Study Protocol Systematic Review

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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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Abstract

Background: Previous studies have reported that microRNA-203 has an effect on the prognosis of with esophageal cancer (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.

Methods: Eligible studies were searched from Google Scholar, Embase, PubMed, Medline, Web of Science, Cochrane Library, China National Knowledge Infrastructure, China Scientific Journal Database, Chinese BioMedical Database and Wanfang Database. Papers in English or Chinese published from their inception to November 2020 will be included without any restrictions. Stata 14.0 and Review Manager 5.3 software were used for data analysis. Hazard ratios (HRs) and its 95% confidence intervals (CIs) were used to assess the prognostic effect of microRNA-203 on overall survival (OS) and disease-free survival (DFS). Methodological quality for each eligible trial will be assessed by using the Newcastle-Ottawa Quality Assessment Scale (NOS).

Results: This study will provide a high-quality evidence-based medical evidence of the correlations between microRNA-203 expression and OS and DFS.

Conclusion: The findings of this meta-analysis will show the effect of high expression of microRNA-203 on the prognosis of EC patients, and may find a new prognostic marker for EC.

INPLASY registration number: INPLASY2020110022.

Abbreviations: CIs = confidence intervals, DFS = disease-free survival, EC = esophageal cancer, GRADE = grading of recommendations assessment, development, and evaluation, HRs = hazard ratios, INPLASY = International platform of registered systematic review and meta-analysis protocols, LASP1 = LIM and SH3 protein 1, NOS = Newcastle-Ottawa Quality Assessment Scale, OS = overall survival, PRISMA-P = preferred reporting items for systematic reviews and meta-analyses protocols.

Keywords: esophageal cancer, microRNA-203, prognosis, meta-analysis

1. Introduction

Esophageal cancer (EC) is one of the malignant tumor seriously threatened human health because of its extremely aggressive nature and poor survival rate.[1–4] According to global cancer statistics, about 572,034 (3.2% of all sites) newly diagnosed cases and 508,585 deaths (5.3% of all sites) occurred worldwide in 2018, ranking the sixth leading cause of tumor-related deaths in all malignant tumors.[1,2] Smoking, red meat consumption, hot tea drinking, low intake of fresh fruit and vegetables, poor oral health, and low socioeconomic status have been proved to be associated with a higher risk of EC.[1,2,5–8] The occurrence of EC varies by geographic area and ethnic group.[9] Its incidence rate can be as high as 30 to 800 cases per 100,000 persons in particular areas of northern Iran, some areas of southern Russia, and in northern China; the incidence in the US is approximately 3 to 6 cases per 100,000 persons.[9,10] Despite the improvement of diagnostic and therapeutic methods in the past decades, the prognosis of EC remains unsatisfactory.[9] Most EC patients already have advanced or metastatic lesions when diagnosed, due to the lack of noticeable clinical symptoms at its early stage.[9,11] The 5-year survival rate of stage III and IV EC patients was about 20% and 10% respectively.[1,9,11] Therefore, actively looking for the related prognostic factors is helpful to improve the overall survival of EC.

MicroRNA is a type of small non-coding single-stranded RNA molecule with a length of 18 to 25 nucleotides.[12–14] MicroRNA can bind with the 3'UTR sequence of messenger RNA (mRNA) to degrade mRNA or inhibit the transcription of mRNA, thereby participating in the biological processes of regulating cell

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proliferation, differentiation, apoptosis and innate immunity.[12,13,15] Some scholars have reported that microRNA may be involved as an oncogene or tumor suppressor gene in the occurrence and development of various tumors including EC.[12,13,16,17]

Several studies have shown that the upregulation of tissue microRNA-203 expression is positively correlated with the survival rate of EC patients.[16–22] Despite intensive clinical studies, the exact association between microRNA-203 and survival in patients with EC has not yet been systematically evaluated. In order to more accurately analyze the effect of high expression of microRNA-203 on the survival of EC patients. Our study comprehensively searched the literature related to the expression of microRNA-203 and the prognosis of EC patients, and used meta-analysis to evaluate the effect of high expression of microRNA-203 on the prognosis of EC patients.

