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Review Article

The Effect of Diabetes Mellitus on Prognosis of Patients with Non-Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis

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Purpose: To quantitatively evaluate the effect of preexisting diabetes mellitus (DM) on the outcomes of patients with non-small-cell lung cancer (NSCLC).
Materials and Methods: Observational studies comparing the prognosis of NSCLC patients with and without diabetes were identified from PubMed, EMBASE, and The Cochrane Central Register of Controlled Trials (CENTRAL). We searched for studies that published in English from inception to March 30, 2019, using search terms related to diabetes and NSCLC. Pooled hazard ratio (HR) and 95% confidence interval (CI) were calculated by a random-effect model and subgroup analyses were performed.
Results: In all, 17 of 1475 identified studies were finally included in the meta-analysis. The result revealed that preexisting diabetes had a significantly negative impact on the overall survival (OS) of patients with NSCLC (HR: 1.31, 95% CI: 1.12–1.54), especially in patients undergoing surgical treatment (HR: 1.46, 95% CI: 1.02–2.09) in comparison with those receiving only non-surgical treatment (HR: 1.33, 95% CI: 0.87–2.03). In addition, preexisting diabetes was more likely to be associated with a worse prognosis among Asian NSCLC patients than Western patients. Sensitivity analysis indicated that the main result was robust, and no evidence of publication bias was found.
Conclusion: Preexisting DM has a negative impact on diabetic NSCLC patients' prognosis.

Keywords: diabetes mellitus, lung cancer, meta-analysis, prognosis

Introduction

Cancer incidence and mortality are rapidly growing worldwide, and lung cancer remains the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.6% of the total cancer deaths in both sexes combined).[1] In China, by 2014 , the incidence rate of lung cancer was approximately 36.5×10^{-5}, of which non-small-cell lung cancer (NSCLC) accounted the most.[2] Over the past 20 years, progress has been substantial and promising with the advent of various targeted therapy and the effective application of immunotherapy in some population with advanced NSCLC, such as the favorable achievement made in the area of Programmed cell death protein-1 (PD-1) and Programmed cell death legand-1 (PD-L1).[3] However, major challenge remains and the prognosis of NSCLC is still unsatisfactory; thus, a further investigation of the relevant factors affecting NSCLC prognosis is warranted. Recent research implied that comorbidities represented an important contributing

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factor to the poor overall prognosis observed in NSCLC patients, and optimized management of coexisting disease would help improve the outcomes remarkably.[4] As one of the most common chronic conditions, diabetes was considered to have potential complex interactions with NSCLC.[5] In 2017, it was estimated that there were about 451 million people with diabetes worldwide,[6] and about 8.7% of NSCLC patients were accompanied by diabetes mellitus (DM).[4] Accumulating epidemiological evidence demonstrated that there was a close link between diabetes and several types of cancer, such as endometrial, breast cancer, and prostate cancer.[7–9] Although a recent meta-analysis indicated that DM was an independent unfavorable prognostic factor for patients with surgically treated NSCLC compared with their non-diabetic counterparts,[10] no high-quality systematic review has been conducted recently to test how DM affected NSCLC patients in all stages, since numerous patients with advanced NSCLC were not eligible for surgical treatment. Large amount of relevant studies was published recently, and inconsistent conclusion existed. Therefore, we conducted this systematic review and meta-analysis of observational studies to quantitively evaluate the effect of preexisting diabetes on the outcomes of patients with NSCLC.

Materials and Methods

Search strategy

We have registered our study on Prospero and the registration number is CRD42019123966. Eligible observational studies that compared the prognosis of NSCLC patients with diabetes and their non-diabetic counterparts were identified from PubMed (Medline), EMBASE, and The Cochrane Central Register of Controlled Trials (CENTRAL). We searched for human studies that published in English from inception to March 30, 2019, using the keywords and/or corresponding Mesh terms including the following: diabetes mellitus or diabetes or diabetic or hyperglycemia, NSCLC or non-small-cell lung cancer. And the reference lists of eligible literatures were also checked for additional information and data, in order to guarantee a systematic research.

Study selection

Titles and/or abstracts of studies retrieved from the databases mentioned above and those from additional sources like reference lists were screened independently by two reviewers to identify the literatures potentially meeting the inclusion criteria. Our overall search target met the three following criteria: (1) evaluating the effect of preexisting DM on survival outcome (overall survival (OS)) of NSCLC patients; (2) observational studies; (2) reporting sufficient information or platitudinous raw data to estimate a hazard ratio (HR) and its corresponding 95% confidence intervals (Cls). Articles were excluded if they (1) were case reports, letters, basic studies, meeting abstracts, and reviews; (2) were of low qualities or were written in languages other than English; (3) failed to provide sufficient reliable information about the OS of the NSCLC patients or HR and their corresponding 95% CIs. When more than one publication reported on the same study or population, only the publication with most complete dataset or reported recently was included. Reports from Japan, Korea, and Taiwan were defined as Asian studies, and those from the United States and Europe were defined as Western studies.

