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Effect of hypoglycemic agents on survival outcomes of lung cancer patients with diabetes mellitus

A meta-analysis

Wen-Xiu Xin, PhD[a,b], Luo Fang, PhD[c], Qi-Lu Fang, MD[a], Xiao-Wei Zheng, MD[a], Hai-Ying Ding, MD[a], Ping Huang, PhD[a,b,*]

Abstract

Background: To assess the association between hypoglycemic agents and prognosis of lung cancer patients with diabetes.

Methods: A comprehensive literature search was performed in PubMed, Web of Science, Embase, and Cochrane Library until May 2017. The search yielded 2593 unique citations, of which 18 articles met inclusion criteria. The hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated by a fixed-effects or random-effects model.

Results: The pooled HRs favoring metformin users were 0.77 for overall survival (OS) (n = 15, 95% CI: 0.68–0.86) and 0.50 for disease-free survival (n = 5, 95% CI: 0.39–0.64). One study assessed the relationship between metformin and cancer-specific survival (CSS), reporting no significant results. No significant association between insulin and OS (n = 2, HR: 0.95, 95% CI: 0.79–1.13) or CSS (n = 2, HR: 1.03, 95% CI: 0.76–1.41) was noted. One study evaluated association of sulfonylureas with lung cancer survival and reported no clinical benefit (HR: 1.10, 95% CI: 0.87–1.40). One study reported no association of thiazolidinediones with lung cancer survival (HR: 1.04, 95% CI: 0.65–1.66).

Conclusions: This meta-analysis demonstrated that metformin exposure might improve survival outcomes in lung cancer patients with diabetes.

Abbreviations: AMPK = adenosine monophosphate-activated protein kinase, CI = confidence interval, CSS = cancer-specific survival, DFS = disease-free survival, DM = diabetes mellitus, EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor, HR = hazard ratio, LKB1 = liver kinase B1, NSCLC = nonsmall cell lung cancer, mTOR = mammalian target of rapamycin, OR = odds ratio, OS = overall survival, PPARγ = peroxisome proliferator-activated receptor gamma, RCT = randomized controlled trial, RR = relative risk, SCLC = small cell lung cancer, SUs = sulfonylureas, T2DM = type 2 diabetes mellitus, TZDs = thiazolidinediones.

Keywords: diabetes, hypoglycemic agents, lung cancer, meta-analysis, prognosis

1. Introduction

Lung cancer has become one of the leading causes of cancer-related mortality in numerous countries.[1] Despite advances in new techniques for detection, diagnosis, and treatment modalities, the overall 5-year survival rate is only about 15% and the prognosis of lung cancer remains poor.[2] Recent researches indicated that there was a close association between the diabetes and cancer. Diabetes is a prevalent metabolic disease worldwide. Approximately 8% to 18% of cancer patients are accompanied by diabetes mellitus (DM),[3] probably due to their increasing global prevalence and the shared risk factors between the diseases, such as cigarette smoking, greater body mass index, and the lack of exercise.[4] Recently, accumulating epidemiological and clinical evidence indicated that DM and insulin resistance predict poor prognosis in many types of cancers, including lung cancer.[5] Several biological mechanisms, including hyperglycemia, hyperinsulinemia, and inflammatory cytokines, might promote the initiation and progression of neoplasms and explain the plausible causal link between DM and cancers.[6,7] It is conceivable that without the influence of above pathophysiological factors, glucose-lowering drugs, such as insulin, insulin sensitizers and secretagoges, may influence the development of tumor.

Metformin has been reported to have anticancer effects by both insulin-dependent and insulin-independent mechanisms.[8] Insulin and sulfonylureas (SUs) can promote cell proliferation and oncogenesis.[9] Thiazolidinediones (TZDs), synthetic ligands of peroxisome proliferator-activated receptor gamma (PPARγ), inhibit cancer cell growth and induce apoptosis.[10–12] A number of epidemiological studies were conducted to investigate the association between antidiabetic agents (metformin, insulin, TZD, and SU) and prognosis of lung cancer. However, results of

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[a] Laboratory of Clinical Pharmacy, [b] Key Laboratory of Head and Neck Translational Research of Zhejiang Province, [c] Zhejiang Key Laboratory of Diagnosis and Treatment Technology on Thoracic Oncology (Lung and Esophagus), Zhejiang Cancer Hospital, Hangzhou, P.R. China.

[*] Correspondence: Ping Huang, Laboratory of Clinical Pharmacy, Zhejiang Cancer Hospital, Hangzhou, People's Republic of China (e-mail: huangpwly@sina.com).

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the association between hypoglycemic agents and lung cancer outcomes were often inconclusive and controversial.

The present meta-analysis of observational studies aimed to quantitatively summarize results to provide a more precise estimation of the association between antidiabetic treatment and clinical outcomes of lung cancer.

2. Materials and methods

2.1. Search strategy

Extensive literature search in PubMed, EMBASE, Web of Science, and The Cochrane Library from inception to 31 May 2017 was performed by 2 study investigators, independently for all the relevant studies addressing the association between the use of hypoglycemic agents and lung cancer. The keywords and/or corresponding Mesh terms were used for searching included: diabetes mellitus or diabetes or diabetic or antidiabetic drugs or hypoglycemic agents or antihyperglycemics; cancer or tumor or neoplasms or carcinoma or malignancy; and lung or pulmonary. All English-language articles were considered. In addition, references cited in the identified studies, recent review articles, meta-analysis, and other relevant studies were also scrutinized to identify potentially pertinent articles which possibly missed in the original search. Attempts were made to E-mail the corresponding authors to obtain additional information when the information was incomplete.

