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Review Article

Efficacy and Safety of Autologous Cytokine-Induced Killer (CIK) Cellular Immunotherapy Combined with Chemotherapy in Non-Small-Cell Carcinoma (NSCLC): A Meta-Analysis

*Cheng Zhong, Haowei Tang, *Qun Wang*

Respiratory Department, Fenghua District People's Hospital, Ningbo, 315000, China

***Corresponding Author:** Email: Wangqundr123@outlook.com

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Abstract

Background: To investigate the efficacy and safety of autologous Cytokine-induced killer (CIK) cellular immunotherapy combined with chemotherapy for non-small-cell carcinoma (NSCLC).

Methods: The literature related to the efficacy and safety of autologous CIK cellular immunotherapy combined with chemotherapy in NSCLC were collected. The Chinese literature databases were collected from CNKI, Wanfang and Weipu, and the English literature were retrieved from Cochrane Library and PubMed. All literature were retrieved until the year of 2022, and evaluated by its method quality and analyzed by RevMan5.3 software.

Results: A Meta-analysis on the 11 included literature showed that the treatment efficacy and disease control rate (DCR) of patients in the observation group were significantly higher than those in the control group ($P < 0.05$), and significantly increased the levels of CD3+, CD4+, CD4+/CD8+ indexes than the control group ($P < 0.05$), and the incidence of bone marrow suppression, liver injury and gastrointestinal symptoms were significantly lower than those of the control group ($P < 0.05$).

Conclusion: Compared with single chemotherapy, CIK combined with chemotherapy in the treatment of patients with NSCLC can improve the efficacy of treatment and DCR, significantly improve their immune function, reduce the incidence of adverse reactions, and is beneficial to the recovery of prognosis.

Keywords: CIK cellular immunity; Chemotherapy; Curative effect; Security; Meta-analysis

Introduction

At present, lung cancer is the most common cancer in clinical, which is also a malignant tumor with the highest incidence, growth rate and mortality. More than 80% of the lung cancer is NSCLC. The onset of NSCLC is insidious and there are no special symptoms in the early stage. When diagnosed, the patient is generally in the middle and late stage of the disease, and the proportion of patients with late distant metastasis and local invasion is not less than 50% (1,2). Surgical treatment is still preferred, however, most of the patients miss the optimal operation time.

Therefore, systemic chemotherapy is usually the treatment for NSCLC (2).

However, systemic chemotherapy may cause acute and subacute toxicity and low effect of anti-tumor immunity, which is also the main reasons for low quality of life, poor tumor response and poor prognosis. It is urgent to find new and effective methods. With the continuous development of molecular biology and tumor immunology technologies, cellular immunotherapy is widely used in the clinical treatment of NSCLC, which can stimulate the immune response of the body by expanding in vitro effector cells and injecting them back, so that the auto-immune system and effector cells can jointly inhibit the development of tumor cells with specific high-killing activities universally (3).

Cytokine-induced killer cells (CIK cells) is a new type of immune active cells, with good cytolytic activity, which has been used the most commonly as cellular immunotherapy in clinical practice, with the characteristics of wide tumor killing spectrum, strong tumor killing activity, high proliferation activity, and has a certain inhibitory effect on a variety of multiple drug-resistant tumor cells (4,5). The combination with chemotherapy drugs has achieved good results in the treatment of NSCLC.

This study evaluated the efficacy and safety of autologous CIK cellular immunotherapy combined with chemotherapy in patients with NSCLC, aiming to provide a reference for the clinical treatment of NSCLC.

Methods

Retrieving literature and relevant data

The literature were retrieved from the establishment of the database to October 2022, Chinese literature was retrieved from databases of CNKI, Wanfang and Weipu, respectively, and English literature were retrieved from platforms of Cochrane Library and PubMed. Chinese keywords included "Autologous CIK Cellular Immunotherapy", "Chemotherapy", "Non-Small Cell Lung Cancer", "CIK Cellular Immunity", "Efficacy and Safety", and English keywords were "Autologous CIK Cellular Immunotherapy", "NSCLC", "CIK Cellular Immunity" and "Efficacy and Safety".

Inclusion and exclusion criteria

Literature inclusion criteria: 1) The literature were on randomized controlled trial, with full text published, in English or Chinese, and the number of cases in a single group of literature was not less than 20; 2) The patients in literature were diagnosed with NSCLC; 3) The patients in the control group were treated with chemotherapy drugs, and those in the observation group were treated with chemotherapy and autologous CIK cellular immunotherapy; 4) The efficacy indexes were efficacy and DCR. Exclusion criteria: 1) The studies were retrospective; 2) The specific information of important data in literature is incomplete; 3) Case reports, case studies and news.

Extracting the data from literature

Two professionals screened the literature, extracted relevant data, and cross-checked the selected information. A third professional was consulted to resolve any disagreement. The extracted literature mainly included: 1) Title, source, author, and publication time of literature; 2) The type and related elements of literature were assessed by risk of bias; 3) Intervention methods and age of patients in the control and research groups; 4) The outcome indexes in the literature included efficacy (efficacy and DCR), immune function (CD3+, CD4+, CD8+, and CD4+/CD8+), and adverse reactions (bone marrow suppression, liver injury, digestive tract symptoms).

Literature quality evaluation

In this study, the quality of literature was evaluated to evaluate randomly generated sequences, allocation concealment, implementation of blinding, presence of other biases, and patient withdrawal and loss to follow-up (6).