Study selection, data extraction, and quality assessment

The process of data extraction was performed in duplicate by two reviewers independently with a predefined information sheet from all the eligible studies. Disagreements between the reviewers were settled by consensus. We extracted following items for each included study: study title, first author's name, study country (region), publication year, study period, sample size, study design, age, length of follow-up, NSCLC subtype, NSCLC stage, treatment method of NSCLC and diabetes, data source, OS, adjusted HR with their 95% CI, and adjusting factors. OS was defined as the primary outcome, and if the studies also provided data other than OS like recurrence rate, progression free survival (PFS) or cancer-specific survival (CSS), they were also extracted as the secondary outcome. In the study conducted by Bartling et al., only the Kaplan–Meier curve was provided; thus, we calculated the HR and 95% CI in accordance to the curve as Tierney et al. recommended.[11] The quality of included studies was assessed using elements of the Newcastle Ottawa scale (NOS),[12] which was recommended by the Cochrane Non-Randomized Studies Methods Working Group. A "star system" judged the included studies on three aspects: the selection of study groups, the comparability between study groups, and the ascertainment of exposure or outcome. Age of patients and stage of NSCLC were, respectively, defined as the most important controlled factors and additional ones when evaluating the comparability between study groups, meanwhile 5 years was defined as an enough long follow-up period. Studies gaining no less

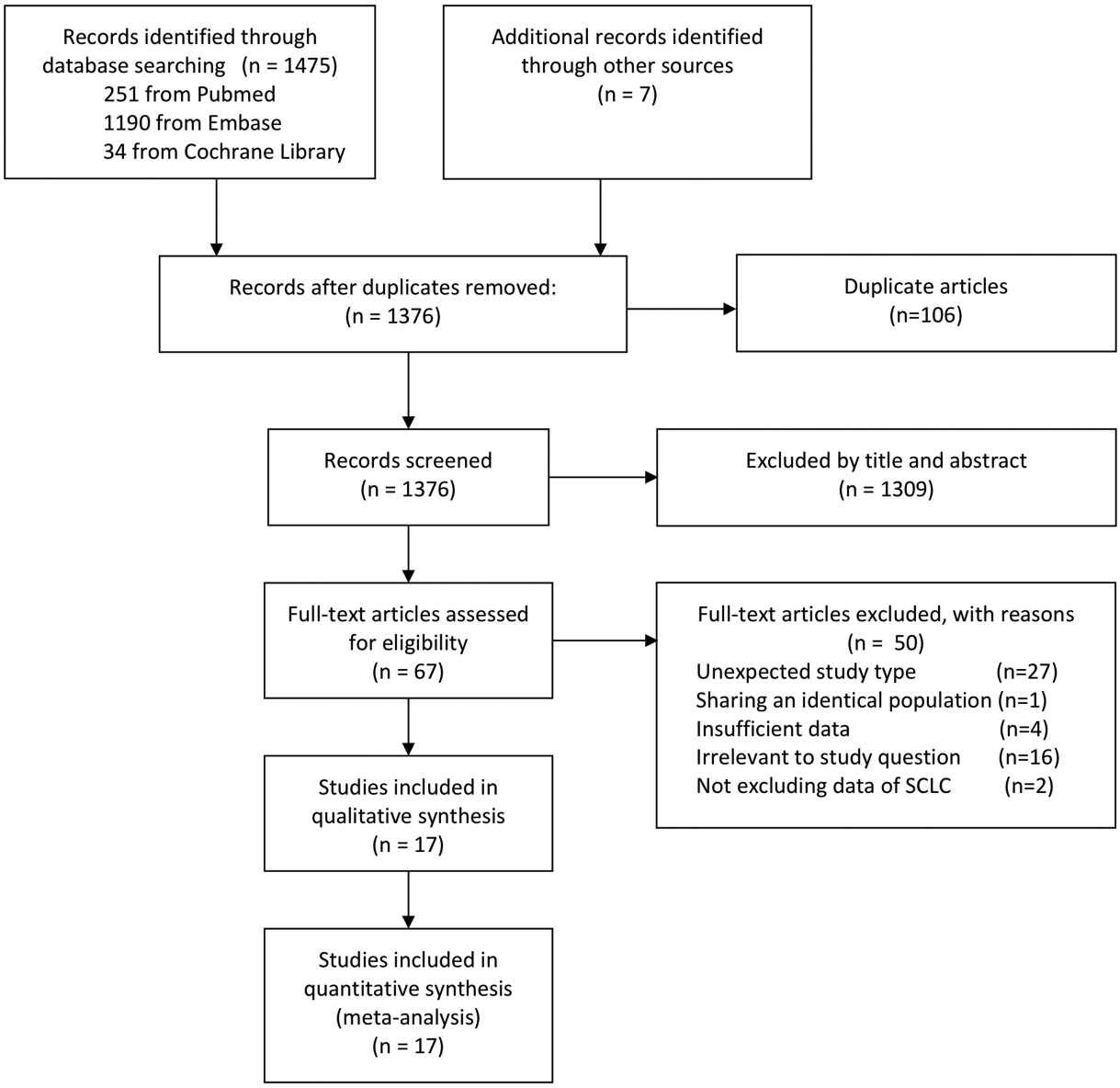

Fig. 1 Flowchart of the article-selection process. SCLC: small cell lung cancer

than 7 stars were considered as high quality, while 5–6 stars indicated medium quality and studies with less than 5 stars were regarded as low quality. This process was conducted by two reviewers independently and the discrepancies were solved by consensus.

