Hindawi
Journal of Clinical Pharmacy and Therapeutics
Volume 2023, Article ID 5575513, 8 pages
https://doi.org/10.1155/2023/5575513

Review Article

The Survival Effect of Metformin on Non-Small Cell Lung Cancer Treated with Chemotherapy: A Systematic Review

Qin Li, Qiao Fan, and Ji Wu

Department of Cardiothoracic Surgery, The Affiliated Hospital of Panzhihua University, Panzhihua 617000, China

Correspondence should be addressed to Qin Li; 2110749339@qq.com

Received 20 January 2023; Revised 15 June 2023; Accepted 16 June 2023; Published 3 July 2023

Academic Editor: Muhammad Iqhrammullah

Objective. Metformin is a common antidiabetic drug that has been reported to serve as an anticancer agent in combination with other therapies. But the effect of the addition of metformin on the survival of non-small cell lung cancer (NSCLC) patients undergoing chemotherapy is still controversial. We conducted this systematic review to evaluate the survival effect of metformin added to chemotherapy in NSCLC patients. *Methods*. Electronic literature search was performed in the PubMed, Embase, and Web of Science databases from their inception up to April 2023. The study region, study design, histological subtype of the NSCLC, tumor stage, treatment strategy, sample size, follow-up duration, diabetes status, and HR of OS or PFS of the included studies were extracted. The quality was assessed through Cochrane collaboration's tool for RCT and the Newcastle–Ottawa scale (NOS) for observational studies, respectively. *Results and conclusions*. Eleven studies with a total of 4606 patients were finally included. Five RCTs showed a high risk of bias due to the open-label nature while six retrospective studies were of high quality. Two studies of NSCLC patients with diabetes reported significant benefits in overall survival from metformin addition, while one study of patients without diabetes reported a negative effect on the survival of metformin addition. The survival impact of metformin added to chemotherapy on unresectable NSCLC patients remains inconclusive. The survival benefit might be more prominent in patients with diabetes, awaiting further evidence.

1. Introduction

Lung cancer remains the type of cancer causing most deaths in the world [1]. There were still a significant number of patients with the advanced stage at diagnosis, most of which were unresectable. Stage IV NSCLC patients could occupy from 2% to 9% of the total patients at diagnosis, while stage III patients could occupy nearly 20% [2, 3]. Although surgery was recommended as the standard of care for most early-stage NSCLC from stage I to IIIB, the role of adjuvant therapy and systemic therapy remained critical in lung cancer management. Postoperative chemotherapy was recommended for early-stage patients undergoing surgery with negative margins but with high-risk characteristics, including poorly differentiated tumors, vascular invasion, visceral pleural involvement, and unknown lymph node status [4]. Patients undergoing surgery and with positive margin or lymph node invasion (N1 or N2) were recommended to receive postoperative chemotherapy or concurrent chemoradiation therapy [4]. Chemotherapy or concurrent chemoradiotherapy was also recommended for NSCLC patients with unresectable advanced disease who are not eligible for targeted therapy or immunotherapy. The survival benefits of chemotherapy required further improvements. The median overall survival (OS) of chemotherapy in advanced NSCLC patients was reported to reach 10 months–26 months [5–7]. The OS of concurrent chemoradiotherapy in unresectable NSCLC patients was from 23% to 32% as reported [8, 9]. Studies pursuing improvement in survival benefits of chemotherapy has always been on the way.

Metformin, the most widely used antidiabetes agent in treating type 2 diabetes, has been extensively studied for its antitumor ability and addictive effects in combination of chemotherapy. Preclinical models have shown that metformin could activate adenosine monophosphate-activated

kinase and inhibit mammalian target of rapamycin, subsequently suppressing protein synthesis and cancer cell growth and proliferation [10, 11]. There have been clinical studies on the impact of metformin on the survival of NSCLC patients undergoing chemotherapy, either in retrospective or prospective design. But due to the differences in study samples and intervention details, consistent results guiding on clinical applications are still lacking.

Herein, the objective was to conduct a systematic review on the impact of metformin on the survival of NSCLC patients undergoing chemotherapy.

2. Methods

2.1. Research Strategy. Electronic literature search was conducted in PubMed, Embase, and Web of Science databases following the preferred reporting items for systematic reviews and meta-analyses guidelines (up to April 2023) [12]. The search terms are shown in Table 1.