Statistical methods

A Meta-analysis was performed on the efficacy and safety of NSCLC with autologous CIK cellular immunotherapy, combined with chemotherapy through RevMan5.3 software. The effects were analyzed by relative risk (RR) or odds ratio (OR) and 95%CI. For continuous variables, the mean, SD and 95%CI were taken as effect statistic. Measurement data were compared with chi-square test, and the magnitude of the heterogeneity were judged combined with I^2 values, whereas, $P>0.10$, $I^2<50\%$, indicating good statistical homogeneity. A Meta-analysis was conducted with a fixed-effects model, whereas, $P\leq0.10$, $I^2\geq50\%$, indicating the presence of statistical heterogeneity, followed by a Meta-analysis with random effect model. For those selected literature data, a meta-analysis could not conduct, however, a descriptive analysis could be performed.

Results

Results of the retrieved literature

Relevant literature were retrieved from databases of Cochrane Library, PubMed, Weipu, Wanfang and CNKI through the established retrieval strategy, and the literature were read and screened according to inclusion and exclusion criteria. Finally, 11 literature were included. The flow chart is shown in Fig. 1.

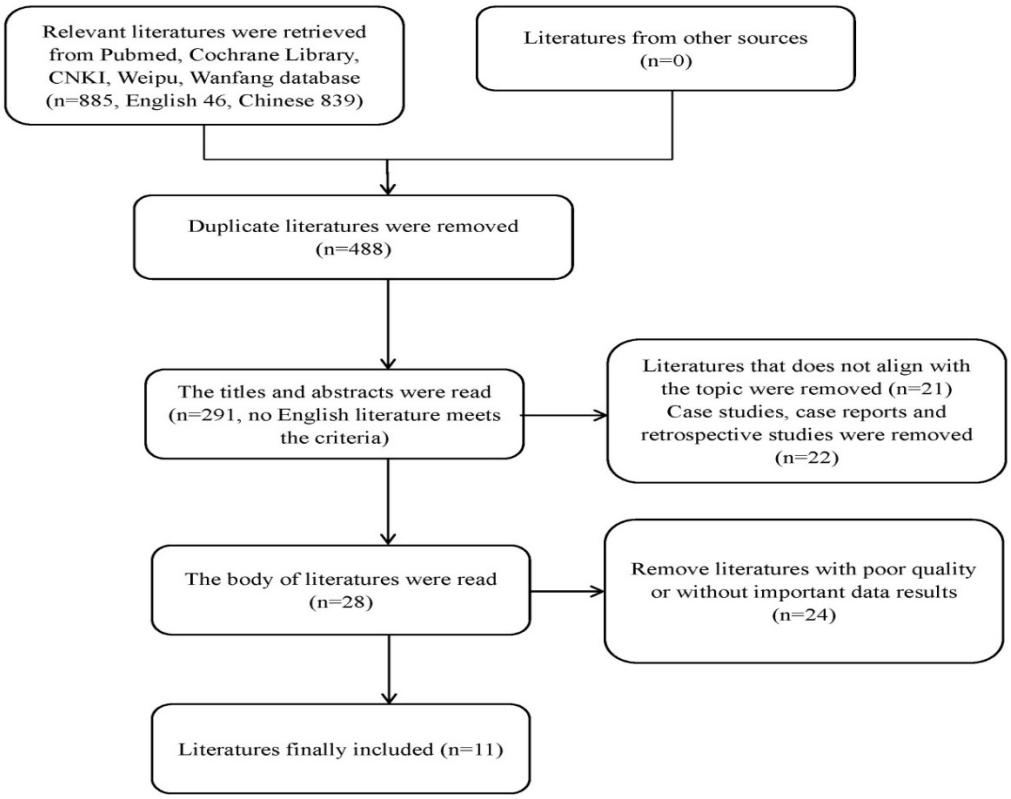


Fig. 1: Flow chart of retrieval and screening of related websites

Basic characteristics of included literature

A total of 11 literature were selected, all of which were randomized controlled trials published from 2015 to 2021. 924 patients were sampled. The control group were treated with chemotherapy, and the research group were treated with chemotherapy combined with CIK cellular immunotherapy. The specific literature information is shown in Table 1.

Table 1: Basic characteristics of included literature

Author / Year	*Sample Size (Patient)*		*Age (Years old)*		*Intervention*		*Outcome Indexes*
	Research Group	Control Group	Research Group	Control Group	Research Group	Control Group	
Ye Ruiping [7] 2016	35	35	41~75	40~72	Chemotherapy combined with CIK cellular immunotherapy	Chemotherapy	A, C, D, E, F, G, H, J
Wang Xiuwen [8] 2017	48	48	38~76	37~74	Chemotherapy combined with CIK cellular immunotherapy	Chemotherapy	A, B, C
He Xiaoyuan [9] 2019	45	45	43~80	42~81	Chemotherapy combined with CIK cellular immunotherapy	Chemotherapy	A, C, D, F
Li Jie [10] 2015	61	61	57.23±8.95	58.19±8.73	Chemotherapy combined with CIK cellular immunotherapy	Chemotherapy	A, C, D, E, F
Li Lei [11] 2016	34	34	58.4±3.5	57.6±4.6	Chemotherapy combined with CIK cellular immunotherapy	Chemotherapy	A, B
Yang Jia [12] 2015	36	36	37~75	38~75	Chemotherapy combined with CIK cellular immunotherapy	Chemotherapy	B, G, H, J
Wang Jinshuo [13] 2015	35	36	59.8±1.3	59.6±2.8	Chemotherapy combined with CIK cellular immunotherapy	Chemotherapy	A, B, C, D, E, F, J
Du Guowei [14] 2016	44	43	68.15±4.33	68.04±4.73	Chemotherapy combined with CIK cellular immunotherapy	Chemotherapy	B, C, D, E, F,
Ding Zhenyu [15] 2015	40	40	The median age was 59.5	The median age was 61.2	Chemotherapy combined with CIK cellular immunotherapy	Chemotherapy	A, B, C
Han Lige [16] 2021	42	41	58.01±7.35	60.25±8.37	Chemotherapy combined with CIK cellular immunotherapy	Chemotherapy	B, C, E, F
Meng Xianlu [17] 2020	43	42	54.72±6.82	55.10±6.49	Chemotherapy combined with CIK cellular immunotherapy	Chemotherapy	B, C, D, E, G, H, J

