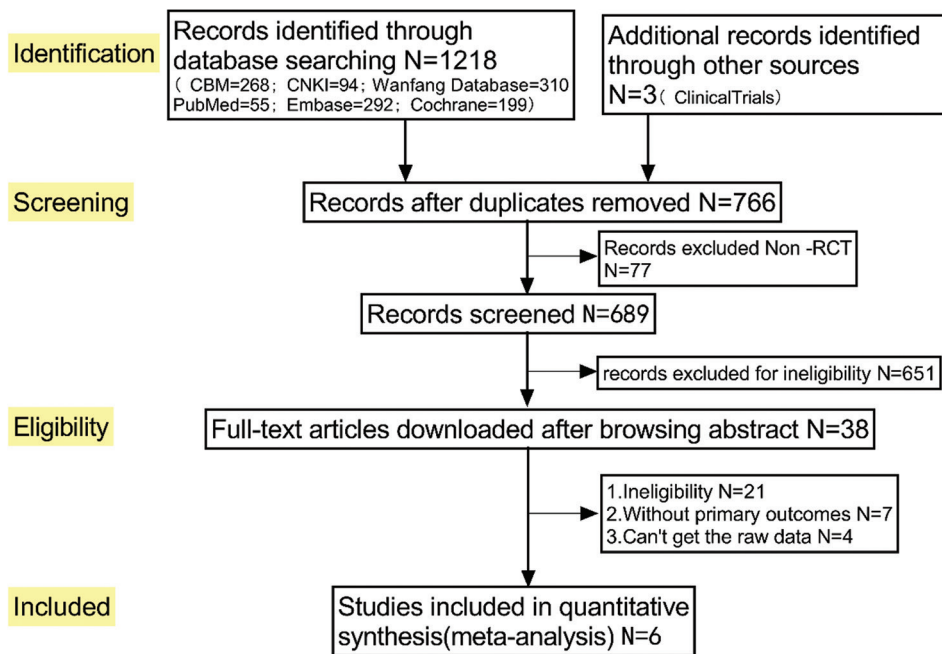


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis flow diagram

Table 2: Results of meta-analysis

Indicators of immune function	Number of studies included	Number of examples/n	SMD (95% CI)		P	
			T ₁	T ₂	T ₁	T ₂
CD3 ⁺	5	312	0.202 (-0.303~0.707)	0.243 (-0.148~0.635)	>0.05	>0.05
CD4 ⁺	6	352	0.157 (-0.404~0.718)	0.234 (0.003~0.466)	>0.05	<0.05
CD8 ⁺	6	352	-0.079 (-0.440~0.283)	0.167 (-0.064~0.397)	>0.05	>0.05
CD4 ⁺ /CD8 ⁺	6	352	0.389 (-0.176~0.954)	0.304 (0.072~0.537)	>0.05	<0.05