2.2. Study Selection. The inclusion criteria of the studies were as follows: (a) randomized controlled trials (RCTs) or observational studies; (b) patients with unresectable NSCLC; (c) chemotherapy (or chemoradiotherapy) with or without metformin was applied to treatment; and (d) the effect of metformin on the survival of unresectable NSCLC patients receiving chemotherapy was reported.

The exclusion criteria were as follows: (a) studies with only abstract published; (b) among studies based on the same population, the study with the most recent or detailed data was selected; and (c) effect estimation of overall survival (OS) or progression-free survival (PFS) was not directly reported or could not be calculated from other supportive data. Two independent reviewers, Q Li and Q Fan, completed the selection process. The disagreements were dealt through discussion.

2.3. Data Extraction and Quality Assessment. The data extraction and quality assessment of the included studies were independently conducted by two reviewers. Data of interest were as follows: first author, publication year, study region, study year, study design, histological subtype of the NSCLC, tumor stage, treatment strategy, sample size, follow-up duration, diabetes status, OS and PFS, and HR of OS or PFS and their corresponding 95% CI. The OS means the length of time that the patients live after the start of treatment. The PFS means the length of time that the patients live until any progression of disease after the treatment. We also reviewed characteristics of study population including age, comorbidities, histology, metastasis, and stage at diagnosis. The quality assessment tools were Cochrane collaboration's tool for RCT and the Newcastle–Ottawa scale (NOS) for observational studies, respectively. The Newcastle–Ottawa scale is a star system that judges the quality of retrospective studies on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest. Two independent reviewers, Q Fan and J Wu, evaluated the quality of the included studies. Any discrepancies would be discussed with a third reviewer Q Li and resolved.

3. Results

3.1. Search Results. The flow chart of the search process is shown in Figure 1. A total of 3399 records were identified through initial database search, and 1930 records were removed due to duplication. The titles and abstracts of the remaining 1469 records were reviewed for eligibility for our study, and 28 potential studies were filtered out. Then, the full text of the 28 studies was carefully read, and 20 studies were excluded according to exclusion criteria. Finally, 11 studies were included in the systematic review [12–22].

3.2. Characteristics of the Included Studies. The characteristics of the 11 included studies are demonstrated in Table 2. All of the studies were published in or after 2010, and the study years were mainly in the past two decades. A total of 4606 patients were included into these studies, of which 1977 (42.92%) patients were treated with chemotherapy (or chemoradiotherapy) plus metformin and the others were treated with chemotherapy (or chemoradiotherapy) alone. Regarding the study design of the included studies, five were RCTs and six were retrospective case-control studies. Patients of four studies were treated with chemoradiotherapy, while the others were treated with chemotherapy.

Characteristics of study populations are given in Table 3. For the ages of patients in the included studies, most had mean or median of age over 55 years. Five of the studies only included patients with diabetes mellitus, four studies only included patients without diabetes mellitus, and the other two studies had diabetic status mixed. Two studies declared to exclude patients with coexisting malignancies other than lung cancer [16, 22]. The comorbidities that were reported or excluded, the metastasis, and the stage at diagnosis are also shown in Table 3.

3.3. Quality Assessment of the Included Studies. The result of the quality assessment is shown in Supplementary Tables 1 and 2. The five RCTs showed a high risk of bias mainly due to the open-label property according to the Cochrane handbook (Supplementary Table 1). The six retrospective studies were of high quality with NOS scores of 7-8 (Supplementary Table 2).

3.4. Effect of Metformin Addition on the OS. Ten of the eleven included studies reported the OS of patients. Of these, only Lin et al. and Chuang et al. reported significant difference between the metformin group and the nonmetformin group [14, 22], in which the metformin group showed better OS. The HR for OS of each included study is shown in Figure 2. Lin et al. showed a significantly protective effect of metformin (HR = 0.77, 95% CI 0.65 to 0.92) [14]. Chuang et al. also reported the protective effect of metformin addition (HR = 0.86, 95% CI 0.78 to 0.94) [22]. But Tsakiridis et al.

Table 1: Search strategies of each database.

