Review Article

Efficacy of metformin adjunctive therapy as the treatment for non-diabetic patients with advanced non-small cell lung cancer: A Systematic review and Meta-analysis

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Background: Currently, the anticancer effects of metformin on different types of lung cancer have been frequently studied. However, the relationship between metformin and prognosis in nondiabetic patients with lung cancer remains controversial. To systematically evaluate the efficacy of metformin adjunctive therapy as the treatment for nondiabetic patients with advanced non-small cell lung cancer (NSCLC) to provide an evidence-based reference for clinical medication. **Materials and Methods:** The literatures related to Phase II or III randomized controlled trials (RCTs) of metformin adjunctive therapy in nondiabetic patients with advanced NSCLC, including EMBASE, PubMed, the Cochrane Library, and Scopus database, were retrieved by computer, and the search time ranged from January 2017 to August 2022. The risk of bias assessment tool recommended by Cochrane Systematic Evaluator Manual 5.1.0 was used to evaluate the quality of the RCTs included. Rev Man 5.3 software and STATA15.0 were used for meta-analysis. **Results:** A total of 8 studies were included (925 patients). Meta-analysis results showed that there were no significant differences in progression-free survival (PFS) (hazard ratio [HR] = 0.95, 95% confidence interval [CI]: 0.66–1.36, P = 0.77), overall survival (OS) (HR = 0.89, 95% CI: 0.61–1.30, P = 0.55, n =7), objective response rate (ORR) (odds ratio [OR] = 1.37, 95% CI: 0.76–2.46, P = 0.30), and 1-year PFS rate (OR = 0.87, 95% CI: 0.39–1.94, P = 0.73, n = 3). Sensitivity analysis showed that PFS and OS indexes were stable. **Conclusion:** Metformin adjunctive therapy can improve the DCR of nondiabetic patients with advanced NSCLC. In addition, the patients cannot obtain a prolonged PFS, OS, 1-year PFS rate, and higher ORR rate.

Key words: Meta-analysis, metformin, non-small cell lung cancer, systematic review

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INTRODUCTION

Lung cancer, one of the most commonly occurring malignancies, remains the leading cause of cancer-related mortality worldwide.[1] According to the statistics, an estimated 2.3 million individuals were diagnosed with cancer globally, with lung cancer accounting for approximately 11.4% of all cases. Approximately 1.8 million people die from lung cancer every year, representing 18% of all cancer-related deaths worldwide.[2] Nonsmall cell lung cancer (NSCLC) is the most common pathological type of lung cancer, including adenocarcinoma, large cell carcinoma and squamous cell carcinoma, accounting for more than 85% of lung cancer.[1,3] Despite some progress that has been achieved in the treatment of lung cancer in the past decades, the 5-year survival rate of patients remains low, and drug resistance contributes to poor prognosis.[1,4] Therefore, multidisciplinary cooperation is essential for the optimal treatment of patients with advanced NSCLC.[5]

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Metformin is a biguanide organic compound, the most commonly used first-line prescription drug for treating type 2 diabetes mellitus, especially for obese patients. In recent years, many studies have shown that metformin has potential anticancer properties,[6-9] leading to improved overall survival (OS) or decreased mortality rates in patients with various solid tumors, including liver cancer, pancreatic cancer, breast cancer, cervical cancer, prostate cancer and colorectal, cancer when addition to standard treatment. Although metformin has been identified as a useful adjunctive therapy for lung cancer patients with diabetes,[10-12] there is a lack of research on its effects in nondiabetic patients, and most studies to date have been retrospective. Some clinical studies have suggested that metformin combined with other anticancer treatments has a synergistic effect,[13,14] while others have produced conflicting results.[15-17] Therefore, the effect of metformin on the prognosis of nondiabetic patients with advanced lung cancer is controversial, and it is necessary to conduct a meta-analysis to confirm its efficacy further. Based on this, we aim to study the relationship between the application of metformin adjunctive therapy and the prognosis of nondiabetic patients with lung cancer.

METHODS

This meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and checklist. The study protocol was registered in the International Prospective Register of Systematic Reviews database with registration number CRD42022367968.

Inclusion and exclusion criteria

The following inclusion criteria were used to select papers for the meta-analysis: (1) randomized controlled trials (RCTs) that reported disease control rate (DCR), progression-free survival (PFS), OS, objective response rate (ORR), and 1-year PFS rate were included in this study; (2) full-text available; (3) papers written in English or Chinese; (4) original papers; (5) publication date from January 2017 to August 2022. Exclusion criteria included:(1) papers not written in English or not available as full-text; (2) studies that reported on nonoriginal data like duplicate studies, case reports, meta, and review papers; (3) animal studies; (4) non-RCTs; (5) diabetic patients. This meta-analysis included the most recently published papers if multiple papers were from the same study and reported the same or overlapping outcomes.

Study design

Phase II or III RCT investigating the efficacy of metformin adjunctive therapy in nondiabetic patients with advanced NSCLC has been published globally and is limited to the English or Chinese language.

Patients

Patients with pathologically or cytologically confirmed inoperable or advanced (stage III or IV or recurrent) NSCLC, age 18 years old, nondiabetic patients, and Eastern Cooperative Oncology Group performance status (ECOG PS) score was 0 or 1, regardless of gender, region, and ethnicity.

Interventions

Control group: Standard antineoplastic agents alone.