SMD=Standard mean difference; CI=Confidence interval

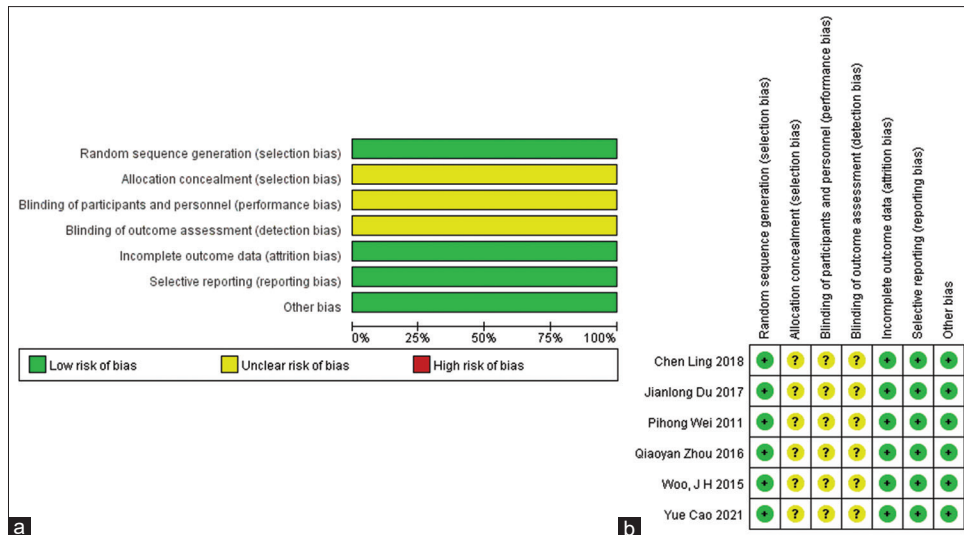


Figure 2: Literature quality evaluation (a) Risk of bias graph, (b) Risk of bias summary

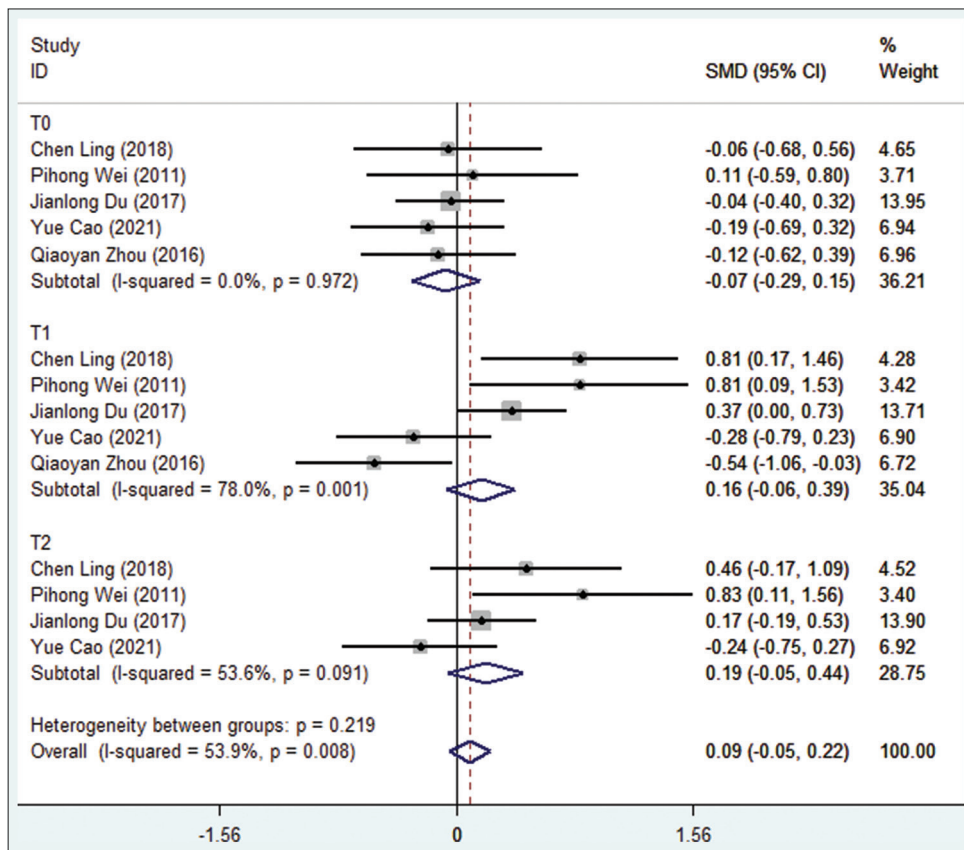


Figure 3: Meta-analysis forest plot of CD3+

groups ($I^2 = 0.0\%$, $P = 0.972$), as shown in Figure 3. The difference in the use of fixed-effect pooled effect sizes was not statistically significant (SMD = -0.07 , 95% CI: $-0.29 \sim 0.15$, $Z = 0.61$, $P = 0.544$); that is, there was no difference in CD3+ between the two groups at T₀, and subsequent meta-analysis could be performed. The effect size of T₁ was combined for heterogeneity testing, and there was some heterogeneity between the selected

