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Research Paper

The Clinical Effect of Metformin on the Survival of Lung Cancer Patients with Diabetes: A Comprehensive Systematic Review and Meta-analysis of Retrospective Studies

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Abstract

Preclinical investigations have revealed an anti-cancer effect of metformin. Several studies of metformin treatment have demonstrated the improved clinical outcomes of lung cancer patients with diabetes; however, the results have been inconsistent among studies. Our systematic review and meta-analysis aimed to summarize the up-to-date effects of metformin on diabetic lung cancer patients.

A systematic search was performed for studies published. Then, these studies were evaluated for inclusion, and relevant data was extracted. The summary risk estimates for the associations of metformin treatment with overall survival (OS) and progression-free survival (PFS) were analyzed using random/fixed-effects models. Analyses stratified by histological type were also conducted. Based on the 10 studies included in our analysis, metformin treatment was found to significantly improve survival, corresponding to reductions of 23% and 47% in OS [hazard ratio (HR)=0.77, 95% confidence interval (95%CI)=0.66-0.9, p=0.001] and PFS (HR=0.53, 95%CI=0.41-0.68, p<0.001), respectively. In addition, significant improvements in the OS for non-small cell lung cancer (NSCLC) (HR=0.77, 95%CI=0.71-0.84, p=0.002) and small cell lung cancer (SCLC) (HR=0.52, 95%CI=0.29-0.91, p=0.022) were observed in association with metformin treatment in analysis stratified by histological type. This stratified analysis also revealed a significant improvement in PFS for both NSCLC (HR=0.53, 95%CI=0.39-0.71, p<0.001) and SCLC (HR=0.54, 95%CI=0.34-0.84, p=0.007). We found that metformin treatment significantly improved the OS and PFS of diabetic lung cancer patients, and our findings suggest that metformin might be an effective treatment option for diabetic patients with lung cancer.

Key words: Lung cancer; Diabetes; Metformin; Survival; Meta-analysis.

Introduction

Diabetes mellitus is the most common metabolic disease, and it is caused by either a deficiency in pancreatic insulin production or resistance of insulin-responsive cells to the insulin produced [1]. Clinically, approximately 20% of patients with cancer have concurrent diabetes, which could be due to the biological links between these two diseases [2]. Previous experimental studies have suggested that an increased neoplastic proliferation rate and an increased risk of tumor progression or metastasis occur in cancer patients with concurrent diabetes mellitus, which could be due to the effects of

hyperinsulinemia, hyperglycemia, and inflammatory cytokines [3-6].

There is increasing interest in investigating the potential use of already-approved medications as anti-cancer agents [7-9]. Metformin is a glucose-lowering agent that improves insulin sensitivity and lowers the circulating insulin level in patients with type II diabetes mellitus [10]. It is the most commonly prescribed oral antidiabetic drug, and it is recommended as the first-line therapy because it is relatively inexpensive, safe, effective, and well-tolerated [11]. Over the past several years, some studies have investigated the effects of metformin treatment on cancer. Basic biochemical studies have provided a better understanding of the mechanisms underlying the anti-tumor activity of metformin and its potential to modulate molecular pathways involved in cancer cell signaling and metabolism [12-14].

Lung cancer is the leading cause of cancer-related death worldwide [15]. Despite advances in surgical and radiotherapy techniques and the availability of new chemotherapeutic agents, the outcomes of patients with lung cancer are still not satisfactory [16]. Thus, there is a need to develop new strategies to improve the efficacies of the current treatment modalities. Several published studies have reported that metformin treatment improves the survival of lung cancer patients with diabetes [17-23]; however, the results of other studies have been inconsistent [24-26]. Therefore, we conducted the present systematic review and meta-analysis to provide reliable and up-to-date evidence on the effects of metformin treatment on lung cancer patient survival and to further evaluate this association according to histologic subgroups.

Material and Methods

Study selection and data extraction

The following computerized bibliographic databases were searched for relevant articles: PubMed (PubMed Central-National Center for Biotechnology Information, PMC-NCBI), EMBASE, and ISI Web of Science (Science Citation Index Expanded). The following search terms were used: “lung cancer”, “diabetes mellitus or diabetes”, “metformin”, “mortality”, “survival”, and “prognosis”. A manual search was performed for references cited in the selected articles and reviews. Articles for which the abstract or full text was not available in English were excluded after review. The search included studies up to April of 2017.

Studies of patients with concurrent lung cancer and diabetes that evaluated the effect of metformin treatment on survival were included. All included studies defined glucose-lowering drug exposure (metformin or non-metformin) in subgroups and further compared metformin-treated patients with non-metformin-treated patients. The criteria for excluding studies in the present analysis were as follows: (1) failure to provide an adjusted hazard ratio (HR) with an estimated 95% confidence interval (95% CI); (2) inclusion of non-diabetic patients in the non-metformin group; and (3) inclusion of patients with type I diabetes mellitus. Two investigators (X. C. and Z. S. W.) independently extracted the following data from each included study: the first author, study region, publication year, study period, study design, tumor histology, tumor stage, length of follow-up, glucose-lowering drug treatment used (metformin or non-metformin), adjusted covariates, and adjusted estimates. A third investigator (X. W.) reviewed the extracted data. Any discrepancies in the course of article selection and data extraction were resolved by group discussion.

