INPLASY PROTOCOL

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Conflicts of interest:
The authors declare that they have no competing interests.

The value of microRNA-203 as a biomarker for the prognosis of esophageal cancer: A protocol for systematic review and meta-analysis

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Review question / Objective: **Whether the high expression of microRNA-203 is in association with poor prognosis in patients with esophageal cancer (EC)?**
Condition being studied: **MicroRNA-203 and esophageal cancer.**
Information sources: **Electronic databases including Google Scholar, Embase, PubMed, Medline, Web of Science, Cochrane Library, China National Knowledge Infrastructure, China Scientific Journal Database, Chinese BioMedical Database and Wanfang Database, will be systematically searched for eligible studies from their inception to November 2020. Language is limited with English and Chinese.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 November 2020 and was last updated on 06 November 2020 (registration number INPLASY2020110022).

INTRODUCTION

Review question / Objective: **Whether the high expression of microRNA-203 is in association with poor prognosis in patients with esophageal cancer (EC)?**

Rationale: **Previous studies have reported that microRNA-203 has an effect on the prognosis of with EC. However, the conclusion is remains controversial. Therefore, this study will try to explore the effect of high expression of microRNA-203 on the prognosis of EC patients.**

Condition being studied: MicroRNA-203 and esophageal cancer.

METHODS

Search strategy: The retrieval strategy will be created based on discussion of all the researchers on the basis of the Cochrane handbook guidelines. The plan searched terms are as follows: "esophageal carcinoma" or "oesophageal carcinoma" or "esophagus carcinoma", "microRNA-203", "miR-203", "prognostic", and "survival". The detailed sample of search strategy for PubMed database is shown in Table 1. Similar search strategies will be modified and used for the other databases.

Participant or population: Patients diagnosed with EC based on pathology and histology will be included. No restrictions regarding age, gender, racial, region, education and economic status.

Intervention: In the experimental group, serum microRNA-203 expression levels were detected in all EC patients confirmed by histopathology.

Comparator: In the control group, the expression levels of serum microRNA-203 were detected in normal participants.

Study designs to be included: All available clinical trials that assessed the effect of high expression of microRNA-203 on overall survival (OS) and disease-free survival (DFS) of patients with EC will be included in this systematic review.

Eligibility criteria: This study will include controlled clinical trials that assessed the effect of high expression of microRNA-203 on OS and DFS of patients with EC. Articles without sufficient available data, animal experiments, case reports and series, literature reviews, meta-analysis, letters, conference abstract, and other unrelated studies will be all excluded from analysis.

Information sources: Electronic databases including Google Scholar, Embase, PubMed, Medline, Web of Science, Cochrane Library, China National Knowledge Infrastructure, China Scientific Journal Database, Chinese BioMedical Database and Wanfang Database, will be systematically searched for eligible studies from their inception to November 2020. Language is limited with English and Chinese.

Main outcome(s): OS and DFS will be taken as prognostic outcomes. hazard ratios (HRs), and 95% confidence intervals (CIs) will be extracted from trials or be estimated from Kaplan-Meier survival curves by established methods.

Data management: Two investigators (Song Wang and Pingping Yu) will be responsible for the data extraction independently. The following data will be extracted from eligible literatures: (I) Study characteristics: first author's name, year of publication, country of study, sample size, microRNA-203 detection method, et al.(II) Participant characteristics: age, gender, race, inclusion and exclusion criteria, et al. (III) Outcome and other data: HRs and 95% CIs of OS and DFS, et al. When any data are missing or insufficient, we will contact original authors by using email. If the data is not available, we will only analyze the currently available data and discuss its potential impact.

Quality assessment / Risk of bias analysis: Two experienced authors (Song Wang and Pingping Yu) will assess the risk of bias for each eligible literature by using the Newcastle-Ottawa Quality Assessment Scale (NOS) independently. This tool comprises of three quality parameters: selection, comparability, and result evaluation. Each study was scored from 0-9 according to these parameters, and ≥7 were judged to be of higher quality. Any disagreements will be resolved via discussion with a third researcher (Zhen Meng).

Strategy of data synthesis: Stata 14.0 (Stata Corp., College Station, TX, USA) and Review Manager 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) statistical software were used for statistical analyses. HRs with corresponding 95% CIs was used

to evaluate the relationship between microRNA-203 expression and OS and DFS. Cochran's Q and Higgins I2 statistic were used to assess heterogeneity among the included clinical trials. P < 0.1 for the Chi2 statistic or an I2 > 50% will be considered as showing considerable heterogeneity. A fixed effect model will be used to calculate the outcomes when statistical heterogeneity is absent; otherwise, the random effects model will be used for analysis.

Subgroup analysis: If the data are available and sufficient, subgroup analysis will be conducted to explore the source of heterogeneity with respect to race, EC types, microRNA-203 detection method, and survival data source.

Sensibility analysis: The sensitivity analysis of each index was carried out by one-by-one elimination method to check the stability of the results. A summary table will report the results of the sensitivity analyses.

Language: Language is limited with English and Chinese.

Country(ies) involved: China.

Other relevant information: (I) Publication bias analysis: If the included studies are sufficient (≥10 trials), we will detect publication biases of included trials using funnel plots, Begg's and Egger regression test. (II) Evidence evaluation: The quality of evidence and the strength of the main result recommendations will be determined by using the guidelines of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).

Keywords: esophageal cancer; microRNA-203; prognosis; meta-analysis.

Dissemination plans: The results may be published in a peer-reviewed journal or disseminated in relevant conferences.

Contributions of each author:
Author 1 - Song Wang - Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Visualization, Writing-original draft.
Author 2 - Pingping Yu - Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing-original draft.
Author 3 - Zhen Meng - Formal analysis, Funding acquisition, Investigation, Methodology, Validation, Writing-review & editing.
Author 4 - Lin Feng - Conceptualization, Project administration, Resources, Software, Supervision, Validation, Writing-review & editing.