Statistical analysis

We qualitatively combined the outcomes information extracted from articles reporting HR with 95% CIs for OS. The inherent heterogeneity among studies was assessed by two statistical methods, Cochrane Q and I^2, in which I^2 <50 indicated moderate heterogeneity and a random-effect model used, whereas a fixed model was used when I^2 >50.[13] The pooled HR was calculated through the DerSimonian-Laird method.[14] Pooled results were presented as p values and 95% CIs, where appropriate, and two-sided $p < 0.05$ was considered to indicate statistical significance. A series of subgroup analyses were performed to investigate the sources of heterogeneity, including the method of treatment, quality of study, study region, statistical methodology, and adjusted factors. Publication bias was evaluated using Begg's funnel plot and the Egger's plot.[15,16] To assess the influence of each study on the overall estimate, sensitivity analysis of prognosis was conducted by repeating the calculation by omitting one study at a time. All analyses were performed using Stata software version 13.0 (Stata Corp, College Station, TX, USA).

Results

Literature search

The process of retrieving articles for inclusion in the meta-analysis is illustrated in the PRISMA Flow diagram (**Fig. 1**). The initial search among the electric databases mentioned above identified 1475 publications, and 7 were retrieved from the references lists of relevant articles. After removing 106 duplicates and screening title/abstract, 67 articles deemed potentially relevant were retrieved for further evaluation. On the basis of reviewing the full text of the 67 articles, 50 that did not meet our eligibility criteria were excluded, leaving 17 studies that provided some estimate of the impact of diabetes on NSCLC prognosis. The 17 publications were ultimately included into the meta-analysis.

Study description and quality assessment

Descriptive data for the studies included in this meta-analysis are summarized in **Tables 1** and **2**. In all, 17 literatures were included, yielding a total of 21328 NSCLC patients: 1655 DM and 19673 non-DM. Type 1 DM (T1DM) and type 2 (T2DM) were not differentiated in these publications. Four studies were from Asia[17–20] and 13 were from western countries.[21–33] Most studies were published within the last 10 years and the sample sizes ranged from 146 to 10378. Seven of the studies[17,19,24,25,27,29,31] investigated the outcomes of patients undergoing surgical treatment, while six studies[18,21,23,26,30,33] focused on those receiving non-surgical treatments like chemotherapy or radiotherapy and three studies[20,22,32] recruited patients receiving both of them. All but one study were retrospective cohort studies while the only exception was designed as a prospective cohort.[31] In all, 13 of the studies[17–20,24–27,29–33] ascertained the diagnosis of preexisting DM in reference to medical records or documented use of anti-diabetic drugs, three retrieved the diagnostic information from local registry system.[21,22,28] In total, 13 studies adopted multivariate regression models to calculate HR while four studies chose univariate models.[17,23,27,33] There were 13 studies that adjusted for age when reporting the HR for OR, which was considered as the most important factor to assure the comparability of cohorts during the process of quality assessment.[17,18,20,22,24–30,32,33] And 11 of the 13 controlled for age and stage,[17,18,20,22,25,26,28–30,32,33] while other potential confounders including gender, smoking, histology type, comorbidities, adjuvant therapy varied across the studies. According to the NOS scale, 10 studies were ranked as high-quality studies (no less than 7 stars), and the mean score was 8, as shown in **Table 3**.

Meta-analysis: DM and NSCLC OS

Of the 17 studies included in this meta-analysis, 16 directly reported a HR with respect to OS of NSCLC patients and data of the remaining were calculated basing on its Kaplan–Meier curve.[27] As shown in **Fig. 2**, a pooled estimate of OS demonstrated that preexisting DM in NSCLC patients was associated with a significantly shorter survival (n = 17, HR: 1.31, 95% CI: 1.12–1.54 by random-effect model). Statistically significant heterogeneity was demonstrated ($\chi^2 = 49.45$, $p < 0.001$, $I^2 = 67.6$) from the primary analysis; thus, we performed a series of subgroup analyses to track the source of heterogeneity and evaluate the impact of diabetes on the prognosis of stratified NSCLC patients. Studies that investigated the outcomes of patients undergoing surgical treatment had an insignificant pooled HR of 1.35 (95% CI: 0.94–1.94, $p = 0.010$, $I^2 = 64.3\%$), but the result became significant when the study conducted by Medairos et al.[29] was dropped (HR = 1.46, 95% CI: 1.02–2.09, $p = 0.018$, $I^2 = 63.3\%$) (**Fig. 3a**). Meanwhile, studies that focusing on patients receiving only non-surgical treatment had a pooled HR of 1.33 (95% CI: 0.87–2.03, $p = 0.001$, $I^2 = 76.2\%$) (**Fig. 3a**). For studies that adjusted for age, the HR was 1.27 (95% CI: 1.08–1.49, $p < 0.001$, $I^2 = 67.2\%$) and for those that adjusted for age and stage, the HR was 1.31 (95% CI: 1.09–1.56, $p < 0.001$, $I^2 = 71.5\%$), while those not adjusting these factors failed to report a significant association. The result from high-quality (defined as no less than 7 stars) studies were similar to the overall estimate (n = 10, HR: 1.36, 95% CI: 1.10–1.69, $p = 0.001$, $I^2 = 69.3\%$, by random model). When stratified by region (Asian and Western) among those high-quality studies, we found a significantly increased risk of worse prognosis in studies conducted in both Asia and western countries, with a more prominent association in Asian studies than in Western ones (Asian: n = 4, HR: 1.89, 95% CI: 1.48–2.40, $p = 0.337$, $I^2 = 11.1\%$; Western: n = 6, HR: 1.09, 95% CI: 1.02–1.20, $p = 0.105$, $I^2 = 45.1\%$, by fixed model) and the heterogeneity decreased (**Fig. 3b**).

