Systematic Review and Meta-Analysis

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Relationships are between metformin use and survival in pancreatic cancer patients concurrent with diabetes

A systematic review and meta-analysis

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Abstract

Background: Increased risk and cancer-related mortality is observed in pancreatic cancer (PC) patients with diabetes mellitus (DM). Whether using metformin as glucose-lowering therapy can result in survival benefit in this group of patients is still unclear.

Methods: A meta-analysis of 21 studies that including 38,772 patients was performed to investigate the association between metformin and overall survival in patients with PC and concurrent DM.

Results: A significant survival benefit was observed in metformin treatment group compared with non-metformin group (hazard ratio [HR] = 0.83, 95% confidence interval [CI]: 0.74–0.91). These associations were observed in both subgroups of Asian countries (HR = 0.69, 95% CI: 0.60–0.79) and Western countries (HR = 0.86, 95% CI: 0.76–0.95), the former was more obvious. Survival benefit was gained for patients at early stage (HR = 0.75, 95% CI: 0.64–0.85) and mixed stage (HR = 0.81, 95% CI: 0.70–0.91), but not for patients at advanced stage (HR = 0.99, 95% CI: 0.74–1.24). Similarly, survival benefit was also observed in patients receiving surgery (HR = 0.82, 95% CI: 0.69–0.94) and comprehensive treatment (HR = 0.85, 95% CI: 0.77–0.93), but not in chemotherapy group (HR = 0.99, 95% CI: 0.67–1.30). No obvious benefit was suggested when pooled by time-varying COX model (HR = 0.94, 95% CI: 0.86–1.03).

Conclusions: These results suggest that metformin is associated with survival benefit in patients with PC and concurrent DM. Further randomized controlled trials and prospective studies with larger sample sizes are required to confirm our findings.

Abbreviations: CI = confidence interval, DM = diabetes mellitus, HR = hazard ratio, OS = overall survival, PC = pancreatic cancer, PFS = progression free survival, RCT = randomized controlled trial, T2DM = type 2 diabetes mellitus.

Keywords: diabetes mellitus, meta-analysis, metformin, pancreatic cancer, survival

1. Introduction

According to the latest data of American cancer statistics in 2019, pancreatic cancer is still the fourth leading cause of cancer-related death, and its incidence is increasing year by year. Siegel RL et al found that in 2019, there will be 56,770 patients diagnosed with pancreatic cancer, among which 45,750 patients will die, most of them within 1 year after diagnosis.[1] Clinically, most of the pancreatic cancer patients are advanced when they first visit, which contributes to poor 5-year survival rates of 2% to 9%,[2] losing the opportunities of radical surgery. So, new adjuvant chemotherapies are urgently required, which are well tolerated by patients with unresectable cancers.

Metformin is a widely used drug for the treatment of type 2 diabetes mellitus via reducing hepatic gluconeogenesis and has been attracting much attention as a potential anti-cancer agent. A number of studies have suggested the association between metformin and reduced cancer risk[3] and better survival outcomes.[4,5] The molecular mechanism of its anticancer effect may be related to the rapamycin-signal pathway and ataxia telangiectasia mutated/liver kinase B1/adenosine 5′-monophosphate-activated protein kinase axis.[6,7] Relationship between diabetes and pancreatic cancer is intricate. There are epidemiologic evidences supporting an association between pancreatic cancer and diabetes mellitus, and there is a significantly higher cancer incidence and cancer-related mortality in those with

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diabetes.[8] Considering all the result above, we are confident that metformin may be one of the promising, safe and effective drugs for the treatment of pancreatic cancer.

Although epidemiologic research and meta-analysis have repeatedly reported the prevention role of metformin use in pancreatic cancer risk,[9,10] the relationship between metformin and prognosis of pancreatic cancer is still ambiguous. New studies in recent years are springing up to clarify the question.[11,12] Therefore, here we perform a meta-analysis to assess the effect of metformin on survival outcome of pancreatic cancer patients with concurrent diabetes mellitus.

2. Materials and methods

2.1. Search strategy

Two reviewers (Yu-Qi Shi and Xiao-Chong Zhou) performed literature search independently in PUBMED from its earliest available date to Feb 04, 2020. EMBASE, Ovid, and Cochrane Library Databases were additionally searched for more relevant articles. The following keywords were used: pancreatic, pancreas, cancer, adenocarcinoma, tumor, neoplasm, mortality, survival, metformin, biguanides, and dimethylbiguanidine. Boolean logic words (AND and OR) were used to combine the key words mentioned above. Full article was investigated if 1 of the 2 reviewers considered it potentially relevant. References of the relevant articles were further screened for earlier original studies. Disagreements were solved by group discussion (Chun-Fang Xu, Yu-Qi Shi Xiao-Chong Zhou, and Peng Du).