Experimental group: Metformin adjunctive therapy (traditional chemotherapy drugs, epidermal growth factor receptor tyrosine kinase inhibitors [EGFR-TKIs], antiangiogenic drugs or chemoradiotherapy).

Outcomes

The included study indicators included PFS, OS, ORR, DCR, and 1-year PFS rate. PFS refers to the duration from the beginning of receiving metformin (MM) combined with anti-tumor drugs to the first disease progression, which could include local recurrence, distant metastasis, deterioration of symptoms, death from any cause, or the last follow-up. OS pertains to the duration from receiving metformin combined with anti-tumor drugs to death for any reason or the last follow-up. ORR denotes the proportion of patients whose tumors showed a significant reduction in size after drug treatment, encompassing complete and partial remission. DCR relates to the proportion of patients whose tumors have shrunk or stabilized and remained for a certain period of time, including cases with complete remission, partial remission, and stabilization.

Data sources and search strategy

For RCT clinical studies on metformin adjunctive therapy in nondiabetic patients with advanced NSCLC, EMBASE, PubMed, Cochrane Library, and Scopus databases were comprehensively searched from January 2017 to August 2022. The search strategies typically used a combination of terms from medical subject headings and free-text keywords, which were as follows: Metformin, NSCLC, and randomized. Meanwhile, RCTs related to metformin adjunctive therapy in nondiabetic patients with advanced NSCLC were manually searched to reduce the incidence of bias.

Data extraction and quality assessment

First of all, 1 researcher (Duan) imported the retrieved documents into Noteexpress software. Duplications were first eliminated using the software of Noteexpress. Subsequently, 2 researchers (Duan and Liao) independently screened the titles, abstract and full text to identify potentially relevant papers. In case of any disagreement over the eligibility for any study between the two reviewers, all these dissensions were thoroughly discussed, and

a full-text assessment was conducted accordingly. 2 investigators (Duan and Liao) independently extracted the following data from each eligible study in a standardized Microsoft Excel sheet, including the last name of the first author, year of publication, gender, study design, clinical trial number, age, gender, clinical trial stage, ECOGPS score, intervention measures, outcome indicators (PFS, OS, ORR, DCR, and 1-year PFS rate). The Cochrane risk bias assessment tool was used to assess the bias risk of RCT, including random sequence generation (selection bias), allocation concealment (selection bias), blinding of investigators and subjects (implementation bias), blinded evaluation of study outcomes (measurement bias), the integrity of outcome data (follow-up bias), selective reporting of study results (reporting bias) and other sources (other bias). Green represents low risk, yellow represents unclear risk, and red represents high risk.

Statistical analysis

Meta-analysis was conducted with Rev Man5.3. Heterogeneity was statistically evaluated by I^2 value, the fixed-effect model was applied for analysis if trials were homogeneous ($I^2 \leq 50\%$ and $P > 0.1$), and the random-effect model was applied for the meta-analysis if statistical heterogeneity was identified ($I^2 > 50\%$ and $P < 0.1$); P value < 0.05 was considered statistically significant unless otherwise noted. For dichotomous data, pooled outcomes were presented as odds ratio (OR) and 95% confidence interval (CI), while OS and PFS were expressed as hazard ratio (HR) and 95% CI for analysis. The subgroups of PFS and OS were analyzed according to the tumor treatment plan. When the number of included literature (n) ≥10, the comparison-corrected funnel plot was used to test for publication bias. Sensitivity analysis was performed by sequential omission of each study to examine the robustness of the pooled results.

RESULTS

Study selection

The study initially identified 341 articles, which included 27 studies from PubMed, 125 from Embase, 145 from the Cochrane Library, 23 from the Scopus database, and 21 from the CNKI database, respectively. After screening the titles and abstracts, 325 articles were further excluded, resulting in a full review of 209 articles. After the strict inclusion and exclusion screening, 8 studies were selected for the systematic review. Figure 1 illustrates the flow diagram of the search strategy and study selection.

Characteristics of included studies

Eight studies were conducted in 2018–2021, with a total of 925 participants. There were 3 studies from China, 1 study from Mexico, 1 study from Korea, 1 study from Canada, 1 study from three countries (US, Canada or Israel) and 1 study from US. Among the included studies, 3 studies focused on subjects receiving metformin with chemoradiotherapy, 2 studies focused on EGFR-TKIs, and 3 studies focused on chemotherapy. Among them, 7 studies reported OS,[18-24] 6 studies reported PFS,[18-20,22-24] 3 studies reported ORR,[21-23] 3 studies reported DCR,[18,23,25] and 6 studies reported 1-year PFS rate.[19,23,24] A summary of study information is provided in Table 1.

Quality assessment

Five studies reported random sequence generation.[18,20,21,24] 3 studies provided information on allocation concealment.[20,21,24] 2 studies used blind methods for subjects and researchers,[20,23] and 2 studies used blind methods for outcome evaluation.[20,23] 7 studies had a low bias of complete data,[18,19,21-25] and 6 trials had a low risk of other biases.[18,20,22-25] All studies had no selective report bias. Risk assessment results revealed that one study had a low risk, one study had an unclear risk, and six studies had a high risk of bias. The quality assessment of 8 RCTs is presented in Figure 2.