Statistical analysis

Adjusted Cox proportional HRs were used for quantitative analysis, and combined HRs for overall survival (OS) and progression-free survival (PFS) were calculated for the patients with lung cancer and diabetes treated (or not) with metformin. Additionally, subgroup analyses according to histological type were performed. Survival curves were estimated for metformin and non-metformin groups according to the method by the Early Breast Cancer Trialists’ Collaborative Group [27]. Heterogeneity across studies was estimated using the χ^2 test and the I^2 statistic, and the proper effect models were chosen accordingly. Statistically significant heterogeneity was defined as an I^2>50% or a χ^2 p-value<0.1[28]. If significant heterogeneity was observed, then the summary estimation was based on a random-effects model, according to the DerSimonian and Laird method [29]. If significant heterogeneity was not observed, then the summary estimation was based on a fixed-effects model. Furthermore, potential obvious heterogeneity was explored through sensitivity analysis. Begg’s and Egger’s tests were used to detect potential publication bias. All statistical analyses were conducted using STATA software version 14.0 (StataCorp, College Station, TX, USA). A two-sided p-value of <0.05 was considered significant all analyses except for the heterogeneity tests.

Results

Meta-analysis database

Figure 1 shows the flow chart for study selection. Initially, 168 articles were retrieved from the computerized bibliographic databases, of which 120 were duplicates. After title screening, 15 studies were recommended for abstract review. Studies that did not report survival information and those that were laboratory investigations, case reports, commentaries, reviews or meta-analyses were excluded from our analysis. Of the abstracts reviewed [30], 14 of the corresponding studies were eligible for further full-text review. We further excluded studies that (1) did not provide statistical data on OS or PFS in the full-text [31], (2) did not provided an adjusted HR with an estimated 95%CI [32, 33], or (3) included non-diabetic lung cancer patients in the non-metformin treatment group [34]. After the full-text review, a total of 10 studies were ultimately included [17-26], which consisted of 10 studies that reported OS [17-26], 5 that reported PFS [18-20, 24, 25], and 5 that presented both measures [18-20, 24, 25]. Two studies included all histological types [21, 26], 6 reported on non-small cell lung cancer (NSCLC) [17, 18, 22, 24, 25], and 2 reported on small cell lung cancer (SCLC) [19, 20]. Among the 10 studies, which consisted of 4,052 patients, 1,719 patients received metformin alone or in combination with another glucose-lowering regimen, and the remaining 2,333 received non-metformin therapy. The detailed characteristics of the included studies are shown in Table 1.

