Systematic Review and Meta-Analysis

Medicine

OPEN

Prognostic value of metformin in cancers
An updated meta-analysis based on 80 cohort studies

Jing Yang, MM[a], Hang Yang, MM[a], Ling Cao, MM[a], Yuzhen Yin, MD[a], Ying Shen, MM[b], Wei Zhu, MD[c,*]

Abstract

Background: Experiments have shown that metformin can inhibit cancer cell growth, but clinical observations have been inconsistent, so we pooled the currently available data to evaluate the impact of metformin on cancer survival and progression.

Methods: PubMed, web of science, Embase, and Cochrane databases were searched. Pooled hazard ratios (HRs) were identified using a random-effects model to estimate the strength of the association between metformin and survival and progression in cancer patients.

Results: We incorporated 80 articles published from all databases which satisfied the inclusion criterion. It showed that metformin was associated with better overall survival (hazard ratio [HR] = 0. 81; 95% confidence interval [CI]: [0.77–0.85]) and cancer-specific survival (HR = 0.79; 95% CI: [0.73–0.86]), and metformin was associated with progression-free survival (HR = 0.76; 95% CI: [0.66–0.87]). In patients with diabetes mellitus, the HR of overall survival was 0.79(95% CI: [0.75–0.83]), progression-free survival was 0.72(95% CI: [0.60–0.85]), and the cancer-specific survival was 0.76(95% CI: [0.68–0.86]). It was proposed that metformin can improve the prognosis of cancer patients with diabetes mellitus.

Conclusion: Based on cohort studies, metformin therapy has potential survival benefits for patients with malignancy, especially with the greatest benefits seen in breast cancer on overall survival, progression-free survival, and cancer-specific survival. And metformin also showed potential benefits in cancer-specific survival in colorectal and prostate cancer.

Abbreviations: AMPK = adenosine monophosphate-activated protein kinase, CI = confidence interval, CSS = cancer-specific survival, EMT = epithelial-mesenchymal transformation, HR = hazard ratio, IGF = insulin-like growth factor, mTOR = mechanistic target of rapamycin, OS = overall survival, PFS = progression-free survival, PTEN = phosphatase and tensin homolog.

Keywords: cancer, cancer-specific survival, meta-analysis, metformin, overall survival, progression-free survival

1. Introduction

Cancer is the first or second leading cause of death before age 70. With the aging of the world population, cancer, as the main cause of death, has become increasingly prominent, which is the most significant obstacle to improving people's life expectancy.[1] Vincent et al reviewed the evidence from genetic studies being compatible with the association between type 2 diabetes and specific cancers. The observational association is unlikely to be driven by a common genetic etiology. It is most likely driven by the specific metabolic characteristics of type 2 diabetes.[2] The previous meta-analyses have extensively studied the relationship between type 2 diabetes and the risk of cancer and cancer death.[3] Diabetes is associated with factors such as hyperinsulinemia, elevated insulin-like growth factor (IGF), hyperglycemia, dyslipidemia, inflammatory cytokines, and intestinal microbiota. These factors are also associated with the occurrence and development of cancer.[4] It is also demonstrated that hyperinsulinemia, obesity, and related metabolic diseases are related to the occurrence of cancer.[5,6]

Metformin belongs to the class of biguanide antidiabetic drugs and is currently the first-line drug treatment for type 2 diabetes. It improves insulin sensitivity by increasing peripheral glucose uptake and utilization, reducing basal and postprandial blood glucose, and decreasing gluconeogenesis of the liver.[7] Scholars have outlined the link between metformin and cancer through some reviews.[7,8] Considering that metformin can interfere with cancer-promoting signaling pathways in various ways, the anticancer effect of metformin is biologically credible. Therefore, many clinical studies, including retrospective

JY and HY these authors contributed equally to this work.

This work was supported by the Wujiang district prospers health through science and education, Grant Number: WWK201908.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Ethical approval was not sought as the study was based entirely on previously published data.

[a] Oncology Center, The Affiliated Jiangsu Shengze Hospital of Nanjing Medical University, Wujiang, Jiangsu Province, P.R. China, [b] Department of Endocrinology, The Affiliated Jiangsu Shengze Hospital of Nanjing Medical University, Wujiang, Jiangsu Province, P.R. China, [c] Department of Oncology, First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, P.R. China.

** Correspondence: Wei Zhu, Department of Oncology, First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province 210029, P.R. China (e-mail: zhuwei@njmu.edu.cn).*

How to cite this article: Yang J, Yang H, Cao L, Yin Y, Shen Y, Zhu W. Prognostic value of metformin in cancers: An updated meta-analysis based on 80 cohort studies. Medicine 2022;101:49(e31799).