studies ($I^2 = 78.0\%$, $P = 0.001$); the results are shown in Figure 3. A sensitivity analysis of the five studies in this study was carried out, as shown in Figure 4, and it was found that none of the studies had a strong impact on the results of the study. The selection of random-effect pooled effect sizes yielded a pooled effect size of 0.202 (95% CI: $-0.303 \sim 0.707$), with no statistically significant difference ($Z = 0.79$, $P = 0.544$) between the

CD3⁺ and inhalation groups in the propofol group at the end of surgery. The effect size of T₂ was combined for heterogeneity testing, and there was some heterogeneity between the selected studies in this study ($I^2 = 53.6%$, $P = 0.091$); the results are shown in Figure 3. The random-effect combined effect size was 0.243 (95% CI: -0.148 ~ 0.635), and the difference was not statistically significant ($Z = 1.22$, $P = 0.223$). There was no difference

between the CD3⁺ and inhalation groups in the propofol group 1 day after surgery. Egger's test was carried out to test the publication bias of the literature in this study, and the P values obtained were all >0.05 ($P_T = 0.746$, $P_{T1} = 0.754$, $P_{T2} = 0.460$). Therefore, it can be judged that the literature in this study is free of the publication bias.

CD4⁺

Six studies (352 patients) reported CD4⁺ T-lymphocyte subsets with no statistical heterogeneity at T₀ ($I^2 = 0.0%$, $P = 0.474$), as shown in Figure 5. The difference in the use of fixed-effect pooled effect sizes was not statistically significant (SMD = -0.10, 95% CI: -0.31 ~ 0.11, $Z = 0.78$, $P = 0.335$); that is, there was no difference in CD4⁺ between the two groups at T₀. The effect size of T₁ was combined for heterogeneity testing, and there was some heterogeneity between the selected studies ($I^2 = 84.3%$, $P = 0.000$), and the results are shown in Figure 5. A sensitivity analysis of the six studies in this study was carried out, and the results are shown in Figure 6. It was found that none of the studies had a strong impact on the study results. The random-effect pooled effect size was 0.157 (95% CI: -0.404 ~ 0.718), the difference was not statistically significant ($Z = 0.55$, $P = 0.584$), and there was no difference between the CD4⁺ and inhalation groups in the propofol group at the

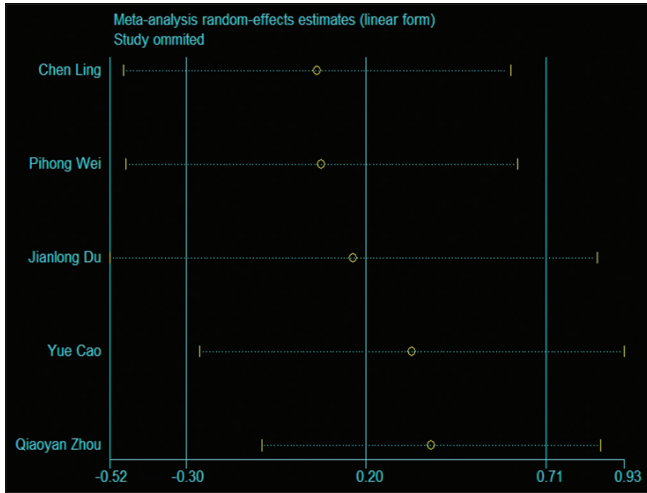


Figure 4: Sensitivity analysis of CD3⁺ (T₁)