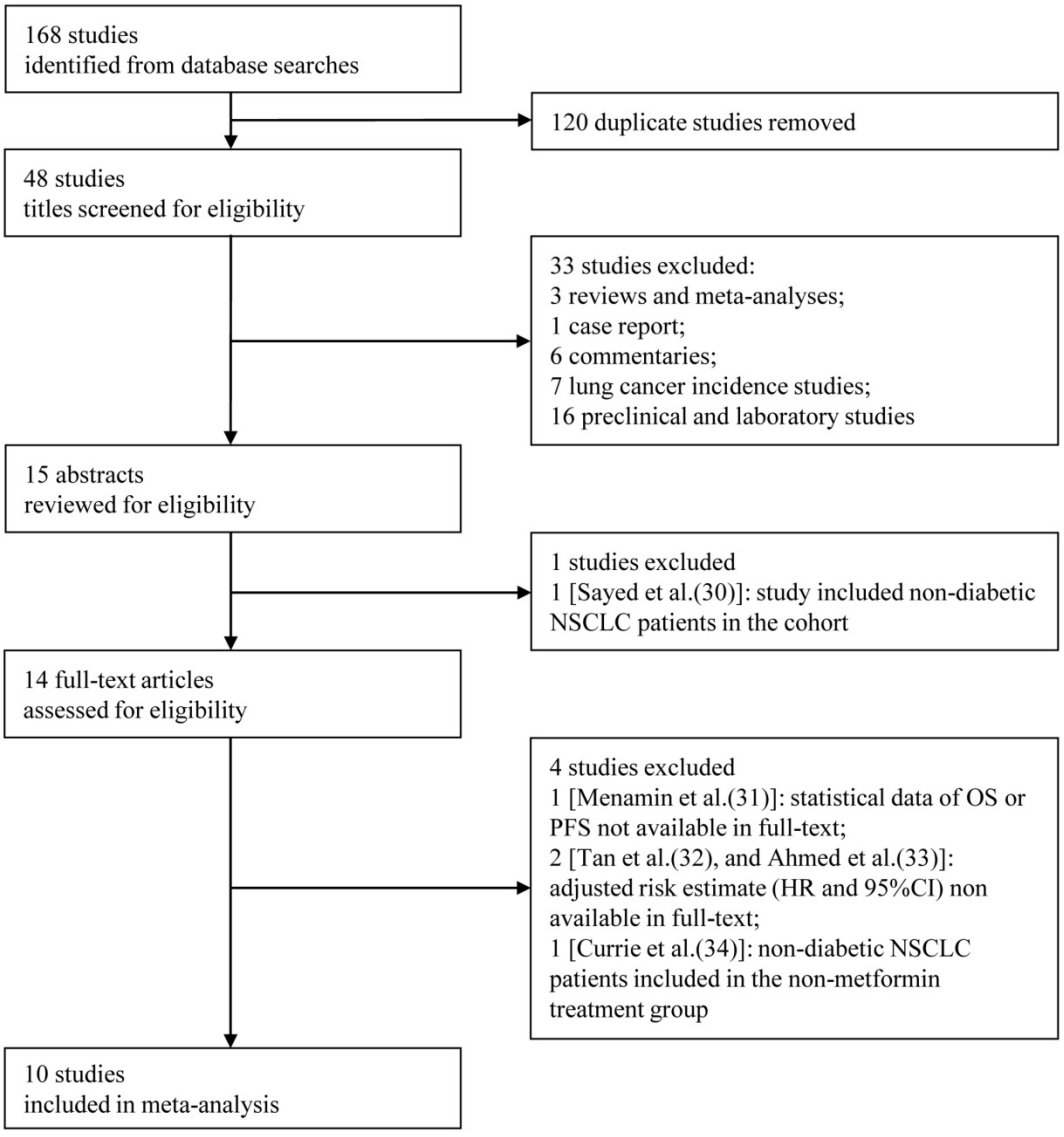

Figure 1. Flow diagram showing the inclusion and exclusion criteria for the studies.

Table 1. Summary characteristics of included studies.

Study (Country)	Year (Study period)	Study Design	Histology	Stage	Follow-up Time (median)	Treatment	Anti-diabetic Treatment	Adjustment Variables	OS	PFS
Lin *et al.* [23] (USA)	2017 (2002-2007)	Retrospective cohort study	NSCLC	I-IV	14.6 months	Surgery Chemotherapy Radiotherapy	Met: 259 Other: 377	Age, sex, race, tobacco use, comorbidities, stage, histology, treatments, insulin/insulin secretogogue/aspirin use	Y	N
Arrieta *et al.* [22] (Mexico)	2016 (2008-2014)	Retrospective cohort study	NSCLC	II-IV	10.8 months	No reported	Met: 111 Other: 75	Gender, smoking, stage, glycemic control	Y	N
Medairos *et al.* [24] (USA)	2016 (2004-2013)	Retrospective cohort study	NSCLC	I-II	19.5 months	Surgery Chemotherapy	Met: 81 Other: 57	Age, gender, T stage, N stage	Y	Y
Wink *et al.* [25] (Netherlands)	2016 (2008-2013)	Retrospective cohort study	NSCLC	III-IV	30 months	Concurrent chemoradiotherapy	Met: 59 Other: 623	Age, gender, stage, PS	Y	Y
Lin *et al.* [17] (USA)	2015 (2007-2009)	Retrospective population-based study	NSCLC	IV	No reported	Chemotherapy TKI Other	Met: 458 Other: 292	Sociodemographic factors, comorbidities, PS, diabetic medications, diabetic severity score, PET use, tumor characteristics, chemotherapy	Y	N
Chen *et al.* [18] (China)	2015 (2006-2014)	Retrospective cohort study	NSCLC	III-IV	No reported	TKI	Met: 44 Other: 46	No reported	Y	Y
Xu *et al.* [20] (China)	2015 (2000-2010)	Retrospective cohort study	SCLC	Limited and extensive	65 months	Chemotherapy surgery	Met: 36 Other: 43	Age, gender, NSE, LDH, tobacco use, stage, PS	Y	Y
Kong *et al.* [19] (China)	2015 (2001-2011)	Retrospective cohort study	SCLC	Limited and extensive	68 months	Chemotherapy surgery	Met: 120 Other: 139	Age, gender, NSE, LDH, smoking, stage, PS	Y	Y
Xu *et al.* [21] (USA)	2015 (1995-2010)	Retrospective cohort study	All	No reported	No reported	No reported	Met: 155/212 Insulin: 19/88 Other: 72/179	Age, sex, race, BMI, tobacco use, insulin use, Charlson Index	Y	N
Mazzone *et al.* [26] (USA)	2012 (1978-2010)	Retrospective case-control study	All	No reported	No reported	No reported	Met: 184 Other: 323	Age, stage	Y	N

Abbreviation: OS, overall survival; PFS, progression-free survival; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; met, metformin; TKI, tyrosine kinase inhibitor; PS, performance status; PET, positron emission tomography; NSE, neuronal specific enolase; LDH, lactate dehydrogenase; BMI, body mass index.