Meta-analysis

Progression-free survival

Six studies[18-20,22-24] reported the HR value of PFS in nondiabetic patients with lung cancer. The heterogeneity test showed that $I^2 = 71\%$, $P = 0.004$. Therefore, the random effect model was used, showing that the difference was

Table 1: Baseline characteristics of included studies for systematic review and meta-analysis

Author, year	Study design	Clinical Trials	Study region	Gender (M/F)	Age (years)	Treatment strategy	Outcome
Arrieta 2019	RCT	NCT03071705	Mexico	47/86	59.4	MM+EGFR-TKI	①②⑤
Tsakiridis 2021	RCT	NCT02115464	Canada	24/30	65.6	MM+Chemoradiotherapy	①②④
Skinner 2021	RCT	NCT02186847	US, Canada, and Israel	97/70	64	MM+Chemoradiotherapy	①②
Guo 2020	RCT	NR	China	82/38	NR	MM+Chemoradiotherapy	①③
Li 2020	RCT	ChiCTR-ONN-17014156	China	41/19	57	MM+Chemotherapy	⑤
Lee 2020	RCT	KCT0005210	Korea	139/25	64	MM+Chemotherapy	①②③
Li 2019	RCT	NCT01864681	China	83/119	59.6	MM+EGFR-TKI	①②③④⑤
Marrone 2018	RCT	NCT01578551	US	9/16	61	MM+Chemotherapy+AAs	①②④

①=OS; ②=PFS; ③=ORR; ④=1-year progression-free survival rate; ⑤=DCR. RCT = Randomized controlled trial; EGFR–TKI = Epidermal growth factor receptor–tyrosine kinase inhibitors; MM = Metformin; AAs = Antiangiogenic drugs; NR = Not reported; PFS = Progression-free survival; OS = Overall survival; ORR = Objective response rate; DCR = Disease control rate

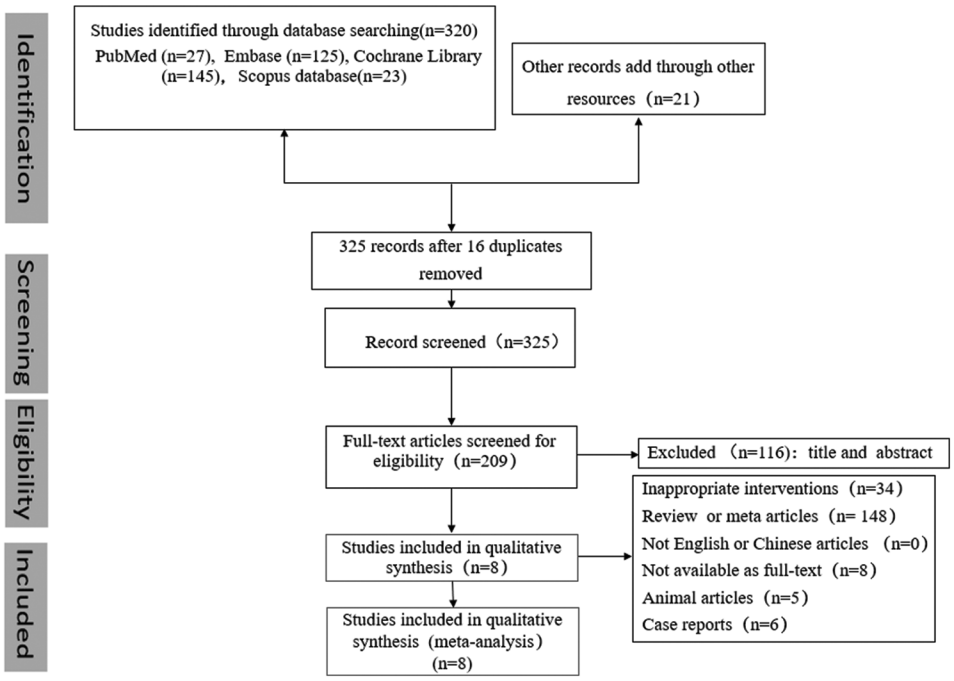

Figure 1: Flow chart of literature screening

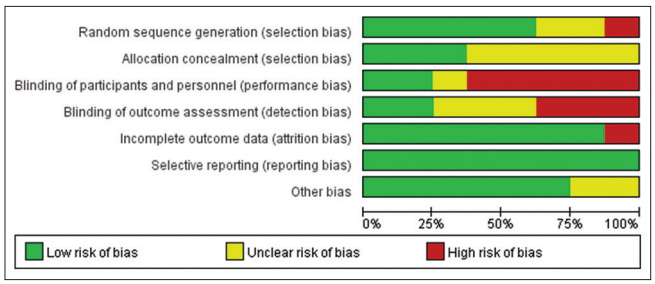

Figure 2: Bias risk assessment of the included randomized controlled trials

not statistically significant (HR = 0.95, 95% CI: 0.66–1.36, P = 0.77, n = 6). Metformin adjunctive therapy did not significantly affect the PFS of nondiabetic patients with advanced NSCLC, as shown in Figure 3.

Overall survival

A total of 7 studies[18-21,22-24] reported the HR value of OS in nondiabetic patients with lung cancer. The heterogeneity test showed that I^2 = 70%, P = 0.003. Thus, a random-effects was used for meta-analysis and the result demonstrated that metformin adjunctive therapy did not significantly improve OS in nondiabetic patients with advanced NSCLC (HR = 0.89, 95% CI: 0.61–1.30, P = 0.55, n = 7), as illustrated in Figure 4.

