INPLASY PROTOCOL

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Conflicts of interest:
None declared.

The association between metformin and hepatocellular carcinoma mortality in patients with type 2 diabetes mellitus: a systematic review and Meta-analysis

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Review question / Objective: **Hepatocellular carcinoma is one of the most common malignant tumors, ranking the second in malignant tumor-related mortality. Although early-stage liver cancer can be effectively treated by radical treatment measures such as surgical resection, liver transplantation, and local ablation, due to the insidious onset and rapid disease progression, most liver cancer patients are diagnosed in the middle and late stages, and the overall treatment effect is not satisfactory. Having type 2 diabetes can lead to an increased incidence of malignancies, including liver cancer. Metformin is an oral biguanide drug that controls hyperglycemia by reducing circulating glucose and improving insulin resistance, activating the AMPK (adenosine phosphate-activated protein kinase) signaling pathway, and inhibiting hepatic gluconeogenesis. of first-line treatment. Metformin was first proposed as an anticancer drug candidate in a 2005 cohort study in Scotland. Subsequent studies have found that metformin can reduce the incidence of liver cancer. In recent years, some studies have suggested that there is a correlation between metformin and the mortality of liver cancer. Some studies have found that metformin can reduce the mortality of liver cancer and prolong the median survival time of liver cancer. However, the clinical results are still controversial. To evaluate the correlation between metformin and type 2 diabetes and liver cancer mortality, this study collected relevant research literature for further meta-analysis. P: Type 2 diabetic patients with hepatocellular carcinoma I: Metformin C: No metformin O: mortality S: cohort study.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 July 2022 and was last updated on 17 July 2022 (registration number INPLASY202270083).

INTRODUCTION

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ablation, due to the insidious onset and rapid disease progression, most liver cancer patients are diagnosed in the middle and late stages, and the overall treatment effect is not satisfactory. Having type 2 diabetes can lead to an increased incidence of malignancies, including liver cancer. Metformin is an oral biguanide drug that controls hyperglycemia by reducing circulating glucose and improving insulin resistance, activating the AMPK (adenosine phosphate-activated protein kinase) signaling pathway, and inhibiting hepatic gluconeogenesis. of first-line treatment. Metformin was first proposed as an anticancer drug candidate in a 2005 cohort study in Scotland. Subsequent studies have found that metformin can reduce the incidence of liver cancer. In recent years, some studies have suggested that there is a correlation between metformin and the mortality of liver cancer. Some studies have found that metformin can reduce the mortality of liver cancer and prolong the median survival time of liver cancer. However, the clinical results are still controversial. To evaluate the correlation between metformin and type 2 diabetes and liver cancer mortality, this study collected relevant research literature for further meta-analysis. P: Type 2 diabetic patients with hepatocellular carcinoma I: Metformin C: No metformin O: mortality S: cohort study.

Condition being studied: Hepatocellular carcinoma is one of the most common malignant tumors, ranking the second in malignant tumor-related mortality. Although early-stage liver cancer can be effectively treated by radical treatment measures such as surgical resection, liver transplantation, and local ablation, due to the insidious onset and rapid disease progression, most liver cancer patients are diagnosed in the middle and late stages, and the overall treatment effect is not satisfactory. Having type 2 diabetes can lead to an increased incidence of malignancies, including liver cancer. Metformin is an oral biguanide drug that controls hyperglycemia by reducing circulating glucose and improving insulin resistance, activating the AMPK (adenosine phosphate-activated protein kinase) signaling pathway, and inhibiting hepatic gluconeogenesis. of first-line treatment. Metformin was first proposed as an anticancer drug candidate in a 2005 cohort study in Scotland. Subsequent studies have found that metformin can reduce the incidence of liver cancer. In recent years, some studies have suggested that there is a correlation between metformin and the mortality of liver cancer. Some studies have found that metformin can reduce the mortality of liver cancer and prolong the median survival time of liver cancer. However, the clinical results are still controversial. To evaluate the correlation between metformin and type 2 diabetes and liver cancer mortality, this study collected relevant research literature for further meta-analysis.

METHODS

Search strategy: Pubmed: (((((((((Metformin[MeSH Terms]) OR (Dimethylbiguanidine[Title/Abstract])) OR (Dimethylguanylguanidine[Title/Abstract])) OR (Glucophage[Title/Abstract])) OR (Metformin Hydrochloride[Title/Abstract])) OR (Hydrochloride, Metformin[Title/Abstract])) OR (Metformin HCl[Title/Abstract])) OR (HCl, Metformin[Title/Abstract])) AND ((((((((((((((((((((((((((((Diabetes Mellitus, Type 2[MeSH Terms]) OR (Diabetes Mellitus, Noninsulin-Dependent[Title/Abstract])) OR (Diabetes Mellitus, Ketosis-Resistant[Title/Abstract])) OR (Diabetes Mellitus, Ketosis Resistant[Title/Abstract])) OR (Ketosis-Resistant Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Non Insulin Dependent[Title/Abstract])) OR (Diabetes Mellitus, Non-Insulin-Dependent[Title/Abstract])) OR (Non-Insulin-Dependent Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Stable[Title/Abstract])) OR (Stable Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Type II[Title/Abstract])) OR (NIDDM[Title/Abstract])) OR (Diabetes Mellitus, Noninsulin Dependent[Title/Abstract])) OR (Diabetes Mellitus, Maturity-Onset[Title/Abstract])) OR (Diabetes Mellitus, Maturity Onset[Title/Abstract])) OR (Maturity-Onset