2.2. Selection criteria

Inclusion criteria of an qualified study in the meta-analysis were as follows: observational study that evaluates the relationship between the use of hypoglycemic agents and prognosis of lung cancer patients with DM; case–control study, cohort study, or population-based quasi-experimental study; the article must have reported sufficient information or platitudinous raw data to estimate a relative risk (RR) or equivalent (i.e., hazard ratio [HR], odds ratio [OR]) and their corresponding 95% confidence intervals (CIs). Considering that diabetes is one of the prognostic factors of lung cancer, we exclude nondiabetic patients. When >1 publication reported on the same study, only the publication with most complete dataset or reported recently was included.

2.3. Data extraction

Data extraction was performed in duplicate by 2 reviewers onto the inclusion criteria listed above from each published article. Disagreements between investigators for inclusion or exclusion were reconciled through group discussion. The following information was collected from the included studies: study title, the first author, study country/period, study design (prospective or retrospective cohort study, randomized controlled trial [RCT], or case–control study), lung cancer stage, lung cancer subtypes, sample size, interventions, length of follow-up, and outcomes. Outcomes included overall survival (OS), disease-free survival (DFS), cancer-specific survival (CSS), and adjusted HRs with their 95% CIs. The fully adjusted HR and their 95% CIs were used as a common measure of associations between hypoglycemic agents and lung cancer.

2.4. Quality assessment

The quality of observational studies was appraised in reference to the Newcastle–Ottawa Scale (NOS), which was recommended by the Cochrane Non-Randomized Studies Methods Working Group.[13] A "star system" was developed to judge the included studies on 3 aspects: the selection of the study groups, the comparability of studies groups, and the ascertainment of exposure or outcome.

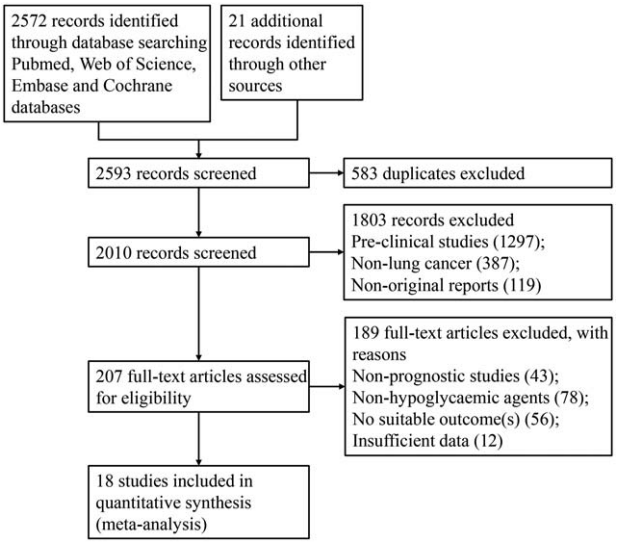

Figure 1. Flowchart the process of selecting the final 18 publications.

2.5. Statistical analyses

The I^2 statistics Higgins and Thompson and Q test were used to analyze heterogeneity across included studies.[14] I^2 values of >50% or Q test of $P<.01$ represented the presence of significant heterogeneity. A DerSimonian–Laird (D-L) random-effects model[15] was selected to calculate the pooled HRs for OS, DFS, and CSS and visualized in forest plots if I^2 values >50%. Otherwise, an inverse-variance fixed-effects model was used if Q test $P<.01$. The subgroup analysis by the potentially important factors, such as lung cancer subtypes, treatment strategy, study region, study design, and potential for immortal time bias, were further performed to examine the potential source of heterogeneity. The presence of publication bias for observational studies was determined using Begg's and Egger's ($P<.05$ indicated the presence of publication bias) regression methods and presented by a funnel plot.[16] Forest plots were distinguished according to first author's name and year of publication to illustrate the HRs with 95% CI. All effects analyses were conducted using Review Manager Version 5.3 software package (Oxford, United Kingdom) and Stata software (Stata Corp, College Station, TX).

3. Results

3.1. Literature search and study characteristics

Figure 1 shows the participant flowchart for the study inclusion in the meta-analysis. After the initial screening, we identified 2593 related publications. A total of 583 duplicates and 1992 irrelevant articles (preclinical studies, nonlung cancer, non-original reports, nonprognostic studies, nonhypoglycemic agents, no suitable outcomes, or no sufficient data) were identified based on titles, abstract, or full-text. Finally, 18 studies,[17–34] including 1 abstract article[22], 14 full-text articles, 2 case–control studies,[18,30] and 16 cohort studies[17,19–29,31–34], were included. Most of the studies were published in recent 5 years. Eight studies

were conducted in the USA,[18–21,27,30,33,34] 5 in China,[23–26,31] 2 in the UK,[17,28] 1 in Germany[29], 1 in Mexico,[32] and 1 in Romania[22]. Of the 18 articles, 10 publications focused on nonsmall cell lung cancer (NSCLC),[19–21,23,25,27,29,32–34] 2 on small cell lung cancer (SCLC),[26,31] 2 on mixed cancers including both NSCLC and SCLC,[18,28] 4 with unavailable information concerned.[17,22,24,30] The sample size of the studies varied from 36 to 7345. Detailed descriptive data for studies included in this meta-analysis are presented in Table 1.