Effect of metformin on survival of all diabetic lung cancer patients

Ten studies were available for inclusion in OS analysis based on metformin treatment of diabetic patients with lung cancer [17-26], of which 7 reported a significant improvement in OS [17-23], 3 found no correlation [21, 24, 25], and 1 reported a decrease in OS [26]. Our meta-analysis revealed that the diabetic lung cancer patients treated with metformin displayed a significant improvement in OS compared with those who did not receive metformin (random-effects model, pooled HR=0.77, 95%CI=0.66-0.9, p=0.001). Significant heterogeneity was observed in our analysis (I^2=63.3%, p=0.001). For the heterogeneity, sensitivity analysis was performed. The details of analysis are summarized in Figure 2(A-B). The estimated survival curve is shown in Figure 4(A). The results of Begg's (p=0.951) and Egger's (p=0.524) tests suggested no evidence of publication bias. Notably, in the study by Xu *et al.* [21], among patients from the Mayo Clinic health records system, metformin treatment was associated with a significant improvement in OS relative to other oral hypoglycemic medications and insulin; however, no benefit of metformin was observed in patients from the Vanderbilt electronic health records system.

Data on PFS were available for 5 studies, all of which reported a significant improvement in the PFS of metformin-treated patients [18-20, 24, 25]. Meta-analysis demonstrated that metformin treatment was associated with increased PFS compared with non-metformin treatment, and this difference was statistically significant (fixed-effects model, pooled HR=0.53, 95%CI=0.41-0.68, p<0.001; heterogeneity, I^2=0%, p=0.829) (Figure 2C). The estimated survival curve is shown in Figure 4(B). No evidence of publication bias was detected (Begg's test, p=0.806; Egger's test, p=0.978).

Effect of metformin on survival of diabetic NSCLC patients

Six studies on NSCLC provided data on OS [17, 18, 22-25]. Four studies reported that the OS of metformin-treated patients was significantly better than that of non-metformin-treated patients [17, 18, 22, 23], whereas the other study did not find a significant association [24, 25]. The pooled HR was 0.77 (95%CI=0.71-0.84 by fixed-effects model, p=0.002) [Figure 3(A)]. The estimated survival curve is shown in Figure 4(C). No significant evidence of heterogeneity was observed in these studies (I^2=24.1%, p=0.253), and no evidence of publication bias was detected (Begg's test, p=0.707; Egger's test, p=0.352).