1.1. Review question

Whether the high expression of microRNA-203 is in association with poor prognosis in patients with EC?

1.2. Study aim/Objective

This study will try to explore the effect of high expression of microRNA-203 on the prognosis of EC patients.

2. Methods

2.1. Study registration

Our meta-analysis protocol will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines.[23] This study has been registered on the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY). The registration number was INPLASY2020110022 (https://inplasy.com/inplasy-2020-11-0022/).

2.2. 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.

2.3. 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.

2.4. Eligibility criteria

2.4.1. Inclusion criteria.

(I) Patients diagnosed with EC based on pathology and histology. No restrictions regarding age, gender, racial, region, education and economic status;
(II) EC Patients are divided into microRNA-203 positive (high) and microRNA-203 negative (low);
(III) Studies that assessed the effect of high expression of microRNA-203 on overall survival (OS) and disease-free survival (DFS) of patients with EC;
(IV) The article provides the relationship between microRNA-203 expression and clinical pathological characteristics.

2.4.2. Exclusion criteria. 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.

2.5. Study selection and data extraction

2.5.1. Study selection. Two experienced authors (SW and PY) will be reviewed independently to identify potential trials by assessing the titles and abstracts. The full text will be further reviewed to determine potential eligible studies. Endnote X7 software will be used for literature managing and records searching. A PRISMA-compliant flow chart (Fig. 1) will be used to describe the selection process of eligible literatures. Excluded

Table 1

Searching strategy in PubMed.

Search Strategy
#1. "microRNA-203" or "miRNA-203" or "miR-203" [Title/Abstract].
#2. "Esophageal cancer" or "Esophageal tumor" or "Esophageal neoplasm" or "Esophageal carcinoma" or "Esophageal malignant" or "Esophageal oncology" or "Oesophageal cancer" or "Oesophageal tumor" or "Oesophageal neoplasm" or "Oesophageal carcinoma" or "Oesophageal malignant" or "Oesophageal oncology" or "Esophagus cancer" or "Esophagus tumor" or "Esophagus neoplasm" or "Esophagus carcinoma" or "Esophagus malignant" or "Esophagus oncology" or "Cancer of the esophageal" or "Cancer of the esophagus" or "Cancer of the oesophageal" or "EC" or "OC" [Title/Abstract].
#3. "Esophageal cancer" or "Oesophageal cancer" or "Esophagus cancer" [MeSH].
#4. #2 or #3.
#5. "Survival" [Title/Abstract]
#6. "Prognosis" [Title/Abstract]
#7. #5 or #6
#8. #1 and #4 and #7
#9. Limit #8 to human
#10. Limit #9 to yr=" -November 2020"

