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REVIEW

# Metformin and colorectal cancer: a systematic review, meta-analysis and meta-regression

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## Abstract

**Purpose** Metformin may have a role in reducing the incidence of colorectal cancer (CRC) and improving survival outcome. This meta-analysis explored the effect of metformin use on colorectal adenoma and cancer incidence, and colorectal oncological outcomes.

**Methods** A database search was conducted on Medline, Embase and CNKI for studies comparing metformin vs. non-metformin users, metformin users vs. non-diabetics and metformin users vs. diabetics with diet-only treatment. Meta-analysis was done with DerSimonian and Laird with risk ratios (RR), and hazard ratios (HR) for survival outcomes.

**Results** We included 58 studies and summarized incidences of colorectal adenoma and cancer, as well as cancer survival outcomes. Metformin users had a significant lower incidence of colorectal adenoma (RR 0.77, CI 0.67–0.88, $p < 0.001$), advanced adenoma (0.61, CI 0.42–0.88, $p = 0.008$) and CRC (RR 0.76, CI 0.69–0.84, $p < 0.001$) respectively compared with non-metformin users. Overall survival (HR 0.6, CI 0.53–0.67, $p < 0.001$) and CRC-specific survival (HR 0.66, CI 0.59–0.74, $p < 0.001$) were higher among metformin users compared with non-metformin users. Further analysis on overall survival of metastatic CRC patients revealed significantly higher survival rates in metformin users (HR 0.77, CI 0.68–0.87, $p < 0.001$).

**Conclusion** This meta-analysis showed that metformin use significantly reduces colorectal adenoma and cancer incidence and improves colorectal cancer outcomes.

**Keywords** Adenoma · Malignant · Incidence · Survival outcomes · Type 2 diabetes mellitus

## Introduction

Type 2 diabetes mellitus (T2DM) is highly prevalent worldwide. It is characterized by chronic hyperglycaemia and is associated with micro- and macrovascular complications. People with T2DM have a lower quality of life measures and had a higher risk of premature death from cardiovascular disease [1]. Growing evidence also suggests that people with T2DM have a higher risk of cancer incidence and death [2]. Several epidemiological studies have reported the higher risk of gastrointestinal cancer, liver cancer, breast cancer and genitourinary cancer with T2DM [2]. Hyperglycaemic milieu and background insulin resistance of T2DM can increase the risk of cancer [2].

Colorectal cancer (CRC) is the third most common cancer in the world, and the second most common cause of cancer death [3]. In a previous meta-analysis of eight studies, T2DM patients have a 21% higher risk of CRC [4]. Others have shown a 36% higher risk of CRC in six case-control studies

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and 29% higher risk of CRC in nine cohort studies among patients with T2DM [5]. There are reports that T2DM patients are less inclined to undergo CRC screening, which might have led to late diagnosis and poorer outcomes [6]. Compared with non-diabetic patients, T2DM patients experience a lower treatment response and higher complications from CRC therapy [6]. Patients with T2DM also have a higher risk of death from CRC [5].

Metformin is the most commonly prescribed oral glucose-lowering drug (GLD) for T2DM due to its efficacy in lowering HbA1c levels, good safety profile, wide availability and its affordability [7]. Interestingly, metformin is emerging as a potential anti-cancer candidate based on findings from several preclinical studies to observational cohorts and prospective trials [8, 9]. The inhibitory effects of metformin on cancer cell growth and proliferation have been attributed mainly to the liver kinase B1 (LKB1)–dependent activation of AMPK and reduction of mammalian target of rapamycin (mTOR) activity [10].

The role of metformin as an anti-cancer agent in CRC is less clear. Some studies have demonstrated benefits in CRC survival outcomes, but some did not [11, 12]. Previous meta-analyses have not successfully provided guidance or explanation on such disparate results [11–14]. This meta-analysis aims to provide an updated and expanded review regarding the role of metformin in both adenoma formation and CRC development, as well as survival outcomes.

## Methods

### Search strategy

The review was synthesized with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Electronic database searches were conducted on Medline, Embase and CNKI from inception to 15th March 2020. Synonyms and keywords were searched for 'Colorectal Cancer' and 'Metformin', and abstracts of potentially eligible studies were imported into EndNote X9 for removal of overlapping data. An example of the search strategy can be found in Supplementary Table 1.