Received: 28 March 2022 / Received in final form: 22 October 2022 / Accepted: 25 October 2022

http://dx.doi.org/10.1097/MD.0000000000031799

and prospective studies, have assessed the risk of metformin and cancer[9–11] and its relationship with the death of cancer [12–14]. There are likewise numerous meta-analyses that summarized these results.[15–17] However, in recent years, there have been continuous clinical trials registered on clinicaltrial.gov, and the results of all previous studies are inconsistent. Although this is not a new topic, there are still discoveries to explore, therefore we did an updated meta-analysis of metformin in cancer prognosis based on cohort studies, mainly to study the relationship between metformin and survival of cancer patients, and try to explore whether it is related to the survival of cancer patients complicated with diabetes mellitus.

2. Materials and Methods

2.1. Protocol

This meta-analysis aimed to understand the relationship between metformin use and cancer prognosis and to draw more robust conclusions based on new research in recent years. The meta-analysis was conducted by the preferred reporting items for systematic reviews and meta-analyses.[18]

2.2. Search strategy

A literature search was carried out using PubMed, Web of Science, Embase, and Cochrane databases from inception to June 2021. We searched for all published and unpublished cohort studies. References in recent review articles were also checked for relevant articles. Although this was a meta-analysis based on cohort studies, we also need to understand the progress of the relationship between metformin and cancer prognosis in clinical trials, which can help improve reliability. We will supplement with clinical trials to assess the conclusions. We searched the following trial registers for ongoing trials: ClinicalTrials.gov (https://clinicaltrials.gov/). The application search engine was chrome. Search terms included: "metformin," "Dimethylbiguanide," and "cancer," "tumor," "neoplasm" or "carcinoma." The search was restricted to English-language articles.

2.3. Study selection

The full text of potentially relevant references was obtained and evaluated in detail to ascertain their eligibility. This research is limited to studies conducted on humans. Two reviewers independently selected the eligible articles. Disagreement between the 2 reviewers was settled by discussing with the 3rd reviewer. Studies considered in this meta-analysis were cohort studies that met the following inclusion criteria: The chief result of the article was overall survival, and secondary outcomes might include progression-free survival or cancer-specific survival; Reported hazard ratio (HR) and 95% confidence interval (CI); Published as a full paper in English. Articles were excluded if they were: editorials, letters, reviews, and case reports; Studies without appropriate data for determining an estimate of HR and 95% CI. In cases of duplicate publications from the same population, only the largest studies were included.

2.4. Data extraction and quality assessment

Two reviewers extracted data independently. The full text of any articles deemed potentially eligible was evaluated for inclusion or exclusion. The following variables were gathered from each study: name of the first author, publication year, cancer site, study design, number of participants, number of metformin use, period of follow-up, HR and its 95% CI, and adjustment factors. In these studies, when multiple estimates of effect (HR) were presented, the most adjusted estimate was extracted; when the adjusted estimate was not available, the crude estimate was extracted.

The quality of non-randomized studies was evaluated according to the Newcastle-Ottawa scale (NOS).[19]

2.5. Statistical analyses

The results of interest were drawn up based on overall survival and cancer-specific survival and cancer progression-free survival. We proceeded to a meta-analysis of all included studies first. If the included studies report risk assessments for cancer-specific survival (CSS) and all-cause mortality (ACM), first calculate the risk estimates for all-cause mortality so as overall survival (OS). Next, we conducted the subgroup analysis according to the tumor site. The same method is used to evaluate progression-free survival (PFS) and CSS.

Heterogeneity was assessed using the I^2 test. When significant heterogeneity ($I^2 > 50\%$) was found, a random-effects model was applied to calculate the pooled effect; otherwise, a fixed-effects model was used. To test the robustness of the association and characterize possible sources of statistical heterogeneity. Sensitivity analysis was carried out according to the diabetic population, in which propensity matching score analysis was utilized, and the cumulative time of taking metformin was > 1 year and using metformin after resection. Publication bias was assessed by funnel plot and Egger test. All analyses were performed using Stata version 14.0 (Stata Corp LP, College Station, TX).

3. Results

3.1. Study characteristics and quality assessment

On the initial search, 5366 eligible citations are using PubMed, web of science, Embase, Cochrane databases, and clinical trials. Then 2199 potentially relevant articles were screened for further review. 523 articles were excluded due to repetition. 877 articles were not observational studies in humans excluded. After carefully looking at the subject and abstract of the article, excluded 439 articles that are not pertinent to the topic of cancer and survival. Then exclude review, letters, non-English studies and non-cohort studies, and meta-analyses, with a total of 56 articles. Finally, we excluded 216 articles that are incongruous with the results indicators we are studying. After reading the literature for quality evaluation, we excluded 8 articles with NOS scores < 7. At last, this meta-analysis incorporated 80 articles,[20–99] published from inception to June 2021. Figure 1 showed the flow diagram for studying inclusion.