Databases	Search strategies
PubMed	("Lung Neoplasms"(Mesh)) and ("Metformin"(Mesh) OR Glucophage OR Glumetza OR Fortamet OR Riomet OR Metformine OR Metformina OR Dimethylguanylguanidine) and (("Chemotherapy, Adjuvant"(Mesh)) OR ("Drug Therapy"(Mesh))
Embase	1: Lung cancer OR Lung Neoplasms 2: Metformin OR Glucophage OR Glumetza OR Fortamet OR Riomet OR Metformine OR Metformina OR Dimethylguanylguanidine 3: Drug Therapy OR Chemotherapy OR Chemotherapy 1 and 2 and 3
Web of Science	TS = ((Lung Neoplasms) AND (Metformin OR Glucophage OR Glumetza OR Fortamet OR Riomet OR Metformine OR Metformina OR Dimethylguanylguanidine) and (Chemotherapy OR Drug Therapy))

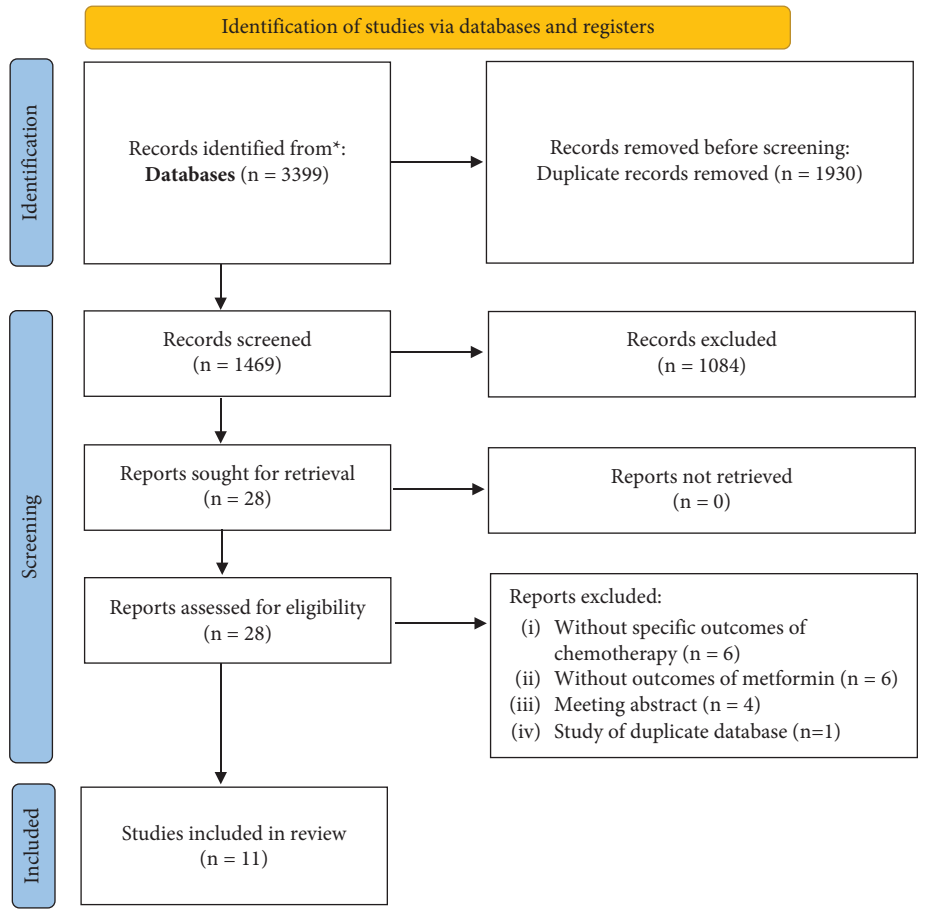

Figure 1: The flowchart of the study election.

showed a negative effect of the metformin group (HR 3.80, 95% CI 1.49 to 9.73) [12].

3.5. Effect of Metformin Addition on the PFS. Six studies reported the PFS of patients. Marrone et al. reported significantly better PFS of the metformin group (median PFS, 9.6 months vs. 6.7 months, and $P = 0.024$) [21]. Wink et al. also showed better PFS of metformin addition (median PFS, 41 months vs. 15 months, and $P = 0.010$). The HR for PFS of each study is shown in Figure 3. Wink et al. showed a significantly protective effect of metformin addition (HR = 0.63, 95% CI 0.41 to 0.96) [15], while Tsakiridis et al. showed a negative effect on PFS of metformin addition (HR = 2.42, 95% CI 1.14 to 5.10).

4. Discussion

4.1. Summary of Evidence. The impact of addition of metformin on the survival of advanced NSCLC patients treated with chemotherapy was inconclusive. While most of the studies included in our systematic review showed

Table 2: Characteristics of the included studies.

