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ORIGINAL RESEARCH

Clinical Effect of Treatment with Metformin for Type 2 Diabetes on Non-Small Cell Lung Cancer Patients Undergoing Immunotherapy: A Retrospective Study

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Purpose: To further identify the clinical impact of metformin on the prognosis of non-small cell lung cancer (NSCLC) with type 2 diabetes who received immunotherapy.

Methods: Stage IV NSCLC patients with type 2 diabetes receiving the immunotherapy from 2017 to 2021 were retrospectively enrolled and divided into the metformin group or non-metformin group according to the treatment strategy for type 2 diabetes (metformin vs other hypoglycemic medicines). The overall response rate (ORR) was primary endpoint, and overall survival (OS), progression-free survival (PFS) and disease control rate (DCR) were secondary endpoints. These outcomes were compared between two groups.

Results: A total of 34 patients were eventually enrolled, including 18 patients in the metformin group. No significant differences in the basic characteristics and incidence of adverse events were observed between two groups. In addition, there was no significant difference in ORR (44.4%, 8/18 vs 25.0%, 4/16, P = 0.236) and DCR (77.8%, 14/18 vs 75.0%, 12/16, P > 0.999) between the metformin and non-metformin groups. Kaplan–Meier survival curve (P = 0.039) and Cox regression analysis indicated that the use of metformin was an independent factor for OS (HR: 0.310, 95% CI: 0.113–0.845, P = 0.022), but not for PFS (Cox regression analysis: P = 0.145).

Conclusion: For NSCLC patients with type 2 diabetes, the combination of metformin and immunotherapy may contribute to OS benefits. However, more high-quality prospective studies with big sample sizes are needed to further clarify the effect of metformin use on the efficacy of immunotherapy in advanced NSCLC patients with diabetes.

Keywords: metformin, non-small cell lung cancer, immunotherapy, prognosis

Introduction

Lung cancer is the most common malignant tumor in the world, with the incidence and mortality ranking first among all malignant tumors.[1] In China, a total of 234, 030 cases were diagnosed with lung cancer in 2018 (accounting for 13.5% of all new-onset malignant tumors), among which, non-small cell lung cancer (NSCLC) is estimated to account for 80% of lung cancer patients, according to data from the National Cancer Institute.[1] However, the prognosis of lung cancer has not improved significantly, and the overall survival (OS) rate is still poor, though significant progress in the diagnosis and treatment of lung cancer has been made in recent decades.[2] The global data show that the age standardized 5-year survival rate of lung cancer fluctuates between 10% and 20% between 2000 and 2014.[3] In China, the age standardized 5-year survival rate of lung cancer showed a slight upward trend between 2003 and 2015, but still remained below 20.0%.[4] Therefore, finding effective methods or means to treat lung cancer has always been a research direction and hotspot in the diagnosis and treatment of lung cancer.

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Chemotherapy has been the most commonly used treatment method for malignant tumor.[5] In recent years, progresses of immune checkpoint inhibitors (ICIs) and monoclonal antibodies targeting immune checkpoints such as Programmed Death-1 (PD-1) and its ligand 1 (PD-L1) in various types of cancer have been made and routinely used in clinical practice.[6,7] Immune drugs represented by PD-1 and PD-L1 inhibitors have been applied in the treatment of lung cancer, becoming the standard treatment choice for advanced NSCLC without driver genes,[8] leading lung cancer into a long-term survival era. However, it should be noted that although immunotherapy has been proven to significantly improve the prognosis of advanced NSCLC patients, some patients still have poor efficacy after immunotherapy, mainly because of primary and/or secondary treatment resistance.[9] Studies show that there are mainly three types of patient subgroups, namely patients who have never shown any response to treatment (primary resistance), patients who initially responded and continued to respond during long-term follow-up, and patients who initially responded but eventually progressed (acquired resistance).[10–12] The reasons for this may include insufficient generation of anti-tumor T cells, insufficient tumor-specific T cell function, or impaired T cell memory formation.[13] Therefore, research on drug resistance in ICIs treatment has a great clinical application value.