Other outcomes

Of the 17 studies in this analysis, several outcomes other than OS were also reported, such as local or distant recurrence rate, PFS and CSS. Because of the limited number of studies demonstrating these data, we did not calculate the pooled HR. Of the five studies that examined

Table 1 Baseline characteristics of the 17 studies included

Studies and years	Country (region)	Recruitment years	Age (year)	Follow-up	Patients with DM		NSCLC stage	Treatment method	NOS
					No./Total	No. %			
Bergamino et al., 2019[33]	Spain	2010–2014	Median: 64 Range: 37–87	NA	56/170	32.9	IIIA–IIIB	Chemotherapy	8
Motoishi et al., 2017[17]	Japan	2007–2015	Mean: 79.5	NA	27/124	17.8	IA–IIIB	Surgery	8
Humar et al., 2017[21]	Slovenia	2005–2010	NA	Median: 9.79 m	18/167	10.8	IIIB–IV	Chemotherapy	6
Hershman et al., 2016[28]	USA	1991–2011	NA	NA	48/222	21.6	IIIB–IV	NA	8
Medaiors et al., 2016[29]	USA	2004–2013	NA	Median: 19.5 m	81/158	51.2	IA–IIB	Surgery	8
Imai et al., 2015[18]	Japan	2002–2009	Median: 64 Range: 40–75	NA	30–159	18.8	IIIA–IIIB	Radiotherapy Chemotherapy	8
Ahmed et al., 2015[23]	USA	1999–2013	Median: 65	Median: 17 m	20/146	13.7	IA–IV	Chemoradiation Therapy	4
Jeon et al., 2015[19]	Korea	2004–2010	Median: 64 Range: 32–81	Median: 40 m	42/271	15.5	I–II	Surgery	7
Inal et al., 2014[30]	Turkey	2001–2012	Median: DM: 60 Non-DM: 58	NA	66/442	14.9	III–IV	Chemotherapy	6
Inachina et al., 2014	Denmark	2007–2015	NA	NA	233/10378	2.2	NA	Surgery or non-surgical treatment	6
Dhillon et al., 2014[24]	USA	2002–2011	Mean: 68.5 Range: 21–93	NA	71/409	17.4	IA–IB	Surgery	4
Luo et al., 2012[20]	Taiwan	2005–2007	Mean: 67.8	Median: 10.5 m	119/229	52.0	IA–IV	Surgery or non-surgical treatment	8
Washington et al., 2012[25]	USA	1995–2005	Median: 67m Range: 21–92	Median: 30 m	122/957	12.7	IA–IIA	Surgery	8
Bartling et al., 2011[27]	German	1998–2003	Mean: 66.7	Maximum: 60 m	55/166	33.1	IA–VI	Surgery	8
Hatlen et al., 2011[26]	Norway	2005–2006	Mean: 64.4	NA	17/436	3.9	IIIB–IV	Chemotherapy	6
Win et al., 2008[31]	UK	? –2006	Mean: 69 Range: 42–85	Range: 3–5y	12/120	10	IA–IIIB	Surgery	5
Van de Poll-France et al., 2007[32]	Netherlands	1995–2002	Mean: 65.7	Maximum: 60 m	581/6690	8.7	IA–VI	Surgery or non-surgical treatment	9

DM: diabetes mellitus; m: month; NA: not applicable; NOS: Newcastle Ottawa scale; NSCLC: non-small-cell lung cancer; y: year

Table 2 Factors adjusted between the DM groups and Non-DM groups

Studies and years	Adjusted factors
Bergamino et al., 2019[33]	Age, gender, smoking, ECOG, stage, comorbidities, radiotherapy dose
Motoishi et al., 2017[17]	Age, gender, BMI, smoking, histology type, surgical procedure, pathological stage, adjuvant therapy, EGFR
Humar et al., 2017[21]	Gender, smoking, histology type, ECOG-PS, IGF1R
Hershman et al., 2016[28]	Age, gender, race, weight loss, LDH, stage IIIB or IV
Medaiors et al., 2016[29]	Age, gender, smoking, race, BMI, comorbidities, ECOG-PS, pathologic stage, procedure, adjuvant chemotherapy
Imai et al., 2015[18]	Age, gender, BMI, ECOG-PS, stage, histology, smoking
Ahmed et al., 2015[23]	Gender, smoking, ethnicity, comorbidities, histology type, stage, ECOG-PS
Jeon et al., 2015[19]	Tuberculosis, stage, size, visceral pleural invasion, positive margin, pathological stage, LVI, BVI, incomplete resection
Inal et al., 2014[30]	Age, gender, ECOG-PS, smoking, weight loss, stage, chemotherapy, metastasis
Inachina et al., 2014	Age, gender, stage, resection
Dhillon et al., 2014[24]	Age, gender, smoking, histology
Luo et al., 2012[20]	Age, gender, smoking, ECOG-PS, BMI, stage, cancer treatment
Washington et al., 2012[25]	Age, gender, surgical procedure, tumor size, stage, histology, adjuvant chemotherapy, visceral pleural invasion
Bartling et al., 2011[27]	Age
Hatlen et al., 2011[26]	Age, gender, histology, stage, smoking, performance status
Win et al., 2008[31]	Shuttle walk distance
Van de Poll-Franse et al., 2007[32]	Age, gender, stage, treatment

