Meta Analysis

The association between metformin use and colorectal cancer survival among patients with diabetes mellitus: An updated meta-analysis

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Abstract

Objective: Recent studies have reported conflicting results on the correlation between metformin use and outcomes in patients with colorectal cancer (CRC). A meta-analysis was performed to evaluate the efficacy of metformin therapy on the prognosis of CRC patients with type 2 diabetes mellitus (T2DM).

Methods: We conducted a systematic search of PubMed, EMBASE, the Cochrane Library, and the Web of Science for related articles up to August 2016. Two investigators independently identified and extracted information. Pooled risk estimates [hazard ratios (*HR*s)] and 95% confidence intervals (*CI*s) were calculated using fixed-effects models. The risk of publication bias was assessed by examining funnel plot asymmetry as well as Egger's test and Begg's test.

Results: Of 81 articles identified, 8 retrospective cohort studies, representing 6098 cases of CRC patients with T2DM who used metformin and 4954 cases of CRC patients with T2DM who did not use metformin, were included in this meta-analysis. There was no significant heterogeneity and quality difference between studies. Metformin users had significantly improved overall survival (OS) (*HR* = 0.82, 95% *CI*: 0.77−0.87, *P* = 0.000). However, Metformin use cannot affect CRC-specific survival (*HR* = 0.84, 95% *CI*: 0.69−1.02, *P* = 0.079) compared to non-users.

Conclusion: This meta-analysis suggests that metformin use may improve survival among CRC patients with T2DM. However, prospective controlled studies are still needed to rigorously evaluate the efficacy of metformin as an anti-tumor agent.

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Keywords: Metformin; Colorectal cancer; Survival; Anti-tumor agent; Meta-analysis

Introduction

Despite the fact that advanced surgical techniques and efficient therapies have been successfully applied in patients with colorectal cancer (CRC), it is still the second most common cancer in males and the third most common malignant tumor in females in the United States,[1]

and CRC is the sixth most common cancer among the Chinese population.[2] Each year, there are about one million newly diagnosed CRC patients around the world.[3] Multiple risk factors of CRC include insulin resistance, obesity, low fiber diet, increasing age, black race, smoking, and metabolic syndromes.[3]

The prevalence of T2DM is predicted to increase from 2.8% in 2000 to 4.4% in 2030.[4] Accumulating preclinical evidence revealed that type 2 diabetes mellitus (T2DM) is related to several types of cancer, including CRC, esophageal cancer, pancreatic cancer, and postmenopausal breast cancer.[5,6] This correlation has mainly been attributed to insulin resistance and factors related to metabolic syndromes, such as hyperinsulinemia and hyperglycemia, which can play additive carcinogenic roles.[7] Preclinical evidence shows a possible therapeutic role for metformin, which is a first-line therapy for many T2DM patients,[8] in blocking CRC progression.[5] Therefore, metformin therapy can be regarded as a potential treatment for CRC patients with T2DM for its anti-tumor effects. Owing to the high prevalence and poor prognosis of CRC, it is possible to speculate that a potential anti-tumor role of metformin may affect public health.

Several recent observational studies have explored the association between metformin use and clinical outcomes in CRC patients with T2DM. Previous meta-analyses of such studies have been inconclusive, as they mainly focused on the prevention of CRC rather than the survival benefits.[9–14] Considering this controversial issue, we conducted a systematic review and quantitative analysis of all retrospective cohort studies to determine whether metformin therapy can improve survival in CRC patients with T2DM.

Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline,[15] which is a revised edition of Quality of Reporting of Meta-Analyses (QUOROM), to rigorously evaluate its quality.

The study did not involve any animals or humans. Therefore, ethical approval was not needed.

Search strategy

Two reviewers (Yu-Lan Liu and Hong-Bo Lei) independently searched PubMed, the Web of Science, EMBASE, and the Cochrane Library databases for all relevant studies up to August 2016. The main search keywords for article title and abstract were "colorectal cancer" in combination with "metformin". Two authors independently reviewed the titles and abstracts of studies identified in the search to exclude unrelated studies. Two researchers (Yu-Lan Liu and Hong-Bo Lei) screened the full texts and references to determine whether there were any additional studies in line with our inclusion criteria.