2.2. Inclusion criteria

Studies were considered eligible if they satisfied all the following items:

(1) randomized controlled trials (RCTs) and non-RCTs (observational, cohort, and case-control) investigating the relationship between metformin use and overall survival (OS);
(2) studies investigating patients diagnosed as pancreatic cancer concurrent with DM;
(3) part of patients were treated with metformin before and/or after diagnosis;
(4) studies providing hazard ratios (HRs) and 95% confidence intervals (CIs), Kaplan–Meier curves or relevant information available to calculate the HRs and 95% CIs.

Abstracts, reviews, meta-analysis articles and studies researching all cancers were ruled out.

2.3. Data collection

Following information from individual study were extracted: first author, year of publication, country, ethnicity of participants, study design, recruitment period, age, sample size, tumor stage, type of DM, other antidiabetic therapy, medical median follow-up, median OS, HR with 95% CI for OS and PFS. Two reviewers conducted data extraction into a predesigned table independently and then checked up with each other. Inconsistency were solved by discussion or consultation with a third reviewer until a consensus was reached. We used multivariate Cox proportional HRs for the quantitative analysis. If multivariate HRs were not available and the corresponding authors did not respond to our request, the univariate HRs were used instead. Data extraction was accomplished by 3 authors (Yu-Qi Shi, Xiao-Chong Zhou, and Peng Du).

2.4. Quality assessment

In light of only 2 RCTs included, the quality assessment was carried out according to the Newcastle–Ottawa scale, which was recommended by the Cochrane Non-Randomized Studies Methods Working Group for quality assessment of observational studies. It assessed study quality by 3 classifications named selection, comparability, and outcome with a total score of 9 stars. Among the 9 stars, 4 stars represented for the appropriate selection of exposure and nonexposure cohort participants; 2 stars represented for the comparability of cohort; and the last 3 stars described the assessment of outcome and follow-up. Studies that scored 5 or more of the 9 stars were considered to be of high quality.

2.5. Statistical methods

We performed analysis using a random-effect model in case that there was significant heterogeneity. We also performed sensitivity analysis to assess whether the summary estimates are robust to inclusion of studies. One study was removed every time, and the rest were analyzed to evaluate whether the results could have been affected significantly by a single study. Heterogeneity was assessed by value of I^2. Publication bias was evaluated by use of Begg funnel plot and Egger linear regression test. A pooled HR >1 suggested that metformin use predicted an unfavorable prognosis for pancreatic cancer patients. Oppositely, a pooled HR <1 suggested a favorable prognosis for those patients. It was regarded as statistically significant if the 95% CI of HR did not overlap 1. $P<.05$ was regarded as statistically significant. All P-values were 2-sided. Stata version 12.0 software (StataCorp, College Station, TX, http://www.stata.com) were used for data analysis. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

3. Result

3.1. Study characteristics

A total of 133 articles were indentified based on the research strategy. After screening the abstracts or full texts, 21 of them were finally included in the meta-analysis[11–31] There were 19 cohorts[11–29] and 2 RCTs[30,31] respectively, containing a total of 38,772 patients recruited between 1986 and 2015, with a sample size ranging from 41 to 13,702. The literature screening process was shown in Figure 1. Characteristics and important information of relevant studies are listed in Table 1. Quality assessment of studies is shown in Table 2.

3.2. Overall and subgroup analysis

Random-effect model was used to conduct the overall meta-analysis. Study-specific HRs and pooled HR which informed association between metformin use and OS of pancreatic cancer were shown in Figure 2. The pooled HR illuminated a protective role of metformin on pancreatic cancer patient concurrent with DM. Metformin administration was associated with a 16% reduced risk for overall mortality compared to those who did not receive (HR = 0.83, 95% CI: 0.74–0.91, $P<.001$, $I^2=79.4$) in absence of significant heterogeneity.