A total of 1,091,593 participants, including 91,249 cases who took metformin were involved. There are 13 sites of cancer included, and 3 articles included all kinds of tumors.[25,53,94] The principal features of eligible studies are presented in Table 1. The quality score for cohort studies and case-control studies is based on the Newcastle-Ottawa scale. NOS scores range from 7 to 9, which are considered high quality (≥7).

3.2. Main analysis

3.2.1. Overall survival. We concluded that metformin use significantly affected the overall survival of cancer (HR = 0.81, 95% CI [0.77–0.85]). Because significant heterogeneity ($P < .001$, $I^2 = 93.9\%$) was observed, a random-effects model was formulated. Among them, 5 kinds of tumors include more than 7 articles. The calculated combined HR for breast cancer with metformin use was found to be 0.77 (95% CI [0.69–0.86]), and the prostate cancer HR was 0.94(95% CI [0.87–1.02]), pancreatic cancer was 0.80(95% CI [0.67–0.95]), lung cancer HR was 0.79(95% CI [0.69–0.92]), colorectal cancer 0.81 (95% CI [0.65–1.01]). It showed that the use of metformin has a significant impact on the overall survival of breast, pancreatic, and lung cancer. Summary data of other tumors were shown in

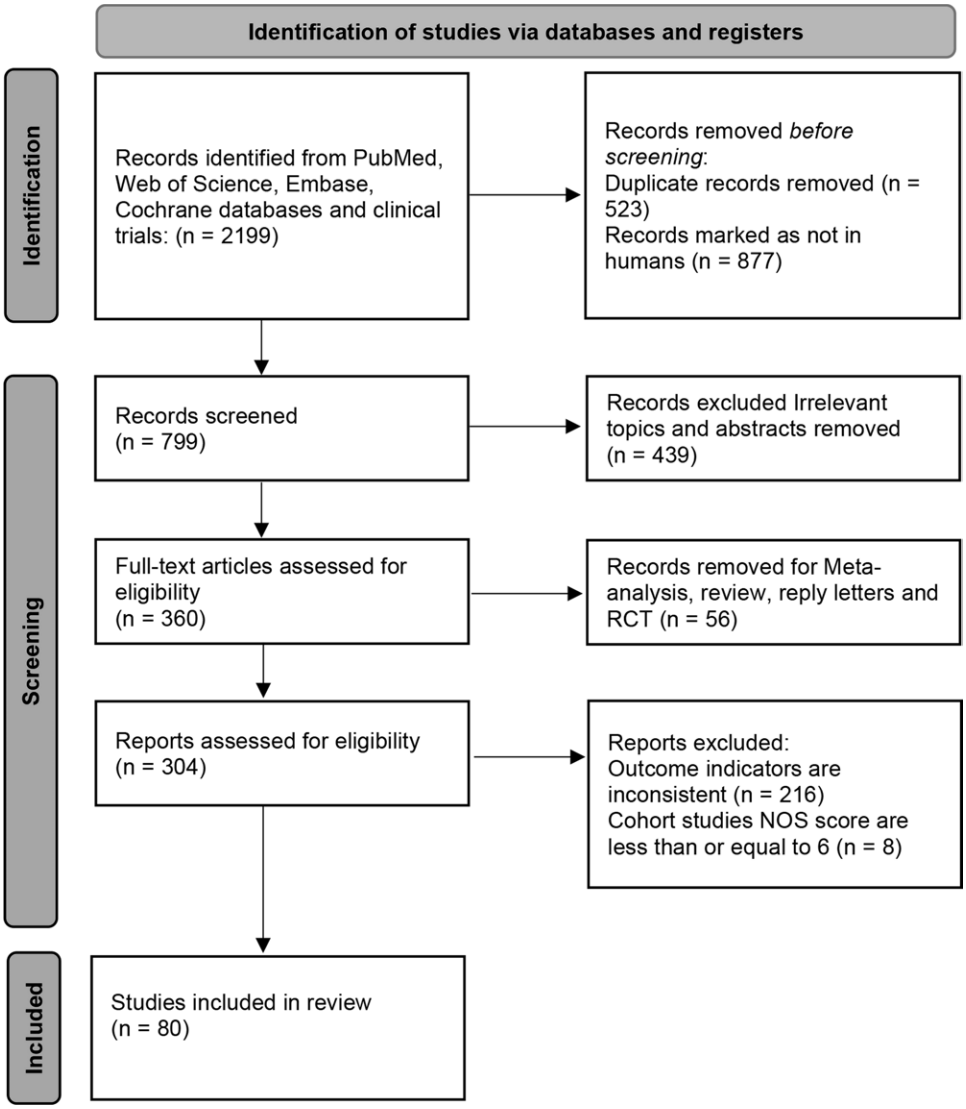

Figure 1. Flowchart of study selection process.

