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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.

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]

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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