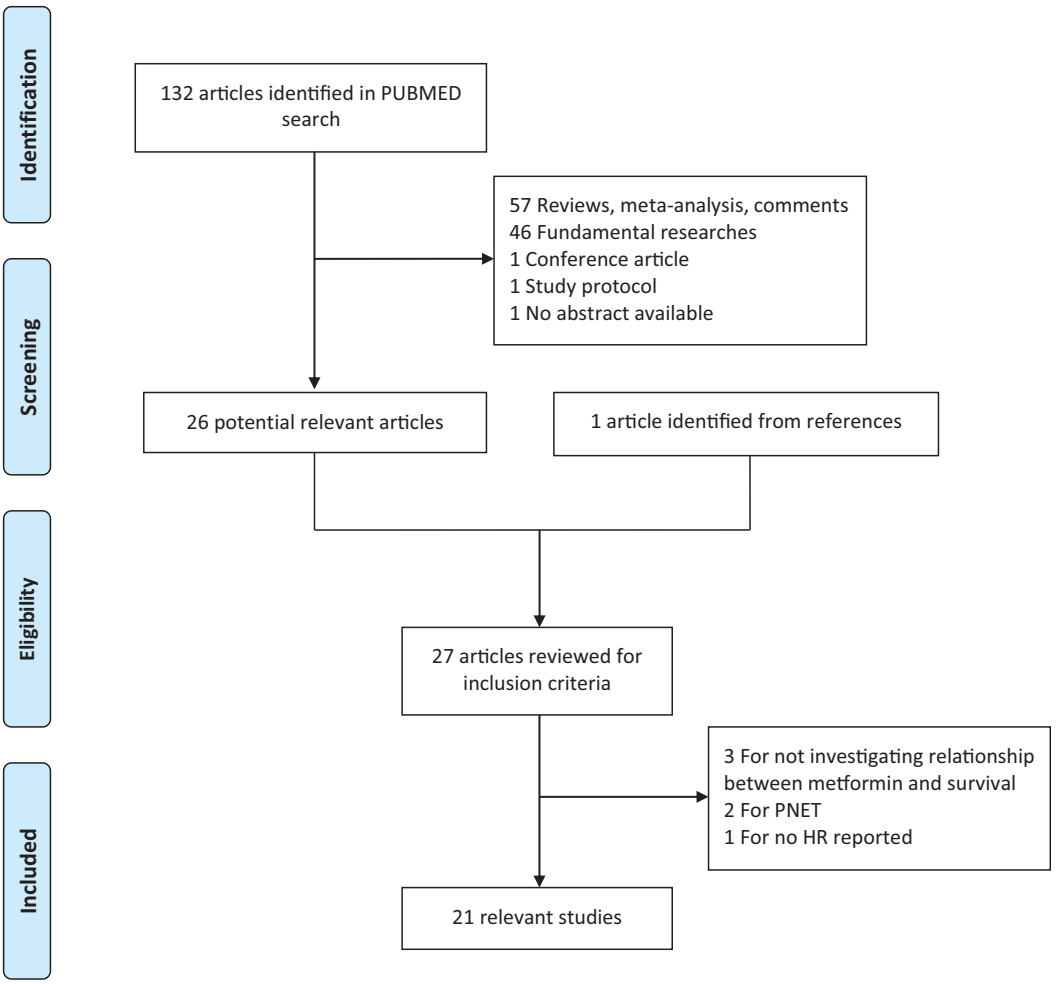

Figure 1. Literature screening process.

All the eligible studies reported HRs for OS of metformin group compared with non-metformin group. Among, 3 studies[12,15,20] also calculated HRs by time-varying model, which were pooled as 0.94 with 95% CI of 0.86 to 1.03, $P = .08$, $I^2 = 60.5$, suggesting no obvious relationship between metformin use and prognosis. However, only 2 authors[22,29] analysed the relationship between metformin use and PFS, showing no protective effect of metformin with no statistical difference (HR = 1.54, 95% CI: 0.94–2.50, $P = .22$, $I^2 = 33.0$). Significant beneficial effect was observed in both Asian and Western countries (HR = 0.69, 95% CI: 0.60–0.79 vs HR = 0.86, 95% CI: 0.76–0.95), but heterogeneity of the former was obvious ($P = .47$, $I^2 = 0.00$). Metformin efficacy was found to be more apparent in subgroup analyses of type 2 diabetes mellitus (HR = 0.77, 95% CI: 0.62–0.92, $P < .001$, $I^2 = 79.9$) and Asian countries.

In subgroup analysis based on cancer stage, survival benefit by metformin adjuvant treatment was obviously observed in patients at early stage (HR = 0.75, 95% CI: 0.64–0.85, $P = .90$) and mixed stage (HR = 0.81, 95% CI: 0.70–0.91, $P < .001$) but not at advanced stage (HR = 0.99, 95% CI: 0.74–1.24, $P = .10$). In subgroup analysis based on treatment strategy, survival benefit was also observed in patients receiving surgery and comprehensive treatment (HR = 0.82, 95% CI: 0.69–0.94, $P = .16$; HR = 0.85, 95% CI: 0.77–0.93, $P = .001$), but not in chemotherapy group (HR = 0.99, 95% CI: 0.67–1.30, $P = .06$). We also conducted subgroup analyses to explore the effect of metformin according to the timing of intake initiation. Metformin use before or after PC diagnosis showed no benefit for OS. Data according to daily metformin use were merely available in studies of E et al[15] and Cerullo et al.[21] Pooled HRs suggested no relationship between metformin and prognosis when daily use range was separated as <1000 mg/d and ≥ 1000 mg/d (Table 3).