Metformin belongs to a class of drugs known as biguanides and underlines that beyond its hypoglycemic effect, metformin may also affect PD-1 blockade. It is a hydrophilic base that exists in the form of cations at physiological pH. Metformin is mainly absorbed by the small intestine and then by the liver, playing a hypoglycemic role.[14] As the main drug for treating type 2 diabetes, it controls blood glucose by reducing glycogen decomposition, inhibiting gluconeogenesis, inhibiting intestinal glucose absorption and increasing insulin sensitivity of surrounding tissues.[15] Recent studies have found that besides its hypoglycemic effect, metformin can also inhibit the occurrence and development of malignant tumor. In addition, the role of metformin in adjuvant anti-tumor and enhancing the sensitivity of chemotherapy drugs has been revealed.[16] Also note that a study has found that metformin may enhance the blocking effect of PD-1 through anti-PD-1 antibodies, suggesting that metformin can reduce tumor hypoxia, thereby enhancing PD-1 blockade.[17] Metformin also inhibits myeloid derived inhibitory cells (MDSCs), thereby enhancing the anti-tumor activity of PD-1 inhibitors.[18] In clinics, a certain proportion of patients receiving ICIs also have diabetes, and type 2 diabetes is very often treated with metformin. Therefore, metformin may have potential clinical application prospects in combination with immunotherapy for lung cancer, which should be further investigated.

Based on this, we reviewed the NSCLC patients with diabetes who received immunotherapy in our hospital from 2017 to 2021 and observed the clinical prognosis of patients who received both metformin and ICI in NSCLC treatment to preliminarily evaluate the impact of metformin on the prognosis of immunotherapy patients.

Method

Study Design

A single-center and retrospective cohort study.

Ethics

This study was approved by the Affiliated Hospital of Chengdu University Ethics Committee (2024-009-03) and promised to comply with the Helsinki Declaration. Based on the experimental type of the retrospective cohort study, all enrolled patients were exempt from the informed consent form.

Inclusive/Exclusive Criteria

The inclusion criteria included 1) age ranged from 18 to 85 years old; 2) patients were diagnosed with stage IV non-small cell lung cancer by cytological or histological evidence and received the immunotherapy from January, 2017, to December, 2021; 3) patients with type II diabetes previously diagnosed; 4) patients in the metformin group received the use of metformin for over 6 months and patients in the non-metformin group did not receive the metformin therapy.

Exclusion criteria included (patients who met any of the following criteria should be excluded): 1) individuals who could not tolerate immunotherapy; 2) active infection, including tuberculosis, hepatitis B, hepatitis C or HIV; 3) individuals who were allergic to immune drugs.

Clinical Data and Outcome Measures

We reviewed the medical records of eligible patients and collected data on basic demographics (age, gender), time of diagnosis, clinical stage at diagnosis (AJCC Version 8), PD-L1 status, diabetes status, prior adjuvant treatment, concurrent chemoradiotherapy, cancer-related surgeries, metformin use, number of ICI cycles, treatment-related adverse reactions, and other relevant information. The post-treatment response evaluation was conducted using the RECIST v.1.1 standard and evaluated through imaging, with grades including complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD).

At the same time, we also recorded and followed up the post-treatment survival of the patients. The overall response rate (ORR) was calculated and defined as the percentage of patients who had achieved PR or CR. Disease control rate (DCR) was defined as the total percentage of patients who had achieved CR, PR, and SD. We calculated the OS rate from the start of treatment to the final follow-up date (December 31, 2022) or date of death, as well as the PFS from the start of treatment to the final follow-up date (December 31, 2022, date of progression or death). We collected basic laboratory data, performance status scores of the Eastern Cancer Cooperation Organization, and reported immune-related adverse events (IrAE) such as fatigue, rash/mucositis, colitis/diarrhea, etc.

The ORR was the primary endpoint of this study, while OS, PFS, and DCR were secondary endpoints.

Statistical Method

We calculate summary indicators for continuous data, such as age, OS and PFS (in months), mean (or geometric mean, depending on the situation), median, standard deviation, and interquartile range at stage IV diagnosis. Histograms of continuous endpoints and Q-Q plots were used to evaluate distribution assumptions. To evaluate survival analysis (OS and PFS, 95% CI), Kaplan Meier method and logarithmic rank test were applied. Cox regression analysis was conducted to explain potential variables that affect survival data, such as age at diagnosis, use of metformin, chemotherapy, radiation therapy, PD-L1 level, and optimal treatment response. Multiple linear regression analysis was conducted to investigate the impact of metformin treatment duration on OS and PFS. Chi-square test and Fisher's exact test were used to compare categorical variables and calculate P-values. Mann Whitney test was used to analyze continuous variables and calculate P-values.