### Selection of studies and data extraction

The outcomes of interest were both CRC neoplasm and oncological outcomes including overall survival, overall survival of patients with stage IV metastatic cancer, cancer-specific

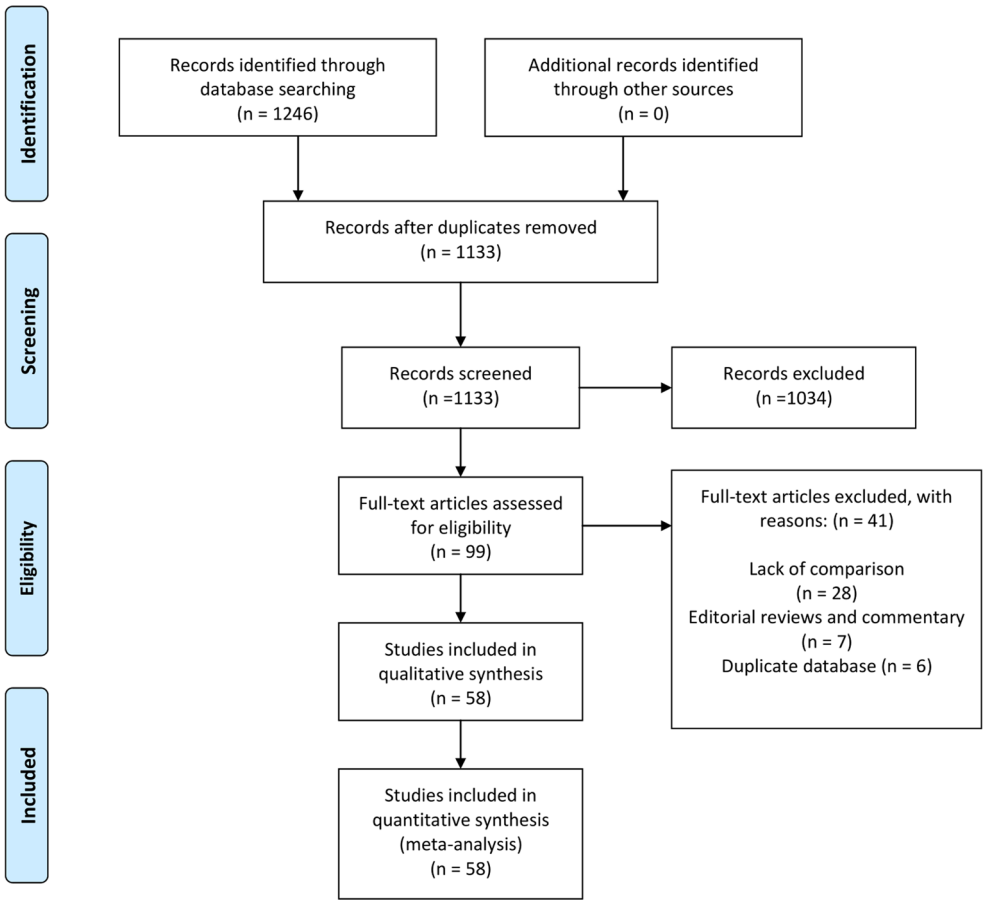


**Fig. 1** PRISMA flowchart

survival, locoregional cancer recurrence and disease-free survival. Reviewing of abstracts and full text were conducted independently by two authors, and discrepancies such as duplicate databases were removed on the basis of consensus and involvement of a third author. The blinded pair then independently extracted general demographics (author, year, country), characteristics of included patients (sample size, age, gender, diabetes) and binary event rates in CRC incidences and oncological outcomes (hazard ratios). When hazard ratios and corresponding confidence interval were unavailable, appropriate formula for estimates was applied [15–17]. Similarly, when mean was not reported, transformation of data was undertaken by pre-existing methods [18, 19].

### Statistical analysis and assessment of quality

Meta-analysis was conducted in risk ratios (RR) for binary variables and hazard ratios (HR) for survival outcomes. Regardless of heterogeneity measures, $I^2$, tau and Cochran Q test, DerSimonian-Laird random effect models was used. In meta-regression, the residual maximum likelihood (REML) model and Knapp-Hartung variance estimator were used after a natural log was applied to the RR/HR to compare with covariates with the influence on the effect size [20, 21]. Publication bias was assessed with Egger's regression test [22]. Statistical analyses were carried out with STATA (16.1 StataCorp LLC) and $p$ values that were less than 0.05 were considered statistically significant.

The quality of the included randomized controlled trials (RCT) studies and non-RCT studies was assessed using the Jadad Scale and Newcastle-Ottawa Scale respectively [23, 24]. The elements of the Jadad Scale (randomisation, blinding and account of all patients) were used to assess biasness in individual studies [24]. Similarly, the Newcastle-Ottawa Scale examines the selection of study groups, comparability and ascertainment of the exposure in case-controls or outcome of interest in cohort studies respectively [23].