Table 2. If there were < 3 literature, they would be not listed in the table.

3.2.2. Progression-free survival. In this meta-analysis, there are 25 articles containing the result of progression-free survival. We draw a conclusion from this analysis that metformin use was associated with reduced cancer progression-free survival (HR = 0.76; 95% CI [0.66–0.87]; I^2 = 67.4%). For breast cancer the pooled HR was 0.64(95% CI [0.44–0.91]; I^2 = 0%), the ovarian cancer HR was 0.37(95% CI [0.25–0.55]; I^2 = 0%), lung cancer HR was 0.61(95% CI [0.48–0.79]; I^2 = 0%). The effect of metformin on PFS of breast cancer, lung cancer, and ovarian cancer was statistically significant, but the effect on other tumors was not obvious, so although the overall results showed that metformin can improve PFS, we need to be cautious when interpreting, the effect on PFS varies by tumor type. Figure 2 showed a forest plot of metformin use and progression-free survival, and summary data of additional tumors were given in Table 2.

3.2.3. Cancer-specific survival. In the included studies, we found that the use of metformin was associated with a significant reduction in cancer-specific survival rates (HR = 0.79; 95% CI [0.73–0.86]). The consequences for breast and prostate cancer were (HR = 0.84; 95% CI [0.73–0.96]) and (HR = 0.83; 95% CI [0.70–0.98]), respectively. And colorectal cancer HR was 0.77(95% CI [0.64–0.94]). The association between metformin use and reduction in CSS remained relatively consistent with OS. However, with 33 articles available for CSS, there is publication bias and further research is needed to better understand this relationship. These results are presented in Figure 3.

3.2.4. Subgroup and sensitivity analysis. If the research method adopted propensity score matching analysis, the result showed that there was an association between metformin use and overall survival (HR = 0.74, 95% CI [0.60–0.91]). For cumulative metformin use for more than 1 year, the HR was 0.82 (95% CI [0.76–0.88]). As an adjuvant treatment after resection treatment, metformin use can improve overall survival (HR = 0.81; 95% CI [0.70–0.93]), and cancer-specific survival (HR = 0.68; 95% CI [0.58–0.80]), but there was little association with progression-free survival (HR = 0.80; 95% CI [0.64–1.00]). Therefore, the role of metformin as adjuvant therapy after surgery needs to be further explored. In patients with diabetes mellitus, the HR of overall survival was 0.79(95% CI [0.75–0.83], and progression-free survival (HR = 0.72; 95% CI [0.60–0.85]), and the cancer-specific survival (HR = 0.76; 95% CI [0.68–0.86]). It was therefore proposed that metformin can improve the prognosis

Table 1

Characteristics of included studies.

Characteristics	Number of studies (%)	Number of metformin use (%)	Number of participants (%)
Outcome indicators, No. (%)			
Overall survival	80 (100)	91,249 (100)	1,091,593 (100)
Progression-free survival	25 (31.25)	5028 (5.51)	65,579 (6.01)
Cancer-SPECIFIC SURVIVAL	33 (41.25)	48,240 (52.87)	201,379 (18.45)
Year of publication, No. (%)			
Before 2015	36 (45)	12,640 (13.85)	101,950 (9.34)
After 2015	44 (55)	78,609 (86.15)	989,643 (90.66)
Disease site, No. (%)			
All	3 (3.75)	3986 (4.37)	37,453 (3.43)
Bladder	2 (2.50)	119 (0.13)	1923 (0.18)
Breast	12 (15)	3936 (4.31)	31,031 (2.84)
Cervical	2 (2.5)	180 (0.20)	966 (0.09)
Colorectal	14 (17.5)	21,485 (23.55)	100,518 (9.21)
Endometrial	5 (6.25)	7571 (8.30)	14,688 (1.35)
Gastric	2 (2.5)	909 (1.00)	2934 (0.27)
Head and neck	5 (6.25)	1294 (1.42)	12,823 (1.17)
Hepatocellular	4 (5.00)	1773 (1.94)	5778 (0.53)
Lung	10 (12.5)	30,464 (33.39)	744,500 (68.20)
Ovarian	3 (3.75)	244 (0.27)	3200 (0.29)
Pancreatic	7 (8.75)	1377 (1.51)	5948 (0.54)
Prostate	9 (11.25)	17,746 (19.45)	129,390 (11.85)
Kidney	2 (2.5)	165 (0.18)	441 (0.04)
Follow-up, No. (%)			
≤5 yr	45 (56.25)	25,945 (28.43)	124,923 (11.44)
>5 yr	20 (25)	32,040 (35.11)	788,792 (72.26)
NA	15 (18.75)	33,264 (36.45)	177,878 (16.3)
Duration of medication use			
≥1 yr	8 (10.0)	26,044 (28.54)	111,572 (10.22)
NA	72 (90.0)	65,205 (71.46)	980,021 (89.78)
Diabetes mellitus status			
Yes	58 (72.5)	37,474 (41.07)	260,580 (23.87)
No	22 (27.5)	53,775 (58.93)	831,013 (76.13)
After resection			
Yes	13 (16.25)	7703 (8.44)	56,293 (5.16)
No	67 (83.75)	83,546 (91.56)	1,035,300 (94.84)
Adjust for drugs			
Yes	18 (22.5)	69,025 (75.64)	915,925 (83.91)
Propensity score analysis			
Yes	6 (7.5)	1960 (2.15)	9720 (0.89)