3.2. Quality assessment of included studies

The NOS statement was used to assess quality of the 18 included studies as shown in Tables 2 and 3. Hypoglycemics exposure assessment varied widely between ever use versus never use, use before or after diagnosis of lung cancer, or time-varying methods. The control group consisted of group not prescribed 1 kind of hypoglycemics but who might have had other kinds of antidiabetic medications. Except 2 case–control studies,[18,30] the other 15 studies used a retrospective cohort design.[17,19–27] Two studies applied hospital-based cohort[25,31] and the others used population-based cohort.[17,19–24,26–29,32–34] Six studies identified the diagnosis of DM or metformin exposure through electronic medical records,[17,20,22,27,28,30] while other studies through interview, registry data, or standardized questionnaires.[18,19,21,23–26,29,31–34] Sixteen studies mentioned the ascertainment of lung cancer via medical records and biopsy-proven lung cancer diagnosis, the rest 2 studies[22,24] were database-driven studies. Data for study were collected from database that contains detailed information. The number of stars ranged from 6 to 9, which showed a high quality of all the eligible studies.

3.3. Metformin exposure and lung cancer outcomes

As summarized in Figure 2A, a pooled estimate of OS demonstrated that metformin exposure in lung cancer patients with diabetes was significantly associated with a 23% decreased risk of all-cause mortality (n = 15, HR: 0.77, 95% CI: 0.68–0.86 by random-effects model). The I^2 statistics and Q test indicated a considerable interstudy heterogeneity ($P < .0001$ for heterogeneity, $I^2 = 70\%$). Considering significant interstudy heterogeneity, studies were further stratified to evaluate HRs of OS by lung cancer subtypes (NSCLC, SCLC, or nondivided subtypes), intervention (chemotherapy or chemoradiation), study region (Asian or Western countries), study design (cohort or case–control study), and potential for immortal time bias (with or without). In all but chemoradiation subgroup, case–control study subgroup, and subgroup with immortal time bias, metformin was still associated with a survival benefit in lung cancer patients. Detailed descriptive data for subgroup analyses of OS of lung cancer are all presented in Table 4.

As summarized in Figure 2B, 5 studies reported adjusted HRs of DFS by metformin use in lung cancer patients with diabetes. In the pooled analyses of the 5 studies, results showed that metformin was significantly associated with a decreased risk of progression or recurrence in lung cancer patients with diabetes compared to nonmetformin users (n = 5, HR: 0.50, 95% CI: 0.39–0.64 by fixed-effect model, $P = .95$ for heterogeneity, $I^2 = 0\%$) without significant heterogeneity. Subgroup analyses based on lung cancer subtypes, treatment strategy, study region, and study design were also performed. In all subgroups, metformin was still associated with an improved DFS in lung cancer patients. Detailed descriptive data for subgroup analyses of DFS of lung cancer are all presented in Table 4.

Among the 18 selected studies, only 1 study carried by Menamin et al[28] examined the association between metformin exposure and lung CSS. In this population-based cohort study, metformin exposure had no association with lung cancer-specific mortality (HR: 0.86, 95% CI: 0.68–1.09).

3.4. Insulin exposure and lung cancer outcomes

Among the 18 selected studies, 2 studies carried by Lin et al[27] and Tseng[24] investigated the prognostic association between insulin exposure and OS of lung cancer patients. In pooled analyses, no effect of insulin use on OS was found in lung cancer patients with diabetes (HR: 0.95, 95% CI: 0.79–1.13 by the fixed-effects model, $P = .72$ for heterogeneity, $I^2 = 0\%$). Two studies[22,28] also reported the association between insulin exposure and CSS of lung cancer. Insulin exposure was also not associated with CSS in lung cancer patients with diabetes on meta-analysis of 2 observational studies (HR: 1.03, 95% CI: 0.76–1.41 by the fixed-effects model, $P = .41$ for heterogeneity, $I^2 = 0\%$) (Fig. 3).

3.5. TZD exposure and lung cancer outcomes

Only 1 study carried by Mazzone et al[18] reported the association between TZD exposure and survival of lung cancer. In this case–control study, no association was found between TZD exposure and risk of lung cancer death (HR: 1.04, 95% CI: 0.65–1.66).

3.6. SUs exposure and lung cancer outcomes

Only 1 study carried by Menamin et al[28] reported the association between SUs exposure and lung CSS. In this cohort study, no association was found between SUs exposure and lung cancer-specific mortality (HR: 1.04, 95% CI: 0.65–1.66).