Inclusion criteria

Inclusion criteria were: (1) study design: retrospective cohort studies; (2) participants: patients with a pathologically confirmed diagnosis of CRC and a T2DM diagnosis before the occurrence of CRC; (3) treatment group: use of metformin; (4) comparison group: non-use of metformin; (5) outcomes: hazard ratios (*HR*s) with 95% confidence intervals (*CI*s) for overall survival (OS) and CRC-specific survival (CS). Studies published in English were included. When there were several publications from the same retrospective cohort, we extracted the useful information from the most recent and complete studies. Studies such as letters, reviews, and comments were excluded.

Data extraction

Data extraction was independently performed by two authors (Yu-Lan Liu and Hong-Bo Lei) following a standard form designed in advance. The following information was extracted from the included articles: authors, year, study design, mean age, country, duration of the study, number of events, outcome assessment, *HR*s with 95% *CI*s, and CRC stage.

Quality assessment

In order to better distinguish the quality of the included studies, the Newcastle-Ottawa Scale[16] was applied for quality assessment of observational studies. All methodological quality of eligible studies was evaluated separately by two authors (Shan Tian and Yan Chen). Any discrepancies were resolved by a third researcher (Wei-Guo Dong). A total of 9 points were enrolled in the scale, and three aspects were included: selection, comparability, and exposure/outcomes. Studies scoring higher than 7 were regarded as high quality, studies scoring 4–6 were seen as good quality, and studies scoring 3 or below were viewed as low quality studies.

Statistical analysis

Pooled *HR*s for OS, CS, and respective 95% *CI*s were estimated by a random-effects model if the

substantial heterogeneity across studies was detected; otherwise, a fixed-effects model was performed. Heterogeneity was assessed with the Cochran's Q statistic[17] and I^2 statistic. For the Q statistic, $P < 0.05$ was considered statistically significant for heterogeneity. For the I^2 statistic, 25−50%, 50−75%, and >75% were regarded as low, moderate, and high heterogeneity, respectively.[18] An I^2 value of ≥50% indicated significant heterogeneity. The source of heterogeneity was investigated by subgroup analysis. Finally, publication bias was evaluated with the application of the Egger's regression and Begg's test, in which $P < 0.05$ was considered representative of statistically significant publication bias. All of the statistical analysis was performed using Stata software program version 11.0 (STATA, College Station, TX, USA).

Results

The literature search yielded 81 studies, and 8 observational studies[19−26] were included in this meta-analysis (Fig. 1). These studies cumulatively included 6098 cases of CRC patients with T2DM who used metformin and 4954 cases of CRC patients with T2DM who did not use metformin. None of these 8 selected studies was industry sponsored.

The characteristics of the included studies are shown in Table 1. The selected studies were all published in the past 4 years (2012−2016). Seven studies[19−22,24−26] reported the *HR*s for OS among CRC patients with T2DM, and four studies[19,21,23,25] reported the *HR*s for CS among CRC patients with T2DM. Of the included studies, four[19,20,22,23] were performed in Europe (Ireland, Netherlands, Denmark, UK), and three[21,24,26] in the United States. The remaining one was performed in Korea.[25] As shown in Table 2, all of the studies scored 6 or higher, suggesting that these studies were of high quality.