Note: Outcome indexes: A: efficacy; B: DCR; C: CD3+ ; D : CD4+ ; E : CD8+ ; F : CD4+/CD8+ ; G: Bone marrow suppression; H: Liver injury; J: Gastrointestinal symptoms

Methodological quality evaluation of included literature

None of the included literature indicated the hidden allocation scheme and the use of blindness was not specifically described, and the risk of bias was low in random sequence method, blind method of literature results, and selective reporting. The quality grade of the included literature were all Grade B, as shown in Fig. 2.

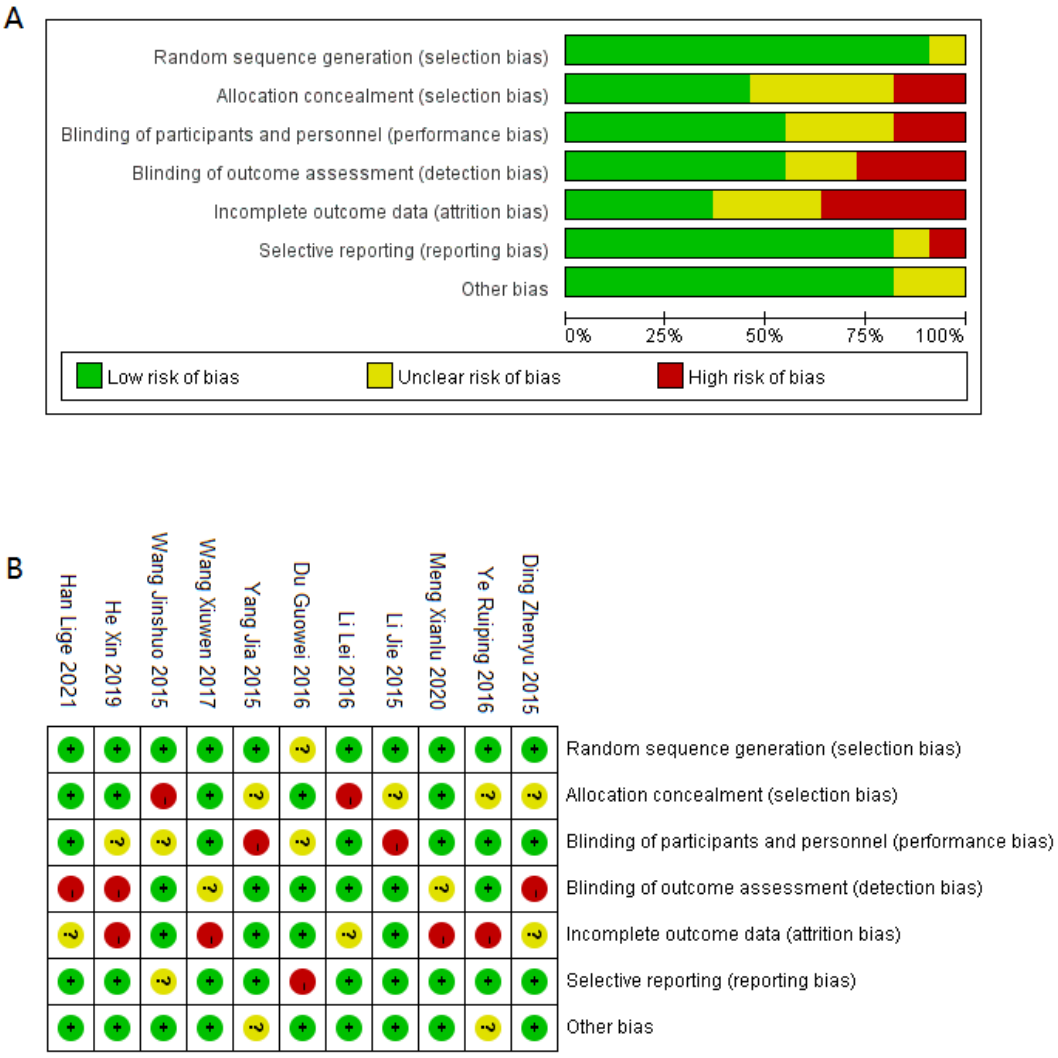
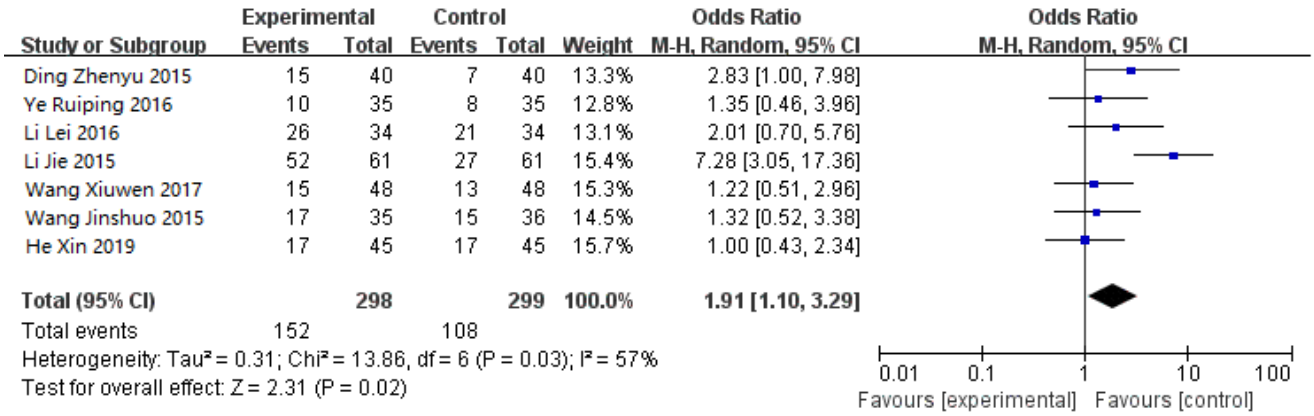