Results

Basic Characteristics of Enrolled Patients

Finally, 34 patients (average age: 66.3 ± 7.8 years, male: 58.8%, median follow-up time: 9.5 months) were included, of which 18 patients took metformin orally for a long time after the diagnosis of type 2 diabetes, and 16 patients used other hypoglycemic treatments. Comparison of clinical data between two groups of patients was shown in Table 1.

Adverse Events During the Treatment Process

During the immunotherapy process, there was no statistically significant difference in the number of newly diagnosed metastases between the two groups (2.1 ± 1.2 vs 2.7 ± 1.3, P = 0.323). In addition, there was no statistically significant difference in the proportions of bone metastases (P = 0.725), brain metastases (P > 0.999), and liver metastases (P > 0.999). There was no significant difference in the incidence of major adverse events during the treatment process, including severe malnutrition (P = 0.230), pneumonia (P > 0.999), acute kidney injury (P = 0.591), immune related adverse reactions (P > 0.999), and readmission (P = 0.323) (Table 2).

Table 1 Comparison of Clinical Data Between the Two Groups of Patients

	Metformin Group (n=18)	Control Group (n=16)	P value
Average diagnosis age	66.6±6.7	66.2±9.2	0.862
Gender			
Male	9 (50.0)	11 (68.8)	0.268
Female	9 (50.0)	5 (31.2)	
Comorbidities			
Hypertension	3 (16.7)	2 (12.5)	>0.999
Cardiovascular disease	3 (16.7)	2 (12.5)	>0.999
COPD	2 (11.1)	1 (6.3)	>0.999
History of malignant tumors	4 (22.2)	3 (18.8)	>0.999
ECOG score			0.898
0	5 (27.8)	3 (18.8)	
1	8 (44.4)	7 (43.8)	
2	3 (16.7)	4 (25.0)	
3	2 (11.1)	2 (12.5)	
Smoker	3 (16.7)	3 (18.8)	>0.999
Median duration of metformin usage (months)	20.3	–	
Median duration of metformin combined with ICIs (months)	4.3	–	
ICIs treatments			0.943
PD-1 inhibitor	6 (33.3)	5 (31.3)	
PD-L1 inhibitor	8 (44.4)	8 (50.0)	
Both	4 (22.3)	3 (18.7)	
Other anti-tumor treatments			
Chemotherapy	5 (27.8)	4 (25.0)	>0.999
Radiotherapy	2 (11.1)	2 (12.5)	>0.999
PD-L1 level			0.868
<1%	7 (38.9)	7 (43.8)	
1–50%	6 (33.3)	4 (25.0)	
>50%	5 (27.8)	5 (31.3)	

Abbreviations: COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; ICIs, immune checkpoint inhibitors; PD-L1, programmed death-ligand 1.

Table 2 Adverse Events During Immunotherapy

	Metformin Group (n=18)	Control Group (n=16)	P value
Number of new metastatic sites during the treatment process	2.1±1.2	2.7±1.3	0.323
Bone metastasis	6 (33.3)	7 (43.8)	0.725
Brain metastasis	4 (22.2)	4 (25.0)	>0.999
Liver metastasis	4 (22.2)	4 (25.0)	>0.999
Other	1 (5.6)	2 (12.5)	0.591
Severe malnutrition	3 (16.7)	0	0.230
Pneumonia	1 (5.6)	1 (6.3)	>0.999
Acute kidney injury	1 (5.6)	2 (12.5)	0.591
Immunotherapy related complications	2 (11.1)	2 (12.5)	>0.999
Readmission	1 (5.6)	3 (18.8)	0.323

Effectiveness Evaluation

Evaluation of Optimal Treatment Response

We evaluated the level of optimal treatment response in patients through imaging techniques such as CT and PET-CT and found that the overall CR, PR, SD, and PD ratios were 2.9% (1/34), 32.4% (11/34), 41.1% (14/34), and 23.5% (8/34),

Table 3 The Evaluation of Therapeutic Effectiveness

	Metformin Group (n=18)	Control Group (n=16)	P value
Therapeutic response			0.574
CR	1 (5.6)	0 (0.0)	
PR	7 (38.9)	4 (25.0)	
SD	6 (33.3)	8 (50.0)	
PD	4 (22.2)	4 (25.0)	
ORR	8 (44.4)	4 (25.0)	0.236
DCR	14 (77.8)	12 (75.0)	>0.999
Time of achieving optimal treatment response	3.3±1.1	3.2±1.3	0.947

Abbreviations: CR, complete remission (CR); PR, partial remission; SD, stable disease; PD, progressive disease; ORR, the overall response rate (ORR); DCR, Disease control rate.