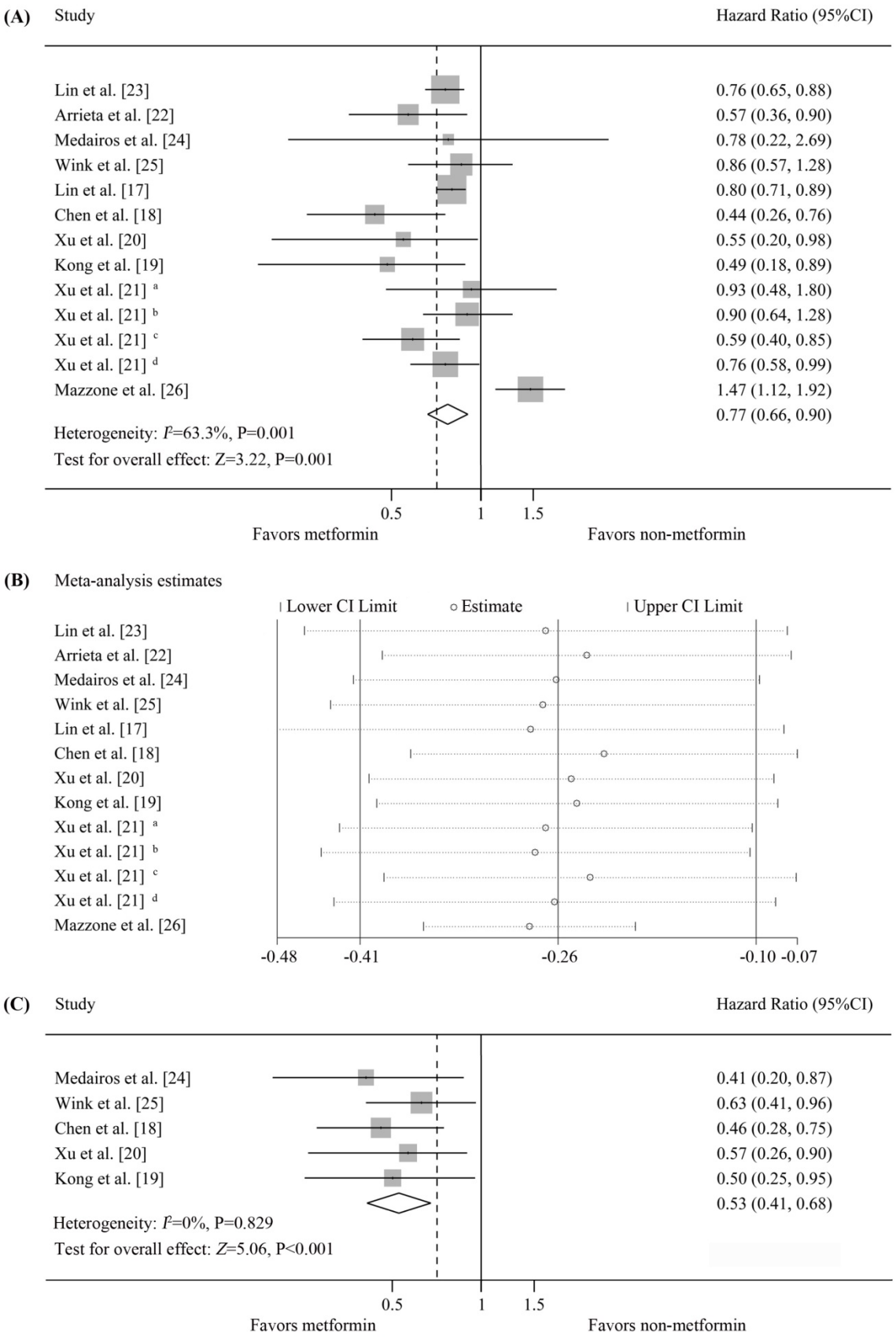

Figure 2. Survival of patients with lung cancer and diabetes who received metformin treatment *vs*. non-metformin treatment. (A) Forest plot of effects of metformin *vs*. non-metformin treatment on the overall survival of all diabetic patients with lung cancer; (B) Forest plot of sensitivity analysis for the heterogeneity of studies included in Figure 2(A); (C) Forest plot of effects of metformin *vs*. non-metformin treatment on the progression-free survival of all diabetic patients with lung cancer. Results from the Vanderbilt electronic health records system: [a] metformin *vs*. insulin, [b] metformin *vs*. other medications; results from the Mayo Clinic electronic health records system: [c] metformin *vs*. insulin, [d] metformin *vs*. other medications.

