INPLASY PROTOCOL

To cite: Xu et al. Circulating long noncoding RNAs as potential biomarkers for stomach cancer: A systematic review and meta-analysis. Inplasy protocol 202120079. doi: 10.37766/inplasy2021.2.0079

Received: 26 February 2021

Published: 26 February 2021

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Support: **2019 Kunshan Key R&D Plan.**

Review Stage at time of this submission: **Piloting of the study selection process.**

Conflicts of interest:
None.

Circulating long noncoding RNAs as potential biomarkers for stomach cancer: A systematic review and meta-analysis

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Review question / Objective: **This meta-analysis aimed to identify the diagnostic performance of circulating lncRNAs in stomach cancer.**
Condition being studied: **Based on 2018 global cancer data, stomach cancer (SC) is the 5th most common neoplasm and the 3rd most deadly cancer, causing an estimated 783, 000 deaths in 2018. Studies have shown that SC patients are often diagnosed at later stages due to the absence of typical early signs. As a result, the overall survival in patients with advanced SC is poor. Blood-based cancer biomarkers are ideal for screening and early detection due to their convenience and low invasiveness. However, the low sensitivity and specificity of conventional blood biomarkers limit their application. Long noncoding RNA (lncRNAs) are RNA molecules greater than 200 nucleotides that modulate gene expression at the levels of transcription, posttranscription and translation, but are not able to encode proteins. An increasing body of evidence has suggested that lncRNAs play a major role during the processes of tumorigenesis and development, which may offer new ideas for the early diagnosis of SC. LncRNAs can also be detected in blood, and circulating noncoding RNAs have become a new source of noninvasive cancer biomarkers, which can serve as new diagnostic biomarkers for SC. This comprehensive systematic review and meta-analysis was conducted to explore the diagnostic accuracy of circulating lncRNAs in SC.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 February 2021 and was last updated on 26 February 2021 (registration number INPLASY202120079).

INTRODUCTION

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METHODS

Participant or population: Patients with stomach cancer (diagnosed using recognized pathological diagnostic criteria). Exclusion: Adolescents (under 18 years of age) and elderly people (over 70).

Intervention: The Index test in this diagnostic meta-analysis is circulating long non-coding RNA. To prevent the missed screening of the included literature, we only designed "long non-coding RNA" in terms of "I" in the search strategy. We then explicitly screened for articles on circular long non-coding RNA in the process of title/abstract screening and full-text reading screening. Sample types include plasma, serum, and plasma/serum exosomes, etc.

Comparator: Not applicable.

Study designs to be included: The meta-analysis, correspondence, single-case reports, review articles, and animal model studies are excluded. There are no other restrictions on the types of research designs that meet the criteria for inclusion.

Eligibility criteria: The following inclusion criteria are used: 1. The expression of lncRNAs was determined in plasma or serum by quantitative reverse transcription-polymerase chain reaction or other molecular techniques; 2. Studies evaluated the diagnosis value of lncRNA for SC; 3. Sufficient data to determine false negatives, true negatives, false positives, and true positives. The exclusion criteria are as follows: 1. Duplicate publications; 2. The meta-analysis, correspondence, single case reports, review articles, and animal model studies.

Information sources: We will search the following databases for relevant English language literature: PubMed (MEDLINE), the Cochrane Library, Web of Science, and EMBASE. All published English articles will be searched until December 31, 2020, regardless of country or article type. The searches will be re-run before the final analysis. If literature data is missing, we will contact study investigators to obtain unreported data or other detailed information. If the missing data is still not available, the article will be eliminated.

Main outcome(s): For a meta-analysis of diagnostic accuracy, the pooled sensitivity, specificity, and the corresponding 95% CIs were used to determine the diagnostic value of circulating lncRNAs on stomach cancer. To quantitatively assess diagnosis accuracy, the area under the curves (AUCs) of summary receiver operating characteristic curves (SROCs) were determined. The SROC curve method is a meta-analysis of multiple different experiments of a certain detection index. According to the weight of their odds ratio, the diagnostic accuracy is comprehensively evaluated by fitting the SROC curve. Measures of effect in Diagnostic meta-analysis are true-positive, false-positive, false-negative, and true-negative.

Additional outcome(s): Fagan's nomogram was applied to judge the clinical value of circulating lncRNAs as a diagnostic method.

Quality assessment / Risk of bias analysis: Two reviewers (Xu J and Cao F) will independently assess the quality of each selected study. The methodological quality and applicability of the included studies were examined using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool using Review Manager software version 5.3. The QUADAS-2 tool is used to assess the quality of diagnostic accuracy studies. The QUADAS-2 tool contains four main areas: process and timing, index testing, reference standards, and patient selection. The risk of prejudice and apprehension were classified as "low", "high" or "unclear". The differences were resolved through discussions among all the researchers. Low-quality articles will be eliminated to ensure the accuracy of the research results.

Strategy of data synthesis: As mentioned above, measures of effect in Diagnostic meta-analysis are true-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TP). Sensitivity, specificity, and sample size are extracted from each selected article. We get TP, FP, FN, and TP by conversion. Sample size of the experimental group is TP + FN, Sample size of the control group is TN + FP, sensitivity = TP / (TP + FN), specificity = TN / (TN + FP)). First, we merge the individual effect sizes: obtain the pooled sensitivity, specificity, negative likelihood ratio, positive likelihood ratio, diagnostic odds ratio, and the corresponding 95% Confidence intervals by Forest plots. Second, The heterogeneity tests are carried out by the Q-test and I^2 statistics. P values of < 0.05 are regarded as statistically significant. An I^2 value > 50% and a P-value < 0.05 indicate significant heterogeneity between the included studies, and a random-effects model is applied. Otherwise, the fixed effects model is applied to evaluate the aggregated results if there is no obvious heterogeneity. Third, taking sensitivity and specificity as the primary combined effect size, it is possible to ignore the negative correlation between sensitivity and specificity. We fit the summary receiver operating characteristic curve. To quantitatively assess diagnosis accuracy, the area under the curves (AUCs) of summary receiver operating characteristic curves is determined. Forth, a sensitivity analysis is used to determine the stability of the results. Deeks' funnel plot examines potential publication bias. A P-value of > 0.1 indicates that there is no publication bias. Fagan's nomogram is applied to judge the clinical value of lncRNAs as a diagnostic method. Statistical analyses are performed using Meta-DiSc 1.4 (Romany Cajal Hospital, Madrid, Spain), Review Manager 5.3 (Cochrane Collaboration, Oxford, England), and STATA 12.0 (Stata Corp LP, TX, USA).

Subgroup analysis: We will consider subgroups such as lncRNA types, race (Asian/Caucasian), specimen (plasma/serum/exosome), and dysregulated state (upregulated/downregulated).

Sensitivity analysis: Sensitivity analysis will be performed to determine the results' stability by executing the "metaninf" command in the Stata software. After omitting the selected study one by one, we assess the sensitivity through changes in the combined estimates of the remaining studies.

Country(ies) involved: China.

Keywords: stomach cancer; circulating lncRNAs; diagnosis; meta-analysis.

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