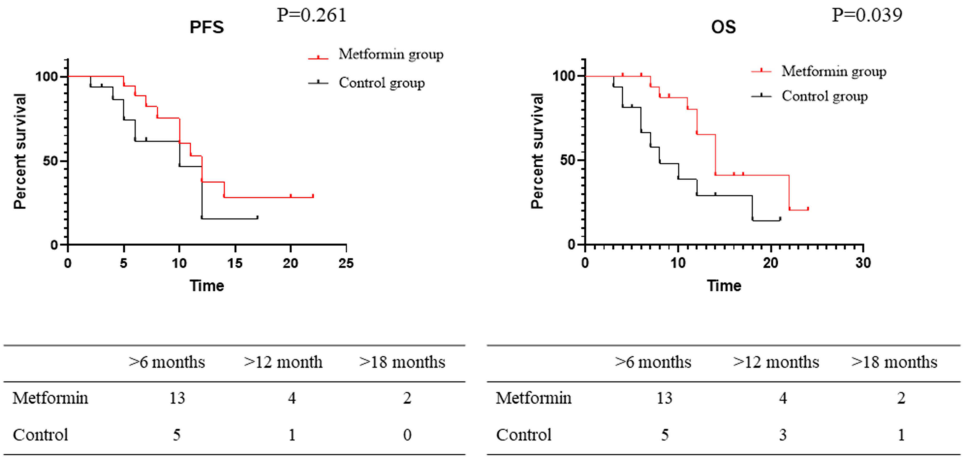
respectively. There was no significant difference in tumor response rate between the two groups (P = 0.574) (Table 3). Furthermore, we analyzed the ORR (44.4%, 8/18 vs 25.0%, 4/16, P = 0.236) and DCR (77.8%, 14/18 vs 75.0%, 12/16, P > 0.999) of the two groups, and no statistically significant difference between the two groups was found. In addition, no statistical difference was observed between the two groups in achieving optimal treatment response time (P = 0.947) (Table 3).

Survival Analysis

Furthermore, the differences in OS and PFS between the metformin group and the control group were analyzed. It was found that on OS, the metformin group was significantly better than the control group (log rank analysis P = 0.039); On PFS, there was no statistically significant difference between the two groups (log rank analysis P = 0.261), as shown in Figure 1.

COX Regression Survival Analysis

Finally, variables including the use of metformin, age, chemotherapy, radiation therapy, PDL-1 levels, and optimal treatment response (ineffective) were included into COX regression. The results showed that the use of metformin (HR: 0.310, 95% CI: 0.113–0.845, P=0.022) and PD-L1 levels (HR: 0.228, 95% CI: 0.078–0.663, P = 0.007) were independent factors affecting patient OS (Table 4). Meanwhile, we conducted PFS risk factor analysis using COX regression and did not find any statistically significant independent risk factors (Table 5).



	>6 months	>12 month	>18 months
Metformin	13	4	2
Control	5	1	0

	>6 months	>12 months	>18 months
Metformin	13	4	2
Control	5	3	1

Figure 1 The comparison of OS and PFS between the metformin group and the control group.

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Table 4 COX Regression Analysis of Overall Survival

	Univariate Analysis			Multivariate Analysis		
	HR	**P value**	**95% CI**	**HR**	**P value**	**95% CI**
Age	0.997	0.909	0.945–1.052		–	
Smoker	0.463	0.310	0.105–2.046		–	
Gender (M)	1.450	0.421	0.586–3.585		–	
Chemotherapy	0.904	0.839	0.339–2.406		–	
Radiotherapy	0.576	0.345	0.183–1.812		–	
Optimal treatment response	0.827	0.537	0.453–1.511		–	
PD-L1 level	0.293	0.015	0.109–0.790	0.228	0.007	0.078–0.663
The use of metformin	0.395	0.054	0.154–1.015	0.310	0.022	0.113–0.845

Note: Variables with a p<0.20 in the univariate analysis were included into the multivariate analysis.