Metformin and morality in CRC patients with T2DM

Metformin use was associated with an 18% lower *HR* for OS (*HR* = 0.82, 95% *CI*: 0.77−0.87, $P = 0.000$) compared with non-metformin use among T2DM patients (Fig. 2). As there was no significant evidence of heterogeneity ($I^2 = 48.1\%$; $P = 0.073$), subgroup analysis was not necessary. We performed sensitivity analyses by excluding one study at a time and recalculating the pooled *HR*s for the remaining studies, and the results demonstrated that the overall pooled estimates were robust. There was no significant publication bias by funnel plot (Fig. 3). We did not
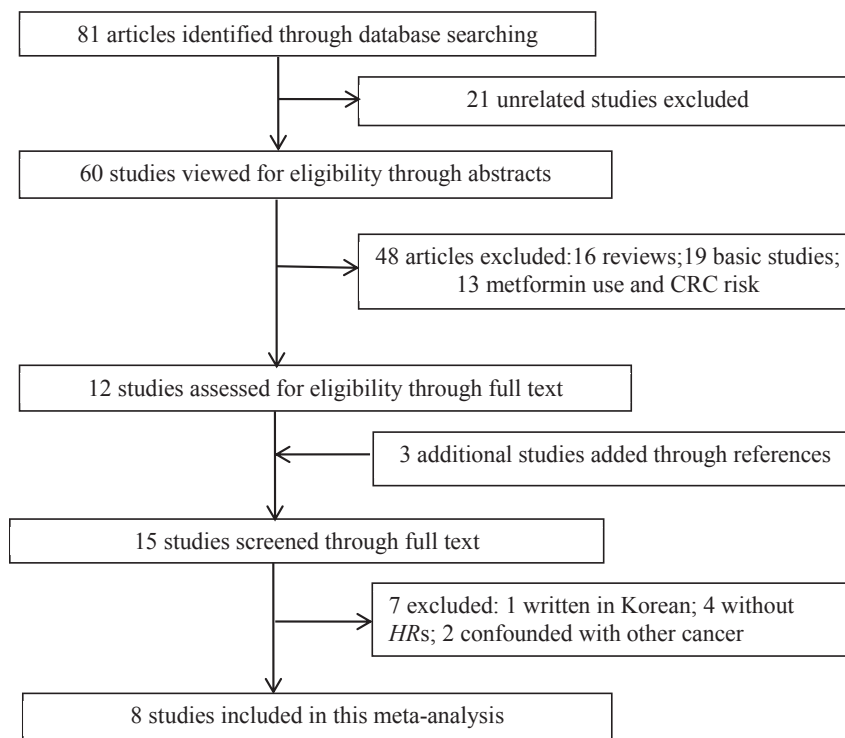

Fig. 1. Flow diagram for study selection. CRC: colorectal cancer; *HR*: hazard ratio.

Table 1
Characteristics of studies included in the meta-analysis evaluating the outcomes of CRC patients treated with metformin.

Authors	Publication year	Design	Country	Duration of the study	Age (metformin vs. non-metformin)	Number of patients (metformin vs. non-metformin)	Outcome assessment	HR (95% CI) for OS	HR (95% CI) for CS	CRC stage
Spillane et al[19]	2013	RCS	Ireland	2001–2006	74 vs. 76	207 vs. 108	OS and CS	0.69 (0.49–0.97)	0.61 (0.37–1.01)	I–III
Zanders et al[20]	2015	RCS	Netherlands	1998–2011	72.3 vs. 71.9	666 vs. 1129	OS	0.78 (0.59–1.01)	–	I–IV
Cossor et al[21]	2013	RCS	USA	1993–1998	–	84 vs. 128	OS and CS	0.86 (0.49–1.52)	0.78 (0.38–1.55)	I–IV
Fransgaard et al[22]	2016	RCS	Denmark	2003–2012	71.7 vs. 71.3	1962 vs. 388	OS	0.85 (0.73–0.93)	–	I–IV
Mc Menamin et al[23]	2016	RCS	UK	1999–2009	–	675 vs. 522	CS	–	1.06 (0.80–1.40)	I–IV
Garrett et al[24]	2012	RCS	USA	2004–2008	–	208 vs. 206	OS	0.6 (0.5–0.8)	–	I–IV
Lee et al[25]	2012	RCS	Korea	2000–2008	–	258 vs. 337	OS and CS	0.66 (0.48–0.92)	0.66 (0.45–0.98)	I–IV
Paulus et al[26]	2016	RCS	USA	2001–2008	–	2038 vs. 2136	OS	0.87 (0.79–0.95)	–	I–IV

CRC: colorectal cancer; HR: hazard ratio; CI: confidence interval; OS: overall survival; CS: CRC-specific survival; RCS: retrospective cohort study; –: no data.

Table 2
Methodological quality of retrospective cohort studies.