## Results

A systematic literature search was conducted based on the search strategy and 1133 studies were derived. Ninety-nine full-text articles were subsequently reviewed to obtain a total of 58 studies for the analyses (Fig. 1). Among the 58 studies, 16 were conducted in USA [25–40], 11 in Korea [41–51], 5 in Taiwan [52–56], 17 in Europe [11, 57–72], 1 in Japan [73], 1 in Singapore [74], 2 in the Middle East [75, 76], 2 in China [77, 78], 1 in Canada [79], 1 in Australia [80] and one particular study that spanned across USA, Canada and Puerto Rico [81]. Four were RCTs [29, 72, 73, 81], nine were case-control studies [25, 31, 32, 34, 45, 57, 62, 63, 70] and forty-five were observational cohort studies. Thirty-four were retrospective cohort studies [11, 26, 28, 30, 35–42, 44, 46–53, 55, 58, 59, 64, 66–69, 74–79], seven were prospective cohort studies [46, 54, 60, 61, 65, 71, 80] and four were cross-sectional studies [27, 33, 43, 56]. The summary results are presented in Table 1.

### Cancer incidence

In total, 1,733,229 patients (metformin $n = 951,275$, non-metformin $n = 781,954$) were studied for incidence of CRC development. All except one study analysed outcomes of interest in patients with T2DM in exception to Higurashi et al. [73] study on using metformin in non-diabetic patients. Eight out of the 33 studies analysed metformin use on colorectal adenoma or/and advanced adenoma incidence, while the remaining 25 studies analysed metformin use on CRC incidence.

### Cancer survival

In cancer survival, 66,873 patients (metformin $n = 12,448$, non-metformin $n = 54,425$) were analysed for their oncological outcomes. There were 46,579 patients without T2DM. Twenty-four studies examined the overall survival of patients; five studies reported on the overall survival of stage IV CRC patients, eight studies on cancer-specific survival, four studies on locoregional cancer recurrence and five studies on disease-free survival.

### Cancer incidence

#### Adenoma formation

There were six studies which compared adenoma formation between metformin and non-metformin users. Pooled analysis of 4328 patients (metformin $n = 1580$, non-metformin $n = 2748$, showed a significant 23% lower adenoma formation among metformin users (RR 0.77, CI 0.67–0.88, $p < 0.001$, Fig. 2). Egger's test for publication bias was not significant ($p = 0.4684$). In advanced adenoma, pooled analysis of 3884 patients (metformin $n = 1388$, non-metformin $n = 2496$) from four studies showed that metformin significantly reduced the risk of advanced adenoma by 39% (RR 0.61, CI 0.42–0.88, $p = 0.008$, Supplementary Fig. 1). Publication bias by Egger's regression was not significant ($p = 0.2751$).

Only one study examined the colorectal adenoma risk between metformin ($n = 457$) and diet control ($n = 1578$) in patients with T2DM and a history of polypectomy [26]. During the median of 4.5 years of follow-up, metformin use was associated with a lower adenoma incidence risk (adjusted HR 0.76, CI 0.65–0.89) compared with diet control. Additionally, one RCT examined the use of metformin (mean dose of 250 mg daily) in 133 non-diabetic patients over 52 weeks [73]. The metformin group ($n = 71$) showed a 40% reduction in the colorectal adenoma formation compared with placebo ($n = 62$) (adjusted RR 0.60, CI 0.39–0.92, $p = 0.016$).