3.3. Sensitivity analysis and publication bias

One study was excluded at a time to calculate pooled HR in sensitivity analysis. The pooled HRs ranged from 0.81 to 0.85, founding no substantial alteration. Results of sensitivity analysis are detailed in Table 4. Publication bias was assessed by Egger regression test and Begg funnel plot and both revealed no obvious publication bias ($t = -0.87$, $P = .40$, Fig. 3A and B).

4. Discussion

Our current meta-analysis based on 21 studies involving 38,772 patients suggests that metformin use in pancreatic cancer patients may be related to longer survival especially in subgroups of Asian countries and early tumor stage. Though results are in agreement

Table 1

Characteristics of relevant studies.

Study	Observation period	Country	Ethnicity	Sample Size (met/non-met)	Age	DM type	Other antidiabetic therapy	Tumor stage	Median follow-up	Median OS time (met/non-met)	Univariate HR (95% CI)	Multivariate HR (95% CI)
Cohort												
Cho, 2019[11]	2006–2015	New Zealand	Caucasian	731 (561/170)	70.0	T2DM	Insulin, sulfonylurea, TZD, Alpha glucosidase inhibitor	NA	259 d	NA	0.46 (0.40–0.54)	0.54 (0.46–0.63)
Toriola, 2019[12]	1998–2013	USA	Caucasian	3811 (2792/1019)	67.8	DM	Insulin, sulfonylurea, TZD, DPP4 inhibitor, meglitinide, Alpha glucosidase inhibitor	I II III IV	4.2 m	4.5/3.7 m	NA	0.89 (0.83–0.98)
Frouws, 2017[13]	1998–2011	Netherlands	Caucasian	907 (77/830)	69	T2DM	Sulfonylurea	I II III IV	NA	5.7/4.0 m	0.76 (0.59–0.98)	0.86 (0.66–1.12)
Jang, 2017[14]	2005–2011	Korea	Asian	764 (530/234)	65	T2DM	insulin, sulfonylurea, TZD, DPP4 inhibitor, others	I II	NA	1.5/1.27 y	0.702 (0.588–0.837)	0.727 (0.609–0.868)
E, 2017[15]	2008–2011	USA	Caucasian	5621 (950/4671)	≥65	DM	Insulin	I II III IV	3.8m	3.98/3.60 m	0.93 (0.87–1.00)	0.91 (0.85–0.98)
Beg, 2017[16]	2006–2009	USA	Caucasian	13702 (2277/11425)	76.1	DM	Insulin, TZD	I II III IV	5.3m	NA	0.94 (0.89–0.98)	1.02 (0.93–1.11)
Amin, 2016[17]	2007–2011	USA	Caucasian	1916 (1098/818)	76.9	DM	Insulin, sulfonylurea, TZD, DPP4 inhibitor, meglitinide, Alpha glucosidase inhibitor	I II III IV	NA	Mean: 5.5/4.2 m	NA	0.88 (0.81–0.96)
Lee, 2016[18]	2005–2013	Korea	Asian	237 (117/120)	66	T2DM	Insulin, sulfonylurea, TZD, DPP4 inhibitor	I II III IV	10.3 m	13.7/8.9 m	0.62 (0.47–0.81)	0.61 (0.46–0.81)
Ambe, 2016[19]	1986–2013	USA	Caucasian	44 (19/25)	68	DM	NA	I II	19 m	39.8/19.3 m	0.54 (0.16–1.86)	NA
Chaiteerakij, 2016[20]	2000–2011	USA	Caucasian	980 (366/614)	67.4	T2DM	NA	I II III IV	9.26 m	9.9/8.9 m	0.88 (0.77–1.01)	0.88 (0.76–1.03)
Cerullo, 2016[21]	2010–2012	USA	Caucasian	3393 (2937/456)	57	DM	NA	I II	16.5 m	20.2 m	0.86 (0.73–1.01)	0.79 (0.57–0.93)
Kozak, 2016[22]	1998–2013	USA	Caucasian	171 (18/153)	69	T2DM	NA	I II III IV	11.23 m	49.8/15.8 m	0.42 (0.299–0.941)	0.60 (0.211–1.675)
Toomey, 2015[23]	1991–2013	USA	Caucasian	132 (18/114)	68	DM	Insulin, sulfonylurea	I II	NA	19.2/17.7 m	NA	0.92 (0.29,2.92)
Choi, 2015[24]	2003–2010	Korea	Asian	183 (56/127)	59.6	DM	Insulin, sulfonylurea	III IV	10.2 m	11.0/7.8 m	NA	0.693 (0.492–0.977)
Cheon, 2014[25]	2005–2011	Korea	Asian	41 (18/23)	69	DM	Others	III IV	NA	273/145 d	1.53 (0.93–2.94)	1.83 (0.84–3.97)
Hwang, 2013[26]	2003–2011	USA	Caucasian	516 (247/269)	72.5	T2DM	Insulin, acarbose, gliptin, sulfonylurea, TZD	III IV	NA	99/114 d	1.13 (0.94,1.36)	1.11 (0.89,1.38)
Nakai, 2012[27]	2001–2011	Japan	Asian	124 (8/116)	66	DM	Insulin, sulfonylurea, TZD	III IV	9.9 m	NA	0.73 (0.22–1.77)	NA
Sadeghi, 2012[28]	2000–2009	USA	Caucasian	302 (117/185)	64	DM	Insulin, sulfonylurea, TZD	I II III IV	11.4 m	15.2/11.1 m	0.68 (0.52,0.89)	0.64 (0.48,0.86)
Currie, 2012[29]	1990–2009	UK	Caucasian	5016 (2843/2173)	71.7	T2DM	Insulin, sulfonylurea	NA	NA	19.2 m	NA	0.93 (0.34,1.52)
RCT												
Reni, 2016[30]	2010–2014	Italy	Caucasian	60 (31/29)	63.5	DM	Insulin, oral agent	IV	NA	6.8/10.4 m	NA	1.56 (0.87–2.8)
Kordes, 2015[31]	2010–2014	Netherlands	Caucasian	121 (60/61)	64/65	DM	placebo	III IV	28.1 m	6.8/7.6 m	1.056 (0.72–1.55)	NA