3.7. Sensitivity analyses and publication bias

Strong heterogeneity ($P < .0001$ for heterogeneity, $I^2 = 70\%$) was observed among the 12 studies on metformin exposure and lung cancer overall mortality. The interstudy heterogeneity may be due to the 2 case–control studies by Xu et al[30] and Mazzone et al[18]. After exclusion of the 2 studies, the corresponding pooled HRs were not changed substantially (HR: 0.82, 95% CI: 0.79–0.86, $P = .01$ for heterogeneity; $I^2 = 49\%$). Sensitivity analyses were performed by sequential omission of each individual studies in the meta-analysis to examine the influence of single dataset on the pooled HRs. The 95% CI of remaining pooled HRs is always <1 when exclude 1 specific study, which means no individual study significantly influenced the pooled HR, indicating a significant association of metformin exposure and OS benefit. Also, the corresponding pooled HRs were not essentially affected in the sensitivity analyses about the effect of metformin on DFS in lung cancer patients with diabetes.

Considering the large variations in the quantitative analyses between metformin use and OS of lung cancer, we performed Egger's test and Begg's funnel plot to evaluate the publication bias. The shapes of the Begg's funnel plot showed some asymmetry qualitatively, yet the quantitative results of Egger's test did not show the evidence of any publication bias ($P = .14$ for metformin on OS) (Fig. 4A). Reasons for asymmetry are hard to define if the included studies are insufficient. Egger's test was not performed since only 5 studies were included when evaluating

Table 1

Baseline characteristics of the eligible studies included in the meta-analysis.

Study, year	Country	Region	Design	Inclusion time	Sample size number	Metformin exposure	Median age, years	Subtype	Cancer ascertainment	Diabetes	Stage	Treatment	Follow-up, months
Ahmed et al, 2015[19]	USA	Western	Cohort	1999–2013	40	Concurrent use during chemoradiation	70.5	NSCLC	Histology Cytology	Diabetes Nondiabetes	I–IV	Chemoradiation	17
Arrieta et al, 2016[32]	Mexico	Western	Cohort	2008–2014	1106	Before diagnosis with NSCLC	61	NSCLC	Medical record	Diabetes Non-diabetes	II–IV	Chemotherapy Targeted therapy	10.8
Chen et al, 2015[25]	China	Asian	Cohort	2006–2014	90	Before the initiation of EGFR-TKI therapy,	64.1	NSCLC	Histology Cytology	Diabetes	III,IV	EGFR–TKI	–
Currie et al, 2012[17]	UK	Western	Cohort	1990–2009	7345	Immediately before cancer diagnosis ≤3 months after cancer diagnosis	71.7	Nondivided	Medical record	Type 1 Type 2	–	–	19.2
Dhillon et al, 2014[20]	USA	Western	Cohort	2002–2011	71	–	–	NSCLC	Pathology	Diabetes Nondiabetes	I	Surgery	44
Fortune et al, 2014[21]	USA	Western	Cohort	2001–2008	5365	–	–	NSCLC	Medical record	Type 2	I–IV	–	–
Kong et l, 2015[26]	China	Asian	Cohort	2001–2011	259	–	–	SCLC	Pathology	Diabetes	–	Chemotherapy	68
Lin et al, 2015[27]	USA	Western	Cohort	2007–2009	750	≤ 6 months before cancer diagnosis	72.5		Histology	Diabetes	IV	Comprehensive	–
Lin et al, 2017[33]	USA	Western	Cohort	2002–2007	636	After NSCLC diagnosis	–	NSCLC	Pathology	Type 2	I–IV	–	14.6
Ioacara et al, 2014[22]	Romania	Western	Cohort	2001–2008	36	–	62	Nondivided	Database	Diabetes	–	–	56.4
Mazzone et al, 2012[18]	USA	Western	C-C	2001–2011	522	Before lung cancer diagnosis	56.2	NSCLC SCLC	Medical record	Diabetes	–	–	–
Medairos et al, 2016[34]	USA	Western	Cohort	2004–2013	215	Within 6 months before the surgical resection		NSCLC	Histology	Type 2	I, II	Surgery	19.5
Menamin et al, 2016[28]	UK	Western	Cohort	1998–2009	1883	Postdiagnosis	–	NSCLC SCLC	Medical record	Type 2	–	Comprehensive	–
Tan et al, 2011[23]	China	Asian	Cohort	2004–2009	99	During first-line chemotherapy and before disease progression	62.6	NSCLC	Medical record	Diabetes	II–IV	Chemotherapy	–
Tseng, 2013[24]	China	Asian	Cohort	1995–2006	–	Before diagnosis	–	Nondivided	Database	Diabetes	–	–	
Wink et al, 2016[29]	Germany	Western	Cohort	2008–2013	682	During the course of radiotherapy	63	NSCLC	Pathology	Diabetes	II–III	Chemoradiation	30
Xu et al, 2015[31]	China	Asian	Cohort	2000–2010	79	Before and after diagnosis of SCLC	63	SCLC	Pathology	Diabetes	–	Chemotherapy	65
Xu et al, 2015[30]	USA	Western	C-C	1995–2010	725	After their cancer diagnosis	65	Nondivided	Medical record	Diabetes	–	–	–

C-C = case–control, EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor, NSCLC = nonsmall cell lung cancer, SCLC = small cell lung cancer; –, none reported.

Table 2

Methodological quality assessment of the 16 cohort studies included in this meta-analysis appraised in reference to the NOS for cohort studies.