Fig. 2: literature bias evaluation

Efficacy

Among the 11 included literature, there were 7 literature on efficacy, including 299 patients in the control group and 298 patients in the observation group. The heterogeneity test among different included literature showed P=0.03, I^2=57%. A Meta-analysis with random effect model showed that the patients in the observation group had a significantly higher efficacy than those in the control group [OR=1.91 (1.10, 3.29), P=0.02]. The presence of publication bias between literature was analyzed with missing plots, as shown in Fig. 3.



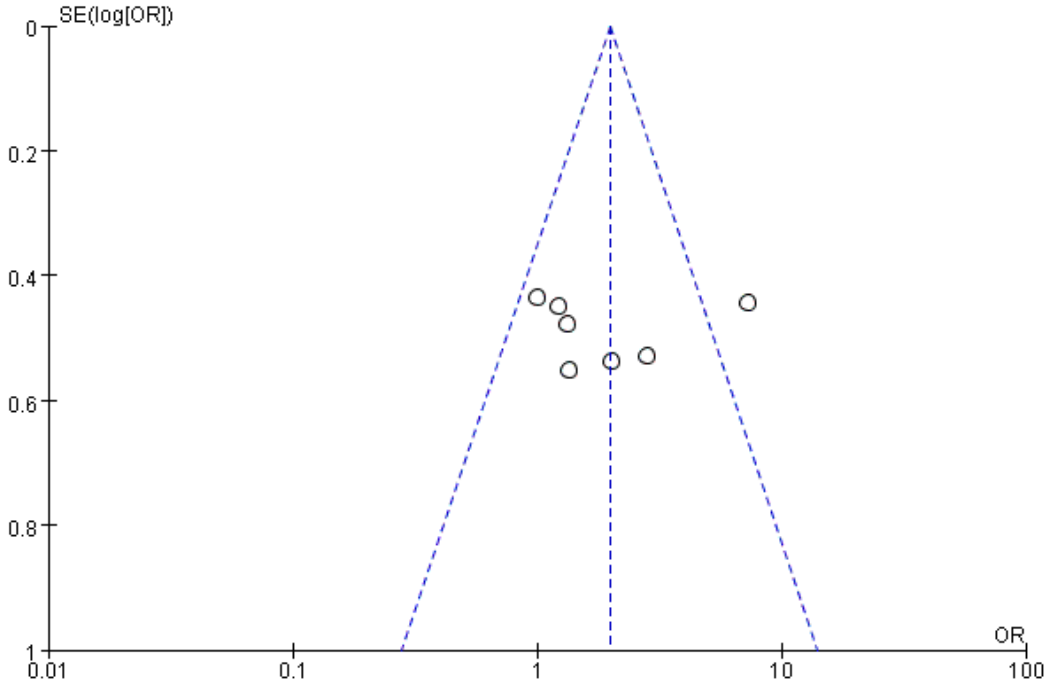


Fig. 3: Forest plot of efficacy through Meta-analysis

Disease control rate

Nine studies reported DCR of NSCLC, including 383 patients in the observation group and 381 patients in the control group. The heterogeneity test between each literature was P=0.96, I^2=0%. A Meta-analysis with a fixed effect model showed that DCR in the observation group was significantly higher than that in the control group [OR = 3.34 (2.40, 4.63), P=0.000]. The presence of publication bias between literature was analyzed with missing plots, as shown in Fig. 4.

CD3+

Nine studies reported CD3+, including 393 patients in the observation group and 391 patients in the control group. The results of heterogeneity test between literature were P =0.000, I^2=100%. A Meta-analysis with random effect model showed that the level of CD3+ in the observation group was significantly higher than that in the control group [OR=15.44 (2.86, 28.01, P=0.02]. The presence of publication bias between literature was analyzed with missing plots, as shown in Fig. 5.