DM = diabetes mellitus, DPP4 = dipeptidyl peptidase-4, HR = hazard ratio, NA = not available, OS = overall survival, RCT = randomized controlled trial, T2DM = type 2 diabetes mellitus, TZD = thiazolidinedione.

Table 2

Quality assessment according to the Newcastle–Ottawa scale.

Study	Selection Representativeness of exposed cohort*	Selection of nonexposed group†	Ascertainment of exposure‡	Outcome of interest was not present at start of study§	Comparability Comparability of cohorts¶	Outcome Assessment of outcome‖	Follow-up long enough for outcomes to occur**	Adequacy of follow up of cohorts††	Score
Cho, 2019[11]	1	1	1	0	2	1	1	1	8
Toriola, 2019[12]	1	1	1	0	2	1	1	1	8
Frouws, 2017[13]	1	1	1	0	2	1	1	0	7
Jang, 2017[14]	1	1	1	0	2	1	1	1	8
E, 2017[15]	1	1	1	0	2	1	1	0	7
Beg, 2017[16]	1	1	0	0	2	1	1	1	7
Amin, 2016[17]	1	1	1	0	2	1	1	1	8
Lee, 2016[18]	1	1	0	0	2	1	1	1	7
Ambe, 2016[19]	1	1	1	0	1	1	1	0	6
Chaiteerakij, 2016[20]	1	1	1	1	1	1	1	1	8
Cerullo, 2016[21]	1	1	1	1	1	1	1	0	7
Kozak, 2016[22]	1	1	1	0	1	1	1	1	7
Toomey, 2015[23]	1	1	0	0	1	1	1	0	5
Choi, 2015[24]	1	1	1	0	2	1	1	1	8
Cheon, 2014[25]	1	1	1	0	2	1	1	1	8
Hwang, 2013[26]	1	1	1	1	2	1	1	1	9
Nakai, 2012[27]	1	1	1	0	1	1	1	0	6
Sadeghi, 2012[28]	1	1	1	0	1	1	1	0	6
Currie, 2012[29]	1	1	1	0	0	1	1	0	5
Reni, 2016[30]	1	1	1	0	2	1	1	1	8
Kordes, 2015[31]	1	1	1	1	2	1	1	1	9

2: Two star; 1: One star; 0: No star.

Star was achieved for each line if.

* The exposed cohort truly or somewhat represented the average in the community.

† The nonexposed cohort was drawn from the same community as the exposed cohort.

‡ Ascertainment of exposure was secure record or structured interview.

§ Outcome of interest was not present at start of study.

¶ Study controls for the most important or any additional factor.

‖ Assessment of outcome was from independent blind assessment or record linkage.

** Follow-up was long enough for outcomes to occur.

†† All subjects follow up of cohorts, subjects lost to follow up unlikely to introduce bias or description provided of those lost.

with previous studies,[32–34] it is so far the most comprehensive meta-analysis containing the newly updated studies.

