INPLASY PROTOCOL

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Corresponding author:
Zhengtong Peng

triumphhope@163.com

Author Affiliation:
Gansu Provincial Hospital

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Conflicts of interest:
The authors declare that there is no conflict of interest.

Relationship between metformin use and survival outcome in patients with cancer: a protocol for systematic review

Wang, JC[1]; Song, X[2]; Zhang, RN[3]; Lian, RN[4]; Peng, ZT[5].

Review question / Objective: **Relationship between metformin use and survival outcome in patients with cancer.**
Condition being studied: **Metformin is one of the most commonly prescribed medication for the management of type 2 diabetes mellitus, several studies have described the good effects of metformin application in cancer, which also has been examined in many systematic reviews (SRs) and meta-analyses. This study aims to systematically appraise the quality of these SRs of the survival benefits from metformin using in common tumors to provide new evidence.**
Information sources: **We will conduct an exhaustive literature search from the following databases: PubMed, EMBASE, and the Cochrane Library.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 November 2020 and was last updated on 27 November 2020 (registration number INPLASY2020110118).

INTRODUCTION

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Condition being studied: **Metformin is one of the most commonly prescribed medication for the management of type 2 diabetes mellitus, several studies have described the good effects of metformin application in cancer, which also has been examined in many systematic reviews (SRs) and meta-analyses. This study aims to systematically appraise the quality of these SRs of the survival benefits from metformin using in common tumors to provide new evidence.**

METHODS

Participant or population: Systematic reviews data from patients with common tumors including pancreatic cancer, breast cancer, gastric cancer colorectal cancer, lung cancer, prostate cancer, ovarian cancer, endometrial cancer, liver cancer, kidney cancer, bladder cancer and some other tumors with a higher incidence or mortality will be included.

Intervention: Survival benefit assessment with use of the metformin before, during, and/or after diagnosis of cancer in patients with or without diabetes.

Comparator: We will include SRs if they explore comparisons of metformin to either: (1) Diabetics: non-use of metformin or use of other hypoglycaemic drugs; (2) Non-diabetics: non-use of metformin or use of placebo.

Study designs to be included: We will include published, peer-reviewed systematic reviews and meta-analyses of RCTs, quasi-RCTs, cohort studies (prospective, retrospective), and case-control studies.

Eligibility criteria: Included criteria: 1.Type of studies. We will include published, peer-reviewed systematic reviews and meta-analyses of RCTs, quasi-RCTs, cohort studies (prospective, retrospective), and case-control studies. All the SRs included must explicitly describe methods of study selection, and explicitly reported the methods of evidence synthesis. 2.Type of participants. SRs data from patients with common tumors including pancreatic cancer, breast cancer, gastric cancer colorectal cancer, lung cancer, prostate cancer, ovarian cancer, endometrial cancer, liver cancer, kidney cancer, bladder cancer and some other tumors with a higher incidence or mortality will be included. There are no limitations on age, race or nationality. 3. Type of interventions. Survival benefit assessment with use of the metformin before, during, and/or after diagnosis of cancer in patients with or without diabetes. There are no restrictions on the dosage taken and the duration of metformin administration. 4. Type of comparators. We will include SRs if they explore comparisons of metformin to either: (1) Diabetics: non-use of metformin or use of other hypoglycaemic drugs; (2) Non-diabetics: non-use of metformin or use of placebo. 5. Type of Outcome measures. We will include SRs that reported meta-estimates at least one of the following outcomes: (1) Primary outcomes: overall survival, progression-free survival, cancer-specific survival; (2) Secondary outcomes: cancer-specific mortality, all-cause mortality. 6. Restrictions. SRs only published/available in the English language will be included in our study. 7. Exclusion criteria. Exclusion criteria of this study as follows:(1) SRs that did not report the relationship between metformin use and survival benefits in cancer patients;(2) Does not report the prognosis for each cancer separately;(3) Does not report the outcome mentioned before;(4) Conference abstract with insufficient data.

Information sources: We will conduct an exhaustive literature search from the following databases: PubMed, EMBASE, and the Cochrane Library.

Main outcome(s): (1) Primary outcomes: overall survival, progression-free survival, cancer-specific survival; (2) Secondary outcomes: cancer-specific mortality, all-cause mortality.

Data management: All citations identified from the literature search will be merged, de-duplicated and stored in a reference manager database (Endnote X8). Two reviewers will independently review all citations by title and abstract to get a result of the broad screen. The second screen will execute by retrieving studies that are potentially relevant in full-text format and checking them against eligibility criteria to determine inclusion again. All the disagreements will be resolved through discussion to reach a consensus or by using a third author to adjudicate. Data collection process Two reviewers will independently collect data by using Microsoft Excel 2019 software. The

following data items from each included study using a predefined data extraction form: authorship, year of publication, databases search and search date, number of included studies and study designs, diabete or not, type of intervention, outcomes and the main findings.

Quality assessment / Risk of bias analysis: The methodological quality and reporting quality of included systematic reviews will be evaluated by using AMSTAR-2 and PRISMA statement respectively.

Strategy of data synthesis: We will summarize and describe the general characteristics of the eligible SRs. Bubble plots will be used to display survival outcomes, methodological and reporting quality of all included systematic reviews. Endnote X8 and EXCEL will be used.

Subgroup analysis: This study will be no subgroup analysis.

Sensibility analysis: This study will be no sensibility analysis.

Country(ies) involved: China.

Keywords: Metformin, cancer, survival outcome, study.

Contributions of each author:

Author 1 - Jiancheng Wang.
Email: 30922329@qq.com
Author 2 - Xia Song.
Email: ery_songxia@lzu.edu.cn
Author 3 - Ruinian Zhang.
Email: zhangrn2017@lzu.edu.cn
Author 4 - Rongna Lian.
Email: lianrn17@lzu.edu.cn
Author 5 - Zhengtong Peng.
Email: triumphhope@163.com