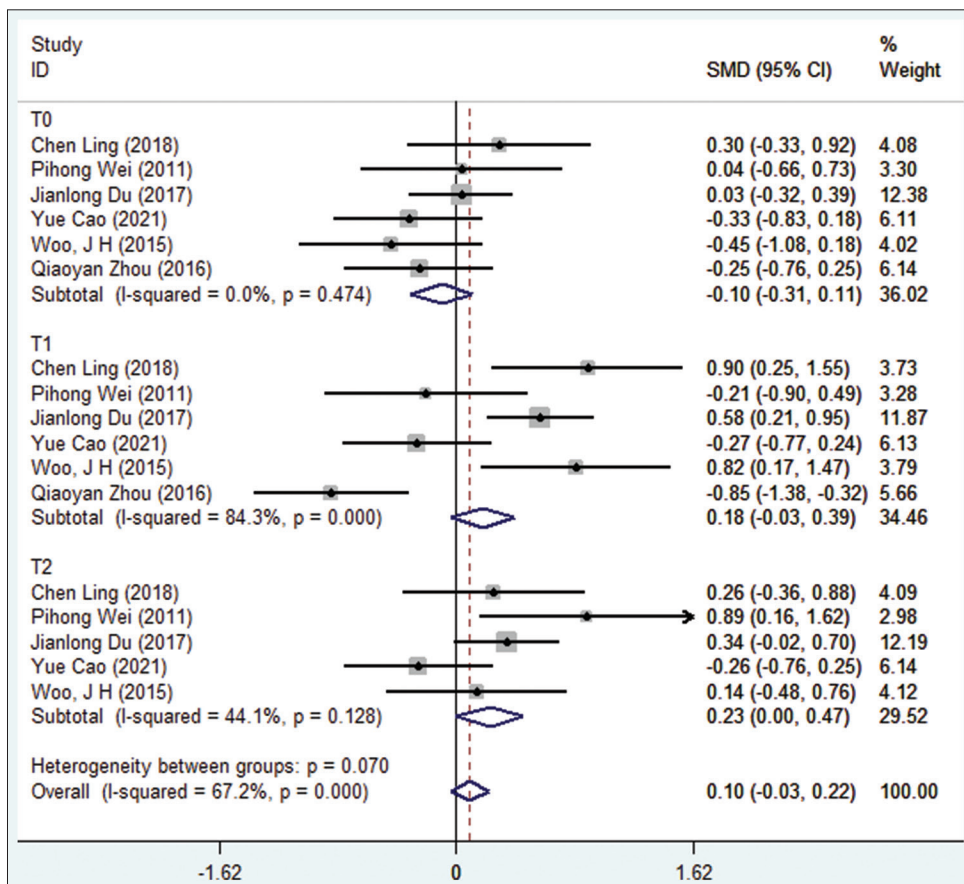


Figure 5: Meta-analysis forest plot of CD4⁺

end of surgery. The effect size of T₂ was combined for heterogeneity testing, and there was no heterogeneity between the selected studies ($I^2 = 44.1\%$, $P = 0.128$), and the result is shown in Figure 5. The fixed-effect combined effect amount was 0.234 (95% CI: 0.003 ~ 0.466), the effect was significant ($Z = 1.98$, $P = 0.047$), and the CD4⁺ in the propofol group was significantly higher than that in the inhalation group by 0.234 1 day after surgery. The P values obtained

by Egger's test were all > 0.05 ($P_{T_0} = 0.769$, $P_{T_1} = 0.817$, $P_{T_2} = 0.789$), so there was no publication bias in the literature in this study.