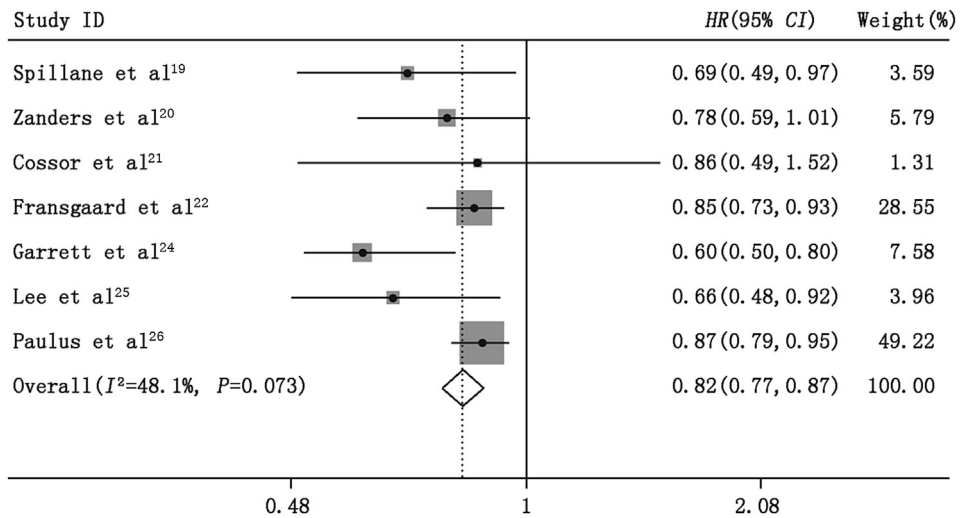| Authors	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor	Outcome assessment	Follow–up long enough for outcomes to occur	Adequacy of follow–up of cohorts	Total quality scores
Spillane et al[19]	+	+	+	+	++	+	–	+	8
Zanders et al[20]	+	+	+	+	++	+	+	–	8
Cossor et al[21]	+	+	+	+	+	+	–	–	6
Fransgaard et al[22]	+	+	+	+	+	+	+	+	8
Mc Menamin et al[23]	+	+	+	+	++	+	+	–	8
Garrett et al[24]	+	+	+	+	+	+	+	+	8
Lee et al[25]	+	+	+	+	+	+	+	–	7
Paulus et al[26]	+	+	+	+	++	+	+	–	8

Fig. 2. Forest plot of *HR* for OS of CRC patients associated with metformin use *vs.* non-use. *HR*: hazard ratio; *CI*: confidence interval; OS: overall survival; CRC: colorectal cancer.
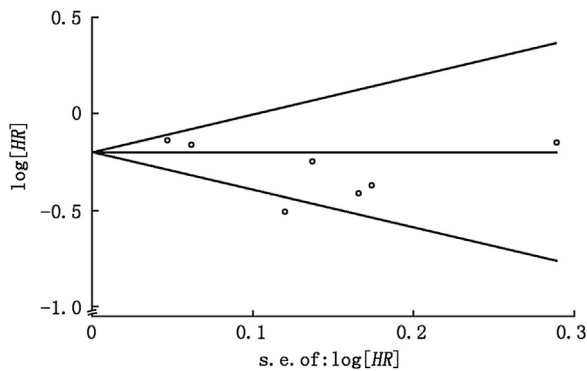

Fig. 3. Funnel plot analysis to detect publication bias. *HR*: hazard ratio.

detect any publication bias based by Egger's test ($t = -2.04$, $P = 0.097$) or Begg's test ($Z = 0.60$, $P = 0.548$).

The pooled *HR* for CS was 0.84 (95% *CI*: 0.69–1.02, $P = 0.079$), with no evidence of heterogeneity ($I^2 = 47.7\%$, $P = 0.125$) (Fig. 4). Subgroup analysis was not performed since there was no evidence of heterogeneity. As only four studies reported CS, it was difficult to confirm whether publication bias existed in our meta-analysis.

Discussion

Our meta-analysis of observational studies explored the association between metformin treatment and CRC outcomes in patients with T2DM, and determined that
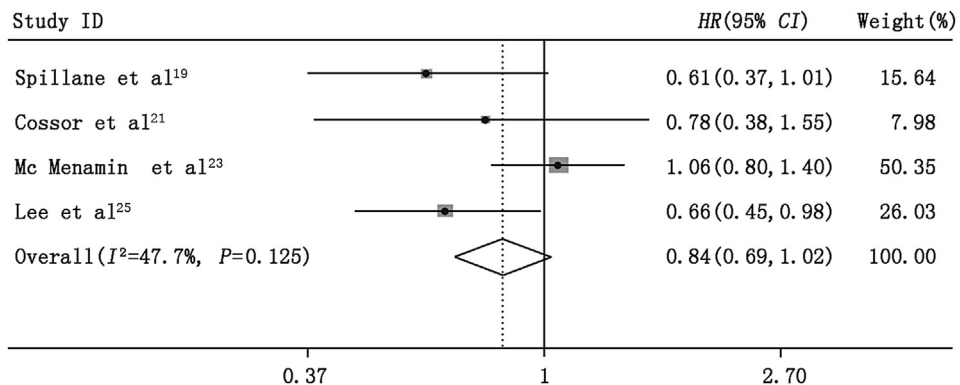