Table 2

Summary pooled HR (95% CI) for subgroup analyses of OS, PFS and CSS using random-effects models.

	OS			PFS			CSS		
Cancer site	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
breast	0.77	0.69–0.86	.000	0.64	0.44–0.91	.013	0.84	0.73–0.96	.009
colorectal	0.81	0.65–1.01	.060	1.00	0.89–1.13	.998	0.77	0.64–0.94	.008
endometrial	0.65	0.44–0.97	.034	0.73	0.37–1.45	.371			
head and neck	0.92	0.77–1.09	.308				0.77	0.41–1.44	.415
hepatocellular	0.75	0.58–0.97	.027						
lung	0.79	0.69–0.92	.002	0.61	0.48–0.79	.000			
ovarian	0.61	0.32–1.16	.131	0.37	0.25–0.55	.000			
pancreatic	0.80	0.67–0.95	.011						
prostate	0.94	0.87–1.02	.141	1.01	0.80–1.28	.941	0.83	0.70–0.98	.030
overall	0.81	0.77–0.85	.000	0.76	0.66–0.87	.000	0.79	0.73–0.86	.001

95%CI = 95% confidence interval, CSS = cancer-specific survival, HR = hazard ratio, OS = overall survival, PFS = progression-free survival.

of cancer patients with diabetes mellitus. Summary data of additional tumors were shown in Table 3.

3.3. Publication bias

In the present meta-analyses, publication bias was observed among studies utilizing Egger test[100] ($P = .015$), and the shape of the funnel plot showed asymmetry in included studies. We considered that there was a potential publication bias in the included literature.

4. Discussion

In our meta-analysis of the relationship between metformin use and cancer prognosis, we found that patients who used metformin showed OS, CSS, and RFS benefits compared with