		Selection (max:*)				Comparability (max:**)		Outcome (max:*)			
Study, year (cohort studies)	Country	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analyses		Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Scores
Ahmed et al, 2015[19]	USA	*	*	*		*		*	*	*	7
Arrieta et al, 2016[32]	Mexico	*	*	*		*	*	*	*	*	8
Chen et al, 2015[25]	China	*	*	*	*	*	*	*	*	*	9
Currie et al, 2012[17]	UK	*	*	*		*	*	*	*		7
Dhillon et al, 2014[20]	USA	*	*			*	*	*	*		6
Fortune et al, 2014[21]	USA	*	*			*	*	*	*		6
Kong et al, 2015[26]	China	*	*			*	*	*	*	*	6
Lin et al, 2015[27]	USA	*	*	*		*	*	*	*	*	7
Lin et al, 2017[33]	USA	*	*	*		*	*	*	*	*	8
Ioacara et al, 2014[22]	Romania	*	*	*		*	*	*	*		6
Medairos et al, 2016[34]	USA	*	*	*		*	*	*	*	*	8
Menamin et al, 2016[28]	UK	*	*		*	*	*	*	*		7
Tan et al, 2011[23]	China	*	*	*	*	*		*	*		7
Tseng, 2013[24]	China	*	*		*	*	*	*		*	7
Wink et al, 2016[29]	Germany	*	*	*		*	*	*	*		7
Xu et al, 2015[31]	China	*	*	*	*	*		*	*	*	8

Each asterisk (*) indicates 1 point on the NOS.
NOS = Newcastle–Ottawa scale.

Table 3

Methodological quality assessment of 2 case–control studies included in this meta-analysis appraised in reference to the NOS for case–control studies.

		Selection (max:*)				Comparability (max:**)	Exposure (max:*)			
Study, year (case–control studies)	Country	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analyses	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate	Scores
Mazzone et al, 2012[18]	USA	*	*		*	*	*	*		6
Xu et al, 2015[30]	USA	*	*			*	*	*		6

Each asterisk (*) indicates 1 point on the NOS.
NOS = Newcastle–Ottawa Scale.

DFS. The shapes of funnel plot did not show obvious asymmetry for DFS qualitatively (Fig. 4B).

4. Discussion

In this meta-analysis, we sought to comprehensively investigate the association of hypoglycemic drugs exposure with clinical outcomes in patients with concurrent lung cancer and diabetes. This meta-analysis demonstrated that metformin treatment in lung cancer patients with diabetes was significantly associated with a 23% increased OS compared with nonmetformin users. Furthermore, our results show that metformin exposure may improve the DFS by 50% compared with those who did not use metformin. However, no association was found between other antidiabetic treatment (insulin, TZDs, and SUs) and prognosis of lung cancer.

Metformin, the first-choice glucose-lowering drug for the treatment of T2DM, has been found to suppress the progression of lung cancer through modifying the expression of proto-oncogenes and tumor suppressor genes in basic studies.[35] The exact antitumor mechanism of metformin is complex and unclear now.[36] Most widely accepted mechanisms now are insulin-dependent and insulin-independent mechanisms. Furthermore, metformin can regulate energy metabolism, protein synthesis, and lipid synthesis via initiating the pivotal liver kinase B1/adenosine monophosphate-activated protein kinase/mammalian target of rapamycin axis, leading to inhibition of the proliferation of cancer cell lines.[36] Although massive experimental evidences have confirmed the effect of metformin on both cancer treatment and chemoprevention,[25,37] clinical events are more complex and epidemiological researches are inconsistent. Several epidemiological studies reported that metformin use among diabetic patients improved the OS of lung cancer patients,[27,31] whereas others showed no statistically significant differences in survival.[19,29] Tian et al[38] recently reported a meta-analysis of metformin and survival outcomes of lung cancer patients with T2DM, the meta-analysis included 6 studies, and the pooled HR of OS was 0.90 (95% CI: 0.84–0.96, $P = .003$), indicating a good prognosis of metformin for lung cancers with T2DM. Since the more recent retrieval time, more retrieval databases, and more inclusive search criteria, our meta-analysis including more studies found that metformin was associated with a 22% reduced risk of all-cause mortality and an increased DFS benefit by 50% in lung cancer patients with DM. The pooled HRs showed that metformin exposure may be associated with a good prognosis in lung cancer patients with diabetes. Furthermore, this study assessed the effect of all class of hypoglycemic agents, including metformin, insulin, SUs, and TZDs, on the prognosis of lung cancer in patients with diabetes, rather than exploring the effect of a single class of hypoglycemic agents.