DM: diabetes mellitus; BMI: body mass index; ECOG-PS: Eastern Cooperative Oncology Group performance status; EGFR: epidermal growth factor receptor; IGF1R: insulin-like growth factor-1 receptor; LDH: lactate dehydrogenase; LVI: lymphatic vessel invasion; BVI: blood vessel invasion.

the impact of diabetes on PFS of NSCLC patients, three found a significant association.[23,28–30,33] Inal et al. found that DM at the time of diagnosis was associated with negative prognostic importance for PFS in advanced stage NSCLC patients receiving first-line platinum-based doublets chemotherapy (HR: 1.83, 95% CI: 1.20–2.79, p = 0.005),[30] and similar result was also reported by Bergamino et al. (HR: 1.68, 95% CI: 1.14–2.47, p = 0.003.[33] In contrast, in the study by Medairos, it was revealed that diabetic NSCLC patients with metformin exposure might be associated with improved PFS compared with those non-diabetic NSCLC patients (HR: 0.415, 95% CI: 0.201–0.887, p = 0.017).[29] The results from Ahmed et al.[23] and Hershman et al.[28] were statistically insignificant, making it difficult to come to a confirmed conclusion with the existence of such a controversy. None of these studies reported a significant association between diabetes and NSCLC patients' local/distant recurrence rate[17,23,25] or CSS.[17]

Sensitivity analysis and publication bias

Sensitivity analysis was performed by sequential omission of each study in the meta-analysis to examine the influence of single data on the pooled HR. The pooled HR and 95% CI remained significant (>1) when excluding a specific study, indicating a robust association between preexisting DM and NSCLC patients' OS (**Fig. 4a**). We evaluated the publication bias by Begg's test and Egger's test. The funnel plot of Begg's test showed some asymmetry yet the quantitative results of both tests did not suggest significant publication bias (Begg's: p = 0.742; Egger's: p = 0.158) (**Figs. 4b** and **4c**).

Discussion

As one of the most common chronic disease, DM has been a tough problem to both physicians and patients for a long period since the incidence of which remains high in today's world.[6] As for those cancer patients who are complicated with diabetes, it is necessary to explore the interactions between the two diseases and to optimize the therapeutic regiment by a proper management of patients' blood glucose level to avoid the negative impact of hyperglycemia. Previous studies[7–9] have suggested that diabetes was closely associated with several types of cancer, thus in our meta-analysis, we included the most updated literatures and evaluate the impact of preexisting DM on NSCLC prognosis. The pooled result demonstrated that preexisting diabetes was a significant negative prognostic factor for NSCLC patients' OS, which was supported by previous studies.[5,7,10] This finding was consistent when studies were limited to those

Table 3 Methodological quality assessment of the 17 studies included in this meta-analysis in reference to the NOS for cohort studies

Study	Selection				Comparability		Outcome			Score
	Represen-tativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertain-ment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis		Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Bergamino et al.[33]	*	*	*	*	*	*	*	*		8
Motoishi et al.[17]	*	*	*	*	*	*	*	*		8
Humar et al.[21]	*	*	*	*			*	*		6
Hershman et al.[28]	*	*	*	*	*	*	*	*		8
Medarios et al.[29]	*	*	*	*	*	*	*	*		8
Imai et al.[18]	*	*	*	*	*	*	*	*		8
Ahmed et al.[23]		*		*		*	*			4
Inachina et al.	*	*	*	*	*	*				6
Jeon et al.[19]	*	*	*	*		*	*	*		7
Inal et al.[30]			*	*	*	*	*	*		6
Dhillon et al.[24]	*	*		*				*		4
Washington et al.[25]	*	*	*	*	*	*	*	*		8
Luo et al.[20]	*	*	*	*		*	*	*	*	8
Bartling et al.[27]		*	*		*	*	*	*	*	7
Hatlen et al.[26]	*	*		*	*	*	*			6
Win et al.[31]	*	*	*	*			*	*		6
Van de Poll-Franse et al.[32]	*	*	*	*	*	*	*	*	*	9