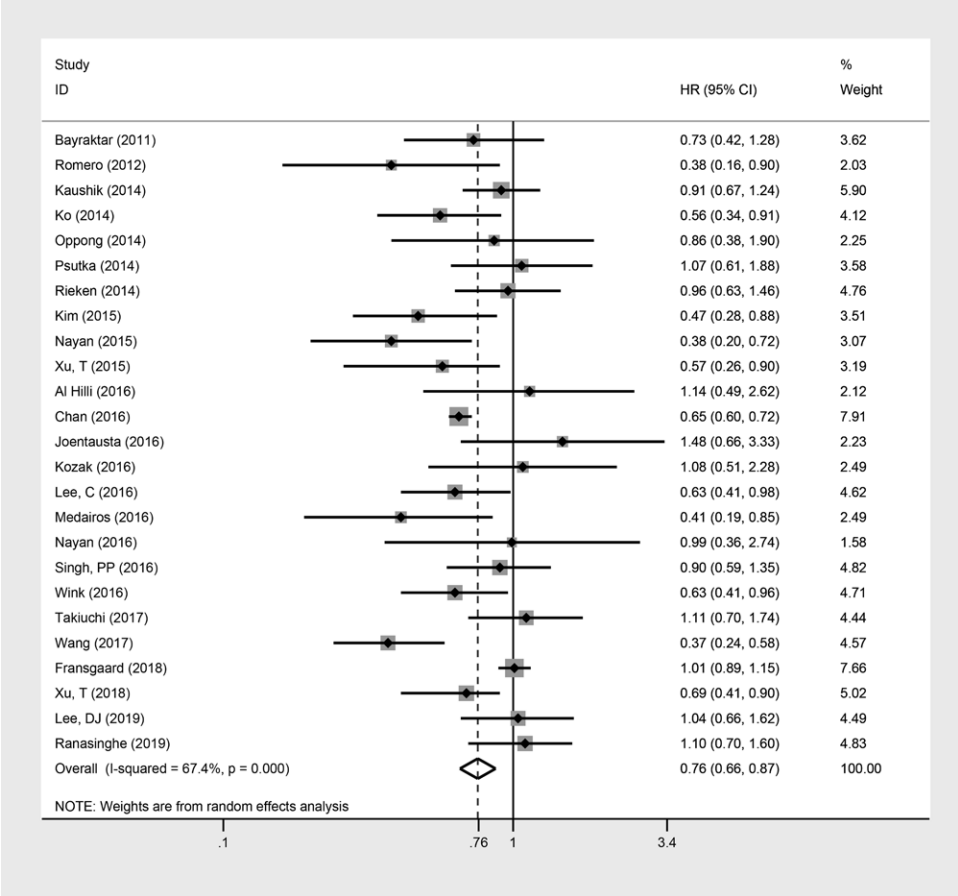

Figure 2. Forest plot of metformin use and progression-free survival.

patients who did not take metformin. Especially in breast cancer, metformin shows prognosis advantages. Metformin use was associated with improving overall survival and progression-free survival in lung cancer. And metformin can increase the overall survival in pancreatic cancer, liver cancer, and endometrial cancer. In ovarian cancer, metformin shows a PFS advantage. Although there were no significant differences in OS and PFS in colorectal and prostate cancers, metformin showed benefits in CSS of the above 2 cancers. We also observed through subgroup analysis of 58 articles, that metformin usage was shown to improve overall and cancer-specific survival and progression-free survival in patients with diabetes mellitus compared with not taking metformin.

As we all know, diabetes mainly produces adverse complications in the cardiovascular,[101] kidney,[102] and nervous tissues.[103] A positive correlation between metabolic syndrome and cancer has been established, and diabetes also increases the risk of cancer. In recent years, it has also been found that the occurrence and development of cancer are often accompanied by a metabolic reprogramming process. Therefore, as a first-line hypoglycemic drug, its anti-tumor mechanism has been extensively studied. In addition to the many observational studies we have described above that explore the role of metformin in cancer, clinical trials have also been conducted in recent years.[104,105] While the results are controversial, the anti-cancer effects of metformin are worth exploring. Metformin belongs to the class of biguanide antidiabetic drugs and is currently the first-line drug treatment for type 2 diabetes.[7] The antitumor mechanism of metformin includes activation of the AMP-activated protein kinase/mechanistic target of rapamycin (mTOR) pathway and direct inhibition of insulin/IGF mediated cell proliferation. It is associated with the activation of adenosine monophosphate-activated protein kinase (AMPK) in the cell. Regulation of the metformin-mediated AMPK-pS6K-mTOR pathway is related to the antiproliferative activity of metformin in human breast cancer cell lines.[106] Phosphorylated AMPK activates and subsequently inhibits the downstream mTOR signaling pathway, down-regulates c-Myc expression, and reduces the level of anti-apoptotic protein p, Induced G1/S phase arrest in the cell cycle.[107] Metformin treatment in breast cancer cells induced mTOR degradation and sequestered the protein in the perinuclear area. This is considerably correlated with the reduction of breast cancer cell proliferation and migration potential.[108] In another area, Metformin may be just an effective inhibitor of IGF-1/IGF1R signaling and can inhibit IGF-1 induced extracellular signal-regulated kinase, Akt activation, and cell proliferation. Thus, metformin inhibits the proliferation of human prostate cancer cells by down-regulating insulin-like growth factor 1 receptor.[109] Since human epidermal growth factor receptor 2, insulin receptor and IGF-I receptor participate in the same downstream signaling through phosphoinositide 3-kinase, AKT, and mTOR, Potential molecular predictors of resistance to human epidermal growth factor receptor 2 include loss of phosphatase and tensin homolog, phosphoinositide 3-kinase/Akt hyperactivation, IGF overexpression, supporting metformin as the potential role of additional therapies related to targeted therapy in breast cancer patients.[110]

In addition, the activation of inflammatory signaling pathways and the initiation of epithelial-mesenchymal transformation (EMT) are closely related to drug resistance, recurrence, and metastasis of tumors. Since EMT is one of the elementary steps of metastasis, metformin inhibits IL-6-induced EMT, cell proliferation, and migration of primary breast cancer cells by