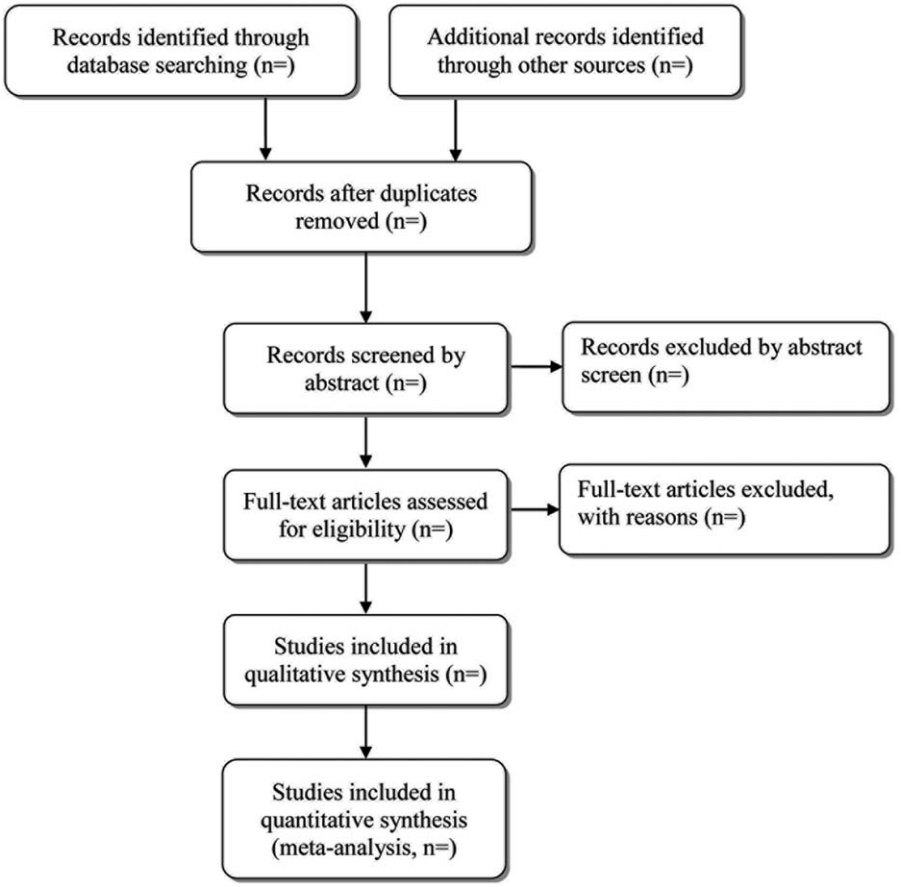

Figure 1. Study selection process for the meta-analysis.

studies and reasons for exclusion will be recorded. Disagreements between the two researchers will be resolved by consensus or by a third independent investigator (ZM).

2.5.2. Data extraction. Two investigators (SW and PY) will be responsible for the data extraction independently. The following data will be extracted from eligible literatures:

Study characteristics: first author's name, year of publication, country of study, sample size, microRNA-203 detection method, et al.

Participant characteristics: age, gender, race, inclusion and exclusion criteria, et al.

Outcome and other data: hazard ratios (HRs), and 95% confidence intervals (CIs) of OS and DFS, et al.

3. Dealing with missing data

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.

3.1. Measures of prognosis

OS and DFS will be taken as prognostic outcomes. HRs with corresponding 95% CIs will be extracted from trials or be estimated from Kaplan-Meier survival curves by established methods.[25]

3.2. Risk of bias assessment

Two experienced authors (SW and PY) will assess the risk of bias for each eligible literature by using the Newcastle-Ottawa Quality Assessment Scale (NOS) independently.[24] 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 (ZM).

3.3. Statistical analysis

Stata 14.0 (Stata Corp., College Station, TX) 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 I^2 statistic were used to assess heterogeneity among the included clinical trials. $P < .1$ for the Chi^2 statistic or an $I^2 > 50\%$ will be considered as showing considerable heterogeneity.[26] 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.

3.4. 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.

3.5. Sensitivity 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.

3.6. Additional analysis

3.6.1. Publication bias analysis. If the included studies are sufficient (≥10 trials), we will detect publication biases of included trials using funnel plots, Begg and Egger regression test.[27–29]

3.6.2. 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).[30]

3.7. Ethics and dissemination

This meta-analysis is a secondary research which based on some previously published data. Therefore, the ethical approval or informed consent was not required in this study. The results may be published in a peer-reviewed journal or disseminated in relevant conferences.