Authors (publication year)	Study regions	Study year	Study design	Treatment strategies	Sample sizes (overall)	Sample sizes (metformin)	Quality assessment[d]
Ahmed (2015)	United States	1999–2013	CCS[a]	Paclitaxel + carboplatin + radiotherapy	166	20	8
Lin (2015)	United States	2007–2009	CCS	Chemotherapy NOS[b]	349	227	7
Sayed (2015)	Egypt	2011–2013	RCT	Gemcitabine/Cisplatin regimen	30	15	High
Wink (2016)	Netherlands	2008–2013	CCS	Cisplatinum/carboplatin + etoposide + radiotherapy	682	59	8
Chuang (2018)	China	2000–2013	CCS	Cisplatin-base chemotherapy	2400	1193	8
Marrone (2018)	United States	2012–2015	RCT	Carboplatin, paclitaxel, and bevacizumab	24	18	High
Xin (2018)	China	2008–2011	CCS	Platinum-based chemotherapy NOS	75	27	8
Skinner (2021)	United States, Canada, and Israel	2014–2016	RCT	Carboplatin + paclitaxel + radiotherapy	167	86	High
Tsakiridis (2021)	Canada	2014–2019	RCT	(Cisplatin + etoposide)/(cisplatin + vinorelbine)/ (carboplatin + etoposide/paclitaxel) + radiotherapy	54	26	High
Lee (2021)	Korea	2014–2018	RCT	Gemcitabine + carboplatin	164	81	High
Wang (2021)	Taiwan China	2004–2013	CCS	Pemetrexed-based platinum doublets NOS	495	225	8

[a]CCS: case-control study; RCT: randomized controlled trials. [b]NOS: not otherwise specific. [c]NA: not available. [d]The quality assessment tools were Cochrane collaboration's tool for RCT and the Newcastle–Ottawa scale (NOS) for observational studies, respectively.

Table 3: Patient characteristics in each included study.

Authors (publication year)	Age of patients[a]	Age limitation	Comorbidities (reported)[b]	Excluded comorbidities	Diabetic status	Histology[c]	Metastasis at diagnosis	Stages
Ahmed (2015)	65 (24–86)	NA	COPD, hypertension, CAD, HLD, and CHF	NA	Mixed	AD, SCC, LCC, poorly differentiated carcinoma, and NSCLC NOS	Limited to one distant metastasis	I–IV
Lin (2015)	72.2 (4.0)	65–80	Charlson Comorbidity Index	Stage IV–V CKD, end-stage renal disease	Yes	AD, SCC, LCC, and NSCLC NOS	Yes without limitation	IV
Sayed (2015)	56 (44–70)	18–80	NA	Diabetes, others such as CHF and chronic lung disease with hyposia	No	AD, SCC, LCC	Yes without limitation	IV
Wink (2016)	63 (29–87)	NA	NA	NA	Yes	AD, SCC, NSCLC NOS	No	II, III
Xin (2018)	NA	NA	NA	NA	Yes	AD, SCC	Yes without limitation	NA
Marrone (2018)	58 (37–74)	≥18	NA	Diabetes, hypertension (>150/>100), history of hemoptysis, thrombotic, and hemorrhagic disorders	No	Nonsquamous NSCLC	Yes without limitation	IIIB-IV
Chuang (2018)	71.2 (9.4)	18–90	Charlson Comorbidity Index	CKD, end-stage renal disease	Yes	NSCLC	NA	I–IV
Skinner (2021)	64 (43–86)	NA	NA	NA	No	AD, adenosquamous, SCC, and NSCLC NOS	No	IIIA-IIIB
Tsakiridis (2021)	65.9 (8.1)	≥18	NA	Diabetes	No	AD, SCC, LCC, and NSCLC NOS	No	III
Lee (2021)	NA	≥18	NA	NA	Mixed	AD, SCC, and NSCLC NOS	Yes without limitation	IIIB-IV
Wang (2021)	67.4 (9.5)	NA	CVA, CAD, CHF, COPD, and CRD	NA	Yes	AD	NA	NA

[a]Age was presented as the mean (SD) or median [range]. [b]COPD, chronic obstructive pulmonary disease. CAD, coronary artery disease; HLN, hyperlipidemia; CHF, congestive heart failure; CVA, cerebral vascular accident; CKD, chronic kidney disease; [c]AD, adenocarcinoma; SCC, squamous cell carcinoma; LCC, large cell carcinoma; NSCLC NOS, non-small cell lung cancer not otherwise specific; NA, not available.