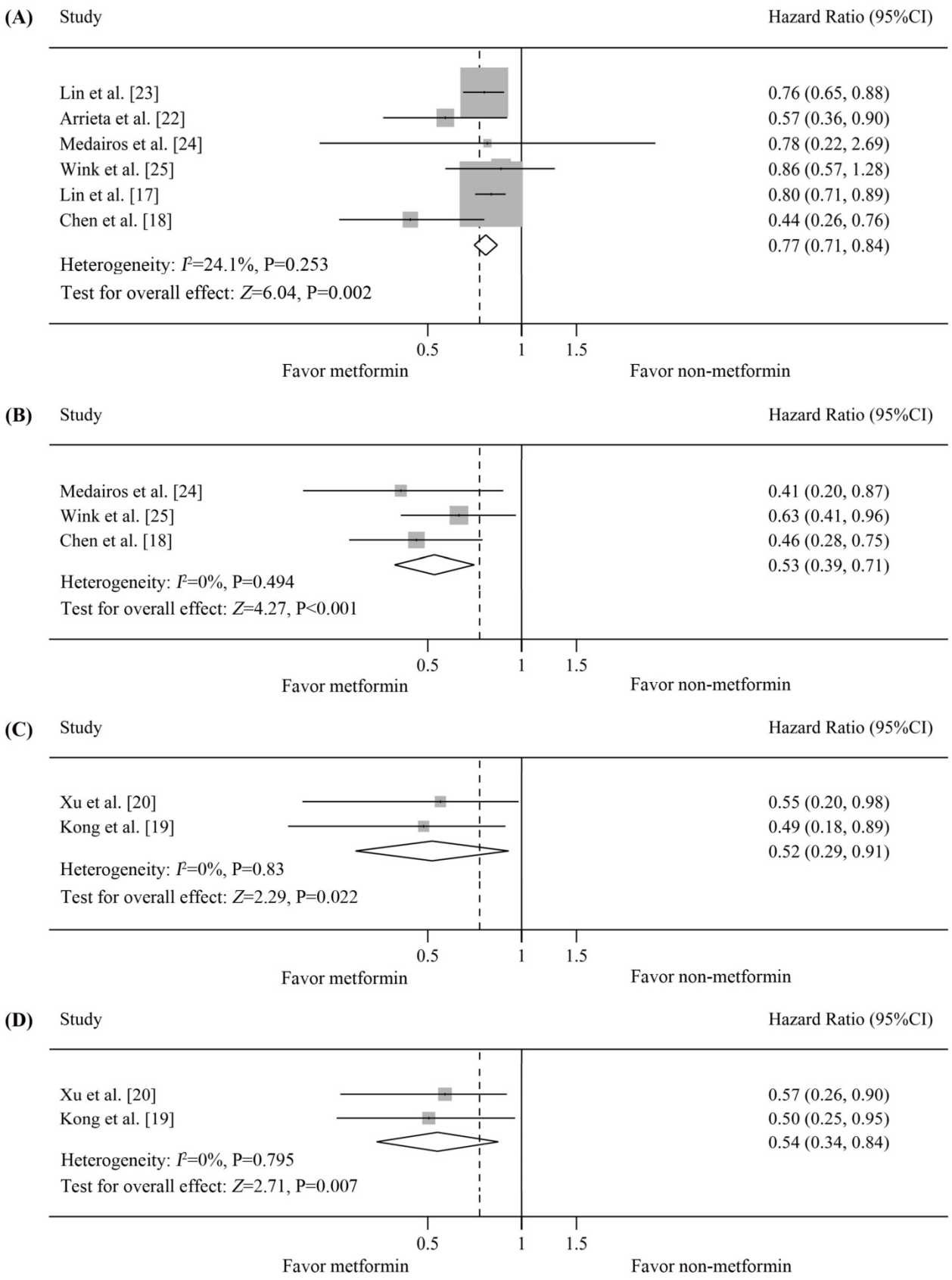

Figure 3. Subgroup analysis according to histological type of the survival of patients with lung cancer and diabetes who received metformin *vs.* non-metformin treatment. (A) Forest plot of effects of metformin *vs.* non-metformin treatment on the overall survival (OS) of diabetic patients with non-small cell lung cancer (NSCLC); (B) Forest plot of effects of metformin *vs.* non-metformin treatment on the progression-free survival (PFS) of diabetic patients with NSCLC; (C) Forest plot of effects of metformin *vs.* non-metformin treatment on the OS of diabetic patients with small cell lung cancer (SCLC); (D) Forest plot of effects of metformin *vs.* non-metformin treatment on the PFS of diabetic patients with SCLC.