Objective response rate

Three studies[21-23] reported ORR in nondiabetic patients with lung cancer, comprising 231 and 246 cases in the metformin adjunctive therapy group and control group, respectively. The heterogeneity test showed that I^2 = 53%, P = 0.12. Thus, a random effect model was employed, showing that the difference was not statistically significant (OR = 1.37, 95% CI: 0.76–2.46, P = 0.30, n = 3). Metformin adjunctive therapy could not enhance the ORR of nondiabetic patients with advanced NSCLC, as depicted in Figure 5.

Disease control rate

Three studies[18,23,25] reported DCR in nondiabetic patients with lung cancer, including 196 and 205 cases in the metformin adjunctive therapy group and control group, respectively. The heterogeneity test showed that I^2 = 0%, P = 0.60. Therefore, a fixed effect model was used for meta-analysis, which revealed that metformin adjunctive therapy improved DCR in nondiabetic patients with advanced NSCLC compared to the control group, with a significant difference (OR = 3.07, 95% CI: 1.28–7.36, P = 0.01, n = 3), as illustrated in Figure 6.

One-year progression free survival rate

Three studies[19,20,23] reported a 1-year PFS rate in nondiabetic patients with lung cancer, including a total of 202 and 208 cases in the metformin adjunctive therapy group and control group, respectively. The heterogeneity test showed that I^2 = 72%, P = 0.03, indicating that a heterogeneity between two the groups. The random effect model was used for meta-analysis and showed that there was no significant difference in the 1-year PFS rate (OR = 0.87, 95%CI: 0.39–1.94, P = 0.73, n = 3), as presented in Figure 7.

Publication bias and sensitivity analysis

The Egger's method was not utilized to evaluate publication bias, owing to the limited number of included studies in the

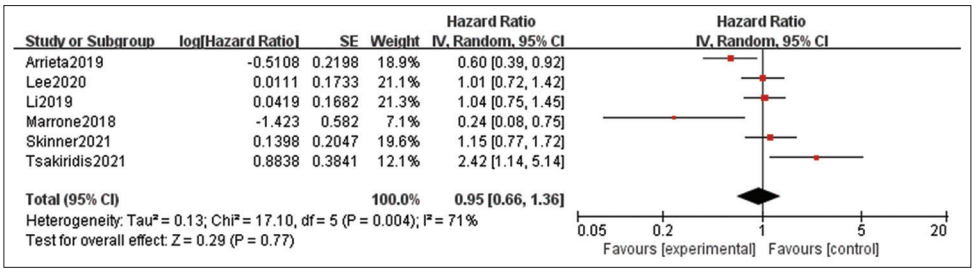

Figure 3: Forest plot for the meta-analysis on PFS of metformin adjunctive therapy

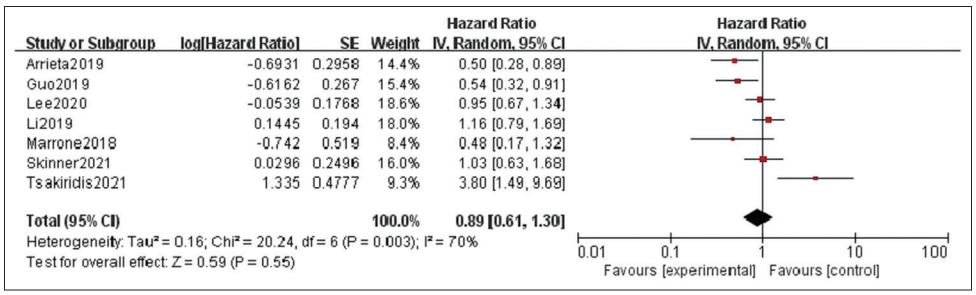

Figure 4: Forest plot for the meta-analysis on OS of metformin adjunctive therapy

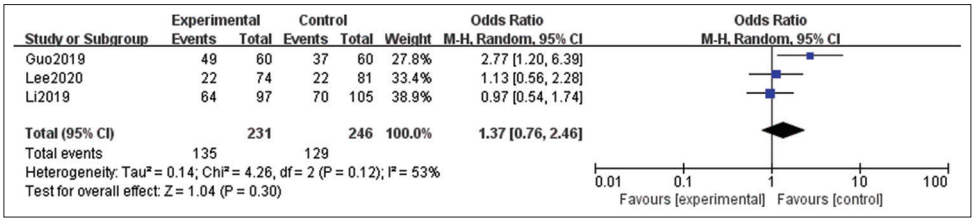

Figure 5: Forest plot for the meta-analysis on ORR of metformin adjunctive therapy

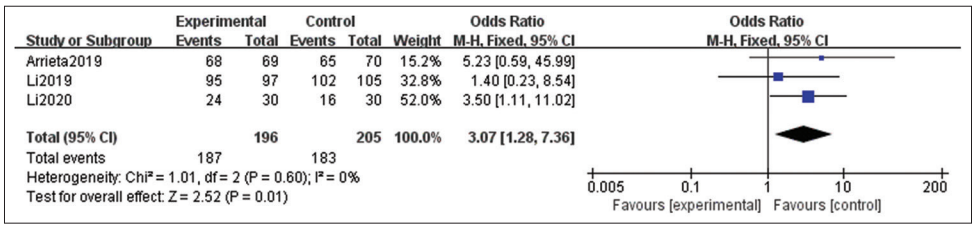

Figure 6: Forest plot for the meta-analysis on DCR of metformin adjunctive therapy