**Table 1** Summary of results

| | No. of articles | Metformin sample size | Control sample size | RR/ HR | CI | *p* value |
|---|---|---|---|---|---|---|
| Adenoma | | | | | | |
| Metformin vs. non-metformin | 6 | 1580 | 2748 | 0.77 | 0.67–0.88 | < 0.001 |
| Metformin vs. diet | 1 | 457 | 1578 | 0.76 | 0.65–0.89 | - |
| Metformin vs. placebo | 1 | 71 | 62 | 0.60 | 0.39–0.92 | 0.016 |
| Advanced adenoma | | | | | | |
| Metformin vs. non-metformin | 4 | 1388 | 2496 | 0.61 | 0.42–0.88 | 0.008 |
| Cancer incidence | | | | | | |
| Metformin vs. non-metformin | 24 | 946,292 | 773,506 | 0.76 | 0.69–0.84 | < 0.001 |
| Metformin vs. diet | 1 | 2875 | 4060 | 1.20* | 0.56–2.56 | - |
| Overall survival | | | | | | |
| Metformin vs. non-metformin | 22 | 11,338 | 6359 | 0.6 | 0.53–0.67 | < 0.001 |
| Metformin vs. non-diabetic | 8 | 3497 | 46,579 | 0.97 | 0.84–1.13 | 0.718 |
| Metformin vs. diet | 3 | 4094 | 1396 | 0.83 | 0.52–1.31 | 0.416 |
| Overall survival—metastatic cancer | | | | | | |
| Metformin vs. non-metformin | 5 | 516 | 615 | 0.77 | 0.68–0.87 | < 0.001 |
| Metformin vs. non-diabetic | 2 | 357 | 36,343 | 1.14 | 0.67–1.94 | 0.625 |
| CRC-specific survival | | | | | | |
| Metformin vs. non-metformin | 8 | 5926 | 2403 | 0.66 | 0.59–0.74 | < 0.001 |
| Metformin vs. non-diabetic | 1 | 84 | 1854 | 1.01 | 0.61–1.67 | 0.969 |
| Recurrence | | | | | | |
| Metformin vs. non-metformin | 4 | 354 | 317 | 0.65 | 0.56–0.76 | < 0.001 |
| Metformin vs. non-diabetic | 2 | 135 | 2113 | 2.1 | 0.42–10.53 | 0.369 |
| Disease-free survival | | | | | | |
| Metformin vs. non-metformin | 4 | 430 | 361 | 0.73 | 0.43–1.24 | 0.25 |
| Metformin vs. non-diabetic | 2 | 135 | 2113 | 1.13 | 0.83–1.54 | 0.425 |
| Metformin vs. diet | 1 | 99 | 67 | 0.68 | 0.32–1.46 | 0.322 |

*Incidence rate ratios

### Malignant lesions

There were 24 studies that reported the association between metformin use on colorectal cancer incidence in patients with T2DM. We included 946,292 metformin users and 773,506 non-metformin users in the analysis. Overall, metformin users had a 24% lower in colorectal cancer incidence compared with non-metformin users (RR 0.76, CI 0.69–0.84, $p < 0.001$, Supplementary Fig. 2). Publication bias was not significant ($p = 0.5939$).

Only one study compared between metformin and diet therapy. In a prospective cohort study of 3 years of follow-up, 2875 metformin users were compared with 4060 on diet-only therapy [71]. The metformin group had a non-significant 20% higher in colorectal cancer incidence rate compared with the diet-only group (incidence rate ratios 1.20, CI 0.56–2.56).

## Cancer survival

### Overall survival

Analysis of 24 studies was performed for three groups including metformin users vs. non-metformin users,