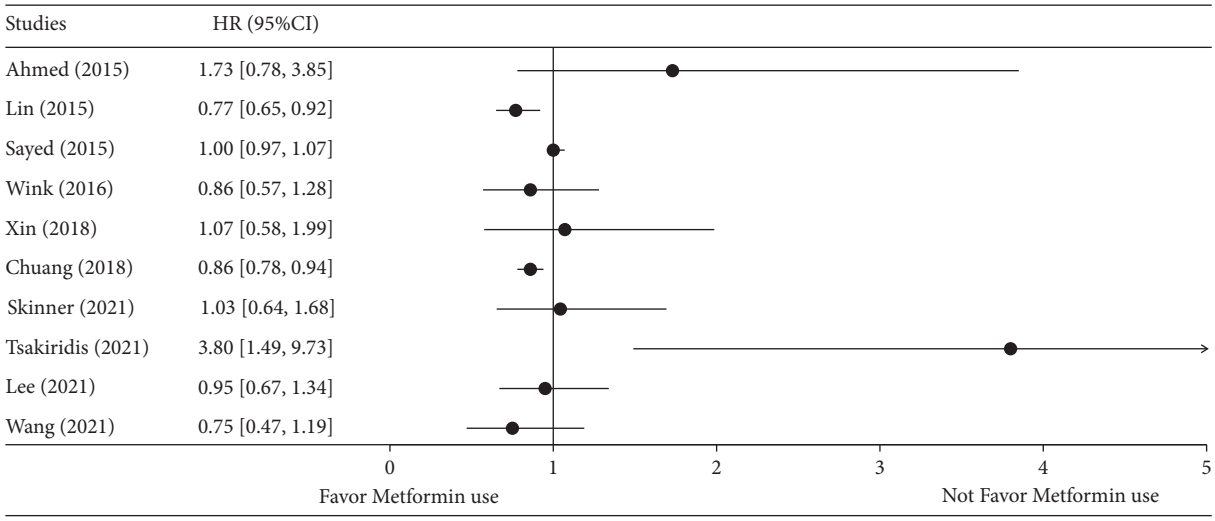

Figure 2: The results of HR for overall survival from the included studies.

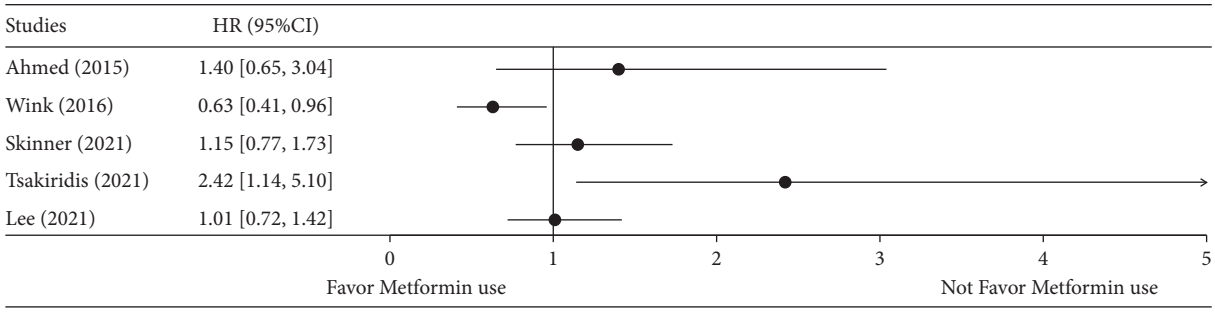

Figure 3: The results of HR for progression-free survival from the included studies.

nonsignificant difference regarding OS and PFS, a comparable number of studies supported or opposed the advantage in survival due to the addition of metformin.

4.2. The Reason for the Addition of Metformin. As reported in the former studies, the median overall survival (OS) of chemotherapy in advanced NSCLC patients reached 10 months–26 months [5–7]. The explorations of new antineoplastic medications never stopped. Metformin, as a common antidiabetes medication, has been shown in the laboratory to have antineoplastic effects. There have been explanations for the mechanism of its antineoplastic effect; the activated AMPK and the suppressed mTOR pathway by metformin have been proposed to explain its inhibition in tumor growth and proliferation [10, 11, 23, 24]. The cytotoxic effects of metformin have also been demonstrated in preclinical studies, both in vivo and in vitro [25, 26]. As a result, metformin was soon put into clinical application in the field of cancer treatment. In addition to its antineoplastic effects on cancer patients, studies have shown metformin's ability to reduce cancer incidence [27–29]. Studies were subsequently performed on the synergistic effect on the survival of metformin with chemotherapy, radiation therapy, targeted therapy with tyrosine kinase inhibitors, and immune-checkpoint inhibitors.