As is well-known, pancreatic cancer is a malignant disease featured by rapid progression and poor prognosis. Surgery is the only potential curative therapeutic approach for pancreatic cancer. However, possibility of surgery is little because about 80% patients are already in an advanced state when they are diagnosed.[35] Therefore, for patients with metastatic or locally advanced inoperable pancreatic cancer, chemotherapy and radiotherapy are considered the standard treatment approach. First line regimens, such as FOLFIRINOX and gemcitabine combined with nab-paclitaxel can only extend limited survival time.[36] Furthermore, patients have a poor toleration for medicine toxicity and numerous side effects. So, new adjuvant agents have been paid more and more attention to improve these the current situation.[37]

Recently, scientists of Japan found a pre-existing diabetes prevalence of 20.7% in cancer patients at any cancer site and diabetes prevalence was especially high in pancreatic cancer.[38] Epidemiological and clinical studies have demonstrated that pancreatic cancer is closely related to diabetes mellitus, being cause and consequence for each other.[8] Patients with pancreatic cancer often suffer from abnormal blood sugar and insulin resistance, which promote the development of diabetes mellitus. In turn, diabetic patients are more likely to develop pancreatic cancer, which is linked with worse prognosis.[39]

Metformin, a traditional anti-diabetic drug, is drawing more and more attention for its anti-cancer effect. Laboratory investigation shows metformin inhibits mitochondrial ATP synthesis to inhibits carcinogenesis via both direct and indirect pathways.[40] For pancreatic cancer patients concurrent with diabetes, a considerable part of them take metformin to control blood sugar. We conducted the meta-analysis attempting to illustrate the association between metformin and clinical survival outcome in these patients. To our knowledge, the present study was the most up to date meta-analysis pooled with 19 cohorts and 2 RCTs, demonstrating a significant survival benefit. As compared to the study of Wan G et al,[34] our analysis included 2 recent cohorts,[11,12] the weight of which add up to 16.50%. Cho et al[11] found that, in individuals with pancreatic cancer–related diabetes, ever users of metformin (adjusted HR = 0.54, 95% CI: 0.46–0.63) had significantly lower risks of mortality compared with never users of antidiabetic medications. Toriola et al[12] observed a survival benefit associated with metformin use (HR = 0.89, 95% CI: 0.83–0.98, $P = .01$) when using the conventional Cox model. However, in multivariable adjusted analyses using the time-varying Cox model, metformin use was not associated with survival: HR = 1.05 (95% CI, 0.92–1.14, $P = .28$). We also

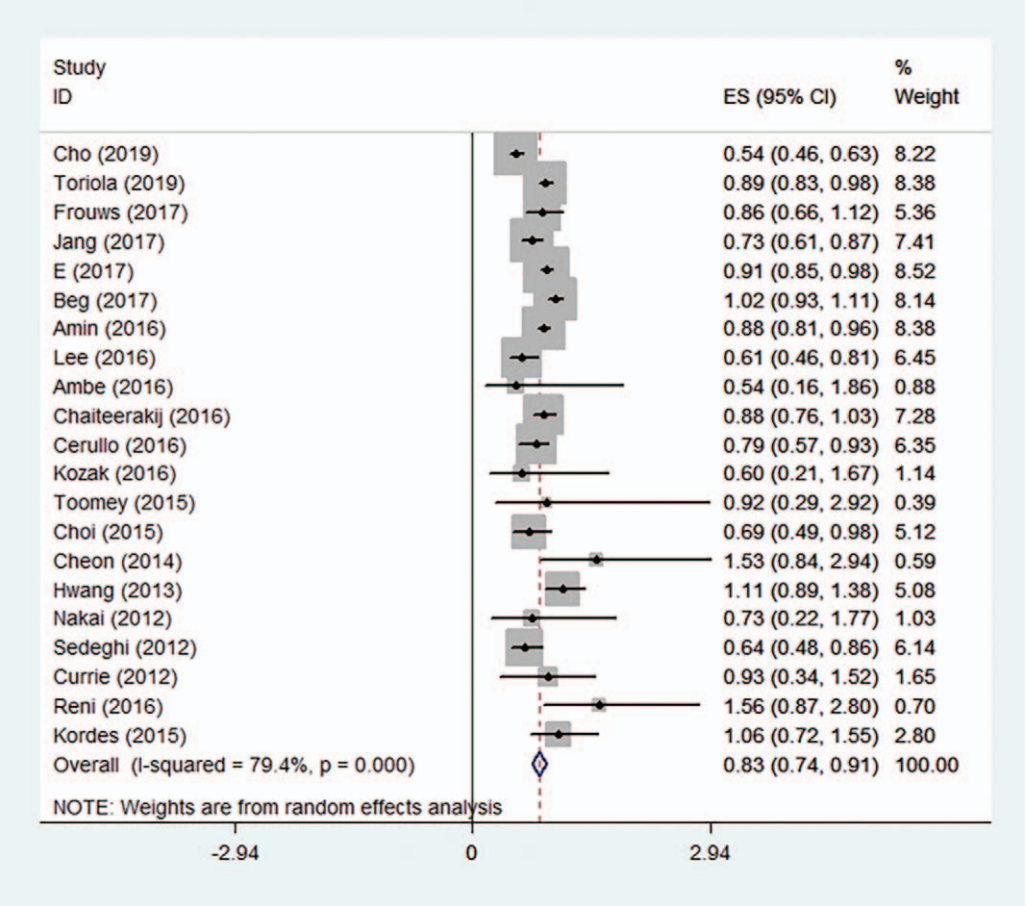

Figure 2. Forest plot showed the association between metformin and OS for pancreatic cancer. Random-effect model was used. For each study, the estimates of HR and 95% CI were plotted with a box and a horizontal line. Closed diamond indicates pooled HR and 95% CI. CI = confidence interval, HR = hazard ratio, OS = overall survival.