The survival association between metformin and lung cancer was further tested through various subgroups such as lung cancer subtypes, treatment strategy, study region, and study design. Subgroup analyses stratified by treatment strategy suggested that a good prognosis between metformin and lung cancer potentially might benefit from chemotherapy patients, not chemoradiation patients. In the subgroup analyses stratified by study region, survival benefit was found in both Asian and Western countries, while a decreased risk of progression or recurrence was only found in Asian countries. Subgroup analysis according to study design revealed that good prognosis can only benefit from cohort studies, not from case–control studies. Details of metformin exposure assessment were not presented in studies by Dhillon

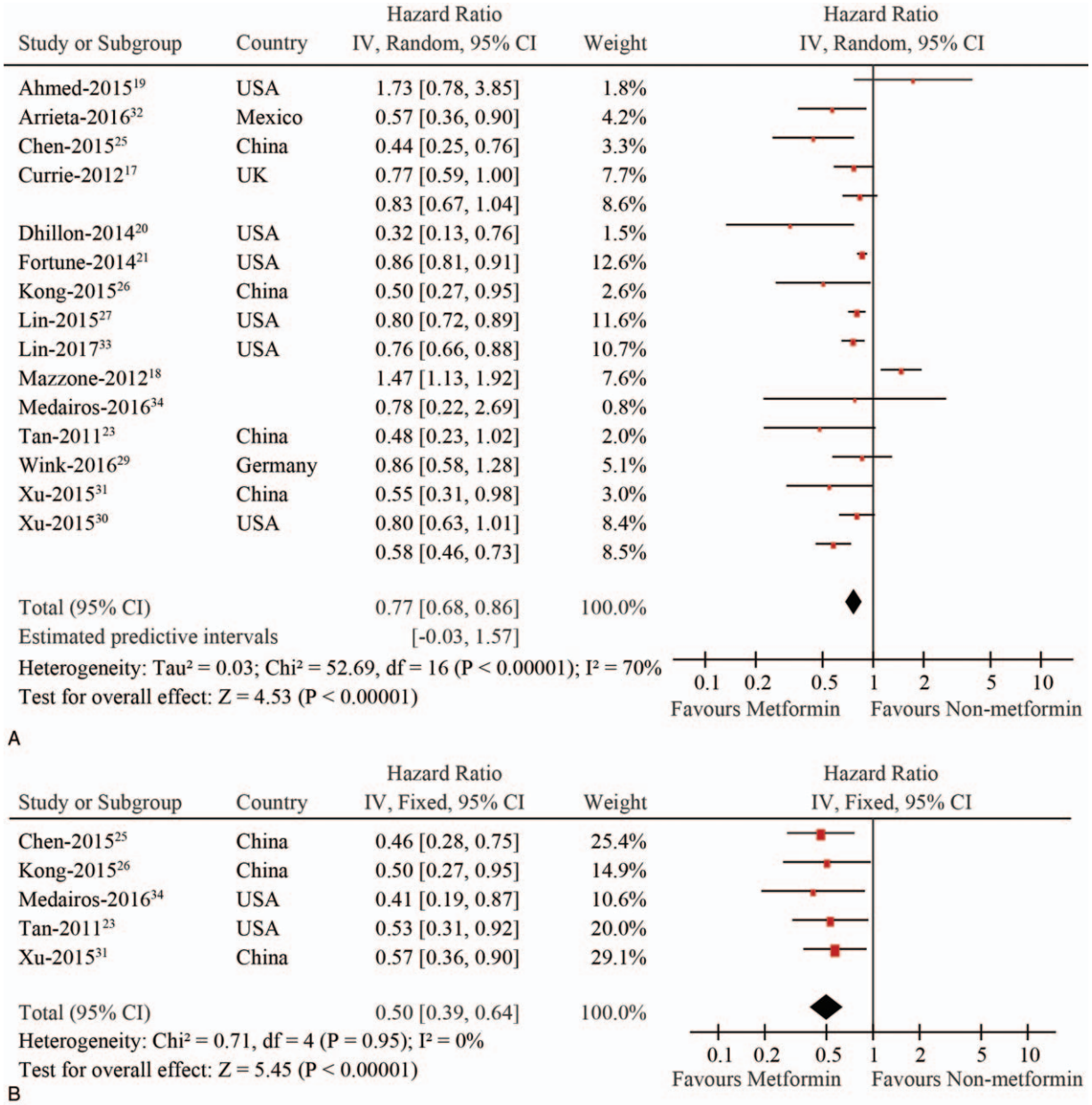

Figure 2. Forest plots on the association of metformin use with survival outcomes for patients with lung cancer: (A) OS; (B) DFS. DFS = disease-free survival, OS = overall survival.

et al[20], Fortune-Greeley et al,[21] and Kong et al[26], the definition of metformin exposure is unclear in the study by Tan et al[23], and metformin use after cancer diagnosis in the studies by Lin et al[33], Currie et al,[17] and Xu et al[30,31], perhaps these studies were prone to immortal time bias. In this meta-analysis, we calculated pooled HRs for OS and DFS after excluding studies deemed to be prone to immortal time bias. After excluding, metformin was still associated with an improved DFS (HR: 0.44, 95% CI: 0.29–0.67, $I^2 = 0\%$), but not associated with an improved OS (HR: 0.85, 95% CI: 0.67–1.09, $I^2 = 76\%$) and the heterogeneity remains, indicating that immortal time bias is not the main source of consistency. The source of heterogeneity was still not well explained even using multiple prespecified criteria for subgroup analysis.

Insulin and SUs can promote oncogenesis by increasing insulin-like growth factor-1 activity and insulin secretion, leading to abnormal stimulation of multiple cellular signaling cascades, strengthening growth factor-dependent cell proliferation, and influencing cell metabolism[9,39]. Our overall evidence did not indicate any relevant role of insulin use in lung cancer outcomes. Likewise, no relevance was found between SUs exposure and lung cancer-specific mortality according to study carried by Menamin et al[28].