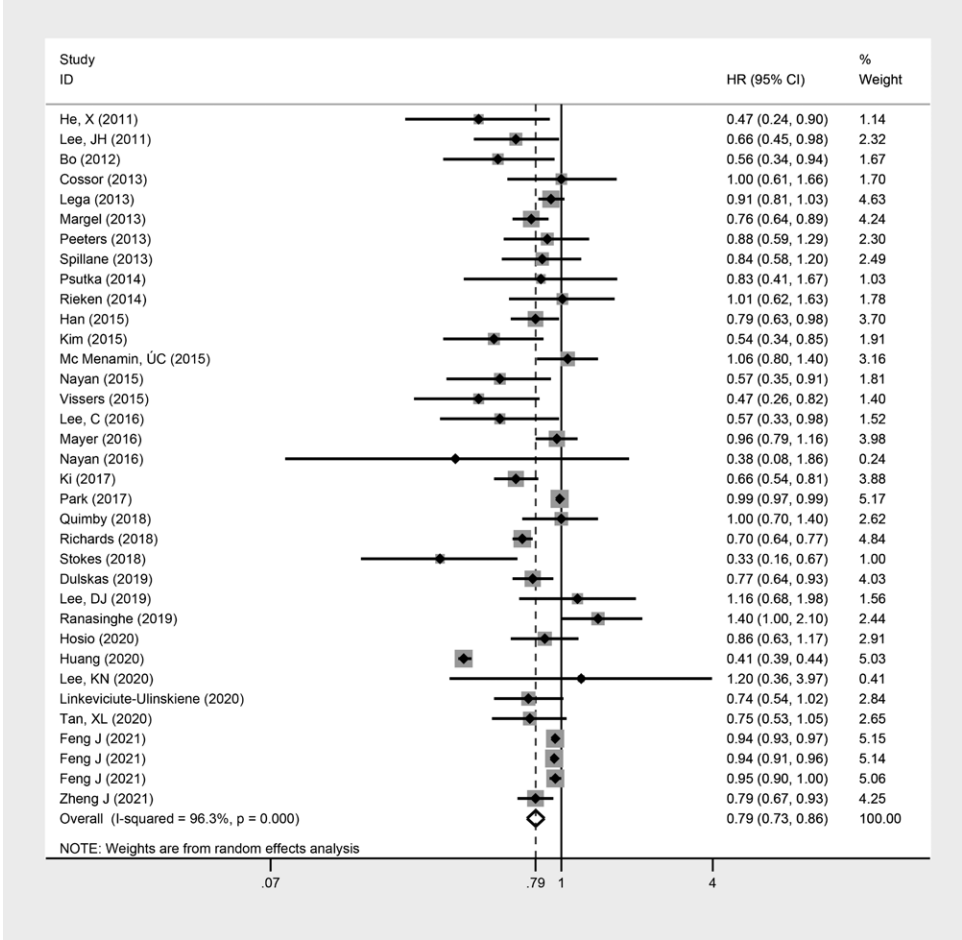

Figure 3. Forest plot of association between metformin use and cancer-specific survival.

Table 3

Summary pooled HR (95%CI) for sensitivity analyses of OS, PFS and CSS using random-effects models.

Study	Outcome	HR (random)	95% CI	Degree of heterogeneity I^2	Numbers of included studies	*P* value
Propensity score matching analysis	OS	0.74	0.60–0.91	19.9	6	.004
Cumulative metformin use more than one year	OS	0.82	0.76–0.88	95.9	8	.000
Metformin use after surgery	OS	0.81	0.70–0.93	66.5	13	.003
Metformin use after surgery	PFS	0.80	0.64–1.00	80.2	10	.046
Metformin use after surgery	CSS	0.68	0.58–0.80	0	5	.000
Patients with diabetes mellitus	OS	0.79	0.75–0.83	72.4	58	.000
Patients with diabetes mellitus	PFS	0.72	0.60–0.85	71.7	19	.000
Patients with diabetes mellitus	CSS	0.76	0.68–0.86	81.0	24	.000

CI = confidence interval, CSS = cancer-specific survival, HR = hazard ratio, OS = overall survival, PFS = progression-free survival.