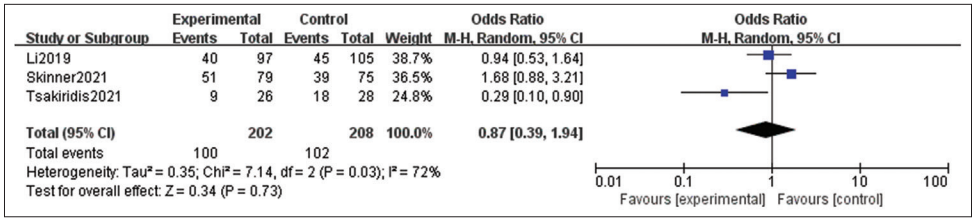

Figure 7: Forest plot for the meta-analysis on the 1-year PFS rate of metformin adjunctive therapy

analyzed outcome indicators, which was less than ten. The fixed/random effect model was implemented to reassess the combined effect amount. The findings indicated that the results of this study were relatively stable, as demonstrated in Table 2.

DISCUSSION

This systematic review and meta-analysis evaluated the combined efficacy of metformin adjunctive therapy in nondiabetic patients with lung cancer. The pooled

Table 2: The result of sensitivity analysis (OS)

Indicators	*n*	Heterogeneity		OR (HR) (95%CI)	*P*
		P	I^2		
PFS					
RE	6	0.004	71%	0.95[0.66, 1.36]	0.77
FE		0.004	71%	0.97[0.81, 1.16]	0.75
OS					
RE	7	0.003	70%	0.89[0.61, 1.30]	0.55
FE		0.003	70%	0.90[0.75, 1.09]	0.30
ORR					
RE	3	0.12	53%	1.37[0.76, 2.46]	0.30
FE		0.12	53%	1.30[0.88, 1.92]	0.19
DCR					
RE	3	0.60	0%	3.00[1.24, 7.28]	0.01
FE		0.60	0%	3.07[1.28, 7.36]	0.01
One-PFS rate					
RE	3	0.03	72%	0.87[0.39, 1.94]	0.73
FE		0.03	72%	1.00[0.68, 1.48]	1.00

PFS=Progression-free survival; OS=Overall survival; ORR=Objective response rate; DCR=Disease control rate; CI=Confidence interval; OR=Odd ratio; HR=Hazard ratio; RE= Random-effect model; FE= Fixed-effect model

analysis results demonstrated that metformin combined with anti-cancer drugs might improve DCR compared with standard antineoplastic, but there was no significant improvement in PFS, OS, ORR or 1-year PFS rate.

Lung cancer is a prevalent public health concern, primarily contributing to be a primary contributor to cancer-related mortalities worldwide. Despite advancements in medical research and healthcare practices, lung cancer remains a significant burden on global health systems and a pressing issue in cancer epidemiology. The clinical manifestations of lung cancer are multifaceted but frequently lacks specificity, leading to diagnostic delays. Consequently, a large number of patients are diagnosed at an advanced stage, which markedly reduces their chances of survival. Specifically, the 5-year survival rate of NSCLC patients is remarkably low. The guidelines advocate for an approach to treating lung cancer that involves combining multidisciplinary therapy with tailored treatment plans for each patient.[26] Numerous investigations have highlighted the lung as a primary site of affliction in individuals with diabetes mellitus.[27,28] In the past decade, renewed interest has been generated regarding the therapeutic re-purposing of metformin as an adjunct to conventional anticancer therapies, particularly in the setting of drug-resistant malignancies.

Metformin, a widely used biguanide anti-diabetic agent, has been the subject of epidemiological research, which has revealed a reduced incidence of cancer among individuals with diabetes who receive metformin therapy. Furthermore, preclinical data suggest that metformin may harbor intrinsic antineoplastic properties.[29-32] Recently, several meta-analyses have demonstrated that the addition of metformin to anti-tumor therapies confers a survival advantage in NSCLC patients with diabetes.[10,33] Nonetheless, the efficacy of metformin in nondiabetic NSCLC patients remains unclear. In the present meta-analysis, we exclusively evaluated NSCLC patients without diabetes who received metformin in conjunction with antineoplastic agents for advanced-stage disease. Our results indicate that the adjunctive administration of metformin solely confers a favorable impact on DCR without significantly enhancing overall survival outcomes.