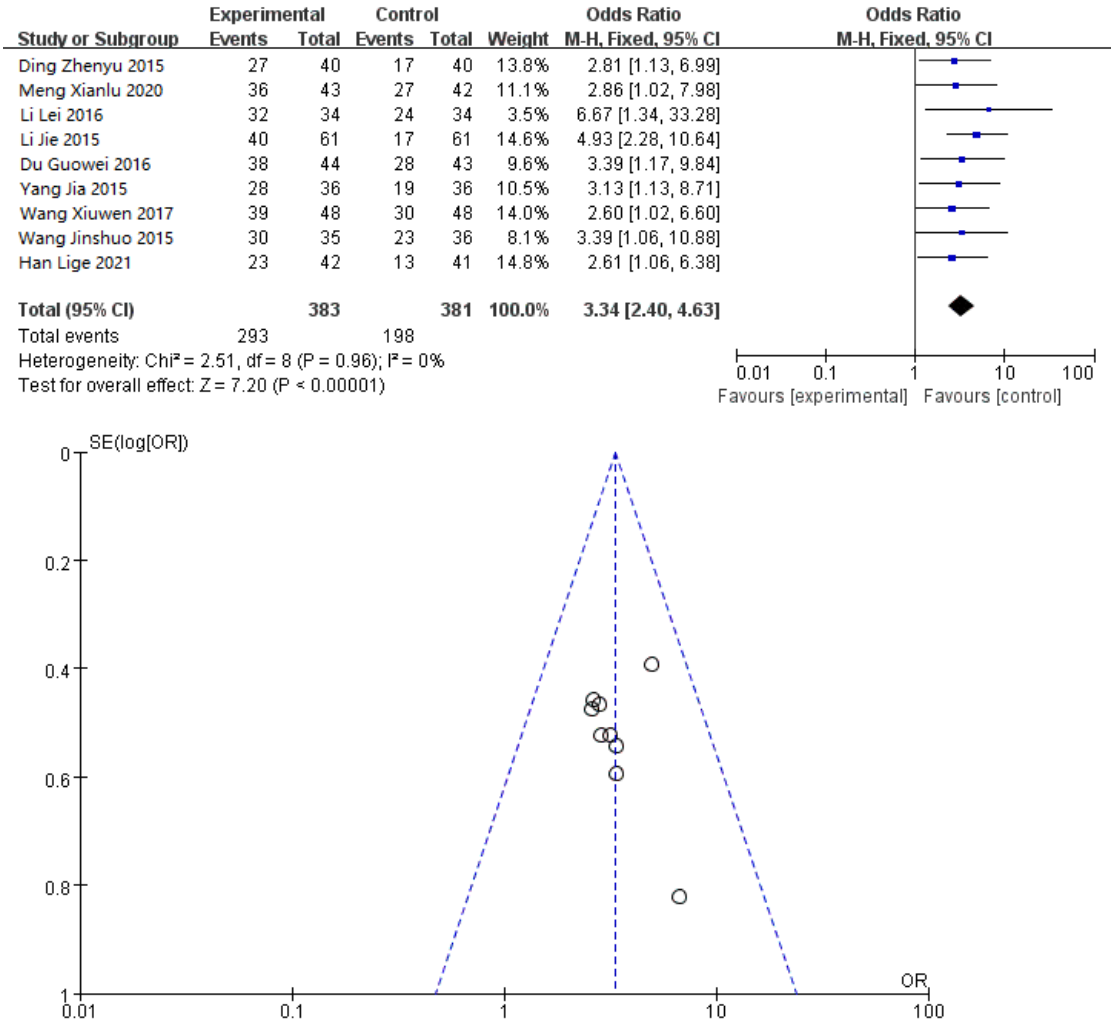


Fig. 4: Forest plot of DCR through Meta-analysis

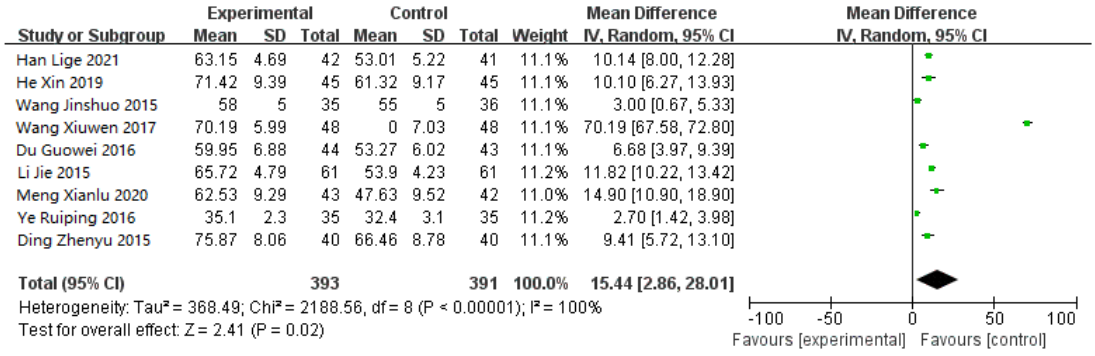


Fig. 5: Forest plot of CD3+ through Meta-analysis

CD4+

Nine studies reported CD4+, including 393 patients in the observation group and 391 patients in the control group. The results of heterogeneity test between literature were P =0.000, I^2=100%. A Meta-analysis with random effect model showed that the level of CD4+ in the observation group was significantly higher than that in the control group [OR=15.44 (2.86, 28.01), P=0.000]. The presence of publication bias between literature was analyzed with missing plots, as shown in Fig. 6.

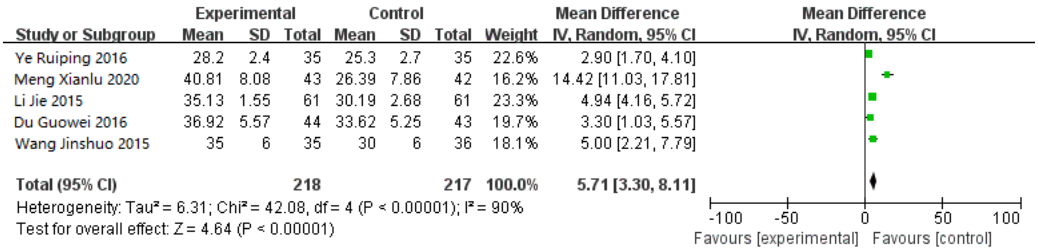


Fig. 6: Forest plot of CD4+ through Meta-analysis

CD8+

Six studies reported CD8+, including 260 patients in the observation group and 258 patients in the control group. The results of heterogeneity test between literature were P =0.000, I^2=97%. A Meta-analysis with random effect model showed that the level of CD8+ in the observation group was significantly higher than that in the control group [OR=1.25 (5.12, 2.62), P=0.53], as shown in Fig. 7.