Table 3

Analysis of association between metformin use and survival of pancreatic cancer concurrent with diabetes mellitus.

Survival	Subgroup		Number of studies	Sample size	HR (95%CI)	*P* for heterogeneity	I^2 (%)
OS (Conventional COX model)	Overall		21	38,772	0.83 (0.74,0.91)	<.001	79.4
	Country	Asian	5	1349	0.69 (0.60,0.79)	.466	0.00
		Western	16	37,423	0.86 (0.76,0.95)	<.001	82.0
	Exposure	Before PC diagnosis	5	13,449	0.91 (0.79,1.03)	.003	74.5
		After PC diagnosis	6	21,215	0.93 (0.68,1.18)	<.001	92.5
	DM type	DM	13	29,450	0.88 (0.81,0.95)	.025	48.5
		T2DM	8	9322	0.77 (0.62,0.92)	<.001	79.9
	Cancer stage	Early	4	4333	0.75 (0.64,0.85)	.895	0.00
		Advances	6	1045	0.99 (0.74,1.24)	.101	45.7
		Mixed stage	11	33,394	0.81 (0.70,0.91)	<.001	87.8
	Treatment Strategy	Surgery	4	4751	0.82 (0.69,0.94)	.163	41.5
		Chemotherapy	5	924	0.99 (0.67,1.30)	.064	55.0
		comprehensive therapy	12	33,097	0.85 (0.77,0.93)	.001	67.1
	Daily metformin use	<1000 mg/d	2	9014	0.91 (0.72,1.11)	.033	78.1
		≥1000 mg/d	2	9014	0.89 (0.54,1.23)	.002	89.8
OS (Time-varying model)	Overall		3	10,412	0.94 (0.86,1.03)	.080	60.5
PFS	Overall		2	231	1.54 (0.94,2.50)	.220	33.0

CI = confidence interval, DM = diabetes mellitus, HR = hazard ratio, OS = overall survival, PC = pancreatic cancer, PFS = progression free survival, T2DM = type 2 diabetes mellitus.

Table 4

Sensitivity analysis.

Excluded study	HR	Lower limit of 95% CI	Upper limit of 95% CI	I^2 (%)	*P*-value
Cho, 2019[11]	0.85	0.79	0.92	55.8	.001
Toriola, 2019[12]	0.82	0.73	0.91	80.0	.000
Frouws, 2017[13]	0.82	0.74	0.91	80.4	.000
Jang, 2017[14]	0.83	0.75	0.92	79.8	.000
E, 2017[15]	0.82	0.73	0.91	79.1	.000
Beg, 2017[16]	0.81	0.72	0.89	76.1	.000
Amin, 2016[17]	0.82	0.73	0.92	80.1	.000
Lee, 2016[18]	0.84	0.75	0.93	78.9	.000
Ambe, 2016[19]	0.83	0.74	0.91	80.3	.000
Chaiteerakij, 2016[20]	0.82	0.73	0.91	80.3	.000
Cerullo, 2016[21]	0.83	0.74	0.92	80.3	.000
Kozak, 2016[22]	0.83	0.74	0.91	80.3	.000
Toomey, 2015[23]	0.83	0.74	0.91	80.4	.000
Choi, 2015[24]	0.83	0.75	0.92	80.1	.000
Cheon, 2014[25]	0.82	0.74	0.90	80.1	.000
Hwang, 2013[26]	0.81	0.73	0.90	79.4	.000
Nakai, 2012[27]	0.83	0.74	0.91	80.4	.000
Sadeghi, 2012[28]	0.84	0.75	0.92	79.5	.000
Currie, 2012[29]	0.82	0.74	0.91	80.4	.000
Reni, 2016[30]	0.82	0.74	0.90	80.0	.000
Kordes, 2015[31]	0.82	0.73	0.90	80.2	.000

CI = confidence interval, HR = hazard ratio.