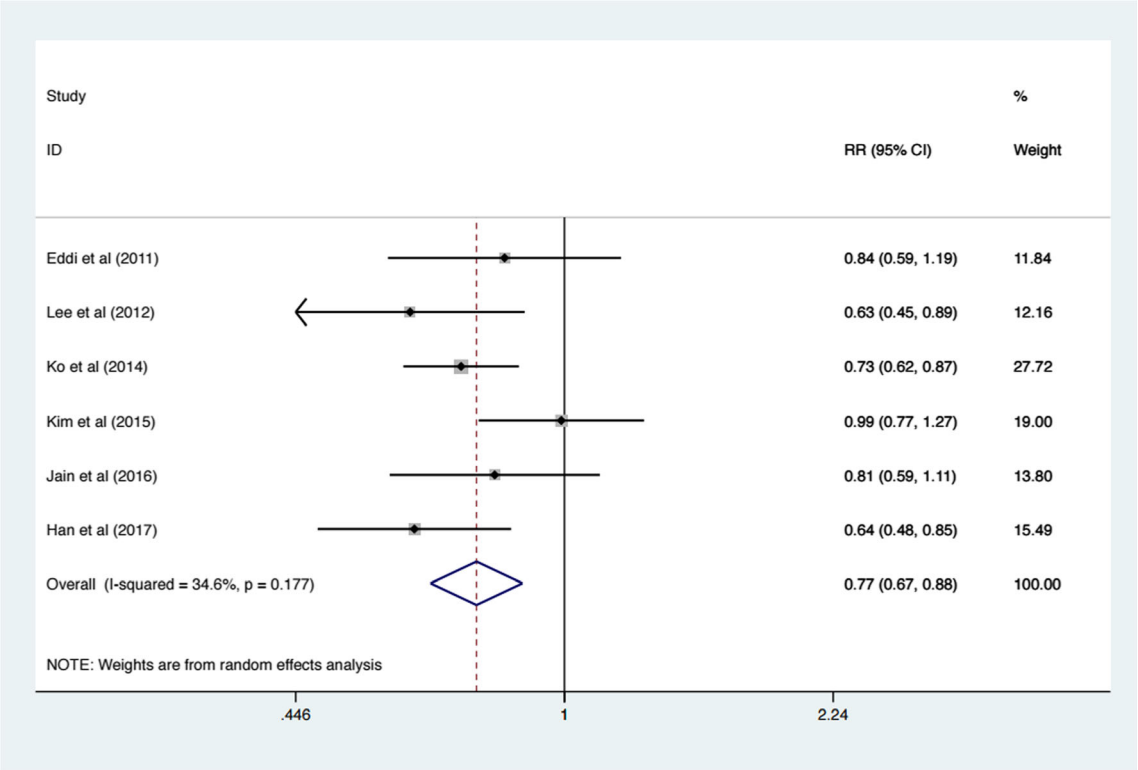


**Fig. 2** Meta-analysis of adenoma incidence

metformin users vs. diet-only therapy patients and metformin users vs. non-diabetic patients. In a pooled analysis of 17,697 patients (metformin $n = 11{,}338$ vs. non-metformin $n = 6359$), there was a significant increase in overall survival in metformin users (HR 0.60, CI 0.53–0.67, $p < 0.001$, Fig. 3). In a pooled analysis of 5490 patients (metformin $n = 4094$ vs. diet-only $n = 1396$), there was no significant difference in overall survival (HR 0.83, CI 0.52–1.31, $p = 0.416$). Pooled analysis of 50,076 patients (metformin $n = 3497$ vs. non-diabetic $n = 46{,}579$) revealed no significant difference in overall survival (HR 0.97, CI 0.84–1.13, $p = 0.718$). Egger's test for publication bias was not significant ($p = 0.222$).

### Overall survival for metastatic colorectal cancer

Analysis of five studies was conducted for two groups including metformin users vs. non-metformin users, and metformin users vs. non-diabetic patients. In a pooled analysis of 1131 diabetic patients (metformin $n = 516$ vs. non-metformin $n = 615$), there was significant higher survival rate among metformin users (HR 0.77, CI 0.68–0.87, $p < 0.001$, Fig. 4). In a pooled analysis of 36,700 patients (metformin $n = 357$ vs. non-diabetics $n = 36{,}343$), there was no difference in survival (HR 1.14, CI 0.67–1.94, $p = 0.625$). Publication bias was not significant ($p = 0.8512$).

### Cancer-specific survival

Analysis of metformin users ($n = 5926$) vs. non-metformin users ($n = 2403$) showed a higher cancer-specific survival among metformin users (HR 0.66, CI 0.59–0.74, $p < 0.001$, Supplementary Fig. 3). There was no significant difference between metformin users ($n = 84$) and non-diabetics ($n = 1854$) (HR 1.01, CI 0.61–1.67, $p = 0.969$, Supplementary Fig. 3). Publication bias was not significant ($p = 0.0533$).

### Risk of colorectal cancer recurrence

In the analysis of four studies, metformin showed a significant lower cancer recurrence (HR 0.65, CI 0.56–0.76, $p < 0.001$, Supplementary Fig. 4) compared with non-metformin users. Analysis of metformin users vs. non-diabetic patients revealed no significant effect on cancer recurrence (HR 2.1, CI 0.42–10.53, $p = 0.369$, Supplementary Fig. 4). Publication bias was significant ($p = 0.006$).

### Disease-free survival

In the analysis of five studies, metformin had no significant effect on disease-free survival for all three groups: metformin users vs. non-metformin users (HR 0.73, CI 0.43–1.24, $p = 0.25$, Supplementary Fig. 5), metformin users vs. diet-only