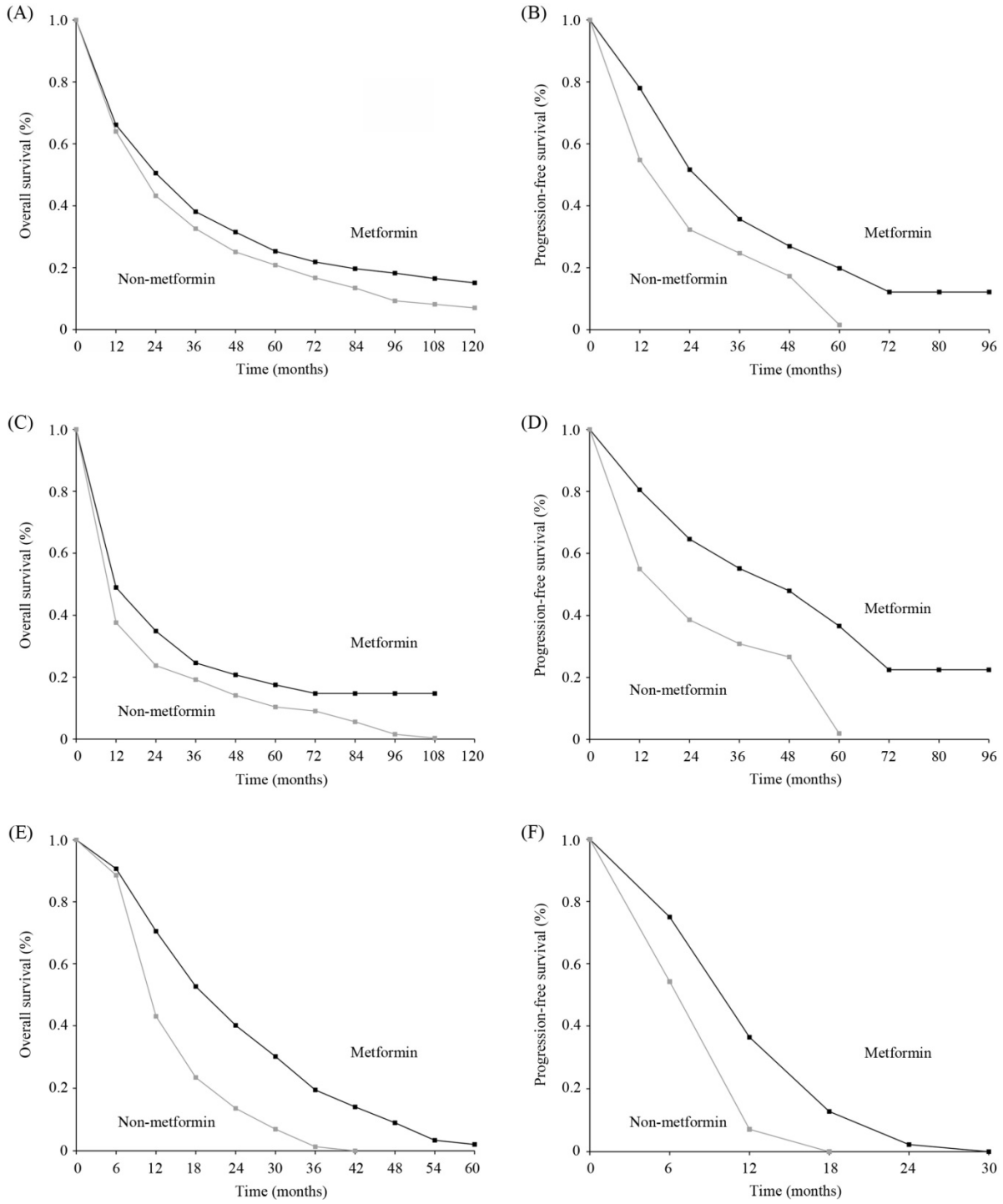

Figure 4. Estimated survival curves. (A) Overall survival (OS) curves for all diabetic patients with lung cancer; (B) Progression-free survival (PFS) curves for all diabetic patients with lung cancer; (C) OS curves for the diabetic patients with non-small cell lung cancer (NSCLC); (D) PFS curves for the diabetic patients with NSCLC; (E) OS curves for the diabetic patients with small cell lung cancer (SCLC); (F) PFS curves for the diabetic patients with SCLC.

PFS data for diabetic NSCLC patients were reported in 3 studies [18, 24, 25], all of which reported that the PFS of metformin-treated patients was significantly better than that of non-metformin-treated patients. Our analysis revealed that PFS was significantly prolonged in metformin-treated patients (pooled HR=0.53, 95%CI=0.39-0.71, p<0.001) [Figure 3(B)]. The estimated survival curve is shown in Figure 4(D). This analysis was based on a fixed-effects model because no evidence of heterogeneity was observed among the included studies (I^2=0%, p=0.494), and no evidence of publication bias was detected (Begg's test, p=0.602; Egger's test, p=0.884).

Effect of metformin on survival of diabetic SCLC patients

Two studies on SCLC in diabetic patients provided OS data, all of which reported a significant improvement in the OS of metformin-treated patients [19, 20]. The pooled HR was 0.52 (95%CI=0.29-0.91 by fixed-effects model, p=0.022) [Figure 3(C)]. The estimated survival curve is shown in Figure 4(E). No evidence of heterogeneity was observed among the data (I^2=0%, p=0.83), and the Begg's test results suggested no evidence of publication bias (p=0.317).

Data on PFS were available for 2 studies [19, 20], all of which reported that the PFS of metformin-treated patients was significantly better than that of non-metformin-treated patients. Our analysis revealed that metformin treatment yielded a significant improvement in PFS compared with non-metformin treatment (fixed-effects model, pooled HR=0.54, 95%CI=0.34-0.84, p=0.007; heterogeneity, I^2=0%, p=0.795) [Figure 3(D)]. The estimated survival curve is shown in Figure 4(F). Publication bias was not observed based on Begg's test (p=0.317).

Discussion

Since 2010, studies of the effects of metformin on cancer survival have increased considerably. Several previous studies have suggested that metformin might modulate the prognosis of diabetic cancer patients, as patients treated with metformin showed significantly better survival than those who received another anti-diabetic medication. Lin *et al.* have reported that metformin treatment improves the survival of diabetic patients with stage IV lung cancer [17], in line with the results of 5 retrospective cohort studies [18-20, 22, 23]. Nevertheless, another 2 recent studies have yielded negative results. Medairos *et al.* have found no evidence of an association between metformin use and OS in a cohort of 215 patients with diabetes and lung cancer [24]. In addition, Wink *et al.* have reported no difference in OS between metformin-treated and non-metformin-treated diabetic lung cancer patients receiving concurrent chemoradiotherapy [25]. Thus, it is important to perform pooled analysis to evaluate the effects of metformin treatment on the survival of diabetic patients with lung cancer to obtain more information for patient management.

Based on data from 10 studies, we demonstrated reductions of 21% and 47% in OS and PFS, respectively, in patients with lung cancer and diabetes who used metformin. In analysis stratified by histological type, we revealed that metformin treatment yielded a significant improvement in OS compared with other anti-diabetic medications in both NSCLC and SCLC. Metformin use was also associated with a significant improvement in PFS for both NSCLC and SCLC.