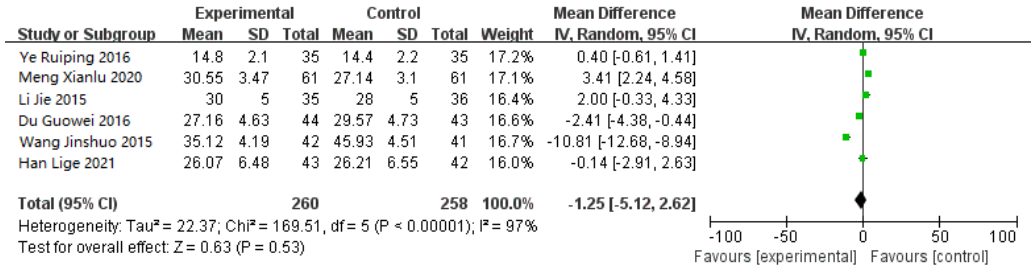


Fig. 7: Forest plot of CD8+ through Meta-analysis

CD4+/CD8+

Six studies reported CD4+/CD8+, including 262 patients in the observation group and 261 patients in the control group. The results of heterogeneity test between literature were P =0.000, I^2=85%. A Meta-analysis with random effect model showed that the level of CD4+/CD8+ in the observation group was significantly higher than that in the control group [OR=0.21 (0.06, 0.36), P=0.01], as shown in Fig. 8.

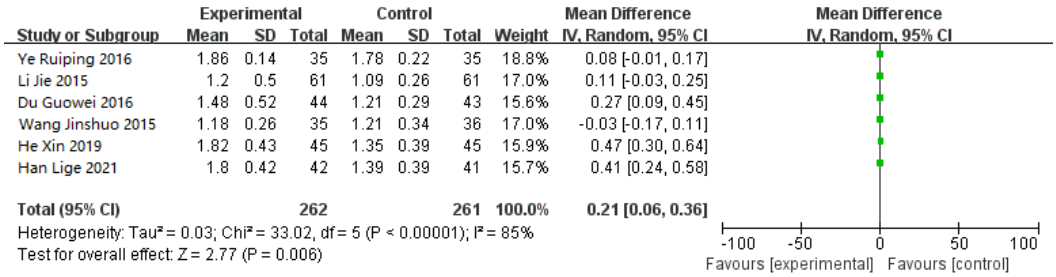


Fig. 8: Forest plot of CD4+/CD8+ through Meta-analysis

Myelosuppression

Three studies reported myelosuppression, including 114 patients in the observation group and 113 patients in the control group. The heterogeneity test among included literature showed P =0.48, I^2=0%. A Meta-analysis with fixed-effects model showed that the incidence of myelosuppression in the observation group was significantly more than that in the control group [OR=0.30 (0.15, 0.61), P=0.00]. The funnel plots are shown in Fig. 9.