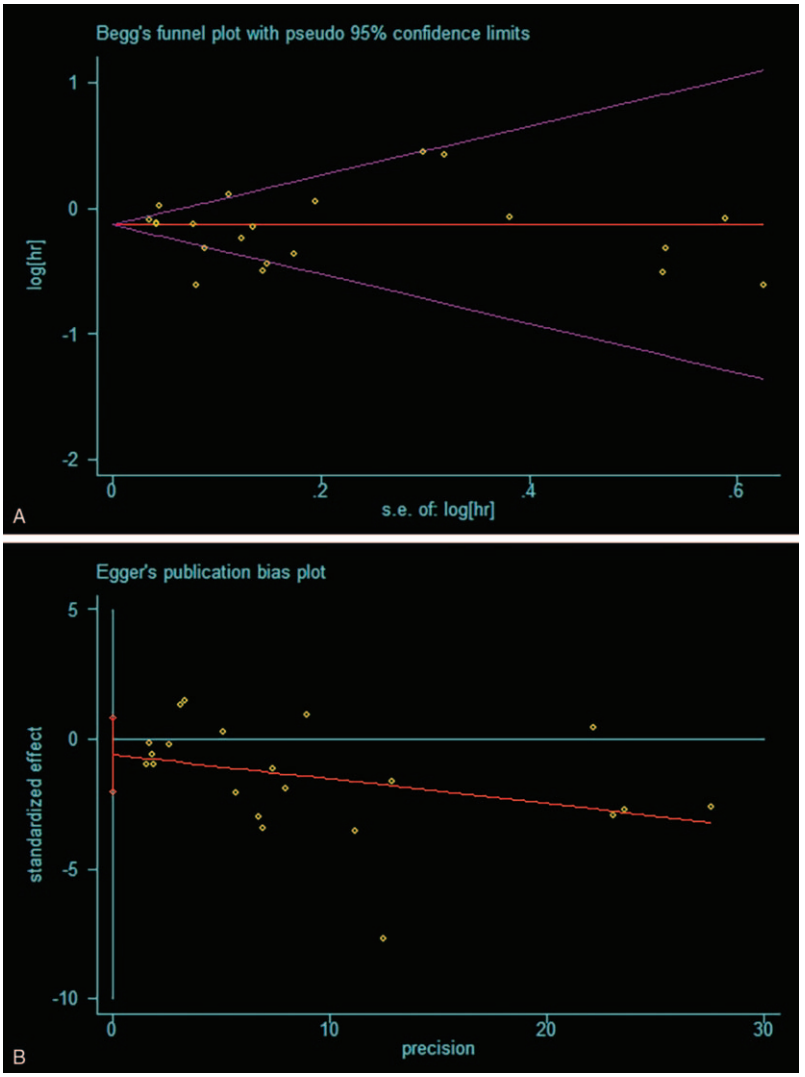

Figure 3. (A and B) Begg Funnel plot and Egger linear regression test for BMI at diagnosis group studies. (A: Begg Funnel plot, B: Egger linear regression). BMI = body mass index.

take studies of Currie et al[29] and Nakai et al[27] into consideration, which were contained in the meta-analysis of Zhou et al.[33] Sensitivity analysis was performed to test the robustness of the conclusions. Also, subgroup analysis was conducted to explore the relationship between metformin effect and ethnicity, DM type, tumor stage, and treatment strategy. Studies included in the analysis are of high quality according to the Newcastle–Ottawa scale scores. At last, no publication bias was surveyed by both Begg test and Egger test.

Limitations of our meta-analysis also need to be considered. When the artificial survival advantage was eliminated by time-varying Cox model, no survival benefit of metformin use was observed. In fact, this analysis method is more accurate for defining metformin exposure status than the conventional Cox model because the analysis takes into account the variation in timing of metformin initiation and considers the period of nonexposure to metformin.[20] More researches are needed to verify the tendency pooled by time-varying Cox model. Subgroup analysis suggested that metformin action may be affected by ethnicity. More survival benefit was observed in Asian population: HR = 0.69, 95% CI: 0.60–0.79, $P = .47$). Even so, since Asian population is retrieved almost from Korea, the representativeness of findings may be limited. Compared to white populations, the tendency of insulin resistance of south Asians is greater when suffered from diabetes.[41] Metformin inhibits hepatic gluconeogenesis and lipogenesis and also increases fatty acid oxidation, as well as enhances insulin sensitivity.[42] However, the underlying mechanism for the discrepancy remains inexplicit. Similar tendency was both found in subgroup analysis of tumor stage and treatment strategy, suggesting the potential importance of metformin action following surgery at early stage. As recommended by guideline, patients at early stage usually receive surgery treatment but chemotherapy at advanced stage.[43] Patients at early tumor stage have more opportunity to have surgery, being free from serious side effects caused by chemotherapy/radiation. It should also not be overlooked that patients at early stage usually survived longer and the cumulative effect of metformin is stronger.

In conclusion, our meta-analysis clarifies the survival benefit of metformin in pancreatic cancer patients concurrent with diabetes mellitus, suggesting metformin as an adjuvant chemotherapy in patients with pancreatic cancer. However, more RCTs and prospective cohorts are needed to confirm the conclusion. Effect of clinical characteristics such as initiation time and dose of metformin, duration and type of diabetes, other hypoglycemic agents and ethnicity should be explored further.

Author contributions

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