Table 5 COX Regression Analysis of Progression-Free Survival

	Univariate Analysis			Multivariate Analysis		
	HR	**P value**	**95% CI**	**HR**	**P value**	**95% CI**
Age	1.108	0.581	0.957–1.082		–	
Smoker	0.639	0.485	0.182–2.249		–	
Gender (M)	0.489	0.146	0.186–1.284	0.450	0.143	0.155–1.311
Chemotherapy	0.939	0.906	0.330–2.674		–	
Radiotherapy	0.884	0.870	0.200–3.897		–	
Optimal treatment response	0.827	0.537	0.453–1.511		–	
PD-L1 level	0.476	0.154	0.172–1.320	0.339	0.058	0.111–1.036
The use of metformin	0.595	0.196	0.224–1.576	0.641	0.423	0.215–1.906

Note: Variables with a p<0.20 in the univariate analysis were included into the multivariate analysis.

Discussion

The important anti-tumor effect of metformin has been extensively studied.[19,20] Metformin can inhibit liver gluconeogenesis by regulating the AMPK/liver LKB1 pathway,[21] which can control protein synthesis and cell proliferation by controlling the energy required by cells, thereby regulating the cell cycle.[22] In addition, it may inhibit the synthesis of unfolded proteins, activate immune responses against cancer cells, inhibit the expression of CD39/73 on MDSCs, and prevent the development of immune tolerance in cancer cells.[22,23] Scharping et al reported that metformin enhances the blockade of PD-1 by anti-PD-1 antibodies, thereby improving T cell function.[17] Eikawa et al reported that the direct effect of metformin on CD8 (+) T cells was crucial for preventing inevitable functional failure in the tumor microenvironment.[24] In addition, metformin has been shown to have direct cytotoxic effects, which can directly kill NSCLC cells.[25]

However, there are still few studies on the relationship or impact of metformin on the treatment of ICIs in lung cancer. Afzal et al investigated the clinical efficacy of metformin combined with ICIs in the treatment of NSCLC patients and enrolled 50 patients who received ICIs plus metformin or did not receive metformin treatment. Their results showed that the total effective rate, DCR, median OS, and PFS time of the combined metformin group were higher than those of the non-combined metformin group, and the same results were obtained in subgroup analysis (second/third line ICIs).[26] These results indicate that NSCLC patients who received both metformin and ICI treatment had a better prognosis. Cortellini et al analyzed 950 NSCLC patients receiving Pembrolizumab (PD1 inhibitor) treatment, and univariate results showed that metformin did not significantly improve the ORR or prolong survival.[27] Jacobi et al included 57 patients with stage IV NSCLC complicated with diabetes and suggested that ORR and DCR in metformin group were relatively higher, although not statistically significant. Meanwhile, there was no significant difference in OS and PFS between the two groups.[28] Chiang et al included 164 patients with diabetes who received immunotherapy and showed that the

combination of metformin could significantly improve patients' OS (HR = 0.53, P = 0.004) and PFS (HR = 0.69, P = 0.042). However, the use of metformin before immunotherapy had no significant effect on the OS (HR = 0.61, P = 0.25) PFS (HR = 0.69, P = 0.32).[29] Their results highly suggested that the combined use of metformin may enhance the sensitivity of immunosuppressive drugs and enhance tumor killing effects. In another study, the authors observed the safety and efficacy of 40 patients with advanced melanoma, renal cell carcinoma, or lung cancer treated with a combination of metformin and nivolumab. The results showed that the high-dose metformin group had significantly longer OS (P = 0.037) and PFS (P = 0.021).[30] Overall, the impact of metformin on the immunotherapy efficacy of NSCLC patients is not yet clear, and more high-quality, large-scale studies are needed in the future to further clarify.

In this experiment, we retrospectively included 34 patients diagnosed as stage IV NSCLC with type 2 diabetes and receiving immunotherapy from 2017 to 2021. The results showed that compared with patients who did not receive metformin treatment, patients who received metformin treatment had an improvement in ORR. Although the difference was not statistically significant, it may be due to the small sample size; However, we can see an increasing trend in the effectiveness of immunotherapy and disease stability among patients receiving metformin combined with immunotherapy. We analyzed the differences in survival between the metformin group and the control group. After analysis, it was found that the metformin group was significantly better than the control group in OS (P = 0.039), which also requires us to have larger sample data in the future to confirm the impact of metformin on the anti-tumor effect of immunotherapy and survival prognosis.