4.3. Characteristics of Patients Receiving Metformin. Chemotherapy was recommended to NSCLC patients who undergo surgery at an early stage but have high-risk features or with positive margins and lymph node invasion. Patients with an advanced stage of NSCLC but not eligible for targeted therapy were also recommended for chemotherapy [4]. Two of our enrolled studies involved patients at an early stage. Wen-Xiu et al. [16] studied NSCLC patients in stage I–IV (28 patients in I-II) for the addition of metformin in platinum-based chemotherapy. Ahmed et al. [13] studied patients in stage I–IV (25 in I-II) treating with platinum-based chemotherapy and radiation therapy. Both studies found no significant effect of metformin on survival, which might be explained by the limited sample size [16]. We were not able to perform subgroup analysis in terms of the stage since no data specific to the stage were provided.

Metformin was originally a type of antidiabetic drug. In our enrolled studies, NSCLC patients with diabetes treated with metformin made up a significant part of the study population. Our subgroup showed that metformin had significant benefits on the survival in patients with diabetes but no significant effect in patients without diabetes. It drove the puzzle of whether metformin's impact on survival was due to its effect on diabetes outcomes. However, studies have reported that the cause of death in patients was primarily cancer progression rather than competing risks due to diabetes

[14, 19]. Meanwhile, all studies on NSCLC patients without diabetes did not conclude that metformin had a beneficial effect on survival. We look forward to further studies to solve the abovementioned puzzle on the metformin effect.

4.4. Timing and Dose of Metformin Use in Enrolled Studies. Lin et al.'s and Chuang et al.'s studies [14, 22] were the only two studies to identify a significant benefit of metformin on survival. In both studies, the study population was already on metformin at the time of lung cancer diagnosis. Study populations in the included retrospective studies were mostly taking metformin prior to lung cancer diagnosis. In those studies, metformin was more likely to be used as a baseline treatment than as add-on chemotherapy. It was unclear whether the effects of metformin had accumulated before chemotherapy or were synergistic with chemotherapy. The included randomized controlled trials started metformin medication after randomization, though still weeks before the initiation of cytotoxic therapy [12, 17, 18].

Wang et al.'s study evaluated the survival benefit of different metformin doses during the first 3 months after lung cancer diagnosis [19]. They found that a daily dose of at least 1500 mg and a cumulative defined daily dose of 21 or higher would bring improved survival outcomes [19]. Among the other three studies that also reported metformin doses, all three planned the full-day doses of 2000 mg [12, 13, 18]. There was less concern about the association between the dose and the survival benefit. We look forward to more concentration on the effect of the metformin dose on survival outcomes.

4.5. Impact on the Survival of Metformin Addition. Two retrospective studies identified significant benefits of metformin addition to survival of patients receiving chemotherapy [14, 22]. But it was surprised to see that one of the included RCTs reported a significantly worse survival outcome of metformin addition. Tsakiridis et al. [12] included 26 patients in the metformin addition group while 28 in the control group. Although the sample size was somewhat limited compared to those two retrospective studies which reported a positive impact of metformin addition, Tsakiridis et al. still identified significant difference between the two groups regarding both OS and PFS [12]. Except for the study design, one of the most prominent differences was that Tsakiridis et al. included patients without diabetes, while studies of Lin et al. [14] and Chuang et al. [22] included patients with diabetes. There might be a hypothesis that metformin could bring a protective effect on survival to those patients with diabetes, which awaited further evidence.

4.6. Implications on Future Direction. The exploration of the role of metformin in cancer treatment remained insufficient. In addition to lung cancer, metformin might have the potential for protective effects on other types of cancer. One study on female patients taking tamoxifen showed that addition of metformin in treatment reduced the tamoxifen-induced endometrial hyperplasia [30]. A randomized trial showed that addition of metformin to colorectal cancer patients following polypectomy could reduce the prevalence of metachronous colorectal cancer [31]. Further investigation into the protective effects of metformin on other cancer is warranted.