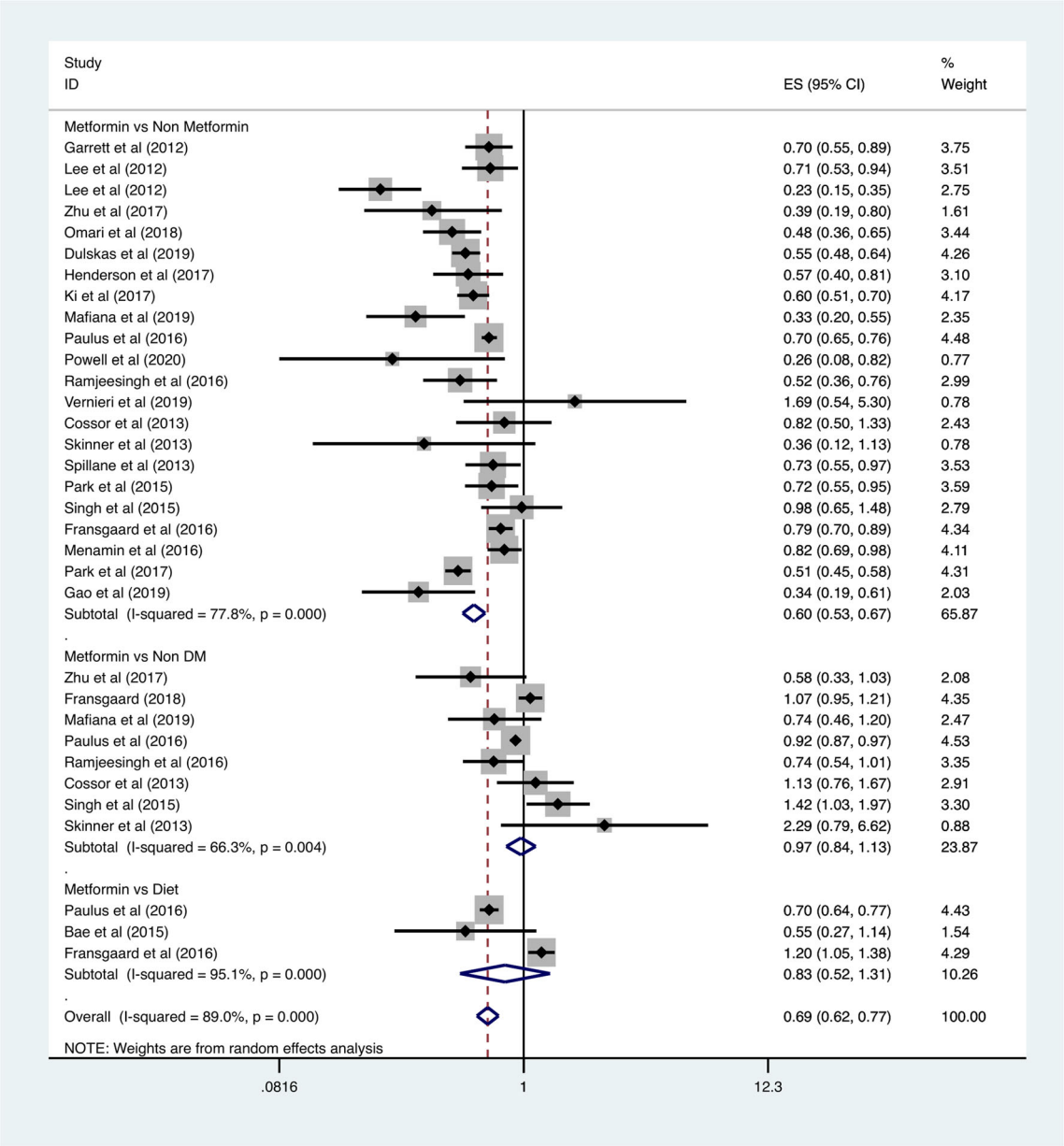


**Fig. 3** Meta-analysis on OS of CRC patients

patients (HR 0.68, CI 0.32–1.46, $p = 0.322$, Supplementary Fig. 5), metformin users vs. non-diabetic patients (HR 1.13, CI 0.83–1.54, $p = 0.425$, Supplementary Fig. 5). Publication bias was not significant ($p = 0.6978$).

## Meta-regression

### Cancer incidence

The full results of the meta-regression are summarized in Supplementary Table 4. Among metformin users, age ($\beta = 0.043$, SE = 0.033, $p = 0.245$) and aspirin use ($\beta = -1.808$, SE = 0.627, $p = 0.102$) were non-significant factors on CRC development. Smoking (current and previous) status was a significant factor ($\beta = -1.416$, SE = 0.357, $p = 0.017$) on CRC development. Among metformin use, there was a larger risk reduction in CRC development among those with current and past smoking.

### Overall survival

We explored the influence of oncological characteristics on the effect size of survival among metformin vs. non-metformin users. Proportion of patients with stage IV had no significant impact on overall survival ($\beta = -0.602$, SE = 0.867, $p = 0.507$). BMI was not a significant predictor in overall survival ($\beta = 0.024$, SE = 0.025, $p = 0.360$).