TZDs, synthetic ligands of PPARγ, improve metabolic control in patients with T2DM through the improvement of insulin sensitivity. TZDs showed an anticancer effect both in preclinical studies[40] and in some clinical trials.[41] A case–control study carried by Mazzone et al[18] found no association between TZDs exposure and OS in lung cancer patients with T2DM.

Table 4

Meta-analysis results of the associations between hypoglycemic agents use and clinical outcomes in lung cancer patients with diabetes.

Hypoglycemic agents	Subgroup		N	HR (95% CI)	*P* values	Test for heterogeneity		
						χ^2	P_h	I^2
Metformin	Overall (OS)		15	0.77 (0.68, 0.86)	<.0001	52.69	<.0001	70%
	Cancer subtypes	NSCLC	9	0.73 (0.61, 0.87)	.0006	20.61	.008	61%
			2	0.53 (0.34, 0.81)	.003	0.04	>.85	0%
		SCLC						
	Treatment strategy	Chemotherapy	5	0.51 (0.40, 0.66)	<.0001	0.59	.96	0%
		Chemoradiation	2	1.12 (0.58, 2.16)	.75	2.35	.13	57%
	Study region	Asian	4	0.49 (0.36, 0.67)	<.0001	0.31	.96	0%
		Western	11	0.81 (0.72, 0.91)	.0003	41.26	<.0001	71%
	Study design	Cohort	13	0.82 (0.79, 0.86)	<.0001	25.62	.02	49%
		C-C	2	0.88 (0.52, 1.47)	.62	27.00	<.0001	93%
	ITB	Without potential ITB	8	0.85 (0.67, 1.09)	.21	28.97	.0001	76%
		With potential ITB	8	0.71 (0.61, 0.82)	<.0001	23.32	.003	66%
	Overall (DFS)		5	0.50 (0.39, 0.64)	<.0001	0.71	.95	0%
	Cancer subtypes	NSCLC	3	0.47 (0.34, 0.66)	<.0001	0.31	.86	0%
		SCLC	2	0.55 (0.38, 0.79)	.001	0.09	.77	0%
	Treatment strategy	Chemotherapy	5	0.50 (0.39, 0.64)	<.0001	0.71	.95	0%
		Chemoradiation	0	–	–	–	–	–
	Study region	Asian	4	0.55 (0.40, 0.67)	<.0001	0.40	.94	0%
		Western	1	0.41 (0.19, 0.87)	–	–	–	–
	Study design	Cohort	5	0.50 (0.39, 0.64)	<.0001	0.71	.95	0%
		C-C	0	–	–	–	–	–
	ITB	Without potential ITB	2	0.44 (0.29, 0.67)	<.0001	0.06	.80	0%
		With potential ITB	3	0.54 (0.40, 0.74)	<.0001	0.10	.95	0%
	Overall (CSS)		1	0.86 (0.68, 1.09)	.21	–	–	–
Insulin	Overall (OS)		2	0.95 (0.79, 1.13)	.57	0.13	.72	0%
	Overall (CSS)		2	1.03 (0.76, 1.41)	.83	0.69	.41	0%
SUs	Overall (CSS)		1	1.10 (0.87, 1.40)	.41	–	–	–
TZDs	Overall (OS)		1	1.04 (0.65, 1.66)	.87	–	–	–

95% CI = 95% confidence interval, C-C = case–control, CSS = cancer-specific survival, DFS = disease-free survival, HR = hazard ratio, ITB = immortal time bias, N = number of studies, NSCLC = nonsmall cell lung cancer, OS = overall survival, P_h = *P* value of the *Q* test for heterogeneity, SCLC = small cell lung cancer.

The strengths of this study include our efforts to provide an accurate and comprehensive analysis. Second, based on the NOS, all the included studies in this meta-analysis were of high quality with stars ranged from 6 to 9. Third, we performed methodological sensitivity analysis and found that no single study significantly influenced the pooled HRs since the 95% CI of pooled HRs is always <1 when randomly exclude 1 study in this meta-analysis, which further demonstrated robustness of this