To the best of our knowledge, the prevailing understanding suggests that metformin exerts its therapeutic effects in individuals with diabetes mellitus by modulating cellular energy metabolism and curtailing hepatic gluconeogenesis through adenylate-activated protein kinase (AMPK) signaling.[10,34] Moreover, *in vitro* and *in vivo* experiments have also confirmed that metformin effectively inhibits the proliferation of lung cancer cells and triggers apoptotic cell death, although the underlying mechanisms behind its anticancer properties are multifaceted. The anticancer activity of metformin is believed to be mediated via various pathways, including the AMPK/LKB1/mTOR signaling axis, nuclear factor erythroid 2-related factor 2 (NRF2) pathway,[35] the miR-381-YAP-Snail signaling cascade,[36] LncRNA-H19,[37,38] the AMPK-CEBPB-PDL1 axis,[39] and others. AMPK serves as an essential modulator of cellular energy homeostasis, and its activity is known to impede cell growth by inhibiting the mammalian target of rapamycin signaling cascade. Specifically, the suppression of mTOR via AMPK activity results in the blockade of the PI3K/PKB/AKT pathway and diminished activation of downstream effectors, such as eukaryotic promoter 4E binding protein 1 and ribosomal protein S6 kinase.[40] Furthermore, mTOR is a critical regulator of cellular proliferation and growth, and research has highlighted that dysregulated mTOR signaling is intimately linked to cell proliferation. Multiple studies have suggested that metformin can facilitate the activation of AMPK's upstream kinase, LKB1, resulting in heightened AMP/ATP ratios and consequent AMPK activation. AMPK activity can impede the mTOR signaling pathway, ultimately suppressing tumor cell proliferation.[40-43] With the shift in the therapeutic focus of NSCLC towards immune checkpoint inhibition, it is imperative to investigate the interaction between metformin and the immune system. In murine models, metformin was found to directly affect CD-81 T cells, which prevented apoptosis of CD81 TILs in the tumor microenvironment, independent of programmed cell death protein 1 (PD-1) and TIM-3 expression.[44] Thus, additional investigations on the potential synergistic effects of checkpoint blockade, with or without chemotherapy, are warranted.

A recent meta-analysis of 24,178 participants from 27 eligible studies showed that metformin is a useful adjuvant drug

for improving survival in patients with early colorectal and prostate cancer.[45] In addition, there is population-based evidence that metformin requires long-term use to exert its anticancer effects.[46] Several important considerations must be considered when evaluating the role of metformin in the treatment of NSCLC. Firstly, the high recurrence and metastasis rates of NSCLC are closely related to the degree of tumor differentiation, thereby impacting treatment outcomes. Secondly, only patients who commenced metformin early or before their NSCLC diagnosis showed improved outcomes.[47] Thirdly, some studies included patients with advanced disease who had not previously received metformin.[23] Given the potential time-dependent effects of metformin exposure, patients may exhibit different responses depending on the duration of metformin exposure. Furthermore, the dose of metformin may not be high enough to be effective, as the antiproliferative effects of metformin are dose-dependent *in vitro*. Clinical data from patients with pancreatic cancer suggest that survival benefits are only achieved with high plasma metformin concentrations (>1 mg/L).[30,48] However, the option of further increasing the dose of metformin is not feasible due to the higher incidence of metformin-induced diarrhea. Moreover, besides metformin exposure, some patients may possess a defect in the LKB1 gene, which encodes a tumor suppressor required for the activation of AMP-activated protein kinase (AMPK) (via AMPK phosphorylation at the Thr172 site), a vital step in the anticancer mechanism of metformin.[30,49] Such mutations in LKB1 can lead to the loss of AMPK function, thereby compromising the effectiveness of metformin in these patients. In the Chinese population, LKB1 was previously shown to be mutated in 10.5% of patients with the EGFR mutation and lung adenocarcinoma.[50] The potential impact of LKB1 inactivation on the metformin-induced enhancement of AMPK-dependent inhibition of proto-oncogenic pathways cannot be disregarded. Furthermore, it is plausible that the anti-tumor effects of metformin could be partially obscured in nondiabetic patients with high levels of AMPK phosphorylation, which are influenced by glucose levels.[51] Finally, the limited sample size and absence of random stratification based on smoking status, EGFR mutant subtype, LKB1 status, or other genetic factors may have contributed to the study's findings. As a result, we need to be careful about interpreting the results. Overall, the findings of this study may offer novel insights for the adjuvant treatment of patients with advanced NSCLC who do not have diabetes and are treated with metformin in combination with antineoplastic agents.

Limitations

This systematic review and meta-analysis also has several limitations. Firstly, subgroup analysis on DCR based on tumor treatment strategy, the dose of MM treatment, and the time was not feasible, owing to the limited number of included studies. However, the sensitivity analysis demonstrated that the results were stable. Secondly, some patients may have received other treatments prior to the study, and the insufficient sample size, patient characteristics, lack of information on metformin exposure time and dose, and insufficient control of confounding factors may have affected the results. Thirdly, some of the included studies lacked double-blind and placebo control. Finally, the language was restricted to Chinese or English, which may have resulted in incomplete data retrieval, potentially affecting the study's outcomes.

CONCLUSION

In nondiabetic patients with advanced NSCLC, metformin combined with antineoplastic drugs has been shown to improve DCR, but no improvement in long-term prognosis has been observed. In addition, the optimal dosage and treatment time of metformin remain unclear and require further investigation. A multi-center, large, high-quality, larger double-blind with more rigorous study designs are still needed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49.
3. Ricciuti B, Leonardi GC, Metro G, Grignani F, Paglialunga L, Bellezza G, *et al.* Targeting the KRAS variant for treatment of non-small cell lung cancer: Potential therapeutic applications. Expert Rev Respir Med 2016;10:53-68.
4. Restifo NP, Smyth MJ, Snyder A. Acquired resistance to immunotherapy and future challenges. Nat Rev Cancer 2016;16:121-6.
5. Eberhardt WE, De Ruysscher D, Weder W, Le Péchoux C, De Leyn P, Hoffmann H, *et al.* 2nd ESMO Consensus Conference in Lung Cancer: Locally advanced stage III non-small-cell lung cancer. Ann Oncol 2015;26:1573-88.
6. White-Al Habeeb NM, Garcia J, Fleshner N, Bapat B. Metformin elicits antitumor effects and downregulates the histone methyltransferase multiple myeloma SET domain (MMSET) in prostate cancer cells. Prostate 2016;76:1507-18.
7. Han K, Pintilie M, Lipscombe LL, Lega IC, Milosevic MF, Fyles AW. Association between metformin use and mortality after cervical cancer in older women with diabetes. Cancer Epidemiol