4. Discussion

EC is one of the well-known and deadliest cancers, and the mortality rate of EC has increasing year by year in the world.[1,2] When detected at early stages, EC can be curatively treated through less invasive methods, resulting in a 5-year survival rate above 90%.[31] However, the 5-year survival rate of advanced EC is only 15% to 25%.[1,32] Therefore, finding biomarkers with high specificity and high sensitivity has important clinical significance for the early diagnosis and prognosis of EC. In recent years, a large number of studies have shown that microRNA-203 plays an important role in the occurrence and development of EC. Takeshita et al[33] found that the expression of microRNA-203 in esophageal squamous cell carcinoma (ESCC) tissues is remarkably lower than that in non-ESCC tissues. There was a significant correlation between the expression levels of microRNA-203 and the relapse-free survival. MicroRNA-203 can significantly inhibit the migration and invasion of ESCC by regulating LIM and SH3 protein 1 (LASP1). He et al[34] indicated that microRNA-203 was down-regulated in EC tissues and was significantly associated with lymph node metastasis and poor overall survival. Therefore, its expression level could potentially be used as a prognostic indicator for EC patient outcomes. Zhang et al[35] showed that the overexpression of microRNA-203 in EC cells dramatically increased cell apoptosis and inhibited cell proliferation, migration and invasion as well as tumor growth. They also found that microRNA-203 may act as novel tumor suppressor in EC through down-regulating the expression of Ran (small GTPase) and microRNA-21. The results of Yu et al[36] demonstrated microRNA-203 could inhibit the proliferation and self-renewal of EC stem-like cells by suppressing stem renewal factor Bmi-1. All in all, we hope that this meta-analysis will provide more accurate and objective evidence for the relationship between microRNA-203 expression and prognosis in EC patients.

The systematic review will also have some limitations. There may be a language bias with the limitation of English and Chinese studies. In addition, the detection method and threshold of microRNA-203 may be different among the included trials. Therefore, there may be a risk of heterogeneity.

Author contributions

Conceptualization: Lin Feng and Song Wang
Data curation: Song Wang and Pingping Yu
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Funding acquisition: Zhen Meng
Investigation: Song Wang, Pingping Yu and Zhen Meng
Methodology: Song Wang, Pingping Yu and Zhen Meng
Project administration: Lin Feng
Resources: Lin Feng and Song Wang
Software: Lin Feng and Song Wang
Supervision: Lin Feng and Song Wang
Validation: Lin Feng and Zhen Meng
Visualization: Song Wang and Pingping Yu
Writing – original draft: Song Wang and Pingping Yu
Writing – review & editing: Lin Feng and Zhen Meng

References

[1] Domper Arnal MJ, Ferrández Arenas Á, Lanas Arbeloa Á. Esophageal cancer: risk factors, screening and endoscopic treatment in western and eastern countries. World J Gastroenterol 2015;21:7933–43.
[2] Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol 2013;19:5598–606.
[3] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
[4] Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019;144:1941–53.
[5] Oze I, Matsuo K, Ito H, et al. Cigarette smoking and esophageal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol 2012;42: 63–73.
[6] Castellsagué X, Muñoz N, De Stefani E, et al. Influence of mate drinking, hot beverages and diet on esophageal cancer risk in South America. Int J Cancer 2000;88:658–64.
[7] Dar NA, Islami F, Bhat GA, et al. Poor oral hygiene and risk of esophageal squamous cell carcinoma in Kashmir. Br J Cancer 2013;109: 1367–72.
[8] Huang FL, Yu SJ. Esophageal cancer: risk factors, genetic association, and treatment. Asian J Surg 2018;41:210–5.
[9] Song Q, Yang W, Meng Z, et al. Protocol for a systematic review and meta-analysis of Kang-ai injection for patients with oesophageal cancer. Medicine 2020;99:e22148.
[10] Pera M. Recent changes in the epidemiology of esophageal cancer. Surg Oncol 2001;10:81–90.
[11] Liu Z, Dong Y, Zhu M, et al. Xiaoaiping injection as adjunct therapy for patients with advanced esophageal carcinoma: a protocol for a systematic review and meta-analysis. Medicine 2020; 99:e20984.
[12] Zhang W, Wei L, Luo R, et al. The value of microRNA-21 as a biomarker for the prognosis of lung cancer: A protocol for systematic review and meta-analysis. Medicine 2020;99:e21483.
[13] Zhang W, Chen J, He G, et al. Impact of mirna-21 on survival prognosis in patients with pancreatic cancer: A protocol for systematic review and meta-analysis. Medicine 2020;99:e22045.
[14] Cheng CJ, Bahal R, Babar IA, et al. MicroRNA silencing for cancer therapy targeted to the tumour microenvironment. Nature 2015;518: 107–10.
[15] Jonas S, Izaurralde E. Towards a molecular understanding of micro-RNA-mediated gene silencing. Nat Rev Genet 2015;16:421–33.