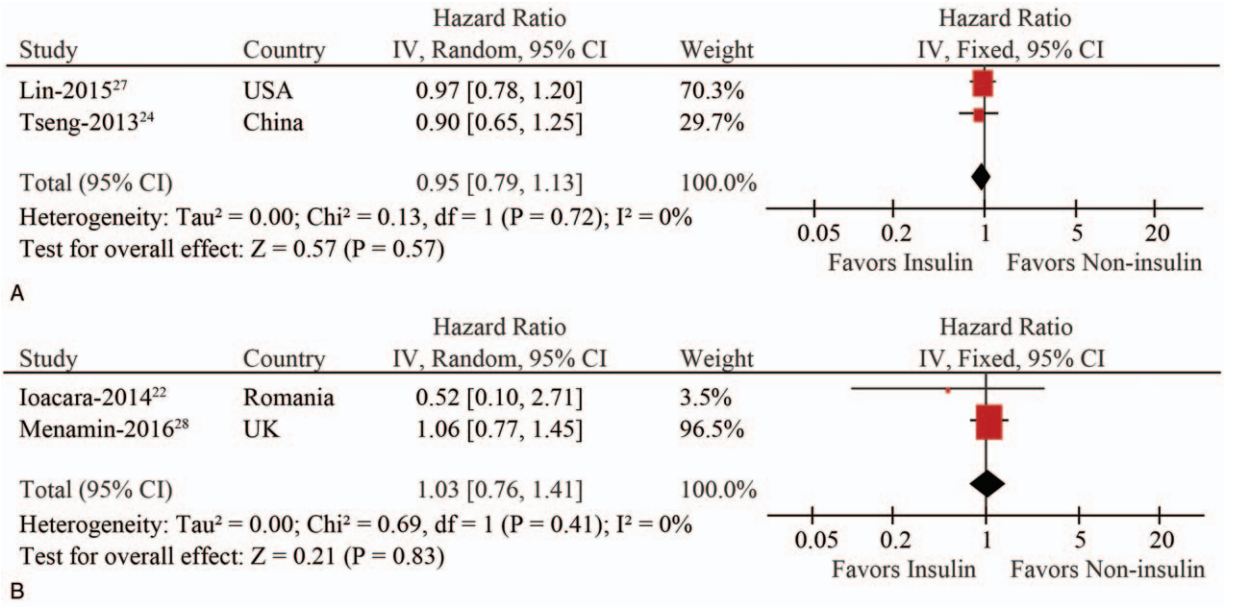

Figure 3. Forest plots on the association of insulin use with survival outcomes for patients with lung cancer: (A) OS; (B) CSS. CSS = cancer-specific survival, OS = overall survival.

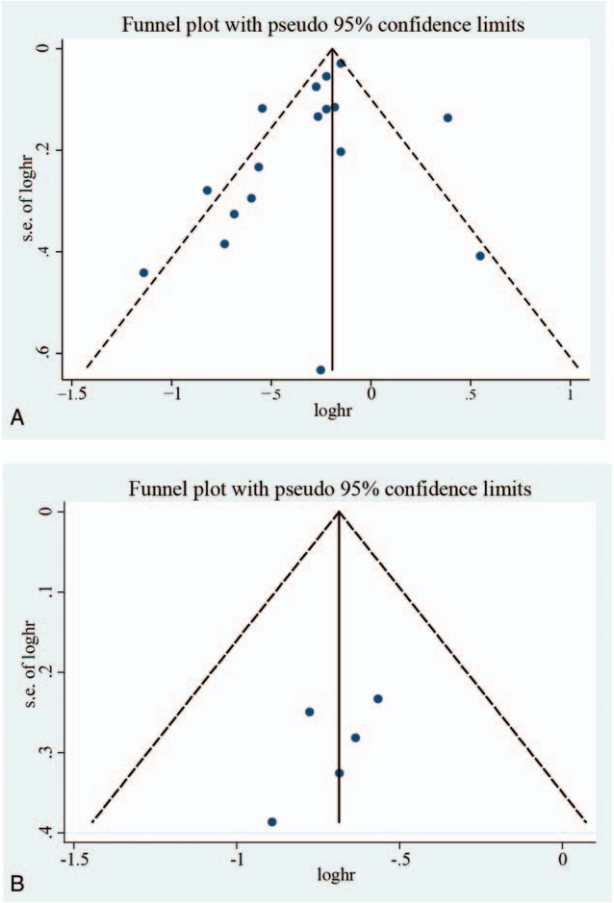

Figure 4. Funnel plot analyses for publication bias: (A) OS; (B) DFS. DFS = disease-free survival, OS = overall survival.

meta-analysis, but nevertheless the clinical heterogeneity in this meta-analysis must be considered in the interpretation. A sensitivity analysis, in which we only included studies restricted to cohort studies, yielded results similar to including all studies. It is important to realize that region, control selection, study design, reference therapy, and study quality were heterogeneous, and the sensitivity of metformin may vary. Finally, concerning publication bias, both qualitative analysis by Begg's test and quantitative analysis by Egger test showed no major bias. We excluded animal studies and in-vitro studies as these studies cannot be generalized to all patients with lung cancer, and may have a potential for selection bias. However, there is a possibility of selection bias in meta-analysis because of nonrandom allocation of metformin to patients with diabetes.

There are several limitations of this present meta-analysis. First, studies included in this meta-analysis are mainly retrospective cohort studies and case–control studies. No RCT or prospective studies was included, which weakened the reliability of evidence. Second, high I^2 indicated high clinical heterogeneity among the eligible studies for OS, which were actualized in a mixture of populations with diverse background therapies and varying inclusion criteria, study population, and adjustment. Third, some of the studies did not report cancer subtype, stage, types of anticancer treatment used, and their effects on outcomes. Finally, the classification of patients based on exposure and nonexposure of metformin in the included studies may be too simple. Most patients with diabetes may use a variety of antidiabetic drugs, with changes in pharmacotherapy over time, which may influence the outcomes.

5. Conclusion

In conclusion, based on the results of this current meta-analysis, metformin exposure seemed to be associated with an improved OS and DFS in lung cancer in patients with diabetic. However, insulin, SUs, and TZDs did not show significant association with lung cancer outcomes. Considering the high heterogeneity across the including studies, high-quality, well-designed, and prospective studies would be required to better understand the association between glucose-lowing drugs and clinical outcome of lung cancer.

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