Fig. 4. Forest plot of *HR* for CS of CRC patients associated with metformin use *vs.* non-use. *HR*: hazard ratio; *CI*: confidence interval; CS: colorectal cancer-specific survival; CRC: colorectal cancer.

metformin use improves the OS of CRC patients, but it cannot prolong the CS of CRC patients with T2DM.

The study of Miranda et al[27] suggested that metformin together with conventional chemotherapy could be an effective treatment regimen for CRC patients with T2DM. Other previous studies found that metformin can improve the survival outcomes of patients with T2DM.[9,28] He et al[9] conducted a meta-analysis, which included six studies, to assess the correlation between metformin use and survival in CRC patients. This meta-analysis revealed an improved OS for metformin users among CRC patients compared with non-users (*HR* = 0.68, 95% *CI*: 0.58−0.81). Mei et al[28] also performed a meta-analysis that included 2461 cases of patients from six retrospective cohort studies. From this study, they drew the conclusion that metformin can reduce the risk of all causes of death by 44% (*HR* = 0.56, 95% *CI*: 0.41−0.77) and the risk of CRC-specific death by 34% (*HR* = 0.66, 95% *CI*: 0.50−0.87) in CRC patients compared to non-users. However, the previous meta-analyses are relatively inconclusive with limited number of included studies. More recently, several relevant large-scale studies have been published, so we conducted an updated systematic review and meta-analysis with the aim to draw a definite conclusion. The results of the present study were in line with the previous ones.

The possible anti-tumor mechanisms of metformin are thought to be because of suppression of the mammalian target of rapamycin (mTOR) signaling pathway, which plays a significant role in the cellular protein translational machinery and cell proliferation.[29] Metformin can inhibit proliferation, metastasis, and invasion of tumor cells, as well as induce tumor cells to undergo apoptosis under high glucose conditions through activation of adenosine monophosphate-activated protein kinase (AMPK) and inhibition of mTOR signaling.[30−32] It has also been shown to block the effect of a high-energy diet on tumor cell growth, reduce insulin resistance, and alleviate the overexpression of fatty acid synthase (FASN).[33,34] Additionally, metformin, as an antitumor agent, exhibits a synergist effect with other chemotherapeutic drugs and cytotoxic effect on cancer stem cells.[35] Furthermore, hyperglycemia is a basic feature of T2MD, considered as a risk factor for the occurrence and development of CRC. High glucose environment leads to aberrant glycosylation, cell proliferation, invasion and metastasis of CRC.[36] Metformin decreases the level of blood glucose by inhibiting liver glucose production and increasing the sensitivity of insulin to the target organs, thus suppressing the hyperglycemia-induced carcinogenesis.

However, our study had several limitations that merit further consideration. First, our results were based on information from observational studies, and no feasible randomized controlled trials (RCTs) were included. Observational studies have methodological shortcomings, and are prone to time-related biases, such as immortal time bias and time-lagging issues.[37] Second, some studies did not adjust for potential confounding factors, such as obesity, CRC stage, population source, and other anti-diabetic medications. Third, the included studies were limited in reporting the dose of metformin among CRC patients with T2DM, so we could not do a subgroup meta-analysis according to metformin dose. Additionally, the studies did not report the effects of any side effects or duration of metformin use on CRC survival. Hence, the observed benefits from duration of metformin use cannot be clearly defined and we cannot completely evaluate its safety. Finally, our analysis was confined to English language studies, so publication bias may have been introduced.

This meta-analysis provides evidence that metformin use can reduce all-cause death among T2DM patients. Well-designed cohort studies and RCTs are needed to confirm these findings and further explore the efficacy and safety of this anti-tumor medicine.

Conflicts of interest

All authors declare that they have no conflicts of interest to disclose.

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