[16] Shao Y, Gu W, Ning Z, et al. Evaluating the prognostic value of microRNA-203 in solid tumors based on a meta-analysis and the cancer genome atlas (TCGA) datasets. Cell Physiol Biochem 2017;41:1468–80.
[17] Xia Y, Wang Y, Wang Q, et al. Increased miR-203-3p and reduced miR-21-5p synergistically inhibit proliferation, migration, and invasion in esophageal cancer cells. Anticancer Drugs 2019;30:38–45.
[18] Hu JM, Chang AM, Chen YZ, et al. Regulatory role of miR-203 in occurrence and progression of kazakh esophageal squamous cell carcinoma. Sci Rep 2016;6:23780.
[19] Okumura T, Shimada Y, Moriyama M, et al. MicroRNA-203 inhibits the progression of esophageal squamous cell carcinoma with restored epithelial tissue architecture in vivo. Int J Oncol 2014;44:1923–32.
[20] Yuan Y, Zeng ZY, Liu XH, et al. MicroRNA-203 inhibits cell proliferation by repressing (Np63 expression in human esophageal squamous cell carcinoma. BMC Cancer 2011;11:57.
[21] Zhang K, Dai L, Zhang B, et al. MiR-203 is a direct transcriptional target of E2F1 and causes G1 arrest in esophageal cancer cells. J Cell Physiol 2015;230:903–10.
[22] Zong M, Feng W, Wan L, et al. MiR-203 affects esophageal cancer cell proliferation, apoptosis and invasion by targeting MAP3K1. Oncol Lett 2020;20:751–7.
[23] Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647.
[24] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[25] Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
[26] Jackson D, White IR, Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. Stat Med 2012;31: 3805–20.
[27] Lin L, Chu H. Quantifying publication bias in meta-analysis. Biometrics 2018;74:785–94.
[28] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
[29] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[30] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
[31] Arantes V, Espinoza-Ríos J. Early esophageal squamous cell carcinoma management through endoscopic submucosal dissection. Rev Gastroenterol Mex 2018;83:259–67.
[32] Le Bras GF, Farooq MH, Falk GW, et al. Esophageal cancer: The latest on chemoprevention and state of the art therapies. Pharmacol Res 2016;113:236–44.
[33] Takeshita N, Mori M, Kano M, et al. MiR-203 inhibits the migration and invasion of esophageal squamous cell carcinoma by regulating LASP1. Int J Oncol 2012;41:1653–61.
[34] He R, Wang J, Ye K, et al. Reduced miR-203 predicts metastasis and poor survival in esophageal carcinoma. Aging 2019;11:12114–30.
[35] Zhang F, Yang Z, Cao M, et al. MiR-203 suppresses tumor growth and invasion and down-regulates miR-21 expression through repressing Ran in esophageal cancer. Cancer Lett 2014;342:121–9.
[36] Yu X, Jiang X, Li H, et al. MiR-203 inhibits the proliferation and self-renewal of esophageal cancer stem-like cells by suppressing stem renewal factor Bmi-1. Stem Cells Dev 2014;23:576–85.