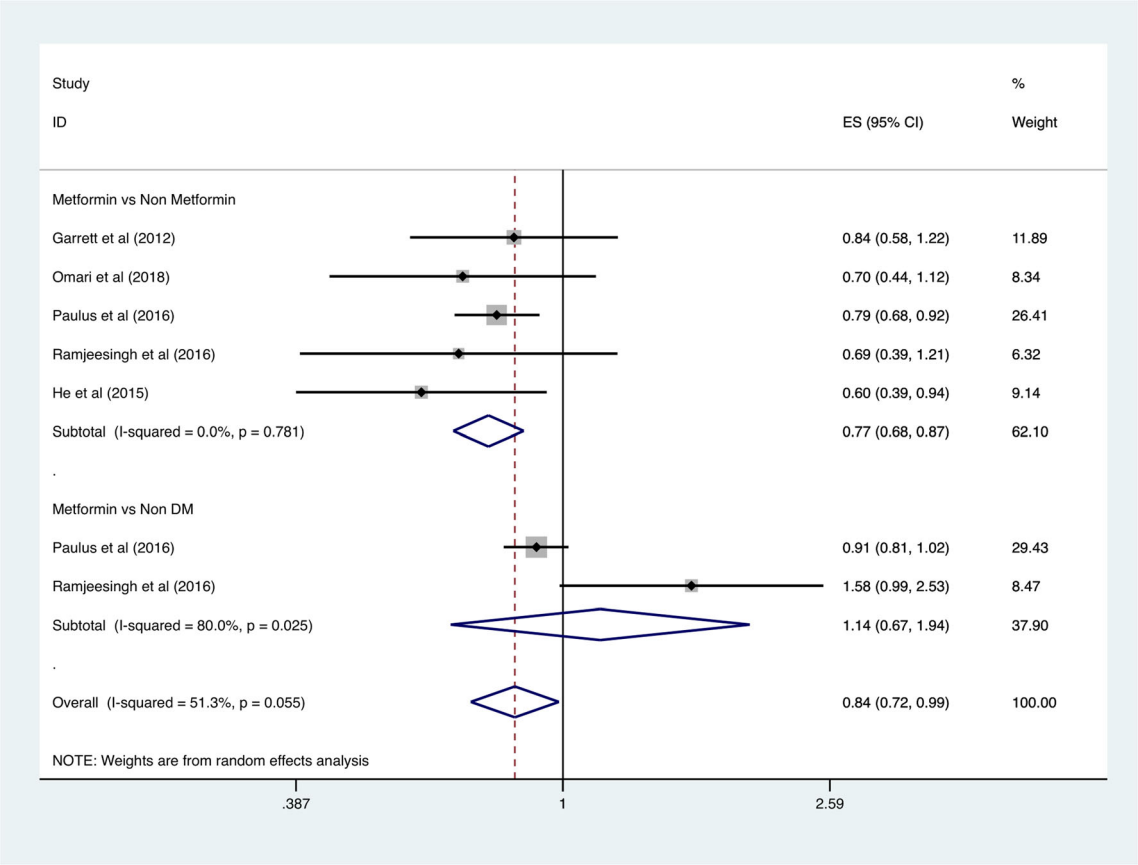


**Fig. 4** Meta-analysis on OS on stage IV CRC patients

## Discussion

In this meta-analysis, metformin reduces colorectal adenoma formation and colorectal cancer incidence. Metformin use is also associated with better cancer survival. For benign lesions, the risk of adenoma and advanced adenoma was significantly lower by 23% and 39% respectively among metformin users. Likewise, cancer incidence in diabetic patients was significantly 24% lower among metformin users. In oncological outcomes, metformin users were generally favoured over non-metformin users in terms of overall survival for both non-metastatic and metastatic cancer, cancer-specific survival and reduced recurrence.

T2DM is characterized by insulin resistance and hyperinsulinemia. There is putative risk of hyperinsulinemia on cancer formation due to its direct effects via cellular activation of PI3K/Akt/mTOR signalling pathways and indirectly through its effect on the insulin-like growth factor (IGF) system and alteration in steroid sexual hormones [82]. In cancer cells, studies have found enhanced expression of insulin-like growth factor receptor (IGF-R) which might lead to increased glucose uptake and high cell proliferation [83]. Hyperglycaemia and oxidative stress pathways may also induce DNA damage and mutation accumulation, contributing to a higher risk of cancer formation [84]. The underlying anti-cancer mechanisms of metformin are likely to involve multiple molecular targets and have been reviewed intensively elsewhere [82]. Briefly, metformin has been shown to induce apoptosis and autophagy through oxidative stress, inflammation and metabolic homeostasis via AMPK and mTOR pathways [85]. Metformin also inhibits mitochondrial mammalian respiratory chain complex I and activates liver kinase B1, a tumour suppressor [10]. These activate downstream target AMPK, thus inhibiting mTOR activity [85, 86]. Metformin also exerts destructive effects on cancer stem cells and may work synergistically with chemotherapy drugs [87, 88], all of which reduce cancer risk and progression, increasing survival probability.

This protective effect of metformin also extends to colorectal adenoma and advanced adenoma formation as studies reported a stronger association to insulin and IGF-1 levels for advanced adenomas [89, 90]. This suggests that IGF-1 might be involved in the progression of benign colorectal lesions and contribute to a higher risk of progression of benign adenoma to carcinoma among people with T2DM [91]. In this meta-analysis, we found that metformin reduces the risk of benign adenoma and advanced adenoma formation, with the risk reduction observed greater for advanced adenoma formation

than benign adenoma. This is not surprising as metformin has been shown to reduce hyperglycaemia, hyperinsulinemia and IGF-1 levels, which all are growth factors in cancer development and progression.