CD8⁺

Six studies (352 patients) reported CD8⁺ T-lymphocyte subsets with no statistical heterogeneity at T₀ ($I^2 = 0.0\%$, $P = 0.565$), as shown in Figure 7. The difference in the use of fixed-effect pooled effect sizes was not statistically significant (SMD = -0.08, 95% CI: -0.29 ~ 0.13, $Z = 0.77$, $P = 0.439$); that is, there was no difference in CD8⁺ between the two groups at T₀. The effect size of T₁ was combined for heterogeneity testing, and there was some heterogeneity between the selected studies ($I^2 = 63.0\%$, $P = 0.019$); the results are shown in Figure 7. A sensitivity analysis of the six studies in this study was carried out, and the results are shown in Figure 8. It was found that none of the studies had a strong impact on the study results. The random-effect pooled effect size was -0.079 (95% CI: -0.440 ~ 0.283), the difference was not statistically significant ($Z = 0.43$, $P = 0.670$), and there was no difference between the CD8⁺ and inhalation groups in the propofol group at the end of surgery. The effect size of T₂ was combined for heterogeneity testing, and there was no heterogeneity between the selected studies ($I^2 = 18.0\%$, $P = 0.300$); the results are

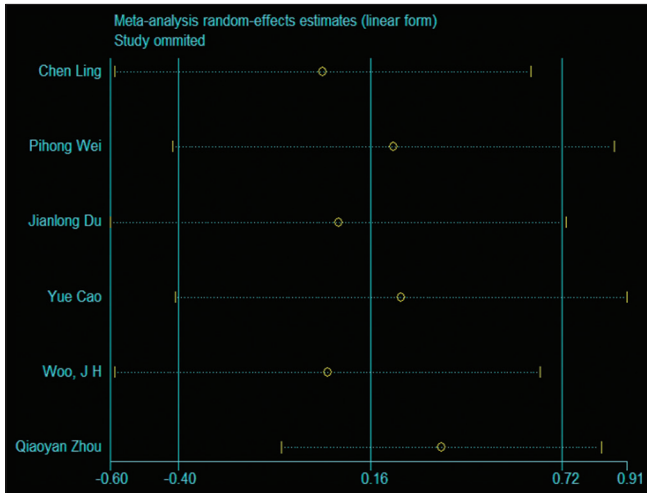


Figure 6: Sensitivity analysis of CD4⁺ (T₁)