4.7. Limitations and the Risk of Bias. Our results should be interpreted with some limitations. First, the five enrolled RCTs were identified as a high risk of bias. This was due to their open-label design since the medication of metformin was hard for blind design. Second, the age limitation, comorbidities, stage and the metastasis status at diagnosis, and the presence of other cancers were not consistent across all included studies, which could be the potential sources of heterogeneity. We reviewed those variables in a table to help comprehensively understand the population characteristics of each study. Third, the different chemotherapy regimen among the enrolled studies was another great source of heterogeneity.

5. Conclusion

Our systematic review showed that the survival impact of metformin in combination with chemotherapy on unresectable NSCLC patients remains inconclusive. The survival benefit of metformin addition might be more prominent in patients with diabetes. More prospective studies are needed to evaluate this effect.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

Supplementary Table 1: risk of bias of the included randomized controlled trials according to the Cochrane collaboration's tool. Supplementary Table 2: quality assessment of the included retrospective case-control studies according to the Newcastle–Ottawa scale. Supplementary Table 3: PRISMA checklist. (*Supplementary Materials*)

References

[1] R. L. Siegel, K. D. Miller, H. E. Fuchs, and A. Jemal, "Cancer statistics, 2021," *CA: A Cancer Journal for Clinicians*, vol. 71, no. 1, pp. 7–33, 2021.

[2] K. Chansky, F. C. Detterbeck, A. G. Nicholson et al., "The IASLC lung cancer staging project: external validation of the revision of the TNM stage groupings in the eighth edition of the TNM classification of lung cancer," *Journal of Thoracic Oncology*, vol. 12, no. 7, pp. 1109–1121, Jul 2017.

[3] Y. She, Z. Jin, J. Wu et al., "Development and validation of a deep learning model for non-small cell lung cancer survival," *JAMA Network Open*, vol. 3, no. 6, Article ID e205842, 2020.

[4] N. C. C. Network, "NCCN clinical practice guidelines in oncology non-small cell lung cancer," 2021, https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

[5] G. V. Scagliotti, P. Parikh, J. von Pawel et al., "Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer," *Journal of Clinical Oncology*, vol. 26, no. 21, pp. 3543–3551, 2008.

[6] C. P. Belani, Y. L. Wu, Y. M. Chen et al., "Efficacy and safety of pemetrexed maintenance therapy versus best supportive care in patients from East Asia with advanced, nonsquamous non-small cell lung cancer: an exploratory subgroup analysis of a global, randomized, phase 3 clinical trial," *Journal of Thoracic Oncology*, vol. 7, no. 3, pp. 567–573, 2012.

[7] J. C. Soria, D. S. W. Tan, R. Chiari et al., "First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study," *The Lancet*, vol. 389, no. 10072, pp. 917–929, 2017.

[8] J. D. Bradley, C. Hu, R. R. Komaki et al., "Long-term results of NRG oncology RTOG 0617: standard- versus high-dose chemoradiotherapy with or without cetuximab for unresectable stage III non-small-cell lung cancer," *Journal of Clinical Oncology*, vol. 38, no. 7, pp. 706–714, 2020.

[9] J. P. Sculier, J. J. Lafitte, T. Berghmans et al., "A phase III randomised study comparing concomitant radiochemotherapy with cisplatin and docetaxel as induction versus consolidation treatment in patients with locally advanced unresectable non-small cell lung cancer," *Lung Cancer*, vol. 117, pp. 32–37, 2018.

[10] R. J. Dowling, M. Zakikhani, I. G. Fantus, M. Pollak, and N. Sonenberg, "Metformin inhibits mammalian target of rapamycin-dependent translation initiation in breast cancer cells," *Cancer Research*, vol. 67, no. 22, pp. 10804–10812, 2007.

[11] R. J. Dowling, P. J. Goodwin, and V. Stambolic, "Understanding the benefit of metformin use in cancer treatment," *BMC Medicine*, vol. 9, no. 1, p. 33, 2011.

[12] T. Tsakiridis, G. R. Pond, J. Wright et al., "Metformin in combination with chemoradiotherapy in locally advanced non-small cell lung cancer: the OCOG-ALMERA randomized clinical trial," *JAMA Oncology*, vol. 7, no. 9, pp. 1333–1341, 2021.

[13] I. Ahmed, A. Ferro, A. Cohler et al., "Impact of metformin use on survival in locally-advanced, inoperable non-small cell lung cancer treated with definitive chemoradiation," *Journal of Thoracic Disease*, vol. 7, no. 3, pp. 346–355, 2015.