NOS: Newcastle Ottawa scale

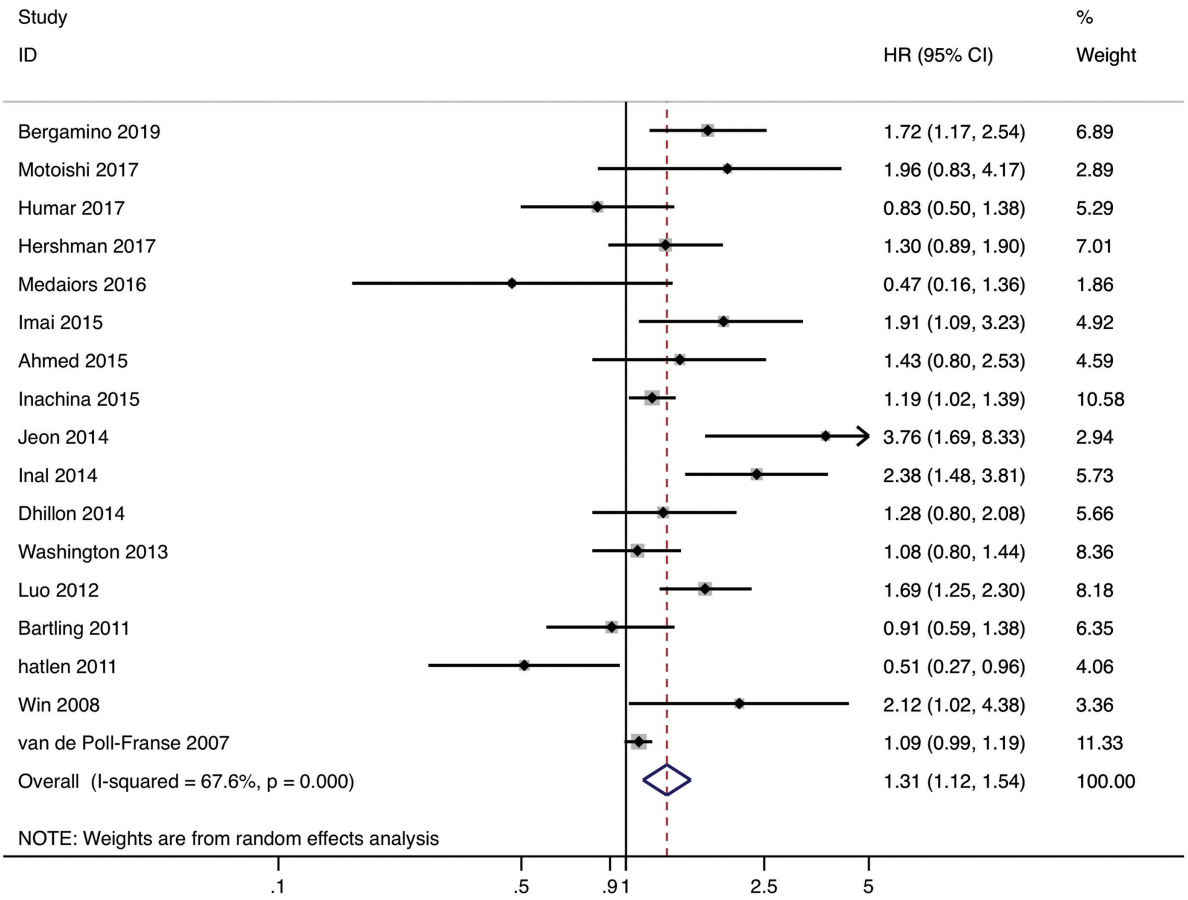

Fig. 2 Meta-analysis of the effect of preexisting diabetes on OS in patients with NSCLC. CI: confidence interval; HR: hazard ratio; NSCLC: non-small-cell lung cancer; OS: overall survival

adjusting for age and/or stage, and sensitivity analysis confirmed the robustness of the main results.

Compared with previous studies, our meta-analysis benefits from our multidisciplinary team consisting of experts in oncology, surgery, and epidemiology and from the rigorous methods, including a comprehensive, systematic review of the published articles. Moreover, it was almost unnecessary for us to estimate the HR of each study based on five-year OS or the raw data since most of the studies (15 of the 16) directly reported the HR, which remarkably decreased the risk of systematic error. In addition, we performed a series of subgroup analyses according to treatment method, study quality, geographic region, study design, and confounding factors to investigate the association in detail and to locate the source of heterogeneity.

When stratifying the studies by treatment method toward cancer, diabetes was significantly associated with a poor prognosis of NSCLC patients who received surgical treatment after excluding Medairos et al.' s study. This phenomenon could be partly explained that the patients enrolled in this study was limited to those with metformin exposure, whereas other studies have no limitations on the choice of therapy to diabetes; thus, the substantial selection bias might considerably influence the pooled HR of surgically treated patients. On the contrary, diabetes had no significant impact on the OS of non-surgically treated patients. On the one hand, the perioperative blood glucose fluctuation could be induced by the stress response to surgical trauma, and it has been suggested that the postoperative blood glucose level was associated with the prognosis of surgically treated patients.[34] The proper blood glucose control has been reported to decrease the inflammation after surgery, thus leading to better long-term outcomes of cancer patients receiving surgery.[35,36] And this effect is more remarkable among diabetic patients since they have a poor glucose tolerance. Therefore, a precise and accurate management