Diabetes Mellitus[Title/Abstract])) OR (Maturity Onset Diabetes Mellitus[Title/Abstract])) OR (MODY[Title/Abstract])) OR (Diabetes Mellitus, Slow-Onset[Title/Abstract])) OR (Diabetes Mellitus, Slow Onset[Title/Abstract])) OR (Slow-Onset Diabetes Mellitus[Title/Abstract])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Noninsulin-Dependent Diabetes Mellitus[Title/Abstract])) OR (Noninsulin Dependent Diabetes Mellitus[Title/Abstract])) OR (Maturity-Onset Diabetes[Title/Abstract])) OR (Diabetes, Maturity-Onset[Title/Abstract])) OR (Maturity Onset Diabetes[Title/Abstract])) OR (Type 2 Diabetes[Title/Abstract])) OR (Diabetes, Type 2[Title/Abstract])) OR (Diabetes Mellitus, Adult-Onset[Title/Abstract])) OR (Adult-Onset Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Adult Onset[Title/Abstract]))) AND ((((((((((((((((((((Liver Neoplasms[MeSH Terms]) OR (Neoplasms, Hepatic[Title/Abstract])) OR (Neoplasms, Liver[Title/Abstract])) OR (Liver Neoplasm[Title/Abstract])) OR (Neoplasm, Liver[Title/Abstract])) OR (Hepatic Neoplasms[Title/Abstract])) OR (Hepatic Neoplasm[Title/Abstract])) OR (Neoplasm, Hepatic[Title/Abstract])) OR (Cancer of Liver[Title/Abstract])) OR (Hepatocellular Cancer[Title/Abstract])) OR (Cancers, Hepatocellular[Title/Abstract])) OR (Hepatocellular Cancers[Title/Abstract])) OR (Hepatic Cancer[Title/Abstract])) OR (Cancer, Hepatic[Title/Abstract])) OR (Cancers, Hepatic[Title/Abstract])) OR (Hepatic Cancers[Title/Abstract])) OR (Liver Cancer[Title/Abstract])) OR (Cancer, Liver[Title/Abstract])) OR (Cancers, Liver[Title/Abstract])) OR (Liver Cancers[Title/Abstract])) OR (Cancer of the Liver[Title/Abstract])) OR (Cancer, Hepatocellular[Title/Abstract])).

Participant or population: Type 2 diabetic patients with hepatocellular carcinoma.

Intervention: Metformin.

Comparator: No metformin.

Study designs to be included: cohort study.

Eligibility criteria: Inclusion criteria1. The research method is a cohort study with complete literature data.2. Subjects The subjects of the study were liver cancer patients with type 2 diabetes mellitus. The cases with metformin application were listed as the case group, and the cases without metformin application were listed as the control group. The diagnosis of liver cancer complied with the diagnostic criteria revised by the Fourth National Liver Cancer Academic Conference; the diagnosis of T2DM was in line with the American Diabetes Association (ADA) or the World Health Organization (WHO) in the clinical application discussed in the Sixth National Endocrinology Academic Conference of the Chinese Medical Association. DM diagnostic criteria.3. Outcome indicators ① After multivariate logistic regression analysis or Cox survival analysis, the original data provide HR value and 95% confidence interval (95% CI); ② The summary results can be expressed by corresponding statistical indicators. Exclusion criteria1. Repeated articles;2. Animal and cell research;3. Unable to obtain the full text, meta-analysis, and review literature;4. The research content is inconsistent;5. Exclude literatures with low quality and incomplete data.

Information sources: CNKI, VIP , Wanfang Database, CBM, Pubmed, Embass, Web of science and the CochraneLibrary, Pubmed.

Main outcome(s): HCC-related mortality.

Additional outcome(s): HCC-related mortality in Asian population; HCC-related mortality in non-Asian populations; HCC-related mortality in treated HCC.

Data management: EndNote: Step 1: Remove duplicate documents. Step 2: Remove meta-analysis, review, etc. Step 3: Read the title and abstract of the article, remove animal experiments and research content that does not conform to the literature. Step 4: Read the full text and remove the literature that does not meet

the research content and that the quality is low.

Quality assessment / Risk of bias analysis: Cochrane tool：Newcastle-Ottawa Scale:1. Selection of study population；2. comparability；3. outcome evaluation. Risk of bias analysis：funnel chart；begg test；egger test.

Strategy of data synthesis: The heterogeneity test was assessed according to the Cochrane manual. When the Q test P≥0.1 and I2<50%, it was considered that there was no statistically significant heterogeneity among the studies, and the fixed effect model was used, otherwise, the random effect model was used.

Subgroup analysis: Subgroup analysis was performed according to whether the study source was from Asia and whether the study subjects were confirmed to have treated HCC.

Sensitivity analysis: The stability of the merged results was assessed by the sensitivity analysis method. If the results did not change much after arbitrarily deleting a document, the results were stable and reliable.

Language: No language limits be imposed on the search.

Country(ies) involved: China.

Keywords: Metformin; Type 2 diabetes; Hepatocellular carcinoma; Mortality; Meta-analysis.

Contributions of each author:

Author 1 - Xiufeng Yu - Topic selection；data collection； quality evaluation; data analysis and article writing.
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