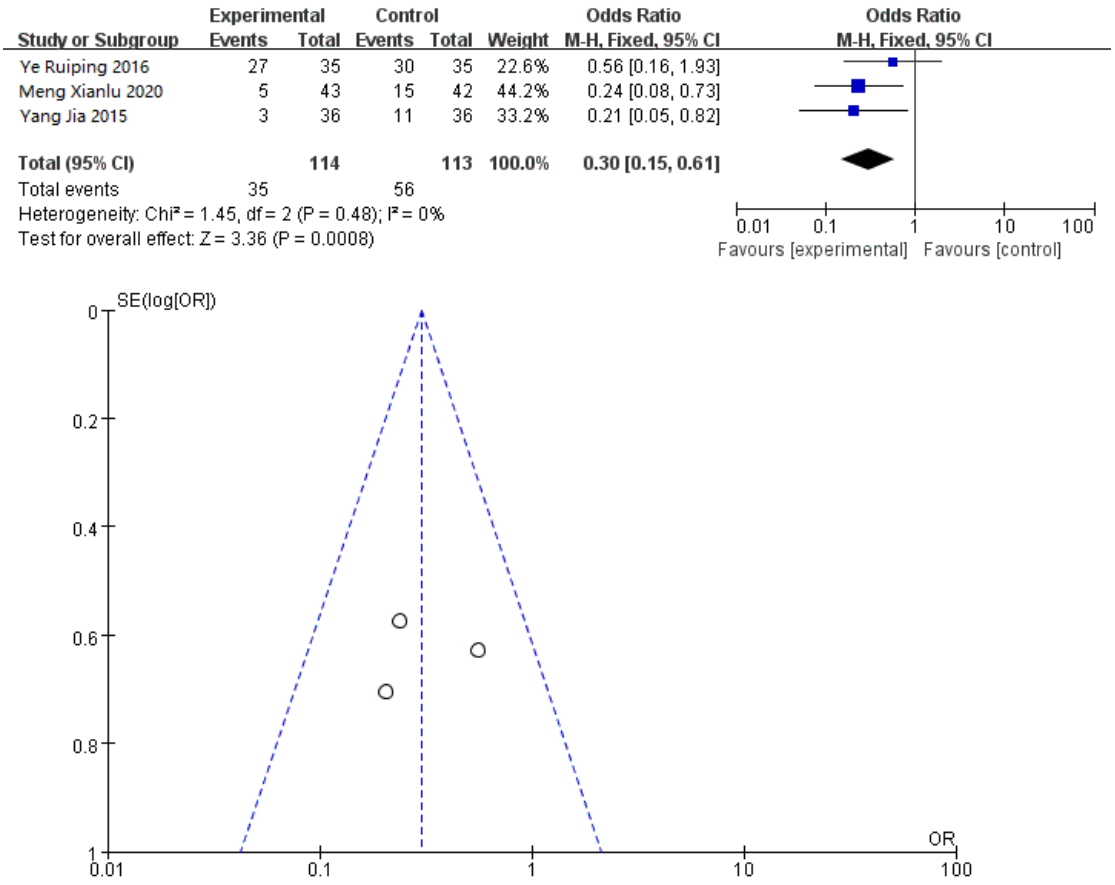


Fig. 9: Forest plots and funnel plots of myelosuppression through Meta-analysis

Liver injury

Three studies reported liver injury, including 114 patients in the observation group and 113 patients in the control group. The heterogeneity test among included literature showed P =0.62, I^2=0%. A Meta-analysis with fixed-effects model showed that the liver injury in the observation group was significantly higher than that in the control group [OR=0.47 (0.24, 0.94), P=0.03]. The funnel plots are shown in Fig. 10.

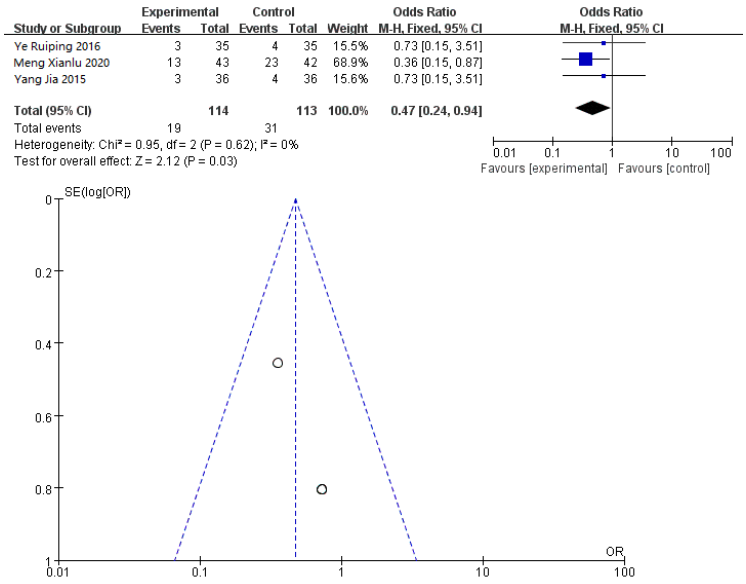


Fig. 10: Forest plots and funnel plots of liver injury through Meta-analysis

Digestive tract symptoms

Four studies reported gastrointestinal symptoms, including 149 patients in the observation group and 149 patients in the control group. The heterogeneity test between included literature showed P =0.99, I^2=0%. A Meta-analysis with fixed-effects model showed that the incidence of gastrointestinal symptoms in the observation group was significantly lower than that in the control group [OR=-0.26 (-0.37, -0.15), P=0.00]. The funnel plots are shown in Fig. 11.

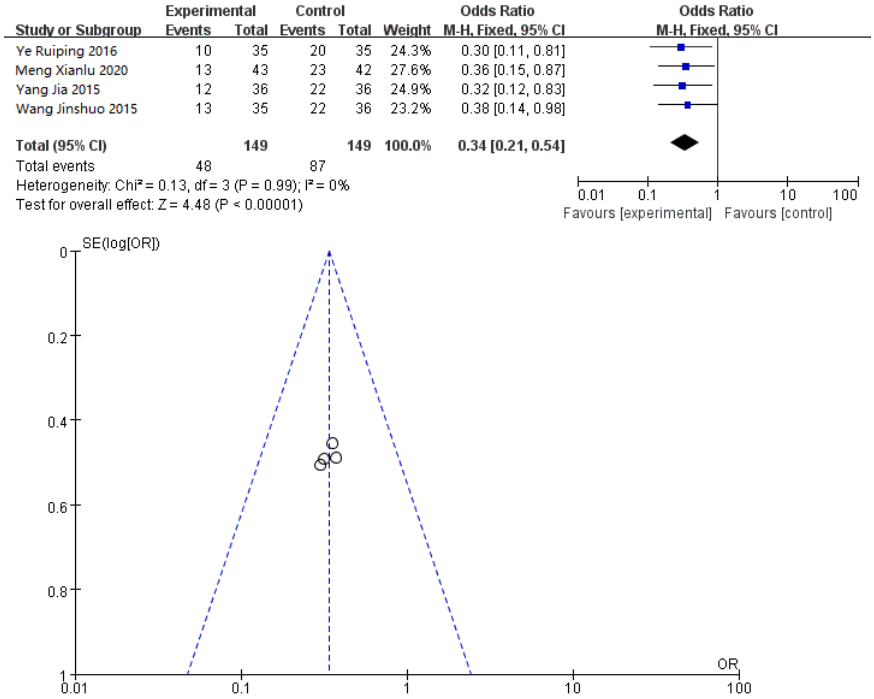


Fig. 11: Forest plots and funnel plots of digestive tract symptoms through Meta-analysis

Discussion

It is a clinical consensus that patients with cancers have low immunity. When the host's immune system is suppressed, the prevalence risk of malignant tumors significantly increases. When tumor cells are rapidly proliferating, the patient's immunity is more prominent. Biological tumor immunotherapy is a new tumor treatment technology that expands isolated mononuclear cells from autologous peripheral blood in vitro and reinjects them into the patient's body to regulate and enhance the patient's immune ability, and can completely eliminate tumor cells (17). CIK is a kind of biological tumor immunotherapy, which integrates the heterogeneous cells obtained by in vitro expanded cytokines into the patient's body, and has the advantages such as high anti-tumor activity, fast value-added rate, unaffected by the anti-tumor effect of multidrug-resistant cancer cells, and anti-apoptotic properties (18). At present, autologous CIK cellular therapy is becoming increasingly important in the clinical treatment for malignant tumors.