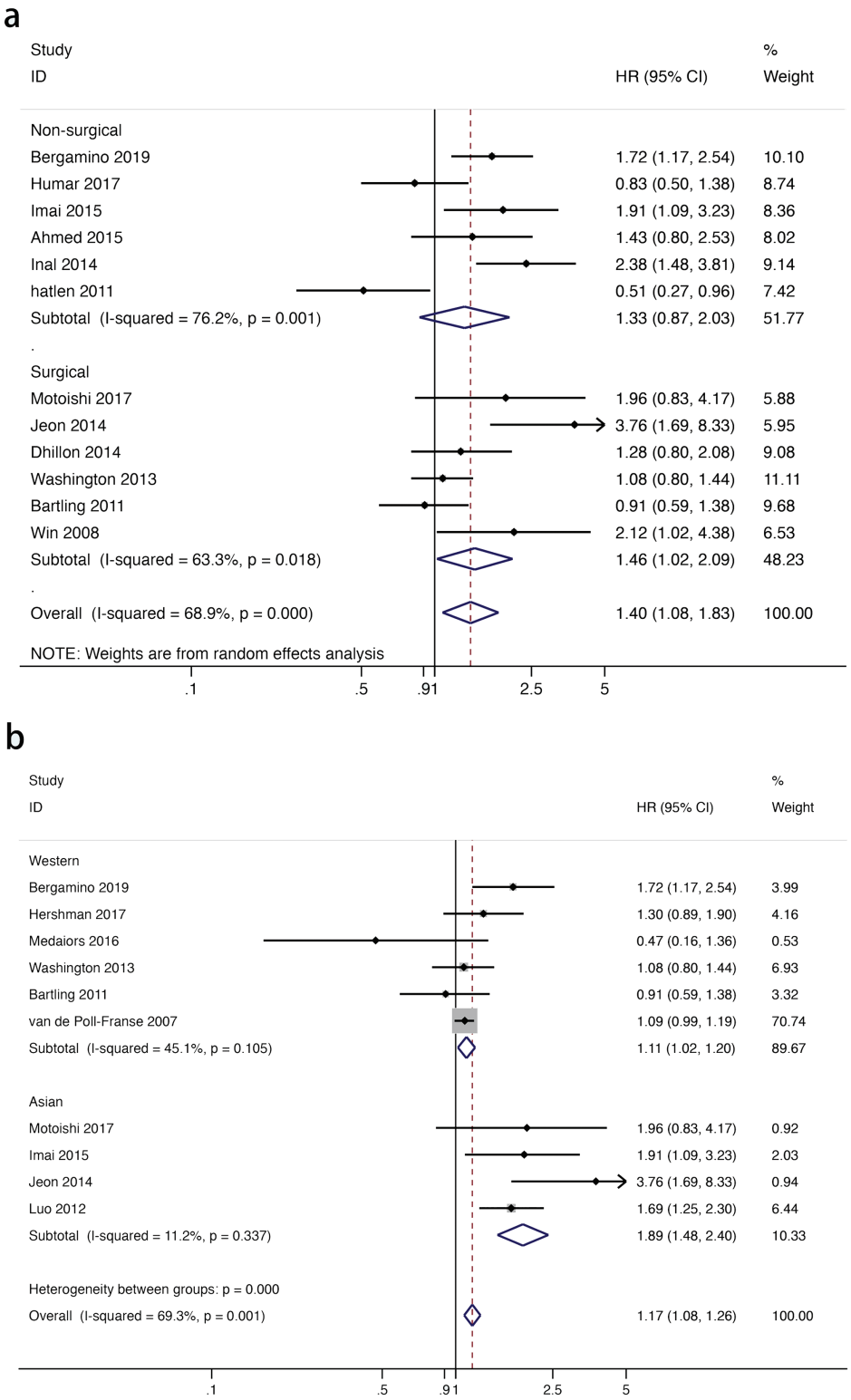

Fig. 3 Subgroup analysis of the effect of preexisting diabetes on OS in patients with NSCLC by (**a**) different treatment method (surgical or non-surgical treatment) and (**b**) geographic regions (Asian or Western, only high-quality studies included). CI: confidence interval; HR: hazard ratio; NSCLC: non-small-cell lung cancer; OS: overall survival