preventing the activation of signal transducer and activator of transcription 3 and NF-κB. Inhibition of signal transducer and activator of transcription 3 activation depends on AMPK activity.[111] Metformin can interfere with the binding of transcription factor IRF-1 to the Yap promoter, thereby damaging Yap expression in lung cancer cells. Decreased activity of the Yap promoter leads to the inhibition of cell proliferation, migration, invasion, and EMT, and increases cell senescence and apoptosis.[112] In addition, metformin down-regulates tumor platelet-derived growth factor-B inhibits angiogenesis and improves vascular maturity. As a consequence, remote transfers are restricted.[113] Metformin has an anti-proliferative effect related to cell cycle arrest and apoptosis, which are transmitted by oxidative stress and activation of AMPK and FOXO3a.[114] From the perspective of the immune microenvironment, metformin can increase the number and the density of infiltrating CD8 + cytotoxic T lymphocytes and enhance the activity of CD8 + T cells.[115–117] Metformin can activate AMP-activated protein kinases and target the cyclooxygenase-2/prostaglandin E2 axis to counteract the immunosuppression of myeloid-derived suppressor cells and partially inhibit the infiltration of tumor-associated macrophages. It can also inhibit the function of macrophages.[115,118] At the same time, metformin in tumor tissues inhibits the ability of macrophages to polarize the M2 phenotype, therefore inhibiting both tumor growth and angiogenesis.[119] Moreover, it has recently been discovered that metformin also increases cytotoxic T lymphocyte activity through the AMPK/programmed death ligand-1 axis. It suggests that the combined use of metformin and immunotherapy has a strong potential.[120] Nevertheless, we may need clinically unachievable doses of metformin to achieve

the effect of inhibiting cancer cells, because, in the clinical trials that have been concluded, no gratifying results have been achieved.[121,122]

Our meta-analysis mainly studied the prognosis effect of metformin on 13 sites of cancers and included the cohort study literature published in recent years with NOS scores not < 7 points, the quality of the studies was high, and the overall study sample size was large. But several limitations should be taken into account when interpreting our results. First, we found heterogeneity between studies in the meta-analysis, which may be resulted from different cancer sites, study designs, population samples, metformin initiation, disease stage, study area, duration of follow-up, combined drugs, and comorbidity. Although it cannot be explained that metformin is beneficial for OS in every cancer type, heterogeneity among different tumors was observed, but the overall study sample size was large, the further stratified analysis did not change the trend of the pooled estimates of OS, therefore did not affect the overall results. Second, in the subgroup analysis of overall survival, there was a large deviation in the number of literature included in each tumor, such as gastric cancer,[54,99] cervical cancer,[38,87] bladder cancer[68,80] there were only < 3 articles. Therefore, it is important to be cautious in explaining the prognosis of metformin and these cancers. Third, because we do not have all the data about the duration of metformin use, we can't make an effective hierarchical analysis. The relationship between the use of metformin and mortality may have different results over time. Similarly, we can't make a hierarchical analysis under the conditions of diversified treatment options and tumor staging. However, we summarized the prognosis of patients after operation, and the benefit of PFS was not obvious in the stratified analysis of postoperative patients. Therefore, we need to be cautious when interpreting this indicator as postoperative adjuvant therapy, and the adjuvant effect of metformin varies by tumor type. Forth, in cancer patients with diabetes mellitus, metformin is positively associated with the improvement of prognosis. But the benefits of OS caused by metformin in cancer patients with diabetes need to consider other causes such as cardiovascular disease comorbidities. Therefore, we cannot satisfactorily eliminate confusion. Fifth, although we have collected 80 cohort studies on metformin and the overall survival of cancer patients and conducted the subgroup analysis, it is the largest sample size study. But the egger test and funnel plot showed publication bias is inevitable in explaining the use of metformin and the prognosis of cancer patients. Due to the nature of observational studies, we cannot say that metformin use is directly causal to improved survival, these results have significant clinical implications until confirmed in randomized clinical trials in cancer patients.

5. Conclusion

The use of metformin in cancer treatment may improve overall and cancer-specific survival, as well as progression-free survival. In particular, we observed that the use of metformin was made in associated with the improvement of overall survival, progression-free survival, and cancer-specific survival in breast cancer. Metformin also shows potential benefits in the CSS of colon cancer and prostate cancer. However, the benefit of PFS in postoperative patients is not obvious, so we need to be cautious when interpreting the role of metformin as postoperative adjuvant therapy. Cancer patients with T2 DM appear to have a better OS with metformin as part of their diabetes therapy. However, because the included articles were observational cohort studies, it cannot directly prove that the use of metformin is related to the improvement of survival rate. It is necessary to interpret the results carefully, and further randomized controlled trials are necessary to verify the results.

Acknowledgments

The authors thank Wang Qiang and Zou Xuan for assisting in preparing and revising this manuscript. We are grateful to all our colleagues in the Department of Oncology, The Affiliated Jiangsu Shengze Hospital of Nanjing Medical University, for their help in this study.

Author contributions

Conceptualization: Wei Zhu.
Data curation: Jing Yang, Ling Cao, Ying Shen.
Funding acquisition: Hang Yang.
Investigation: Hang Yang.
Methodology: Ying Shen.
Project administration: Yuzhen Yin.
Software: Jing Yang.
Writing – original draft: Jing Yang.
Writing – review & editing: Ying Shen, Wei Zhu.

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