Notably, the study conducted by Mazzone *et al.* is the only one showing the reduced survival of diabetic lung cancer patients who received metformin [26]. Conversely, 6 other included studies provided evidence of a positive effect of metformin treatment on survival [17-20, 22, 23]. There are several possible reasons for these discrepant findings among studies. First, differences in adjustments for patient characteristics could have led to bias in the results among studies. Second, Mazzone *et al.* included diabetic lung cancer patients of all stages, and they did not control for differences in lung cancer treatments in their analyses. Moreover, the unknown and potential interactions between metformin and the different histological lung cancer subtypes could have influenced the clinical outcomes of these populations; these possibilities merit additional research.

In the present meta-analysis, the findings of Medairos *et al.* and Wink *et al.* suggested that the treatment of diabetic NSCLC patients with metformin was associated with improved PFS but that it had no effect on OS [24, 25]. To the best of our knowledge, preclinical studies have demonstrated that metformin may act by preventing progression; thus, simply comparing patients treated (or not) with metformin may not capture its effects. The examination of time-dependent cumulative variables for metformin exposure is important to further evaluate whether it influences the clinical outcomes of patients with cancer and diabetes [35]. Margel *et al.* have demonstrated that the cumulative duration of metformin treatment is associated with a significant improvement in the survival of diabetic prostate cancer patients [36]. In addition, Vissers *et al.* and Peeters *et al.* both have reported an improvement in the cancer-specific survival of diabetic breast cancer patients with cumulative metformin exposure [37, 38]. A longer follow-up duration and the assessment of time-dependent cumulative variables may be required to identify an association between metformin treatment and OS in diabetic lung cancer patients, especially for patients with early-stage disease. With regard to the relationship between dose-response and survival, Medairos *et al.* have demonstrated no evidence of a significant association between PFS and metformin use with increasing daily dosages [24]. Similar results have been reported in one colorectal cancer study [39]. To date, few studies have used dose-response variables for modeling metformin treatment; thus, further investigations are required to address this issue.

Cancer and diabetes are being diagnosed concurrently in individuals with increasing frequency

[4]. Studies have revealed that the relationship between cancer and metformin treatment is complex and that factors affecting one or more parts of the cancer signaling network could be associated with cancer mortality. In laboratory studies, metformin has been shown to inhibit cell proliferation, reduce colony formation, and cause partial cell cycle interruption in several cancer cell lines [40-42]. These studies have suggested that metformin-induced activation of AMPK pathways may inhibit downstream cellular growth and proliferation in tumor cells, at least by inhibiting protein synthesis to some extent [13, 40]. Metformin regulates the insulin level by ameliorating insulin sensitivity [1]. Additional *in vivo* studies have demonstrated that metformin exerts less anti-tumor activity in mice fed a control diet than in those fed a high-energy diet [43]. These findings suggest that the reduction in the endogenous insulin level by metformin may contribute to its anti-tumor activity [12]. Other *in vitro* studies have reported similar findings that metformin may kill cancer cells, reduce the cancer burden and enhance the effectiveness of breast cancer treatment [44-46]. Further, an observational study conducted by Jiralerspong *et al.* has reported increased pathologically complete responses of early-stage breast cancer patients undergoing neo-adjuvant therapy who had received metformin treatment compared with those who had received non-metformin treatment [47]. Based on the growing evidence of anti-cancer mechanisms of metformin reported in preclinical studies along with the results of retrospective analyses of the association between metformin and survival, metformin is considered a potential adjunctive cancer therapy [48].

Our meta-analysis has several limitations. First, the designs of the included retrospective studies differed, and the adjusted estimates used in these studies were not adjusted by the same variables. All of these factors could have caused heterogeneity among the studies. Although we applied a random-effects model that takes potential heterogeneity into consideration, careful interpretation of the heterogeneity is necessary. Second, the grouping of patients according to metformin/non-metformin treatment could be an oversimplified comparison. Most of the patients with lung cancer and diabetes received one or more glucose-lowering medications and other medications with dosage changes during the follow-up period. It is extremely difficult to evaluate the effects of intricate interactions among various medications on clinical outcomes.

Conclusions

In conclusion, our results provide an overview of recent evidence on the effects of metformin treatment in diabetic lung cancer patients, and they demonstrate a significant improvement in survival following metformin treatment. However, due to some limitations, our results should be interpreted cautiously. Further prospective, high-quality studies on the effects of metformin treatment in diabetic lung cancer patients must be conducted to confirm our findings.

Abbreviations

HR, hazard ratio; 95%CI, 95% confidence interval; OS, overall survival; PFS, progression-free survival; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor; PS, performance status; PET, positron emission tomography; NSE, neuronal specific enolase; LDH, lactate dehydrogenase; BMI, body mass index.

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Authors' contributions

Conception and design: XC, ZSW, and XW; Collection and assembly of data: All authors; Data analysis and interpretation: All authors; Manuscript writing: XC, ZSW, XDW, and XW; Final approval of manuscript: All authors.

Competing Interests

The authors have declared that no competing interest exists.

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