There is a strong link between the occurrence of lung cancer and the decline of immune capacity (19). Therefore, the body's immune capacity of advanced patients with NSCLC is reduced, which easily leads to the decline of immune surveillance ability, resulting in the occurrence of immune escape. The immunosuppression of CIK is mainly completed by the activation of immune cells such as T lymphocytes and NK cells. However, T lymphocytes are a major participant in the cellular immunity of the body, and the immune response of their core cells involves two cell subsets, CD4+ and CD8+. And the body's immune balance is mainly maintained by the interaction between these two types of immune cells. CD4+/CD8+ are indexes for the body's immune regulation and are important to measure the severity of diseases (20). When the ratio of CD4+/CD8+ is lower than their normal level, it can be considered that the immune regulation of the body is disordered and it is easy to form malignant tumors. Only when the ratio of CD4+/CD8+ is at a normal level, CD4+/CD8+ has an anti-tumor effect. CD3+ is a mature lymphocyte with the highest immune activity in the body's immunity (21). Among the literature selected in this study, the levels of CD3+, CD4+ and CD4+/CD8+ in patients with NSCLC who were treated with chemotherapy combined with CIK cellular immunotherapy were significantly higher than those treated with chemotherapeutic agents alone, indicating that chemotherapy combined with CIK cellular immunotherapy could improve the levels of CD3+, CD4+, and CD4+/CD8+ in patients with NSCLC, improving the treatment effect of NSCLC.

This is similar to a Meta-analysis conducted by Li X et al., which shows that the combination of CIK cellular immunotherapy and chemotherapy has a clear effect on the treatment for NSCLC (22). There is a study (23) confirmed that in patients with NSCLC, high levels of CD8+ T cells in the tumor were positively correlated with increased survival rate and decreased overall recurrence rate. And in the literature selected in this study, there was no difference in the ratio of CD8+ in peripheral blood between the two groups, possibly because CD8+ T cells had infiltrated into tumor cells, which also indirectly indicated that cellular immune function had been enhanced. At the same time, it also showed that CIK immunotherapy could enhance the therapeutic efficacy of chemotherapy in patients with NSCLC, and could not increase the incidence of adverse effects occurring during the treatment, including myelosuppression, liver injury, gastrointestinal symptoms, etc.

In addition, the treatment efficacy and disease control rate of patients receiving CIK combined chemotherapy are significantly lower than those receiving single chemotherapy. In addition, the efficacy and DCR of the treatment for patients receiving CIK combined chemotherapy were significantly lower than those receiving chemotherapy alone. Therefore, the use of CIK cellular immunotherapy or chemotherapy can significantly reduce the burden of tumors and restore or alleviate immune suppression in the body. The combination of the two treatments can improve

the immune capacity of patients, reduce the incidence of adverse reactions, and control the deterioration of malignant tumors to a certain extent. Therefore, the combination of CIK immunotherapy and chemotherapy should be recognized.

The limitations of this study are as follows: The quality of literature selected in this study was not high, which was Grade B. The included literature did not indicate the hidden allocation scheme and the use of blind method was not described in detail. The risk of bias in random sequence method, blind method of literature results and selective reporting were all low, and there were certain limitations in terms of methodology. The clinical trial conditions in the selected literature were different, and there was clinical heterogeneity. Due to the lack of sufficient clinical data, the long-term efficacy and safety of patients with NSCLC could not be accurately evaluated. As the studies included in the literature were all domestic clinical studies, which also indicates the limitations of the conclusions of this study to some extent. Despite the above limitations, the strength of evidence in the evaluation of this study was reduced. However, due to the strict inclusion criteria of this study, the baseline comparability of included studies was relatively good, the Meta-analysis was standardized, and the bilateral symmetry of funnel plots of DCR, efficacy and adverse reactions of patients after treatment was relatively good, indicating that publication bias has little impact on the results of this study. The results of this study have high reliability, so the results obtained through the Meta-analysis were reliable and stable, which could provide evidence-based reference for clinical treatment of NSCLC and further studies.

Systematic evaluation can not only analyze and evaluate the existing clinical studies, and facilitate the guidance of clinical practice, but also indicate the direction of future studies. According to the limitations of the evaluation of this study, several suggestions can be made: The process of reporting RCT should be standardized, especially the methodological quality should be described concretely. The end points should be described in detail, and the follow-up and record of safety and long-term efficacy should be strengthened. Economic indexes related to the report are collected to facilitate the economic evaluation of the intervention. More high-quality, large-sample clinical studies should be conducted to verify the conclusions obtained from this Meta-analysis. At present, it is still an important issue in clinical research that which chemotherapy drugs should be combined with CIK immunotherapy to improve the therapeutic effect of patients.

Conclusion

Compared with the single chemotherapy treatment for patients with NSCLC, the combination of CIK with chemotherapy for patients with NSCLC can improve the efficacy and DCR, and significantly improve their immune function, reduce the incidence of adverse reactions, and restore the prognosis.

Journalism Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

No funding was received in this study.

Conflict of Interest

The authors declare that there is no conflict of interest.

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