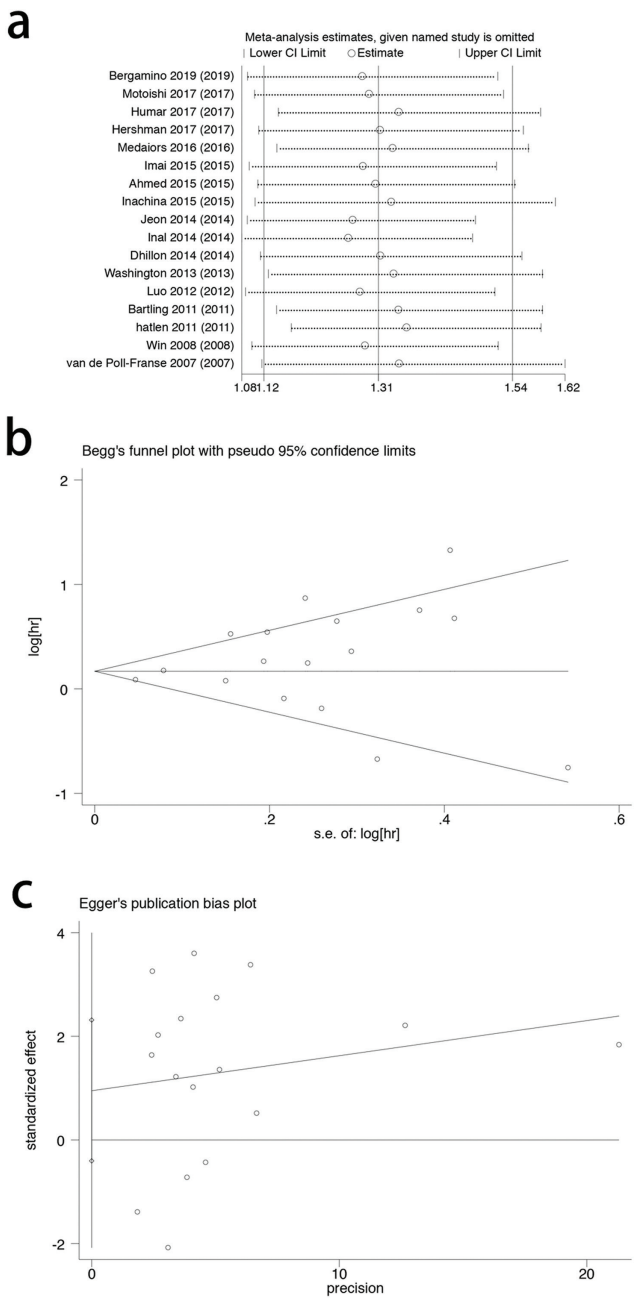

Fig. 4 (**a**) Sensitivity analysis. (**b**) Begg's funnel plots analyses for the potential publication bias among the studies. (**c**) Egger's plots analyses for the potential publication bias among the studies. CI: confidence interval; HR: hazard ratio

of perioperative blood glucose level, especially in patients with diabetes, is demanded. In addition, diabetes is considered to promote cancer development via the insulin-like growth factor 1 receptor (IGF-1R) signal pathway. Ding et al. found higher IGF-1R expression in relatively early stage of NSCLC with DM, and similar results from other malignancies also demonstrated that IGF-1R promoted malignant development at early stages while during later stage IGF-1R signaling was not required for further progression.[37–39] On the other hand, only five studies focusing on diabetic non-surgically treated NSCLC patients were included in this meta-analysis, which limited the representation of the pooled result. Further research is warranted to clarify the role of preexisting diabetes in advanced NSCLC patients receiving chemotherapy, radiotherapy, and immunotherapy.

Moreover, when stratifying by geographic region, we found a significantly increased risk of worse prognosis in studies conducted in both Asia and western countries, with a more prominent association in Asian studies Western ones, whose result was only marginally significant. Several literatures focusing on the association between diabetes and the risk or mortality of cancer also demonstrated similar result in patients with gastric and breast cancer.[40–42] This could be partially explained by different ethnic backgrounds, dietary habits, and disease prevalence. A high level of heterogeneity among studies existed, and difference in geographic region, follow-up time, study design, and adjusted factors are considered to be the source of heterogeneity. When the analysis was restricted to high-quality studies (no less than 7 stars), the subgroup analysis of geographic region was consistent and the heterogeneity was almost eliminated, indicating that ethnic and lifestyle difference among the studies might substantially contribute to the observed heterogeneity.

Although the exact underlying molecular mechanism linking diabetes and cancer remains unconfirmed, several mechanisms have been proposed: (1) hyperinsulinemia and insulin resistance caused by diabetes promote cancer growth through IGF-1 signal pathway. The IGF system, consisting of IGF, IGF receptor (IGF-R) and IGF-binding protein (IGF-BP), was considered to be an important factor that affected cancer development in T2DM patients; (2) hyperglycemia directly contributes to the cancer development. As a consequence of hyperglycemia, the formation of irreversible advanced glycation end-products was suggested to alter the tumor microenvironment[43]; and (3) difference in cancer comorbidities and treatment choice. People with diabetes have an elevated risk of developing several kinds of comorbidities such as diabetic nephropathy, coronary heart disease, peripheral sensory neuropathy, and infection, which consequently decreases their tolerance of specific chemotherapy regime.[44] Therefore, cancer patients with diabetes are less likely to receive aggressive treatment, which to some extent affects the prognosis of cancer patients.[32]

Several limitations of the study deserve mention. First, only observational studies rather than randomized controlled trial were included in this meta-analysis, limiting the strength of the pooled the result. Second, despite we almost eliminated the heterogeneity when stratifying the high-quality studies by geographic region, high level of heterogeneity still existed in several subgroups. Third, besides age and stage, other confounding factors, such as ascertainment of DM, definition of OS, follow-up length, smoking and histology varied across the studies, making it difficult to accurately assess the impact of DM on OS.

Although the result was favorable, it is important to notice that these data do not necessarily suggest a causal relationship between diabetes and worse cancer prognosis, as most results concerning PFS, recurrence rate, or CSS were controversial or had no statistical significance. Moreover, none of the included studies, respectively, investigate the impact of diabetes on patients with different histological type of NSCLC. In addition, only 5 of the 16 studies reported the diabetic therapeutic regime. It has been suggested that some hypoglycemic medicine such as metformin has a positive impact on cancer outcomes.[45] Besides, several other details of diabetes, such as the subtype, severity, age subgroup, and time of diagnosis should also be taken into consideration when evaluating the impact of diabetes on cancer prognosis. Therefore, further research is warranted to evaluate the interaction of diabetes and anti-diabetic drugs on the prognosis of NSCLC.

Conclusion

The main finding of our study is that preexisting DM has a negative impact on NSCLC patients' OS, especially in the surgically treated subgroup and Asian subgroup. Therefore, our study underscores the importance to assess the possible relationships between diabetes and NSCLC. Important research questions include the prognosis of diabetic NSCLC patients receiving a specific treatment method like immunotherapy, and whether tighter control of blood glucose level would improve the survival of NSCLC patients. Finally, integrated clinical attention and better-designed studies toward the complex interactions between diabetes and cancer are urgently warranted.

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Disclosure Statement

The author reports no conflicts of interest in this work.

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