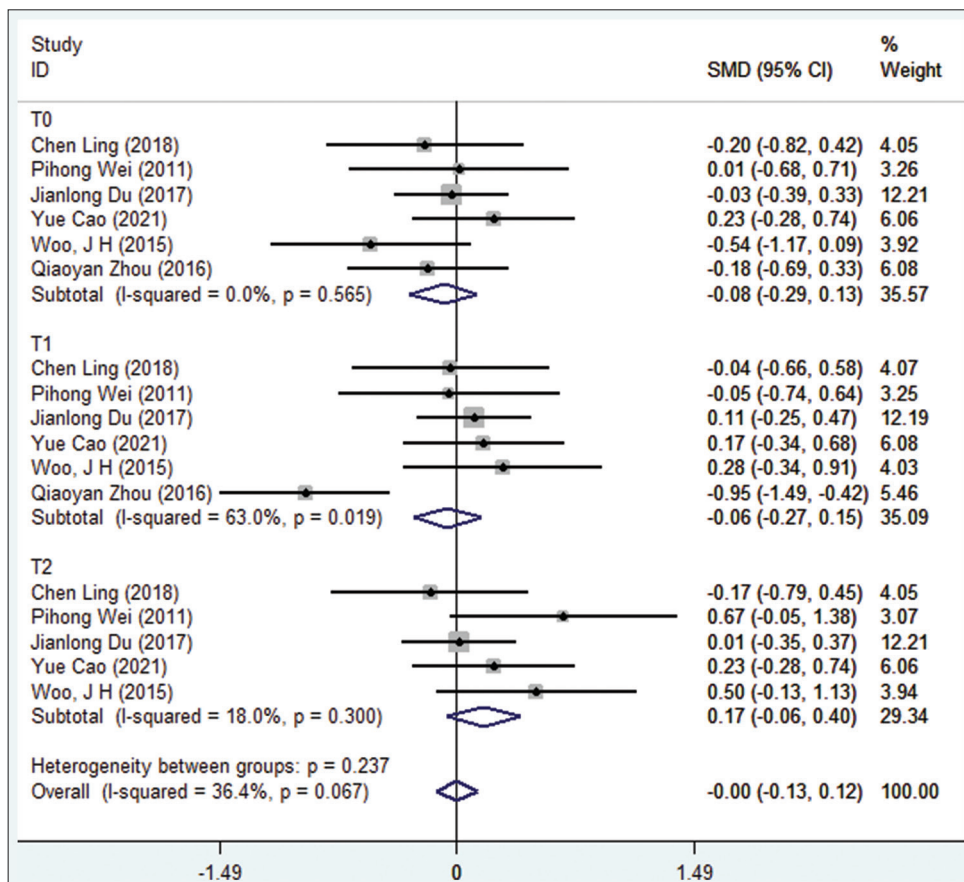


Figure 7: Meta-analysis forest plot of CD8⁺

shown in Figure 7. The fixed-effect combined effect size was 0.167 (95% CI: -0.064 ~ 0.397), and the difference was not statistically significant ($Z = 1.41, P = 0.157$). There was no difference between the CD8⁺ and inhalation groups in the propofol group 1 day after surgery. The P values obtained by Egger's test were all > 0.05 ($P_{T_0} = 0.496, P_{T_1} = 0.761, P_{T_2} = 0.283$), so there was no publication bias in the literature of this study.

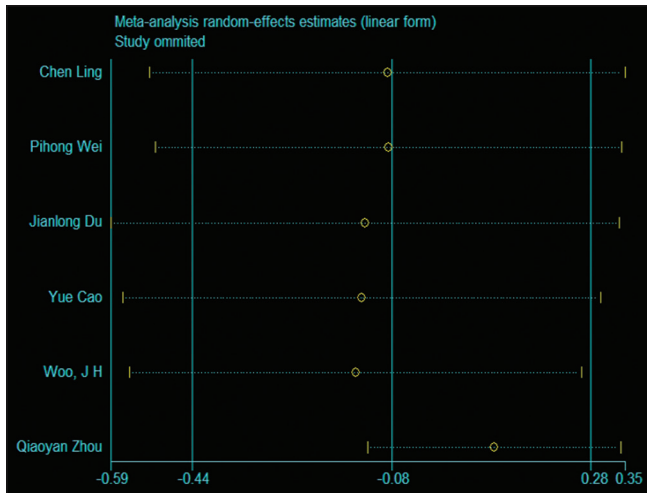


Figure 8: Sensitivity analysis of CD8⁺ (T₁)

CD4⁺/CD8⁺

Six studies (352 patients) reported the CD4⁺/CD8⁺ ratio with no statistically significant heterogeneity between groups at T₀ ($I^2 = 23.3%, P = 0.259$), as shown in Figure 9. The difference in the use of fixed-effect pooled effect sizes was not statistically significant (SMD = -0.04, 95% CI: -0.25 ~ 0.17, $Z = 0.37, P = 0.709$), so there was no difference in the ratio between the two groups at T₀, and subsequent meta-analysis could be performed. The effect size of T₁ was combined for heterogeneity testing, and there was some heterogeneity between the selected studies ($I^2 = 84.2%, P = 0.000$), and the result is shown in Figure 9. A sensitivity analysis of the six articles in this study is shown in Figure 10, and it was found that none of the studies had a strong impact on the study results. The random-effect pooled effect size was 0.389 (95% CI: -0.176 ~ 0.954), and the difference was not statistically significant ($Z = 1.35, P = 0.177$). There was no difference between CD4⁺/CD8⁺ in the propofol group and the inhalation group at the end of surgery. The effect size of T₂ was combined for heterogeneity testing, and there was no heterogeneity between the selected studies ($I^2 = 48.0%, P = 0.103$); the results are shown in Figure 9. The fixed-effect combined effect amount was 0.304 (95% CI: 0.072 ~ 0.537), and the effect was significant ($Z = 2.56, P = 0.010$). The ratio in the propofol group was significantly higher than that