Biomarkers Prev 2016;25:507-12.
8. Chen PH, Zhu GZ, Li L, Chen Y, Dai HQ, Su WJ, *et al.* Distinct effects of anti-diabetic medications on liver cancer risk and patient survival. J BUON 2020;25:2147-53.
9. Lega IC, Shah PS, Margel D, Beyene J, Rochon PA, Lipscombe LL. The effect of metformin on mortality following cancer among patients with diabetes. Cancer Epidemiol Biomarkers Prev 2014;23:1974-84.
10. Cao X, Wen ZS, Wang XD, Li Y, Liu KY, Wang X. The clinical effect of metformin on the survival of lung cancer patients with diabetes: A comprehensive systematic review and meta-analysis of retrospective studies. J Cancer 2017;8:2532-41.
11. Zhang J, Wu J, He Q, Liang W, He J. The prognostic value of metformin for advanced non-small cell lung cancer: A systematic review and meta-analysis. Transl Lung Cancer Res 2018;7:389-96.
12. Xiao K, Liu F, Liu J, Xu J, Wu Q, Li X. The effect of metformin on lung cancer risk and survival in patients with type 2 diabetes mellitus: A meta-analysis. J Clin Pharm Ther 2020;45:783-92.
13. Currie CJ, Poole CD, Jenkins-Jones S, Gale EA, Johnson JA, Morgan CL. Mortality after incident cancer in people with and without type 2 diabetes: Impact of metformin on survival. Diabetes Care 2012;35:299-304.
14. Arrieta O, Barron FB, Padilla MS, Ramirez-Tirado LA, Flores-Estrada D, Cruz-Rico G, *et al*. Combination of metformin plus TKI vs. TKI alone in EGFR(þ) LUNG adenocarcinoma: A randomized phase II study. J Clin Oncol 2018;36:15s.
15. Arrieta O, Varela-Santoyo E, Soto-Perez-de-Celis E, Sánchez-Reyes R, De la Torre-Vallejo M, Muñiz-Hernández S, *et al.* Metformin use and its effect on survival in diabetic patients with advanced non-small cell lung cancer. BMC Cancer 2016;16:633.
16. Ahmed I, Ferro A, Cohler A, Langenfeld J, Surakanti SG, Aisner J, *et al.* Impact of metformin use on survival in locally-advanced, inoperable non-small cell lung cancer treated with definitive chemoradiation. J Thorac Dis 2015;7:346-55.
17. Xiaofeng L, Xi C, Lin W, Shuang C. Effect of metformin for advanced non-small cell lung cancer adjuvant therapy: A meta-analysis. Mod Oncol 2022;30:1967-72.
18. Arrieta O, Barrón F, Padilla MS, Avilés-Salas A, Ramírez-Tirado LA, Arguelles Jiménez MJ, *et al.* Effect of metformin plus tyrosine kinase inhibitors compared with tyrosine kinase inhibitors alone in patients with epidermal growth factor receptor-mutated lung adenocarcinoma: A phase 2 randomized clinical trial. JAMA Oncol 2019;5:e192553.
19. Tsakiridis T, Pond GR, Wright J, Ellis PM, Ahmed N, Abdulkarim B, *et al.* Metformin in combination with chemoradiotherapy in locally advanced non-small cell lung cancer: The OCOG-ALMERA randomized clinical trial. JAMA Oncol 2021;7:1333-41.
20. Skinner H, Hu C, Tsakiridis T, Santana-Davila R, Lu B, Erasmus JJ, *et al.* Addition of metformin to concurrent chemoradiation in patients with locally advanced non-small cell lung cancer: The NRG-LU001 phase 2 randomized clinical trial. JAMA Oncol 2021;7:1324-32.
21. Guo JL, Zhu B, Zheng Y, Wang YX, Wen YY, Wang HH. The curative effect study of metformin combined with concurrent radiotherapy and chemotherapy in patients with non-small cell lung cancer. Chin J Ration Drug Use 2020;17:63-6.
22. Li RY, Lin ZY, Li J, Fei J, Xu D, Gong P. Changes of IGF-1 and mTOR expressions in peripheral blood of patients with non-small cell lung cancer before and after chemotherapy combined with metformin and analysis on their therapeutic effects. J Jilin Univ (Med Ed) 2020;46:108-15.
23. Lee Y, Joo J, Lee YJ, Lee EK, Park S, Kim TS, *et al.* Randomized phase II study of platinum-based chemotherapy plus controlled diet with or without metformin in patients with advanced non-small cell lung cancer. Lung Cancer 2021;151:8-15.
24. Li L, Jiang L, Wang Y, Zhao Y, Zhang XJ, Wu G, *et al.* Combination of metformin and gefitinib as first-line therapy for nondiabetic advanced NSCLC patients with EGFR mutations: A randomized, double-blind phase II trial. Clin Cancer Res 2019;25:6967-75.
25. Marrone KA, Zhou X, Forde PM, Purtell M, Brahmer JR, Hann CL, *et al.* A randomized phase II study of metformin plus paclitaxel/carboplatin/bevacizumab in patients with chemotherapy-naïve advanced or metastatic nonsquamous non-small cell lung cancer. Oncologist 2018;23:859-65.
26. National Health Commission of the People's Republic of China. Guidelines for the diagnosis and treatment of primary lung cancer (2022 edition). Chin J Ration Drug Use 2022;19:1-28.
27. Zhang Y, He J. The development of targeted therapy in small cell lung cancer. J Thorac Dis 2013;5:538-48.
28. Lin CC, Chang CT, Li TC, Kao A. Objective evidence of impairment of alveolar integrity in patients with non-insulin-dependent diabetes mellitus using radionuclide inhalation lung scan. Lung 2002;180:181-6.
29. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. BMJ 2005;330:1304-5.
30. Pollak MN. Investigating metformin for cancer prevention and treatment: The end of the beginning. Cancer Discov 2012;2:778-90.
31. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care 2006;29:254-8.
32. Shaw RJ, Lamia KA, Vasquez D, Koo SH, Bardeesy N, Depinho RA, *et al.* The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. Science 2005;310:1642-6.
33. Yao L, Liu M, Huang Y, Wu K, Huang X, Zhao Y, *et al.* Metformin use and lung cancer risk in diabetic patients: A systematic review and meta-analysis. Dis Markers 2019;2019:6230162.
34. Moro M, Caiola E, Ganzinelli M, Zulato E, Rulli E, Marabese M, *et al.* Metformin enhances cisplatin-induced apoptosis and prevents resistance to cisplatin in co-mutated KRAS/LKB1 NSCLC. J Thorac Oncol 2018;13:1692-704.
35. Sun X, Dong M, Gao Y, Wang Y, Du L, Liu Y, *et al.* Metformin increases the radiosensitivity of non-small cell lung cancer cells by destabilizing NRF2. Biochem Pharmacol 2022;199:114981.
36. Jin D, Guo J, Wu Y, Chen W, Du J, Yang L, *et al.* Correction: Metformin-repressed miR-381-YAP-snail axis activity disrupts NSCLC growth and metastasis. J Exp Clin Cancer Res 2022;41:339.
37. Hashemi M, Moazeni-Roodi A, Sarabandi S, Karami S, Ghavami S. Association between genetic polymorphisms of long noncoding RNA H19 and cancer risk: A meta-analysis. J Genet 2019;98:81.
38. Liu K, Li B, Wu XT, Ming HD. Mechanism study of metformin inhibiting migration and invasion of non-small cell lung cancer A549 cell through LncRNA-H19. J Clin Surg 2022;30:719-21.
39. Lu T, Li M, Zhao M, Huang Y, Bi G, Liang J, *et al.* Metformin inhibits human non-small cell lung cancer by regulating AMPK-CEBPB-PDL1 signaling pathway. Cancer Immunol Immunother 2022;71:1733-46.
40. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell 2017;168:960-76.
41. Chen YQ, Chen G. Combined therapeutic effect and molecular mechanisms of metformin and cisplatin in human lung cancer xenografts in nude mice. J Cancer Res Ther 2015;11:324-30.
42. Zhang Y, Feng X, Li T, Yi E, Li Y. Metformin synergistic pemetrexed suppresses non-small-cell lung cancer cell proliferation and invasion *in vitro*. Cancer Med 2017;6:1965-75.
43. Guo Q, Liu Z, Jiang L, Liu M, Ma J, Yang C, *et al.* Metformin inhibits growth of human non-small cell lung cancer cells via liver kinase B-1-independent activation of adenosine monophosphate-activated