Tan et al and the Afzal team also reported that patients receiving chemotherapy combined with metformin treatment had better ORR and DCR, although this difference was not statistically significant in this study.[9,31] Overall, the sample size of the studies, including our experiment, was relatively small, and the generalizability of the conclusions was limited due to clinical retrospective studies and confounding factors. However, our results provide a basis for our future large-scale, high-quality research, that metformin may affect the anti-tumor effect of NSCLC immunotherapy, although it is currently unclear what leads to the improvement of ORR; however, metformin blocking the increase of PD-1, combined with the previous increase in PD-1 expression during chemotherapy, may play a role in this regard. In the future, we need to study this observation in further basic and clinical research.

Finally, the patients included in our study are all NSCLC patients with type 2 diabetes, so the use of metformin is within the scope of conventional treatment. A review article by Levy et al mentioned that the incidence rate of cancer in diabetes patients treated with metformin was reduced, and the anti-tumor effect of metformin seemed to be dose dependent. The higher the dose of metformin, the stronger its anti-tumor effect.[32] Although it is currently believed that metformin is one of the safest hypoglycemic drugs for type 2 diabetes patients, it does not cause hypoglycemia, and has good metabolic effects.[33] It has good safety under various non-diabetes conditions.[34] However, it should be fully recognized that metformin treatment still has certain potential side effects, mainly including fatigue, diarrhea, bloating, muscle pain, abdominal pain, lactic acidosis, etc.[33] The safety and effectiveness of metformin for immunotherapy combination therapy in the future need to be further evaluated.

In the future research on the effect of metformin on the treatment in NSCLC patients with type 2 diabetes, in addition to expanding the sample size as much as possible, we believe that the following aspects need to be considered and integrated into practice: 1) The dose of metformin is theoretically related to its anti-tumor effect, and the minimum dose to improve the treatment effect of ICI in NSCLC patients should be determined as far as possible; 2) NSCLC includes various subtypes such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, with high heterogeneity among different pathological subtypes. The mechanism of action of metformin on the efficacy of ICI treatment in different types of NSCLC patients may be different, so there are differences in clinical efficacy, which requires stratified analysis. 3) Previous studies have suggested that combination chemotherapy can enhance the therapeutic efficacy of ICIs in NSCLC patients, and metformin can improve the efficacy of chemotherapy. Therefore, further evidence is needed to determine whether the combination of the three can achieve better therapeutic effects. 4) At the same time, the timing of using metformin should also be clear, that is, there may be some differences in the effectiveness of taking metformin only during ICIs treatment and taking metformin before, during, and after treatment.

Finally, it should be noted that this study has certain limitations and shortcomings, mainly including a small sample size and retrospective research nature, which require the generalizability and reliability of our conclusions to be verified by large samples and high-quality research data. Second, achieving glycemic control typically requires a combination of medications rather than relying on a single agent. Among the 18 patients, we analyzed who were prescribed metformin, 4

also utilized insulin, while 12 incorporated additional anti-diabetic agents alongside metformin. These included sulfonylurea secretagogues, alpha-glucosidase inhibitors, and thiazolidinedione derivatives that function as sensitizers. Although there is currently no evidence to demonstrate that the use of these hypoglycemic agents affects immunotherapy, we cannot dismiss this possibility. In addition, due to retrospective analysis limitations, we are unable to collect complete clinical data related to patients, including detailed radiotherapy, chemotherapy treatment history, specific drugs of ICIs, etc. These data may have a significant impact on the results of our analysis. Therefore, in the future, we will design prospective studies to expand the sample data and further validate our results and conclusions. Furthermore, given the heterogeneity of NSCLC subtypes, subgroup analyses could reveal differential effects of metformin based on tumor characteristics. This could refine treatment strategies and lead to more personalized approaches.

Conclusion

For NSCLC patients with type 2 diabetes, the combination of metformin and immunotherapy may contribute to OS benefits, but not to ORR, DCR or PFS. However, more high-quality prospective studies with big sample sizes are needed to further clarify the effect of metformin use on the efficacy of immunotherapy in advanced NSCLC patients with diabetes.

Data Sharing Statement

The data used to support the findings of this study have not been made available for protection of privacy.

Ethics Approval

This study was approved by the Affiliated Hospital of Chengdu University Ethics Committee (2024-009-03) and promises to comply with the Helsinki Declaration.

Patient Consent

All data were anonymous and aggregated; therefore, the requirement to obtain written informed consent from patients was waived by the Affiliated Hospital of Chengdu University Ethics Committee.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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