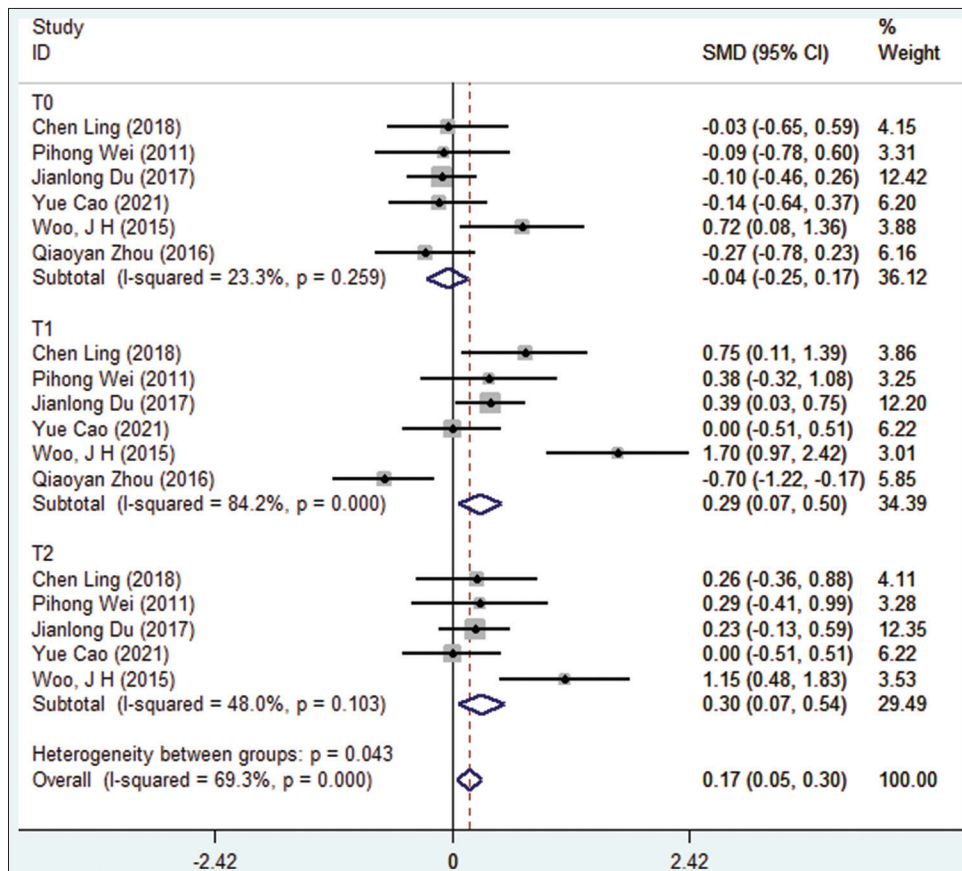


Figure 9: Meta-analysis forest plot of CD4⁺/CD8⁺

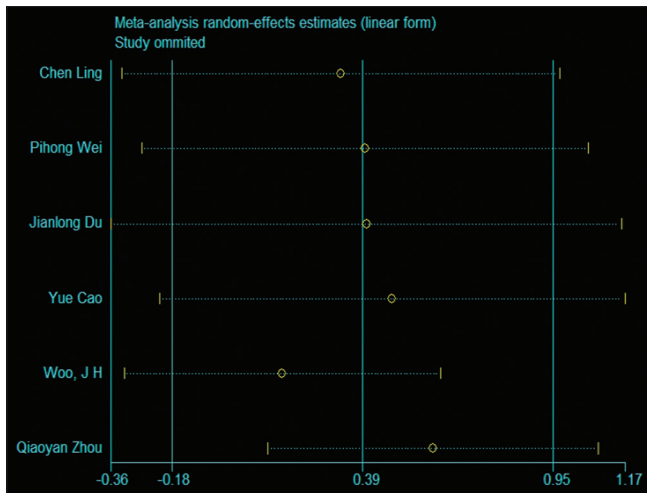


Figure 10: Sensitivity analysis of CD4⁺/CD8⁺ (T₁)

in the inhalation group by 0.348 1 day after surgery. The *P* values obtained by Egger's test were all >0.05 ($P_{T0}=0.422$, $P_{T1}=0.504$, $P_{T2}=0.442$), so there was no publication bias in the literature of this study.