Our study also showed that the meta-regression for age and aspirin use did not alter the effect of metformin on CRC formation. Aspirin has been shown to reduce incidence of colorectal neoplasia; thus, our results may be interpreted independently of the effects of aspirin [92]. Additionally, our meta-regression suggested metformin had a larger risk reduction on CRC formation among those with current and previous smoking. Cigarette smoking is a modifiable risk factor for CRC. Cigarette smoking leads to higher inflammation, DNA mutation and angiogenesis which leads to higher risk of gastrointestinal cancer [93]. Cigarette smoking is also a risk factor for T2DM and its related complications. It is therefore plausible that metformin might exert a greater anti-neoplastic effect in people with T2DM and history of current or previous smoking. We recognize that the risk of cardiovascular diseases (CVD) triples for patients with T2DM and current smoking compared with non-diabetic non-smokers [94]. Thus, diabetic smokers might suffer from premature death from CVD, which might lead to a false observation of a lower risk of CRC incidence among current and past smokers. Admittedly, our analysis is limited by the amount of data available as definitions of duration and dose of smoking vary between studies.

In assessing oncological outcomes, our analysis showed that metformin users had an increased overall survival for non-metastatic and metastatic CRC, CRC-specific survival and reduced recurrence risk compared with non-metformin users. However, there was no significant effect observed in disease-free survival. Several studies including Hosono et al. suggests metformin's potential in reducing risk of colorectal adenoma and subsequent cancer recurrence by suppressing formation of aberrant crypt foci [95]. Different oncological treatment regimens used in different studies might account for the lack of consistency in the effect of metformin on disease-free survival [96]. For example, the use of high dose of oxaliplatin-fluoropyrimidine chemotherapy may overinflate metformin's true anti-cancer properties [72]. We were unable to adjust for the use of chemotherapeutic agents as only four studies specified the treatment regimen.

Interestingly, majority of the subgroup analysis performed involving metformin vs. diet therapy or metformin vs. non-diabetic did not reveal significance in all oncological outcomes including overall survival and CRC-specific survival. Spillane et al. demonstrated that high doses of metformin reduced cancer-specific mortality to that of non-diabetics [69]. T2DM is associated with poorer cancer survival outcomes; thus, it is probable that metformin improves the survival outcomes of patients with T2DM to that of T2DM patients on diet-only therapy or non-diabetic patient [82, 85, 97]. Other factors such as duration and metformin dose [54], glycaemic control [98] and tumour biology [99] may affect survival and would require further investigations.

In metastatic colorectal cancer, the overall survival was 23% higher among metformin users compared with non-metformin users. Metastatic progression involves various steps, including (1) invasion and spread of cancer cells, and (2) secondary tumour development at distant sites [100]. Metformin may prevent the invasion and further metastatic spread of colorectal cancer cells, metformin through reduction of epithelial-mesenchymal transition (EMT) [101]. Specifically, EMT is a suggested mechanism where epithelial cells are transformed into undifferentiated mesenchymal cells, which can freely metastasize to distant sites and establish new colonies [102]. Metformin has been shown to reduce EMT via PI3K/Akt/mTOR pathway [103], and also by repressing IL-6 signalling [104] and Wnt/beta-catenin pathway [105]. In addition, metformin has been shown to suppress angiogenesis which might attenuate cancer cell invasion and reduce distant metastasis [106]. The use of metformin in refractory colorectal cancer is currently undergoing investigations, as seen from ongoing phase II clinical trials in Brazil (NCT01930864) and USA (NCT03800602).

### Limitation

This meta-analysis has several limitations. Firstly, we did not assess the effect of other GLDs such as sulfonylureas or insulin on colorectal cancer incidence and survival due to a lack of information provided in the articles. Studies have suggested that the use of non-metformin antidiabetic pharmacotherapy may lead to increased cancer risk and reduced survival [107]. Since metformin users may have been prescribed other antidiabetic medication simultaneously, confounders might be present. Also, many of our studies were observational in nature and are prone to time-related bias which may overestimate the protective effects of a drug [108].

## Conclusion

Currently, metformin is the most common prescribed oral GLD for T2DM due to its efficacy, good safety profile and, importantly, affordability. Specifically, for colorectal lesions, metformin use in people with T2DM is associated with a lower incidence of benign adenoma and cancer formation, and better oncological outcomes. Further investigations are required to further understand the interplay between the anti-tumour and antidiabetic effect of metformin.

**Code availability** Not applicable.

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**Data availability** All data available upon request.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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