protein kinase. Mol Med Rep 2016;13:2590-6.
44. Eikawa S, Nishida M, Mizukami S, Yamazaki C, Nakayama E, Udono H. Immune-mediated antitumor effect by type 2 diabetes drug, metformin. Proc Natl Acad Sci U S A 2015;112:1809-14.
45. Coyle C, Cafferty FH, Vale C, Langley RE. Metformin as an adjuvant treatment for cancer: A systematic review and meta-analysis. Ann Oncol 2016;27:2184-95.
46. Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. Diabetes Care 2010;33:1304-8.
47. Lin J, Gill A, Zahm SH, Carter CA, Shriver CD, Nations JA, *et al.* Metformin use and survival after non-small cell lung cancer: A cohort study in the US Military health system. Int J Cancer 2017;141:254-63.
48. Kordes S, Pollak MN, Zwinderman AH, Mathôt RA, Weterman MJ, Beeker A, *et al.* Metformin in patients with advanced pancreatic cancer: A double-blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol 2015;16:839-47.
49. Sanchez-Cespedes M, Parrella P, Esteller M, Nomoto S, Trink B, Engles JM, *et al.* Inactivation of LKB1/STK11 is a common event in adenocarcinomas of the lung. Cancer Res 2002;62:3659-62.
50. Gao B, Sun Y, Zhang J, Ren Y, Fang R, Han X, *et al.* Spectrum of LKB1, EGFR, and KRAS mutations in Chinese lung adenocarcinomas. J Thorac Oncol 2010;5:1130-5.
51. Wu D, Hu D, Chen H, Shi G, Fetahu IS, Wu F, *et al.* Glucose-regulated phosphorylation of TET2 by AMPK reveals a pathway linking diabetes to cancer. Nature 2018;559:637-41.