[14] J. J. Lin, E. J. Gallagher, K. Sigel et al., "Survival of patients with stage IV lung cancer with diabetes treated with metformin," *American Journal of Respiratory and Critical Care Medicine*, vol. 191, no. 4, pp. 448–454, 2015.

[15] K. C. J. Wink, J. S. A. Belderbos, E. M. T. Dieleman et al., "Improved progression free survival for patients with diabetes and locally advanced non-small cell lung cancer (NSCLC) using metformin during concurrent chemoradiotherapy," *Radiotherapy & Oncology*, vol. 118, no. 3, pp. 453–459, 2016.

[16] X. Wen-Xiu, Z. Xiao-Wei, D. Hai-Ying et al., "Impact of metformin use on survival outcomes in non-small cell lung cancer treated with platinum," *Medicine*, vol. 97, no. 51, Article ID e13652, 2018.

[17] Y. Lee, J. Joo, Y. J. Lee 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*, vol. 151, pp. 8–15, 2021.

[18] H. Skinner, C. Hu, T. Tsakiridis 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 Oncology*, vol. 7, no. 9, pp. 1324–1332, 2021.

[19] J. L. Wang, Y. T. Tsai, C. H. Lin et al., "Benefits of metformin combined with pemetrexed-based platinum doublets as a first-line therapy for advanced lung adenocarcinoma patients with diabetes," *Biomolecules*, vol. 11, no. 8, p. 1252, 2021.

[20] R. Sayed, A. S. Saad, L. El Wakeel, E. Elkholy, and O. Badary, "Metformin addition to chemotherapy in stage IV non-small cell lung cancer: an open label randomized controlled study," *Asian Pacific Journal of Cancer Prevention*, vol. 16, no. 15, pp. 6621–6626, 2015.

[21] K. A. Marrone, X. Zhou, P. M. Forde 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," *The Oncologist*, vol. 23, no. 7, pp. 859–865, 2018.

[22] M. C. Chuang, Y. H. Yang, Y. H. Tsai et al., "Survival benefit associated with metformin use in inoperable non-small cell lung cancer patients with diabetes: a population-based retrospective cohort study," *PLoS One*, vol. 13, no. 1, Article ID e0191129, 2018.

[23] M. A. Pierotti, F. Berrino, M. Gariboldi et al., "Targeting metabolism for cancer treatment and prevention: metformin, an old drug with multi-faceted effects," *Oncogene*, vol. 32, no. 12, pp. 1475–1487, 2013.

[24] M. Foretz, B. Guigas, L. Bertrand, M. Pollak, and B. Viollet, "Metformin: from mechanisms of action to therapies," *Cell Metabolism*, vol. 20, no. 6, pp. 953–966, 2014.

[25] H. Ashinuma, Y. Takiguchi, S. Kitazono et al., "Antiproliferative action of metformin in human lung cancer cell lines," *Oncology Reports*, vol. 28, no. 1, pp. 8–14, 2012.

[26] A. Leone, E. Di Gennaro, F. Bruzzese, A. Avallone, and A. Budillon, "New perspective for an old antidiabetic drug: metformin as anticancer agent," *Cancer Treatment and Research*, vol. 159, pp. 355–376, 2014.

[27] S. Gandini, M. Puntoni, B. M. Heckman-Stoddard et al., "Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders," *Cancer Prevention Research*, vol. 7, no. 9, pp. 867–885, 2014.

[28] H. Noto, A. Goto, T. Tsujimoto, and M. Noda, "Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis," *PLoS One*, vol. 7, no. 3, Article ID e33411, 2012.

[29] Z. J. Zhang, Y. Bi, S. Li et al., "Reduced risk of lung cancer with metformin therapy in diabetic patients: a systematic review and meta-analysis," *American Journal of Epidemiology*, vol. 180, no. 1, pp. 11–14, 2014.

[30] S. R. Davis, P. J. Robinson, F. Jane et al., "The benefits of adding metformin to tamoxifen to protect the endometrium a randomized placebo-controlled trial," *Clinical Endocrinology*, vol. 89, no. 5, pp. 605–612, 2018.

[31] T. Higurashi, K. Hosono, H. Takahashi et al., "Metformin for chemoprevention of metachronous colorectal adenoma or polyps in post-polypectomy patients without diabetes: a multicentre double-blind, placebo-controlled, randomised phase 3 trial," *The Lancet Oncology*, vol. 17, no. 4, pp. 475–483, 2016.