DISCUSSION

This meta-analysis included six randomized controlled trials comparing the effects of propofol anesthesia and inhalation anesthesia on postoperative immune function in breast cancer patients, with selected indicators of immune function limited to the cellular level. The results showed that there was no difference in the effects on T-lymphocytes between propofol anesthesia and inhalation anesthesia at the end of surgery and 1 day after surgery, but on the postoperative day, patients with propofol anesthesia had higher activities of CD4⁺ cells and CD4⁺/CD8⁺ than those with inhalation anesthesia.

Perioperative immunosuppression predisposes individuals to tumor recurrence and metastasis.^[18] Cellular immunity plays an important role in antitumor effects, and T-lymphocytes are the most important cell population and an important indicator reflecting the level of immunity. CD3⁺, CD4⁺, and CD8⁺ are the main effector cells of T-lymphocytes. CD3⁺ is a characteristic marker representing T-lymphocytes. Peripherally mature T-lymphocytes have CD3⁺ distribution on the surface, and the decrease in the ratio of CD3⁺ is related to impaired cellular immune function. Peripheral mature T-lymphocytes are divided into two cell subsets, CD4⁺ and CD8⁺, according to the difference in CD differentiation antigens on the cell surface. CD4⁺ T cells can secrete some cytokines, which play a role in assisting the body's immune function, promoting the immune response, and inducing Type IV hypersensitivity reactions. CD8⁺ T cells detect and specifically kill cancer cells,^[19] which are key to cellular immunity associated with the prognosis of

cancer. The CD4⁺/CD8⁺ ratio is considered to be positively correlated with the function of cellular immunity,^[20] and a decrease in the ratio indicates that the body's immunity may be in a state of suppression or disorder, which is an indicator of disease severity and poor prognosis.

Propofol can enhance antitumor immunity by enhancing the activity of CD8⁺ T cells,^[10] which can preserve the activity of lymphocytes. Inhalation anesthetics have been shown to reduce circulating lymphocytes and induce apoptosis of T-lymphocytes.^[3,4,8,18,21,22] This may be related to the fact that propofol does not increase the damage to DNA in white blood cells.^[23] Although the precise mechanisms by which volatile anesthetics inhibit lymphocyte functions remain elusive, the induction of apoptosis, the decrease in mitochondrial membrane potential, the release of cytochrome C from mitochondria, interference with the MAPK cascade, the induction of mitochondrial reactive oxygen species, and abnormal calcium release from the endoplasmic reticulum suggest possible mechanisms for the volatile anesthetic-induced inhibitory effects on lymphocytes.^[18] The results of the effects of propofol and inhalation anesthetics on T-lymphocyte subsets suggest that propofol may have potentially beneficial effects on long-term prognosis after breast cancer surgery.

Limitations of the study

There are some limitations in the review. First, the number of included RCTs was small, with only six RCTs participating in this meta-analysis, five of which (312 patients) were from Asia. Different populations have different sensitivities to propofol and inhalation anesthetics, and the results may also be influenced by genetics, environment, and lifestyle. Second, some of the results are heterogeneous, and there are nonnegligible biases in the meta-analyses.

CONCLUSION

There was no difference in the effects of propofol and inhalation anesthetics on T-lymphocytes immediately after surgery, but the inhibitory effects of inhalation anesthetics on CD4⁺ and CD4⁺/CD8⁺ ratios were stronger 1 day after surgery.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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